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PERSPECTIVE

Current Scientific Considerations to Verify Physiologically-Based Pharmacokinetic Models and Their Implications for Locally Acting Products

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Challenges to verify physiologically-based pharmacokinetic (PBPK) models are significant for locally acting product (LAP) given action-site drug concentration is not easily measurable and when systemic pharmacokinetics (PK) do not reflect action-site drug delivery or are not detectable. As such, regulatory or scientific programs that generate clinically relevant *in vitro/in vivo* data for the product or data from an array of products with relevant formulation properties and use conditions become critical for model verification.

CURRENT CONSIDERATIONS TO VERIFY PBPK MODELS

In both drug development and regulatory settings, PBPK modeling has become a key methodology that integrates up-to-date knowledge on drug substance, formulation, and *in vitro/ex vivo/in vitro* drug release and its interplay with the human physiological system to describe the overall drug absorption, biodistribution, metabolism, disposition, and drug-exposure changes following permutations in the human physiological system. For new drug development, PBPK has been mainly employed to assess drug–drug interactions, support initial dose selection in pediatric and first-in-human trials, and potentially serve as additional scientific evidence in specific populations.[1] For generic drug development, oral PBPK models have been mainly used to establish biopredictive dissolution methods and conduct virtual bioequivalence (BE) simulations by incorporating formulation effects. Nonoral PBPK methods have been used to inform BE study designs, identify critical quality attributes (CQAs), set clinically relevant specifications, and develop regulatory standards for LAPs.[2,3]

Historically, various terms with slight differences in meaning have been used to describe model verification. They include *model validation*, *verification*, *qualification*, and *evaluation*. The European Medicines Agency PBPK guidance[4] also differentiated *model verification* from *platform qualification*. In the published standards of the American Society of Mechanical Engineers for establishing the credibility of medical devices,[5] the model credibility assessment includes verification, validation, and uncertainty quantification. In this commentary, model verification will be used to refer to the entire model evaluation process to qualify the model to inform decision making.

The US Food and Drug Administration (FDA) PBPK format and content guidance[6] states that model verification "should provide sufficient information to clearly demonstrate that the proposed PBPK model is appropriate for the modeling purpose or question asked." The European Medicines Agency PBPK guidance[4] states that the level of model verification depends on the "regulatory impact or impact on success of drug development." Consistent with these two guidances and the fit-for-purpose principle used for top-down modeling approaches such as population PK or exposure–response analyses, model verification for purpose will be considered as the guiding principle for PBPK modeling in this commentary. **Table 1** summarizes the current general considerations for PBPK model verification.

PBPK MODEL VERIFICATIONS FOR LAPs

Use of LAP PBPK models

For LAPs, the assessment of action-site drug concentration and/or BE can be challenging because the measurement of drug concentrations at the site of action in humans may not be feasible or ethical. As clinical efficacy and safety data serve as the pivotal information for new drug approval, comparative clinical end-point BE studies can serve as surrogate measures to assess exposure equivalence at the site of action for generic drug development. However, comparative clinical end-point BE studies are costly, and they can often be insensitive to formulation or dose differences when the drug exposure and clinical response relationship is flat. If systemic PK exposure is measurable and related to the exposure at the site of action, it could be used to evaluate BE for products such as the lidocaine topical delivery system (see the FDA draft product-specific guidance (PSG)). Similarity of the physicochemical properties and drug release can also be sufficient evidence for BE (see PSG). PBPK models can help identify which of these approaches is most appropriate for a specific drug.

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Compared with PBPK model verifications for drug–drug interaction evaluation and biopharmaceutics use, which mainly rely on systemic PK data, model verifications for LAPs are unique and challenging. The FDA has initiated nine external research projects with external collaborators to advance PBPK and/or computational fluid dynamics modeling for orally inhaled, ophthalmic, dermal, and intranasal LAPs under the Generic Drug User Fee Amendments I regulatory science program in fiscal years 2012–2017 (**Table 2**). They have critically supported developing PSGs, addressing application review questions and providing responses to pre–Abbreviated New Drug Application questions regarding using alternative approaches to replace comparative clinical end-point studies to assess BE.

