# Physiologically Based Pharmacokinetic (PBPK) Modeling and Simulation Approaches: A systematic review of published models, applications and model verification

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**Running Title:**

Review of the use of PBPK modeling

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**Abbreviations:**

AUC, Area under the plasma concentration-time curve; ACAT, advanced compartmental absorption and transit; ADAM, advanced dissolution, absorption and metabolism; ADME, absorption, dissolution, metabolism and excretion; $C_{max}$, maximum concentration in plasma; $C_{ss,avg}$, average concentration at steady state; DDI, drug-drug interaction; EMA, European Medicines Agency; FDA, US Food and Drug administration; [I], inhibitor concentration; IND investigational new drug; IVIVE, in vitro-to-in vivo extrapolation; $K_i$, inhibition constant for P450 inhibition; NDA, new drug application; PBPK, physiologically based pharmacokinetic; PK, pharmacokinetic; PKPD, pharmacokinetic/pharmacodynamic

## Abstract

Modeling and simulation of drug disposition has emerged as an important tool in drug development, clinical study design and regulatory review, and the number of physiologically based pharmacokinetic (PBPK) modeling related publications and regulatory submissions have risen dramatically in recent years. However, the extent of use of PBPK modeling by researchers, and the public availability of models has not been systematically evaluated. This review evaluated PBPK-related publications to 1) identify the common applications of PBPK modeling, 2) determine ways in which models are developed, 3) establish how model quality is assessed and 4) provide a list of publically available PBPK models for sensitive P450 and transporter substrates as well as selective inhibitors and inducers. PubMed searches were conducted using the terms PBPK and physiologically based pharmacokinetic model to collect published models. Only papers on PBPK modeling of pharmaceutical agents in humans published in English between 2008 and May 2015 were reviewed. A total of 366 PBPK-related articles met the search criteria with the number of articles published per year rising steadily. Published models were most commonly used for drug-drug interaction (DDI) predictions (28%), followed by interindividual variability and general clinical pharmacokinetic predictions (23%), formulation or absorption modeling (12%) and predicting age related changes in pharmacokinetics and disposition (10%). 106 models of sensitive substrates, inhibitors and inducers were identified. An in-depth analysis of the model development and verification revealed a lack of consistency in model development and quality assessment practices demonstrating a need for development of best-practice guidelines.

**Introduction**

Prediction of disposition characteristics of new drug candidates can identify pharmacokinetic liabilities such as poor bioavailability, high clearance, potential for DDIs, or the need for dose adjustments in special populations (Chen et al., 2012; Di et al., 2013; Jones et al., 2009; Obach et al., 1997; Shardlow et al., 2013; Zhao et al., 2011). Such predictions can help decision making regarding development progression, dose selection and clinical study strategies (Chen et al., 2012; Di et al., 2013; Jones et al., 2015, 2009; Obach et al., 1997; Rowland et al., 2011; Shardlow et al., 2013; Zhao et al., 2011). A variety of allometric scaling, in vitro-to-in vivo extrapolation (IVIVE) and in silico methods has been developed over the years to enable predictions of human pharmacokinetics prior to first in human dosing. More than 30 different methods exist to predict human volume of distribution (Di et al., 2013) including interspecies scaling (Lombardo et al., 2013a) and in silico methods. Generally in vivo animal data, LogP values, plasma protein binding and blood to plasma ratios are used to predict human steady state volume of distribution and tissue-to- plasma partitioning (Berezhkovskiy, 2004; Poulin and Theil, 2000, 2002; Poulin et al., 2001; Rodgers and Rowland, 2006; Rodgers et al., 2005). While interspecies scaling allows predictions of human volume of distribution, its utility in the prediction of human clearance is limited due to species differences in the expression and substrate specificity of drug metabolizing enzymes and transporters (Di et al., 2013; Obach et al., 1997). Instead, IVIVE tools have been developed to predict hepatic bioavailability and whole organ clearances from in vitro intrinsic clearance, protein binding and permeability data as well as in vivo blood flows. (Cho et al., 2013; Houston, 1994; Iwatsubo et al., 1997; Lombardo et al., 2013b; Obach et al., 1997). While further efforts are needed to improve IVIVE, particularly for transporters and non-P450 enzymes, IVIVE has become an important tool in the process of predicting human exposures and effective dosages.

Quantitative methods to predict pharmacokinetics range in complexity from static mechanistic predictions of specific PK parameters to dynamic PBPK models used to predict plasma concentration time curves. Static mechanistic methods typically use one or two in vitro parameters to predict specific human PK

parameters, and can therefore be easily adopted in screening programs to prioritize and triage compounds based

on undesirable pharmacokinetics. Static prediction methods have been used extensively to predict human

metabolic (Gillette, 1971; Iwatsubo et al., 1997; Obach et al., 1997; Rowland et al., 1973) and transporter

mediated clearance (Barton et al., 2013; Liu and Pang, 2005; Varma et al., 2013) as well as drug interactions

(Fahmi et al., 2008; Mayhew et al., 2000; Obach et al., 2007; Wang et al., 2004). Yet, while static models are

very useful for predictions of overall drug exposures in humans or the overall magnitude of DDIs, they rely on

steady state assumptions and hence cannot predict the overall shape of the plasma-concentration time curve,

time-varying changes in enzyme or transporter inhibition or the distribution kinetics of new drugs. In contrast

PBPK models provide simulated concentration versus time profiles of a drug and its metabolite(s) in plasma or

an organ of interest, and allow for estimation of maximum plasma concentrations, absorption kinetics,

distribution kinetics and drug elimination simultaneously. While the simultaneous modeling of drug disposition

processes provides multiple advantages (Almond et al., 2009; Di et al., 2013; Fahmi et al., 2009; Galetin, 2014;

Huang and Rowland, 2012; Jamei et al., 2009a; Rostami-Hodjegan and Tucker, 2007; Rowland et al., 2011;

Shardlow et al., 2013; Tsamandouras et al., 2013; Varma et al., 2015a), it also makes PBPK modeling labor

intensive and requires considerably more parameter estimates and more detailed physiological and drug specific

data than static predictions. The simulated concentration time profiles can aid in selection of optimal sampling

times or dosing strategies in different study populations including vulnerable subjects (Rowland et al., 2011).

They can also aid in design of DDI studies in which the timing of the dosing of the perpetrator drug and the

victim drug is critical (Shardlow et al., 2013; Zhao et al., 2009), or in situations where perpetrator

concentrations fluctuate over the sampling and dosing interval (Almond et al., 2009; Di et al., 2013; Fahmi et

al., 2009; Pang and Durk, 2010).  Additionally, the simulated concentrations can be linked to pharmacodynamic

endpoints in order to allow for pharmacokinetic/pharmacodynamic (PKPD) simulations. Furthermore, because

PBPK models account for sequential metabolism and permeability limited processes, they may provide

advantages for predicting bioavailability when compared to static models (Chow and Pang, 2013; Fan et al.,

2010). This can have important implications for first in human dose selection, particularly for drugs with active or toxic metabolites. In some cases, PBPK models incorporate interindividual variability, thus allowing for the prospective simulation of the population variability in the pharmacokinetics of a given drug. Population variability is not typically accounted for in static models but can provide insight into variability in exposure and drug response in a given population (Brown et al., 2012; Cubitt et al., 2011; Jamei et al., 2009a; Rostami-Hodjegan and Tucker, 2007). Finally, the separation of drug specific parameters and physiological parameters within the model, can result in a more mechanistic understanding of sources of interindividual variability than what can be provided by population and compartmental modeling techniques (Rostami-Hodjegan and Tucker, 2007; Tsamandouras et al., 2013; Vinks, 2013). However, detailed understanding of physiological variables in the population of interest is required but not always available, which can hinder the use of PBPK modeling in special populations.

In recent years, the number of publications (Rostami-Hodjegan et al., 2012; Rowland et al., 2011) and regulatory submissions (Huang et al., 2013; Sinha et al., 2014; Zhao et al., 2011) referencing or including PBPK modeling has increased substantially. The development of user friendly software tools such as Simcyp®, GastroPlus™ and PK Sim® have made modeling more accessible to those without extensive modeling and/or programming experience (Chen et al., 2012; Huang et al., 2013; Zhao et al., 2011). However, it is possible that many users are not completely familiar with or aware of the assumptions made and equations used during model building and implementation. As such, the increased implementation of PBPK modeling has led to a need for comprehensive software and modeling-focused education as well as need for confirming the sound knowledge of users in absorption, dissolution, metabolism and excretion (ADME) principles and fundamental physiology (Jones et al., 2015). A recommendation for presence of a modeling expert for advice and review of models has also been made to ensure appropriate decision-making and interpretation of the modeling (Jones et al., 2015). Advancements in computer science and physiologically based mathematical models have led to the expansion of the potential applications of PBPK modeling. For example, more complex absorption models

such as advanced dissolution, absorption and metabolism (ADAM) models (Jamei et al., 2009b) and advanced

compartmental absorption and transit (ACAT) models (Agoram et al., 2001) have been developed that enable

the use of PBPK modeling for the simulation of food effects (Heimbach et al., 2013; Patel et al., 2014; Shono et

al., 2009; Turner et al., 2012; Xia et al., 2013a; Zhang et al., 2014), the impact of drug properties on absorption

kinetics (Kambayashi et al., 2013; Parrott et al., 2014), and intestinal interactions (Fenneteau et al., 2010). The

development of sophisticated models that allow for the simulation of multiple inhibitors or inducers, relevant

metabolites, and multiple mechanisms of interaction have permitted the prediction of complex DDIs involving

enzymes, transporters and multiple interaction mechanisms (Chen et al., 2015; Dhuria et al., 2013; Gertz et al.,

2013, 2014; Guo et al., 2013; Kudo et al., 2013; Rekic et al., 2011; Sager et al., 2014; Shi et al., 2015; Siccardi

et al., 2013; Varma et al., 2012, 2013; Wang et al., 2013a; Zhang et al., 2009). Furthermore, the mechanistic

understanding of ADME changes that occur in different age groups or disease states has improved and

consequently PBPK modeling has been used to simulate drug disposition in special populations including

hepatic (Johnson et al., 2014) and renal impairment populations (Li et al., 2012; Lu et al., 2014; Sayama et al.,

2014; Zhao et al., 2012a), children (Leong et al., 2012) and pregnant women (Andrew et al., 2008; Gaohua et

al., 2012; Horton et al., 2012; Ke et al., 2012, 2013a, 2013b; Lu et al., 2012).

In the past 10 years, PBPK modeling has become increasingly accepted by regulatory agencies as a

means of informing clinical study strategy and, as a result, it has become a useful tool in drug development

(Huang et al., 2013; Leong et al., 2012; Sinha et al., 2014; Zhao et al., 2012b). PBPK approaches have been

included in regulatory guidance on hepatic impairment (European Medicines Agency Committee for Medicinal

Products for Human Use, 2005), pediatrics (U.S. Food and Drug Administration Center for Drug Evaluation

and Research (CDER), 2014), DDIs (European Medicines Agency Committee for Medicinal Products for

Human Use, 2012; Japan Ministry of Health, Labor and Welfare, 2014; U.S. Food and Drug Administration

Center for Drug Evaluation and Research (CDER), 2012), and pharmacogenetics (European Medicines Agency

Committee for Medicinal Products for Human Use, 2011; U.S. Food and Drug Administration Center for Drug

Evaluation and Research (CDER), 2013) as a means of guiding clinical study design and labeling decisions.

Hence, in addition to being used to inform internal development decisions (Chen et al., 2012; Jones et al., 2015, 2009; Shardlow et al., 2013), PBPK modeling is increasingly being used in investigational new drug (IND) and new drug applications (NDA) (European Medicines Agency Committee for Medicinal Products for Human Use, 2014; Huang et al., 2013; Sinha et al., 2014). The FDA Office of Clinical Pharmacology has been tracking the use of PBPK modeling in regulatory submissions since 2008 (Huang et al., 2013; Pan, 2014). Based on 2013 submissions, the models included in regulatory filings were most commonly used for DDI (60%), pediatric (21%) and absorption (6%) predictions (Pan, 2014). PBPK models have been used during the review process to inform dose selection and optimal design for clinical studies (Leong et al., 2012) and in some cases to directly inform labeling (Zhao et al., 2012b). For example, cabazitaxel is predicted to cause in vivo CYP3A4 inhibition based on its $I/K_i$ ratio, but modeling and simulation suggested minimal risk for DDI in vivo. As a result the label states that a "a post-marketing requirement for the effect of cabazitaxel on the pharmacokinetics of a sensitive CYP3A4 substrate is therefore not necessary" (Huang and Rowland, 2012; Huang et al., 2013; U.S. Food and Drug Administration Center for Drug Evaluation). Additional examples of PBPK-informed labeling between 2008 and 2014 are included in recent reviews (Huang et al., 2013; Jones et al., 2015; Sinha et al., 2014; Zhao et al., 2012b).

