Applications of Physiologically Based Pharmacokinetic (PBPK) Modeling and Simulation During Regulatory Review

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Physiologically based pharmacokinetic (PBPK) modeling and simulation is a tool that can help predict the pharmacokinetics of drugs in humans and evaluate the effects of intrinsic (e.g., organ dysfunction, age, genetics) and extrinsic (e.g., drug–drug interactions) factors, alone or in combinations, on drug exposure. The use of this tool is increasing at all stages of the drug development process. This report reviews recent instances of the use of PBPK in decision-making during regulatory review. The examples are based on Center for Drug Evaluation and Research reviews of several submissions for investigational new drugs (INDs) and new drug applications (NDAs) received between July 2008 and June 2010. The use of PBPK modeling and simulation facilitated the following types of decisions: the need to conduct specific clinical pharmacology studies, specific study designs, and appropriate labeling language. The report also discusses the challenges encountered when PBPK modeling and simulation were used in these cases and recommends approaches to facilitating full utilization of this tool.

Physiologically based pharmacokinetic (PBPK) models estimate the pharmacokinetic (PK) profile or exposure in "a target tissue or organ after a drug dose by taking into account the rate of absorption into the body, distribution among target organs and tissues, metabolism, and excretion" (http://www.epa.gov/opp00001/science/comptox-glossary.html#p). The development of PBPK models can be traced back to 1937, when Teorell derived several formulas to describe drug concentrations over time in blood and tissues.[1] Although his model was a rudimentary one, its emphasis on drug distribution and concentration as a function of time in tissues other than blood make this probably the first PBPK model. For several decades, efforts have been made to refine PBPK models that can be applied in drug development and the evaluation of environmental toxins (ref. 2 and the references therein). Over the past two decades, the advancements in computer science and the explosion of knowledge in biomedical sciences supported development of the highly sophisticated, population-based PBPK modeling and simulation tools that are now available.[3–6]

An important role of clinical pharmacologists is to identify optimal dosing regimens for individual patients. In order to achieve this, the effects of intrinsic (e.g., organ dysfunction, age, genetics) and extrinsic (e.g., drug–drug interactions) patient factors (**Figure 1a**) on drug exposure and response need to be evaluated during drug development.[7] PBPK modeling and simulation can help predict the pharmacokinetics of drugs in humans, including the effect of intrinsic and extrinsic factors on ADME (absorption, distribution, metabolism, and excretion). These predictions aid in the selection of optimal dosing regimens. **Figure 1b** illustrates components of a PBPK model, including drug-dependent and drug-independent system components. The system components are based on decades of knowledge of body fluid dynamics (e.g., secretion of gastric acid and bile, blood flow, urine flow), tissue size and composition, abundance and distribution of drug receptors, drug-metabolizing enzymes, and membrane transporters in various organ and tissue compartments. The drug-dependent component of the model enables the study of ADME processes and mechanisms of action at the cellular level by dividing the organs into tissue and intracellular spaces. Consequently, changes in the magnitude and time course of drug exposure and drug action in the tissue of interest can be investigated.

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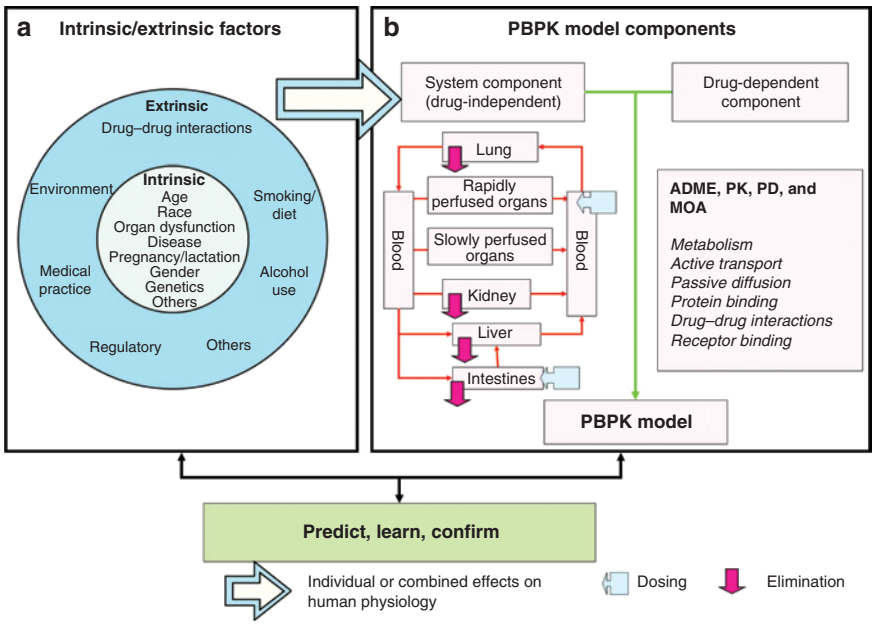

Figure 1 Application of physiologically based pharmacokinetic (PBPK) modeling and simulation to evaluate the effect of various extrinsic and intrinsic factors on drug exposure and response. (**a**) Intrinsic and extrinsic patient factors that can affect drug exposure and response (taken from Huang and Temple[7]). (**b**) Components of PBPK modeling (drug-dependent component and drug-independent (system) component). The figure indicates that the effects of individual or combined intrinsic/extrinsic factors on drug exposure are projected via both drug-dependent and drug-independent (system) components of the PBPK model. ADME, absorption, distribution, metabolism, and excretion; MOA, mechanism of action; PD, pharmacodynamics; PK, pharmacokinetics.