The use of systemic PK data to verify LAP PBPK model

For LAPs, systemic PK can potentially be used to establish BE in combination with appropriate product characterization(s) and/or *in vitro* testing(s) given that systemic PK metrics can sufficiently reflect local drug delivery at the site of action. A critical use for PBPK is to determine when and what systemic PK metrics can be used as surrogates for local exposure at the site of action. A sufficiently verified PBPK model can help evaluate whether the systemic drug exposure reflects local drug delivery, especially through the shape of PK curve. For example, the application of PBPK models predicted a correlation between systemic mesalamine plasma PK and its gastrointestinal distribution for this gastrointestinal LAP.[7] An FDA contract titled "Correlation of Mesalamine Pharmacokinetics With Local Availability," based on intubation techniques to simultaneously measure gastrointestinal physiology and drug concentration, successfully supported their predicted correlations with the plasma drug PK profile. As a result, the FDA revised six PSGs for mesalamine delayed-release and extended-release oral products to recommend BE studies with PK end points including partial area under the curve metrics instead of using comparative clinical end points.[8] When systemic PK data do not reflect drug concentration at the site of action, it can disqualify a LAP PBPK model that fails to predict the general characteristics of the systemic PK profile.

Of note, to link local to systemic drug exposure, it is scientifically justifiable to consider a hybrid PBPK model for LAPs to combine a mechanistic local drug distribution and absorption model with a conventional compartment PK model or a minimal PBPK model that characterizes systemic drug PK following drug absorption.

New technologies to generate action-site drug concentration and relevant *in vitro*/*ex vivo* testing information

The PBPK model-based mechanistic understanding of the correlation between systemic PK profile or product-quality attributes and local drug delivery, as verified by directly measuring drug concentration at the action site or indirectly measuring relevant *in vitro* or *ex vivo* data, can dramatically reduce the regulatory burden for LAP developments.

Ideally, *ex vivo*/*in vitro* data can be generated from a realistic model that serves as a good representation of local environment and the geometry of the site where the product has been applied. For example, data generated from *in vitro* permeation testing using excised human skin and *in vitro* actuation of orally inhaled drug products in realistic mouth–throat models can serve as relevant *ex vivo*/*in vitro* data to verify the input component of the PBPK models as developed for dermal and inhalation products, respectively.

The measurement of *in vivo* PK data at or near the site of action requires techniques that are less invasive to humans without major ethical concerns. Great progress has been made in recent years. For orally inhaled products, *in vivo* data using gamma scintigraphy with radiolabeled aerosols have been used to estimate central and peripheral deposition amounts.[9] For topical dermatological products, dermal microdialysis and open-flow microperfusion techniques have been directly applied to measure local cutaneous concentrations, which involve using tiny hollow filaments ("probes") inserted into the dermis layer of the skin.[10] For ophthalmic products, the FDA conducted an internal research project to measure the distribution of dexamethasone in different tissues of the eye following topical ocular administration of tobramycin/dexamethasone suspension to male New Zealand white rabbits. The data will be used to verify a dexamethasone rabbit ocular compartmental absorption and transit PBPK model. The ultimate goal is for the ocular PBPK model to be extrapolated to explore the impact of formulation characteristics such as particle size and viscosity on the ophthalmic bioavailability (BA) of suspension drug products in humans.

Verification of the effects of drug formulation and product factors on local and systemic drug exposures

Locally acting drug products cover a wide range of dosage forms, including solutions, emulsions, lotions, ointment, and implants. The PBPK models for these products should describe the complex interplay between product attributes and human physiology, correlate CQAs to *in vivo* drug exposure at the site of action, and relate drug exposure to therapeutic performance. Predicting the observed differences between dosage forms of the same active ingredient can be a part of model verification.

Science-based *in vitro* and *in vivo* information can critically support the verification of the identified CQAs. For example, considering rheology as a CQA for an ophthalmic drug product, research (Grant 1U01FD004719) found that both the viscosity and particle size of Q1/Q2 (qualitatively and quantitatively the same) ophthalmic budesonide suspensions can influence *in vivo* rabbit ocular BA with an increase in viscosity resulting in improved BA. Data from formulations with different CQA can certainly be used to verify relevant PBPK models.

Model performance can also be supported by the use of data from other products. Model verification using multiple molecules and formulations with relatively rich *in vitro* and *in vivo* data and with a range of physicochemical properties and formulation parameters that cover those for the product being tested can critically enhance model credibility.