Despite the increasing use of PBPK modeling, there are many challenges that limit the utility of PBPK modeling and simulation. In general IVIVE using PBPK models requires considerably more experimental and in silico data than static models. Due to the large number of parameters required for PBPK modeling and limited availability of in vivo data to verify individual parameters, model predictions can be confounded by lack of confidence in individual parameters. For example, for drugs that have not been administered intravenously to humans, distribution and absorption parameters cannot be validated or verified experimentally, introducing uncertainty into model parameters and output. The application of PBPK modeling to predict PK in disease populations is hindered by lack of in vivo data in patient populations, poor understanding of the physiological

changes that occur in certain populations and limited knowledge of tissue specific changes in enzyme and

transporter expression (Edginton and Joshi, 2011; Jones et al., 2015; Sjöstedt et al., 2014). Furthermore,

absolute abundances of transporters and non-P450 enzymes in the liver and other tissues are not well

established, resulting in poor IVIVE of the kinetics of non-P450 substrates and permeability limited drugs

(Edginton and Joshi, 2011; Harwood et al., 2013; Jones et al., 2015, 2012; Varma et al., 2012). Additionally, a

lack of selective substrates and inhibitors for some non-P450 enzymes and transporters has prevented model

validation against in vivo data (Jones et al., 2015). While efforts are being made to characterize tissue specific

transporter expression, current models of the disposition of transporter substrates rely on the incorporation of

empirical scaling factors (Varma et al., 2015a). Although scaling factors have allowed for predictions of the

kinetics of a number of uptake transporter substrates (Gertz et al., 2014; Jamei et al., 2014; Kudo et al., 2013;

Varma et al., 2012, 2014, 2015b), it is not possible to experimentally verify whether unbound tissue exposures

are adequately predicted (Chu et al., 2013; Jones et al., 2015; Varma et al., 2015a). This could have important

implications for IVIVE of efflux clearance, metabolism-transporter interplay and predictions of

pharmacological effect. The utility of PBPK modeling in the prediction of therapeutic protein disposition is still

relatively limited as discussed in a recent white paper (Jones et al., 2015). While a number of PBPK models

have been used to accurately predict the kinetics of monoclonal antibodies (Baxter et al., 1995; Cao and Jusko,

2014; Chetty et al., 2015; Elmeliegy et al., 2014; Ferl et al., 2005; Li et al., 2014a; Shah and Betts, 2012; Zhao

et al., 2015), model structures are inconsistent (Chetty et al., 2012; Jones et al., 2015). Limited data on target

expression and changes in disease populations result in the risk for overparameterization with PBPK models,

and thus there is an effort to move towards reduced PBPK models for therapeutic proteins (Chetty et al., 2015;

Diao and Meibohm, 2015; Elmeliegy et al., 2014; Li et al., 2014a).

Another current challenge in the PBPK modeling field is determining how to assess model quality. To

date, neither the FDA nor EMA have issued a formal guidance regarding model quality assessment during

regulatory review. However, the FDA has acknowledged the use of the best practice methods proposed by the

World Health Organization International Programme for Chemical Safety (World Health Organization, 2010;

Zhao et al., 2012b). These practices include ensuring the physiological plausibility of the input parameters,

demonstrating the ability of the model to predict the pharmacokinetics in an independent data set, and

confirming that sensitivity and uncertainty analysis support the model quality. The recommendation to establish

a guideline for reporting a qualification of PBPK models was made at the 2014 MISG New Technologies

Forum on Physiologically Based Modeling and Simulation (Ministerial Industry Strategy Group, 2014) and the

EMA released a concept paper on the reporting and quality assessment of PBPK models with the goal of

publishing a draft guidance in 2015 (European Medicines Agency Committee for Medicinal Products for

Human Use, 2014). However, while some basic guidelines for assessing model quality prior to regulatory

review are accepted or in development, no standards exist for how model quality should be evaluated in peer-

reviewed publications. Additionally, no formal analysis of the literature has previously been performed to

evaluate what quality assessment methods are typically used in peer-reviewed publications, if any.

Despite the growth of the PBPK modeling field and the well-established use of PBPK models in

regulatory submissions, the overall public availability of PBPK models is unclear and the breath of use of PBPK

modeling by the research community has not been systematically evaluated. The PBPK models used in

regulatory submissions are not publically available to the outside research community, which prevents the broad

use of models that have been accepted by regulatory agencies. Furthermore, the applications of the models in

regulatory submissions may be driven primarily by the needs of drug developers and may not reflect how PBPK

modeling is used in the larger research community. Identifying and compiling a list of the publicly available

models could be beneficial to future research efforts since published models could be used either unchanged, or

as a starting point in future modeling efforts. Furthermore, determining the common applications of the

published PBPK models will provide insight into current modeling interests as well as highlight under-

represented applications. This review evaluates recent PBPK publications and identifies the common

applications of PBPK modeling, how models are typically developed, ways in which model quality is assessed

and provides a list of publically available PBPK models with focus on enzyme probes and marker substrates and important perpetrators of DDIs.

**Literature search strategy**

PubMed searches were conducted using the search terms PBPK and physiologically based pharmacokinetic model within the abstract or title of the manuscript.  Papers were selected for review if they were published in English between 2008 and May 20, 2015 and focused on PBPK modeling of pharmaceutical agents in humans.  The number of papers referenced is likely an underrepresentation of the overall body of literature on PBPK modeling due to the strict search criteria and the search terms used.  Publications were categorized as a review, commentary, letter to the editor, or an original data paper containing one or more PBPK models. Papers that focused on the development of new modeling software or a modeling strategy were classified as prediction method papers.  Original data papers were further categorized by the primary application of the models.

Models for FDA and EMA recommended probe substrates, inhibitors and inducers (European Medicines Agency Committee for Medicinal Products for Human Use, 2012; U.S. Food and Drug Administration Center for Drug Evaluation and Research (CDER), 2012) were identified within the original data papers.  Complete lists of the compounds recognized by the regulatory agencies are shown in **Supplemental Tables 1** and **2**. Models for these compounds were included in our analysis if 1) they were original published models, 2) enough information was provided to allow for replication of the model in an appropriate software program and 3) the simulation results were compared to observed in vivo data. A number of models were excluded because they were default library files in a simulation software package, the model input parameters were not reported or the simulation results were not compared to in vivo data.  Compound models were categorized as substrates, inhibitors and/or inducers based on their classification in the FDA or EMA DDI guidance (European Medicines Agency Committee for Medicinal Products for Human Use, 2012; U.S. Food and Drug Administration Center

for Drug Evaluation and Research (CDER), 2012) if the model was built with the clearance pathways or

interaction parameters that permitted it to be used for the specified purpose. Models for FDA substrates,

inhibitors and inducers that lacked the appropriate clearance pathways or inhibition/induction parameters to

allow them to be used according to their FDA or EMA classification were placed into a category of their own.

For each FDA and EMA recommended substrate, inhibitor or inducer that met the search criteria, information

regarding the simulated formulation, genotype, and software used was extracted.  Furthermore, the source of the

clearance input parameter (in vitro or in vivo), the type of independent quality assessment data set used and the

a priori model acceptance criteria were collected.  Finally, the type of model (full or minimal PBPK) was

determined.  PBPK models were considered to be minimal if the model included no more than 5 compartments

including the gastrointestinal tract, blood, liver, and up to two additional compartments.  More complex models

were considered to be "Full PBPK".

**PBPK Modeling Articles by Year and Application**

A total of 366 PBPK-related articles meeting our search criteria were published since 2008.  While it is

unlikely that the literature search identified all of the papers presenting PBPK modeling in the literature, the

search likely provides adequate and representative coverage of the existing models and practices. The number

of articles published per year rose steadily with time from 9 articles in 2008 to 94 articles published in 2014

(**Figure 1A**).  Of the papers identified, 74% were original data papers that included one or more PBPK models

while 26% were reviews, commentaries, letters to the editor or prediction methods papers.  The original data

papers were analyzed in order to identify the common applications of PBPK models. The distribution of the

model applications is shown in **Figure 1B**.  The published PBPK models were most commonly used for DDI

predictions (28%).  The majority of the DDI prediction models were used to simulate P450-mediated DDIs

(81%), while the remainder of the models focused on transport DDIs (10%) or a combination of P450 and

transporter mediated interactions (10%).  Additionally, models were commonly used to predict interindividual

variability and general clinical pharmacokinetics (23%), absorption kinetics (12%) and age related changes in

pharmacokinetics (10%). This distribution of model applications is distinctly different from what has been reported for regulatory submissions to the FDA. The models included in FDA regulatory filings were primarily used for DDI predictions (60%), followed by pediatrics (21%) and absorption (6%) predictions (Pan, 2014). Based on this analysis the use of PBPK modeling to evaluate interindividual variability and overall drug disposition characteristics is far more common in the broader research community than in regulatory review. This difference reflects the fact that both the FDA guidance on pediatrics (U.S. Food and Drug Administration Center for Drug Evaluation and Research (CDER), 2014) and DDIs (U.S. Food and Drug Administration Center for Drug Evaluation and Research (CDER), 2012) include PBPK modeling as a potentially useful tool for guiding clinical study design but PBPK modeling is currently not included in FDA guidance on bioequivalence or first in human studies.

**Published Models of FDA and EMA Recommended Substrates, Inhibitors and Inducers**

Each of the 271 original data papers identified included at least one PBPK model of a pharmaceutical agent. The majority of the papers included models of approved drugs while only 21 papers (8%) used PBPK modeling to simulate the pharmacokinetics of drugs in development. The published PBPK models included default models from software libraries, as well as original models. Of the published original models, the models for FDA and EMA recommended sensitive substrates, inhibitors and inducers were further evaluated. While these models only represent a fraction of the published PBPK models, these compounds represent a group of drugs for which PBPK models are particularly useful, since the models can be used in DDI predictions or to validate altered expression levels or activity of transporters and enzymes in new physiological models. 56 papers were found that included models for FDA and EMA listed sensitive substrates, inhibitors and inducers. In these papers, 107 original models representing 61 different compounds were identified. These models were analyzed to gain insight into how peer reviewed models are commonly developed and how authors assess overall model quality. For each model, information about model development was documented, including the software used, the complexity of the model (full or minimal PBPK), the source of the clearance input value and

the type of dosing simulated. Additionally, information regarding model quality and quality assessment was documented, including whether the simulated population matched the observed population, if an independent dataset was used to verify model quality and the type of criteria authors used to determine if a model performance was acceptable. The compounds modeled, the model development methods and quality assessment criteria are provided in **Tables 1-6** along with references to the original publications.

*How were the models developed?*

PBPK models can vary in complexity from full PBPK models where all of the distribution organs and tissues are represented as separate perfused compartments to more simplified, minimal PBPK models in which tissues with similar kinetics are lumped (Bois et al., 2010; Cao and Jusko, 2012; Leahy, 2003; Nestorov et al., 1998; Parrott et al., 2005; Pilari and Huisinga, 2010; Tsamandouras et al., 2013). The majority of the models for the FDA and EMA substrates, inhibitors and inducers listed in Tables 1-6 were full PBPK models (72%) as opposed to minimal PBPK models (27%). Full PBPK models will typically fit the experimental data better than minimal models due to the larger number of parameters used, which increases the degrees of freedom in the model. Yet confidence in any individual parameter is decreased when moving from minimal to full PBPK model. Minimal PBPK models can be used to reduce model complexity while still allowing for mechanistic simulations in only the compartments of interest (Cao and Jusko, 2012; Nestorov et al., 1998; Pilari and Huisinga, 2010; Tsamandouras et al., 2013). One advantage of full PBPK modeling is the ability to simulate the exposure of a drug or its metabolites in specific tissues that are not accessible to clinical sampling. This can be particularly important if the pharmacological or toxicological effects are driven by the concentrations in that tissue (Tsamandouras et al., 2013). However, none of the models listed in Tables 1-6 and only 13 of the 271 original data papers used simulated tissue concentrations to address pharmacology and toxicology questions (**Table 7**). Instead, full PBPK models were generally used to enable the systematic prediction of distribution kinetics to simulate plasma concentration-time profiles. All of the models that were used to simulate kinetics in special populations in which distribution kinetics can be highly altered, such as pediatrics and pregnancy,

incorporated full PBPK models. Full PBPK was also used in all but two of the models for transporter substrates and inhibitors due to the need to capture permeability rate limited processes.

PBPK models are comprised of system-specific parameters and drug-specific parameters. System specific parameters include blood flow, organ volumes, enzyme and transporter expression, and plasma protein concentrations (Galetin, 2014; Jamei et al., 2009a; Rowland et al., 2011). Drug-specific parameters include intrinsic clearances, volume of distribution, solubility and physicochemical parameters, tissue partitioning, plasma protein binding affinity and membrane permeability. As a result, drug-dependent parameters are independent of the system parameters, allowing for mechanistic extrapolation of human pharmacokinetics from in vitro and in silico data in a "bottom-up" approach (Galetin, 2014; Jamei et al., 2009a; Rostami-Hodjegan et al., 2012; Rowland et al., 2011; Tsamandouras et al., 2013). While "bottom-up" approaches are generally considered to be more mechanistic, in many cases sufficient in vitro data or characterization of all drug elimination pathways is not available to allow bottom-up predictions, or existing in vitro data does not predict in vivo disposition well enough. Similarly, in many cases, the knowledge of the biological system is too limited to allow for "bottom-up" predictions of disposition kinetics in the population of interest. The "bottom-up" approach is usually not the method of choice in situations where PBPK models are built to specifically evaluate the disposition characteristics of a drug that has been administered to humans or to a special population. In these situations, the model is built to fit the data rather than for predictive IVIVE purposes and a combination of "top-down" and "bottom-up" approaches is often used. Several reviews have provided excellent discussions of the utility and setbacks of these combination or "middle-out" approaches to model development (Jamei et al., 2009a; Li et al., 2014b; Tsamandouras et al., 2013). In general, when using middle-out approaches, in vitro intrinsic clearances are back- calculated from in vivo clearance by assigning the fractions of the in vivo clearance associated with each clearance pathway, or scaling factors are assigned to the in vitro or in vivo clearance value(s) in order to accurately predict the observed data. Parameter estimation methods and

sensitivity analysis can also be used in instances where in vitro data is unavailable and in vivo $f_m$'s are not known.