Publications in the literature describe the use of PBPK modeling in critical areas of clinical pharmacology, including pediatrics,[8–11] formulation effect,[12,13] organ impairment,[14,15] and drug–drug interactions.[16–21] The dynamic models that incorporate interindividual variability of intrinsic factors can help determine optimal dosing regimens and sampling schemes at the time of designing clinical pharmacology studies.[16,19,21–24]

From July 2008 to June 2010, the Office of Clinical Pharmacology in the Center for Drug Evaluation and Research of the US Food and Drug Administration (FDA) used PBPK modeling and simulation while reviewing numerous submissions to assist in several types of decisions relating to the need to conduct specific clinical pharmacology studies (both premarketing and postmarketing), the design of the studies, and the appropriate language in the labeling. In this report, we provide a summary of these submissions and their regulatory implications, and we present lessons learned from these reviews.

RESULTS

Summary of PBPK modeling and simulations included in IND and NDA submissions

From July 2008 to June 2010, the FDA reviewed seven investigational new drug (IND) and six new drug applications (NDA) submissions containing PBPK modeling and simulations conducted by the sponsors. In addition, FDA reviewers conducted PBPK modeling and simulations to support clinical pharmacology reviews of another four NDA submissions for which the sponsors did not use PBPK. As a comparison, in the 3 years before 2008, FDA received only two submissions containing PBPK modeling and simulations. Many of the PBPK modeling and simulation evaluations addressed questions relating to drug–drug interactions; others addressed pediatric dosing, the impact of hepatic impairment on drug exposure, and the impact of multiple factors on drug exposure (**Table 1**). A scheme of PBPK modeling and simulations can be generalized to include five basic steps, as outlined in **Figure 2**. In step 1, the drug's clearance pathways are identified and quantified. In step 2, drug-dependent parameters are incorporated into PBPK models. Step 3 compares the predicted concentration–time profiles with those obtained from available *in vivo* human studies. Step 4 consists of refining the model on the basis of the results from step 3. Finally, in step 5, the refined PBPK model is used for predicting PK profiles under various scenarios that have not been studied experimentally. In addition, the mean and upper/lower boundaries that reflect variability or uncertainty are simulated.

Four case studies that posed different regulatory questions regarding the use of PBPK modeling and simulation are described in the following sections of this report.

Representative case studies

Case 1. Specific regulatory question: Can PBPK simulations rule out CYP2C9 inhibition by drug A, even though the ratio of *in vivo* inhibitor concentration (*I*: maximum plasma concentration at the highest proposed dose) to *in vitro* inhibition constant (K_i) of CYP2C9 (I/K_i) is >0.1?

Synopsis: *In vitro* drug interaction data indicate that drug A is a reversible inhibitor of CYP2C9, with an estimated I/K_i ratio of ~2, where *I* is the maximal plasma concentration of drug A. The 2006 draft FDA drug interaction guidance indicates that a clinical drug interaction study should be conducted when the

Table 1 Summary of general regulatory questions addressed using PBPK modeling and simulations

Cases	Main enzymatic pathways; interacting drug/ substrate relationships	Regulatory questions addressed related to PBPK modeling and simulations
1	NME is a CYP inhibitor *in vitro* ($I/K_i > 0.1$)	Can PBPK simulations predict the magnitude of DDI with a CYP substrate *in vivo*?
2	NME is a CYP substrate	An *in vivo* DDI study with a CYP inhibitor has been conducted when NME was dosed orally. Can PBPK simulation predict the magnitude of DDI when NME is given intravenously?
3	NME is a CYP substrate and also renally excreted	Can PBPK simulations predict the magnitude of DDI in subjects with varying degrees of renal impairment (mild, moderate, or severe)?
4	NME is a CYP inhibitor *in vitro* ($I/K_i > 0.1$) NME is metabolized by multiple CYPs in the liver	Can PBPK simulations predict the magnitude of DDI with a CYP substrate *in vivo*? Can PBPK simulations predict the magnitude of DDI with CYP inhibitors? Can PBPK simulations predict PK in subjects with hepatic impairments?
Others	NME is a substrate of a polymorphic CYP *in vitro*	Can PBPK simulations predict the PK in extensive, intermediate, or poor metabolizers of this CYP?
	NME is a CYP substrate and a DDI study using a specific inhibitor dose has been conducted *in vivo*	Can PBPK simulations predict the magnitude of DDI using a different inhibitor dose as recommended by the FDA?
	NME is a CYP substrate and an *in vivo* DDI study has been conducted with a CYP inhibitor	Can PBPK simulations predict the magnitude of DDI with a CYP inducer?
	NME is a TDI of a CYP	Its single-dose PK data are available: Can PBPK simulations predict dose- and time-dependent PK after multiple dosing? Can PBPK simulations predict TDI *in vivo*?
	NME is metabolized by multiple CYPs	Can PBPK simulation be used to predict fractional metabolism based on enzyme kinetic studies *in vitro*?
	NME's adult PK data are available	Can PBPK simulations help determine the optimal doses for pediatric studies?
	NME is metabolized in the liver	*In vivo* data are available in hepatically impaired subjects taking lower than recommended doses of NME. Can PBPK simulations predict PK of NME in hepatic impairment patients taking recommended doses?
	NME and its metabolite are both inhibitors of a CYP	Can PBPK simulation predict the DDI potential of the NME?

