BASICS OF PHYSIOLOGICALLY-BASED PHARMACOKINETIC (PBPK) MODELING AND CONSIDERATIONS FOR BUILDING PBPK MODELS:

Use of PBPK Modeling Strategies in Drug Discovery and Development

Punam Sandhu, Ph.D.
Pharmacokinetics, Pharmacodynamics and Drug Metabolism
MSD

Society for Study of Xenobiotics (SSX), Bengaluru, India
3rd Annual SSX Meeting (October 2018)

Overview

- Applications of Physiologically-Based Pharmacokinetic (PBPK) approaches
- Implementation of physiologically-based pharmacokinetic modeling
- Examples of PBPK modeling & simulation in drug development
- Development of PBPK models for special populations
- Overview of PBPK in Clinical Pharmacology reviews of regulatory submissions
- Use of PBPK approaches in regulatory submissions and product labeling
  - Current state of PBPK applications and considerations for future state
  - Examples of impact on product labeling of approved drugs

Physiologically-Based Pharmacokinetic Modeling Allows Integration of Data from A Variety of Sources

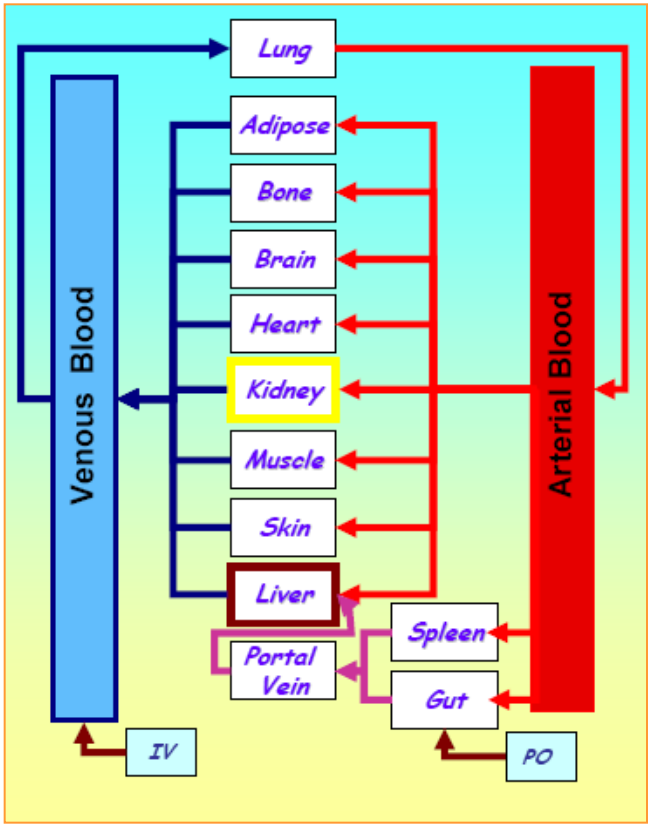


Figure adapted from simCYP workshop material

- PBPK is a mathematical concept which can describe the distribution and elimination of drugs from the body
  - Animals and human
  - In silico absorption models
- Clearance parameters can be estimated using various in vitro and/or in vivo techniques
- Since the model is written in terms of real physiological relationships, it is easy to incorporate factors that cause perturbations in Absorption, Distribution, Metabolism & Excretion (ADME) properties.
  - Solubility, Induction, inhibition, PGx, disease, etc.

Example of system parameters

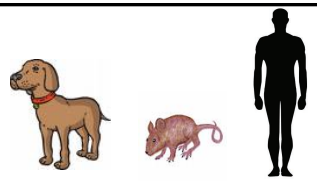
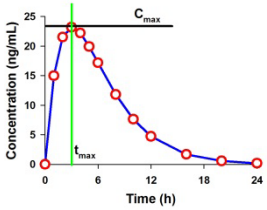
- organ size/composition
- blood flow rates
- GI tract physiology (pH, transit times, etc.)
- age, sex, race

Example of compound parameters

- plasma protein binding
- permeability
- solubility
- metabolic clearance
- physiochemical properties

Poulin and Theil, J Pharm Sci 89: 16-35, 2000
Poulin and Theil, J Pharm Sci 91: 129-56, 2002
Poulin and Theil, J Pharm Sci 91: 1358-70, 2002
Berezhkovskiy, J Pharm Sci 93: 1628-40, 2004
Rodgers and Rowland, J Pharm Sci 95: 1238-57, 2006
Rodgers and Rowland, Pharm Res 24: 918-33, 2007

Examples of Diverse Applications of PBPK Models

preclinical/clinical study design

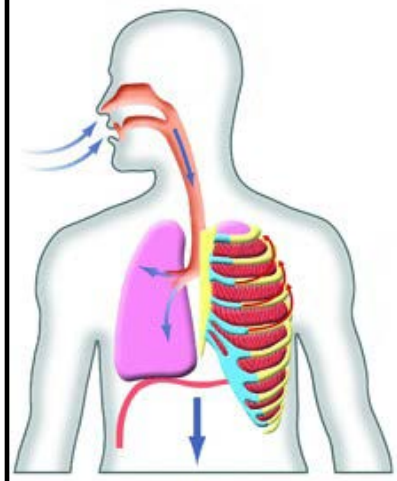
victim and perpetrator DDI

pediatrics

mechanistic insight

hepatic/renal impairment

ethnic and pharmacogenetic impact



inhaled therapeutics

intrinsic/extrinsic factors

Ontogeny - Age Dependency of Metabolism

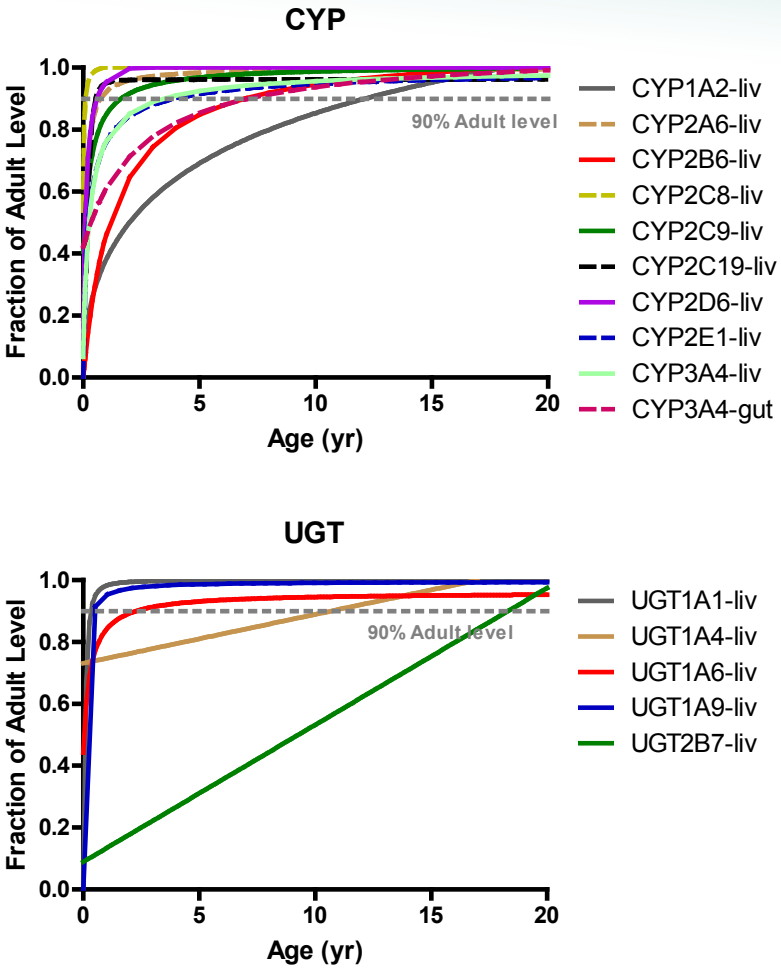
Enzyme-Specific Time of Maturation

Enzymes	Location	Fractional expression at birth relative to adult	Time to 90% adult expression*
CYP1A2	Hepatic	<0.05	~10-12 yr
CYP2A6	Hepatic	<0.05	~9-10 m
CYP2B6	Hepatic	<0.05	6-8 yr
CYP2C8	Hepatic	~0.3	~1-2 mon
CYP2C9	Hepatic	~0.4	~1.5-2 yr
CYP2C19	Hepatic	~0.2	6-8 mon
CYP2D6	Hepatic	<0.05	6-8 mon
CYP2E1	Hepatic	<0.05	3-4 yr
CYP3A4	Hepatic	<0.05	1-3 yr
CYP3A4	Gut	~0.4	~ 7-8 yr
UGT1A1	Hepatic	<0.05	~4-5 m
UGT1A4	Hepatic	~0.7	~10-11 yr
UGT1A6	Hepatic	~0.4-0.5	~ 1.5-2 yr
UGT1A9	Hepatic	<0.05	~5-6 mon
UGT2B7	Hepatic	~0.1	~19-20 yr