Table 1 Current considerations for model verification

Category	Current considerations		Practice
Guiding principle	The level of verification needed should depend on the regulatory impact of the modeling, intended use, or modeling purpose[a]		
	The regulatory impact is directly linked to the risk to the patients in case the modeling predictions lead to erroneous regulatory decisions		
	Procedures used for model verification for both the drug and the system models should be discussed[a]		
Input parameters	Validity and biological plausibility of input parameters		Pharmacological/biological knowledge and mechanism of action
	Uncertainty around the determination or prediction of parameter values[a]	Subject to important assumptions	Sensitivity analysis for assumption model and different model structures
		Key experimentally determined parameters that may not reflect *in vivo* situation	Sensitivity analysis for parameters involved
		Multiple reported values in the literature	
		Parameter value(s) fit during the model building	Sensitivity analysis and pharmacological/physicochemical plausibility; a joint sensitivity analysis, where two or more parameters are tested simultaneously, may be the preferred choice
		Difficult to be determined experimentally	Model fitting and pharmacological/physicochemical plausibility
	Results of sensitivity analyses for uncertain parameters should be discussed in the context of the simulation conditions and potential clinical relevance		
	In some instances, model parameters may be refined during model verification. Such modifications are important aspects of model refinement and should be described and justified		If the assumptions of the model parameters cannot be confirmed during modification, further verification to predict clinical scenarios that were not previously evaluated should also be submitted
Assumptions	Influence on modeling outcomes for the assumptions made		Sensitivity of modeling outcome to different parameter values[a] and structures that reflect the assumptions made
Model structure	The model structure should provide a mechanistic framework of the systemic or local ADME process being modeled by representing the realistic *in vivo* drug absorption process and accounting for the impact of product quality attribute(s) on drug *in vivo* dissolution and absorption		
Data for verification	Validation data should be related to the intended purpose of the model		Whether the data are from products with similar route of administration, physicochemical properties. To qualify the system model of a PBPK platform, compounds with similar ADME characteristics to that of the intended use should be included in a prespecified data set. The number of drug compounds included in the data set and the range of pharmacokinetic properties covered by the data set will affect the confidence in the PBPK platform and what it may be qualified for. It is considered that, e.g., 8 to 10 compounds is indicative of a sufficient number. If possible, it should be ensured that there are additional drugs included in the qualification set that were not used in the platform building. The model qualification should show the ability of the PBPK platform to predict observed outcomes with adequate precision, for a wide variety of drugs based on certain types of background information
Model building	Clarity on the model building and optimization processes		A systematic approach interplaying with current existing data for model verification
Model use	The impact of a simulation also depends on how much weight of evidence the PBPK simulation will have in a certain scenario (i.e., how much other data are available to support a certain decision), the therapeutic context, and the resulting treatment recommendations		
	To decide if an intended use can be established for high regulatory impact decisions, considerations need to be given as to whether the science is mature enough. This would include valid system data (including abundance data if relevant) and demonstrated *in vitro–in vivo* correlations. It could also include demonstrating the interplay between physiology and the drug substance/drug product		
	The qualification will only be valid for situations covered by the qualification data set, e.g., only for the specific enzyme(s), site of inhibition (e.g., liver, intestine), and the type of background data (including pharmacokinetic data, the system parameters, and the population used) on which the simulations were based		
	The evaluation of the drug model for a certain purpose should focus on evaluating the parts of the drug model that are central to the intended purpose		
	Model verification should provide sufficient information to clearly demonstrate that the proposed PBPK model is appropriate for the modeling purpose or question asked for the particular drug product and study population and is robust enough to respond to perturbations in uncertain parameters		

The contents are mainly adopted and paraphrased from the European Medicines Agency guidance.[4]
ADME, absorption, distribution, metabolism, and excretion; PBPK, physiologically-based pharmacokinetic.
[a]Contents that are also covered in the US Food and Drug Administration guidance on PBPK analyses—format and content.[6]

Table 2 Summary of Generic Drug User Fee Amendments I modeling grants for locally acting products