CYP, cytochrome P450; DDI, drug–drug interactions; FDA, US Food and Drug Administration; NME, new molecular entity; PBPK, physiologically based pharmacokinetic; PK, pharmacokinetic; TDI, time-dependent inhibitor.

I/K_i ratio is >0.1 (ref. 25). The sponsor's PBPK simulations indicated that because drug A has a short half-life, there would be minimal drug interaction with the CYP2C9 substrate warfarin. The FDA's PBPK analysis included metabolites in the model. These metabolites have longer half-lives and higher systemic exposure than drug A does (e.g., the AUC of one metabolite is 10-fold higher than that of drug A). The inhibition potential of the metabolites is not known. The FDA's PBPK model used a conservative approach, assuming the same inhibition potency for metabolites as for the parent drug. The resulting PBPK simulation suggested that coadministration of drug A can inhibit CYP2C9 and increase the exposure of warfarin.

Conclusion: PBPK modeling does not rule out the potential for drug A to inhibit the metabolism of a CYP2C9 substrate. Although PBPK simulation may provide more information than the I/K_i ratio, the lack of metabolite inhibition data limited the utility of the PBPK simulation in this specific case. The sponsor is conducting *in vitro* inhibition studies of the metabolites and will incorporate the data in the PBPK model. If the PBPK model that includes actual metabolite inhibition data indicates that administration of drug A does not significantly inhibit metabolism of a CYP2C9 substrate, an *in vivo* interaction study between drug A and warfarin may not be needed. However, if the model indicates significant inhibition of CYP2C9, a clinical study of the interaction between drug A and warfarin is warranted.

Case 2. Specific regulatory question: Can PBPK modeling and simulation predict the magnitude of interaction between a strong CYP3A inhibitor and a sensitive CYP3A substrate administered intravenously, on the basis of the data from an interaction study between the inhibitor and the substrate administered orally?

Synopsis: Sildenafil is a sensitive CYP3A substrate that undergoes significant first-pass metabolism. After oral administration, 92% of the drug was absorbed with an absolute bioavailability of 38%.[26] It is also metabolized by CYP2C9. Oral administration of sildenafil with ritonavir, a strong CYP3A inhibitor, resulted in a greater than 10-fold increase in sildenafil AUC. In order to predict the magnitude of interaction between ritonavir (or other strong CYP3A inhibitors) and sildenafil administered intravenously, the sponsor constructed a PBPK model for sildenafil and ritonavir, and conducted simulations for the new administration route of sildenafil. The results indicated a smaller degree of drug interaction (AUC increased by approximately threefold) when sildenafil is given intravenously vs. orally. The smaller magnitude of interaction with intravenous administration as compared with oral administration of sildenafil is expected and is consistent with literature data for midazolam, another CYP3A-sensitive substrate with significant first-pass metabolism. Data in the literature comparing drug interactions of midazolam after oral and intravenous administration in the presence and absence of a strong CYP3A inhibitor showed a