For the models shown in **Tables 1-6**, in vitro clearance values (bottom-up approach) were used for clearance parameters in 35% of the cases. The most common alternative to IVIVE was back-calculating in vitro intrinsic clearance data from in vivo clearance (21%).  Because this approach incorporates the fractional contribution of individual enzymes into the model, models developed using this technique can potentially be used to simulate pharmacokinetics in situations where enzyme expression levels or activity are altered. However, the reliability of the back-calculations to capture the true intrinsic clearances requires knowledge of the fractional contribution of each enzyme to in vivo clearance and an understanding of the true systemic clearance and bioavailability, which may not be available.   18% of the models used in vivo clearance as an input parameter.  While this can be a reliable way to ensure that the total body clearance is captured, no specific elimination pathways are accounted for and thus the model is not useful for predicting the effects of an inhibitor or inducer, or the consequences of changes in enzyme or transporter expression levels.  In 17% of the models, a scaling factor was applied to the in vitro or in vivo clearance value(s) in order to accurately predict the observed data.  Scaling factors were particularly common for transporter substrates, likely due to the current limitations in IVIVE of transporter-mediated clearance (Harwood et al., 2013; Li et al., 2014b).  Finally, parameter estimation methods and sensitivity analysis were performed to determine the in vitro CL values required to capture the true in vivo clearance for 9% of the models.  While these approaches can permit extrapolation to observed in vivo clearance, caution should be exercised when estimating input parameters.  In cases where in vitro parameter values and their variability are well understood, low prediction success could indicate that the model is lacking a critical pharmacokinetic process (Jones et al., 2015; Tsamandouras et al., 2013)

*What Makes a Good Model and How is Model Quality Assessed?*

Best practices of model assessment have been proposed by the World Health Organization (World Health Organization, 2010) and have been discussed in the context of regulatory review (Caldwell et al., 2012; European Medicines Agency Committee for Medicinal Products for Human Use, 2014; Ministerial Industry Strategy Group, 2014; Zhao et al., 2012b). However, no requirements or guidelines exist regarding how to determine the quality of a PBPK model in general research applications and prior to publication. In regulatory guidance the criteria for assessing model validity is often presented in the context of whether the model meets the performance requirements for its specific purpose. However, in the research literature the specific goal or purpose for the model is often not specified, and PBPK modeling is frequently used to explain observed clinical findings or to support a particular mechanistic hypothesis rather than predict drug disposition in a specific population or clinical situation. In order to establish the scope of current practices in the PBPK models that have been published for various purposes and applications, an evaluation of the current state of model development and quality assessment was conducted. The compound models listed in **Tables 1-6** were assessed to 1) identify the criteria that were typically used in peer-reviewed publications to determine if a model was adequate and 2) determine if models were tested against multiple in vivo data sets.

It is considered good practice to assess the quality of a model against in vivo data that was not used in the model development process and in situations where one of the parameters is altered, such as in a DDI or an alternative genotype population (Jones et al., 2015; McLanahan et al., 2012; Sinha et al., 2014; World Health Organization, 2010; Zhao et al., 2012b). Our analysis revealed that the pharmacokinetic simulations of 97% of the models were compared to pharmacokinetics in independent study populations. When an independent dataset was used to test a model, the dataset typically described the pharmacokinetics after a single dose or DDI, or for an alternative population, formulation or dosing regimen. The distribution of the types of in vivo data sets used to assess the quality of the models is shown in **Figure 2A**. Most of the models were assessed using multiple types of data sets (57%), DDI data (15%) or pharmacokinetic data from alternative populations (9%). Only 3% of the models were not compared to an independent data set. However, despite the fact that most

models were assessed against data that was not used in model development, the simulated populations were

rarely matched with the population demographics of the clinical study subjects, or the population demographics

used in the simulations were not reported (**Tables 1-6**). The simulated age, gender and genotypes were reported

to match the observed population for only 32% of the models. Additionally, the simulated genotypes were only

specified for 21% of the models. It is possible that the demographics of the clinical study and the simulated

population were matched in many of the papers but not reported. However, reporting the strategy for how the

simulated populations were made to reflect the observed would provide greater confidence for the reader that

the simulated population was reasonably representative of the true observed population. The population

specific parameters used in PBPK models such as enzyme and transporter abundance, organ volume, blood

flow, plasma protein binding and glomerular filtration rate are dependent on the population demographics such

as age, gender, genotype and disease state. Similarly, the interindividual variability in the physiological

parameters is dependent on the population demographics. Thus, ensuring that the demographics of the

simulated population match those of the observed population may improve the accuracy of both mean PK

parameters (Steere et al., 2015) and predicted population variability. More careful reporting of the simulated

and observed study populations would also be critically important when model performance is assessed. As has

been highlighted in the literature (Abduljalil et al., 2014), PBPK simulations are often compared to clinical

studies with small study populations, and the true inter- and intra-individual variability of the observed PK

parameters of the compound of interest are not known. This can lead to a situation in which one clinical study

does not accurately predict the PK parameters observed in another study with the same compound (Abduljalil et

al., 2014). In such situations, a PBPK model cannot meet the common acceptance criteria for both studies

simultaneously. Yet, the simulated population variability was rarely compared to the observed in the literature

evaluated, and we found no papers in our analysis in which a priori model acceptance criteria were driven by

knowledge of the variability in the PK parameters of the drug of interest in the target population. The 90%

confidence interval is, however, generally shown in simulated plasma concentration-time curves (Jones et al.,

2015), and several studies used the simulated 90% confidence interval of the plasma concentration curves as a criterion for model acceptance (Bui et al., 2015; Chetty et al., 2015; Sager et al., 2014).

Determination of model performance was inconsistent and largely subjective in a majority of the papers. In 56% of the published models in **Tables 1-6**, the authors did not specify a priori a criterion by which they would decide if their model was successful or not (**Figure 2b**). A recent publication from the IQ PBPK working group suggests that criteria should be predefined regarding whether a model is fit-for purpose (Jones et al., 2015). However there is no consensus on what criteria should be applied for the different modeling purposes. The IQ working group suggested that for drugs with a broad therapeutic window, a common 2-fold criteria for the model would be acceptable, but for drugs with narrow therapeutic index more stringent criteria would be appropriate (Jones et al., 2015). On the other hand for PBPK models used for risk assessment, the IQ proposed that acceptance criteria should reflect the effect of accuracy on dose selection. Yet, this recommendation is not consistent with the methods used to evaluate model performance in the literature. Overall, in the papers (**Tables 1-6**) in which the acceptance criteria were specified a priori, 4 standard choices were employed for model acceptance. For 22% of the models, the authors specified that predicted pharmacokinetic parameter(s) (i.e. AUC, $C_{ss,avg}$, $C_{max}$) in a given population must be within 2-fold of the observed value in order for the model to be considered acceptable. In 7% of the cases, predicted mean pharmacokinetic parameters were required to be within 25-30% of the observed mean. In addition, for 10% of the models, the predicted fold change in AUC or $C_{max}$ between different simulated populations or study conditions had to be within 2-fold of the observed fold change for the model to be acceptable. Finally, for 4% of the models, the authors specified that the predicted fold change in AUC and $C_{max}$ needed to be within 30% of the observed fold-change. When the acceptance criteria were analyzed according to the types of applications, a more striking discrepancy with the proposed guidance was observed (**Figure 2C**). For models built for narrow therapeutic index drugs only 17% (2 papers) used a 30% difference as the standard for model acceptance. 50% (6 papers) of the papers had no criteria and 33% (4 papers) considered a 2-fold difference to be an acceptable

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criteria for these drugs. Similarly, for P450 sensitive substrates, which are expected to clinically report on <2-fold changes in clearance, only 3% (1 paper) used <30% difference in fold change as an acceptance criteria for the PBPK models, and 42% (13 papers) considered <2-fold difference in PK parameters or in fold changes acceptable. 16% of the papers (5 papers) used the <30% difference in PK parameters as an acceptance criteria for P450 sensitive substrates. For P450 inducers, there were no models that required a <30% difference in PK parameters and for transporter substrates, inhibitors and inducers, nearly all papers (84%) had no specified acceptance criteria. Taken together, this data suggests that there is a lack of consistency in model quality assessment, which does not reflect the different purposes for which the models were developed. The data also suggests that there is a need for more rigorous evaluation of model quality assessment during peer review. The issue of the lack of strict peer review requirements for published models has been discussed previously in the literature (McLanahan et al., 2012), but it has not been formally addressed by the larger research community.

Based on the analysis of the PBPK models used to simulate drug absorption, more stringent criteria of model assessment were used in this field, likely adapted from bioequivalence standards. For some absorption models, model performance was determine to be high if error was <25%, medium if error was 25-50%, low if error was 50%-2-fold and inaccurate if error was >2-fold (Sjögren et al., 2013). Importantly, many of the absorption models systematically evaluated model performance in terms of the plasma concentration-time curves rather than specific PK parameters using a similarity factor ($f_1$ or $f_2$) to calculate the % difference between the simulated and measured plasma concentrations at each measured time point (Fei et al., 2013; Kambayashi et al., 2013; Shono et al., 2009; Wagner et al., 2012; Wang et al., 2013a). In addition, many absorption models were evaluated using statistical criteria such as linear regression between observed and predicted parameters or concentrations and method of residuals (Kambayashi et al., 2013; Shono et al., 2009; Turner et al., 2012). A critical model evaluation criterion used in some studies evaluating PBPK models of biologics (Cao et al., 2013; Kletting et al., 2010) was discrimination between different models using statistical criteria that account for the added degrees of freedom in the model. The Akaike information criterion and

correlation analyses were used to specifically differentiate between developed PBPK models and identify the model that best fitted the observed data (Cao et al., 2013; Kletting et al., 2010). Adaptation of some of these methods and criteria into PBPK modeling in other research areas may provide good standardization of model acceptance criteria.

**Conclusions**

PBPK modeling is increasingly being used in peer-reviewed publications to provide mechanistic predictions of pharmacokinetics and disposition in diverse populations and dosing regimens. Since 2008, 106 models of sensitive substrates, inhibitors and inducers have been published, with applications ranging from DDIs to pregnancy. However, there is a relative lack of consistency in how models are developed and how model quality is assessed. Published models use "bottom-up", "top-down" and "middle-out" approaches to estimate clearance input values and vary in complexity. While model performance was found to be tested against model-independent data sets 97% of the time, model acceptance criteria and the extent to which the simulated populations reflect the observed population were not always specified. Thorough and consistent reporting of model development techniques and quality assessment could increase reader confidence and result in more widespread acceptance of published models. Thus, the development of best-practice guidelines for peer-review submissions might be beneficial. **Table 8** includes suggestions for the information that should be included in peer-reviewed publications containing PBPK models. These suggestions are consistent with best-practice guidelines for regulatory review (European Medicines Agency Committee for Medicinal Products for Human Use, 2014; Ministerial Industry Strategy Group, 2014; World Health Organization, 2010; Zhao et al., 2012b), but also acknowledge that guidelines for peer-reviewed models may not require the same degree of reporting detail as what has been proposed for regulatory submissions.

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**Authorship Contributions**

Participated in research design:  Sager, Yu, Ragueneau-Majlessi, Isoherranen

Performed data analysis: Sager

Wrote or contributed to the writing of this manuscript: Sager, Yu, Ragueneau-Majlessi, Isoherranen

# References

Abduljalil, K., Cain, T., Humphries, H., and Rostami-Hodjegan, A. (2014). Deciding on Success Criteria for Predictability of Pharmacokinetic Parameters from In Vitro Studies: An Analysis Based on In Vivo Observations. Drug Metab. Dispos. *42*, 1478–1484.

Agoram, B., Woltosz, W.S., and Bolger, M.B. (2001). Predicting the impact of physiological and biochemical processes on oral drug bioavailability. Adv. Drug Deliv. Rev. *50*, S41–S67.

Almond, L.M., Yang, J., Jamei, M., Tucker, G.T., and Rostami-Hodjegan, A. (2009). Towards a quantitative framework for the prediction of DDIs arising from cytochrome P450 induction. Curr. Drug Metab. *10*, 420–432.

Andrew, M.A., Hebert, M.F., and Vicini, P. (2008). Physiologically based pharmacokinetic model of midazolam disposition during pregnancy. In 30th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, 2008. EMBS 2008, pp. 5454–5457.

Ball, K., Bouzom, F., Scherrmann, J.-M., Walther, B., and Declèves, X. (2014). Comparing translational population-PBPK modelling of brain microdialysis with bottom-up prediction of brain-to-plasma distribution in rat and human. Biopharm. Drug Dispos. 485–499.

Ballesta, A., Zhou, Q., Zhang, X., Lv, H., and Gallo, J.M. (2014). Multiscale Design of Cell-Type–Specific Pharmacokinetic/Pharmacodynamic Models for Personalized Medicine: Application to Temozolomide in Brain Tumors. CPT Pharmacomet. Syst Pharmacol *3*, e112.

Baneyx, G., Parrott, N., Meille, C., Iliadis, A., and Lavé, T. (2014). Physiologically based pharmacokinetic modeling of CYP3A4 induction by rifampicin in human: Influence of time between substrate and inducer administration. Eur. J. Pharm. Sci. *56*, 1–15.

Barton, H.A., Lai, Y., Goosen, T.C., Jones, H.M., El-Kattan, A.F., Gosset, J.R., Lin, J., and Varma, M.V. (2013). Model-based approaches to predict drug–drug interactions associated with hepatic uptake transporters: preclinical, clinical and beyond. Expert Opin. Drug Metab. Toxicol. *9*, 459–472.

Baxter, L.T., Zhu, H., Mackensen, D.G., Butler, W.F., and Jain, R.K. (1995). Biodistribution of monoclonal antibodies: scale-up from mouse to human using a physiologically based pharmacokinetic model. Cancer Res. *55*, 4611–4622.

Berezhkovskiy, L.M. (2004). Volume of distribution at steady state for a linear pharmacokinetic system with peripheral elimination. J. Pharm. Sci. *93*, 1628–1640.

Bois, F.Y., Jamei, M., and Clewell, H.J. (2010). PBPK modelling of inter-individual variability in the pharmacokinetics of environmental chemicals. Toxicology *278*, 256–267.

