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REVIEW

PBPK modeling and simulation in drug research and development



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Abstract Physiologically based pharmacokinetic (PBPK) modeling and simulation can be used to predict the pharmacokinetic behavior of drugs in humans using preclinical data. It can also explore the effects of various physiologic parameters such as age, ethnicity, or disease status on human pharmacokinetics, as well as guide dose and dose regimen selection and aid drug–drug interaction risk assessment. PBPK modeling has developed rapidly in the last decade within both the field of academia and the pharmaceutical industry, and has become an integral tool in drug discovery and development. In this mini-review, the concept and methodology of PBPK modeling are briefly introduced. Several case studies were discussed on how PBPK modeling and simulation can be utilized through various stages of drug discovery and development. These case studies are from our own work and the literature for better understanding of the absorption, distribution, metabolism and excretion (ADME) of a drug candidate, and the applications to increase efficiency, reduce the need for animal studies, and perhaps to replace clinical trials. The regulatory acceptance and industrial practices around PBPK modeling and simulation is also discussed.

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1. Introduction

The concept of physiologically based pharmacokinetic (PBPK) models was first introduced by Teorell in 1937¹. For several decades, growing efforts have been made to refine PBPK models so that they can be applied in drug development². Thanks to the advancement in computing power and increasing access to preclinical data, especially *in vitro* data, on absorption, distribution, metabolism and excretion (ADME). PBPK modeling and simulation currently receives extensive attention during drug discovery and development^{3,4}, and in submissions for regulatory filing and reviews^{5,6}. As a unique tool, PBPK models can be used to estimate the pharmacokinetic (PK) profile of a compound based on its preclinical ADME data and can be used to assess the exposure in a target organ after the administration of a drug by taking into account the rate of absorption and disposition in that organ, as well as metabolism within that organ if it is applicable. Based on the PK data generated from one dose schedule, the PBPK model can be used to evaluate the PK profile of different dose schedules and/or dose routes. Based on the PK data from one ethnic population, the PBPK model can be used to predict the PK profile in different ethnic populations as well as populations of various age and disease stages. This mini-review describes the PBPK methodology used in drug discovery and development and specific examples of its application together with the regulatory acceptance and industrial common applications.

2. PBPK methodology

PBPK models are made up of compartments corresponding to the different physiological organs of the body, linked by the circulating blood system. Each compartment is exactly described by a tissue volume and blood flow rate that is specific to the species of interest. Each tissue is defined with assumptions of either perfusion-rate-limited or permeability-rate-limited. Perfusion-rate-limited kinetics tends to exist for small lipophilic molecules where the blood flow to the tissue proved to be the limiting process of the absorption. Permeability-rate-limited kinetics occurs for more hydrophilic and larger molecules where the permeability across the cell membrane becomes the limiting process of absorption⁷. Drug is disposed *via* the exile blood flow after being metabolized in the organ, if applicable.

A schematic of a PBPK model is shown in Fig. 1. The mass balance differential equations used in these models have been described previously⁸ and follow the principles shown below.

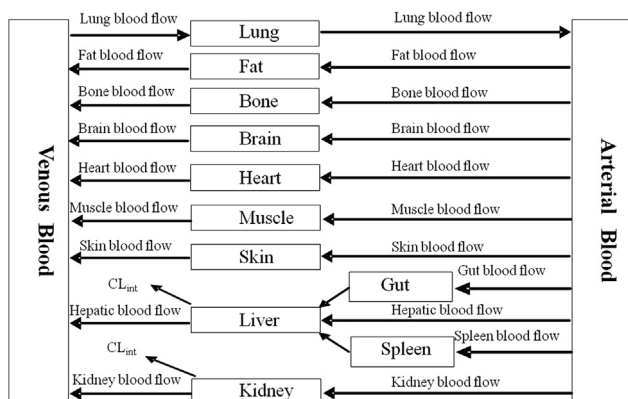


Figure 1 Schematic of a PBPK model.

Non-Eliminating tissues:

$$VT \times dCT/dt = Q_T \times C_A - Q_T \times CV_T \quad (1)$$

where Q is blood flow (L/h), C is concentration (mg/L), V is volume (L); and T represents tissues, A represents arterial, V represents venous.

$$CV_T = C_T / (K_p / B:P) \quad (2)$$

where K_p is tissue to plasma partition coefficient of the compound and B:P is the ratio of blood to plasma.

Eliminating tissues:

$$VT \times dCT/dt = Q_T \times C_A - Q_T \times CV_T - CL_{int} \times CV_u T \quad (3)$$

where CL_{int} is the intrinsic clearance of the compound (L/h), and u is unbound.

Different from the conventional PK models, PBPK model is composed of two main parts—an anatomical “backbone” which contains species specific physiological parameters that are independent of the drug and hence can be applied to any compounds, and a drug-specific part which consists of the individual drug's ADME properties applied to the relevant processes within each tissue compartment. Parameters for incorporating into PBPK models are either drug-dependent (*e.g.*, binding to blood, f_{ub} ; tissue-to-plasma distribution coefficient, K_{PT} ; tissue permeability–surface area product, P_{ST} ; enzymatic activity, V_{max}/K_m) or drug-independent (*e.g.* blood flows, Q_T ; tissue volumes, V_T ; tissue composition). The accuracy of the PBPK prediction of ADME parameters by the model not only depends on the present knowledge of animal or human physiology, but also on the physicochemical and biochemical properties of the test compounds.

3. The key points in PBPK model construction

3.1. Acquisition of drug dependent parameters

PBPK modeling is a bottom-up approach that integrates a large number of drug specific data, parameters on species physiology (system data), and a good understanding of all active processes affecting the pharmacokinetic properties of a drug. System-dependent parameters (*e.g.*, tissue volume, blood flow, glomerular filtration rate, amount of microsomal protein/hepatocytes per gram of liver, plasma protein, enzyme, and transporter abundance) for human and preclinical species are available in the literature and have been compiled in the commercial PBPK platforms, including GastroPlus (www.simulations-plus.com), PKSIM (www.systemsbiology.com/products/pk-sim.html), Simcyp (www.simcyp.com), ADMEWORKS DDI Simulator (http://www.fqs.pl/chemistry_materials_life_science/products/ddi_simulator), CLOEPK (<http://www.cyprotex.com/insilico/>), and many other modeling software. For example, PBPK models in humans specify ethnic population (specific system parameters) account for variability (standard deviation or range) and the covariation between these parameters in that ethnic population. Drug dependent parameters include physicochemical properties (molecular weight, pK_a , basic or acidic nature of the drug), solubility ($\log D$) and permeability, blood cell and plasma protein binding (*e.g.* fraction unbound in plasma ($f_{u,p}$), blood plasma partitioning [B:P]), transporter contribution to drug disposition, and *in vitro* data on the metabolism by hepatic or extrahepatic enzymes (*e.g.*, intrinsic clearance (CL_{int})). A lack of sufficient *in vitro* and *in vivo* data may hamper the use of this approach. These compound-specific parameters are often deter

Table 1 Data requirement for building a PBPK model in Simcyp®.

