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Meeting Report

Theme: Dissolution and Translational Modeling Strategies Enabling Patient-Centric Product Development
Guest Editors: Marilyn N. Martinez, Sandra Suarez, and Andreas Abend

Dissolution and Translational Modeling Strategies Toward Establishing an *In Vitro-In Vivo* Link—a Workshop Summary Report

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ABSTRACT. This publication summarizes the proceedings of day 2 of a 3-day workshop on "Dissolution and Translational Modeling Strategies Enabling Patient-Centric Product Development." Patient-centric drug product development from a drug product quality perspective necessitates the establishment of clinically relevant drug product specifications via an *in vitro-in vivo* link. Modeling and simulation offer a path to establish this link; in this regard, physiologically based modeling has been implemented successfully to support regulatory decision-making and drug product labeling. In this manuscript, case studies of physiologically based biopharmaceutics modeling (PBBM) applied to drug product quality are presented and summarized. These case studies exemplify a possible path to achieve an *in vitro-in vivo* link and encompass (a) development of biopredictive dissolution methods to support biowaivers, (b) model-informed formulation selection, (c) predicting clinical formulation performance, and (d) defining a safe space for regulatory flexibility via virtual bioequivalence (BE). Workflows for the development and verification of absorption models/PBBM and for the establishment of a safe space using dissolution as an input are described with examples. Breakout session discussions on topics, such as current challenges and some best practices in model development and verification, are included as part of the Supplementary material.

KEY WORDS: clinically relevant dissolution specifications; IVIVC/IVIVR; physiologically based biopharmaceutics modeling (PBBM); safe space; virtual bioequivalence.

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INTRODUCTION

The integration of dissolution testing and translational biopharmaceutics modeling toward enabling patient-centric drug product development was the theme of a workshop (1,2) held at the University of Maryland's Center of Excellence in Regulatory Science and Innovation (M-CERSI) in May 17–19, 2017. Challenges and practical applications linking *in vitro* data to clinical systemic exposure were discussed during day 2 of this event via podium presentations and breakout sessions by scientists from the US Food and Drug Administration (FDA), international regulatory agencies, global pharmaceutical companies, and academia. Invited speakers shared case examples of physiologically based absorption modeling, PBAM (also referred to in this manuscript as physiologically based biopharmaceutics modeling (PBBM), population-PK *in vitro-in vivo* correlation (IVIVC), and PB-IVIVC/IVIVR (*in vitro-in vivo* relationship). The challenges faced during absorption model development, common reasons for lack of success of IVIVCs, and unmet needs were discussed by working groups. The current article summarizes the plenary talks and breakout sessions held during workshop day 2. Other related publications have focused on the role of dissolution in drug product development (workshop day 1, (3)) and regulatory applications of clinically relevant dissolution testing (workshop day 3 (4)).

BACKGROUND

The emergence of readily available physiologically based oral absorption and physiologically based pharmacokinetic (PBPK) models has led to a significant increase in the use of these methods in the pharmaceutical industry. This has prompted the issuance of general PBPK guidance from regulatory agencies, such as the FDA and European Medicines Agency (EMA) (5,6). While current PBPK guidance focuses on the application of these models for the prediction of drug-drug interactions (DDIs), physiologically based modeling is used for formulation optimization and selection to perform food effect and bioequivalence (BE) predictions, to establish IVIVC, and to conduct virtual trial simulations (5–8).

To accurately predict *in vivo* drug product performance (*e.g.*, systemic exposure) reflecting drug product variants, the model should consider the interactions between physiology and the pharmaceutical formulation. Specifically, a dissolution-based modeling approach should be able to predict the clinical impact of formulation variations in parameters measured in the chain of production, such as solid-state characteristics, particle size distributions, tablet tensile strength, porosity, and excipient qualities by (1) using *in vitro* data as an input to the absorption component of the model; (2) relying on the integration of mechanistic absorption into the model to account for fundamental physiologically related mechanisms, *e.g.*, intestinal transit times, dependences on luminal pH, or particle size-driven drug release/dissolution; and (3) the integration of systemic disposition/metabolism component to simulate plasma concentration *vs.* time profiles. For the purpose of this article, these modeling approaches, which combine absorption modeling, biopredictive dissolution testing, and PBPK, are referred to as PBBM.

Currently, PBBM entails the incorporation of biorelevant and/or biopredictive dissolution data, typically from different formulation variants (*e.g.*, different composition or manufacturing process) in the model. This can be considered analogous to the process of establishing IVIVCs. A future opportunity would be to mechanistically link input dissolution data to specific formulation characteristics, *e.g.*, a mechanistic model that would be able to separately describe disintegration, granule, and active pharmaceutical ingredient (API) dissolution taking into account hydrodynamics and concentration gradients in the gastrointestinal (GI) tract.

PBBM has shown utility in several cases, *e.g.*, development of model-based IVIVC and establishing safe space (4) criteria for a drug product. PBBM is built on the assumption that the *in vitro* dissolution/release of the drug can be qualitatively and quantitatively translated to an *in vivo* setting, *i.e.*, the experimental methods must be biopredictive. As such, biopredictive dissolution/release profiles from *in vitro* experimental methodologies are critical not only for the purpose of gaining an enhanced drug product understanding but also for generating reliable PBBM predictions, which are necessary for regulatory flexibility.

The breakout sessions summarized in the Supplementary material examined some of the gaps described above. Presented case examples discussing the link of *in vitro* data with *in vivo* outcomes are summarized below, and further details of the presentations can be found online (1). Commonly used abbreviations discussed at the workshop (1) can be found in Table I.

PRESENTATIONS AND CASE EXAMPLES

Challenges and Strategies in Establishing an In vitro-In vivo Link, Dr. Paul Seo, FDA (9)

During the Office of Pharmaceutical Science reorganization to the Office of Pharmaceutical Quality in early 2015, the Division of Biopharmaceutics was formed in the Office of New Drug Products. The reorganization was a prime opportunity to align the functions and strategy of biopharmaceutics-related scientific and regulatory issues. One of the primary goals was to emphasize linking drug product quality to clinical performance, a subset of the discussion involved "clinically relevant specifications." The presentation provided background information on the operational logistics of biopharmaceutics assessment for innovator (New Drug Application—NDA) and generic drug (Abbreviated New Drug Application—ANDA) applications and then proceeded to focus on the current and future states of IVIVCs at the FDA.

The findings of an analysis regarding IVIVCs in NDAs submitted to the FDA were presented. It was found that since 2008, approximately 54 IVIVCs were submitted using the NDA or Investigational New Drug (IND) application pathway. Solid oral dosage forms comprised at 74% of the 54 IVIVCs. Despite agency recommendations and considering the breadth and quantity of applications, the number of IVIVCs received remained low (10). The presentation inferred that the barriers to IVIVC are possibly due to the

Table I. Commonly Used Terms (Modified From (4))

Term	Definition
Clinically relevant	The term "clinically relevant" implies the establishment of a link between drug product quality attributes (*e.g.*, *in vitro* dissolution, purity), CMAs/CPPs, and *in vivo* performance (*e.g.*, systemic exposure).
Safe space	Boundaries defined by *in vitro* specifications (*i.e.*, dissolution or other relevant drug product quality attributes), within which drug product batches are anticipated to be bioequivalent to one another, or less optimally, but still possible, bioequivalent to the pivotal clinical batch(es).
Biorelevant dissolution method	A set of testing conditions for monitoring *in vitro* dissolution designed to closely mimic a relevant biological fluid and a physiological environment. Biorelevant may or may not be biopredictive.
Biopredictive dissolution method	A set of testing conditions for which *in vitro* dissolution profiles are capable of predicting pharmacokinetic profiles. These are typically based on classical or mechanistic IVIVC or PBBM.
Clinically relevant dissolution specifications	A set of *in vitro* dissolution testing conditions and acceptance criterion(ia) that can identify and reject drug product batches that are not expected to be bioequivalent to clinical pivotal product batches.
Clinically relevant drug product specification (CRDPS)	CRDPS are those specifications that demonstrate consistent *in vivo* drug product performance (*i.e.*, efficacy and safety). These specifications are established to identify and accept only drug product batches that are bioequivalent to clinical pivotal product batches.
Discriminating dissolution specifications	A set of *in vitro* dissolution testing conditions that along with the acceptance criterion(ia) are able to differentiate drug products manufactured under target conditions *vs.* drug products that are intentionally manufactured with meaningful variations (*i.e.*, formulation and manufacturing variants) for the relevant manufacturing variables (*e.g.*, drug substance particle size, compression force, tablet hardness).
QC dissolution specification	A set of *in vitro* testing conditions and acceptance criterion(ia) intended to ensure that a drug product adheres to a defined set of quality criteria that meet the requirements established by regulatory agencies.
IVIVC	A quantitative relationship validated based on a method of analysis conforming to current regulatory expectations, which links *in vitro* release to *in vivo* exposure.
IVIVE	*In vitro* to *in vivo* extrapolation, in the context of PBPK absorption modeling and simulation, refers to the quantitative transposition of experimental results or observations made *in vitro* to predict the systemic exposure, provided the PBPK absorption model has been adequately validated (*e.g.*, able to adequately predict failed BE batches).
IVIVR	A relationship, which fails the aforementioned definition (for an IVIVC) and has no regulatory application unless a safe space, is established (*e.g.*, when combined with bracketing approach).
PBBM	Physiologically based biopharmaceutics model(s) or modeling. PBBM is based on the same principles as PBAM and encompasses all areas of biopharmaceutics.
PBPK	Physiologically based pharmacokinetic(s) (33).
PBPK absorption modeling (PBAM)	Physiologically based pharmacokinetic(s) absorption models include ACAT (Advanced Compartmental Absorption Transit) and ADAM (Advanced Dissolution, Absorption, and Metabolism) as well as other mechanistic models, which mimic physiological conditions and incorporate dissolution information while accounting for relevant physicochemical and physiological factors leading to a prediction of systemic exposure versus time (8).