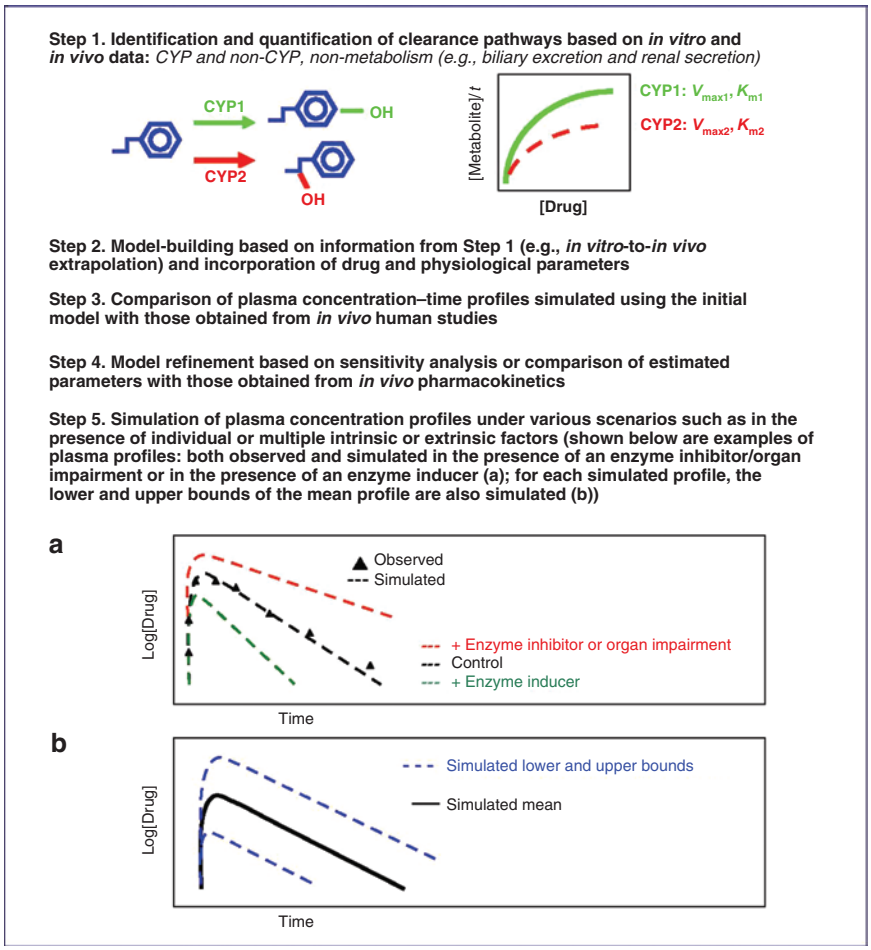

Figure 2 General processes in PBPK modeling and simulations. CYP1 and CYP2 represent two CYP isoforms involved in the metabolism of the new molecular entity (NME); CYP, cytochrome P450; K_m, Michaelis–Menten constant; V_{max}, maximum rate of reaction; [Metabolite] and [Drug], concentrations of metabolite and substrate drug.

decreased extent of inhibition after intravenous administration of the substrate as compared to oral administration of the substrate (Table 2).

The FDA's independent PBPK analysis also indicated that the magnitude of the effect of a strong CYP3A inhibitor on sildenafil concentrations is smaller when sildenafil is administered intravenously as compared with when it is administered orally (http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022473s000_ClinPharmR.pdf). However, the quantitative effect of ritonavir on intravenously administered sildenafil cannot be confirmed because of two potential limitations. First, the contribution of CYP3A to the overall clearance of sildenafil ($f_{m,CYP3A}$) cannot be confirmed. *In vitro* data showed that CYP3A and CYP2C9 contributed 80% and 20%, respectively, to the formation of UK-103,320, a metabolite of sildenafil. These data were used in the sponsor's PBPK model to represent the metabolism of sildenafil. However, several primary metabolites including UK-103,320 have been reported *in vivo*.[26] Therefore, the *in vitro* f_m values calculated based on UK-103,320 formation may not represent the *in vivo* contribution to sildenafil metabolism by each CYP isoform. Because the magnitude of drug–drug interaction is influenced by f_m,[27] confirmation of $f_{m,CYP3A}$ is critical. Second, the PBPK model did not consider concurrent induction of CYP3A by ritonavir.[28] As the induction of CYP3A by multiple doses of ritonavir may offset the strong CYP3A inhibition effect of the drug, accurate prediction of the magnitude of the drug–drug interaction between ritonavir and intravenous sildenafil would need to consider both induction and inhibition in the model. Therefore the magnitude of drug–drug interaction may depend on the dosing regimen (e.g., duration of pretreatment) of ritonavir.

Conclusion: On the basis of the PBPK model and the midazolam drug interaction literature, the FDA agreed with the sponsor's conclusion that a smaller degree of drug–drug interaction is anticipated between a strong CYP3A inhibitor and sildenafil when the latter drug is administered intravenously as compared to oral administration. It was therefore found to be acceptable to include the following wording in the sildenafil injection product label: "Predictions based on a pharmacokinetic model suggest that drug–drug interaction with CYP3A inhibitors will be less than those observed after oral sildenafil administration." However, several limitations prevent the use of PBPK modeling to determine the quantitative effect of the interaction between ritonavir and the sildenafil injection product.

Table 2 Summary of PK parameters of midazolam and sildenafil with and without coadministration of CYP3A inhibitors (clarithromycin, ketoconazole, ritonavir, saquinavir, or erythromycin)

	PK parameters				AUCR (± inhibitor)		
	CL_{iv} (L/h)	F_{oral}	F_g	F_h	p.o.	i.v.	Reference
Midazolam	27.8	0.31	0.42	0.74	—	—	Gorski[42], 1998[a]
Midazolam+clarithromycin	10.1	0.75	0.83	0.90	7.0	2.7	Gorski[42], 1998
Midazolam+ketoconazole (200 mg)	—	—	—	—	11.0	3.4	Lucksiri[43], 2005[b]
Midazolam+ketoconazole (400 mg)	—	—	—	—	15.0	4.2	Lucksiri[43], 2005
Sildenafil	40.8	0.38	0.69	0.55	—	—	Muirhead[26], 2002a[c]
Sildenafil+ritonavir	—	—	—	—	11	—	Muirhead[44], 2000[d]
Sildenafil+saquinavir	—	—	—	—	3.1	—	Muirhead[45], 2000
Sildenafil+erythromycin	—	—	—	—	2.6	—	Muirhead[45], 2002b[e]

AUCR: AUC ratio = $AUC_{with\ inhibitor}/AUC_{without\ inhibitor}$.