**** May be confounded by pubescent changes, at least for some CYPs.***

Implication:

- **Age-dependent CLint changes as a result of enzyme ontogeny.**



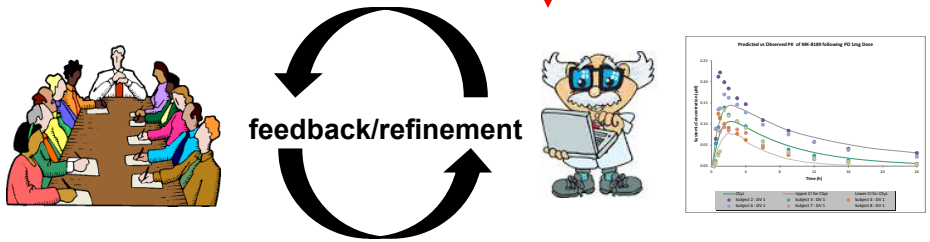
Johnson TN et al. Clin Pharmacokinet 2006; 45: 931-956.
Miyagi SJ, et al. Drug Metab Dispos 2011, 39:912-919.
Miyagi SJ, et al. Drug Metab Dispos 2012, 40:1321-1327.
Miyagi SJ and Collier AC Drug Metab Dispos 2007, 35:1587–1592.
SIM-CYP Pediatric modeling training slides.2012 (from Georgy Hartmann)

High-Level Workflow for the Initiation and Support of PBPK Modeling in Drug Development

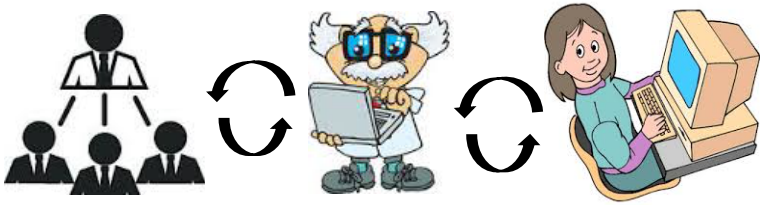
Question from program team

Group lead assigns a modeler

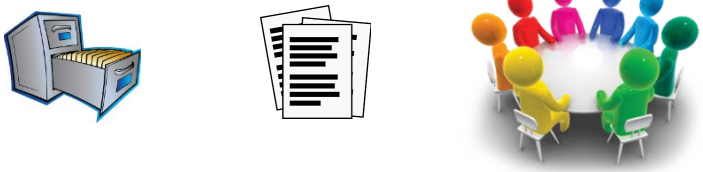
PBPK modeler works with team to build and qualify model



Draft model reviewed along with fit-for-purpose qualification/QC plan. Scientific rigor and appropriateness of model to answer team questions discussed.

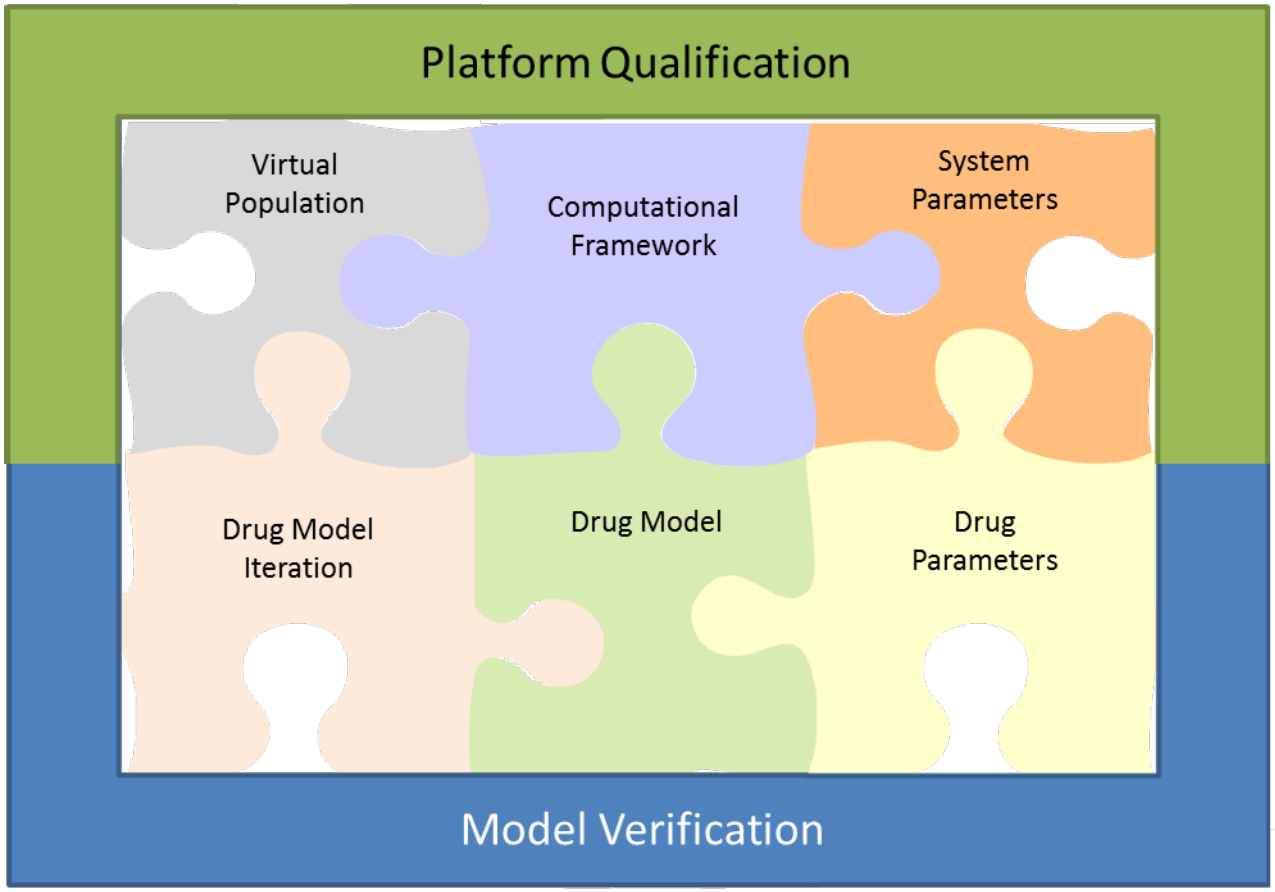


Further refinement of model as needed



Final PBPK model and interpretation is provided to program team to enable decision making.

Components of a PBPK Modeling Package



Platform Qualification

- A PBPK platform is an integrated environment which allows building and running PBPK models
- Several commercial PBPK software platforms available (simCYP, GastroPlus, PK-SIM)
- The platform includes several components such as:
  - Graphical User Interface
  - Computational Framework
  - System Parameters
  - Drug Parameters
- The PBPK models within a platform are developed to handle specific tasks based on certain assumptions
- See slides in Supplemental Material section for additional information on platform qualification

M Shebley, P Sandhu, AE Riedmaier, M Jamei, R Narayanan, A Patel et al., PBPK Model Qualification & Reporting Procedures for Regulatory Submissions. *Clin. Pharmacol. Ther.,* 2018, 104 (1), 88-110.