following factors: (1) IVIVC is viewed as "difficult"; (2) low acceptance rates of models (approximately 40%), (3) resource barriers, including knowledge, cost, and time; (4) ethical considerations; and (5) being regarded as an "all or nothing" approach. Moreover, some common reasons for unsuccessful IVIVCs were presented. It was found that traditional dissolution methods may not be biopredictive, formulation variants do not provide adequate difference in release profiles or were not appropriate (*e.g.*, release controlling excipient addition/deletion), and there was often lack of *a priori* planning of incorporating IVIVCs in the drug development.

Following the current state of IVIVC, the presentation moved on to future agency directions with regard to establishing an *in vitro*/*in vivo* link from a biopharmaceutics perspective. Emphasis was placed on the current lack of *in silico* modeling approaches presented in the quality section of dossiers received by FDA. It was stated that as agency resources become more constrained, advancing model-informed drug development (MIDD) (an element of Prescription Drug User Fee Amendments VI (11)) in the quality space could provide not only regulatory relief but also a deeper understanding of critical manufacturing process and formulation impacts *in vivo*. Moreover, PBAM was highlighted as a promising tool that has seen increased usage across disciplines at the agency, serving various functions in drug application review.

Within the biopharmaceutics discipline, it was found that since 2009, approximately 19 NDA submissions involved PBAM to support quality topics (10). Of the 19 submissions, approximately 75% of the PBAM models were found acceptable for their intended purpose. A balanced approach weighing the decision risk and the totality of available data contributed to the high acceptance rate of the models. Considering the successful applications of this "mechanistic" approach, the Division of Biopharmaceutics is also exploring

the applicability of mechanistic modeling and simulation to low-risk/high-reward ANDAs for generic drug products. It was noted that PBAM was used in a variety of justifications, including (1) dissolution method/acceptance criteria, (2) particle size distribution setting, (3) IVIVR, (4) risk assessment, (5) oral absorption in special populations, (6) supportive evidence of Biopharmaceutics Classification System (BCS), (7) effect of gastric pH, and (8) effect of food. Specific case examples of PBAM justification were provided, which included dissolution method and acceptance criteria selection, widening of specifications or parameters (*e.g.* dissolution, particle size, milling methods, dwell times) while maintaining ability to reject non-bioequivalent (non-BE) batches, and Scale-Up and Post-Approval Changes (SUPAC) level 3 changes.

Challenges and future directions were discussed. Early challenges included an overall reluctance by applicants to attempt PBBM upfront due to a perceived low acceptance rate or lack of experience. Submission of early development data to support PBBM was seen as a challenge, as no guidance on PBBM has been issued yet. Specific to ANDAs, no real avenue for engagement with regulatory authorities prior to submission was seen as a hurdle. Based on these early observations, the regulatory authorities intend to provide more clarity through publications, guidance, and regular use of written responses to recommend and promote collaboration of physiologically based biopharmaceutics model building and "mechanistic" IVIVC/R.

Application of Stochastic Deconvolution in IVIVC Development, Maziar Kakhi, PhD, FDA (12)

A recent review (10) shows that for regulatory submissions over the past decade, the acceptance of IVIVCs has been about 40% and the number of submissions per year has been reducing. Most IVIVC submissions employ two-stage, numerical deconvolution, and while it is not being asserted that this approach directly contributes to the low IVIVC acceptance and submission rates, such classical methods of deconvolution do present numerous drawbacks. For example, they are limited to linear, time-invariant systems, do not allow for a mathematically rigorous treatment of inter-subject variability, and require the administration of a reference (unit impulse response (UIR)) formulation. It is also not possible with numerical deconvolution to distinguish between *in vivo* release and subsequent absorption, which may be influential when trying to correlate *in vitro* to *in vivo* release. In this latter scenario, properly validated mechanistic/physiologically based absorption models can provide additional insights. However, in environments where complete mechanistic knowledge of the system dynamics is not available, a synergy of first-principle concepts, stochastic methods, and statistical approaches can provide an efficient, accurate, and insightful strategy for model development. Stochastic deconvolution is being proposed as one such possible approach representing a parameter estimation method embedded within a non-linear mixed effects population-PK formalism. In this approach, traditional compartmental kinetics requiring the solution of ordinary differential equations expressing mass balances is coupled to an absorption rate coefficient modeled as a mixed effect whose random component is described by a Wiener process.

A "proof of principle" example (13) has been presented, which demonstrates stochastic deconvolution's ability to reproduce very accurately *a priori* specified (*i.e.*, known) absorption profiles using simulated PK data for linear, non-linear, and time-invariant systems. The latter two scenarios are representative of Michaelis–Menten kinetics and enterohepatic circulation. It is noted that numerical deconvolution is not able to address non-linear and time-invariant systems.

A further example (13) is presented, which applies stochastic deconvolution to PK data generated for an IVIVC study of extended-release (ER) formulations of a BCS class III drug substance. By means of a full population-PK/stochastic deconvolution, scenarios were considered in which immediate release (IR) data were either retained or excluded to inform parameter estimation. The resulting fraction absorbed profiles were then used to model level A IVIVCs. All the considered stochastic deconvolution scenarios and numerical deconvolution yielded on average similar results with respect to the IVIVC validation. These results could be achieved with stochastic deconvolution without recourse to IR data for UIR characterization. Unlike numerical deconvolution, this also implies that in crossover studies where certain individuals do not receive an IR treatment, their ER formulation data alone can still be included as part of the IVIVC analysis. While the IVIVC development strategy employed in this study followed the current guidance recommendations of internal validation based on mean prediction errors (PE), it is hoped that increased application and testing of population-PK IVIVC methodologies could encourage the extension of validation criteria, so that inter-subject variability can be incorporated and a more rigorous picture of formulation performance evaluated.

Novel Approaches in Human PK Study Design (Stable Isotopes Technique) to Overcome the Challenges in the Conduct of Dedicated BA/BE Studies (Case Studies), Timothy H. Montague, PhD, GlaxoSmithKline (14)

Establishing BE of a product has been a challenge to the development of many compounds and therefore is a critical component in the drug development process. That importance has increased over time, especially with the desire to link *in vitro* data (*e.g.*, dissolution) to *in vivo* data and to support quality by design (QbD). The biggest challenge is how to develop this *in vitro*/*in vivo* link in the most efficient manner possible. Based on the product being developed and the number of critical quality attributes (CQAs) and critical process parameters (CPPs) for the product, the size and number of studies needed to define the appropriate design space could be quite large. Additionally, if the compound/product exhibits high *in vivo* variability, then the number of subjects needed for making a statistically significant conclusion could become quite high. Therefore, a method or study design that could deal with these issues could add significant value to the drug development process.

The application of stable isotope-labeled compounds to bioavailability questions described first by Heck *et al.* (15) may be one approach to overcome this challenge. Utilization

of a stable isotope-labeled drug substance provides the ability to measure plasma concentrations of an enriched and non-enriched drug substance from the same plasma sample (*i.e.*, subject). Thus, by co-administrating an enriched and non-enriched drug substance, it has been demonstrated that the variability of the statistical test used to compare formulations can be reduced (15) and subsequently reduce the required number of subjects to be studied.

The proposed approach here is a variation to that proposed by Heck *et al.* (15), which uses a stable isotope-labeled drug (SIL) as an internal control such that each subject in each dosing period will receive a small dose of the compound in question containing enriched isotope (SIL) in addition to the randomized formulation (reference or test). The two pharmacokinetic (PK) parameter values (*e.g.*, AUC) obtained for each subject/dosing period (non-enriched and SIL) should be highly correlated, $\rho > 0.95$ (16). Thus, when the statistical analysis "adjusts" for the SIL, the resulting variability of the statistical test is reduced, and subsequently, the required sample size is similarly reduced. Simulations indicated that the application of the stable isotope approach would result in a greater than 70% reduction in the residual mean square error and correspondingly, a greater than 80% reduction in the required sample size when the correlation between non-enriched and enriched concentrations was greater than or equal to 0.90 (16) (Fig. 1).