F_g, bioavailability in the gut; F_h, bioavailability in the liver; F_{oral}, oral bioavailability.

[a]Gorski 1998: i.v. and p.o. midazolam was given before and on day 7 of oral clarithromycin (500 mg b.i.d. day 1–7). [b]Lucksiri 2005: i.v. and p.o. midazolam was given before and during 7-day oral ketoconazole (200 or 400 mg q.d., i.v. midazolam on day 6, p.o. midazolam on day 7). [c]Muirhead 2002(a): i.v. sildenafil 25 mg; p.o. sildenafil 50 mg. Blood pharmacokinetic parameters were calculated. Complete absorption and predominant liver metabolism after i.v. administration were assumed. [d]Muirhead, 2000: p.o. sildenafil before and on day 6/7 of b.i.d. oral ritonavir (300 mg b.i.d. on day 1, 400 mg b.i.d. on day 2, and 500 mg b.i.d. on days 3–7), or p.o. sildenafil before and on day 6/7 of oral saquinavir (1,200 mg t.i.d.). [e]Muirhead, 2002(b): p.o. sildenafil before and on day 5 of b.i.d. oral erythromycin (500 mg).

Case 3. Specific regulatory question: Can PBPK modeling and simulation determine the combined effect of multiple factors (e.g., moderate renal impairment + moderate enzyme inhibitor)?

Synopsis: Rivaroxaban is an orally administered direct factor X_a inhibitor approved in Europe for the prevention of venous thromboembolism in adult patients undergoing elective hip or knee replacement surgery. The product information (SmPC) and public assessment report (EPAR) is available on the EMA homepage (http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000944/human_med_001155.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d125). Rivaroxaban is eliminated via two major routes: (i) ~36% of the dose is excreted renally as unchanged drug, with net secretion (likely mediated by P-glycoprotein and/or breast cancer-resistant protein) and filtration contributing at a ratio of approximately 5:1 and (ii) hepatic metabolism by CYP3A (~18%), CYP2J2 (~14%), hydrolysis (~14%), and an uncharacterized pathway (~8%). Coadministration of rivaroxaban with ketoconazole or other strong CYP3A/P-glycoprotein inhibitors such as ritonavir resulted in an increase in rivaroxaban AUC by ~2.5-fold, which is considered clinically relevant. However, studies with other inhibitors such as erythromycin and clarithromycin reported 1.3- and 1.5-fold increases in rivaroxaban AUC, respectively; these were not deemed clinically relevant. The sponsor considered erythromycin to be a weak-to-moderate CYP3A4/P-gp inhibitor and clarithromycin to be a strong CYP3A4 /weak-to moderate P-gp inhibitor in these studies. Further, the PK of rivaroxaban was evaluated in subjects with renal impairment, as estimated by creatinine clearance (CL_{Cr}). As compared with the corresponding values in healthy volunteers (CL_{Cr} > 80 ml/min), rivaroxaban AUC values were increased 1.4- to 1.6-fold in subjects with values of CL_{Cr} down to 15 ml/min (EMA Review). The EMA review and Summary of Product Characteristics noted that rivaroxaban was not recommended in patients with severe renal impairment (CL_{Cr} < 15 ml/min), that the changes in exposure in patients with mild to moderate renal impairment were not deemed clinically relevant, and that severe renal impairment with CL_{Cr} of 15–29 ml/min required that caution be exercised while prescribing the drug regimen. It was considered important to address the question of whether a combination of factors (e.g., mild to moderate renal impairment plus concomitant administration of a mild to moderate CYP3A4 inhibitor)—each of which by itself would not be deemed clinically relevant—could result in a clinically relevant change in rivaroxaban exposure.

To project the extent of drug–drug interaction in patients with various degrees of renal impairment and who are on a regimen of rivaroxaban with CYP/efflux transporter inhibitors, the reviewers constructed a semi-PBPK model. The utility and the associated designs of semi-PBPK models have been reviewed elsewhere[19,20,29,30] and are not discussed in detail here. Confidence in the final model was assessed by visual comparison of simulated rivaroxaban plasma concentration-vs.-time profiles with those observed from clinical studies[31] in which the drug had been administered in a similar manner.

The semi-PBPK model evaluated drug–drug interaction at the organ level (liver and kidney), and the effect of renal impairment, using a time-based inhibitor concentration model. In addition, the model considered concurrent inhibition of hepatic CYP enzymes and kidney efflux transporter(s) and the possible effect of renal impairment on hepatic enzyme activity.[32,33] Because the absolute oral bioavailability of rivaroxaban is nearly 100% (EMA Review), first-pass metabolism and efflux transport in the gut wall were not considered in the model.

The effect of erythromycin on the elimination of rivaroxaban was then evaluated. The inhibition of the renal secretion of rivaroxaban by efflux transporters and the CYP2J2-mediated

elimination pathway were assumed to be reversible, whereas inhibition of CYP3A4 was assumed to be time-dependent (or irreversible inhibition in the presence of erythromycin, http://www.druginteractioninfo.org, accessed July 2010). Next, using the semi-PBPK model, the reviewers assessed the effect of coadministration of erythromycin along with rivaroxaban in subjects with renal impairment.

