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PERSPECTIVE

Translational Modeling Strategies for Orally Administered Drug Products: Academic, Industrial and Regulatory Perspectives

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ABSTRACT During non-clinical and clinical development of a new molecular entity (NME), modeling and simulation (M&S) are routinely used to predict the exposure and pharmacokinetics (PK) of the drug compound in humans. The basic methodology and output are generally understood across all functional disciplines. However, this understanding is mostly restricted to traditional methods such as those in simplified kinetic models and void of adequate mechanistic foundation to address questions beyond the observed clinical data. In the past two decades, alternative and more mechanistic methods, particularly for describing absorption, distribution, excretion and metabolism (ADME) of drugs have been developed and applied under the general umbrella of physiologically-based pharmacokinetic (PBPK) methods. Their mechanistic nature gives the ability to ask many other questions which were not traditionally asked and provide some logically and evidenced-based potential answers. Whilst traditional PK methods are mainstream and understood by most scientists, mechanistic absorption models alongside other PBPK approaches are still deemed eclectic, despite making significant strides in the fundamental science as well as regulatory acceptance. On November 3rd, a short course was held at the annual American Association of Pharmaceutical Scientists (AAPS) meeting in San Antonio, Texas. The different talks were tailored to provide a basis or rationale for the subject, introduction to fundamental principles with historical perspective, a critique of the state-of-the-art, examples of successful application of the methods across different phases of the drug development process and the specific standards these mechanistic models should meet to be fully reliable from a regulatory perspective.

KEY WORDS oral absorption · physiologically-based biopharmaceutics modeling · physiologically-based pharmacokinetic modeling · product quality · regulatory

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ABBREVIATIONS

AAPS	American association of pharmaceutical scientists
ADME	Absorption, distribution, metabolism and excretion
API	Active pharmaceutical ingredient
AUC	Area under the curve
BCS	Biopharmaceutics classification system
BDDCS	Biopharmaceutics drug disposition classification system
BE	Bioequivalence
C_{max}	Maximal concentration
CMC	Chemistry, manufacturing and controls
CMC	Critical micellar concentration
CRDPS	Clinically relevant drug product specifications
CYP	Cytochrome P450

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DDI	Drug-drug interaction
DMPK	Drug Metabolism and Pharmacokinetics
EMA	European Medicines Agency
ER	Extended-release
FaSSIF	Fated state simulated intestinal fluid
FeSSIF	Fed state simulated intestinal fluid
HFHC	High-fat, high-calorie
HFLC	High-fat, low-calorie
HPβCD	hydroxypropyl-β-cyclodextrin
IR	Immediate-release
IVIVC	*In vitro-in vivo* correlation
IVIVP	*In vitro-in vivo* prediction
IVIVR	*In vitro-in vivo* relation
LFLC	Low-fat, low-calorie
M&S	Modeling and simulation
MR	Modified-release
NDA	New drug approval
NME	new molecular entity
PBBM	Physiologically-based biopharmaceutics modeling
PBPK	Physiologically-based pharmacokinetic(s)
PCDPD	Patient centric drug product development
PK	Pharmacokinetics
QbD	Quality by Design
QC	Quality control
SmPC	Summary of product characteristics
U.S. FDA	United States Food & Drug Administration

INTRODUCTION: GENERAL OVERVIEW OF THE COURSE

Over the years, a notable switch has been observed in the field of pharmacokinetic (PK) modeling where traditional approaches representing oral absorption as a simple first-order reaction have been revised and, in particular cases, replaced by more mechanistic modeling approaching considering the complex interactions a drug needs to face before reaching systemic circulation (e.g., luminal precipitation, transporter-dependent absorption, interaction of drug molecules with colloidal species and endogenous constituents). This specific part of 'mechanistic oral absorption modeling' has been brought under the term 'physiologically-based biopharmaceutics modeling (PBBM)', which is integrated and optimized in current physiologically-based pharmacokinetic (PBPK) platforms as applied by formulation scientists in the pharmaceutical industry.

The first part of this course was intended as an introduction to the discipline of 'Mechanistic Absorption and PBPK modeling'. There is a major gap of knowledge between the small group regular PBPK-users and those who are outside the core discipline of M&S. Also, the majority of traditional PK scientists are trained in compartmental PK (through, for example, Phoenix WinNonlin® or PKPlus™). Hence, the nuances and advantages of PBPK modeling (e.g., the impact of precipitation on luminal concentrations and systemic exposure) are presented here so as to enhance the understanding and utilization of these mechanistic approaches. The first talks were tailored to provide an introduction to fundamental principles with historical perspective and examples of successful application of the methods across different phases of the drug development process.

In the second part of this workshop, the specific standards that these mechanistic models should meet to be fully reliable from a regulatory perspective were thoroughly discussed. Regulatory authorities encourage the inclusion of PBPK and PBBM strategies to the application in support of regulatory decision-making. PBPK modeling could be essential in understanding the mechanistic phenomena such as underlying drug interactions in the human body which are otherwise difficult or impossible to ascertain in a clinical setting. Moreover, since drug products are given to specific patient populations, the nuances of that population and its impact on the PBPK modeling exercise should be determined. There is still a gap where validation of these settings and methods are still subjective and open to a variety of interpretations. As pharmaceutical companies are investing in these tools and techniques, this course discussed these aspects and their validation from a regulatory perspective. Recently, the European Medicines Agency (EMA) and U.S. Food & Drug Administration (FDA) have both released a guideline that describes the expected content of PBPK modeling and simulation reports included in the regulatory submission, mostly applied to look at drug-drug interactions (DDI). Followed correctly, this opens an opportunity to potentially grant requesting biowaivers.

PHYSIOLOGICALLY-BASED PHARMACOKINETIC (PBPK) MODELING: INTRODUCTION AND STATE-OF-THE-ART - AMIN ROSTAMI-HODJEGAN, PHD

The first talk emphasized the importance of PBPK modeling as an explorative tool to assess drug concentrations in the different organs of the human body, after being exposed to a drug via a certain route (e.g., oral, ocular, intravenous). From this basis, PBPK modeling has already played a pivotal role in the field of pharmaceutical drug development and environmental toxicology (i.e., predicting the exposure to a certain hazardous pollutant in the different organs of the human body) (1,2). The fact that PBPK models are able to predict drug concentrations, one may consider using alternative test methods and strategies that reduce, refine, and/or replace vertebrate animal testing (3R principle) (3).

