Challenges in Using PBPK Models for Locally Acting Drug Products to Inform Regulatory Decision Makings

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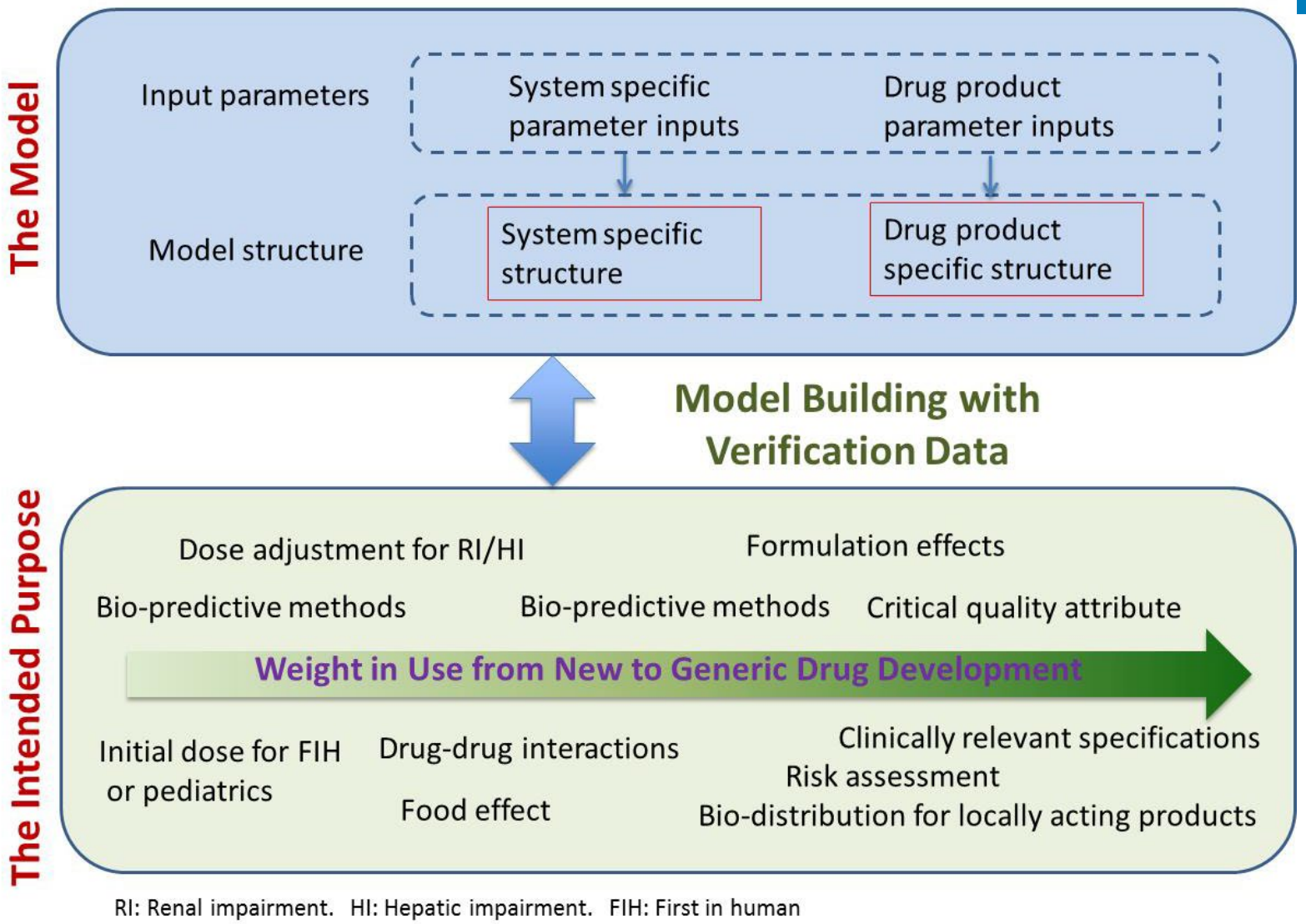
Outline

- Current Considerations to Verify Physiologically Based Pharmacokinetic (PBPK) Models
- PBPK Model Verifications for Locally Acting Products (LAPs)
  - Challenges
  - The use of systemic PK data to verify LAP PBPK models
  - New technologies to generate action site drug and relevant in vitro/ex vivo testing information
  - Verification of effects of drug formulation and product factors on local and systemic drug exposures