Parameter	Unit convert to	<i>In vitro</i> test system
Molecular weight	g/mol	Physicochemistry property measurement, less prefer an <i>in silico</i> prediction
log P		Octanol:water partition coefficient
p K_a (s)		Physicochemistry property measurement, less prefer to use an <i>in silico</i> prediction
Compound type	Base, acid, neutral	Based on the chemical structure or pH-dependent solubility test
pH-dependent solubility	$\mu\text{g/mL}$	Measured in buffer with different pH
Plasma protein binding	f_u	<i>In vitro</i> in human plasma (pay attention to whether compound binds to AGP)
Blood–plasma partitioning	B:P	<i>In vitro</i> in human blood
Apparent permeability	10^{-6} cm/s	Caco-2, MDCK
Intrinsic clearance in microsomes, or S9, or hepatocytes, or rhCYP	$\mu\text{L}/\text{min}/\text{mg}$ for microsomes and S9, $\text{uL}/\text{min}/\text{million cells}$ for hepatocytes, $\text{uL}/\text{min}/\text{pmol}$ for rhCYP	<i>In vitro</i> assay, or use <i>in vivo</i> clearance if available
Protein concentration in <i>in vitro</i> test	mg/mL	<i>In vitro</i> assay for intrinsic clearance
<i>In vitro</i> test matrix binding	f_u	Measure the free fraction using the same protein concentration in the <i>in vitro</i> test system
V_{max} and K_m (if study for saturable PK; study metabolic-mediated DDI as a victim)	pmol/min/mg, $\mu\text{mol/L}$	The same <i>in vitro</i> system where intrinsic clearance was determined
Percent of enzyme (e.g. CYP) contribution to the metabolism (study DDI as a victim; study metabolic-mediated DDI as a perpetrator)	f_m	<i>In vitro</i> reaction phenotyping
Reversible inhibition, IC_{50}	$\mu\text{mol/L}$	Human liver microsomes or suitable <i>in vitro</i> system
Mechanism-based CYP inhibition, k_{inact} , K_I	h^{-1} , $\mu\text{mol/L}$	Human hepatocytes with positive controls in 3 donors
CYP Induction, J_{max} , EC_{50}	fold induction, $\mu\text{mol/L}$	

Some transporter data can be incorporated; when clinical data become available, CL, V_{ss} , f_a , K_a , etc., can be incorporated to refine the initial model.

mined using *in vitro* assays or sometimes *in silico* models. Table 1 lists the input data required for building a basic PBPK model, in this case, for Simcyp simulation.

3.2. Combination of “bottom-up” and “middle-out” methods to create and refine a PBPK model

PBPK modeling typically uses a “bottom-up” approach and is initially constructed based on preclinical data during the early drug discovery stage. Compound-specific parameters generated using *in vitro* models are used to predict *in vivo* PK profile in preclinical species and humans. For example, a “bottom-up” methodology for the clinical PK profile prediction proposed by Jones et al.⁹ is described as following:

- (1) Verification of intravenous disposition prediction in preclinical species, for example, assessment of most appropriate K_p prediction methodology taking into account method assumptions, assessment of the prediction accuracy and the physicochemical properties of the particular compound;
- (2) Verification of oral absorption prediction in preclinical species over a range of doses to further assess prediction accuracy;
- (3) Simulation of disposition and absorption in humans—using appropriate CL and K_p prediction methods selected based on the preclinical verification step. Once preclinical or clinical *in vivo* data are available, the mechanistic PBPK models can be further refined and updated (“middle-out” approach) and applied

prospectively to simulate unstudied scenarios and, when appropriate, these predictions can be incorporated into regulatory submissions, product labels, additional post-approval studies, and next generation follow-on drugs¹⁰.

During this stage, mismatches between simulation and observation may frequently occur and parameter sensitivity analysis is critical to identify the inputs that have the most influence on a simulated profile. The selection of which parameters to focus upon for the parameter sensitivity analysis requires a good understanding of the nature of each input data, as well as how they may impact the simulated profile. It is also important to have an understanding of how the input data are generated and the associated errors, and also an awareness of the reasonable range of input values.

4. Applications of PBPK modeling during drug research and development

PBPK models are routinely applied from the early discovery stage, where there is limited data captured for any compound of interest, to late drug development, where large amounts of data are available⁹. PBPK modeling can be categorized into three major roles, that can be used to inform regulatory communications, that have impacted clinical development decisions and that promote the mechanistic understanding of clinical observations¹¹.