Accurately and precisely predicting peripheral or systemic concentrations of a drug applying a PBPK model, all depends

on the input data derived from *in vitro* experiments (4,5). Related to intestinal absorption, apparent permeability of the compound of interest with a set of reference compounds can be measured in the Caco-2 system while interactions with uptake/efflux transporters can be performed using rat hepatocytes to determine K_m and V_{max} values (Michaelis-Menten kinetics). The integration of relevant concentrations of enzymes/transporters in PBPK models should be monitored in order to ensure relevant predictions towards the outcome of a drug and/or metabolites in the organ of interest. Based on collaborative research among different groups, large variability in measured concentrations of clinically relevant transporters and metabolizing enzymes was observed using mass spectrometry (6). As these values are of utmost importance for simulation software companies, a white paper was published communicating the standard operating procedures to quantify these proteins in, for instance, liver samples. In the case of healthy subjects, a wide variety of physiological data is available in the literature that can assist PBPK platforms to become biorelevant. However, in the case of specific populations (e.g., pregnant/lactating women), less information is available in the literature with respect to the impact of specific physiologic variables (e.g., V_{ss}, blood flow rates) on the systemic exposure of the drug due to ethical barriers (7,8). Nevertheless, the combination of a 'bottom-up' and a 'top-down' approach can actually estimate the values of the underlying physiological variables in order to explain the observed plasma concentrations of a drug (9).

Assuming that each and every person is unique, PBPK models are able to simulate individual concentration-time profiles using a stochastic modeling approach. Incorporation of variability in these underlying physiological processes is crucial to see the entire picture. In addition, a parameter sensitivity analysis (PSA) can be used to show the impact of a physiological variable on the systemic outcome of a drug in a certain physiological range (from a minimal to a maximal value) (10). A clear overview of how PBPK modeling fulfills drug development and regulatory recommendations have been shown by Zhao *et al.*, emphasizing that the principle of 'predict, learn and confirm' can only be assessed when measuring and understanding the impact of intrinsic/extrinsic factors on drug concentrations throughout the entire body (11). At this point, a total of 254 submissions were reviewed by the office of clinical pharmacology (U.S. FDA) including 94 new drug approvals (NDA). Each submission might contain more than 1 area of application. As depicted in Fig. 1, PBPK modeling is mostly applied in the area of drug-drug interactions (60%) and less in the field of absorption and/or food-effect modeling (4%) (12).

Figure 2 depicts the general components of a PBPK analysis package for submission to regulatory health authorities.

The green frame represents the PBPK platform components that undergo qualification; the blue frame represents the PBPK components that undergo model verification. The model iteration is considered a verification step when new data emerge (i.e., clinical observations) and new learnings are applied to the drug model. The model iteration is an essential step towards verification of the parameters and assumptions that were originally implemented, including newly generated data to confirm prior assumptions and optimize parameters where necessary, a process that is generally accepted as good modeling practice across various areas of modeling and simulation (13).

In the case of generic drug development, PBPK modeling is recently accepted to support bioequivalence (BE) evaluation which includes dermal PBPK as part of the support of not conducting a comparative clinical endpoint study with a similar formulation. The PBPK helped regulatory authorities to understand the systemic to local link and an *in vivo* BE study supported the BE assessment (14).

Also for NDA or generic drug products, the impact of excipients/manufacturing process/buffers/surfactants can be thoroughly explored when adjusting the biopharmaceutical input data (solubility, dissolution, and permeability in presence and absence of these constituents) and performing simulations for the population of interest (15). Based on the simulate outcome, confidence intervals can judge whether plasma AUC and C_{max} are in the prescribed confidence intervals (80–125%) to decide if the drug product can be considered BE or non-BE.

MECHANISTIC MODELING OF ENABLING FORMULATIONS IN PHARMACEUTICAL INDUSTRY – MICHAEL B. BOLGER, PHD

As many compounds suffer from a low aqueous solubility, enabling formulations (e.g., salts, solid dispersions, lipidic formulations, nanocrystalline API, and cyclodextrin-based solutions) are of utmost importance to tackle this hurdle and to create sufficient intraluminal concentrations as a driving force for intestinal absorption. In the second talk, Mike Bolger (Simulations Plus, Inc.) gave a comprehensive overview about how to explore the use of Physiologically-based Biopharmaceutics Modeling (PBBM) principles towards an understanding of *in vitro* absorption, distribution, excretion and metabolism (ADME) and *in vivo* data in preclinical studies to predict absorption and PK in human, especially for low aqueous compounds that require an enabling formulation to achieve sufficient therapeutic concentrations.

The apparent solubility in presence of bile salts and phospholipids can be greater than the intrinsic aqueous solubility as a function of pH due to the fact that more drug can be solubilized in the presence of micelles when concentrations of bile salts and phospholipids reach or exceed the critical micellar concentration (CMC). Only then, micellar structures will

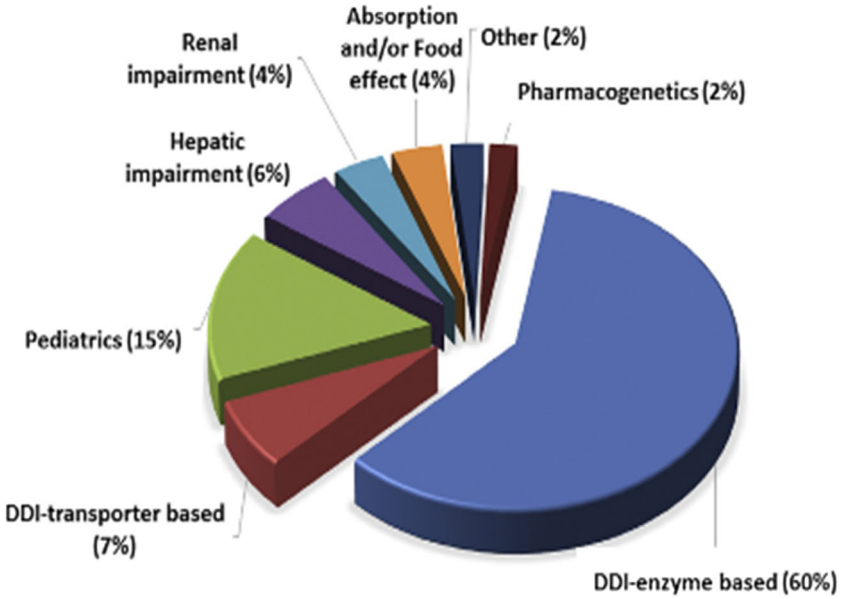

Fig. 1 PBPK modeling and simulation areas of intended applications in IND/NDA submissions reviewed by the US FDA's Office of Clinical Pharmacology from 2008 to 2017. A total of 254 submissions were reviewed by OCP including 94 NDAs from 2008 to 2017. Each submission might contain more than 1 area of application. For example, 1 submission may include one or more PBPK models to support enzyme-, transporter-mediated DDI assessment, effect of organ impairment on PK assessment, and food effect assessment. Figure adopted from Grimstein and co-workers with permission (12). Copyright Elsevier 2019.