Bosgra, S., van de Steeg, E., Vlaming, M.L., Verhoeckx, K.C., Huisman, M.T., Verwei, M., and Wortelboer, H.M. (2014). Predicting carrier-mediated hepatic disposition of rosuvastatin in man by scaling from individual transfected cell-lines in vitro using absolute transporter protein quantification and PBPK modeling. Eur. J. Pharm. Sci. *65*, 156–166.

Brantley, S.J., Gufford, B.T., Dua, R., Fediuk, D.J., Graf, T.N., Scarlett, Y.V., Frederick, K.S., Fisher, M.B., Oberlies, N.H., and Paine, M.F. (2014a). Physiologically based pharmacokinetic modeling framework for quantitative prediction of an herb-drug interaction. CPT Pharmacomet. Syst. Pharmacol. *3*, e107.

Brantley, S.J., Gufford, B.T., Dua, R., Fediuk, D.J., Graf, T.N., Scarlett, Y.V., Frederick, K.S., Fisher, M.B., Oberlies, N.H., and Paine, M.F. (2014b). Physiologically Based Pharmacokinetic Modeling Framework for Quantitative Prediction of an Herb–Drug Interaction. CPT Pharmacomet. Syst. Pharmacol. *3*, e107.

Brown, J., Crison, J., and Timmins, P. (2012). Predicting feasibility and characterizing performance of extended-release formulations using physiologically based pharmacokinetic modeling. Ther. Deliv. *3*, 1047–1059.

Bui, K.H., Zhou, D., Agbo, F., and Guo, J. (2015). Effect of Multiple Intravenous Doses of Lanicemine (AZD6765) on the Pharmacokinetics of Midazolam in Healthy Subjects. J. Clin. Pharmacol.

Caldwell, J.C., Evans, M.V., and Krishnan, K. (2012). Cutting Edge PBPK Models and Analyses: Providing the Basis for Future Modeling Efforts and Bridges to Emerging Toxicology Paradigms. J. Toxicol. *2012*, e852384.

Cao, Y., and Jusko, W.J. (2012). Applications of minimal physiologically-based pharmacokinetic models. J. Pharmacokinet. Pharmacodyn. *39*, 711–723.

Cao, Y., and Jusko, W.J. (2014). Survey of monoclonal antibody disposition in man utilizing a minimal physiologically-based pharmacokinetic model. J. Pharmacokinet. Pharmacodyn. *41*, 571–580.

Cao, Y., Balthasar, J.P., and Jusko, W.J. (2013). Second-generation minimal physiologically-based pharmacokinetic model for monoclonal antibodies. J. Pharmacokinet. Pharmacodyn. *40*, 597–607.

Chen, Y., Jin, J.Y., Mukadam, S., Malhi, V., and Kenny, J.R. (2012). Application of IVIVE and PBPK modeling in prospective prediction of clinical pharmacokinetics: strategy and approach during the drug discovery phase with four case studies. Biopharm. Drug Dispos. *33*, 85–98.

Chen, Y., Mao, J., and Hop, C.E.C.A. (2015). Physiologically Based Pharmacokinetic Modeling to Predict Drug-Drug Interactions Involving Inhibitory Metabolite: A Case Study of Amiodarone. Drug Metab. Dispos. *43*, 182–189.

Chetty, M., Mattison, D., and Rostami-Hodjegan, A. (2012). Sex differences in the clearance of CYP3A4 substrates: exploring possible reasons for the substrate dependency and lack of consensus. Curr. Drug Metab. *13*, 778–786.

Chetty, M., Li, L., Rose, R., Machavaram, K., Jamei, M., Rostami-Hodjegan, A., and Gardner, I. (2015). Prediction of the Pharmacokinetics, Pharmacodynamics, and Efficacy of a Monoclonal Antibody, Using a Physiologically Based Pharmacokinetic FcRn Model. Front. Immunol. *5*.

Cho, H.-J., Kim, J.-E., Kim, D.-D., and Yoon, I.-S. (2013). In vitro–in vivo extrapolation (IVIVE) for predicting human intestinal absorption and first-pass elimination of drugs: principles and applications. Drug Dev. Ind. Pharm. *40*, 989–998.

Chu, X., Korzekwa, K., Elsby, R., Fenner, K., Galetin, A., Lai, Y., Matsson, P., Moss, A., Nagar, S., Rosania, G.R., et al. (2013). Intracellular Drug Concentrations and Transporters: Measurement, Modeling, and Implications for the Liver. Clin. Pharmacol. Ther. *94*, 126–141.

Cubitt, H.E., Yeo, K.R., Howgate, E.M., Rostami-Hodjegan, A., and Barter, Z.E. (2011). Sources of interindividual variability in IVIVE of clearance: an investigation into the prediction of benzodiazepine clearance using a mechanistic population-based pharmacokinetic model. Xenobiotica *41*, 623–638.

CY Chow, E., and Sandy Pang, K. (2013). Why we need proper PBPK models to examine intestine and liver oral drug absorption. Curr. Drug Metab. *14*, 57–79.

Damle, B., Varma, M.V., and Wood, N. (2011). Pharmacokinetics of Voriconazole Administered Concomitantly with Fluconazole and Population-Based Simulation for Sequential Use. Antimicrob. Agents Chemother. *55*, 5172–5177.

Darwich, A.S., Pade, D., Rowland-Yeo, K., Jamei, M., Asberg, A., Christensen, H., Ashcroft, D.M., and Rostami-Hodjegan, A. (2013). Evaluation of an In Silico PBPK Post-Bariatric Surgery Model through Simulating Oral Drug Bioavailability of Atorvastatin and Cyclosporine. CPT Pharmacomet. Syst. Pharmacol. *2*, e47.

Dhuria, S., Einolf, H., Mangold, J., Sen, S., Gu, H., Wang, L., and Cameron, S. (2013). Time-Dependent Inhibition and Induction of Human Cytochrome P4503A4/5 by an Oral IAP Antagonist, LCL161, In Vitro and In Vivo in Healthy Subjects. J. Clin. Pharmacol. *53*, 642–653.

Di, L., Feng, B., Goosen, T.C., Lai, Y., Steyn, S.J., Varma, M.V., and Obach, R.S. (2013). A Perspective on the Prediction of Drug Pharmacokinetics and Disposition in Drug Research and Development. Drug Metab. Dispos. *41*, 1975–1993.

Diao, L., and Meibohm, B. (2015). Tools for predicting the PK/PD of therapeutic proteins. Expert Opin. Drug Metab. Toxicol. 1–11.

Djebli, N., Fabre, D., Boulenc, X., Fabre, G., Sultan, E., and Hurbin, F. (2015). Physiologically-based Pharmacokinetic Modeling for Sequential Metabolism: Effect of CYP2C19 Genetic Polymorphism on Clopidogrel and Clopidogrel Active Metabolite Pharmacokinetics. Drug Metab. Dispos. dmd.114.062596.

Edginton, A.N., and Joshi, G. (2011). Have physiologically-based pharmacokinetic models delivered? Expert Opin. Drug Metab. Toxicol. *7*, 929–934.

Edginton, A.N., Ahr, G., Willmann, S., and Stass, H. (2009). Defining the Role of Macrophages in Local Moxifloxacin Tissue Concentrations using Biopsy Data and Whole-Body Physiologically Based Pharmacokinetic Modelling. Clin. Pharmacokinet. *48*, 181–187.

Elmeliegy, M., Lowe, P., and Krzyzanski, W. (2014). Simplification of Complex Physiologically Based Pharmacokinetic Models of Monoclonal Antibodies. AAPS J. *16*, 810–842.

Emoto, C., Fukuda, T., Cox, S., Christians, U., and Vinks, A.A. (2013). Development of a Physiologically-Based Pharmacokinetic Model for Sirolimus: Predicting Bioavailability Based on Intestinal CYP3A Content. CPT Pharmacomet. Syst. Pharmacol. *2*, e59.

European Medicines Agency Committee for Medicinal Products for Human Use (2005). Guideline on the Evaluation of the pharmacokinetics of medicinal products in patients with impaired hepatic function.

European Medicines Agency Committee for Medicinal Products for Human Use (2011). Guideline on the use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products.

European Medicines Agency Committee for Medicinal Products for Human Use (2012). Guideline on the Investigation of Drug-Drug Interactions.

European Medicines Agency Committee for Medicinal Products for Human Use (2014). Concept Paper on Qualification and reporting of physiologically-based pharmacokinetic (PBPK) modeling and analyses.

Fahmi, O.A., Maurer, T.S., Kish, M., Cardenas, E., Boldt, S., and Nettleton, D. (2008). A Combined Model for Predicting CYP3A4 Clinical Net Drug-Drug Interaction Based on CYP3A4 Inhibition, Inactivation, and Induction Determined in Vitro. Drug Metab. Dispos. *36*, 1698–1708.

Fahmi, O.A., Hurst, S., Plowchalk, D., Cook, J., Guo, F., Youdim, K., Dickins, M., Phipps, A., Darekar, A., Hyland, R., et al. (2009). Comparison of Different Algorithms for Predicting Clinical Drug-Drug Interactions, Based on the Use of CYP3A4 in Vitro Data: Predictions of Compounds as Precipitants of Interaction. Drug Metab. Dispos. *37*, 1658–1666.

Fan, J., Chen, S., C.Y. Chow, E., and Sandy Pang, K. (2010). PBPK Modeling of Intestinal and Liver Enzymes and Transporters in Drug Absorption and Sequential Metabolism. Curr. Drug Metab. *11*, 743–761.

Fei, Y., Kostewicz, E.S., Sheu, M.-T., and Dressman, J.B. (2013). Analysis of the enhanced oral bioavailability of fenofibrate lipid formulations in fasted humans using an in vitro–in silico–in vivo approach. Eur. J. Pharm. Biopharm. *85*, 1274–1284.

Fenneteau, F., Poulin, P., and Nekka, F. (2010). Physiologically based predictions of the impact of inhibition of intestinal and hepatic metabolism on human pharmacokinetics of CYP3A substrates. J. Pharm. Sci. *99*, 486–514.

Ferl, G.Z., Wu, A.M., and DiStefano, J.J. (2005). A Predictive Model of Therapeutic Monoclonal Antibody Dynamics and Regulation by the Neonatal Fc Receptor (FcRn). Ann. Biomed. Eng. *33*, 1640–1652.

Friedman, E.J., Fraser, I.P., Wang, Y.-H., Bergman, A.J., Li, C.-C., Larson, P.J., Chodakewitz, J., Wagner, J.A., and Stoch, S.A. (2011). Effect of Different Durations and Formulations of Diltiazem on the Single-Dose Pharmacokinetics of Midazolam: How Long Do We Go? J. Clin. Pharmacol. *51*, 1561–1570.

Galetin, A. (2014). Rationalizing Underprediction of Drug Clearance from Enzyme and Transporter Kinetic Data: From In Vitro Tools to Mechanistic Modeling. In Enzyme Kinetics in Drug Metabolism, S. Nagar, U.A. Argikar, and D.J. Tweedie, eds. (Humana Press), pp. 255–288.

Gaohua, L., Abduljalil, K., Jamei, M., Johnson, T.N., and Rostami-Hodjegan, A. (2012). A pregnancy physiologically based pharmacokinetic (p-PBPK) model for disposition of drugs metabolized by CYP1A2, CYP2D6 and CYP3A4. Br. J. Clin. Pharmacol. *74*, 873–885.

Gérard, C., Bleyzac, N., Girard, P., Freyer, G., Bertrand, Y., and Tod, M. (2010). Influence of Dosing Schedule on Organ Exposure to Cyclosporin in Pediatric Hematopoietic Stem Cell Transplantation: Analysis with a PBPK Model. Pharm. Res. *27*, 2602–2613.

Gérard, C., Bleyzac, N., Girard, P., Freyer, G., Bertrand, Y., and Tod, M. (2011). Links Between Cyclosporin Exposure in Tissues and Graft-Versus-Host Disease in Pediatric Bone Marrow Transplantation: Analysis by a PBPK Model. Pharm. Res. *28*, 531–539.

Gérard, C., Stocco, J., Hulin, A., Blanchet, B., Verstuyft, C., Durand, F., Conti, F., Duvoux, C., and Tod, M. (2014). Determination of the Most Influential Sources of Variability in Tacrolimus Trough Blood Concentrations in Adult Liver Transplant Recipients: A Bottom-Up Approach. AAPS J. *16*, 379–391.

Gertz, M., Cartwright, C.M., Hobbs, M.J., Kenworthy, K.E., Rowland, M., Houston, J.B., and Galetin, A. (2013). Cyclosporine Inhibition of Hepatic and Intestinal CYP3A4, Uptake and Efflux Transporters: Application of PBPK Modeling in the Assessment of Drug-Drug Interaction Potential. Pharm. Res. *30*, 761–780.

Gertz, M., Tsamandouras, N., Säll, C., Houston, J.B., and Galetin, A. (2014). Reduced Physiologically-Based Pharmacokinetic Model of Repaglinide: Impact of OATP1B1 and CYP2C8 Genotype and Source of In Vitro Data on the Prediction of Drug-Drug Interaction Risk. Pharm. Res. 1–16.

Gillette, J.R. (1971). Factors Affecting Drug Metabolism. Ann. N. Y. Acad. Sci. *179*, 43–66.

Guo, H., Liu, C., Li, J., Zhang, M., Hu, M., Xu, P., Liu, L., and Liu, X. (2013). A mechanistic physiologically based pharmacokinetic-enzyme turnover model involving both intestine and liver to predict CYP3A induction-mediated drug–drug interactions. J. Pharm. Sci. *102*, 2819–2836.

Harwood, M.D., Neuhoff, S., Carlson, G.L., Warhurst, G., and Rostami-Hodjegan, A. (2013). Absolute abundance and function of intestinal drug transporters: a prerequisite for fully mechanistic in vitro–in vivo extrapolation of oral drug absorption. Biopharm. Drug Dispos. *34*, 2–28.