The stable isotope method is only appropriate under the assumptions that (1) formulations are qualitatively and quantitatively the same and (2) subject/period are qualitatively and quantitatively the same. Thus, this may not be valid for formulations with different components, drug interaction studies, food effect studies, and similar studies.

A clinical study was conducted to (1) confirm that the stable isotope approach would allow reduction in the number of subjects required to draw statistical inferences in both a crossover and parallel design (objective 1); (2) confirm that for formulations that were qualitatively and quantitatively the same, the methodology would result in unbiased results in the case of both known equivalence (objective 2) and (3) known inequivalence (objective 3) in both a crossover and parallel design; and (4) evaluate the effect of food on the correlation between stable isotope-labeled (SIL) and unlabeled PK to determine if it would introduce bias into the results (objective 4).

The study was conducted as four-way crossover study in 17 healthy volunteers in which one of four regimens (A, B, C, D) was administered in each period. In addition, enriched formulation (SIL) was administered in each period. Regimens A and B were the same oral formulation and dose. Regimen C was the same oral formulation as regimen A, but the dose was 25% higher. Regimen D was the same formulation and dose as regimen A, but administered with food (food know to decrease C_{max}). The SIL was administered as an aqueous solution and a dose that was 10% of regimen A.

The correlation between non-enriched and enriched (SIL) was as expected for AUC, but slightly lower than expected for C_{max} (0.85–0.89). Analysis of the data from all four study regimens (crossover design) resulted in a large reduction in variability for the statistical test both in the context of crossover and parallel group designs.

The pilot study identified some considerations for the synthesis and manufacturing of compound with a stable isotope. Synthesis of two different stable isotope-labeled compounds may be required if one is needed as an internal standard (typically with additional 13C atoms) for analytical purposes. When the drug in question is administered at low doses, the accuracy of administration of the stable isotope (at no more than 10% of actual dose) needs to be assessed. For poorly water-soluble drug substances, the use of solid state *vs.* solution state needs to be considered for the enriched formulation, and the impact on absorption should be

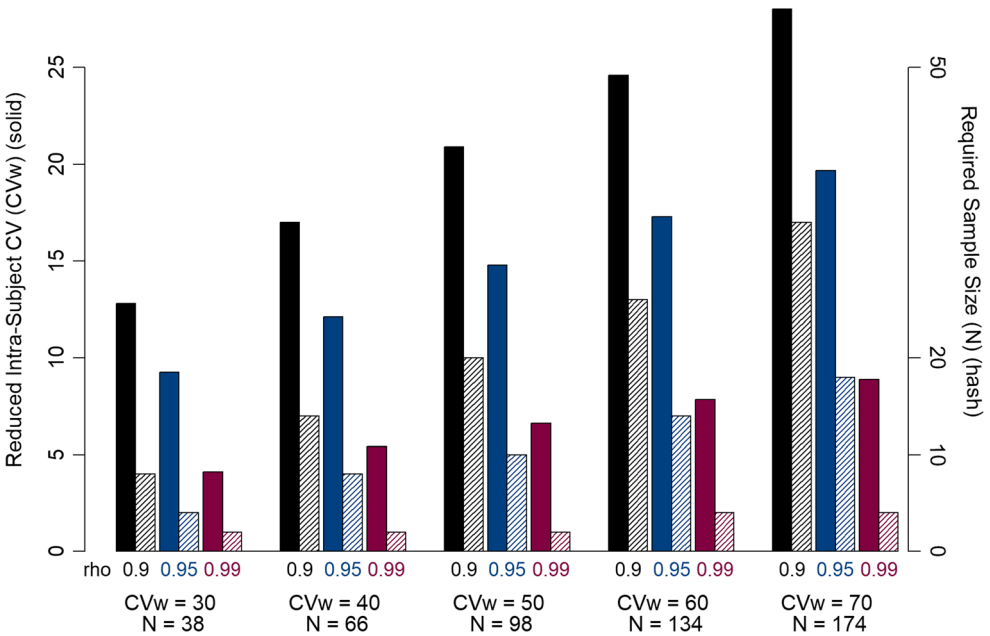

Fig. 1. Reduced variability as a function of sample size. Higher levels of reduced variability are possible with higher N. Solid bars represent intra-subject CV (CVw), and hashed bars represent required sample size to provide 90% power to demonstrate bioequivalence, as a function of the non-enriched and SIL correlation coefficient (rho)

assessed. Finally, the resource and cost for synthesis to produce a metabolically stable labeled compound need to be considered.

In summary, the isotope methodology can be a valuable tool for reducing the size of relative bioavailability and BE clinical studies, which in turn can help (1) provide *in vivo* data for QbD development to set clinically relevant specifications or (2) make conducting these studies for highly variable drugs or in difficult to recruit patient populations (*e.g.*, oncology patients). However, utilization of this method is limited to situations in which (1) the formulations are qualitatively and quantitatively the same and (2) the subject/period is qualitatively and quantitatively the same.

Development of Canagliflozin: Physiologically Based Absorption Modeling During Late-Stage Formulation and Process Optimization, Nico Holmstock, PhD, Janssen (17)

PBAM was used to assess the potential effects of particle size distribution of canagliflozin API on its oral bioavailability for non-particle-engineered (NPE) and particle-engineered (PE) API lots produced by two different crystallization processes. In addition to PBAM, also other approaches were used: evaluation of physicochemical characteristics, cross-study comparisons of human PK data, and a bioavailability study in beagle dogs. GastroPlus™ (Simulations Plus, Inc.) was used to develop a model of canagliflozin describing its *in vivo* absorption and PK across three dose levels (50, 100, and 300 mg) using available PK data (Fig. 2). A sensitivity analysis was performed to identify the most critical formulation properties affecting the absorption and plasma exposure (Fig. 3). Estimates of BE between the NPE and PE API lots were obtained using the virtual trial simulations accounting for variability in PK and physiological parameters. These data demonstrated that the differences in particle size distribution between NPE and PE API lots would not be expected to lead to any meaningful differences in the oral bioavailability of canagliflozin tablets and ultimately not affect the exposure of canagliflozin. The population-derived plasma C_{max} and AUC values would be bioequivalent between the tablets manufactured with NPE and PE API, regardless of the dose. Based on the similar physicochemical characteristics of NPE and PE API lots and similar bioavailability of tablets manufactured with NPE and PE API lots, it can be concluded

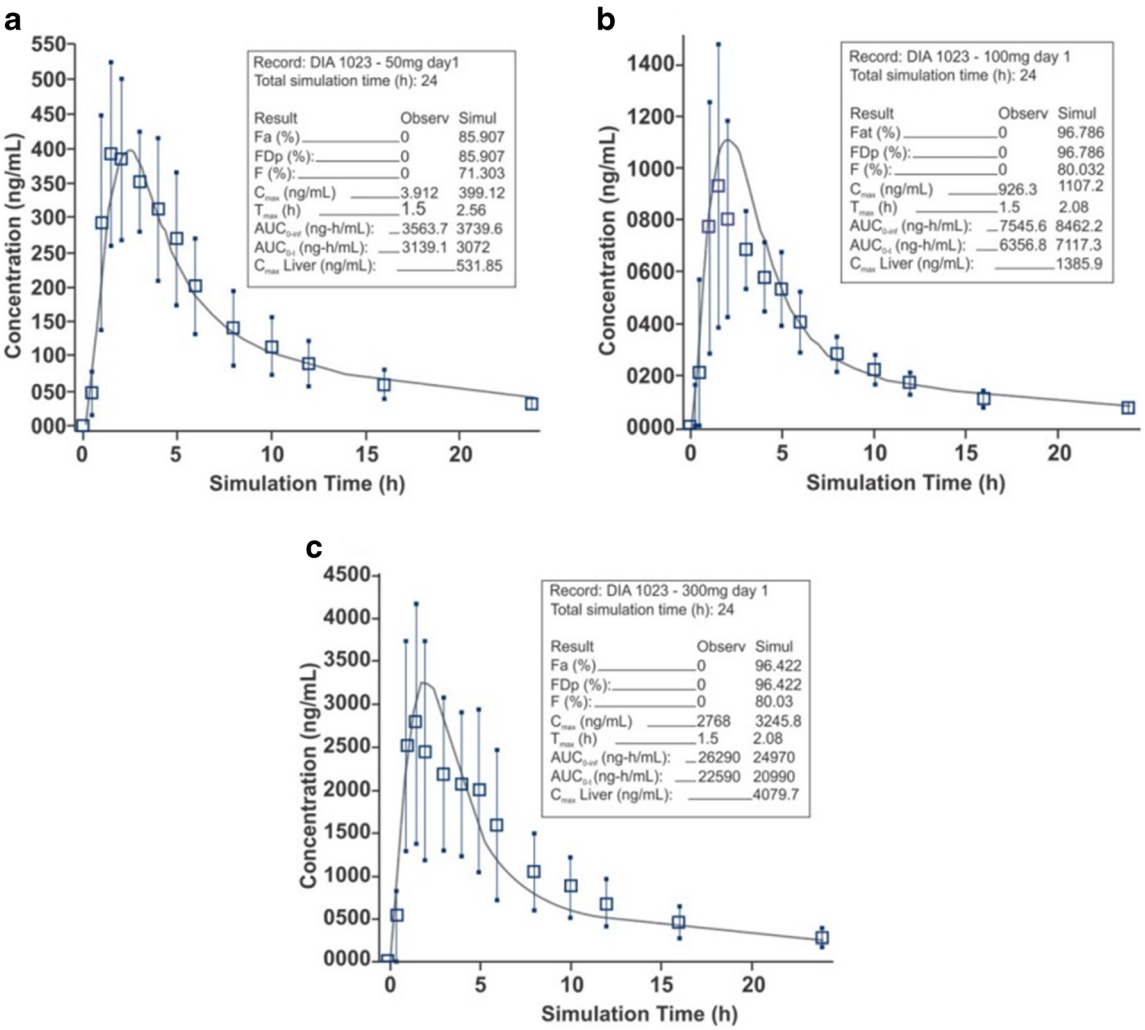

Fig. 2. Simulated (line) versus observed (squares) plasma concentrations of canagliflozin after oral dosing of 50 (**a**), 100 (**b**), and 300 mg (**c**) at day 1 as a function of time