be present to enhance the drug's solubility. Based on the work of Mithani (16), the impact of bile salts and/or phospholipids as an enhancer of drug solubility can be predicted using the following equation:

$$Sol_{bile,pH} = Sol_{aq,pH}\left(1 + \frac{Mwt_{H_2O}}{\rho_{H_2O}} \times SR \times C_{bile}\right) \quad (1)$$

With $Sol_{bile,\ pH}$ representing the *in vivo* solubility in a specific compartment (e.g., duodenum) with specific pH and bile salt concentration; $Sol_{aq,\ pH}$ representing the buffer solubility at a given pH; $\frac{Mwt_{H_2O}}{\rho_{H_2O}}$ is the ratio of the molecular weight of water and the density of water; SR is the solubilization ratio and C_{bile} is the *in vivo* concentration of bile salts in a given region (e.g., duodenum). According to the work by Mithani *et al.* the solubilization ratio can be estimated from the octanol/water LogP value, using the following equation:

$$Log\ SR = 2.23 + 0.61 \times LogP \quad (2)$$

Besides solubility as a key issue, the dissolution rate for these compounds is also affected; dissolution of the drug molecule is rather unfavorable than favorable from a thermodynamic point of view. Therefore, enabling formulations, such as nanocrystalline API particles, are an interesting approach to circumvent this problem as the particle size is strongly reduced. This formulation method should be distinguished from the use of nanoparticles as carriers of drug API. The resulting increase in surface area for interaction with the surrounding gastrointestinal (GI) fluid greatly facilitates dissolution. Besides

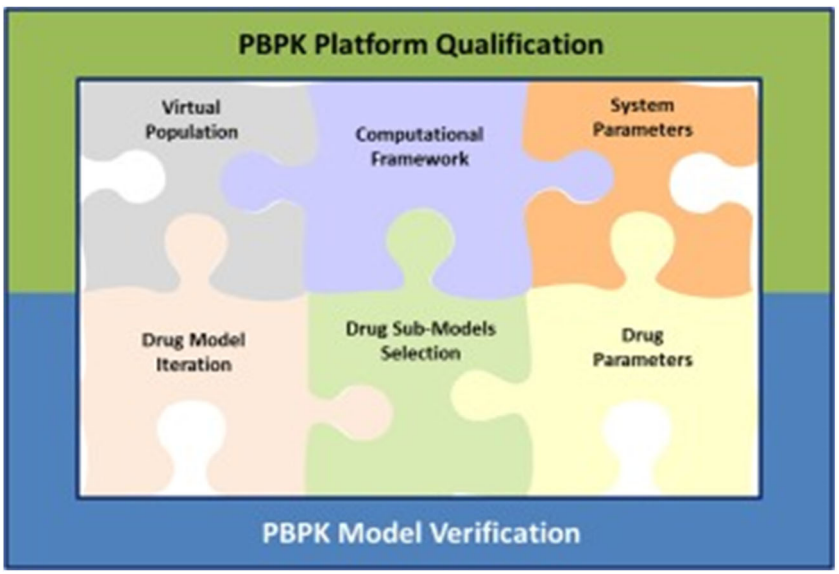

Fig. 2 General components of a PBPK analysis package for submission to regulatory health authorities. Green frame represents the PBPK platform components that undergo qualification; blue frame represents the PBPK components that undergo verification. Adopted from Shebley *et al.* with permission (13). Copyright Wiley 2018.

nanocrystalline API particles, amorphous drugs can more easily dissolve because of the absence of the crystal lattice. For these formulations, supersaturated concentrations of the drug can be achieved along the GI tract (17–19). With 'supersaturated concentrations', we refer to a state where luminal concentrations are reached that are higher than the *in vivo* solubility of the drug in that specific region of the GI tract. These supersaturated concentrations generate a high driving force for intestinal absorption and the level of supersaturation depends on the dose of the enabled formulation. Nevertheless, the supersaturated state is a meta-stable state, and the drug will have the tendency to precipitate until its level of solubility. The rate and extent of precipitation increases as the level of supersaturation increases with dose amount. Two different classes of drugs can be classified that show different precipitation kinetics (20,21):

1. class 1 drugs that are classified as fast precipitating drugs and the precipitate is characterized by a crystalline solid-state;
2. class 2 drugs that are classified as slow precipitating drugs and the precipitate is characterized by a transition through a liquid-liquid phase transition to an amorphous solid-state (20).

The question pops up how PBPK modeling can handle these processes carefully, taking into account the propensity of a drug to supersaturate and precipitate. This was elucidated by a couple of case examples including a solid dispersion of Nimodipine (Nimotop®) and a cyclodextrin-based solution of compound X. For both cases, low and high doses were explored.

For the first example (Nimotop®), precipitation was initially handled as a first-order precipitation process assuming that the drug precipitates with first-order kinetics until its level of solubility. The initial fast dissolution of the enabled formulation was modeled using a Weibull function based on fitting to *in vitro* dissolution data. For the 30 mg dose, a fitted precipitation time was found to be approximately 10-fold slower than for a dose of 90 mg to adequately reflect the systemic exposure of the drug. In a second experiment, precipitation was handled using the preferred method, the mechanistic nucleation and growth approach. This method takes into account that the amorphous solid dispersion with solubility 10 times higher than the crystalline solubility and 3 μm particle radius will drive the solid dispersion into solution at a supersaturated concentration that depends on the dose. This mechanistic nucleation model has only two factors that need to be fitted to explain the observed data for all of the doses. These factors are: (i) a surface integration factor and (ii) an exponential correction factor. One set of fitted parameters are applicable to any dose strength and have been used across species to predict first in human exposure.