5. Lead optimization or candidate evaluation, a case study

Unlike late development stages where PK data from animal can be used to refine the PBPK model built on *in vitro* data, in drug discovery, these processes mainly rely on the use of physicochemical properties, *in vitro* data, and increasingly *in silico* data. This example illustrates the use of a PBPK absorption model (GastroPlus v. 8.5) in the prediction of human oral bioavailability from preclinical studies for a candidate compound. YQA-14 is a novel and selective dopamine D₃ receptor antagonist, with the potential to treat drug addiction. Earlier compounds in its structural class tend to have poor oral bioavailability in humans due to the pronounced metabolism from aldehyde oxidase (AO). The aim of this study was to simulate the clinical pharmacokinetic behavior of YQA-14 using a PBPK model to assess the likelihood of developing YQA-14 as a clinical candidate¹². YQA-14 is a lipophilic and basic compound with three pK_a values (6.91, 9.30, and 10.91) and a logD_{7.4} value of 2.15. At pH 6.5, the solubility of YQA-14 was 0.004 mg/mL. It was stable in human liver cytosolic fractions (less AO metabolism liability compared to the previous candidates), and the liver microsomal clearances and *in vivo* clearances were moderate in rats, dogs (*in vitro* and *in vivo*) and humans (*in vitro* only). It also had moderate bioavailability in preclinical species. For human PK prediction, a “bottom-up” full PBPK model was first built by inputting the main parameters obtained from *in vitro* studies (Table 2). This model was then validated and modified by *in vivo* PK profiles of rats and dogs (Fig. 2). After oral administration, YQA-14 was rapidly absorbed in preclinical species with a T_{max} around 0.5–1 h; this is consistent with the high permeability obtained from the Caco-2 assessment. Oral bioavailability in rats and dogs were 15.6% and 45.9%, respectively. Because rats have a higher hepatic clearance, both *in vitro* and *in vivo*, then might have a higher pre-system metabolism. Poor solubility could be another reason for the lower bioavailability in rats because a higher dose was given to rats compared to dogs. After the preclinical model was validated, physicochemical properties, models/modules used to predict tissue distribution, compound dissolution and precipitation information, combined with respective *in vitro* human data (clearance, plasma protein and microsomal binding, and RBC partitioning) were utilized to simulate human plasma concentration vs. time profiles of YQA-14 at 287 mg QD, a therapeutic dose extrapolated from the

rat pharmacology study. A bioavailability of 16.9% was predicted in humans. However, after decreasing the oral dose from 287 mg to 57.4 mg (the low end of the projected human efficacious dose), the predicted bioavailability increased from 16.9% to 35.1%, whereas no change in elimination parameters such as t_{1/2} was observed, suggesting that solubility did play a role in the absorption of YQA-14 in humans. These acceptable PK properties make YQA-14 an improved candidate for further development as a potential dopamine D₃R antagonist for the treatment of drug addiction in clinic.

6. Drug–drug interaction (DDI) potential prediction, a case study

This example demonstrates the potential of using PBPK modeling in the prediction of DDI risk¹³. Naturally occurring furanocoumarin compounds psoralen (PRN) and isopsoralen (IPRN) are bioactive constituents in herbaceous plants. They are widely used as active ingredients in many Chinese herbal medicines. Both PRN and IPRN showed potent reversible inhibition of CYP1A2 in human liver microsomes (HLMs). In addition, time-dependent inhibition of CYP1A2 was observed with IPRN but not PRN. In an attempt to assess the potential DDI risk, Simcyp simulations were conducted to predict phenacetin (a CYP1A2 substrate) AUC changes under the co-administration of PRN or IPRN by allowing perpetrator and victim dosed at the same time once a day for 10 days. A reduced PBPK model was built using the basic physicochemical data listed in Table 3¹⁴. Simulations were performed in healthy subjects (n=100, 50% men, aged 40–65 years) by using a Simcyp population-based simulator (version 11, Simcyp Ltd., Sheffield, UK). A population of smokers was constructed by modifying the CYP1A2 abundance in healthy subjects from 52 to 94 pmol/mg microsomal protein to mimic individuals who smoke 20 cigarettes per day¹⁴. The Simcyp default phenacetin profile was used without further modification. The maximum allowed daily doses of PRN and IPRN (60 mg, Chinese Pharmacopoeia Commission, 2010) were used to predict the worst-case scenario of DDI. Fig. 3 presents the 10-day simulations of plasma concentration–time profiles of a 1500 mg daily dose of phenacetin with a 60 mg daily dose of PRN or IPRN. The results showed that PRN increased the AUC of phenacetin by 1.71-fold and 2.12-fold in healthy volunteers and smokers, respectively, whereas IPRN increased the AUC of phenacetin by 3.24-fold and 5.01-fold in healthy volunteers and smokers, respectively. It is worth noting that in this simulation, the smoker population has lower basal AUC because of their high CYP1A2 activity. Co-administration of the moderate reversible inhibitor PRN was not able to bring the AUC back to the level of a healthy volunteer, suggesting an incomplete balance of the higher CYP1A2 activity induced by the smoke. However, when a more potent inhibition IPRN was applied (both reversible and time-dependent CYP1A2 inhibitor), the AUC in the smoke population was comparable to the level of healthy volunteer suggesting that the inhibition and inactivation effects by IPRN balanced off the CYP1A2 activity induced by smoke. On the other hand, the change of clearance and AUC were more profound when the co-administration IPRN or PRN in smoke population.

7. Human PK and DDI prediction to avoid clinical DDI trials, a case study

Orteronel (TAK-700) is an oral, nonsteroidal, reversible, selective 17,20-lyase inhibitor that was in development for the treatment of

Table 2 Input data used in the GastroPlus™ PBPK model.

Parameter	Value
Molecular weight (g/mol)	442.95
pK _a	6.91, 9.30, 10.91
logD at pH 7.4	2.15
Caco-2 permeability (10 ⁻⁶ cm/s)	19.90, 22.13
(propranolol, control)	
Aqueous solubility at pH 6.5 (mg/mL)	0.004
R _{hp} in rat, dog, human	0.70, 0.67, 0.65
%F _u in rat, dog, human plasma and human liver microsomes	1.29, 1.05, 0.96, 64
CL _{int} in rat, dog and human liver microsomes (mL/min/kg)	57.60, 6.42, 13.46
<i>In vitro</i> predicted hepatic clearance in rat, dog and human (mL/min/kg)	31.60, 5.49, 8.05
<i>In vivo</i> clearance, rat, dog (mL/min/kg)	29.7, 8.3
Dose (rat, dog, and human, mg/kg, QD)	25, 5, 4.1

This table is adapted from Ref. 12 with permission.