The Eco-System of PBPK Modeling



RI: Renal impairment. HI: Hepatic impairment. FIH: First in human

Thoughts Collected from Guidance for Modeling 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* 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*.		
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*	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	
		Paremter value(s) fit during the model building	Sensitivity analysis and pharmacological/physico-chemical 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/physico-chemical 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	Influnce on modeling outcomes for the assumptions made		Sensitivity of modeling outcome to different parameter values* 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 adminstration, 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 pre-specified data set. The number of drug compounds included in the dataset and the range of pharmacokinetic properties covered by the dataset will affect the confidence in the PBPK platform and what it may be qualified for. It is considered that e.g. eight to ten 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 dataset, 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. for the particular drug product and study population and is robust enough to respond to perturbations in uncertain parameters.		

Note: Contents are mainly adopted from the EMA guidance. *: Contents that are also covered in the FDA guidance re: PBPK analyses—format and content.

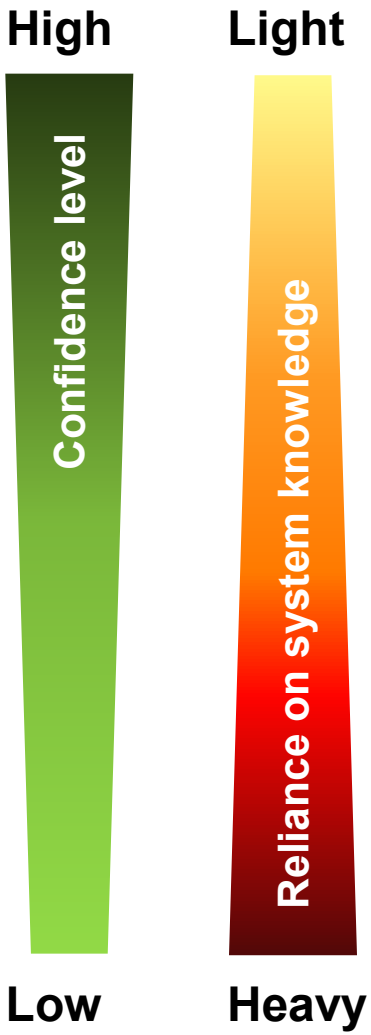
Guiding Principle for PBPK Modeling

- FDA guidance: Model verification "should provide sufficient information to clearly demonstrate that the proposed PBPK model is appropriate for the modeling purpose or question asked"
- EMA PBPK guidance: The level of model verification depends on the "regulatory impact or impact on success of drug development"
- Nomenclature for this presentation: Modeling and Verification for purpose
  - In references to these two guidances and in line with the fit-for-purpose principle as used for top down modeling approaches such as population pharmacokinetics or exposure-response analyses

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM531207.pdf
https://www.ema.europa.eu/documents/scientific-guideline/guideline-qualification-reporting-physiologically-based-pharmacokinetic-pbpk-modelling-simulation_en.pdf

Confidence Levels on PBPK Applications in NDA

	Applications	Status
Drug-drug Interactions	*Drug as enzyme substrate*	• *Substrate/inhibitor models verified with key clinical data can be used to simulate untested scenarios and support labeling*
	Drug as enzyme perpetrator	• *Use to confirm the lack of enzyme inhibition* • *Additional evidence needed to confirm predictive performance for positive interactions*
	Transporter-based	• *In vitro-in vivo extrapolation not mature* • *Complicated by transporter-enzyme interplay* • *Predictive performance yet to be demonstrated*
Specific populations	*Organ impairments (hepatic and renal)*	• *Predictive performance yet to be improved* • *System component needs an update*
	Pediatrics	• *Allometry is reasonable for PK down to 2 years old* • *Less than 2 years old ontogeny and maturation need to be considered*
Others with limited experiences	*Pregnancy, ethnicity, geriatrics, obesity, disease states* *Food effect, formulation change, PH effect (including DDIs on gastric PH)* *Tissue concentration*	



Wagner, CPT-PSP, 2015

Slide from Ping Zhao, 2016 ASCPT

Challenges to Verify Locally Acting Products (LAPs)