Cyclodextrins can be applied as solubility-enhancing excipients for poorly soluble drugs. Drugs demonstrate a variety of affinities for the core of these structures, being more hydrophobic than hydrophilic (22–24). As GI transit and absorption occur the equilibrium of the cyclodextrin-drug complex will shift resulting in a relatively low concentration of free drug and an increasing concentration of free cyclodextrin. The cyclodextrin equilibrium generally prevents supersaturation and precipitation. Also, due to the lower concentration gradient, less mass per unit time is absorbed resulting in lower C_{max} and longer T_{max}. Capturing the dynamic interplay between free and complexed drug can be challenging. For two different doses of compound X, formulated as a solution in the presence of hydroxypropyl-β-cyclodextrin (HPβCD) and in the absence of cyclodextrin, precipitation characteristics were described applying the mechanistic nucleation model. Based on the simulated results, there was no precipitation of the cyclodextrin-solubilized solutions when the equilibrium of free compound X, complexed compound X, and HPβCD were taken into consideration. As the dose of compound X is increased and the amount of HPβCD is increased, the concentration gradient for free drug decreased while the permeability remained constant. However, as the dose increased, the unbound C_{max} in the duodenal enterocytes increased to a level that resulted in saturation of gut enzymes and a decrease in gut first-pass extraction and due to low unbound liver concentrations, the liver first-pass extraction remained constant.

MECHANISTIC MODELING OF ENABLING FORMULATIONS: AN ACADEMIC PERSPECTIVE – BART HENS, PHD

The third talk was demonstrating how mechanistic modeling can be applied in an academic setting. Based on EMA guidelines, PBPK modeling can be used to support a regulatory decision, however, the PBPK platform needs to be qualified for the intended use and the predictive performance needs to be demonstrated. As stated by the U.S. FDA guideline, the following information should be included in the submission to facilitate a timely review (25):

- Name and version of the software;
- Schematic view of the model structure and mathematical equations (or relevant references) based on established theoretical or biological knowledge;
- Parameterization of system information and sources of parameter values, such as databases used to describe the population variability and correlation between parameters;
- User's manual (i.e., instructions on how to run the code).

From an academic point of view, it is interesting to evaluate the impact of certain physiological variables on the systemic outcome of a drug and to what extent a PBPK model should rather be simple, complex or even more complex to adequately reflect the luminal and systemic behavior of a drug. Two specific case examples were presented. In the first case, a mechanistic absorption model was developed for the weakly acidic (Biopharmaceutics Classification System (BCS) class 2a) compound ibuprofen. Simulations were performed in commercially available software (GastroPlus™) and user-customized software (Phoenix WinNonlin®) platforms. In the second case example, simulations were performed for the basic compound (BCS class 2b) posaconazole, using the Simcyp® Simulator and GastroPlus™. For both test compounds, a clinical data set was available as a reference to validate the obtained simulations derived from both modeling platforms. In two independent clinical studies, luminal concentrations of posaconazole (17) and ibuprofen (26) were obtained by measuring these concentrations in the aspirated GI fluids of healthy subjects after oral administration of the drug product. For both compounds, gastric and intestinal concentrations were measured after oral administration of the drug by aspirating the fluids via an aspiration catheter, positioned along the GI tract. Simultaneously, the pH of the aspirates was measured. In parallel, blood samples were collected to determine the systemic concentrations. In the case of ibuprofen, GI motility was recorded by water-perfused manometry.

Using the Phoenix WinNonlin® platform, we aimed to reflect the luminal and systemic concentrations of ibuprofen under fasting state conditions starting with the simplest model, assuming a first-order kinetic process for dissolution, gastric emptying, and absorption (27). However, this model was not fully able to capture all the individual luminal and systemic concentration-time profiles. In a second step, the model was revised and dissolution was handled as pH-dependent and gastric emptying was handled as a first-order process until the time of appearance of phase 3 contractions (i.e., strong, repetitive contractions known as the house-keeper wave to remove any solid material directly out of the stomach into the small intestine) post-dose after which the remaining dose was directly transferred to the duodenal compartment (28). The mechanistic model focused on the integration of phase III contractions to simulate a house-keeper wave that is responsible for the direct release of ibuprofen particles from the stomach into the small intestine. In the different compartments of the small intestine, the dissolution of ibuprofen is driven by the regional pH, determining the fraction dissolved and undissolved. Afterward, a statistical analysis was performed to see how both scenarios matched with the observed luminal and systemic concentrations. In addition to this model, an advanced compartmental absorption and transit (ACAT™) model was developed in GastroPlus™ to assess the impact of dynamic pH, fluid volumes and gastric emptying on the systemic performance of ibuprofen. A comparison of these simulations was made with simulations performed by default settings. Implementation of the measured pH, residual fluid volumes and time to phase 3 contractions post-dose was done in separate time-dependent cat.-files which ran in the GastroPlus™ platform to reflect more dynamic simulations. In terms of luminal dissolution and absorption, the dynamic settings properly reflected the *in vivo* data, which could not be stated for the default settings. To evaluate the sensitivity of each physiological variable towards the systemic exposure of ibuprofen, sensitivity analyses were performed showing the importance of residual pH and rate of gastric emptying as key variables determining the systemic outcome of the drug.

In the case of posaconazole, a weak base, precipitation should not be neglected in the design of your workspace. Using the Simulator *in vitro* analysis (SIVA®) toolkit, Hens and colleagues modeled their *in vitro* data in this toolkit and were able to determine the precipitation rate constants that could be implemented in the Simcyp® Simulator to adequately reflect the luminal and systemic concentration-time profiles (29). Using GastroPlus™, precipitation was fitted as a first-order kinetic process, but fluids were handled as dynamic based on the residual fluids measured by MRI in healthy subjects after drinking 240 mL of water (30). These fluid volumes were implemented in the .cat-files together with the measured pH data from the aspirated GI fluids (31). Especially for these poorly soluble compounds (BCS class 2/4), the application of these dynamic fluids is demonstrating better results in terms of systemic outcome compared to the default settings where each segment of the GI tract has a certain volume that remains constant during the entire simulation run. In addition, when dealing with an ionized compound, the impact of pH should definitely be considered as this will determine the ratio of dissolved *versus* undissolved drug along the GI tract (32).

USING PBPK MODELING TO TACKLE DEVELOPMENTAL CHALLENGES – TYCHO HEIMBACH, PHD

PBPK modeling may predict or describe the PK of drugs in healthy volunteers or specific populations. Readily available software platforms, recent regulatory guidance, new in silico ADMET tools, as well as increased awareness in academic institutions, all have promoted interests in expanding PBPK in model-informed drug development. PBPK has become a scientifically important tool in drug development to identify drug development risks and to facilitate regulatory interactions or approvals. Verified PBPK models allow a mechanistic understanding of ADME processes, including food-effects on drug absorption, or drug-drug interactions (DDI). Case

examples highlight how PBPK modeling can e.g., i) impact clinical trial designs, ii) biowaiver studies, iii) inform the dosing regimen in specific populations, iv) inform product labeling language. The evolving roles of PBBM will also be covered (33). The session is expected to benefit both pharmaceutical scientists in academia or the industry interested in learning about PBPK opportunities and limitations. The impact of food on the systemic outcome of the drug was discussed for the in-house compound NVS B, whereas a pediatric PBPK model was described for nilotinib. Finally, a bioavailability (BA)/bioequivalence (BE) assessment was shown for the in-house compound NVS345.