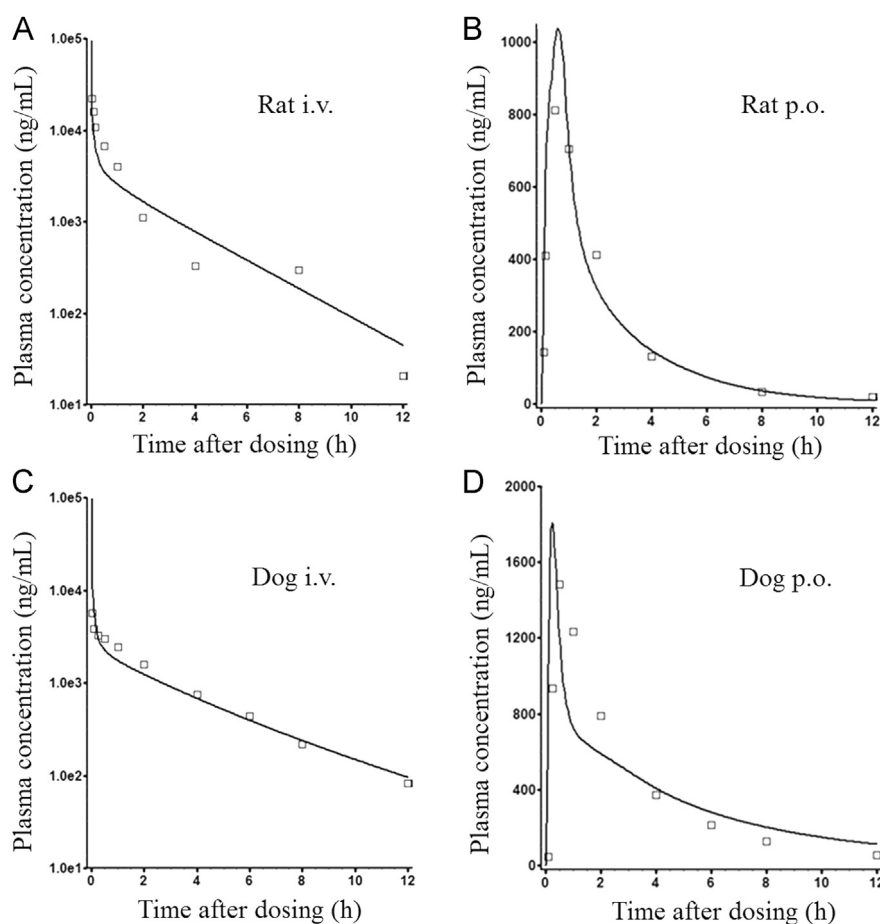


Figure 2 Observed (\square) and PBPK model-simulated (—) plasma concentration–time profiles of YQA-14 in rats (A and B) and dogs (C and D) after a single i.v. (A and C) or (p.o.) (B and D) administration. Observed plasma concentration–time profiles (OBS) were obtained for rats and dogs after single i.v. and p.o. administration of YQA-14 at 25 and 5 mg/kg, respectively ($n=3$ rats/group; $n=4$ dogs/group). This figure is adapted from Ref. 12 with permission.

patients with metastatic castration-resistant prostate cancer. *In vitro* CYP inhibition study in human liver microsomes showed that orteronel is a moderate inhibitor in CYP1A2, 2C8, 2C9, and 2C19, with IC_{50} values of 17.8, 27.7, 30.8 and 38.8 $\mu\text{mol/L}$, respectively. However, it showed no inhibition in CYP2B6, 2D6 or 3A4/5 ($IC_{50} > 100 \mu\text{mol/L}$, Table 4)¹⁵. The C_{max} of orteronel in patients who had consumed a high-fat meal was at average of 9.18 $\mu\text{mol/L}$ and thus, the $[I]/IC_{50}$ ratio calculated using a basic static model showed that orteronel could cause as high as 1.84-fold of DDI. Following the FDA DDI guidance¹⁶, if basic static models show that a perpetrator has the potential of causing DDI (*i.e.* $[I]/IC_{50} > 0.1$), following up DDI assessment using a PBPK model under the dynamic conditions with both substrate and inhibitor is recommended. A PBPK model was then built with physicochemical and preclinical data and oral clearance from a human phase I trial because *in vitro* metabolic clearance does not reflect the total body clearance (Table 5). The resulting model well described the observed clinical PK (Fig. 4). This model was then used to simulate DDI potential with a set of sensitive CYP probe substrates, theophylline, repaglinide, (*S*)-warfarin, and omeprazole for CYP1A2, 2C8, 2C9, and 2C19, respectively (built in compound profiles within the Simcyp software, no further modification was made). The DDI potential of orteronel toward these 4 CYPs at the dynamic concentration scenario was simulated. As shown in Table 6, orteronel would not cause DDI with any of the 4 CYPs

with AUC changes all less than 1.25-fold, with the criteria considered as no DDI by the FDA¹⁶.

8. Dose guidance for renal impairment patients, a case study

This case illustrates how PBPK modeling can inform appropriate dosing of renal impairment (RI) patients in phase I/III studies and thereby enable characterization of safety and efficacy in the RI patients during the late stage of drug development¹⁷. Data from human ADME study revealed that orteronel (see last example) is a drug that is primarily cleared by kidney excretion. The extent of orteronel biotransformation is minimal, with cytochrome P450 isozymes having only a minor role. Thus, patients with renal impairment may have increased exposure to orteronel because of their impaired urinary excretion capability. A PBPK model was built as described in the last case study. The predicted PK profile was then validated using clinical PK data before applying the model to simulate PK profile of orteronel in moderate (glomerular filtration rate (GFR), 30–60 mL/min) or severe (GFR, < 30 mL/min) RI patients. By comparing the PBPK model outputs with the population PK analysis results from phase 2 trials, it was demonstrated that PBPK modeling can accurately predict the effect of moderate and severe RI on the PK profile of orteronel (*i.e.* fold increase in AUC). In this model, exposure to orteronel

Table 3 Input data of PRN and IPRN for Simcyp[®] simulation.

Parameter	PRN	IPRN
Molecular weight	186.17	186.17
$\log D_{7.4}$	1.63	1.32
Blood–plasma partition co-efficient (B/P)	0.82	0.65
Plasma protein binding (f_u)	0.283	0.126
Microsomal protein binding at 0.5 mg/mL (f_u)	0.745	0.906
Apparent permeability value: P_{app} (10^{-6} cm/s) Caco-2 (calibration compound atenolol $P_{app} = 1.40 \times 10^{-6}$ cm/s)	51.6	44.6
Microsomal clearance ($\mu\text{L}/\text{min}/\text{mg}$)	14.5	8.0
CYP1A2 IC_{50} ($\mu\text{mol}/\text{L}$)	0.26	0.22
CYP1A2 K_i ($\mu\text{mol}/\text{L}$)		0.40
CYP1A2 k_{inact} (min^{-1})		0.05

For reversible inhibition, K_i were estimated using $\text{IC}_{50}/2$;

Both compounds are in neutral condition under physiological pH, thus $\text{p}K_a$ was not available;

1400 mg phenacetin QD $\times 10$ and 60 mg PRN or IPRN QD $\times 10$ were applied;

This table is adapted from Ref. 14 with permission.