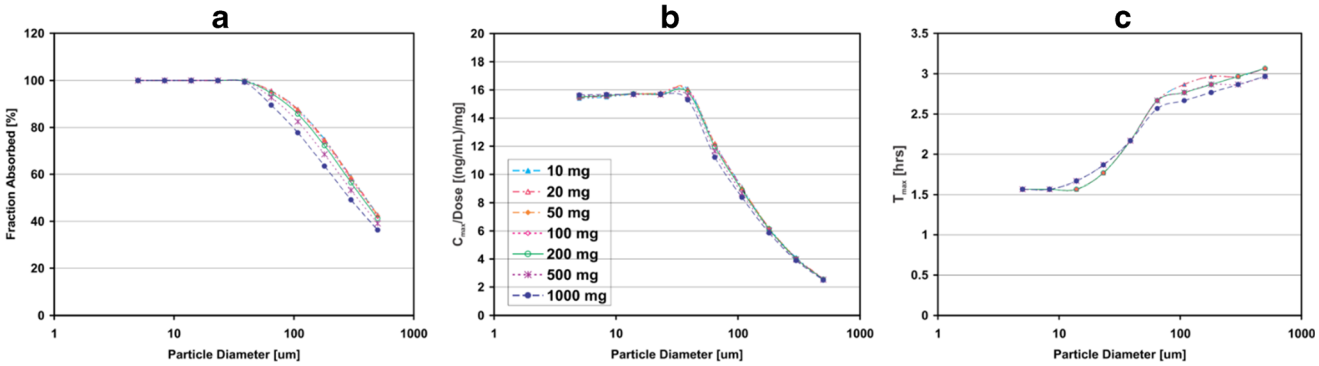

Fig. 3. Parameter sensitivity analysis of predicted fraction absorbed (**a**), C_{max} (**b**), and T_{max} (**c**) toward particle diameter

that data from clinical studies using NPE API lots can be used to support PK-labeling statements for drug product manufactured with PE API lots.

PBPK Absorption Modeling Challenges in Predicting Clinical Outcomes Across BCS/BDDCS (Biopharmaceutics Drug Disposition Classification System) Classes (Proton Pump Inhibitor Effects, Formulation Assessments, Food Effects): PBBM Case Studies From an Industry Perspective, Tycho Heimbach, PhD, Novartis (18)

Common questions for the *in vivo* performance of weakly basic drugs are (a) does food alter or enhance systemic exposure; (b) can co-administration of proton pump inhibitors result in reduced systemic bioavailability in patients; and (c) will the proposed to be marketed formulation have similar systemic availability compared to a proof of concept formulation? *In vitro* data was used in combination with a PBAM to describe or anticipate systemic exposure in the clinic. Specifically, in the presented example, pH-solubility data as well as solubility data in fasted and fed state were incorporated using PBBM to "mechanistically" describe a lack of food effects or lack of proton pump inhibitor interactions and to aid in a science-driven formulation selection for the final marketed tablet formulation. Drug E exhibited high solubility at or below pH 4.5 (>2.4 mg/mL) and lower (moderate) solubility at pH 6.8 (0.8 mg/mL) and pH 7.5 (0.3 mg/mL) in phosphate buffer devoid of surfactants. In biorelevant media, the solubility was moderate to high with similar values in both FaSSiF and FeSSiF (>2 mg/mL) yielding dose numbers of 1 to 1.1 for a 600-mg dose (19). Drug E permeability (P_{eff}) was moderate (0.9×10^{-4} cm/s), converted from a measured Caco-2 permeability of 0.18×10^{-5} cm/s. Drug E observed fraction absorbed from a non-optimized formulation in a human ADME study was 70% and was estimated to be >85% with capsule and tablet formulations. Drug E shows overall dose-proportional exposure over a dose range of 50–600 mg in clinical studies. Pharmacokinetics was also linear in the rat (up to 100 mg/kg) and the dog (up to 25 mg/kg).

For model development, commercial platforms were used integrating physicochemical/biopharmaceutics *in vitro* data. The disposition parameters were estimated "top-down" using clinical pharmacokinetic data from healthy subjects and were consistent with preclinical scaling methods. Default PBPK parameters in GastroPlus™ and Simcyp® were used. Parameter sensitivity analyses for percent mass absorbed were conducted, and a diagnostic plot showed that drug absorption is slower than dissolution (Fig. 4). Simulated *vs.* observed mean human PK profiles following oral 600-mg dose using PBAM are shown below in Fig. 5.

The PBAM and PBPK approach was considered to be of high-regulatory impact (20,21) as PBAM was used in lieu of

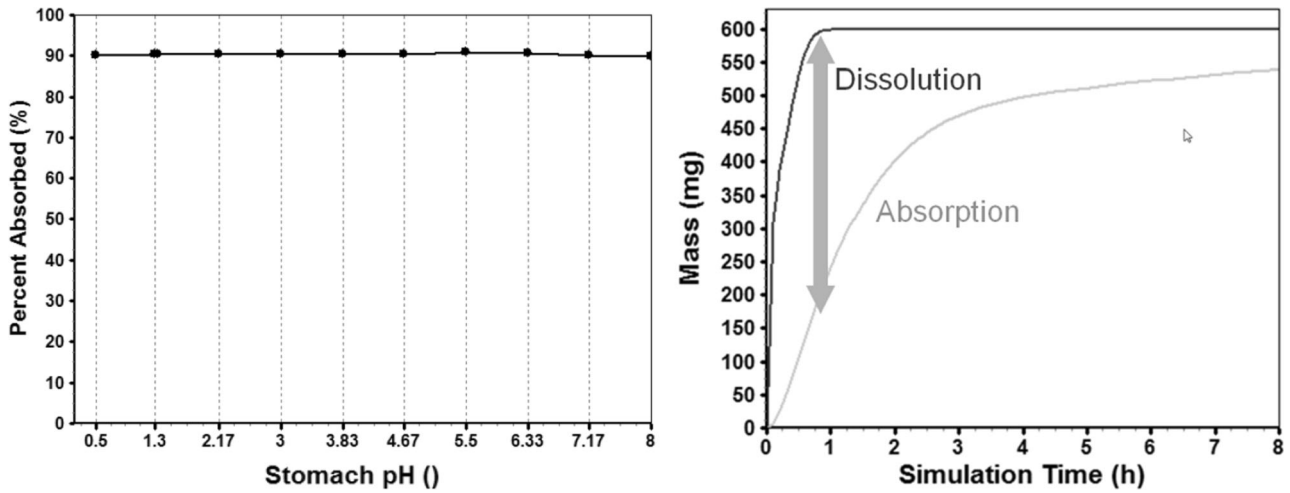

Fig. 4. (Left) Drug E's extent of absorption from the gastrointestinal tract is not altered and constant over a pH range from pH 1 to pH 8; (right) for drug E, the rate of dissolution is not rate-limiting systemic availability