With respect to PBBM, this format of modeling aims to establish an *in vivo-in vitro* link and to (i) develop a biopredictive dissolution method to support biowaivers, (ii) construct model-informed formulation selection, (iii) predict clinical performance and to (iv) design a safe space for regulatory flexibility via virtual BE. This opens the debate if we may shift from *in vitro-in vivo* correlation (IVIVC) to *in vitro-in vivo* predictions (IVIVP).

A pediatric PBPK model was developed in the Simcyp® simulator for nilotinib, taking into account the enzyme ontogeny, organ sizes and blood flows as known for the specified age groups of (i) 2 to 6 years, (ii) 6 to 12 years and (iii) 12 to 18 years old (34). In the first set of experiments, the adult PBPK model was validated against reference data. After validation, the model was adapted to physiological characteristics as observed for these defined age ranges. Moreover, important PK parameters such as K_a, CL and V_d were scaled towards the specific age range. The question that arose was if it is possible to scale the dosage strength based on the body surface area (BSA) for children aging from 2 to 6 years old as for this population PK data is rather scarce. Based on the simulated outcomes, it could be concluded that a BSA dosing approach is adequate in this population.

In a second case example, a successful PBPK DDI assessment was shown for panobinostat (Farydak®), an orally active hydroxamic acid-derived histone deacetylase (HDAC) inhibitor for the treatment of relapsed and refractory multiple myeloma (35,36). This marketed drug is approved by the U.S. FDA and EMA as a combination therapy with bortezomib and dexamethasone. This compound is characterized by high permeability and rapid absorption. Disposition of the compound is mediated by 53–70% non-CYP metabolism (hydrolysis, reduction, glucuronidation and one- and two-carbon chain shortening) and 30–47% CYP metabolism, predominantly by CYP3A4 and minor CYP2D6 > CYP2C19. Clinical studies were performed to evaluate the interaction with a CYP3A4 inhibitor (ketoconazole) and an inducer (rifampin) (37,38). The simulated data captured the observed data nicely well: the model informed the user that 40% of the drug was cleared by the contribution of CYP3A4, in line with the 30–47% as measured by human mass balance studies. The impact of these interactions was noted in the patient leaflet and summary of product characteristics (SmPC) stating that *'Simulations using PBPK models, predicted an approx. 70 % decrease in systemic exposure of panobinostat in the presence of strong inducers of CYP3A. Avoid co-administration of Farydak® with strong CYP3A inducers [see Drug Interactions (7.2)].'*

A final example of predicting a food effect and a food-effect under achlorhydric conditions was shown for the in-house molecular entity NVS345, a BCS class 2 compound. Reliable solubility and dissolution data, also in bio-relevant media such as fed (FeSSIF) and fasted (FaSSIF) state simulated intestinal fluid were available. ACAT built-in physiological parameters such as pH, transit times, volume and bile salt concentration across the intestinal tract were used to simulate fasted and high-fat, high-calorie (HFHC) meal conditions. For co-administration with ranitidine (H_2-antagonist inhibiting gastric secretion), pH in stomach was set to 6.50 (in fasted and fed state simulations). To simulate the food effect for low–fat, low-calorie (LFLC) and high-fat, low-calorie (HFLC) meal, several adjustments in the ACAT model were applied. The following scheme was applied to support the reliability of biopharmaceutics PBPK simulation of food effects (Fig. 3).

In terms of plasma C_{max} and AUC, the model was able to reflect the observed data when NVS345 was administered (i) in the fasted state, (ii) in the fasted state with ranitidine, (iii) with a low-fat meal, (iv) with a high-fat meal and (v) with a low-fat meal in presence of ranitidine. In the fasted state, absorption was limited by dissolution and precipitation, whereas intestinal permeability was the rate-limiting factor for the fed state conditions.

To commercialize this drug product, post-pivotal changes to the formulation of NVS345 were required for product commercialization (final formulation 2). A constant Z-factor was fitted with respect to *in vitro* dissolution data of NVS345 in biorelevant media (FaSSIF and FeSSIF) for both formulations. The BE study was conducted in the fasted and fed (HFHC) state with the highest dose strength (200 mg) to satisfy both the guidance (greatest differentiation of formulations in the fasted state) and clinical administration (product administered after food). For both cases, BE was shown both in the fasted and fed state for C_{max} and AUC_{last}/AUC_{inf}.

REGULATORY REQUIREMENTS FOR A PBPK MODEL: PERSPECTIVE FROM THE EMA – ANDERS LINDAHL, PHD

Industrial scientists should be aware of how a PBPK workspace needs to be built from a regulatory point of view and, even more important, how it will be evaluated by regulatory authorities. Anders Lindahl (Swedish Medical Products Agency) identified the most useful EMA guidelines for