Heimbach, T., Xia, B., Lin, T., and He, H. (2013). Case Studies for Practical Food Effect Assessments across BCS/BDDCS Class Compounds using In Silico, In Vitro, and Preclinical In Vivo Data. AAPS J. *15*, 143–158.

Horton, S., Tuerk, A., Cook, D., Cook, J., and Dhurjati, P. (2012). Maximum Recommended Dosage of Lithium for Pregnant Women Based on a PBPK Model for Lithium Absorption. Adv. Bioinforma. *2012*.

Houston, J.B. (1994). Utility of in vitro drug metabolism data in predicting in vivo metabolic clearance. Biochem. Pharmacol. *47*, 1469–1479.

Hsu, V., Vieira, M. de L.T., Zhao, P., Zhang, L., Zheng, J.H., Nordmark, A., Berglund, E.G., Giacomini, K.M., and Huang, S.-M. (2014). Towards Quantitation of the Effects of Renal Impairment and Probenecid Inhibition on Kidney Uptake and Efflux Transporters, Using Physiologically Based Pharmacokinetic Modelling and Simulations. Clin. Pharmacokinet. *53*, 283–293.

Hu, Z.-Y., Edginton, A.N., Laizure, S.C., and Parker, R.B. (2014). Physiologically Based Pharmacokinetic Modeling of Impaired Carboxylesterase-1 Activity: Effects on Oseltamivir Disposition. Clin. Pharmacokinet. *53*, 825–836.

Huang, S.-M., and Rowland, M. (2012). The Role of Physiologically Based Pharmacokinetic Modeling in Regulatory Review. Clin. Pharmacol. Ther. *91*, 542–549.

Huang, S.-M., Abernethy, D.R., Wang, Y., Zhao, P., and Zineh, I. (2013). The utility of modeling and simulation in drug development and regulatory review. J. Pharm. Sci. *102*, 2912–2923.

Hyland, R., Dickins, M., Collins, C., Jones, H., and Jones, B. (2008). Maraviroc: in vitro assessment of drug–drug interaction potential. Br. J. Clin. Pharmacol. *66*, 498–507.

Iwatsubo, T., Hirota, N., Ooie, T., Suzuki, H., Shimada, N., Chiba, K., Ishizaki, T., Green, C.E., Tyson, C.A., and Sugiyama, Y. (1997). Prediction of in vivo drug metabolism in the human liver from in vitro metabolism data. Pharmacol. Ther. *73*, 147–171.

Jamei, M., Dickinson, G.L., and Rostami-Hodjegan, A. (2009a). A Framework for Assessing Inter-individual Variability in Pharmacokinetics Using Virtual Human Populations and Integrating General Knowledge of Physical Chemistry, Biology, Anatomy, Physiology and Genetics: A Tale of "Bottom-Up" vs "Top-Down" Recognition of Covariates. Drug Metab. Pharmacokinet. *24*, 53–75.

Jamei, M., Turner, D., Yang, J., Neuhoff, S., Polak, S., Rostami-Hodjegan, A., and Tucker, G. (2009b). Population-Based Mechanistic Prediction of Oral Drug Absorption. AAPS J. *11*, 225–237.

Jamei, M., Bajot, F., Neuhoff, S., Barter, Z., Yang, J., Rostami-Hodjegan, A., and Rowland-Yeo, K. (2014). A Mechanistic Framework for In Vitro-In Vivo Extrapolation of Liver Membrane Transporters: Prediction of Drug-Drug Interaction Between Rosuvastatin and Cyclosporine. Clin. Pharmacokinet. *53*, 73–87.

Japan Ministry of Health, Labor and Welfare (2014). Drug interaction guideline for drug development and labeling recomendations (draft).

Johnson, T.N., Zhou, D., and Bui, K.H. (2014). Development of physiologically-based pharmacokinetic model to evaluate the relative systemic exposure to quetiapine after administration of IR and XR formulations to adults, children and adolescents. Biopharm. Drug Dispos. *35*, 313–371.

Jones, H., Chen, Y., Gibson, C., Heimbach, T., Parrott, N., Peters, S., Snoeys, J., Upreti, V., Zheng, M., and Hall, S. (2015). Physiologically based pharmacokinetic modeling in drug discovery and development: A pharmaceutical industry perspective. Clin. Pharmacol. Ther. *97*, 247–262.

Jones, H.M., Gardner, I.B., and Watson, K.J. (2009). Modelling and PBPK Simulation in Drug Discovery. AAPS J. *11*, 155–166.

Jones, H.M., Barton, H.A., Lai, Y., Bi, Y., Kimoto, E., Kempshall, S., Tate, S.C., El-Kattan, A., Houston, J.B., Galetin, A., et al. (2012). Mechanistic Pharmacokinetic Modeling for the Prediction of Transporter-Mediated Disposition in Humans from Sandwich Culture Human Hepatocyte Data. Drug Metab. Dispos. *40*, 1007–1017.

Kambayashi, A., Blume, H., and Dressman, J. (2013). Understanding the in vivo performance of enteric coated tablets using an in vitro-in silico-in vivo approach: Case example diclofenac. Eur. J. Pharm. Biopharm. *85*, 1337–1347.

Kaspera, R., Kirby, B.J., Sahele, T., Collier, A.C., Kharasch, E.D., Unadkat, J.D., and Totah, R.A. (2014). Investigating the contribution of CYP2J2 to ritonavir metabolism in vitro and in vivo. Biochem. Pharmacol. *91*, 109–118.

Ke, A.B., Nallani, S.C., Zhao, P., Rostami-Hodjegan, A., and Unadkat, J.D. (2012). A PBPK Model to Predict Disposition of CYP3A-Metabolized Drugs in Pregnant Women: Verification and Discerning the Site of CYP3A Induction. CPT Pharmacomet. Syst. Pharmacol. *1*, e3.

Ke, A.B., Nallani, S.C., Zhao, P., Rostami-Hodjegan, A., and Unadkat, J.D. (2013a). Expansion of a PBPK Model to Predict Disposition in Pregnant Women of Drugs Cleared via Multiple CYP Enzymes, Including CYP2B6, CYP2C9 and CYP2C19. Br. J. Clin. Pharmacol. *77*, 554–570.

Ke, A.B., Nallani, S.C., Zhao, P., Rostami-Hodjegan, A., Isoherranen, N., and Unadkat, J.D. (2013b). A Physiologically Based Pharmacokinetic Model to Predict Disposition of CYP2D6 and CYP1A2 Metabolized Drugs in Pregnant Women. Drug Metab. Dispos. *41*.

von Kleist, M., and Huisinga, W. (2009). Pharmacokinetic–pharmacodynamic relationship of NRTIs and its connection to viral escape: An example based on zidovudine. Eur. J. Pharm. Sci. *36*, 532–543.

Kletting, P., Kull, T., Bunjes, D., Mahren, B., Luster, M., Reske, S.N., and Glatting, G. (2010). Radioimmunotherapy with Anti-CD66 Antibody: Improving the Biodistribution Using a Physiologically Based Pharmacokinetic Model. J. Nucl. Med. *51*, 484–491.

Kudo, T., Hisaka, A., Sugiyama, Y., and Ito, K. (2013). Analysis of the Repaglinide Concentration Increase Produced by Gemfibrozil and Itraconazole Based on the Inhibition of the Hepatic Uptake Transporter and Metabolic Enzymes. Drug Metab. Dispos. *41*, 362–371.

Leahy, D.E. (2003). Progress in simulation modelling for pharmacokinetics. Curr. Top. Med. Chem. *3*, 1257–1268.

Leong, R., Vieira, M.L.T., Zhao, P., Mulugeta, Y., Lee, C.S., Huang, S.-M., and Burckart, G.J. (2012). Regulatory experience with physiologically based pharmacokinetic modeling for pediatric drug trials. Clin. Pharmacol. Ther. *91*, 926–931.

Li, G., Wang, K., Chen, R., Zhao, H., Yang, J., and Zheng, Q. (2012). Simulation of the pharmacokinetics of bisoprolol in healthy adults and patients with impaired renal function using whole-body physiologically based pharmacokinetic modeling. Acta Pharmacol. Sin. *33*, 1359–1371.

Li, J., Guo, H., Liu, C., Zhong, Z., Liu, L., and Liu, X. (2015). Prediction of Drug Disposition in Diabetic Patients by Means of a Physiologically Based Pharmacokinetic Model. Clin. Pharmacokinet. *54*, 179–193.

Li, L., Gardner, I., Dostalek, M., and Jamei, M. (2014a). Simulation of Monoclonal Antibody Pharmacokinetics in HumansUsing a Minimal Physiologically Based Model. AAPS J. *16*, 1097-1109.

Li, R., Barton, H.A., Yates, P.D., Ghosh, A., Wolford, A.C., Riccardi, K.A., and Maurer, T.S. (2014b). A "middle-out" approach to human pharmacokinetic predictions for OATP substrates using physiologically-based pharmacokinetic modeling. J. Pharmacokinet. Pharmacodyn. *41*, 197–209.

Li, R., Ghosh, A., Maurer, T.S., Kimoto, E., and Barton, H.A. (2014c). Physiologically Based Pharmacokinetic Prediction of Telmisartan in Human. Drug Metab. Dispos. *42*, 1646–1655.

Liu, L., and Pang, K.S. (2005). The Roles of Transporters and Enzymes in Hepatic Drug Processing. Drug Metab. Dispos. *33*, 1–9.

Lombardo, F., Waters, N.J., Argikar, U.A., Dennehy, M.K., Zhan, J., Gunduz, M., Harriman, S.P., Berellini, G., Rajlic, I.L., and Obach, R.S. (2013a). Comprehensive Assessment of Human Pharmacokinetic Prediction Based on In Vivo Animal Pharmacokinetic Data, Part 1: Volume of Distribution at Steady State. J. Clin. Pharmacol. *53*, 167–177.

Lombardo, F., Waters, N.J., Argikar, U.A., Dennehy, M.K., Zhan, J., Gunduz, M., Harriman, S.P., Berellini, G., Liric Rajlic, I., and Obach, R.S. (2013b). Comprehensive Assessment of Human Pharmacokinetic Prediction Based on In Vivo Animal Pharmacokinetic Data, Part 2: Clearance. J. Clin. Pharmacol. *53*, 178–191.

Lu, C., Suri, A., Shyu, W.C., and Prakash, S. (2014). Assessment of cytochrome P450-mediated drug–drug interaction potential of orteronel and exposure changes in patients with renal impairment using physiologically based pharmacokinetic modeling and simulation. Biopharm. Drug Dispos. *35*, 543–552.

Lu, G., Abduljalil, K., Jamei, M., N. Johnson, T., Soltani, H., and Rostami-Hodjegan, A. (2012). Physiologically-based Pharmacokinetic (PBPK) Models for Assessing the Kinetics of Xenobiotics during Pregnancy: Achievements and Shortcomings. Curr. Drug Metab. *13*, 695–720.

Mayhew, B.S., Jones, D.R., and Hall, S.D. (2000). An In Vitro Model for Predicting In Vivo Inhibition of Cytochrome P450 3A4 by Metabolic Intermediate Complex Formation. Drug Metab. Dispos. *28*, 1031–1037.

McLanahan, E.D., El-Masri, H.A., Sweeney, L.M., Kopylev, L.Y., Clewell, H.J., Wambaugh, J.F., and Schlosser, P.M. (2012). Physiologically Based Pharmacokinetic Model Use in Risk Assessment—Why Being Published Is Not Enough. Toxicol. Sci. *126*, 5–15.

Meyer, M., Schneckener, S., Ludewig, B., Kuepfer, L., and Lippert, J. (2012). Using Expression Data for Quantification of Active Processes in Physiologically Based Pharmacokinetic Modeling. Drug Metab. Dispos. *40*, 892–901.

Ministerial Industry Strategy Group (2014). MISG New Technologies Forum on Physiologically-based Pharmacokinetic (PBPK) Modeling and Simulation.

Nestorov, I.A., Aarons, L.J., Arundel, P.A., and Rowland, M. (1998). Lumping of whole-body physiologically based pharmacokinetic models. J. Pharmacokinet. Biopharm. *26*, 21–46.

Neuhoff, S., Yeo, K.R., Barter, Z., Jamei, M., Turner, D.B., and Rostami-Hodjegan, A. (2013a). Application of permeability-limited physiologically-based pharmacokinetic models: Part II - prediction of p-glycoprotein mediated drug–drug interactions with digoxin. J. Pharm. Sci. *102*, 3161–3173.

Neuhoff, S., Yeo, K.R., Barter, Z., Jamei, M., Turner, D.B., and Rostami-Hodjegan, A. (2013b). Application of permeability-limited physiologically-based pharmacokinetic models: Part II - prediction of p-glycoprotein mediated drug–drug interactions with digoxin. J. Pharm. Sci. *102*, 3161–3173.

Obach, R.S., Baxter, J.G., Liston, T.E., Silber, B.M., Jones, B.C., Macintyre, F., Rance, D.J., and Wastall, P. (1997). The Prediction of Human Pharmacokinetic Parameters from Preclinical and In Vitro Metabolism Data. J. Pharmacol. Exp. Ther. *283*, 46–58.

Obach, R.S., Walsky, R.L., and Venkatakrishnan, K. (2007). Mechanism-Based Inactivation of Human Cytochrome P450 Enzymes and the Prediction of Drug-Drug Interactions. Drug Metab. Dispos. *35*, 246–255.

Ogungbenro, K., and Aarons, L. (2015). A Physiologically Based Pharmacokinetic Model for Clobazam and Stiripentol in Adults and Children. Pharm. Res. *32*, 144-157.