- Measurement of drug concentrations at the site of action in human may not be feasible or ethical
- Systemic drug concentrations may not reflect local concentrations
- Plasma/blood PK may not be detectable

The Use of Systemic PK Data to Verify LAP PBPK Model

- Disqualify a LAP PBPK model that fails to predict the general characteristics of the systemic PK profile
- PBPK model can help evaluate whether the systemic drug exposure can reflect local drug delivery, especially through the shape of PK curve
  - PBPK models predicted a correlation between systemic mesalamine plasma PK and its gastrointestinal distribution
  - FDA contract successfully supported their predicted correlations
  - Findings are implemented in bioequivalence assessment in product specific guidances

Measurement of in vivo Gastrointestinal Release and Dissolution of Three Locally Acting Mesalamine Formulations in Regions of the Human Gastrointestinal Tract. Yu A, Baker JR, Fioritto AF, Wang Y, Luo R, Li S, Wen B, Bly M, Tsume Y, et al.Mol Pharm. 2017 Feb 6;14(2):345-358.

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

- Directly measuring drug concentration at the action site
  - Measurement of in vivo PK data at or near the site of action
  - Techniques that are less invasive to human without major ethical concerns
- Indirectly measuring relevant in vitro or ex vivo data
  - Data from realistic models that serve as a good representation of local environment and the geometry of the site

Examples of Techniques for Verification Data Generation

- Orally inhaled products:
  - Data from realistic mouth-throat models
  - Gamma scintigraphy with radiolabeled aerosols
- Topical dermatological products:
  - In vitro permeation testing using excised human skin
  - Dermal microdialysis and open flow microperfusion techniques to measure local cutaneous concentrations
- Ophthalmic products
  - Techniques to measure the distribution of dexamethasone in different tissues of the eye in rabbits

Verification of Effects of Drug Formulation and Product Factors

- Science based in vitro/in vivo data that
  - Are applicable to different dosage forms
  - Characterize the complex interplay between product attributes and human physiology
  - Correlate critical quality attribute to action site drug exposure
- Data should be sensitive to formulation effects, including dose and concentration differences, on local drug distribution

The Use of Data from Other Products

- Verification will only be valid for situations covered by the verification dataset
- 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 the ones for the product being tested can critically enhance model credibility

Modeling Grants/Contracts of GDUFA I Regulatory Science Program on LAPs

Category of Products	Grant	Objective	Status
Modeling of orally inhaled drug products	U01FD004570	Develop CFD models of orally inhaled drug products (OIDPs) 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 (MDIs) and dry powder inhalers (DPIs) and which account for differences in aerodynamic particle size distribution (APSD), breathing pattern, and airway geometry.
	U01FD005214	develop a model which can predict deposition, distribution, absorption, metabolism, and excretion of OIDPs using a combined approach with CFD and PBPK methods	Lung airflow may be modeled using a quasi-3D approach as a means of improving on the efficiency of fully 3D CFD simulations. Results have indicated that the inclusion of cartilaginous rings in the lung model may increase the deposition fraction predictions from DPI 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 due to inter-subject variability in small airway deposition of MDI 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 2D surface model which models mucociliary motion and predicts both dissolution and absorption of deposited mometasone furoate.
	U01FD005201	develop a model which can predict deposition, distribution, and absorption of intranasal corticosteroids (ICSs) 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 which deposit on a regional basis in the nasal cavity. A PBPK model which predicts intravenous, nasal, and oral absorption and distribution from ICS 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 PK as compared with in vivo data.
Modeling of ophthalmic drug products	U01FD005211	Advance the ocular PBPK and mechanistic absorption modeling (MAM) 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 MAM/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 which 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 3D 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 towards model development and validation is taking place.
	U01FD005225	Develop the physiologically based absorption and pharmacokinetic modeling and simulation platform for non-gastro-intestinally 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

Conclusions

- Model verification for LAP PBPK models serves as a key step in using model to inform regulatory and drug development decisions
- Verifying such models can be challenging, mainly attributable to 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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Thank you!