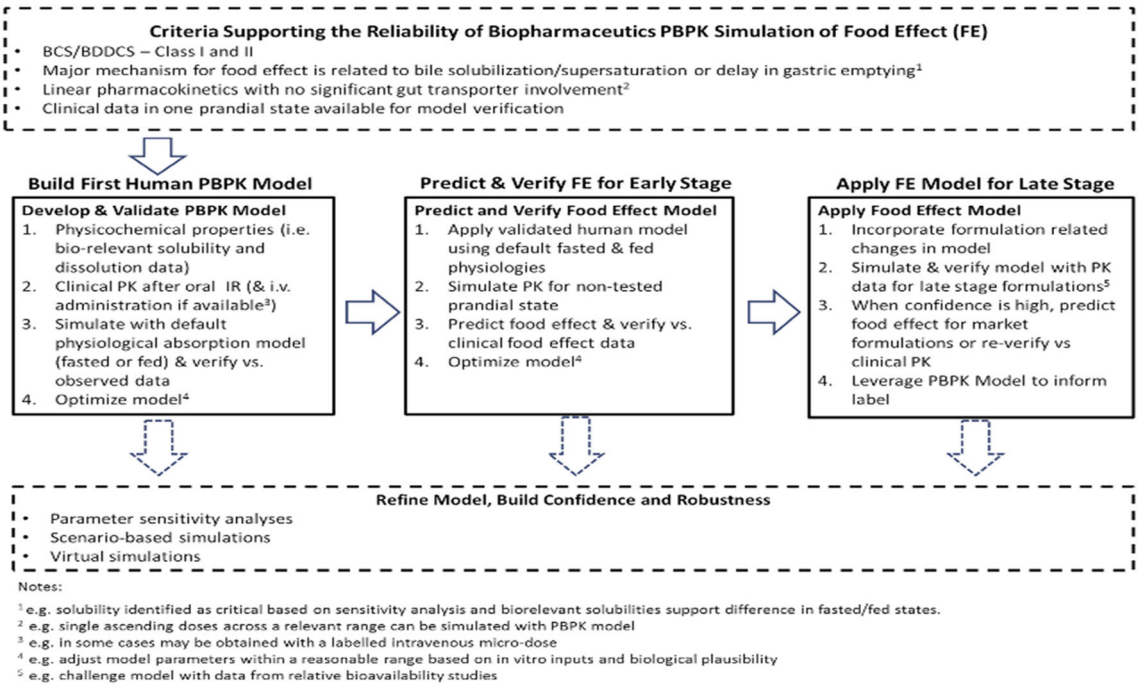

Fig. 3 Workflow for food effect predictions for BCS I and BCS II compounds. BCS, Biopharmaceutics classification system; IR, immediate-release; BDDCS, Biopharmaceutics Drug Disposition Classification System. Adopted from Tistaert and co-workers with permission (39). Copyright Elsevier 2019.

PBPK applications, taught the audience how a PBPK platform can be qualified and shared the top three things that assessors look at when evaluating a PBPK platform application.

The use of PBPK modeling was first introduced in EMA regulatory guidelines less than 10 years ago. The 'Investigation of drug interactions' guideline that appeared in 2012 (40) mentioned that *'PBPK models need to be qualified for its purpose. In general, the performance of the model needs to be supported by relevant in vivo data.'*

In December 13 of 2018, a new EMA guideline entitled 'Guideline on the reporting of PBPK modeling and simulation' was adopted, and came into effect on the 1st of July 2019 (41). Up until now, most applications sent to EMA using PBPK modeling are situated in the field of 'drug-drug interactions (DDI)'. Although PBBM is widely used in the pharmaceutical industry, the simulated data are rarely submitted to regulatory authorities. The reason for this phenomenon is because of (i) lack of recognized regulatory framework or guidance, (ii) lack of alignment in vision and approach across regulatory regions, (iii) lack of real case studies in the public domain where PBPK models have been used in regulatory interactions (42). The aim of the new guideline is to describe the expected content of PBPK modeling and simulation reports included in regulatory submissions. Moreover, this guideline clearly describes the documentation needed to support the qualification of a PBPK platform for the intended use. The platform can be commercially available, but there is no restriction in using an in-house built platform. When mentioning 'qualification of a PBPK platform', the EMA authorities are referring to certify that a PBPK platform can be used for an intended regulatory purpose (e.g., show for an extended-release formulation that the platform can also predict the extended-release of another drug compound). The user can refer to literature data to confirm this. The level of qualification depends on the regulatory impact of the simulation (e.g., high impact examples are, for instance, changes in SmPC, dose, posology to include children). To evaluate the predictive performance of the platform, one should assess the ability of the model to predict the range of the observed outcome of the representative *in vivo* PK studies or pop-PK analyses. The simulated outcomes should be compared with the observed data and when drug disposition would be simulated in a new population, the drug model evaluation should include simulation of the observed exposure in other populations. A parameter sensitivity analysis (PSA) should be conducted in order to point out these underlying variables that can cause quantitative changes in the model output. For instance, in case of oral absorption modeling for a drug product belonging to BCS class 2 or 4, GI pH, particle size and uncertain parameters that are hard to measure (e.g., precipitation time) should be included in the sensitivity analysis report. Applicants should be aware of what an assessor always looks for in a PBPK model:

1. Is the simulation platform suitable for the purpose?
2. Is the drug model capable of predicting the observed PK data of the compound?

3. What are the most important parameters in the model; how are they justified and how will the uncertainty in these parameters affect the predicted outcome?

A final take-home message was shared with the audience and should be considered when starting a PBPK application:

1. Read the EMA PBPK guideline before you start the modeling job;
2. Follow carefully the EMA guideline;
3. Guide the assessor through the PBPK model

   a. Qualification of the platform
   b. Parameter sensitivity analysis
   c. Evaluation of the drug model

CURRENT STATE AND FUTURE EXPECTATIONS OF PBBM TO SUPPORT DRUG PRODUCT DEVELOPMENT, MANUFACTURING CHANGES AND PROCESS CONTROLS: FDA PERSPECTIVE – SANDRA SUAREZ SHARP, PHD

'A quality product of any kind consistently meets the expectations of the user, drug products are no different.' Patients expect safe and effective medicinal products with every dose they take. Recently, the Agency is advocating the implementation of "Patient Centric" where the patient's perspectives are taken into consideration during drug product development and during the FDA's evaluation of new medicines. In more specific terms, patient centric drug product development (PCDPD), from a drug product quality perspective, is the development of science- and risk-based drug product specifications, in-process controls and control strategy that are linked to meaningful *in vitro*/ clinical *in vivo* tests, resulting in consistent product performance (e.g., safety and efficacy profiles) in the indicated patient population. Specifically, the establishment of clinically relevant drug product specifications (CRDPS) is part of PCDPD (43) and the identification of a safe space ensures CRDPS. One role of biopharmaceutics is to identify the drug substance and dosage form factors that affect the *in vitro* and *in vivo* performance to limit/mitigate the risk to patients. PBBM can facilitate this role. Some key considerations in the evaluation of risk from biopharmaceutics perspective are summarized in Fig. 4.

The use of PBBM is gaining substantial attention not only by the pharmaceutical industry but among several regulatory agencies for its application in support of drug product quality. This is evident by the significant increase in the last five years in the number of applications submitted to the Agency containing PBBM which includes widening acceptance criteria for certain attributes in drug product specifications and in support of biowaiver request. Physiologically based models are predicated on leveraging the scientific community's knowledge and experience through pooling existing/new data such as physicochemical, *in vitro* characterization, preclinical and clinical data and formulation variants. These unique features of physiologically based models increase the likelihood of establishing an IVIVR or IVIVC which are the basis for defining a safe space. As such, defining a safe space is a feature that characterizes PBBM.

In practice, the following schematic flow (Fig. 5) could be applied to guide applicants through the development and validation of a PBBM.