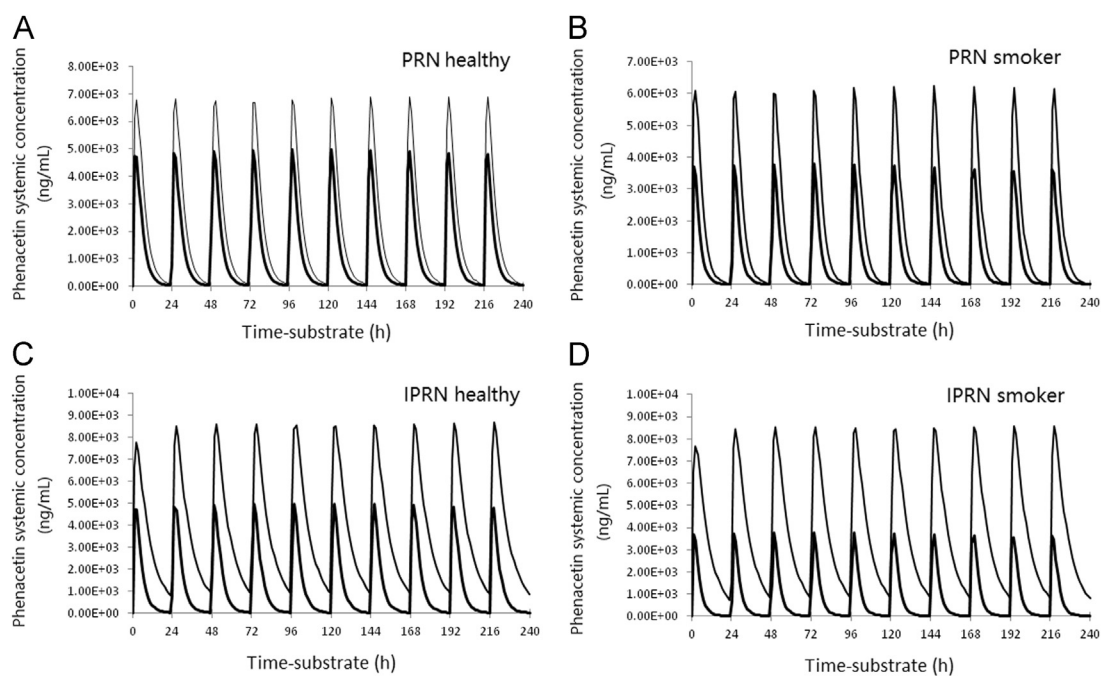


Figure 3 Simcyp simulation results of phenacetin AUC_{0-24} at 1400 mg daily $\times 10$ days in the presence of IPRN (60 mg daily $\times 10$ days) and absence of IPRN in healthy subjects (A) and smokers (B), or the presence of PRN (60 mg daily $\times 10$ days) and absence of PRN in healthy subjects (C) and smokers (D). The outer curves represent phenacetin concentration in the presence of PRN or IPRN. This figure is adapted from Ref. 14 with permission. IPRN, isopsoralen; PRN, psoralen.

increased as a reversed function of the estimated proportion of orteronel cleared by the kidney, aligning with the degree of renal impairment. The AUC for orteronel, when given at the clinical dose of 400 mg BID, was predicted to increase by 52% in patients with moderate RI and 83% in patients with severe RI compared with the healthy population group. Furthermore, the PBPK simulation also predicted that a reduced dose of orteronel of 220 mg BID (or a rounded dose of 200 mg BID) would achieve exposures in severely impaired subjects comparable to those seen in subjects with normal renal function treated at 400 mg BID (Fig. 5). Then a PopPK model was built to determine if dose adjustments might be required for renal RI patients in the clinical setting. Results of the PopPK suggested that patients with mild RI

may not require dose adjustments as they were predicted to have only a 20% higher exposure compared to the healthy subjects (a scenario not included in the PBPK modeling). Patients with severe RI given orteronel 200 mg BID were predicted to have similar orteronel plasma concentrations as control subjects given 400 mg BID. In summary, this case demonstrates that for a drug being eliminated primarily *via* renal route, the PBPK modeling approach can play a key role for guiding dose selection. This analysis helped the inclusion of patients with RI in phase III trials with appropriate dose adjustment. That could serve as an alternative to a dedicated RI study, or suggests that a reduced-size study in severe RI patients may be sufficient to assess the exposure risk in other RI patients.

Table 4 Orteronel $[I]/K_i$ values and predicted AUC ratio using static model.

Parameter	CYP1A2	CYP2C8	CYP2C9	CYP2C19
Orteronel IC_{50} ($\mu\text{mol/L}$)	17.8	27.7	30.8	38.8
$[I]/K_i$	1.03	0.66	0.60	0.47
Substrate (f_m)	Theophylline (0.90)	Repaglinide (0.64)	(S)-warfarin (1.00)	Omeprazole (0.87)
AUC ratio	1.84	1.34	1.60	1.39

Abbreviations: CYP, cytochrome P450; $[I]$, inhibitor concentration that is the total plasma maximum concentration (C_{max}); IC_{50} , 50% inhibitory concentration; K_i , inhibition dissociation constant.

Note: The mean C_{max} in the subjects with the high-fat meal was $9.18 \mu\text{mol/L}$. $K_i = IC_{50}/2$, assuming competitive inhibition. The f_m was adapted from Simcyp[®] v 11. AUC ratio was calculated using the basic static equation: $AUCR = 1/(f_m/(1+[I]/K_i)+(1-f_m))$.

This table is adapted from Ref. 15 with permission.

Table 5 Orteronel input data for PBPK M&S.