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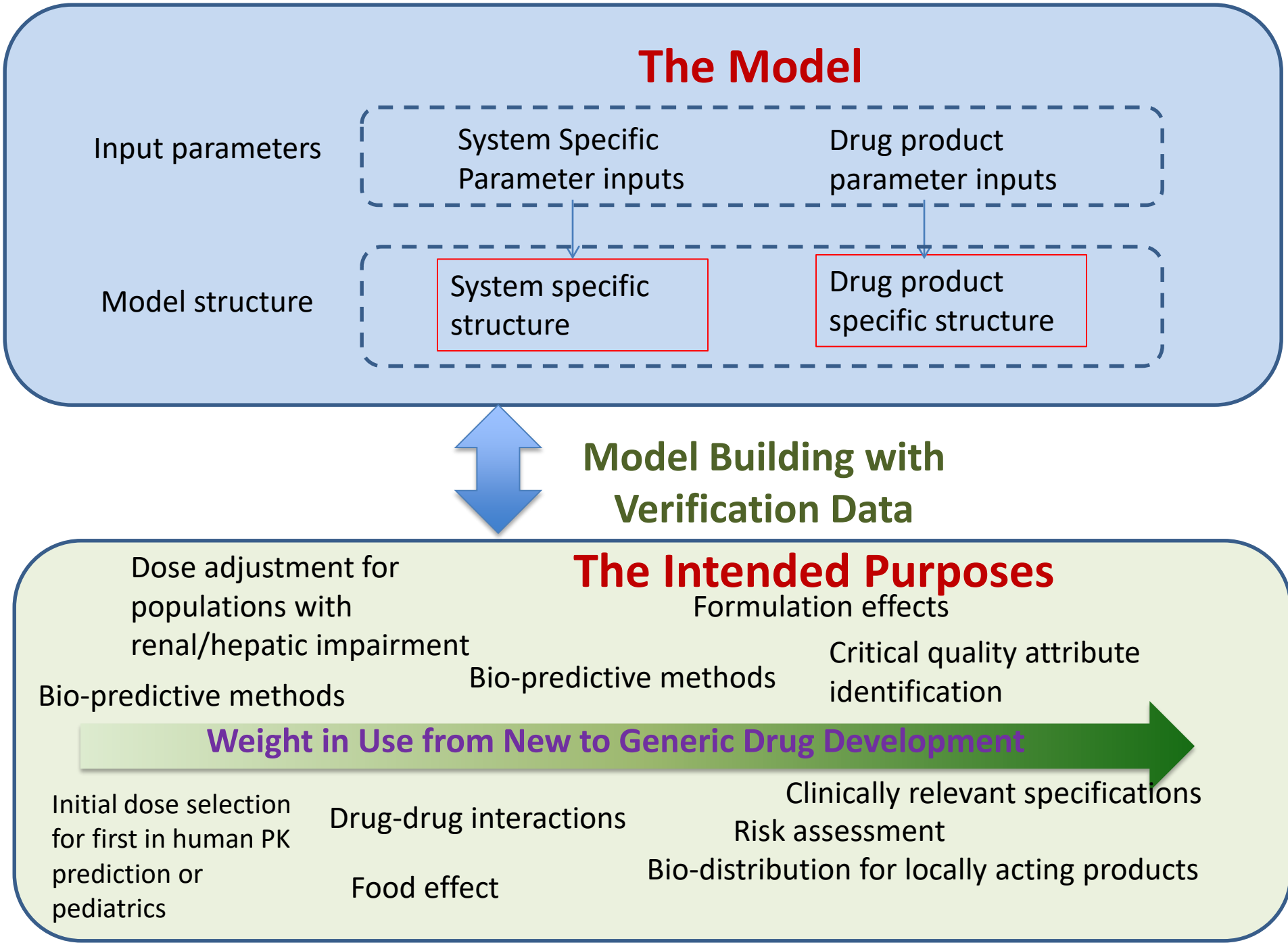
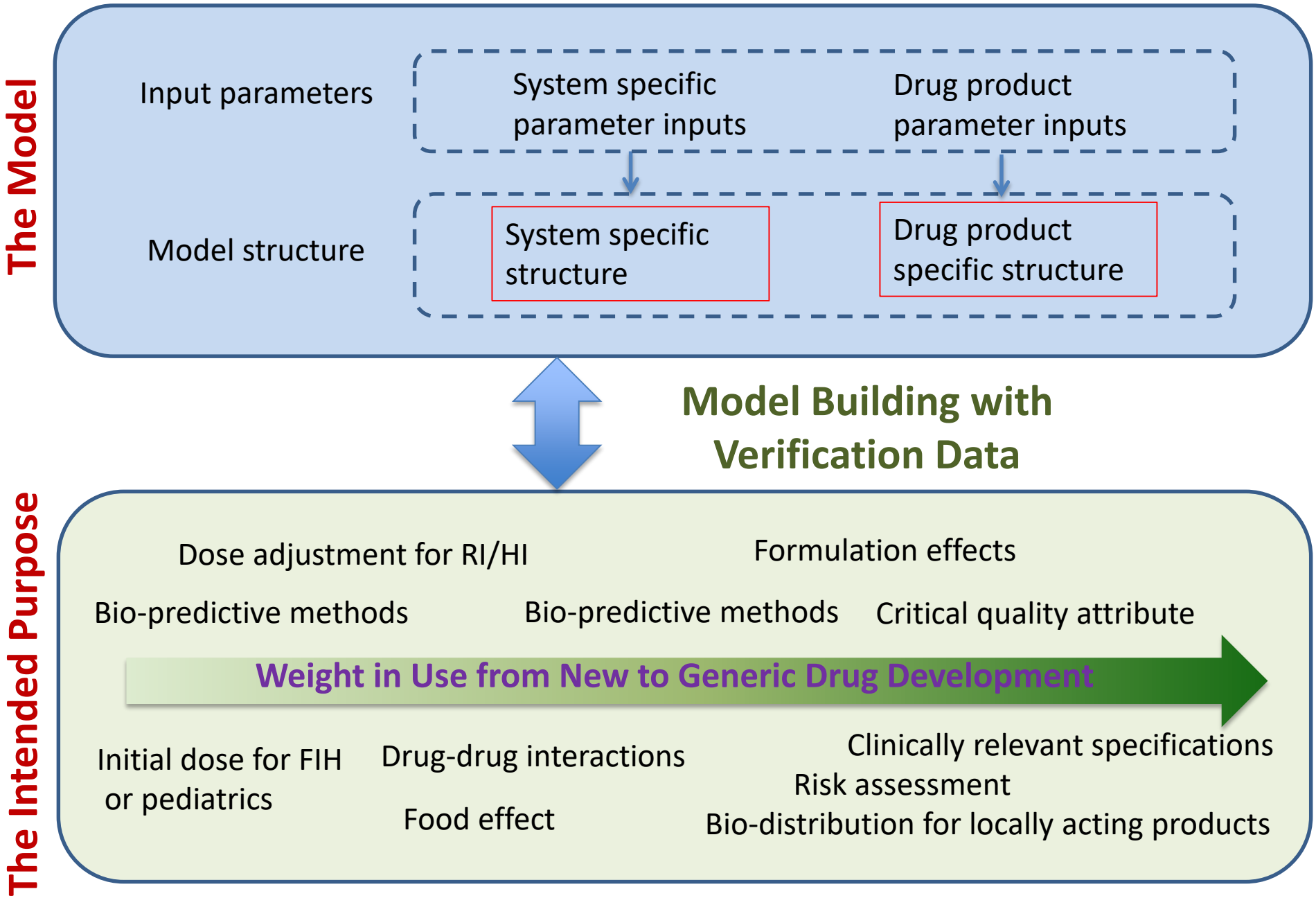
Gaps and Research Needs

- Leveraging model complexity and model performance
- Developing methods and data sets for model validation
- Understanding physiology and pathology in various populations
- Understanding within-subject variability
- Developing in vivo relevant in vitro testing
- Building confidence in complicated mechanism based models


The Model
Input parameters
System Specific Parameter inputs
Drug product parameter inputs
Model structure
System specific structure
Drug product specific structure
Model Building with Verification Data
The Intended Purposes
Dose adjustment for populations with renal/hepatic impairment
Formulation effects
Critical quality attribute identification
Bio-predictive methods
Bio-predictive methods
Weight in Use from New to Generic Drug Development
Initial dose selection for first in human PK prediction or pediatrics
Drug-drug interactions
Food effect
Clinically relevant specifications
Risk assessment
Bio-distribution for locally acting products



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Revisiting Model Qualification