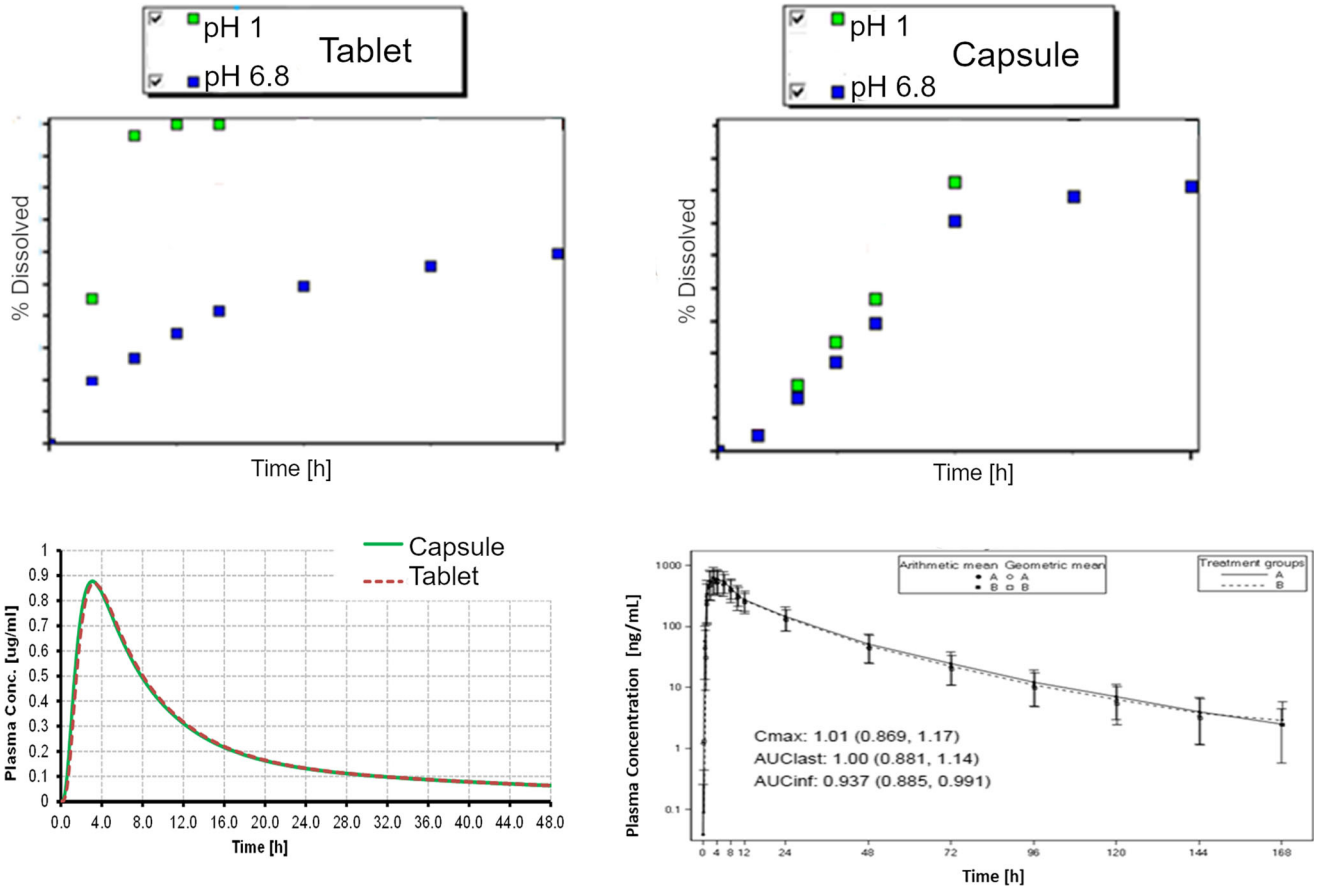

Fig. 5. Differences in representative dissolution rates between prototype capsule (hard gelatin capsule, HGC) formulations and tablet (film-coated tablet, FCT) formulations (top) were predicted to be bioequivalent and with no significant impact on systemic exposure (bottom left). This was consistent with clinical observations for the tablet (treatment A) *vs.* capsule (treatment B) (bottom right)

PPI as well as DDI (not shown) *in vivo* studies. Similar to examples in the literature, PBBM demonstrated that AUC and C_{max} were not significantly altered over a pH range of < 1 to 8 (22). For Drug E, absorption was independent of pH (Fig. 4, left panel), and dissolution was not rate-limiting for absorption (Fig. 4, right panel). While the tablet had a slower dissolution (Fig. 5, top) relative to the capsule, no impact on the systemic PK profile had been predicted. As predicted, the final formulation had similar exposure to an earlier prototype capsule formulation (Fig. 5, bottom).

Physiologically Based Absorption Modeling and IVIVC Used in Drug Product Development Projects, Andrés Olivares-Morales, Ph.D., Roche (23)

Three case studies of successful application of PBAM in drug development were presented. Case 1 introduced work to evaluate the impact of pharmaceutical properties on the pharmacokinetics of bitopertin (24). Bitopertin is a neutral BCS class 2 compound, and a PBAM was developed in GastroPlus™ (Simulations Plus, Inc.) to support drug product development. Model development followed a "learn and confirm" cycle that integrates *in vitro*, *in silico*, and *in vivo* preclinical data to build confidence in the model predictions (25). The PBAM was subsequently validated with clinical pharmacokinetic profiles obtained from single ascending dose (SAD) and multiple ascending dose (MAD) studies; the model was able to describe well the PK profiles from both studies. Based on parameter sensitivity analysis (PSA), the PBAM demonstrated that the particle size had a significant impact on bitopertin's absorption. These predictions were later on corroborated *in vivo* as the model accurately predicted the outcome of a relative bioavailability (BA) trial between capsules and tablets containing coarse- *vs.* finely milled API. The established PBBM played a key role into the establishment of a particle size specification range that would allow flexibility, yet minimized the risk of affecting bitopertin's absorption following a QbD paradigm.

The second case study described a "mechanistic" absorption model, by Stillhart *et al.* (26), to characterize the *in vivo* release and absorption of basmisanil, a poorly soluble BCS class 2 compound currently under development by Roche. The PBAM development for basmisanil followed similar steps as described before for bitopertin. However, given the availability of a human intravenous (IV) microdose study, these data were incorporated into the model development to better characterize the compound's disposition and thus allowing focusing the attention only on the "mechanistic" absorption predictions. The development model was validated against the data obtained in a SAD study, where the PBAM adequately captured the dissolution rate- and solubility-limited exposure of basmisanil as a function of dose (C_{max} and AUC). However, when the model was used to predict the relative bioavailability

between granules-in-sachet formulation *vs.* a newly developed film-coated tablet, the model was not able to capture the differences in exposure between the two formulations. The reasons for such difference were investigated via imaging techniques and *in vitro* dissolution testing of drug product and its intermediates. A link was established between the distribution of drug particles in the tablet matrix and its release profile in biorelevant media, suggesting that the drug load and tablet manufacturing process had a significant impact on the overall *in vivo* performance. A discriminatory dissolution method was developed using FeSSIF in a USP Apparatus II. This dissolution method did not establish sink conditions but was able to capture the differences in dissolution rate between the granules-in-sachets and film-coated tablet formulations. The dissolution profiles were used to build a "mechanistic" IVIVR in GastroPlus™ using a deconvolution approach. Not only the IVIVR was able to capture the difference in exposure between the two formulations but also IVIVR along with virtual BE simulations predicted the *in vivo* performance for both dissolution rate- and solubility-limited absorption dose ranges (C_{max} and AUC; dose range between 1.5- and 1250-mg basmisanil). The novel dissolution method combined with a "mechanistic" modeling approach along with virtual BE assessment allowed its use to guide formulation development for basmisanil.

A third case study showcased a "mechanistic" absorption model by Olivares *et al.* (27) to explain the higher bioavailability of oxybutynin's OROS® formulation compared to its IR tablet. Oxybutynin (OXY) is a BCS class 1 compound displaying short half-life and a low oral bioavailability (*ca.* 6%) predominantly due to high CYP3A-mediated presystemic extraction (hepatic and intestinal). Interestingly, when switching from an IR formulation to a sustained release OROS® formulation, OXY's bioavailability increases up to 70%. Therefore, a model was built to mechanistically investigate and explain such differences. OXY's model development followed a similar approach as the aforementioned case studies, combining *in vivo* disposition data with a PBAM that allows focusing on the prediction of the oral absorption and bioavailability. The newly developed model adequately captured the bioavailability differences between the two formulations using only *in vitro* and *in silico* inputs for the absorption-related parameters. In addition, a successful IVIVC was obtained for the OROS® formulation using only a release profile obtained for this formulation. Due to the "mechanistic" nature of the model, an analysis of the fraction absorbed, f_a, and fraction of drug escaping gut wall metabolism, F_G, and of differences between formulations was possible. This analysis provided evidence that the differences in bioavailability were likely due to a reduced intestinal CYP3A4-mediated first-pass metabolism in the OROS® formulation, rather than an increase colonic absorption (the f_a is reduced from 1 to almost 0.3 when switching from IR to OROS® formulation). In conclusion, the model suggested that the major driver of higher bioavailability observed for OXY OROS is the intestinal first-pass metabolism rather than the differences in fraction absorbed in the enterocytes between the two formulations. This particularly can affect CYP3A4 substrates due to the uneven distribution of the CYP3A4 enzymes along the GI tract.

In summary, three examples demonstrated that "mechanistic" absorption/dissolution modeling provided further insights with respect to the key factors contributing to oral drug absorption and bioavailability. The use of the right *in vitro* experimental and modeling approaches, such as "mechanistic-deconvolution," can guide clinical design and address team's questions related to formulation. Finally, one key aspect to all our examples was the validation of the modeling approaches with external datasets. This step was essential to generate confidence in the utility of PBAM and to gain acceptance from project teams, peers, and health authorities in order to allow their use for addressing absorption-related questions.