PBPK Modeling Considerations

- It's desirable to consider a fit-for-purpose model to ensure stage appropriate investment in the PBPK model

Stage	Examples
Exploratory	• Used in discovery to aid in dose selection for animal studies • Help identify key properties for mitigating DDI potential
Internal Decision Making	• Inform candidate selection • Help guide team in terms of DDI strategy
M&S for Regulatory Submissions	• Assess need for clinical trials • Responding to regulatory inquiries around a clinical trial design • Design of early phase clinical studies (e.g. inclusion/exclusion criteria)

Framework for Building and Evaluating a PBPK Modeling Project

1. Questions the model will address
2. How will decisions/path forward be impacted by M&S?
3. Description of the model and its relevance to questions being raised
4. What are the assumptions that need to be made?
5. What data will be used and how will model capture uncertainty? (sometimes new data needs to be generated for model qualification)
6. Is the model qualified?

1. Questions the Model will Address

- The most important modeling activity is identifying the question that the model will address
- Linking the question to be addressed to the decision is important in defining the scope and value of the modeling activity
- Involves collaboration with the project team to come up with pre-specified and fit-for-purpose qualification metrics. The metrics should be clearly communicated and agreed upon prior to initiating the modeling effort
  - Example: AUC, Cmax, Tmax and $T_{1/2}$ need to be modeled within 2-fold of the observed value (widely used acceptance criterion to qualify a model as fit for purpose) for the model to be qualified

2. How Will Decisions/Path Forward be Impacted by M&S

- Identify a direct link of how model results will impact actions taken, or decisions made by the project team.
  - Example PBPK driven decision: Potent inhibitors and inducers of CYP3A4 will be excluded from early clinical development if the model predicted AUC GMR are >2-fold (inhibitors) or <0.5 (inducers).

- Place impact of modeling project into the appropriate “Tier” to ensure the right level of qualification/validation of the model (i.e., fit-for-purpose).
  - Exploratory vs for internal decision making vs for use in regulatory submissions

3. Description of the Model and its Relevance to Questions Being Raised

- Do the PBPK models appropriately incorporate the system (i.e. physiological) and drug specific properties required to address the question?

- Are the models being structured/parameterized in such a way that a meaningful result could be generated?

- *Example:* PK in different populations was simulated by incorporating system parameters that are known to vary between populations (differences in enzyme expression, organ size, and blood flows) with compound-specific properties (fractional intrinsic clearance through the various processes involved in drug elimination).

4. What Are The Model Assumptions & How Are They Supported?

- With every question being asked, there are assumptions being made

- Some of these assumptions are at the level of the program, and not dependent on whether a model is going to be applied or not
  - Example *program* assumption: 30% target occupancy at trough is required for efficacy.
  - Example *model* assumption: The inhibitory effect of Compound Z on CYP450 is modeled as a competitive inhibitor based on in vitro data.

5. How Does the Model Capture Uncertainty in the Data? (1)

- **Working with experimentalists to evaluate existing data and need for any additional experiments to qualify the model.**
- The source of every model parameter needs to be clearly stated, e. g. which parameters are fixed vs. fitted to data.

- Example:

Parameter	Value	Uncertainty	Source
fm,CYP3A4	0.8	0.7 - 0.9	measured in vitro
CLrenal	2	%CV = 27	measured in vivo
fu,mic	0.9	NA	educated guess

5. How Does the Model Capture Uncertainty in the Data? (2)

- Insufficient knowledge, data, or representation of the physiology results in limitations and assumptions in the model and uncertainty in identification of model parameters or structure. This translates into uncertainty in model output
- When uncertainty around an input parameter cannot be explicitly incorporated into the model (e.g. Monte-Carlo simulation), then a sensitivity analysis needs to be conducted to demonstrate potential impact on results.
- Examples of uncertainty in model results:
  - Fraction excreted unchanged is 20% based on preclinical BDC data, but human ADME data is not yet available.
    - Uncertainty in fraction excreted could impact conclusions from the model about potential for victim DDI
  - Fraction metabolized by a specific enzyme (e.g. CYP3A) is 70%, but metabolic pathways for remaining 30% are unknown

6. Is the Model Qualified?

- Identifying a metric for the essential behaviors of a system, together with acceptable deviation from it, is a challenge vital to model qualification

- Two key properties of a qualification metric are (1) the metric needs to be pre-specified, and (2) the metric should be fit-for-purpose
  - Pre-specification of metrics eliminates potential bias and increases confidence in the qualification outcome.
  - A fit for purpose metric will quantitatively assess the deviation of model output from experimental results, and whether the model is appropriate for decision making within the constraints of available knowledge and data

- The PBPK model needs to be structure/parameterized in a way where all relevant physiological and drug specific properties are accounted for

PBPK Modeling Approaches and Their Applications

Modeling Approach	Data Availability	Examples of Modeling Scenarios	General Applications
Bottom-Up	Physiochemical properties and blood binding (LogP, pKa, fu_p, B/P)	Projection of human drug distribution	Provide mechanistic understanding
	In vitro permeability and pharmaceutics information	Projection of human PK parameters and FIH dose	
	In vitro metabolism substrate/perpetrator data	Enzyme DDI projection (victim and perpetrator)	
	In vivo ADME information in preclinical species		
Top-down	Clinical concentration-time profiles from single or multiple ascending doses with summary of PK parameters	Development of model and identify parameters and their inter-subject variability as well as identifying covariates	Support clinical trial decisions
Middle-out	Physiochemical properties and in vitro ADME data may be available, but key in vitro quantitative or mechanistic data may be lacking	Refined predictions of DDI (perpetrator or victim)	Provide mechanistic understanding and support clinical trial decisions
	Clinical concentration-time profiles after single and multiple ascending doses with summary of PK parameters	Special populations (pediatrics, organ impairment),	
	May have clinical DDI data available as a victim and/or perpetrator for key CL pathway(s)	Formulation optimization or selection; in silico bioequivalence	
	In vivo human ADME or mass-balance data		

Examples of PBPK Modeling and Simulation in Drug Development:

Developing the Models for Special Populations

Impact of Intrinsic and Extrinsic Factors on PBPK Modeling

The disposition of a drug is altered by various intrinsic and extrinsic factors.

.

Intrinsic factors

- Age
- Body Surface Area (Weight)
- Disease State
- Gender
- Genetic Polymorphisms
- Organ Impairment
- Race