Parameter	Value
Compound type	Monoprotic base
Molecular weight	307.35
$\log D_{7.4}$	1.322
pK_a	6.600
Blood–plasma partition coefficient (B/P)	1.39
Plasma protein binding (f_u)	0.403
Main binding protein	HSA
Microsomal protein binding at 0.5 mg/mL ($f_{u,\text{mic}}$)	0.961
f_u (gut)	1
f_a	0.86
K_a (L/h)	0.79
Q_{gut} (L/h)	8.394
Apparent intrinsic permeability value: P_{app} (10^{-6} cm/s) Caco-2	9.05
Calibration compound (propranolol) value: P_{app} (10^{-6} cm/s) Caco-2	25.1
Clinical oral clearance (CL/F), (L/h)	16.9
Human ADME clearance routes (renal, hepatic, other)	53%, 28%, 19%
Clinical oral clearance, %CV	15.7
Clinical volume of distribution (V_d/F), (L/kg)	1.4
Clinical volume of distribution, %CV	30.2
CYP1A2 K_i ($\mu\text{mol/L}$) ^a	8.9
CYP2C8 K_i ($\mu\text{mol/L}$) ^a	13.8
CYP2C9 K_i ($\mu\text{mol/L}$) ^a	15.4
CYP2C19 K_i ($\mu\text{mol/L}$) ^a	19.4

Abbreviations: %CV, percent coefficient of variation; ADME, absorption, distribution, metabolism, excretion; f_a , fraction absorbed; f_u , fraction unbound; f_u (gut), apparent unbound fraction in enterocytes; HSA, human serum albumin; IC_{50} , 50% inhibitory concentration; K_a , first-order absorption rate constant; K_i , reversible inhibition constant; $\log D_{7.4}$, logarithm of the octanol–water partition coefficient at pH 7.4; P_{app} , apparent passive permeability; pK_a , logarithmic acid dissociation constant; Q_{gut} , hypothetical blood flow term that is used to indicate complex interplay among passive intestinal permeability, active transport, enterocyte drug binding, blood flows to enterocytes, and gut metabolism.

This table is adapted from Ref. 15 with permission.

^aAll inhibition was assumed conservatively to be reversible; K_i values were calculated: $IC_{50}/2$.

9. Bridge healthy adults to special populations

PBPK models can be utilized to extrapolate the drug pharmacokinetic behavior in healthy volunteer to patient populations that are a challenge to obtain PK profiles for, such as predicting doses and drug exposures in children and infants¹⁸ and patients suffered from impaired renal or liver function^{11,15}. The work of Parrott and colleagues¹⁹ exemplified the usage of a mechanistic PBPK model in predicting the pharmacokinetics of a neuraminidase inhibitor oseltamivir and its active metabolite oseltamivir carboxylate (OC) which are for the treatment and prophylaxis of influenza A and B infections in infants and neonates. In their strategy (Fig. 6), the

simulation of pharmacokinetics in adult animal species was first conducted. After a reasonable simulation of pharmacokinetics in the adult animal is achieved with a refinement, prediction of human pharmacokinetics was performed using information captured during the refinement of the animal model. For prediction of juvenile PK profile in humans, the same methodology is followed. First, a juvenile animal model is generated, which accounts for age-dependent differences that are known to impact the PK behavior of the drug, then the model was verified by comparison with the data obtained from a juvenile animal study. Finally, the prediction of juvenile humans was done using a PBPK model that accounted for age dependency in humans and information gathered

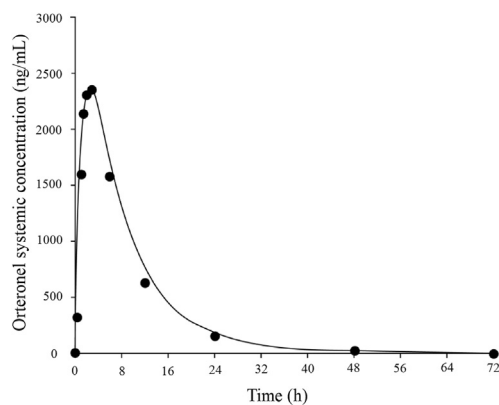


Figure 4 Simulated and actual mean orteronel concentration-versus-time curves. The line represents the simulated mean area under the concentration-versus-time curve after a single dose of orteronel at 400 mg; the circles represent the actual data points from the high-fat diet group ($n=42$) treated with a single dose of orteronel 400 mg. This figure was adapted from Ref. 15 with permission.

Table 6 DDI analysis: simulated area under the concentration–time curve ratios for orteronel.

CYP/substrate	Dose	Orteronel IC ₅₀ (μmol/L)
CYP1A2/theophylline (SV)	125 mg TID	17.8
CYP2C8/repaglinide (SV)	0.25 mg BID	27.7
CYP2C9/(S)-warfarin (Sim)	10 mg QD	30.8
CYP2C19/omeprazole, enteric-coated (SV)	20 mg BID	38.8

Abbreviations: BID, twice daily; CYP, cytochrome P450; DDI, drug–drug interaction; IC₅₀, 50% inhibitory concentration; QD, once daily; Sim, profile based on *in vitro* data; SV, profile based on *in vivo* data; TID, 3 times daily.

This table was adapted from Ref. 15 with permission.

from adult human and juvenile animal studies for refinement. This provided the first insight of drug exposure in juveniles since a PK study in this population is hard to come by.

10. Regulatory submission

PBPK modeling has been gaining acceptance at various regulatory bodies as part of submission package. Discussion of modeling and simulation approaches can be found in the updated DDI guidance from both the European Medicines Agency (EMA)²⁰ and the U.S. Food and Drug Administration (FDA)¹⁶. Recently, The FDA hosted a workshop at their White Oak Campus in Silver Spring, MD, USA. At the workshop, the director of the Center of Drug Evaluation and Research (CDER), Dr. Janet Woodcock, concluded that “the modeling work performed thus far at CDER has contributed tremendously to overall drug development, in terms of safety and efficacy, which ultimately result in patient benefits”⁶. Both FDA scientists and industrial and academic representatives agreed that the current advance in PBPK modeling enable us to predict investigational drugs as a substrate of drug metabolizing enzyme with high confidence, especially when the drug is