The Utility of PBPK Absorption Modeling and Simulation as a Tool to Increase the Success of Developing Biopredictive Dissolution Methods: Success and Limitations (Case Studies from Regulatory Perspective), Ho-Pi Lin, Ph.D., FDA (28)

PBAM is a promising approach for promoting clinically relevant pharmaceutical quality-based risk assessment and specifications due to its capacity in linking *in vitro* characteristics with *in vivo* clinical performance. Using clinical PK data generated during drug product development and dissolution profiles as model inputs for PBAM, two case studies, successful versus failed, were presented and summarized below.

Case study—drug product A is an IR tablet formulation designed for a BCS class 4 API. During product development, a clinical test formulation (CTF), at lower strength, was first tested in humans. Two formulations at higher strength were subsequently tested and showed that one was bioequivalent and the other was bioinequivalent to the CTF. These clinical PK data gathered during drug product development were leveraged to guide the development of a clinically relevant dissolution method, by which the non-BE formulation can be rejected. Specifically, a human PBAM using GastroPlus™ ACAT model was developed and validated and further used to prove the clinically relevant nature of the proposed dissolution method and to support the proposed dissolution acceptance criterion for all strengths. The model parameters were obtained either from clinical observations or optimized by fitting the PBAM to the observed PK profile after IV and oral administration. The PBPK model was successfully validated internally and externally (*e.g.*, PE were not more than 10%). The PBAM was further supported by successful prediction of observed clinical BE data by repeated *in silico* BE simulation comparing several dosing regimens using the respective dissolution profiles. This analysis supported the applicant's assertion that the proposed dissolution method is clinically relevant. Further, the validated PBAM was employed to support the proposed dissolution acceptance criterion for all strengths. In this regard, a virtual batch (representing virtual dissolution profile with the proposed Q value) and the reference pivotal BE batch were estimated to be bioequivalent based on the virtual BE simulations; this supported the proposed dissolution acceptance criterion.

Case Study—drug product B containing BCS class 1 API was designed as an extended-release formulation. A dissolution method capable of distinguishing meaningful changes in CQAs was developed. For PBAM building, IV data were

used to derive PK parameters, such as clearance and volume of distribution. For oral absorption, PBAM was subsequently established using the dissolution profile from a CTF at lower strength. The dissolution profile observed in higher strength of the same formulation was used for PBAM validation. Three additional formulations, showing slow, medium, and fast dissolution profiles, were used to perform virtual BE studies (actual PK data were not available for the three formulations). Simulated results showed the formulation with a medium dissolution rate was the only one BE to the CTF. Together with results showing that slow and fast formulations were non-BE to CTF, the clinical relevance of the dissolution method was claimed by the applicant. The claim was not accepted by FDA in part due to insufficient clinical data to properly validate the model. Adequate model validations are essential components for building a reliable model and its subsequent application. It may be beneficial to involve the regulatory agency at the early stage of model building and validation to increase the success rate of model.

The Utility PBPK Absorption Modeling and Simulation as a Tool to Develop Biopredictive Dissolution Methods, Liang Zhao, PhD, FDA and Eleftheria Tsakalozou, PhD, FDA (29)

The Office of Generic Drugs within the FDA is using PBAM to support product specific guidance development, pre-ANDA regulatory interactions, ANDA review consults, and the assessment of post-marketing signals. These efforts include assessments on *in vivo* locally acting product performance (mesalamine suppositories), alcohol dose-dumping potential (metformin hydrochloride ER tablets), release mechanism change risks (venlafaxine), identification of CQAs on product *in vivo* performance (prasugel), and approval of lower strength(s) based on *in vitro* dissolution performance when BE has been assessed at a higher strength for a generic drug product (fingolimod, OXY). The agency encourages the generic industry to follow a MIDD approach when proposing novel BE assessment methods.

To highlight how PBAM can be leveraged for regulatory decision-making, the case of OXY hydrochloride ER tablets was presented. The regulatory interest in this case stemmed from different drug delivery mechanisms between the innovator OXY drug product Ditropan XL® and its generic drug products; the brand name product was an OROS® osmotic delivery technology non-disintegrating tablet (reference drug product), while the generic drug products were formulated as enteric-coated matrix tablets (test drug product). The change in the delivery mechanism resulted in an increase in the time of C_{max} (T_{max}) in both fasting and fed states for the test compared to the reference product and a multi-peak PK profile only for the test formulations in the fasting state.

To quantitatively describe the delay in OXY absorption when formulated as an enteric-coated matrix rather than an OROS® 15-mg tablet (increased Tmax) and to assess the risk of not conducting *in vivo* BE studies for the lower strength OXY ER drug products (5 and 10 mg), an IVIVR was developed for both the reference and the test product. More specifically, a PBAM was developed in GastroPlus™ (version 9.0) by coupling the Advanced Compartmental and Transit (ACAT™) model with a one-compartment model to describe systemic disposition. Sensitivity analysis showed that the *in vitro* dissolution data employed for model development were critical in capturing the early absorption phase for both reference and test products as well as the multi-peak PK profile for the test products (Optimization Module™). The developed models reasonably described the mean observed data, summarized from five FDA-approved ANDAs, falling within the 95% prediction intervals of the simulated PK profiles. The previous models were further leveraged to develop IVIVRs utilizing the IVIVCPlus™ Module. However, in this particular example, the traditional Wagner-Nelson (WN) deconvolution method performed better than the "mechanistic" absorption modeling approach; the estimated % PE of exposure PK parameters were lower with the WN than with the PBAM method. Further analysis using the IVIVR supported the approval of the low-strength (5 and 10 mg) OXY test drug products based on the *in vivo* studies on the higher strength (15 mg).

Furthermore, the developed IVIVR along with virtual BE constituted the first step toward identifying biopredictive dissolution conditions for OXY ER drug products.

***In Silico* PBPK Modeling in Support of drug Product Dissolution and drug Substance Particle Size Specifications, Xavier Pepin, Ph.D., AstraZeneca (30)**

During the development of the IR formulation of Priadel® 200 mg, dissolution specifications were developed for product dissolution at the release and end of product shelf life. Failing to meet dissolution specifications at end of product shelf life was leading to batch destruction and significant costs associated to warehouse management for the manufacturing plant. Dissolution specifications were proposed to be changed post-approval by shifting them toward earlier time points. PBPK absorption modeling was used to support this change. A model was built in GastroPlus™ v7 based on the solubility, permeability of the drug, and disposition parameters obtained from a top-down analysis of an internal clinical trial with the reference formulation. Lithium carbonate is a highly soluble and highly permeable drug in the upper part of the intestine (permeability drops in the colon). The clearance is only renal, and there is no metabolism for this ion. The model was validated using historical data for several formulations of lithium, showing different dissolution rates covering the space for Priadel® 200-mg dissolution current and proposed specifications. Dissolution rate was entered in GastroPlus™ model using Weibull equation to fit the observed *in vitro* dissolution for various test products. The model validation was successful, showing PE of 9% on C_{max}, 7% on AUC, and 18% on T_{max} for the five formulations of the validation set. The model was then used to test virtual batches that would dissolve following the initial and the proposed new dissolution specifications at the end of the product shelf life. Exposure ratios calculated from this model were used to justify the new proposed dissolution specifications between which all products were anticipated to be bioequivalent. The post-approval change was accepted by the UK and Irish authorities in Spring 2012.

In another case example for Zurampic® 200-mg tablets, the objective was to evaluate the impact of *in vitro* dissolution on *in vivo* performance. This was achieved by

creating a safe space with dissolution data. High-regulatory impact was achieved as a biowaiver was granted based on PBPK absorption BA/BE modeling. During FDA review of the Zurampic® submission, the sponsor was challenged on the product dissolution specification: The FDA proposed to perform BE study between batch ELAB, which dissolved at the proposed specification and clinical reference 12A015 that exhibited faster dissolution, or perform PBBM to compare batches. Lesinurad, the active ingredient in Zurampic® tablets, is a BCS class 2 drug with low solubility at low pH (solubility = 6 μg/mL, 37°C at pH 1.6), but is very soluble in intestinal conditions. A model was set up using GastroPlus™ v9.0 using a clinical trial where the oral reference formulation was administered together with IV-microtracer to develop 10 individual models and evaluate the gastric emptying patterns of individual subjects (lesinurad pharmacokinetic profiles show absorption peaks in 30% of the subjects, which can be explained by gastric emptying patterns).

The model validation consisted of reproducing the clinical outcome of a study where a non-bioequivalent batch to the clinical reference was tested. During the course of this validation, four different methods to integrate dissolution data were tested. The only option, which could reproduce the clinical outcome, was to fit the *in vitro* dissolution data to a product representative particle size distribution (P-PSD) using a mechanistic model. This P-PSD allowed to explain dissolution rates in other medium compositions (31).

The GastroPlus™ approach taken consisted of running virtual clinical trials using reference and virtual batches to determine safe space where products are anticipated to be bioequivalent (Fig. 6). The same model was also used to show that the proposed drug substance particle size specifications were acceptable.