Just as the EMA, the U.S. FDA published new guidelines related of PBPK modeling in August 2018 entitled 'PBPK analyses – format and content: guidance for industry'. Similar to the EMA guideline, the applicant should provide information with respect to the model verification/validation. Moreover, the input of dissolution data (cf., clinically relevant dissolution testing) must be incorporated as part of a PBBM model development and validation for supporting manufacturing/control changes (e.g., there should be a clear rank-order correlation between *in vitro* dissolution testing and PK). Incorporation of biorelevant dissolution data is not mandatory. However, it may be relevant to conduct biorelevant dissolution testing alongside simpler dissolution testing to support major CMC changes and bridging studies. PBBM could then be extremely useful to bridge these gaps. Lastly, selection of a dissolution modeling approach should be based on drug product understanding and not on the best fit of the dissolution data (e.g., the use of 'raw' dissolution data is not suitable, which may only be appropriate for highly soluble compounds). In the case of modified-release (MR) drug products, the use of empirical functions (for instance a Weibull function) is justifiable.

In the case of virtual BE trials (for a generic drug product or a commercialized product compared to batch formulation phase 3), the estimated intra- and inter-subject variability for PK parameters (such as plasma C_{max} and AUC) should be comparable to the observed inter- and intrasubject variability. The number of subjects for virtual BE trials should be justified and comparable to the number of subjects that were recruited for the *in vivo* BE trial. The number of virtual BE trials used to estimate the probability of concluding BE should be justified. Finally, a clear description of the methods/algorithms used to determine the intra-subject variability in virtual BE should be included.

The concept of safe space is derived from the well-known IVIVC notion where drug product changes whose mean dissolution profiles fall within the boundaries defined by the extremes of bioequivalent dissolution profiles are expected to be bioequivalent. Similar to IVIVC, extrapolation outside this space is not appropriate unless reinforced by additional clinical data. In addition, when using safe space to support

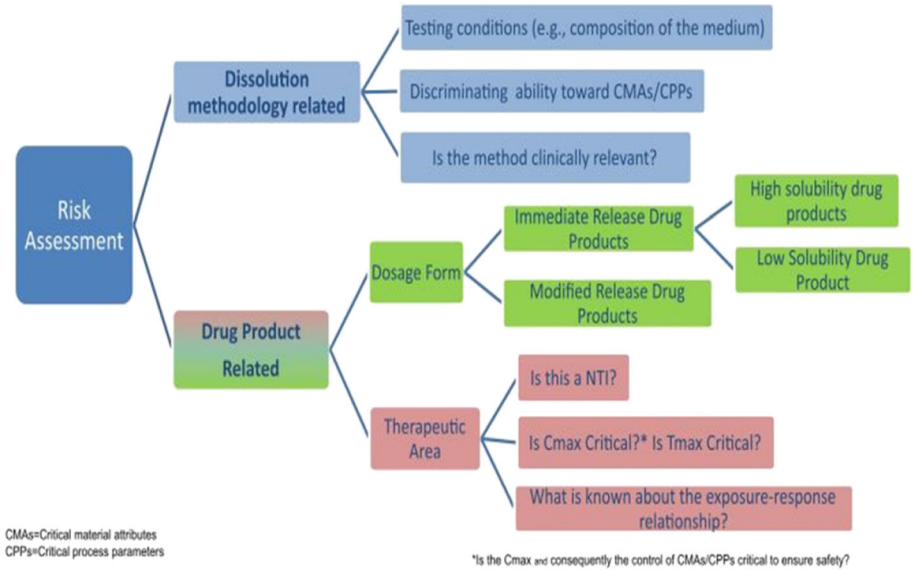

Fig. 4 Key considerations in the assessment of risk from biopharmaceutics perspective.

dissolution or other critical quality attributes' acceptance criteria, the resulting limits are based on mean values of the input variable which must include dissolution profiles data. The determination of a safe space heavily relies on the drug product's prior knowledge and a thorough understanding of the drug product's critical quality attributes and their interaction which is usually attained via implementation of Quality by Design (QbD) principles. The "spatial dimensions" of the drug product design space (s) resulting from QbD studies may or may not be similar to that defined under safe space which should be derived by evaluating the clinical impact of critical portions within the design space(s). As such, the establishment of safe space allows applicants not only to implementing patient centric drug product quality but also to gain regulatory flexibility by reducing the number of clinical studies that may be needed in support of major manufacturing changes. In a nut shell, safe space provides an opportunity for taking a major step in accelerating drug product development lowering the cost of drug product development.

There are several approaches for defining a safe space which include the development of an *in vitro-in vivo* relationship (IVIVR) or an IVIVC via either conventional or mechanistic

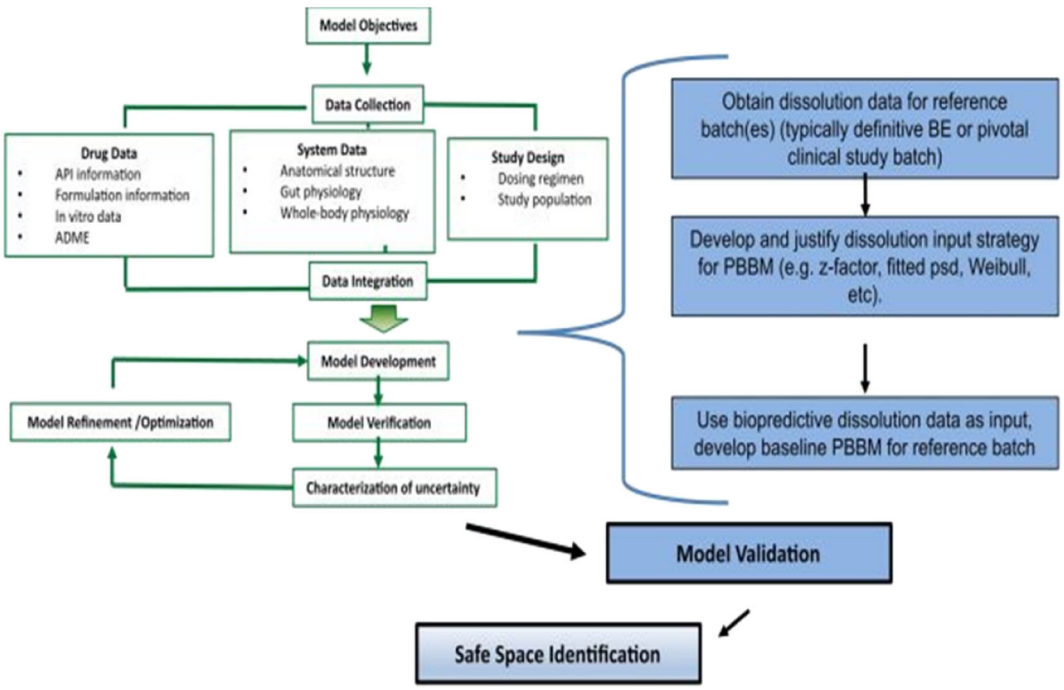

Fig. 5 PBBM general workflow in model development, verification and validation.