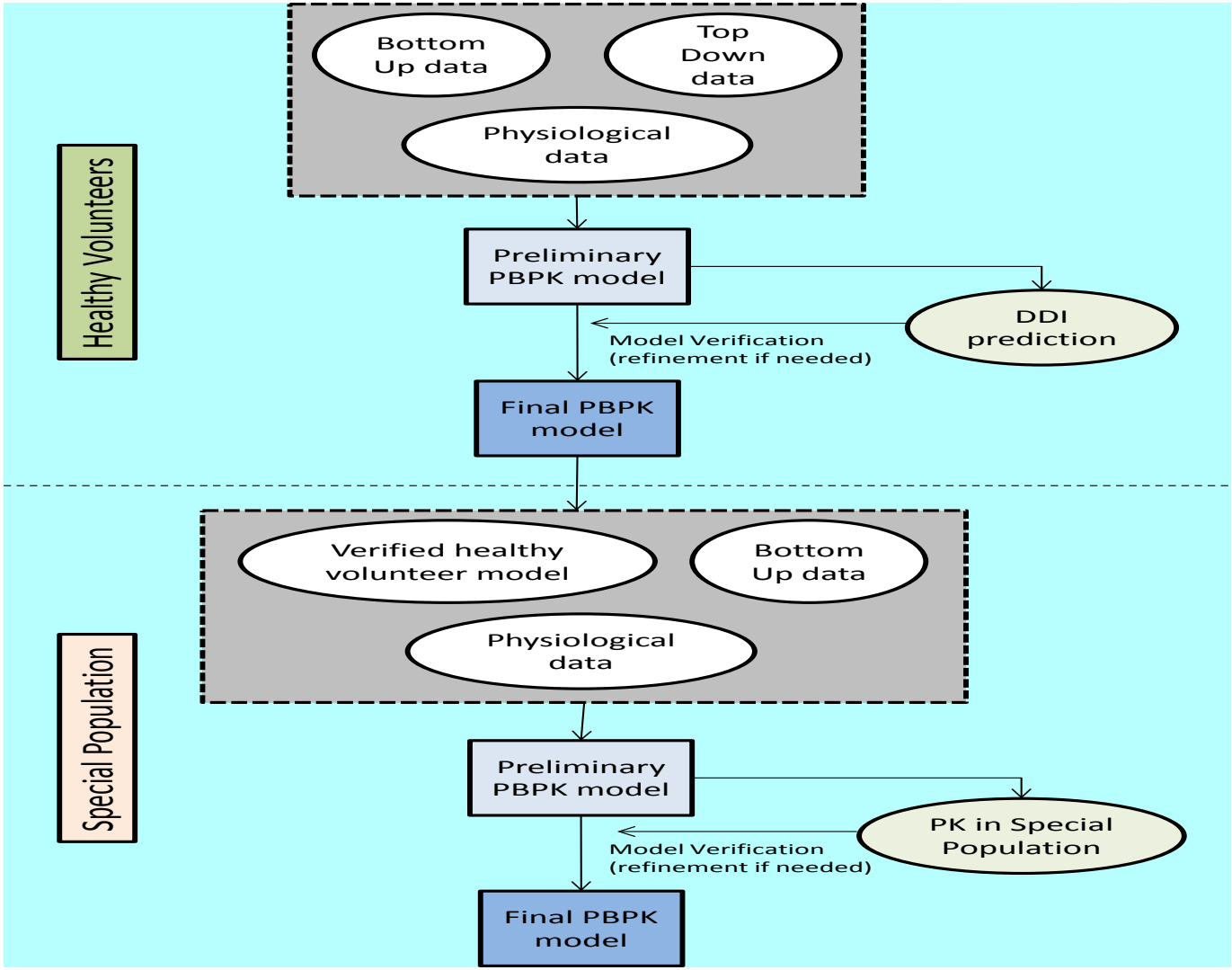
Extrinsic factors

- Alcohol Use
- Concomitant Drug Use
- Diet
- Smoking

Considerations for PBPK Approaches in Special Populations

- Pharmacokinetics is dependent upon various pathological and physiological variables that can affect exposure in subjects
- Pathological variables that affect PK
  - Renal insufficiency, hepatic insufficiency, obesity, cardiac function
- Physiological variables that affect PK
  - Age (e.g. children vs adults vs elderly)
  - Race (e.g. Caucasian vs African vs Asian populations)
  - Ethnicity (e.g. Chinese vs Japanese)
- Developing models for an oncology population
  - Albumin binding and alpha-acid glycoprotein binding are key factors
- Other special population considerations
  - Pregnancy, Pharmacogenomics (CYP poor vs extensive metabolizers)

Qualification of Special Populations Using PBPK M & S

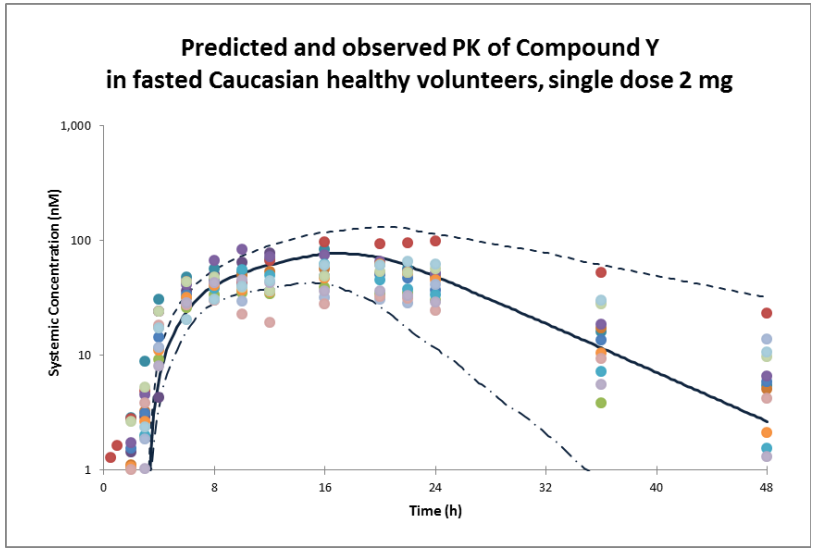


Characterizing a PBPK Model for Compound Y to Predict Exposure in Japanese Population

- Objective:
  - Simulation of single dose and multiple dose healthy volunteer (HV) PK for the controlled-release (CR) intermediate formulation
  - Prospective modeling and simulation of PK in Japanese population based on PK in HV
- Key Assumptions for Simcyp PBPK Model Development:

Model Considerations	Input	Source
Dosing Regimen	CR formulation 2 mg QD for 4 days	---
Absorption Model	ADAM Model (colon transit time 16 hr)	simCYP (see slide 31)
Distribution Model	Full PBPK Model	simCYP
Vss	0.25 L/kg	Predicted (consistent with reported Vd/F of 0.31 L/kg)
fm	CYP3A4=0.86; CYP2C9=0.12; CYP1A2=0.02	From recombinant CYP data
Clint	CYP3A4=0.109; CYP2C9=0.028; CYP1A2=0.0067 µL/min/pmol	From retrograde model based on reported CL/F = 2.67 L/hr and fm
Protein Binding	3.8%	Measured
Blood-to-Plasma Ratio	0.9	Measured

Predicted vs. Observed PK of Compound Y: Single Dose 2 mg CR Formulation (Intermediate) in Caucasian HV Population

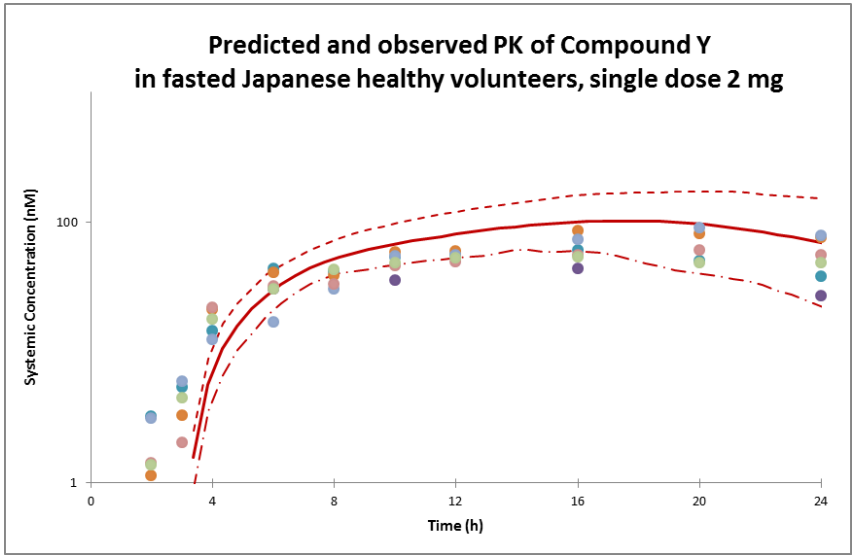


- Solid curve represents predicted geometric mean (GM) plasma concentrations. Dashed curves are 5th / 95th percentiles.
- Colored data points are observed individual concentrations.

	C_{max} (nM)	T_{max} (hr)	C_{24h} (nM)	C_{48h} (nM)	AUC_{0-48} (nM*hr)	T ½ (hr)
Observed N=14 GM (%CV)	*56.7* *(33)*	*20* *(10 – 24)*	*43.7* *(38)*	*4.84* *(2.80-8.36)*	*1350* *(36)*	*7.8* *(6.5-9.4)*
Predicted N=500 Caucasian HV GM (90% CI)	83 (46-134)	17.8 (13.6-20.4)	47.2 (11.1-113)	2.65 (0.05-31.9)	1613 (672-3234)	6.3 (3.0-13.5)

- The Simcyp PBPK model was able to describe the PK of Compound Y in Caucasian HV
- The predicted PK parameters for Caucasian HV were within a 2-fold range of the observed parameter values, therefore meeting the acceptance criteria.