Summary and Recommendations of Meeting Breakout Sessions

In this section, a summary of the discussions that took place during meeting breakout sessions is presented. More detailed information of this topic can be found in the Supplementary material related to workshop day 2. Two general topics were examined in the breakout sessions:

1. Knowledge gaps to increase the use of PBPK and physiologically based biopharmaceutics models for regulatory decision-making: challenges with API space and formulation attributes.
2. Which data should be submitted to support the validation/verification of PBPK absorption models for regulatory decision-making? What are the recommended validation/verification acceptance criteria for physiologically based biopharmaceutics modeling and simulation?

It should be noted that the questions raised reflect the actual terminology used at the time of the workshop and may not reflect the current terminology use in this manuscript. A summary of commonly used terms is shown in Table I.

Key discussion points are captured below and further summarized in Fig. 7 in the context of PBBM, depicting a model development workflow for regulatory submission. A recurring theme was the concept of the safe space. To this end, the authors have summarized a general thought process via a workflow tree relying on biopredictive dissolution testing and physiologically based modeling (Fig. 8). A generalized approach toward establishing a safe space via virtual BE is illustrated in Fig. 9, and (hypothetical) dissolution profiles are shown as an example. PBBM defined a dissolution profile, which is bioequivalent to the pivotal batch.

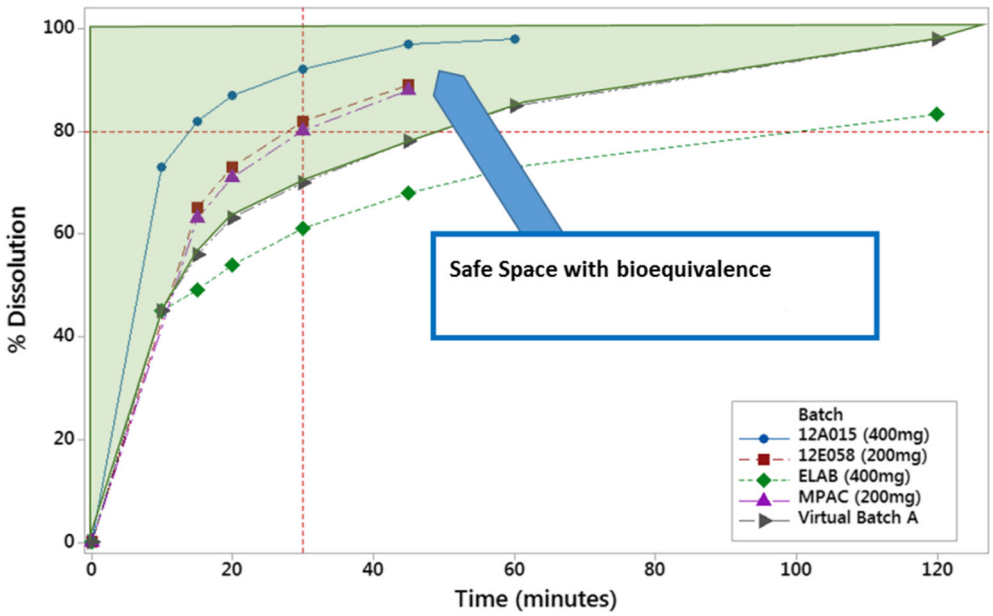

Fig. 6. *In vitro* dissolution space where lesinurad products are predicted to be bioequivalent based on physiologically based biopharmaceutics modeling. Reprinted with permission from Mol. Pharmaceutics 2016, 13, 9, 3256–3269. Copyright (2016) American Chemical Society

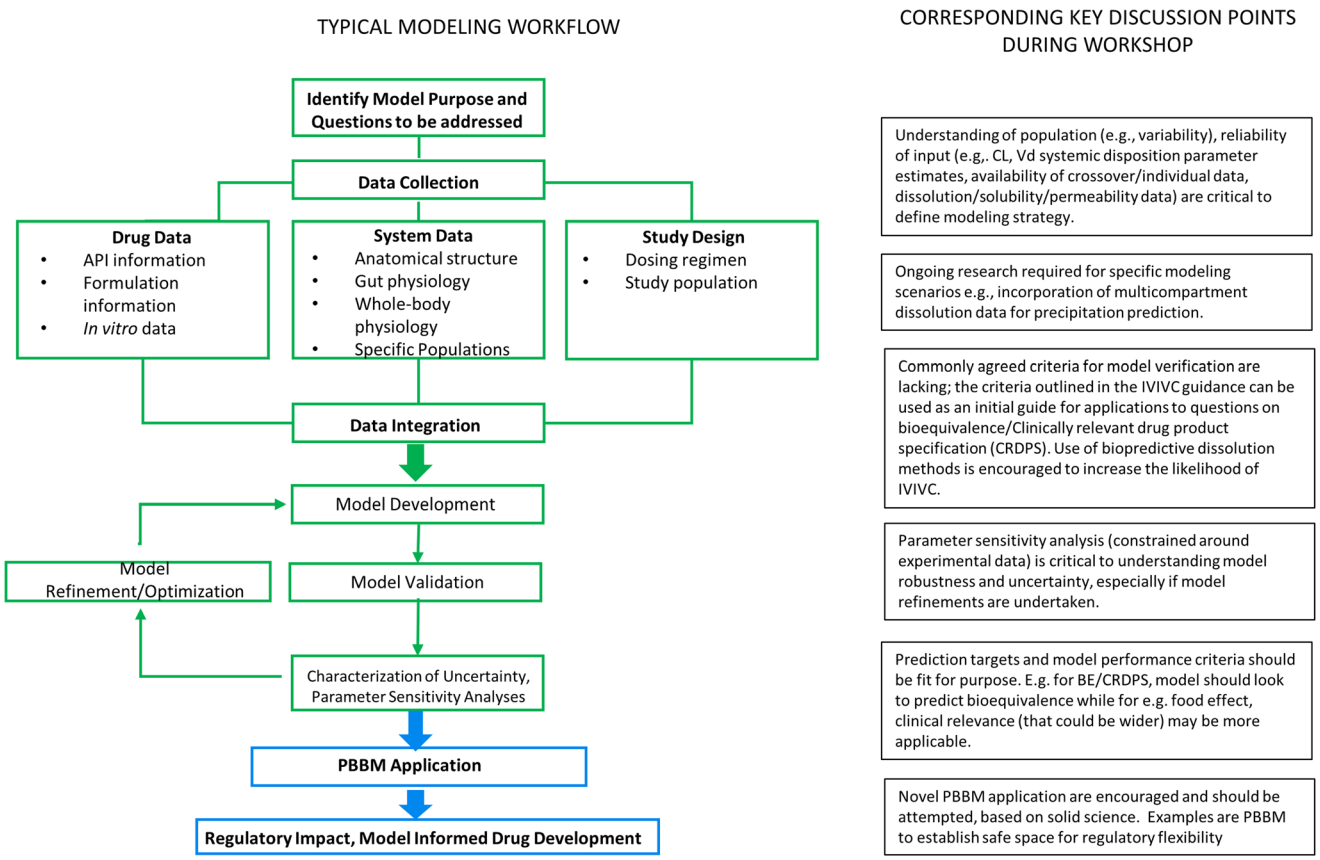

Fig. 7. A typical physiologically based biopharmaceutics modeling workflow should include key modeling objectives to be addressed. Key input parameters should be justified. Adequately qualified characterization of the population variability parameters should be included

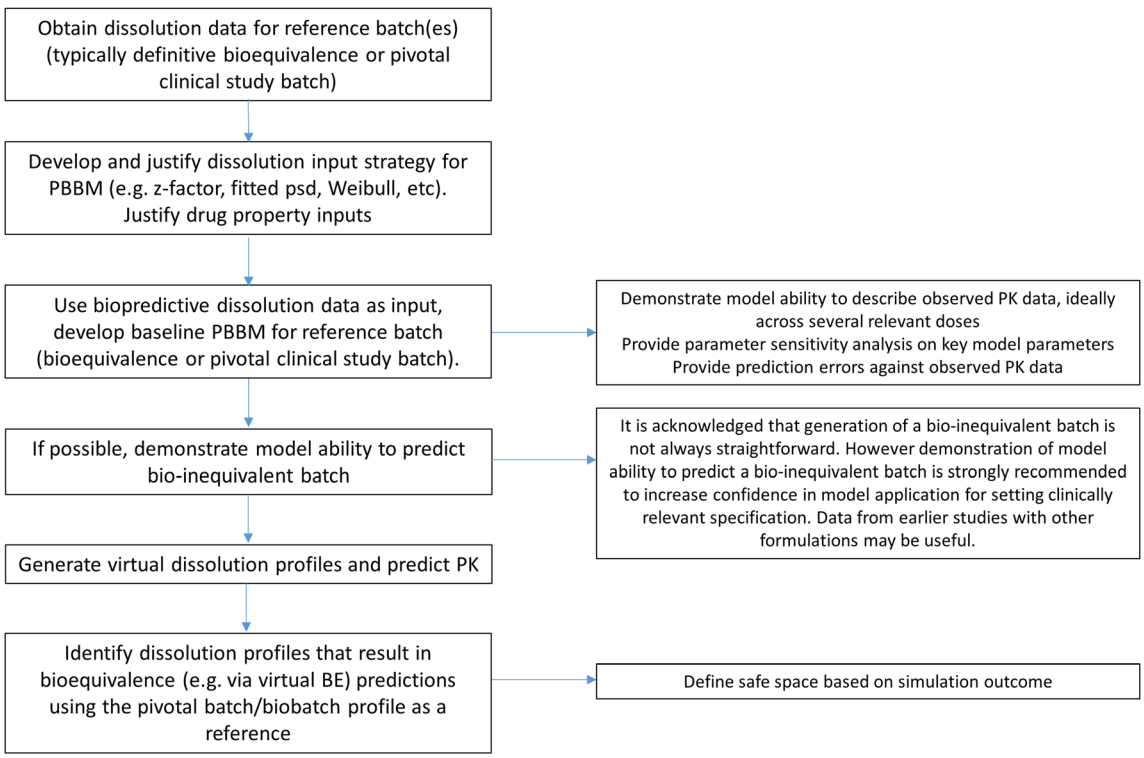

Fig. 8. Example workflow for application of physiologically based biopharmaceutics modeling toward establishing a safe space for clinically relevant specifications for immediate release products. A qualified baseline model is required, which is developed/verified following the workflow presented in Fig. 7