Pan (2014). Application of FDA Physiologically based Pharmacokinetic Knowledgebase in Evaluating Model Predictability for Drug-Drug Interactions (Atlanta, Georgia).

Pan, X., Wang, P., Hu, N., Liu, L., Liu, X., Xie, L., and Wang, G. (2011). A Physiologically Based Pharmacokinetic Model Characterizing Mechanism-based Inhibition of CYP1A2 for Predicting Theophylline/Antofloxacin Interaction in both Rats and Humans. Drug Metab. Pharmacokinet. *26*, 387–398.

Pang, K.S., and Durk, M.R. (2010). Physiologically-based pharmacokinetic modeling for absorption, transport, metabolism and excretion. J. Pharmacokinet. Pharmacodyn. *37*, 591–615.

Parrott, M.N., Davies, B., Hoffmann, G., Koerner, A., Lave, T., Prinssen, E., Theogaraj, E., and Singer, T. (2011). Development of a Physiologically Based Model for Oseltamivir and Simulation of Pharmacokinetics in Neonates and Infants. Clin. Pharmacokinet. *50*, 613–623.

Parrott, N., Jones, H., Paquereau, N., and Lavé, T. (2005). Application of Full Physiological Models for Pharmaceutical Drug Candidate Selection and Extrapolation of Pharmacokinetics to Man. Basic Clin. Pharmacol. Toxicol. *96*, 193–199.

Parrott, N., Hainzl, D., Scheubel, E., Krimmer, S., Boetsch, C., Guerini, E., and Martin-Facklam, M. (2014). Physiologically Based Absorption Modelling to Predict the Impact of Drug Properties on Pharmacokinetics of Bitopertin. AAPS J. 16, 1077-1084.

Patel, N., Polak, S., Jamei, M., Rostami-Hodjegan, A., and Turner, D.B. (2014). Quantitative prediction of formulation-specific food effects and their population variability from in vitro data with the physiologically-based ADAM model: A case study using the BCS/BDDCS Class II drug nifedipine. Eur. J. Pharm. Sci. *57*, 240–249.

Péry, A.R.R., Brochot, C., Zeman, F.A., Mombelli, E., Desmots, S., Pavan, M., Fioravanzo, E., and Zaldívar, J.-M. (2013). Prediction of dose-hepatotoxic response in humans based on toxicokinetic/toxicodynamic modeling with or without in vivo data: A case study with acetaminophen. Toxicol. Lett. *220*, 26–34.

Pilari, S., and Huisinga, W. (2010). Lumping of physiologically-based pharmacokinetic models and a mechanistic derivation of classical compartmental models. J. Pharmacokinet. Pharmacodyn. *37*, 365–405.

Polasek, T.M., Polak, S., Doogue, M.P., Rostami-Hodjegan, A., and Miners, J.O. (2009). Assessment of inter-individual variability in predicted phenytoin clearance. Eur. J. Clin. Pharmacol. *65*, 1203–1210.

Poulin, P. (2015). A Paradigm Shift in Pharmacokinetic–Pharmacodynamic (PKPD) Modeling: Rule of Thumb for Estimating Free Drug Level in Tissue Compared with Plasma to Guide Drug Design. J. Pharm. Sci. *104*, 2359-2368.

Poulin, P., and Theil, F.-P. (2000). A priori prediction of tissue:plasma partition coefficients of drugs to facilitate the use of physiologically-based pharmacokinetic models in drug discovery. J. Pharm. Sci. *89*, 16–35.

Poulin, P., and Theil, F.-P. (2002). Prediction of pharmacokinetics prior to in vivo studies. 1. Mechanism-based prediction of volume of distribution. J. Pharm. Sci. *91*, 129–156.

Poulin, P., Schoenlein, K., and Theil, F.-P. (2001). Prediction of adipose tissue: Plasma partition coefficients for structurally unrelated drugs. J. Pharm. Sci. *90*, 436–447.

Rajoli, R.K.R., Back, D.J., Rannard, S., Freel Meyers, C.L., Flexner, C., Owen, A., and Siccardi, M. (2014). Physiologically Based Pharmacokinetic Modelling to Inform Development of Intramuscular Long-Acting Nanoformulations for HIV. Clin. Pharmacokinet. *54*, 639–650.

Rekic, D., Roshammar, D., Mukonzo, J., and Ashton, M. (2011). In silico prediction of efavirenz and rifampicin drug-drug interaction considering weight and CYP2B6 phenotype. Br. J. Clin. Pharmacol. *71*, 536–543.

Rodgers, T., and Rowland, M. (2006). Physiologically based pharmacokinetic modelling 2: Predicting the tissue distribution of acids, very weak bases, neutrals and zwitterions. J. Pharm. Sci. *95*, 1238–1257.

Rodgers, T., Leahy, D., and Rowland, M. (2005). Physiologically based pharmacokinetic modeling 1: Predicting the tissue distribution of moderate-to-strong bases. J. Pharm. Sci. *94*, 1259–1276.

Rostami-Hodjegan, A., and Tucker, G.T. (2007). Simulation and prediction of in vivo drug metabolism in human populations from in vitro data. Nat. Rev. Drug Discov. *6*, 140–148.

Rostami-Hodjegan, A., Tamai, I., and Pang, K.S. (2012). Physiologically based pharmacokinetic (PBPK) modeling: It is here to stay! Biopharm. Drug Dispos. *33*, 47–50.

Rowland, M., Benet, L.Z., and Graham, G.G. (1973). Clearance concepts in pharmacokinetics. J. Pharmacokinet. Biopharm. *1*, 123–136.

Rowland, M., Peck, C., and Tucker, G. (2011). Physiologically-Based Pharmacokinetics in Drug Development and Regulatory Science. Annu. Rev. Pharmacol. Toxicol. *51*, 45–73.

Sager, J.E., Lutz, J.D., Foti, R.S., Davis, C., Kunze, K.L., and Isoherranen, N. (2014). Fluoxetine- and Norfluoxetine-Mediated Complex Drug–Drug Interactions: In Vitro to In Vivo Correlation of Effects on CYP2D6, CYP2C19, and CYP3A4. Clin. Pharmacol. Ther. *95*, 653–662.

Sayama, H., Takubo, H., Komura, H., Kogayu, M., and Iwaki, M. (2014). Application of a Physiologically Based Pharmacokinetic Model Informed by a Top-Down Approach for the Prediction of Pharmacokinetics in Chronic Kidney Disease Patients. AAPS J. *16*, 1018–1028.

Shah, D.K., and Betts, A.M. (2012). Towards a platform PBPK model to characterize the plasma and tissue disposition of monoclonal antibodies in preclinical species and human. J. Pharmacokinet. Pharmacodyn. *39*, 67–86.

Shardlow, C.E., Generaux, G.T., Patel, A.H., Tai, G., Tran, T., and Bloomer, J.C. (2013). Impact of Physiologically Based Pharmacokinetic Modeling and Simulation in Drug Development. Drug Metab. Dispos. *41*, 1994–2003.

Shi, J., Fraczkiewicz, G., Williams, W., and Yeleswaram, S. (2015). Predicting drug-drug interactions involving multiple mechanisms using physiologically based pharmacokinetic modeling: a case study with ruxolitinib. Clin. Pharmacol. Ther. *97*, 177–185.

Shono, Y., Jantratid, E., Janssen, N., Kesisoglou, F., Mao, Y., Vertzoni, M., Reppas, C., and Dressman, J.B. (2009). Prediction of food effects on the absorption of celecoxib based on biorelevant dissolution testing coupled with physiologically based pharmacokinetic modeling. Eur. J. Pharm. Biopharm. *73*, 107–114.

Siccardi, M., Marzolini, C., Seden, K., Almond, L., Kirov, A., Khoo, S., Owen, A., and Back, D. (2013). Prediction of drug-drug Interactions Between Various Antidepressants and Efavirenz or Boosted Protease Inhibitors Using a Physiologically Based Pharmacokinetic Modelling Approach. Clin. Pharmacokinet. *52*, 583–592.

Sinha, V., Zhao, P., Huang, S.M., and Zineh, I. (2014). Physiologically Based Pharmacokinetic Modeling: From Regulatory Science to Regulatory Policy. Clin. Pharmacol. Ther. *95*, 478–480.

Sjögren, E., Westergren, J., Grant, I., Hanisch, G., Lindfors, L., Lennernäs, H., Abrahamsson, B., and Tannergren, C. (2013). In silico predictions of gastrointestinal drug absorption in pharmaceutical product development: Application of the mechanistic absorption model GI-Sim. Eur. J. Pharm. Sci. *49*, 679–698.

Sjöstedt, N., Kortejärvi, H., Kidron, H., Vellonen, K.-S., Urtti, A., and Yliperttula, M. (2014). Challenges of Using In Vitro Data for Modeling P-Glycoprotein Efflux in the Blood-Brain Barrier. Pharm. Res. *31*, 1–19.

Steere, B., Baker, J.A.R., Hall, S.D., and Guo, Y. (2015). Prediction of In Vivo Clearance and Associated Variability of CYP2C19 Substrates by Genotypes in Populations Utilizing a Pharmacogenetics-Based Mechanistic Model. Drug Metab. Dispos. *43*, 870–883.

Teeguarden, J.G., Housand, C.J., Smith, J.N., Hinderliter, P.M., Gunawan, R., and Timchalk, C.A. (2013). A multi-route model of nicotine–cotinine pharmacokinetics, pharmacodynamics and brain nicotinic acetylcholine receptor binding in humans. Regul. Toxicol. Pharmacol. *65*, 12–28.

Thiel, C., Schneckener, S., Krauss, M., Ghallab, A., Hofmann, U., Kanacher, T., Zellmer, S., Gebhardt, R., Hengstler, J.G., and Kuepfer, L. (2014). A Systematic Evaluation of the Use of Physiologically Based Pharmacokinetic Modeling for Cross-Species Extrapolation. J. Pharm. Sci. *104*, 191–206.

Tornio, A., Filppula, A.M., Kailari, O., Neuvonen, M., Nyrönen, T.H., Tapaninen, T., Neuvonen, P.J., Niemi, M., and Backman, J.T. (2014). Glucuronidation converts clopidogrel to a strong time-dependent inhibitor of CYP2C8 a phase 2 metabolite as perpetrator of drug-drug interactions. Clin. Pharmacol. Ther. *96*, 498–507.

Tsamandouras, N., Rostami-Hodjegan, A., and Aarons, L. (2013). Combining the "bottom-up" and "top-down" approaches in pharmacokinetic modelling: Fitting PBPK models to observed clinical data. Br. J. Clin. Pharmacol. *79*, 48–55.

Turner, D.C., Yin, F., Kindt, J.T., and Zhang, H. (2012). Understanding pharmacokinetic food effects using molecular dynamics simulation coupled with physiologically based pharmacokinetic modeling. Biopharm. Drug Dispos. *33*, 510–521.

U.S. Food and Drug Administration Center for Drug Evaluation Postmarketing Requirements, Drug Approval Package for Cabazitaxel.

U.S. Food and Drug Administration Center for Drug Evaluation and Research (CDER) (2012). Guidance for Industry: Drug interaction studies- study design, data analysis, implications for dosing, and labeling.

U.S. Food and Drug Administration Center for Drug Evaluation and Research (CDER) (2013). Guidance for Industry: Clinical Pharmacogenomics: Premarket Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling.

U.S. Food and Drug Administration Center for Drug Evaluation and Research (CDER) (2014). General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products.

Varma, M.V., Pang, K.S., Isoherranen, N., and Zhao, P. (2015a). Dealing with the complex drug–drug interactions: Towards mechanistic models. Biopharm. Drug Dispos. *36*, 71–92.

Varma, M.V.S., Lai, Y., Feng, B., Litchfield, J., Goosen, T.C., and Bergman, A. (2012). Physiologically Based Modeling of Pravastatin Transporter-Mediated Hepatobiliary Disposition and Drug-Drug Interactions. Pharm. Res. *29*, 2860–2873.

Varma, M.V.S., Lin, J., Bi, Y.-A., Rotter, C.J., Fahmi, O.A., Lam, J.L., El-Kattan, A.F., Goosen, T.C., and Lai, Y. (2013). Quantitative prediction of repaglinide-rifampicin complex drug interactions using dynamic and static mechanistic models: delineating differential CYP3A4 induction and OATP1B1 inhibition potential of rifampicin. Drug Metab. Dispos. Biol. Fate Chem. *41*, 966–974.

Varma, M.V.S., Scialis, R.J., Lin, J., Bi, Y.-A., Rotter, C.J., Goosen, T.C., and Yang, X. (2014). Mechanism-Based Pharmacokinetic Modeling to Evaluate Transporter-Enzyme Interplay in Drug Interactions and Pharmacogenetics of Glyburide. AAPS J. *16*, 736–748.

Varma, M.V.S., Lin, J., Bi, Y., Kimoto, E., and Rodrigues, D. (2015b). Quantitative Rationalization of Gemfibrozil Drug Interactions: Consideration of Transporters-Enzyme Interplay and the Role of Circulating Metabolite Gemfibrozil 1-O-β-Glucuronide. Drug Metab. Dispos. dmd.115.064303.

Vieira, M.L.T., Zhao, P., Berglund, E.G., Reynolds, K.S., Zhang, L., Lesko, L.J., and Huang, S.-M. (2012). Predicting Drug Interaction Potential With a Physiologically Based Pharmacokinetic Model: A Case Study of Telithromycin, a Time-Dependent CYP3A Inhibitor. Clin. Pharmacol. Ther. *91*, 700–708.

Vinks, A.A. (2013). The Future of Physiologically Based Pharmacokinetic Modeling to Predict Drug Exposure in Pregnant Women. CPT Pharmacomet. Syst. Pharmacol. *2*, e33.