PBPK Model Well Described PK of Compound Y in Japanese HV Population : Single Dose 2 mg CR Formulation (Intermediate)

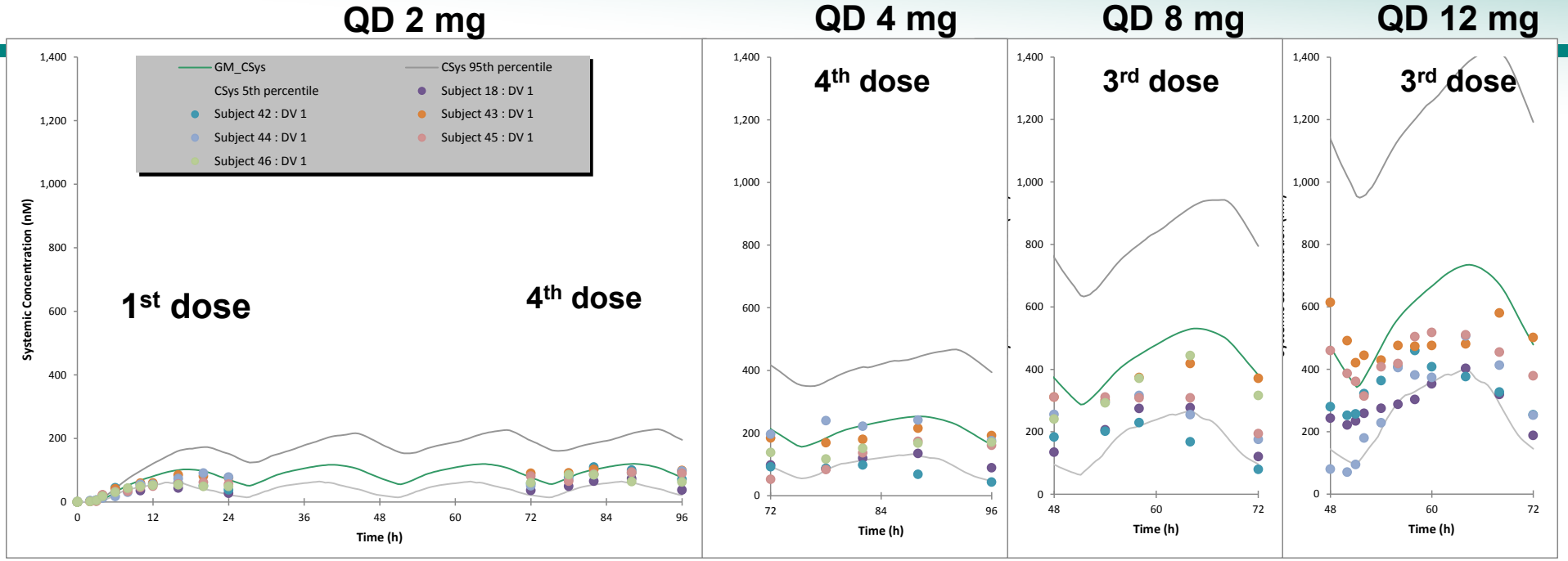


- Solid curve represents predicted geometric mean (GM) plasma concentrations. Dashed curves are 5th / 95th percentiles.
- Colored data points are observed individual concentrations.
- No re-fitting was done.

	C_{max} (nM)	T_{max} (hr)	C_{24h} (nM)	AUC_{0-48} (nM*hr)	T ½ (hr)
Observed N=5 Japanese HV; GM (%CV)	*68.8 (23)*	*16 (16 – 20)*	*57.3 (31)*	*1030 (21)*	*Not reported*
Predicted N=100 Japanese HV; GM (90% CI)	102 (55-173)	17.7 (13.7-20.6)	59.0 (13.3-153)	2040 (809-4510)	7.0 (3.1-16.2)

- For Japanese population, an a priori prediction was made and later confirmed by the data; the VPC supports the prediction.

Predicted vs. Observed PK of Compound Y in Japanese Healthy Volunteers



- Compound Y was given in multiple ascending doses; QD 2mg (D1-4), 4mg (D5-8), 8mg (D9-11), 12mg (D12-14).
- Curves represent simulated geometric mean (green) and 5th / 95th percentiles (grey) of plasma concentrations from N=100 subjects (Simcyp Japanese population), and are overlayed with observed (data points) individual concentrations from N=6 Japanese subjects. No re-fitting was done.

- **Conclusion:** The Simcyp PBPK model was able to adequately describe the PK of Compound Y in Japanese healthy volunteers over the dose ranges.

Predicted vs. Observed PK of Compound Y in Japanese Healthy Volunteers: Multiple Rising Doses 2, 4, 8 and 12 mg QD using CR formulation

		QD 2 mg (4 doses)	QD 4 mg (4 doses)	QD 8 mg (3 doses)	QD 12 mg (3 doses)
Japanese, Observed, N=5 GM (%CV)	$AUC_{0-\tau}$ (nM*hr)	1990 (9.86)	3440 (42.5)	6630 (30.4)	9570 (19.7)
	C_{max} (nM)	97.3 (9.21)	172 (35.9)	335 (27.0)	522 (12.1)
Simcyp v15.1 (ADAM model, CR formulation) N=100 GM (90%CI)	$AUC_{0-\tau}$ (nM*hr)	2288 (2081-2515)	5142 (4694-5634)	9390 (8580-10290)	14090 (12870-15430)
	C_{max} (nM)	126 (117-136)	267 (246-289)	512 (475-552)	768 (712-828)

- **Conclusion:** The Simcyp ADAM model was able to adequately describe the PK of Compound Y CR formulation in Japanese HVs following multiple doses in a dose range of 2 to 12 mg QD. The geometric mean C_{max} and AUC_{0-24h} were predicted within ± 55% of the observed values.

Cmax and AUC Ratios of Various Compounds Following Oral or Intravenous Administration to Non-Japanese and Japanese Healthy Subjects at the Clinical Dose

Compound	Dose	Non-Japanese Subjects		Japanese Subjects	
		C_{max} Ratio[a]	AUC Ratio[a]	C_{max} Ratio[a]	AUC Ratio[a]
A	10 mg	0.846	0.933	0.930	1.09
B	2 mg	1.37	1.26	1.63	1.50
C	160 mg	1.05	1.14	1.08	1.00
D	400 mg	1.01	0.957	0.722	0.926
E	100 mg	0.699	1.10	0.808	1.41
F	100 mg	1.02	0.805	0.955	0.835
G	8 mg/kg	Not Applicable[b]	1.07	Not Applicable[b]	1.03
H	20 mg	0.698	1.02	1.12	2.71
I	150 mg	0.703	1.43	0.582	1.47

[a]Ratios of predicted values to observed values (predicted/observed).
[b]Cmax ratio for Compound G is not applicable as the compound is administered intravenously

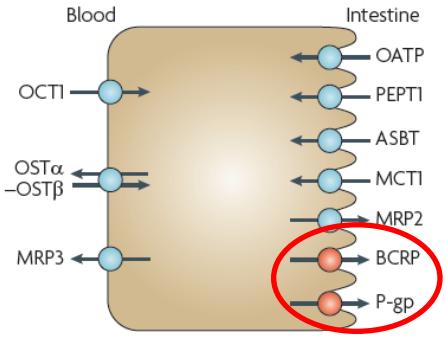
Conclusion: The PBPK models were able to successfully predict PK in the Japanese population

Y Matsumoto, T Cabalu, P Sandhu, G Hartmann, T Iwasa, H Yoshitsugu, C Gibson, N Uemura., Application of PBPK Modeling to Predict Pharmacokinetics in Healthy Japanese Subjects. *Clin. Pharmacol. Ther., 2018 (In Press).*