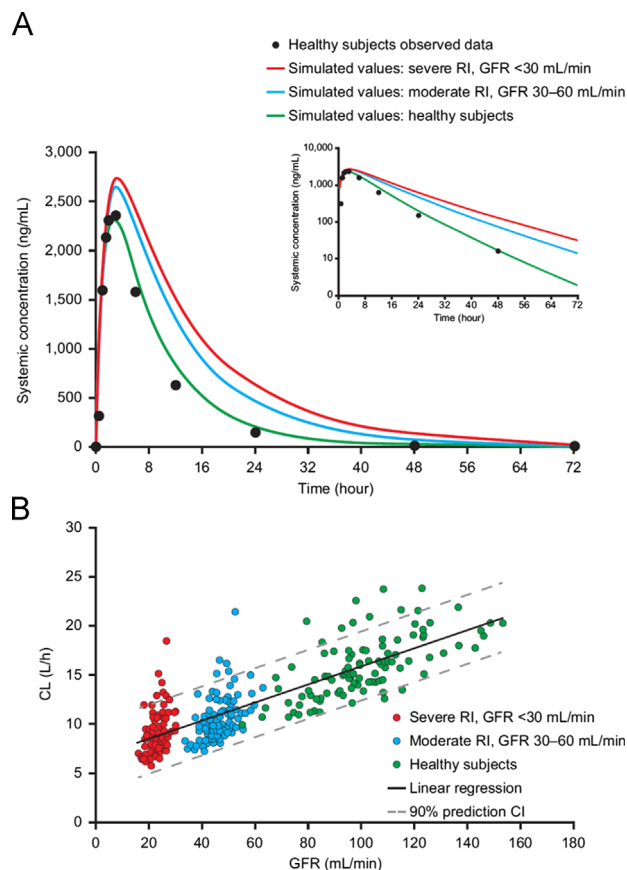


Figure 5 Physiologically based pharmacokinetic (PBPK) simulation of orteronel in (A) healthy subjects (observed and simulated values), subjects with moderate renal impairment (simulated values), and subjects with severe renal impairment (simulated values), and (B) regression of orteronel clearance vs. glomerular filtration rate (GFR) based on PBPK simulations in healthy subjects, subjects with moderate renal impairment, and subjects with severe renal impairment. Observed data for healthy subjects (high-fat diet group, $n=42$) were obtained from clinical study C21007. The clinical scenario assumed 100% bioavailability with all uncharacterized metabolism treated as hepatic clearance (orteronel dose: 400 mg BID for 10 days). CL, total clearance; RI, renal impairment. This figure was adapted from Ref. 17 with permission.

primarily metabolized by CYP3A and 2D6^{21,22}. Among compounds in the BCS classification, the PK profile of type I compounds with high solubility and high permeability usually can be predicted quite well from their preclinical data. On the other hand, prediction of exposure changes due to CYP induction has not been well validated, neither had the compounds of mix of CYP inducer and time-dependent inhibitor. PK prediction involving transporters is still not reliable due to poor understanding of the scaling factors used to extrapolate *in vitro* data to *in vivo* disposition. The same is true for metabolism and disposition in the gut. Due to the complexity of the metabolism, absorption, and transporter activity involved at the different segments of the gastrointestinal tract, and the unique nature of the of individual compound, PBPK modeling for gut absorption (F_g) has yet to be optimized^{22,23}. Drug metabolizing enzyme-transporter interplay, PK prediction in organ impairment population, and allometry scaling down to children younger than 2 years of age (ontogeny

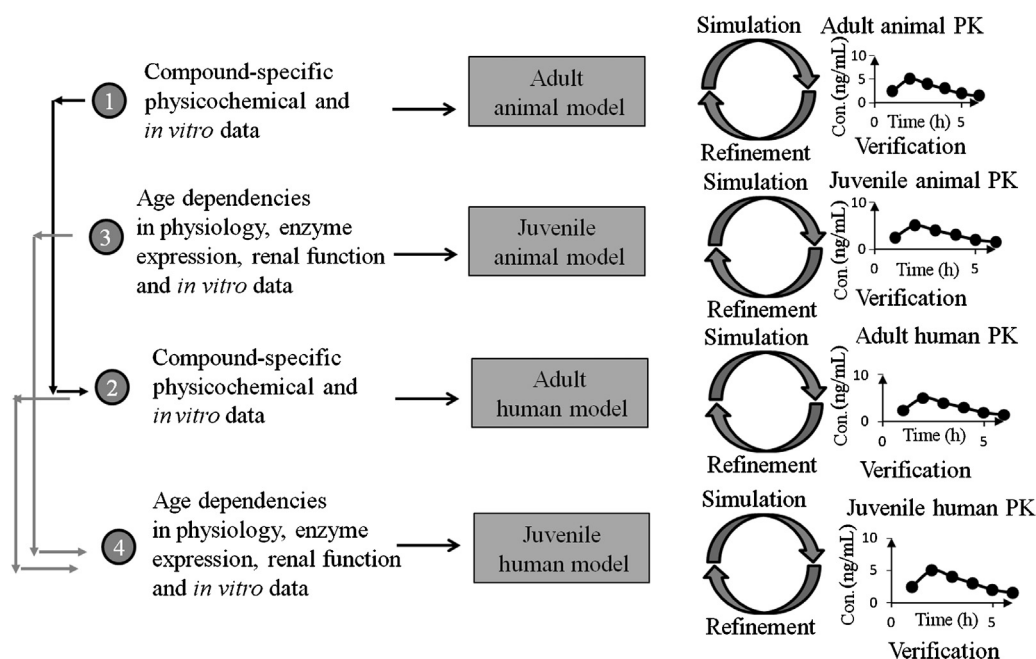


Figure 6 PBPK modeling strategy employed to predict exposure in neonates and infants. A stepwise approach is followed with verification against *in vivo* data at each step. Simulations in juveniles are based on a model incorporating age dependencies in physiology and incorporating data from relevant *in vitro* systems. Verification in juvenile animals allows for model refinement before prediction in children. This figure was adapted from Ref. 19 with permission.

and maturation), are among the areas that still need more research. There are much experiences lacked in the area of pregnancy, obesity, and the geriatric population, as well as food effect, formulation, and pH effects. The prediction of intracellular concentration is also often a challenge^{24,25}.

As PBPK modeling advances, the FDA has seen an increase in modeling work in submission packages. Much of the modeling work is cited in drug product labels to illustrate the degree or lack of DDI risk with co-administration of market drugs^{5,6,22,26–30}. From July 1, 2008 to December 31, 2013, there were 112 PBPK packages submitted to the FDA including 5 run by the agency. Among these packages, most of the studies (76/112) were DDI-related. Most of the DDI simulation (45/76) had no clinical data available for comparison, and of these eight studies were for perpetrators. Most of the DDI submissions were for CYP inhibition risk evaluation, only 8 cases were for CYP induction and 1 was for transporter inhibition. A few cases (3) had clinical data available for building and optimizing the final models²². In most situations, the PBPK models were included in the submission of IND or NDA.