Wagner, C., Jantratid, E., Kesisoglou, F., Vertzoni, M., Reppas, C., and B. Dressman, J. (2012). Predicting the oral absorption of a poorly soluble, poorly permeable weak base using biorelevant dissolution and transfer model tests coupled with a physiologically based pharmacokinetic model. Eur. J. Pharm. Biopharm. *82*, 127–138.

Wang, Y.-H. (2010). Confidence Assessment of the Simcyp Time-Based Approach and a Static Mathematical Model in Predicting Clinical Drug-Drug Interactions for Mechanism-Based CYP3A Inhibitors. Drug Metab. Dispos. *38*, 1094–1104.

Wang, J., Xia, S., Xue, W., Wang, D., Sai, Y., Liu, L., and Liu, X. (2013a). A semi-physiologically-based pharmacokinetic model characterizing mechanism-based auto-inhibition to predict stereoselective pharmacokinetics of verapamil and its metabolite norverapamil in human. Eur. J. Pharm. Sci. *50*, 290–302.

Wang, Y., Wang, Z., Zuo, Z., Tomlinson, B., Lee, B.T.K., Bolger, M.B., and Chow, M.S.S. (2013b). Clinical Pharmacokinetics of Buffered Propranolol Sublingual Tablet (Promptol[TM])—Application of a New "Physiologically Based" Model to Assess Absorption and Disposition. AAPS J. *15*, 787–796.

Wang, Y.-H., Jones, D.R., and Hall, S.D. (2004). Prediction of Cytochrome P450 3a Inhibition by Verapamil Enantiomers and Their Metabolites. Drug Metab. Dispos. *32*, 259–266.

World Health Organization (2010). International Programme on Chemical Harmonization Project. Characterization and Application of Physiologically Based Pharmacokinetic Models in Risk Assessment. Harmonization Project Document No. 9.

Wu, C., Sun, L., Sun, J., Yang, Y., Ren, C., Ai, X., Lian, H., and He, Z. (2013). Profiling biopharmaceutical deciding properties of absorption of lansoprazole enteric-coated tablets using gastrointestinal simulation technology. Int. J. Pharm. *453*, 300–306.

Wu, F., Gaohua, L., Zhao, P., Jamei, M., Huang, S.-M., Bashaw, E.D., and Lee, S.-C. (2014). Predicting Nonlinear Pharmacokinetics of Omeprazole Enantiomers and Racemic Drug Using Physiologically Based Pharmacokinetic Modeling and Simulation: Application to Predict Drug/Genetic Interactions. Pharm. Res. *31*, 1919-1929.

Xia, B., Heimbach, T., Lin, T., Li, S., Zhang, H., Sheng, J., and He, H. (2013a). Utility of Physiologically Based Modeling and Preclinical In Vitro/In Vivo Data to Mitigate Positive Food Effect in a BCS Class 2 Compound. AAPS PharmSciTech *14*, 1255–1266.

Xia, B., Heimbach, T., Gollen, R., Nanavati, C., and He, H. (2013b). A Simplified PBPK Modeling Approach for Prediction of Pharmacokinetics of Four Primarily Renally Excreted and CYP3A Metabolized Compounds During Pregnancy. AAPS J. *15*, 1012–1024.

Xu, L., Chen, Y., Pan, Y., Skiles, G.L., and Shou, M. (2009). Prediction of Human Drug-Drug Interactions from Time-Dependent Inactivation of CYP3A4 in Primary Hepatocytes Using a Population-Based Simulator. Drug Metab. Dispos. *37*, 2330–2339.

Yan, G.Z., Generaux, C.N., Yoon, M., Goldsmith, R.B., Tidwell, R.R., Hall, J.E., Olson, C.A., Clewell, H.J., Brouwer, K.L.R., and Paine, M.F. (2012). A Semiphysiologically Based Pharmacokinetic Modeling Approach to Predict the Dose-Exposure Relationship of an Antiparasitic Prodrug/Active Metabolite Pair. Drug Metab. Dispos. *40*, 6–17.

Yeo, K.R., Kenny, J.R., and Rostami-Hodjegan, A. (2013). Application of in vitro-in vivo extrapolation (IVIVE) and physiologically based pharmacokinetic (PBPK) modelling to investigate the impact of the CYP2C8 polymorphism on rosiglitazone exposure. Eur. J. Clin. Pharmacol. *69*, 1311–1320.

Zane, N.R., and Thakker, D.R. (2014). A Physiologically Based Pharmacokinetic Model for Voriconazole Disposition Predicts Intestinal First-pass Metabolism in Children. Clin. Pharmacokinet. *53*, 1171–1182.

Zhang, H., Xia, B., Sheng, J., Heimbach, T., Lin, T.-H., He, H., Wang, Y., Novick, S., and Comfort, A. (2014). Application of physiologically based absorption modeling to formulation development of a low solubility, low permeability weak base: mechanistic investigation of food effect. AAPS PharmSciTech. *15*, 400–406.

Zhang, X., Quinney, S.K., Gorski, J.C., Jones, D.R., and Hall, S.D. (2009). Semiphysiologically Based Pharmacokinetic Models for the Inhibition of Midazolam Clearance by Diltiazem and Its Major Metabolite. Drug Metab. Dispos.. *37*, 1587–1597.

Zhao, Y., and Hu, Z.-Y. (2014). Physiologically based pharmacokinetic modelling and in vivo [I]/Ki accurately predict P-glycoprotein-mediated drug-drug interactions with dabigatran etexilate. Br. J. Pharmacol. *171*, 1043–1053.

Zhao, J., Cao, Y., and Jusko, W.J. (2015). Across-Species Scaling of Monoclonal Antibody Pharmacokinetics Using a Minimal PBPK Model. Pharm. Res. 1–13.

Zhao, P., Ragueneau-Majlessi, I., Zhang, L., Strong, J.M., Reynolds, K.S., Levy, R.H., Thummel, K.E., and Huang, S.-M. (2009). Quantitative Evaluation of Pharmacokinetic Inhibition of CYP3A Substrates by Ketoconazole: A Simulation Study. J. Clin. Pharmacol. *49*, 351–359.

Zhao, P., Zhang, L., Grillo, J.A., Liu, Q., Bullock, J.M., Moon, Y.J., Song, P., Brar, S.S., Madabushi, R., Wu, T.C., et al. (2011). Applications of physiologically based pharmacokinetic (PBPK) modeling and simulation during regulatory review. Clin. Pharmacol. Ther. *89*, 259–267.

Zhao, P., Vieira, M. de L.T., Grillo, J.A., Song, P., Wu, T.-C., Zheng, J.H., Arya, V., Berglund, E.G., Atkinson, A.J., Sugiyama, Y., et al. (2012a). Evaluation of Exposure Change of Nonrenally Eliminated Drugs in Patients With Chronic Kidney Disease Using Physiologically Based Pharmacokinetic Modeling and Simulation. J. Clin. Pharmacol. *52*, 91S – 108S.

Zhao, P., Rowland, M., and Huang, S.-M. (2012b). Best practice in the use of physiologically based pharmacokinetic modeling and simulation to address clinical pharmacology regulatory questions. Clin. Pharmacol. Ther. *92*, 17–20.

Zhu, L., Zhang, Y., Yang, J., Wang, Y., Zhang, J., Zhao, Y., and Dong, W. (2015a). Prediction of the pharmacokinetics and tissue distribution of levofloxacin in humans based on an extrapolated PBPK model. Eur. J. Drug Metab. Pharmacokinet. doi: 10.1007/s11095-015-1703-5.

Zhu, L., Yang, J., Zhang, Y., Wang, Y., Zhang, J., Zhao, Y., and Dong, W. (2015b). Prediction of Pharmacokinetics and Penetration of Moxifloxacin in Human with Intra-Abdominal Infection Based on Extrapolated PBPK Model. Korean J. Physiol. Pharmacol. Off. J. Korean Physiol. Soc. Korean Soc. Pharmacol. *19*, 99–104.

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**Figure Legends**

**Figure 1: Summary of the PBPK literature analyzed.** Panel A shows the number of articles per year that contain one or more PBPK models of pharmaceutical agents in humans. Panel B shows the distribution of the PBPK model applications in the original data papers.

**Figure 2: Summary of the model details in the evaluated literature.** The distribution of the acceptance criteria used in PBPK models of FDA probe substrates and inhibitors is shown in panel A. All publications included in the analysis contained models that were verified against in vivo data. The types of in vivo data sets used to verify the quality of the models are summarized in panel B.

## Table 1. P450 Sensitive Substrates

| Enzyme | Compound | Application | Minimal or Full PBPK | Oral or IV | Clearance[a] | Simulated genotype specified? | Age, sex, genotype matched?[b] | Verification[c] | Acceptance Criteria[d] | Software[e] | Citation |
|---|---|---|---|---|---|---|---|---|---|---|---|
| CYP1A2 | Caffeine | Allometry | Full | Oral | SF | No | N.S | A,D | 1 | PK Sim | (Thiel et al., 2014) |
| CYP2B6 | Efavirenz | DDI | Minimal | Oral | In vitro | Yes | N.S | A, E | 1 | Simcyp | (Siccardi et al., 2013) |
| | Efavirenz | DDI | Full | Oral | In vitro | Yes | S | D,E | 1 | Simcyp | (Rekic et al., 2011) |
| | Efavirenz | Absorption | Full | Oral | In vitro | No | N.S | B | 5 | Matlab | (Rajoli et al., 2014) |
| CYP2C8 | Repaglinide | Diabetes | Full | Oral | In vitro | No | N.S. | B,D | 3 | WinNonlin | (Li et al., 2014b) |
| | Repaglinide | RI | Full | Oral | BC | Yes | N.S. | D | 1 | Simcyp | (Zhao et al., 2012a) |
| | Repaglinide | DDI | Minimal | Oral | PE | No | N.S | B, E | 1 | Napp | (Kudo et al., 2013) |
| | Repaglinide | DDI | Full | Oral | BC | No | N.S | C,E | 1 | Simcyp | (Varma et al., 2013) |
| CYP2C19 | Clobazam | Pediatrics | Full | Oral | In vitro | No | N.S. | B,D,E | 1 | Matlab | (Ogungbenro and Aarons, 2015) |
| | Omeprazole | Clinical PK | Minimal | Both | BC | Yes | N.S. | B,E | 1 | Simcyp | (Wu et al., 2014) |
| CYP2D6 | Metoprolol | Pregnancy | Full | Oral | In vitro, SF | Yes | S, G | D, E | 2 | Simcyp, Matlab | (Ke et al., 2013b) |
| | Dextromethorphan | Pregnancy | Full | Oral | PE | No | S, G | D, E | 2 | Simcyp, Matlab | (Ke et al., 2013b) |
| | Dextromethorphan | Allometry | Full | Oral | SF | No | N.S | A,D | 1 | PK Sim | (Thiel et al., 2014) |
| CYP3A4 | Alfentanil | DDI | Full | Oral | BC | No | N.S. | C, E | 5 | Gastroplus | (Baneyx et al., 2014) |
| | Alfentanil | DDI | Full | Oral | In vitro | No | N.S. | E | 5 | WinNonlin | (Guo et al., 2013) |
| | Buspirone | DDI | Full | Oral | In vitro | No | N.S. | E | 5 | WinNonlin | (Guo et al., 2013) |
| | Indinavir | Pregnancy | Full | Both | In vitro, SA | No | S | C, D, E | 2 | Simcyp, Matlab | (Ke et al., 2012) |
| | Maraviroc | DDI | Minimal | Oral | In vitro | No | N.S. | A,E | 1 | Simcyp | (Hyland et al., 2008) |
| | Midazolam | Pregnancy | Full | Oral | In vitro | No | S | A, D | 2 | Simcyp, Matlab | (Ke et al., 2012) |
| | Midazolam | DDI | Full | Oral | BC | No | N.S | C, D | 5 | Gastroplus | (Baneyx et al., 2014) |
| | Midazolam | DDI | Full | Oral | PE | No | N.S | A | 4 | Berkeley M. | (Brantley et al., 2014) |
| | Midazolam | Pregnancy | Full | Oral | In vivo | No | S | B,D | 3 | Gastroplus | (Xia et al., 2013b) |
| | Midazolam | DDI | Minimal | Oral | In vitro | No | N.S. | E | 5 | WinNonlin | (Wang et al., 2013a) |
| | Midazolam | DDI | Full | Oral | In vitro | No | N.S. | E | 5 | WinNonlin | (Guo et al., 2013) |
| | Midazolam | Allometry | Full | Oral | SF | No | N.S | A, D | 1 | PK Sim | (Thiel et al., 2014) |
| | Quetiapine | Pediatrics | Both | Oral | BC | No | A, S | D, E | 1 | Simcyp | (Johnson et al., 2014) |
| | Sildenafil | RI | Full | Oral | BC | Yes | N.S. | D | 2 | Simcyp | (Zhao et al., 2012a) |
| | Simvastain | DDI | Full | Oral | In vitro | No | N.S. | E | 5 | WinNonlin | (Guo et al., 2013) |
| | Simvastatin | DDI | Minimal | Oral | In vitro | No | N.S. | A, E | 5 | WinNonlin | (Wang et al., 2013a) |

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| Triazolam | DDI | Full | Oral | In vitro | No | N.S. | E | 5 | WinNonlin | (Guo et al., 2013) |
| Triazolam | DDI | Full | Oral | BC | No | N.S. | C, E | 5 | Gastroplus | (Baneyx et al., 2014) |

[a] BC= back-calculated from in vivo data, PE= parameter estimate, SA= sensitivity analysis, SF= scaling factor from mice. [b] Age, sex and genotype are denoted as A, S and G, respectively. N.S.= not specified. [c] Data sets used in model verification included: (A) Single dose PK, (B) alternative dosing regimen, (C) alternative formulation, (D) alternative population, (E) DDI. [d] Acceptance criteria fell into 5 categories: (1) Not specified, (2) Ratio of PK parameter(s) must be within 30% of observed, (3) Ratio of PK parameter(s) must be within 2 fold of observed, (4) PK parameters must be within 30% of observed, (5) PK parameters must be within 2 fold of observed. [e] Berkeley M= Berkeley Madonna