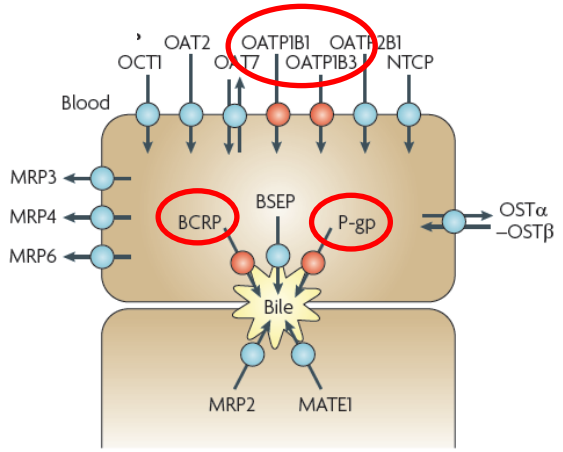
Compound X: (Anti-Infective)

- Substrate and/or inhibitor of CYP3A & drug transporters (OATP1B1/1B3, P-gp, BCRP)

Intestine:



Hepatocyte:



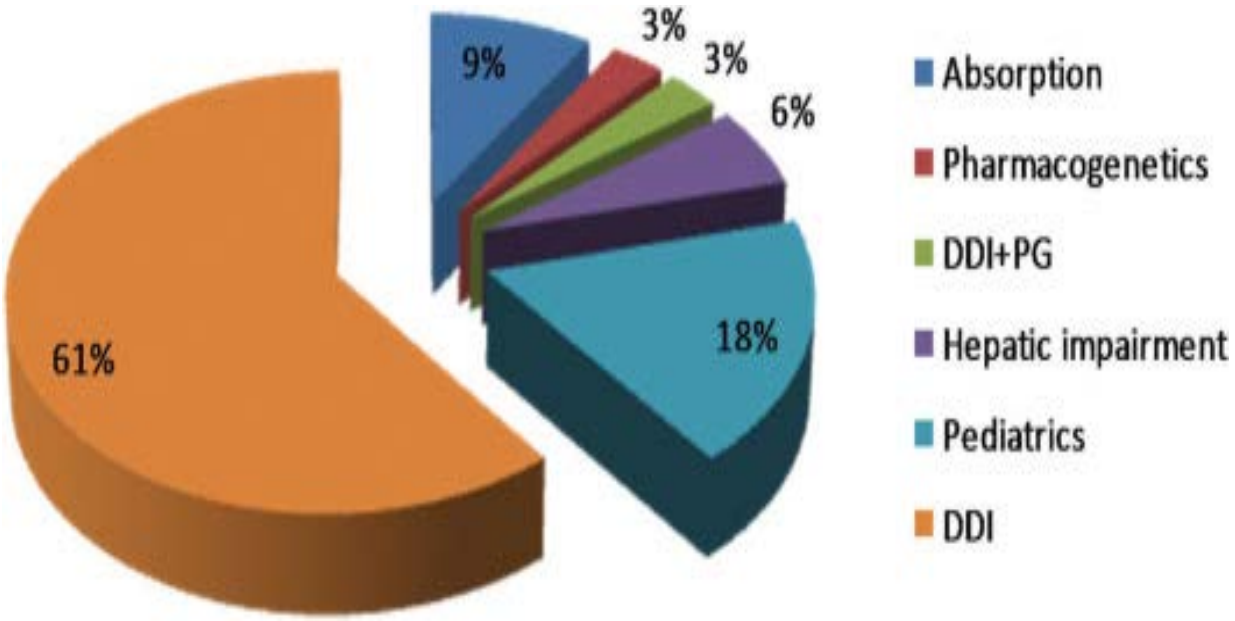
- Highly liver-targeted via hepatic uptake transporters
  - Liver:Plasma ratio is time, concentration, species-dependent
  - Liver:Plasma ratio saturates at different point for each species
  - ***Challenge***: In vitro to in vivo extrapolation of transporter data is difficult
- Non-linear, time-dependent plasma PK in humans
  - ***Challenge:*** Determining underlying mechanism of nonlinear PK
- Different PK in most sub-populations (Japanese/non-Japanese, elderly/young, male/female, healthy/patients)
  - ***Challenge:*** Determining underlying mechanism of sub-population PK difference & impact on safety/efficacy
  - ***Challenge***: Predict PK in sub-populations not studied (e.g., Japanese / elderly / female / HCV)

Building a PBPK Model for Compound X to Understand Exposure Differences in Various Sub-Populations

- The general PBPK model was customized to incorporate three active processes:
  - 1) saturable metabolism by CYP3A
  - 2) saturable efflux transport at the apical side of intestinal enterocytes representing the net transport rate due to P-gp, and
  - 3) saturable influx transport at the basolateral membrane of hepatocytes representing OATP-mediated influx into liver
- The PBPK model successfully described the key ADME and plasma disposition properties of Compound X, including:
  - Greater than dose-proportional PK
  - Dose-dependent bioavailability and clearance
- Model provided a basis for:
  - Understanding underlying mechanism driving non-linear PK
  - Understanding the effects of various intrinsic factors (Japanese race, age, gender, HCV infection) on the plasma PK of Compound X
  - Extrapolating non-Japanese PK database to Japanese

PBPK Modeling and Simulation in Regulatory Submissions and Product Labeling

PBPK M&S in Clinical Pharmacology Reviews of FDA Approved Drugs (2008 to 2012)



Huang SM, Abernethy DR, Wang Y, Zhao P, Zineh I. J Pharm Sci. (2013) 102, 2912-2923

While in most cases, the primary objective of PBPK modeling was DDI predictions, there are several examples (OLYSIO/SOVRIAD/simeprevir, EDURANT/rilpivirine, and FARYDAK/Panobinostat) where it has been used successfully for other applications.

The Opportunity

PMDA's Challenge to Accelerate Clinical Development and Review of New Drugs in Japan

K Ichimaru[1], S Toyoshima[1] and Y Uyama[1]

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 88 NUMBER 4 | OCTOBER 2010

- Active efforts within the Pharmaceutical & Medical Devices Agency (PMDA) to shorten drug development times in Japan to resolve the "drug lag"
  - *'Despite the improvements in operational activities such as review and scientific consultation for new drugs and the shortening of the review time for drug approval, the increase of staff numbers alone would not be sufficient to achieve the goal of resolving the problem of "drug lag.""*
- PBPK modeling may be one tool which could, in some cases, offer an opportunity for streamlined and accelerated drug development path

Regulatory Agency Specific Requests for PBPK Modeling from Sponsors

- Build a model to consider nonlinear PK or explain potential mechanisms of nonlinear PK
- Build a full PBPK model to consider P-gp contribution to the biliary excretion of the drug
- Simulate DDI or drug exposure at steady-state or using different dosing regimens. Provide sensitivity analysis of inhibition parameters.
- Simulate drug concentrations in tissues to explore the reason for certain AEs observed in the clinic. Simulate drug plasma concentrations in disease populations.

Products Containing Dosing Recommendations Informed by PBPK Strategies

2011	2012	2013	2014	2015	2016	2017
Rilpivirine	Ponatinib	Ibrutinib	Blinatumomab	Alectinib	Ribociclib	Acalabrutinib
Rivaroxaban		Simeprevir	Eliglustat	Aripiprazole	Naldemidine	Abemaciclib
		Macitentan	Ruxolitinib	Cobimetinib		Ertugliflozin
		Skyla	Olaparib	Panobinostat		Letermovir
			Naloxegol	Lenvatinib		
			Ceritinib	Sonidegib		
				Osimertinib		
				Dolutegravir		
FDA PBPK Reviews (Total ~ 230; prior to 2010 <20)						
14	16	47	38	40	40	35
EMA PBPK Reviews (Total ~ 60)						
5	3	9	10	11	11	13

Sources:
V Sinha & P Zhao, ASCPT Annual Meeting, San Diego 2016;
PharmaPendium

Current Status of PBPK Applications

Scenario	PBPK Application	Current Status
Drug-Drug Interactions	Drug as enzyme substrate	- Substrate/inhibitor models qualified with key clinical data can be used to simulate untested scenarios and support labeling
	Drug as enzyme perpetrator	- Use to determine the lack of enzyme inhibition - Additional evidence from clinical trials needed to confirm predictive performance for positive interactions
	Transporter-mediated	- In vitro-in vivo extrapolation not mature due to lack of information - Complicated by transporter-enzyme interplay - Predictive performance yet to be adequately demonstrated
Specific populations	Organ Impairment (hepatic and renal)	- Predictive performance needs improvement - System components need update
	Pediatrics	- Allometry is reasonable for PK down to 2 years old in most cases - Less than 2 years old, ontogeny and maturation need to be considered
Additional specific populations and situations	Pregnancy, ethnicity, geriatrics, obesity, disease states, food effect, formulation changes, pH effects, and tissue concentrations	- Limited experience to draw conclusions - High confidence in predicting effects of BCS Class I & II drugs for absorption