The model predicted that, as renal function decreased by 0% (no impairment), 25%, 50%, 75%, and 90%, the rivaroxaban exposure (AUC) in the presence of erythromycin would increase by 1.2-, 1.5-, 2.0-, 3.0-, and 4.1-fold, respectively, as compared with rivaroxaban exposure in subjects with normal renal function in the absence of erythromycin. Therefore, these preliminary findings suggest the possibility that a moderate CYP3A4 inhibitor (such as erythromycin) that by itself might increase rivaroxaban by only ~1.2 fold could result in a twofold or more increase in rivaroxaban exposure in subjects with mild to moderate renal impairment. Additional simulations (data not shown) suggested that altered plasma protein binding of rivaroxaban in patients with impaired renal function may also impact the prediction of the exposure change.

Conclusion: The FDA reviewers concluded that several mechanisms needed to be incorporated into the PBPK model in order to adequately evaluate the magnitude of *in vivo* drug–drug interactions in subjects with renal impairment. Furthermore, in their briefing document to the Cardiovascular and Renal Drugs Advisory Committee (19 March 2009), the FDA reviewers indicated that, in view of the notable dual pathway of elimination of rivaroxaban, "The potential effect of concurrent renal impairment and the use of a moderate/strong CYP3A4 inhibitor on rivaroxaban exposure is of particular concern, given [that] this interaction can result in an increased exposure greater than the sum of its parts, and this interaction was not evaluated or modeled by the applicant" (http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM181524.pdf).

This analysis also supports the EMA's cautionary language regarding the potential for multiple impairments in its product information for rivaroxaban. This approach may also provide additional context for the regulatory question of whether a dedicated clinical study to quantify the PK and pharmacodynamic effects should be considered so that the dose may be optimized for this scenario.

Case 4. Specific regulatory questions: Can PBPK modeling and simulation indicate whether *in vivo* interaction studies are needed for a drug that is a CYP3A inhibitor *in vitro*? Can PBPK modeling and simulation indicate whether *in vivo* interaction and organ impairment studies are needed for a drug that is a CYP3A substrate?

Synopsis: Intended for intravenous infusion, cabazitaxel is predominantly metabolized *in vivo* by CYP3A isoenzymes (http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/201023s000ClinPharmR.pdf). Cabazitaxel also inhibits CYP3A *in vitro* with an I/K_i ratio of > 0.1. The reviewers constructed a PBPK model for cabazitaxel on the basis of *in vitro* and *in vivo* metabolism data and *in vivo* PK parameters. The model was used to predict the outcome of the following scenarios that lacked *in vivo* data:

I. *In vivo* drug–drug interaction with a CYP3A substrate, midazolam
II. *In vivo* drug–drug interaction with a CYP3A inhibitor, ketoconazole
III. *In vivo* drug–drug interaction with a CYP3A inducer, rifampin
IV. PK of cabazitaxel in patients with various degrees of hepatic impairment

With this model, the simulated PK profile for cabazitaxel was comparable to the observed *in vivo* PK data. For scenario I, although I/K_i is > 0.1, the model predicted minimal drug–drug interactions when cabazitaxel and midazolam were coadministered, possibly because of the rapid disappearance of cabazitaxel in plasma during the distribution phase, its relatively high plasma protein binding, and the absence of inhibition of gut metabolism, as cabazitaxel is administered intravenously. The FDA reviewers also conducted a sensitivity analysis that incorporated a several-fold higher I/K_i ratio, in order to confirm the absence of CYP3A inhibition by cabazitaxel *in vivo* (Midazolam AUC ratio with and without inhibitor <1.1). For scenarios II and III, the PBPK model indicated that a drug–drug interaction was possible (i.e., the estimated ratio of cabazitaxel AUC with the inhibitor ketoconazole to that without was 2.2, and the corresponding ratio for the inducer rifampin was 0.6). For scenario IV, the PBPK model predicted higher increases in cabazitaxel exposure with higher degrees of hepatic impairment (the AUC is 2.5-fold higher in subjects with a Child-Pugh score of C as compared with healthy subjects).

Conclusion: The PBPK simulations indicate that an *in vivo* drug–drug interaction study with midazolam as a substrate is not required, even though cabazitaxel has an I/K_i > 0.1. The simulations confirmed the need to conduct *in vivo* drug–drug interaction studies with CYP3A inhibitor(s) and inducer(s). The simulations assisted the design of a PK study in hepatic impairment by supporting the use of a lower dose of cabazitaxel in patients with severe hepatic impairment in the planned hepatic impairment study.

DISCUSSION

The improvement in our understanding of human physiology and biochemistry, drug ADME, and mechanism of action; the availability of tools that allow us to model nonclinical and clinical pharmacology data; and the advancement of information technology have made it possible for us to utilize a systems-biology approach such as PBPK modeling to evaluate drug exposure changes due to individual patients' intrinsic and/or extrinsic factors (**Figure 1**). In this report, we present our regulatory experience in using PBPK modeling and simulations in addressing clinical pharmacology questions. The experience indicates that knowledge regarding both the system component and the drug-dependent component are essential in constructing an appropriate PBPK model.