11. Common industrial application for PBPK modeling

In the pharmaceutical industry, PBPK modeling is used for purposes, such as mechanistic studies, aiding internal drug discovery or clinical development decisions, and informing regulatory communication including filing at various stages (*e.g.*, IND and NDA). It is mostly applied at the development stage. Below are a few outlines of its routine applications:

- 1) At the lead optimization stage of drug discovery, PBPK modeling can provide human PK prediction at clinical dose and dose schedule. A high projected dose (*e.g.*, > 1 g/day) may

discourage further investment in that drug PK candidate if it is not a first-in-class drug candidate. For a similar reason, if a drug needs to be administrated multiple times a day, it may face challenge in marketing if it is neither a first-in-class nor a best-in-class drug candidate.

- 2) At the candidate selection stage of drug discovery, should a drug candidate be partially metabolized by polymorphic enzymes, such as CYP2D6 or 2C19, a PBPK model can be applied to simulate the exposure in population including poor metabolizer to determine whether poor metabolizers need to be excluded in the first-in-human (FIH) trials. The model can be further refined with the data from FIH healthy volunteer trials to help to design a DDI study (*e.g.*, dose adjustment) in the poor metabolizer population.
- 3) At the drug development stage, DDI risk simulation is the most popular application for PBPK modeling. Whether a drug candidate is a substrate of drug metabolizing enzymes or a perpetrator, a DDI risk simulation with standard care medications can assess the risk of co-medication with these standard care market drugs. Oftentimes, the most potent perpetrator or the most sensitive substrate is used in the initial simulations to assess the worst case scenario. If enough safety margins are presented at the worst case scenario, then clinical trials with moderately sensitive substrates or perpetrator may get waived.
- 4) Many drugs are cleared *via* hepatic metabolism. Some may be excreted *via* renal excretion. Thus, exposure simulation in organ impairment patients is important to know. There are successful examples of such a simulation described above and in the literature^{11,15}.
- 5) In DDI trial, dependent on the half-life of the substrate, the dose frequency and dose duration of the inhibitor need to be optimized to cover the duration of the exposure of the substrate as much as possible. The more exposure overlap between the substrate and the inhibitor, the better we can capture the DDI

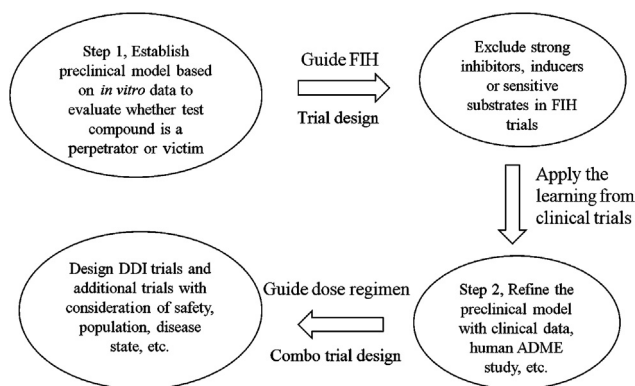


Figure 7 Application of physiologically based pharmacokinetic modeling and simulation in various stages of drug discovery and development. Models were initially built with preclinical data, and later refined with available clinical information. This figure was adapted from Ref. 15 with permission.

potential between these two drugs³¹. In a crossover study design, the washout period is changed upon the application of an inhibitor and therefore needs to be simulated prior the study. A lengthy washout period is costly and also not convenient to the patients, whereas a washout period too short would affect the data quality.

- 6) For many high clearance compounds and substrate of CYP3A4/5, the CYP3A4/5 inhibitor ritonavir is often used to enhance the exposure. PBPK modeling can be used to simulate whether, in the presence of ritonavir, the exposure of the drug candidate can reach the level of efficacious exposure. When DDI liability cannot be avoided, for example part of the chemical structure is responsible for the pharmacological activity but also carries DDI liability, modeling and simulation can be applied to evaluate whether alternative routes of administration (*e.g.*, intravenous) would reduce the DDI liability. Drugs target for inhalation or other non-conventional routes are better evaluated using PBPK modeling to get the feasibility test.

12. Conclusions

PBPK modeling is a useful tool for the prediction of human PK profile from preclinical data. Once FIH PK data or human ADME data becomes available, the model can be further fine-tuned as illustrated in Fig. 7¹⁵. It is a good tool for evaluating and optimizing clinical trial design, for example, to select the dose and dose schedule. It helps to understand the individual variability and parameters that have the most impact on human PK profile through sensitivity analysis. Hence, PBPK modeling provides a practical solution for extrapolating PK profile from healthy population to some ethnic, special age, or disease populations where clinical PK study is the hardest to conduct. In the DDI prediction area, PBPK modeling can help to determine the washout period in a crossover study design to set the minimal but sufficient clinical trial duration. It can also be applied as an alternative to DDI trials in some special populations, such as pediatrics and organ-impairment patients where the actual DDI trial is hard to conduct due to logistical or ethical issues. Thus, it can sometimes provide waiver for conducting unnecessary clinical DDI trials which then speeds up the drug development process and put fewer burdens on patients. Conducting DDI trials with multiple

perpetrators in patients is also not ethical and practical, the PBPK modeling, in this case, can provide information about “what if” all of those drugs are co-administered together. On the other hand, as discussed earlier, PBPK modeling is a bottom-up approach, its results dependent on the quality of the input data. Although software are available for the prediction of physicochemical properties of compounds, such as $\log P$ and pK_a , in authors experience, it is critical to use measured values to get a reliable PBPK prediction, especially when predicting human PK profile, rather than the AUC ratio for DDI purpose. For example, for a set of clinical candidates (about 40 compounds), the number of compounds for which the predicted PK profile within two fold of observed clinical values dropped from about 70% to half of that when *in silico* predicted $\log P$ and pK_a were used (unpublished data). Transporter is another emerging area of PBPK modeling, however, most of the data generated are qualitative to answer the question of yes or no of whether a compound is a substrate of a transporter. PBPK modeling relies on kinetic data, such as the clearance of the compound *via* that transporter. Thus, additional data of transporter clearance are needed for PBPK modeling.

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