C Wagner, P Zhao, Y Pan, V Hsu, J Grillo, SM Huang and V Sinha.
CPT Pharmacometrics Syst. Pharmacol. (2015) 4, 226-230

Use of PBPK for Hepatically / Renally Impaired and Specific Populations

Current Gap	Future Proposal	Benefits
- ~50 to 80% NMEs approved in 2013 / 2014 did not include clear dosing recommendations for severe renal / hepatic impairment - ~15 to 30% NMEs did not include dosing recommendations for mild renal / hepatic impairment - Changes in PK and/or dosing recommendations rarely provided for use in pregnant women - In majority of the cases, no useful information in label for other specific populations	- Initial PBPK efforts can focus on dose recommendations for use in hepatically / renally impaired patients For PBPK efforts, need to focus on - Physicochemical properties, ADME - Creating models for clearance pathways for each specific population - Based on model prediction accuracy, can make recommendations for sub-population (mild, moderate or severe) e.g. XARELTO / Rivaroxaban	- Predicting exposure in sub-populations can prevent unnecessary conduct of lengthy trials - Early dosing predictions can help recruit patients from specific populations in pivotal/Phase III trials - In some situations M & S might be the only way to predict dosing (e.g. pregnant patients) P Jadhav, J Cook, V Sinha, P Zhao, A Rostami-Hodjegan, V Sahasrabudhe, N Stockbridge, and JR Powell. J Clin Pharm, 2015, 55(10), 1073-1078.

Example 1: CERDELGA™ / Eliglustat (EGT)

- **Indication:** For patients with Gaucher disease type 1 who are CYP2D6 extensive metabolizers (EMs), intermediate metabolizers (IMs), or poor metabolizers (PMs)

- **Properties:** Eliglustat is a CYP2D6 and CYP3A substrate. Co-administration of CERDELGA with drugs that inhibit CYP2D6 and CYP3A may significantly increase the exposure to eliglustat and result in prolongation of the PR, QTc, and/or QRS cardiac interval, which could result in cardiac arrhythmias.

- **Objectives of PBPK modeling:** To predict effects of moderate and strong CYP3A or CYP2D6 inhibitors on EGT exposure in CYP2D6 EMs, IMs and PMs

Eliglustat: PBPK Modeling and Labeling Implications

Co-administration with CYP2D6 Inhibitors

- For CYP2D6 EMs and IMs taking strong or moderate CYP2D6 inhibitors reduce the EGT dosage to 84 mg once daily

Co-administration with CYP3A Inhibitors

- For CYP2D6 EMs taking strong or moderate CYP3A inhibitors: reduce the EGT dosage to 84 mg once daily
- Not recommended for CYP2D6 PMs taking weak CYP3A inhibitors
- Not recommended for CYP2D6 IMs and PMs taking moderate CYP3A inhibitors
- Contraindicated for CYP2D6 IMs and PMs taking a strong CYP3A inhibitor

Co-administration with CYP2D6 & 3A Inhibitors

- Contraindicated in CYP2D6 EMs and IMs taking a strong or moderate CYP2D6 inhibitor with a strong or moderate CYP3A inhibitor

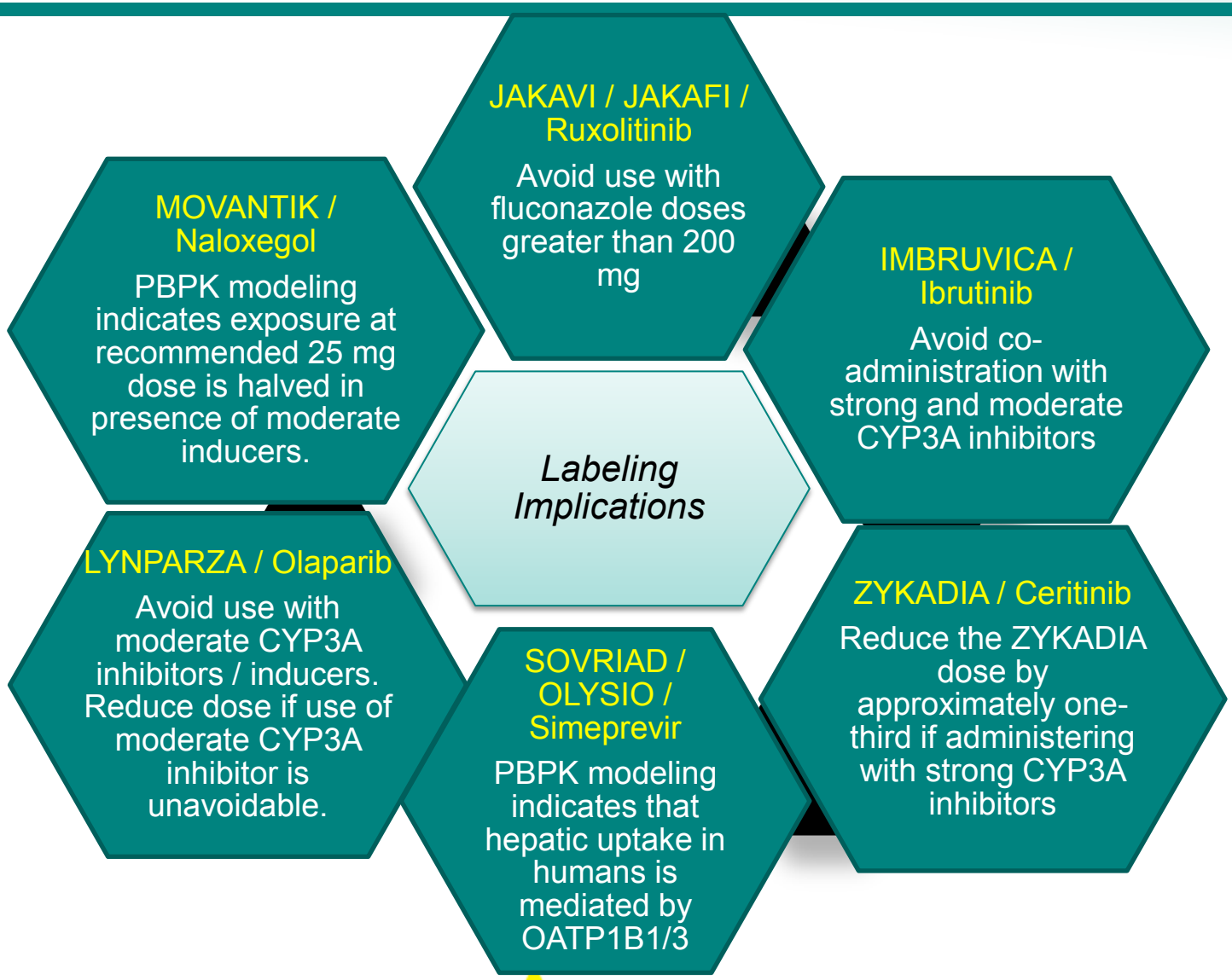
Example 2: FARYDAK / Panobinostat

- **Indication:** FARYDAK, in combination with bortezomib and dexamethasone, is indicated for the treatment of patients with multiple myeloma

- **Properties:** The human oxidative metabolism of panobinostat via the cytochrome P450 system primarily involves CYP3A isozymes.

- **Use of PBPK modeling and labeling implications:**
  - The aqueous solubility of panobinostat is pH dependent, with higher pH resulting in lower solubility. Coadministration of FARYDAK with drugs that elevate the gastric pH was not evaluated in vitro or in a clinical trial; however, altered panobinostat absorption was not observed in simulations using PBPK models.
  - Simulations using PBPK models, predicted an approximately 70% decrease in the systemic exposure of panobinostat in the presence of strong inducers of CYP3A. Avoid coadministration of FARYDAK with strong CYP3A inducers.