Table 3. Important parameters needed for comprehensive evaluation of complex drug interactions

Type of study	Parameters estimated
In vitro ADME and interaction	Enzyme/transporter involved in elimination and interaction Drug distribution (e.g., $f_{u,p}$ and B/P) Interaction mechanisms and parameters (e.g. K_i) Initial f_m estimation
Phase I dose escalation (oral administration)	CL/F_{oral} V/F_{oral} Likely f_e, CL_r and metabolite data
Absolute oral bioavailability	CL V Likely CL_r and metabolite data F_{oral}
In vivo mass balance (e.g., studies in humans using radiolabeled material)	Confirm f_m Confirm f_a Confirm f_e, CL_r

B/P, blood to plasma ratio; CL, clearance; CL_r, renal clearance; F_a, fraction absorbed; f_e, fraction of the dose excreted unchanged in the urine; F_{oral}, oral bioavailability; $f_{u,p}$, unbound fraction in plasma; K_i, reversible inhibition constant.; V, volume of distribution.

Modified from Zhao *et al.*[21]

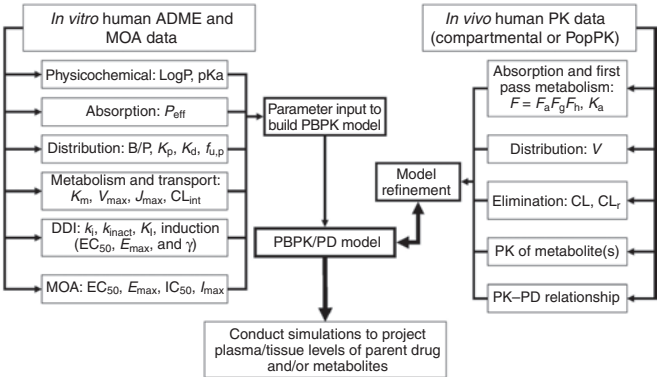

Figure 3 General scheme to incorporate drug-dependent parameters into a PBPK model. ADME, absorption, distribution, metabolism, and excretion (although "absorption" in this figure refers specifically to the passive processes of drug entry into systemic circulation, parameters such as jejunum permeability (P_{eff}), measurable *in vitro*, may be affected by active processes by transporters, and an array of factors influencing drug absorption have been reviewed by Jamei *et al.*[12]); AUC, area under the concentration-vs.-time curve; B/P, blood to plasma ratio; C_{max}, maximum concentration; CL, clearance; CL_{int}, intrinsic clearance; CL_r, renal clearance; DDI, drug–drug interactions; EC_{50} or IC_{50}, concentration causing half of the maximal effect of induction or inhibition; E_{max} or I_{max}, maximum effect of induction or inhibition; F, bioavailability; F_a, fraction absorbed; F_g, bioavailability in the gut; F_h, bioavailability in the liver; $f_{u,p}$, unbound fraction in plasma; γ, Hill coefficient; J_{max}, maximum rate of transporter-mediated efflux/uptake; K_a, first-order absorption rate constant; K_d, dissociation constant of drug–protein complex; K_i, reversible inhibition constant; K_I, apparent inactivation constant, concentration causing half of the maximal inactivation; k_{inact}, apparent maximum inactivation rate constant; K_m, Michaelis–Menten constant, substrate concentration causing half of the maximal reaction or transport; K_p, tissue-to-plasma partition coefficient; LogP, logarithm of the octanol–water partition coefficient; MOA, mechanism of action; PD, pharmacodynamics; P_{eff}, jejunum permeability; PK, pharmacokinetics; PopPK, population pharmacokinetics; V, volume of distribution; V_{max}, maximum rate of metabolite formation.

The four cases presented in this article describe the potential advantages of PBPK models over traditional models (e.g., compartmental models). PBPK models incorporate all available, relevant PK and physiology information, allowing the models to predict the effect of multiple factors on the drug concentration–time profile. The fact that these models are based on physiology helps scientists who are not clinical pharmacologists to understand the modeling results and incorporate them in drug development decisions. PBPK provides a more realistic prediction of the potential for drug–drug interactions than the static approach (such as the use of I/K_i) that has traditionally been used. The PBPK-based drug–drug interaction predictions are more realistic because they consider multiple factors and mechanisms that impact the interactions.[16–21]

As depicted in **Figure 2**, characterization and quantitative determination of elimination pathways of a drug and its metabolites is an important first step when conducting PBPK modeling and simulations. Based on our review of the submissions containing PBPK simulations, we noted that the lack of necessary information regarding clearance pathways has often hampered the proper use of the PBPK approaches. Without a thorough understanding of the ADME processes for an individual drug, it is difficult to quantify the effect of intrinsic and extrinsic factors on the PK of the drug. In order to appropriately characterize and quantify the contribution of specific enzymes and/or transporters to the overall disposition, several *in vitro* and *in vivo* studies appear to be indispensible under the current drug development paradigm (**Table 3**).