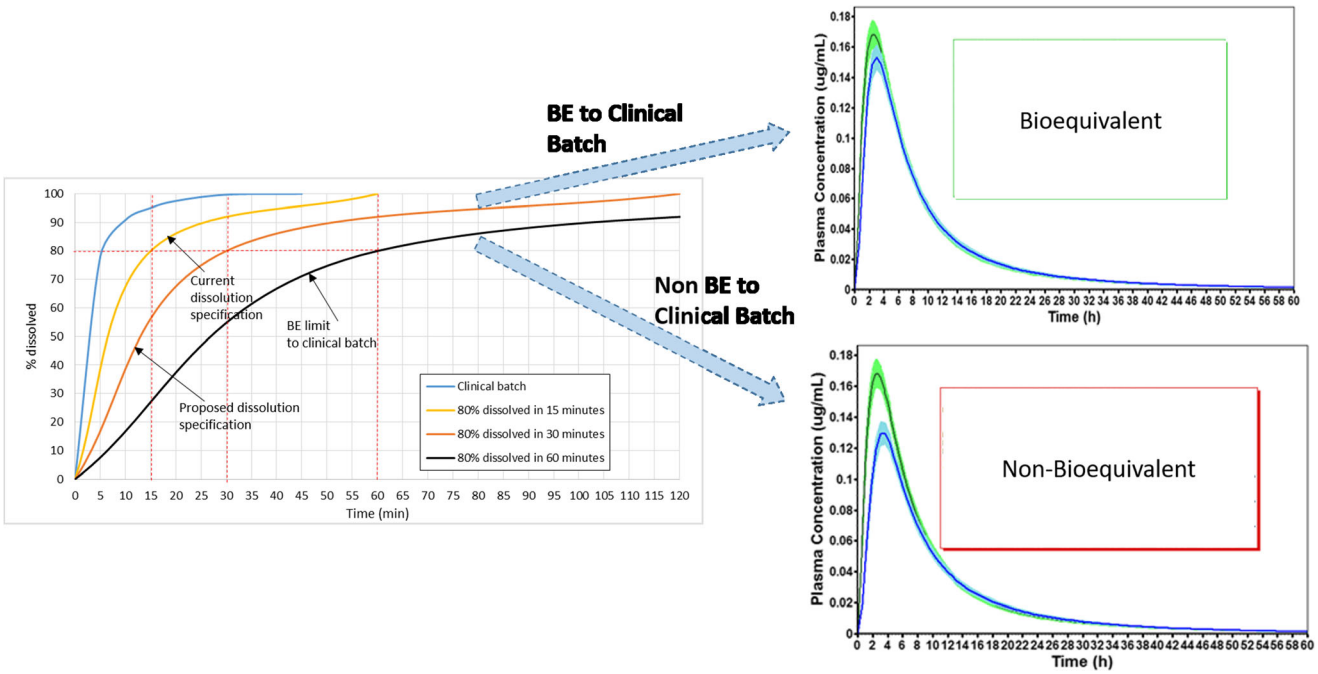

Fig. 9. A hypothetical example for application of physiologically based biopharmaceutics modeling toward establishment of the safe space. In this case, the safe space is established via virtual bioequivalence simulation for a hypothetical dissolution profile (80% in 30 min) between previously studied dissolution rates (80% in 15 and 80% in 60 min). The outcome of the virtual bioequivalence (BE) simulations is validated against observed clinical data prior to simulating the proposed "acceptable" dissolution profile. Thus, PBBM defines a dissolution profile (orange), which is bioequivalent and may be proposed as acceptance criterion as it shows virtual BE. It is bracketed by the yellow dissolution profile, which is BE to the pivotal batch, and the black dissolution profile, which is non-BE using PBBM, consistent with clinically observed data. Figure 9 has been modified from reference (32). A safe space example as applied to a drug development compound is described in Fig. 6

1. PBBM applications are strongly encouraged by FDA and are finding increased usage in the pharmaceutical industry. Nevertheless, it was recognized that there are still numerous challenges associated with *a priori* modeling of some processes (*e.g.*, API precipitation, drug release from a matrix of excipients, GI motility and hydrodynamics, transporter-mediated absorption, formulation disintegration, and non-oral routes of administration). In addition, there is still somewhat limited experience with PBBM in the regulatory setting, for example in the case of *in vitro* approaches in lieu of conducting *in vivo* studies or the prediction of food effects. In this regard, workshop attendees recognized that, to date, no specific PBBM guidance has been issued by regulatory agencies. Regulatory scientists encouraged sponsors/applicants to more frequently follow PBBM approaches in support of their submitted applications, thereby increasing the pool of experience upon which the new guidance can be based. FDA scientists engaged in biopharmaceutics review indicated that they intend to begin using standard wording in IND communications to encourage the use of PBBM.
2. The discussions focused on two distinct aspects of PBBM: (a) verification *vs.* validation of models as related to regulatory submissions and (b) specific input scenarios for simulations (*e.g.*, use of dissolution data). A general PBPK guidance, "*Physiologically Based Pharmacokinetic Analyses—Format and Content Guidance for Industry*," was issued by the FDA (6) that focuses on the format and content for submission of such models. These guidelines, in principle, are applicable to physiologically based modeling approaches, such as PBBM. The case examples presented throughout the conference, as well as the discussions during the breakout sessions, emphasized that for adequate verification, the quantification of model-related input parameters (*i.e.*, experimental or optimized) requires appropriate justification. Parameter sensitivity analysis of key model parameters should be provided.
3. The need to better describe and predict the variability in humans was identified as a topic of additional research. For drugs where high absorption variability is a concern, appropriate physiology variability data determined from GI biomarkers (pH, transit times, *etc.*) can be included in virtual physiological human population files as a means to further improve the link to *in vitro* dissolution. The need to conduct a sensitivity analysis to establish which physiological variable(s) critically impact *in vivo* dissolution was also stressed in the context of understanding sources of variability.
4. In discussing how to model systemic drug disposition in a PBBM, the participants stated that, in principle, minimal PBPK or whole-body PBPK models can be used. Specifically, attendees discussed that when the

focus of the modeling effort is on *in vivo* dissolution and absorption, it may be appropriate to combine a mechanistic absorption model with a minimal PBPK model (*e.g.*, simple systemic compartmental model that lumps major physiologic attributes from whole-body PBPK models). Such a simplification was considered acceptable, provided that the drug disposition does not compromise the ability to adequately describe processes governing the drug bioavailability (*e.g.*, if there is interplay between absorption and first-pass metabolism).

5. Clinically relevant dissolution methods were discussed without specifically identifying an *in vitro* dissolution method best-suited for PBBM. It was stressed that establishing an *in vitro-in vivo* link can be done using multiple approaches. Evaluation of *in vivo* absorption profiles (obtained by deconvolution) may serve as a blueprint to accelerate the development of a quality control (QC)/clinically relevant dissolution method (31). The use of biorelevant dissolution data integrated into PBBMs was also mentioned as a feasible path for defining a safe space.

CONCLUSION

Biopharmaceutics modeling to establish physiologically based relationships linking clinically relevant dissolution data to clinical outcomes remains a challenge and offers major opportunities. Regulatory agencies, such as the FDA, and scientists from the industry presented case examples of population-PK and PBBM approaches to inform clinical trials, develop IVIVCs, and set clinically relevant dissolution specifications using the safe space approach. This workshop (1,2) covered new terms, such as PBBM, in the biopharmaceutics community. There was an identified need for a specific PBBM regulatory guidance to further promote the development and application of PBBM to drug product quality. Likewise, regulatory agencies encouraged the use of novel, PBBM approaches to be included in regulatory submissions in support of drug product quality. The generation of a safe space for gaining regulatory flexibility using PBBM was highlighted (4).

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of Interest The authors declare that there are no conflicts of interest.

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