approaches. In addition, the boundaries of the safe space can be further supported by relying on exposure-response analysis for efficacy and safety allowing, in some cases the expansion of this space beyond what is defined by IVIVR/IVIVC. A general workflow in the development of safe space via "mechanistic" IVIVR and IVIVC is depicted in Fig. 6. Identifying a safe space via a physiologically based approach necessitates the development of baseline and absorption models similarly to the way it is performed when developing a PBPK model. Briefly, the disposition model should be derived from intravenous PK data as much as possible. Other data (e.g., PK from oral solution) may be acceptable with justification. The absorption model should be built using data from drug product reference batches, typically the definitive BE or pivotal clinical study batch. These data are essential for the development and justification of the dissolution input strategy for PBBM. Once the model has been refined as needed and verified using approaches such as parameter sensitivity analysis, the predictive power of the model is confirmed by validating the model using an independent set of data fit for purpose.

It is pertinent to emphasize that the drug product's safe space should be built based on a thorough understanding of the relationship among the critical material attributes (CMAs), critical process parameters (CPPS), dissolution and systemic exposure. To this end, formulation variants (at least two) that follow a rank order relationship are needed when building a safe space via IVIVR. The boundaries of the safe space are then defined by a bracketing approach. This bracketing approach relies on identifying the virtual mean dissolution profiles representing the extremes in formulation/process differences and dissolution acceptance criteria that are BE based on virtual bioequivalence trials. It should be noted that when the boundaries on the safe space fall outside the data used to develop and validate the PBBM model, additional dissolution and clinical PK data are needed, preferably non-BE data to support the proposal. Building a safe space via IVIVC follows similar steps as described above, but in this case since at least three formulation variants are needed to build the correlation (which usually include considerable formulation changes that are likely to result in non-BE to the refence batch and the opposite bound), additional non-BE may not be needed.

There are no regulatory hurdles for the use of innovative modeling approaches in support of drug product quality. FDA encourages the development of conventional or physiologically based "mechanistic" IVIVCs as they are considered the "gold standard" for gaining regulatory flexibility throughout the drug product's life cycle. When these paths fail, the data generated during drug product development along with the conduct of dedicated PK studies (whenever possible) may be leveraged to define a safe space. To this end, FDA encourages the use PBBM approaches to be included in regulatory submissions to underpin drug product quality. Building confidence on this approach is essential and a stepping stone toward regulatory policy. Briefly, building a safe space is

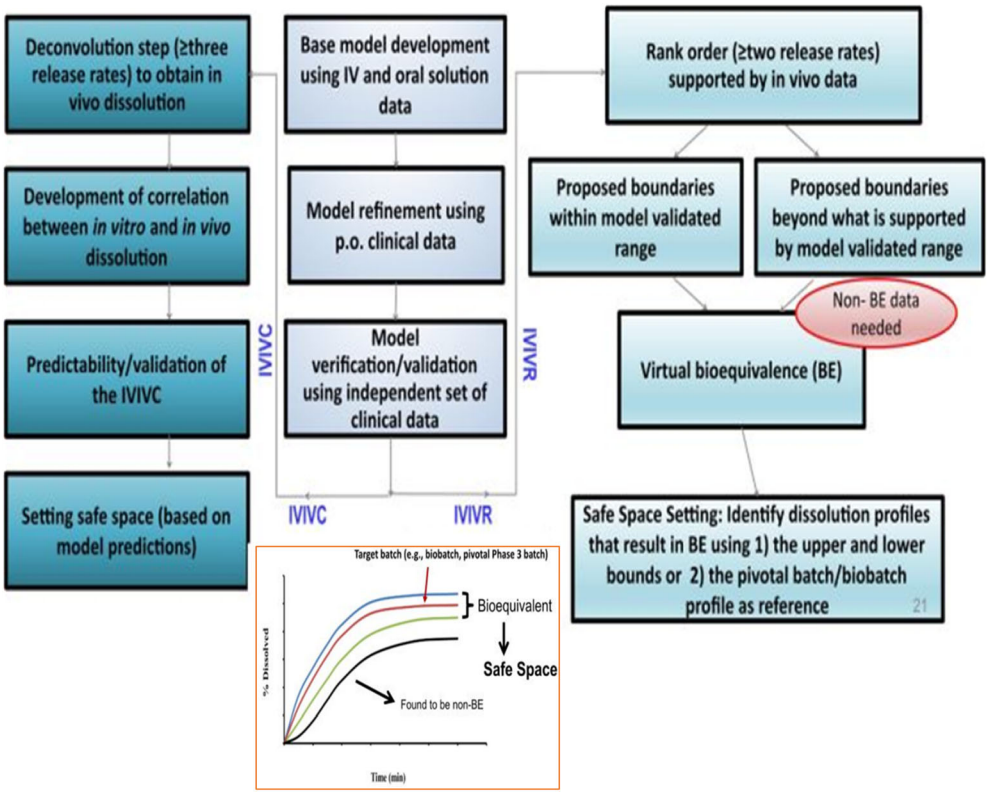

Fig. 6 General workflow in the development of safe space via PBBM (adapted from Zhao and Suarez, 2019, with permission (43)).

relevant not only for gaining regulatory flexibility, but a stepping stone toward setting clinically relevant drug product specifications and towards "Patient-centric" Drug product development.

CONCLUSION & FUTURE PERSPECTIVES

In conclusion, industrial scientists should be aware of how a PBPK workspace needs to be built from a regulatory point of view and, even more important, how it will be evaluated by regulatory assessors. Clinically relevant *in vitro* experiments should be carried out that will define the so-called safe space which assures product efficacy and safety for the patient. As most of the submitted applications handle DDI, industrial scientists should be encouraged to do the same for absorption and/or food-effect modeling purposes. Based on a 2016 survey, it was stated that there was a lack of clear regulatory guidelines for guidance and a kind of lack with respect to the alignment in vision and approach across different regulatory regions (42). To tackle these hurdles, EMA and U.S. FDA came up with new guidelines in 2018 which were thoroughly discussed in this manuscript. Followed correctly, this opens an opportunity to potentially requesting biowaivers in the near future for orally administered drug products, regardless of its classification according to the BCS (44). The different talks were tailored to provide a basis or rationale for the subject, introduction to fundamental principles with historical perspective, a critique of the state-of-the-art, examples of successful application of the methods across different phases of the drug development process and the specific standards these mechanistic models should meet to be fully reliable from a regulatory perspective.

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COMPLIANCE WITH ETHICAL STANDARDS

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