Figure 3 summarizes a general scheme to incorporate drug-dependent parameters into a PBPK model. Physicochemical parameters such as LogP, pKa, and polar surface area (experimentally determined or calculated based on chemical structure using *in silico* models) can be used to calculate tissue partitioning characteristics.[34–38] These parameters are also used when estimating microsomal protein binding and effective permeability that are not experimentally determined. *In vitro* metabolism and enzyme inhibition/induction parameters that are intended to describe drug clearance and drug–drug interaction mechanisms are experimentally determined and incorporated as input into PBPK models. A subsequent important step is the integration of *in vivo* knowledge to refine the PBPK model and to qualify the PBPK model by comparing the simulated PK profiles with those

from available *in vivo* studies. For example, in order to carry out simultaneous evaluation of autoinhibition and multiple-dose effect on drug pharmacokinetics, one sponsor constructed the initial PBPK model using *in vitro* enzyme inhibition data and subsequently obtained PK parameters from phase 1 single-dose data to refine the enzyme kinetic parameters. Similar techniques were employed by reviewers when separately constructing PBPK models during the review process, using a variety of tools (see Methods).

During earlier stages of drug development, comprehensive drug-dependent parameters may not be available and the construction of a PBPK model relies largely on *in vitro* and *in silico* data. These initial models can be used to address certain regulatory questions in a qualitative manner as well as in candidate selection or optimization of clinical study designs. As the compound progresses to later stages of drug development, PBPK models could be iteratively refined to incorporate additional quantitative information on drug disposition from available *in vivo* studies. An adequately constructed PBPK model can play a critical role in designing clinical pharmacology studies by projecting drug PK profiles under various scenarios. It can also help in determining whether there is a need for additional studies, including postmarketing requirement or commitment studies, as part of risk–benefit assessment of new molecular entities.

This report focuses primarily on the utility of PBPK in assessing the mean drug exposure changes caused by intrinsic and/or extrinsic factors. Besides their deterministic features, population-based PBPK models can provide information related to variability and uncertainty of the PK profiles in patient subgroups.[39]

Despite the progress in the development of population-based PBPK modeling tools and their increased utility in pharmaceutical research, drug development, and regulatory review, quantitative prediction of certain clinical pharmacology scenarios is not possible because of several knowledge gaps. These gaps reside in both drug-independent (system-) and drug-dependent components. Like other modeling and simulation exercises, the use of PBPK is associated with various assumptions, which may vary depending on the stage of drug development and the regulatory questions to be addressed. One major knowledge gap is our insufficient understanding of developmental-related, disease-related, and organ dysfunction-related changes in human physiology. For example, knowledge regarding how renal impairment quantitatively affects the activities of individual metabolizing enzymes or transporters is critical in the construction of a PBPK model to assess the extent of drug interactions in patients with varying degrees of renal impairment. Similarly, we need an improved understanding of the effects of age on drug-metabolizing enzymes and transporters and renal function in both pediatric and geriatric populations. In addition, adequate characterization of the clearance pathways for drugs and their metabolites, and of the effects (induction and inhibition of specific enzymes and transporters) of interacting drugs is required. Besides the necessity to bridge these knowledge gaps, there is also a need for continued research to formulate and refine best practices in the use of PBPK approaches during drug development and regulatory review.[40,41] At the FDA, efforts have been undertaken to streamline the process of using PBPK during regulatory review, including criteria for conducting separate confirmatory PBPK modeling and simulations when reviewing PBPK data submitted by the sponsors.

In summary, between July 2008 and June 2010, the Office of Clinical Pharmacology at CDER, FDA, reviewed submissions for approval of INDs and NDAs that incorporated PBPK simulations. In this report, we summarize general schemes of PBPK simulation and propose procedures to obtain necessary data to construct PBPK models. In order to fully utilize PBPK in drug development and regulatory review, it is critical to adequately define mechanisms of drug disposition and understand general physiological perturbations related to diseases, age, and organ dysfunction.

METHODS

The Office of Clinical Pharmacology at the FDA has reviewed numerous submissions for approval of INDs and NDAs that included the use of PBPK modeling and simulations. Additional modeling and simulations were conducted by the FDA clinical pharmacology reviewers using a variety of software products. For example, when estimation of PK parameters using compartmental analysis was needed, mean concentration-vs.-time profiles (PK profiles) were digitized using GetData software (version 2.24, http://getdata-graph-digitizer.com). PK parameters were estimated by means of compartmental analyses using WinNonlin (version 5.2, Pharsight, Cary, NC). In other instances, PK of metabolites was considered important. Parameters for metabolites were obtained by fixing PK parameters of the parent drug in a model that incorporates metabolism. In one case, the values for volume of distribution, formation clearance, and elimination clearance of metabolites were estimated using NONMEM software or by manually adjusting the parameters in a PBPK simulator. PBPK simulators used in the submissions by sponsors and in the FDA reviews include Simcyp (Sheffield, UK), PK-Sim (Bayer Technologies, Leverkusen, Germany), and Gastroplus (Simulation Plus, Lancaster, CA). Other in-house PBPK models were developed using software such as SAAMII (University of Washington, Seattle, WA).

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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