Other Examples of Labeling Implications Based on PBPK Modeling



Summary: Usefulness of PBPK Applications (1)

- PBPK approaches provide a mechanistic opportunity to explain differences in exposure in populations
- Help describe/understand characteristics of clinical data to facilitate extrapolation to different populations
- Diverse applications of the use of PBPK models in drug discovery and development
- Use of PBPK modeling for Compound Y (a central nervous system drug) helped predict exposure of a controlled-release formulation in Caucasian and Japanese populations following single and multiple dosing

Summary: Usefulness of PBPK Applications (2)

- Use of PBPK modeling for Compound X (anti-infective) helped understand the exposure differences in clinical data attributed to:
  - Greater than dose proportional PK
  - Differences in PK between non-Japanese and Japanese healthy volunteers
  - Differences in PK between young and elderly individuals
  - Differences in PK between healthy individuals and HCV patients

- This helps streamline the enrollment of subjects in clinical trials and minimizes duplication of data (e.g. facilitates with bridging strategies in case of ethnic sensitivity concerns)

- Can help shorten drug development times to address the “drug lag” which has been identified as a concern for drug development (Ichimaru, Toyoshima and Uyama, Clin. Pharmacol. Ther., 2010, 88(4), 454-457).

Consortium White Paper on Use of PBPK Approaches

- Comprised of 35 PBPK modeling scientists
- Represented by 25 companies & Prof. Malcolm Rowland from the simCYP Consortium
- Authors: Mohamad Shebley[1*], Punam Sandhu[2], Arian Emami Riedmaier[1], Masoud Jamei[3], Rangaraj Narayanan[4], Aarti Patel[5], Sheila Annie Peters[6], Venkatesh Pilla Reddy[7], Ming Zheng[8], Loeckie de Zwart[9], Maud Beneton[10], Francois Bouzom[11], Jun Chen[12], Yuan Chen[13], Yumi Cleary[14], Christiane Collins[15], Gemma L. Dickinson[16], Nassim Djebli[12], Heidi J Einolf[17], Iain Gardner[3], Felix Huth[17], Faraz Kazmi[9], Feras Khalil[18], Jing Lin[19], Aleksandrs Odinecs[20], Chirag Patel[21], Haojing Rong[22], Edgar Schuck[23], Pradeep Sharma[7], Shu-Pei Wu[24], Yang Xu[25], Shinji Yamazaki[26], Kenta Yoshida[13], and Malcolm Rowland[27]

- Author Affiliations: [1]AbbVie Inc., [2]Merck & Co. Inc., Kenilworth, NJ, USA, [3]Certara, [4]rangaraj.narayanan@gmail.com, [5]GlaxoSmithKline, [6]Merck KGaA, Germany, [7]AstraZeneca, Cambridge, UK, [8]Bristol-Myers Squibb, [9]Johnson & Johnson, [10]Servier, [11]UCB Biopharma, [12]Sanofi, [13]Genentech, [14]Roche Innovation Center Basel, [15]Astellas, [16]Eli Lilly & Company, [17]Novartis, [18]Grünenthal GmbH, [19]Sunovion Pharmaceuticals Inc., [20]Nektar Therapeutics, [21]Takeda Pharmaceuticals International Co., [22]Shire, [23]Eisai, [24]Vertex Pharmaceuticals, [25]Amgen, [26]Pfizer, [27]The University of Manchester, U.K.
- *Clin. Pharmacol. Ther.*, 2018, **104 (1),** 88-110.

Acknowledgements

- SSX ORGANIZING COMMITTEE

- Chris Gibson
- Nancy Agrawal
- Tjerk Bueters
- Tammie Cabalu
- Luzelena Caro
- Anne Chain
- Xioayan Chu
- Ed Feng
- Wei Gao
- Georgy Hartmann
- Takashi Iwasa
- Filippos Kesisoglou
- Yuki Matsumoto
- Akira Ohshima
- Conrad Raab
- Lisa Shipley
- Vikram Sinha
- Ying-Hong Wang
- Larissa Wenning
- Rebecca Wrishko
- Hiroyuki Yoshitsugu
- MSD simCYP User Group
- PPDM Team Members
- Prof. Naoto Uemura (Oita University, Japan)
- Masoud Jamei (simCYP, Certara, UK)
- Iain Gardner (simCYP, Certara, UK)
- simCYP Consortium Members

Abbreviations

- ADAM: Advanced Dissolution, Absorption and Metabolism
- ADME: Absorption, Distribution, Metabolism, Excretion
- AE: Adverse Event
- AUC: Area Under the Curve
- BA: Bioavailability
- BCRP: Breast Cancer Resistance Protein
- CI: Confidence Interval
- CL: Clearance
- Cl_{int}: Intrinsic Clearance
- C_{max}: Maximal Drug Concentration
- CR: Controlled Release
- CYP: Cytochrome P450
- DDI: Drug-Drug Interaction
- EGT: Eliglustat
- EMs: Extensive Metabolizers
- FIH: First-In-Human
- F_m: Fraction metabolized
- GMR: Geometric Mean Ratio
- HCV: Hepatitis C Virus
- HV: Healthy Volunteer
- IMs: Intermediate Metabolizers
- K_i: Inhibitory Constant
- K_m: Concentration of substrate required for enzyme to achieve half V_{max}
- M&S: Modeling & Simulation
- NME: New Molecular Entity
- OAT: Organic Anion Transporter
- OATP: Organic Anion Transporting Polypeptide
- PBPK: Physiologically Based Pharmacokinetic
- PG/PGx: Pharmacogenomics
- P-gp: P-Glycoprotein
- P.O. Per Os administration
- PMs: Poor Metabolizers
- QD: Once-a-Day
- $T_{1/2}$: Half-life
- UGT: Uridine 5'-Diphospho-Glucuronosyl Transferase
  V_{max}: Time to reach C_{max}
- V_{max}: Maximum velocity of enzyme
- VPC: Visual Predictive Check

Thank you for your time and attention.

Questions?

SUPPLEMENTAL MATERIAL

Platform Qualification (1)

- A PBPK platform is an integrated environment which allows building and running PBPK models
- The platform may or may not include compound or population-specific databases
- The platform includes several components such as:
  - Graphical User Interface
  - Computational engine
  - Data structures
  - Various models
- The PBPK models within a platform are developed to handle specific tasks based on certain assumptions

M Shebley, P Sandhu, AE Riedmaier, M Jamei, R Narayanan, A Patel et al., PBPK Model Qualification & Reporting Procedures for Regulatory Submissions. *Clin. Pharmacol. Ther.,* 2018, 104 (1), 88-110.

Platform Qualification (2)

- Computational Framework Includes:
  - Design Qualification
    - Intended purpose of the software platform
  - Installation Qualification
    - Robust reproduction of the results on the user's computer

- System Parameters Include:
  - Tissue and Organ Compartments
    - Tissue volume, surface area, pH, gastric emptying time, intestinal transit time
    - Abundance of drug metabolizing enzymes and transporters and genotype
    - Demographics (age, gender, ethnicity, disease state)

Platform Qualification (3)

- Drug Parameters include the following properties:
  - Physiochemical (molecular weight, pKa, Log P, blood to plasma ratio, fraction unbound in plasma)
  - Absorption (fraction absorbed, apparent permeability, solubility)
  - Distribution (volume of distribution, tissue:plasma partition coefficients)
  - Elimination (in vitro intrinsic clearance (CL), fraction metabolized by a specific CYP or UGT (fm), fraction unbound in microsomes, in vivo plasma CL, renal CL)
  - Drug Interactions (K_i/K_{inact} for CYP, K_i for UGT or transporter mediated interactions)
  - Involvement of transporters (intestinal, liver, kidney, brain)
  - Sensitivity Analysis
    - To assess impact of uncertainty in specific parameters or modeling assumptions e.g. K_i range for CYP3A, fraction metabolized (f_m) by a specific enzyme