Category of products	Grant	Objective	Status
Modeling of orally inhaled drug products	U01FD004570	Develop CFD models of orally inhaled drug product delivery to human lungs, where these predictions would be used to evaluate the impact of certain drug product and physiological characteristics on total and regional deposition	The project has been completed, and a collection of CFD models were validated with *in vitro* and *in vivo* data capable of predicting total and regional deposition from metered dose inhalers and dry powder inhalers and that account for differences in aerodynamic particle size distribution, breathing pattern, and airway geometry
	U01FD005214	Develop a model that can predict deposition, distribution, absorption, metabolism, and excretion of orally inhaled drug products using a combined approach with CFD and PBPK methods	Lung airflow may be modeled using a quasi–three-dimensional approach as a means of improving on the efficiency of fully three-dimensional CFD simulations. Results have indicated that the inclusion of cartilaginous rings in the lung model may increase the deposition fraction predictions from dry powder inhaler delivered drug. The multiscale modeling approach employed by this study is capable of predicting PK profiles that match well with experimental data in some cases
	U01FD005837	Use CFD to predict differences because of intersubject variability in small airway deposition of metered dose inhaler drug delivery to asthmatic patients	A new methodology for applying heterogeneous constriction to a healthy subject lung model will be expected, and the project will include an *in vivo* data set generated using gamma scintigraphy to provide a basis for the validation of the CFD simulations
Nasal	U01FD004570	Develop a nasal model in addition to the already developed lung models	This nasal model incorporates a two-dimensional surface model that models mucociliary motion and predicts both dissolution and absorption of deposited mometasone furoate
	U01FD005201	Develop a model that can predict deposition, distribution, and absorption of intranasal corticosteroids using a combined approach with CFD and PBPK methods	To date, a method was developed to estimate numbers of API particles with respect to particle size that deposit on a regional basis in the nasal cavity. A PBPK model that predicts intravenous, nasal, and oral absorption and distribution from intranasal corticosteroid devices and includes considerations for dissolution, mucociliary clearance, glucocorticoid receptor binding, plasma protein binding, and metabolism in the gastrointestinal tract and the liver showed accurate prediction of fluticasone propionate pharmacokinetics when compared with *in vivo* data
Modeling of ophthalmic drug products	U01FD005211	Advance the ocular PBPK and mechanistic absorption modeling software through a combination of expanding the existing knowledge base for ocular drug absorption and pharmacokinetics and implementing enhanced physiological models for human and animal eyes in the OCAT mechanistic absorption modeling/PBPK model	The expanded knowledge base of ocular physiology and the observed variability in system parameters were used to develop more sophisticated objective function equations that allow for simultaneous fitting of parameters that influence ocular and plasma compartment concentrations. Melanin binding was incorporated in the developed model. The OCAT model has been developed for brimonidine in rabbit
	U01FD005219	Develop a model that can predict delivery, distribution, and absorption of ophthalmic drug products using a combined approach with CFD and PBPK methods in human and animal subjects	A two-dimensional CFD model has been developed to provide an enhanced understanding of fluid transport between different regions of the eye
Modeling of dermal drug products	U01FD005232	Develop PBPK models on dermal absorption of drug products following three different approaches: an analytical solution based on Laplace transformations, a compartmental modeling approach, and a three-dimensional numerical analysis mimicking the geometry of the stratum cornea and processes that occur when a product is applied on the skin	Overall, a systematic approach in dermal PBPK model development has been established, and significant progress toward model development and validation is taking place
	U01FD005225	Develop the physiologically based absorption and pharmacokinetic modeling and simulation platform for non-gastrointestinally absorbed drug products in humans with focus on the skin as the formulation application area	Up to now, the following aims (updating volunteer physiology, incorporation of hydration level of stratum corneum as part of the model, collection of skin pH in different anatomical sites of body and its variability, accounting the role of skin appendages on absorption, ability to model drug effect on local skin physiology, addition of deep tissue compartment) have been successfully completed

API, active pharmaceutical ingredient; CFD, computational fluid dynamics; PBPK, physiologically-based pharmacokinetic.

CONCLUSIONS

Model verification for LAP PBPK models is a key step in using models to inform regulatory and drug development decisions. Verifying such models can be challenging, mainly attributable to the difficulty in obtaining drug concentration at the site of action. Advancing technologies to generate relevant *in vitro* and *in vivo* data that directly and indirectly reflect local drug delivery, leveraging systemic PK, and/or using additional data from relevant drug products can collectively serve as a weight-of-evidence approach for model verification.

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