**Table 2: Summary of PBPK models published for narrow therapeutic index substrates**

| Enzyme | Compound | Application | Model Type | IV or Oral | Clearance[a] | Simulated genotype specified? | Age, sex, genotype matched?[b] | Verification[c] | Acceptance Criteria[d] | Software[e] | Citation |
|---|---|---|---|---|---|---|---|---|---|---|---|
| CYP1A2 | Theophylline | Pregnancy | Full | Oral | BC | No | S | B, D | 2 | Simcyp, Matlab | (Ke et al., 2013b) |
| | Theophylline | DDI | Minimal | Both | In vitro | No | N.S. | B, E | 1 | Matlab | (Pan et al., 2011) |
| CYP2C9 | Phenytoin | Clinical PK | Minimal | Oral | In vitro | Yes | A, S, G | B | 1 | Simcyp | (Polasek et al., 2009) |
| | Warfarin | DDI | Full | Oral | PE | No | A, S, G | A | 4 | Berkeley M. | (Brantley et al., 2014) |
| CYP3A4 | Cyclosporine | Pediatrics | Full | IV | In vivo, SF | No | A | C | 1 | AdaptII | (Gérard et al., 2010) |
| | Cyclosporine | DDI | Full | Oral | In vitro | No | N.S. | E | 5 | WinNonlin | (Guo et al., 2013) |
| | Cyclosporine | DDI | Full | Both | PE | No | N.S. | C, E | 5 | Matlab | (Gertz et al., 2013) |
| | Cyclosporine | Allometry | Full | Oral | SF | No | N.S | A, D | 1 | PK Sim | (Thiel et al., 2014) |
| | Quinidine | DDI | Full | Oral | In vitro | No | N.S. | E | 5 | WinNonlin | (Guo et al., 2013) |
| | Sirolimus | Clinical PK | Full | Oral | In vitro, PE | No | A, S | B, D, E | 1 | Simcyp | (Emoto et al., 2013) |
| | Tacrolimus | DDI | Full | Oral | In vitro | No | N.S. | E | 5 | WinNonlin | (Guo et al., 2013) |
| | Tacrolimus | Clinical PK | Minimal | Oral | BC | Yes | A, S, G | D, E | 1 | PKquest | (Gérard et al., 2014) |

[a] BC- back-calculated from in vivo data, PE= parameter estimate, SF= scaling factor. [b] Age, sex and genotype are denoted as A, S and G, respectively. N.S.= not specified.
[c] Data sets used in model verification included: (A) Single dose PK, (B) alternative dosing regimen, (C) alternative formulation, (D) alternative population, (E) DDI. [d] Validation Criteria fell into 5 categories. (1) Not specified, (2) Ratio of PK parameter(s) must be within 30% of observed, (3) Ratio of PK parameter(s) must be within 2 fold of observed, (4) PK parameters must be within 30% of observed, (5) PK parameters must be within 2 fold of observed. [e] Berkeley M= Berkeley Madonna

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## Table 3. PBPK models and model details for recognized P450 inhibitors

| Enzyme | Compound | Application | Minimal or Full PBPK | Oral or IV | Clearance[a] | Additional Inhibition Parameters | Simulated genotype specified? | Age, sex, genotype matched?[b] | Verification[c] | Acceptance Criteria[d] | Software | Citation |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | **Strong Inhibitors** | | | | | | |
| CYP2C8 | Gemfibrozil | DDI | Minimal | Oral | PE | CYP3A4 | No | N.S. | A, B, E | 1 | Napp | (Kudo et al., 2013) |
| CYP2D6 | Paroxetine | Pregnancy | Full | Oral | In vitro | CYP3A4 | Yes | S, G | D, E | 2 | Simcyp, Matlab | (Ke et al., 2013b) |
| | Fluoxetine | DDI | Minimal | Oral | In vitro | CYP1A2 CYP2C9 CYP2C19 | Yes | N.S. | E | 1 | Simcyp | (Siccardi et al., 2013) |
| CYP3A4 | Clarithromycin | DDI | Minimal | Oral | In vivo | - | Yes | A, S, G | A, B, E | 3 | Simcyp | (Wang, 2010) |
| | Clarithromycin | DDI | Minimal | Oral | In vivo | - | No | A, S, G | B, E | 3 | Simcyp | (Xu et al., 2009) |
| | Itraconazole | DDI | Minimal | Oral | PE | - | No | N.S. | A, B, E | 1 | Napp | Kudo et al., 2013 |
| | Ritonavir | DDI | Minimal | Oral | In vitro | CYP2C9 CYP2D6 | Yes | N.S. | A, E | 1 | Simcyp | (Siccardi et al., 2013) |
| | Ritonavir | Clinical PK | Minimal | Oral | In vitro | CYP3A5 CYP2D6 CYP2J2 | Yes | N.S. | D | 1 | Simcyp | (Kaspera et al., 2014) |
| | Telithromycin | RI | Full | Oral | BC | P-gp | Yes | N.S. | D, E | 1 | Simcyp | (Zhao et al., 2012a) |
| | Telithromycin | DDI | Full | Oral | BC | P-gp CYP3A5 | No | N.S. | A, B, E | 1 | Simcyp | (Vieira et al., 2012) |
| | | | | | | **Moderate Inhibitors** | | | | | | |
| CYP2C9 | Amiodarone | DDI | Full | Both | BC | CYP2D6 CYP3A4 | No | N.S. | A, E | 1 | Simcyp | (Chen et al., 2015) |
| CYP2C19 | Omeprazole | Clinical PK | Minimal | Both | BC | - | Yes | G | B, D, E | 1 | Simcyp | (Wu et al., 2014) |
| CYP3A4 | Diltiazem | DDI | Minimal | Oral | In vivo | - | No | A, S, G | B, E | 3 | Simcyp | (Xu et al., 2009) |
| | Diltiazem | DDI | Minimal | Oral | In vitro | - | No | N.S. | A, B, E | 1 | WinNonlin | (Zhang et al., 2009) |
| | Diltiazem | DDI | Minimal | Oral | In vivo | CYP2D6 | No | A, S | B | 1 | Simcyp | (Friedman et al., 2011) |
| | Erythromycin | DDI | Minimal | Oral | In vivo | CYP2C8 | No | A, S, G | B, E | 3 | Simcyp | (Xu et al., 2009) |
| | Verapamil | DDI | Minimal | Oral | In vitro | CYP2C8 OATP1B1 | No | N.S. | A, B, C, E | 5 | WinNonlin | (Wang et al., 2013a) |
| | Verapamil | DDI | Full | Oral | BC | - | No | A, S | A, E | 1 | Simcyp | (Neuhoff et al., 2013a) |
| | Verapamil | DDI | Minimal | Oral | In vivo | - | No | A, S, G | B, E | 3 | Simcyp | (Xu et al., 2009) |
| | | | | | | **Weak Inhibitors** | | | | | | |
| CYP2C8 | Trimethoprim | DDI | Minimal | Oral | In vivo | - | Yes | N.S. | B, E | 1 | Simcyp | (Yeo et al., 2013) |

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[a] PE= parameter estimation from in vivo data, BC= back-calculated from in vivo data. [b] Age, sex and genotype are denoted as A, S and G, respectively. N.S.= not specified. [c] Data sets used in model verification included:  (A) Single dose PK, (B) alternative dosing regimen, (C) alternative formulation, (D) alternative population, (E) DDI.  [d] Validation Criteria fell into 5 categories.  (1) Not specified, (2) Ratio of PK parameter(s) must be within 30% of observed, (3) Ratio of PK parameter(s) must be within 2 fold of observed, (4) PK parameters must be within 30% of observed, (5) PK parameters must be within 2 fold of observed.

**Table 4: PBPK models published for P450 inducers**

| Enzyme | Compound | Application | Model Type | IV or Oral | Clearance[a] | Simulated genotype specified? | Age, sex, genotype matched?[b] | Verification[c] | Acceptance Criteria[d] | Software | Citation |
|---|---|---|---|---|---|---|---|---|---|---|---|
| CYP2B6 and CYP3A4 | Efavirenz | DDI | Minimal | Oral | In vitro | Yes | N.S | A, E | 1 | Simcyp | (Siccardi et al., 2013) |
| | Efavirenz | Absorption | Full | Oral | In vitro | No | N.S. | B | 5 | Matlab | (Rajoli et al., 2014) |
| | Efavirenz | DDI | Full | Oral | In vitro | Yes | S | D, E | 1 | Simcyp | (Rekic et al., 2011) |
| CYP3A4 | Carbamazepine | DDI | Full | Oral | In vitro | No | N.S. | B, E | 5 | WinNonlin | (Guo et al., 2013) |
| | Etravirine | Absorption | Full | Oral | In vitro | No | N.S. | B | 5 | Matlab | (Rajoli et al., 2014) |
| | Rifampin | DDI | Full | Oral | BC | No | N.S. | E | 5 | Gastroplus | (Baneyx et al., 2014) |
| | Rifampin | DDI | Full | Oral | In vivo | No | N.S. | B, E | 5 | WinNonlin | (Guo et al., 2013) |
| | Rifampin | DDI | Full | Oral | BC | No | A, S, G | A | 1 | Simcyp | (Neuhoff et al., 2013b) |

[a] BC= back calculated from in vivo data. [b]Age, sex and genotype are denoted as A, S and G, respectively. N.S.= not specified. [c]Data sets used in model verification included: (A) Single dose PK, (B) alternative dosing regimen, (C) alternative formulation, (D) alternative population, (E) DDI. [d]Validation Criteria fell into 5 categories. (1) Not specified, (2) Ratio of PK parameter(s) must be within 30% of observed, (3) Ratio of PK parameter(s) must be within 2 fold of observed, (4) PK parameters must be within 30% of observed, (5) PK parameters must be within 2 fold of observed.

**Table 5: Summary of the PBPK models published for transporter substrates, inhibitors and inducers**

| Transporter(s) | Compound | Application | Minimal or Full | Oral or IV | Clearance[a] | Simulated genotype specified? | Simulations age, sex, genotype matched?[b] | Verification[c] | Acceptance Criteria[d] | Software[e] | Citation |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Inducers** | | | | | | | | | | | |
| P-gP | Rifampin | Transport | Minimal | Oral | BC | No | A,S | A, E | 1 | Simcyp | (Neuhoff et al., 2013b) |
| **Inhibitors** | | | | | | | | | | | |
| OAT1, OAT3 | Probenecid | DDI | Full | Both | BC | No | N.S. | C | 1 | Simcyp | (Hsu et al., 2014) |
| OATP1B1 | Gemfibrozil | DDI | Minimal | Oral | PE | No | N.S. | A, B, E | 1 | Napp | (Kudo et al., 2013) |
| | Gemfibrozil | Transport | Full | Oral | BC | Yes | N.S. | E | 1 | Simcyp | (Varma et al., 2015a)* updated Varma et al 2012 |
| | Cyclosporine | Transport | Full | Oral | In vivo | Yes | N.S. | A, E | 1 | Simcyp | (Varma et al., 2012) |
| OATP1B1, 1B3 | Cyclosporine | Transport | Full | Oral | BC | No | A, S, G | B | 1 | Simcyp | (Jamei et al., 2014) |
| BCRP | Cyclosporine | DDI | Full | Both | PE | No | N.S. | C, E | 5 | Matlab | (Gertz et al., 2013) |
| P-gp | Verapamil | DDI | Full | Oral | BC | No | A, S | A, E | 1 | Simcyp | (Neuhoff et al., 2013b) |
| **Substrates** | | | | | | | | | | | |
| BCRP OATP1B1, 1B3 | Rosuvastatin | Transport | Full | Oral | BC, PE, SA | No | A, S | B, E | 1 | Simcyp | (Jamei et al., 2014) |
| OATP1B1, OAT3 | Pravastatin | Clinical PK | Full | Both | In vitro, SF | No | N.S. | C | 1 | Matlab, PK Sim | (Meyer et al., 2012) |
| OATP1B1 | Pravastatin | Transport | Full | Both | In vitro, SF | No | N.S. | A, B, E | 1 | Simcyp | (Varma et al., 2012) |
| | Atorvastatin | Absorption | Full | Oral | In vitro | No | AS | D | 1 | Simcyp | (Darwich et al., 2013) |
| | Bosentan | Transport | Full | IV | In vitro, SF | No | N.S. | None | 1 | Berkeley M. | (Jones et al., 2012) |
| | Fluvastatin | Transport | Full | IV | In vitro, SF | No | N.S. | None | 1 | Berkeley M. | (Jones et al., 2012) |
| | Glyburide | DDI | Full | Both | In vitro | Yes | G | B, C, E | 1 | Simcyp | (Varma et al., 2014) |
| | Glyburide | Pregnancy | Full | Oral | BC | No | S | B, D, E | 2 | Simcyp, Matlab | (Ke et al., 2013a) |
| | Repaglinide | Transport | Full | IV | In vitro, SF | No | N.S. | None | 1 | Berkeley M. | (Jones et al., 2012) |
| | Repaglinide | RI | Full | Oral | BC | Yes | N.S. | D | 1 | Simcyp | (Zhao et al., 2012a) |
| | Repaglinide | DDI | Minimal | Oral | In vivo | No | N.S. | E | 1 | Napp | (Kudo et al., 2013) |
| | Repaglinide | DDI | Full | Both | BC | No | N.S. | C, E | 1 | Simcyp | (Varma et al., 2013) |
| OATP1B3 | Telmisartan | Transport | Full | Both | In vitro, SF | No | N.S. | C | 1 | Matlab | (Li et al., 2014c) |
| OATP1B1,1B3 | Rosuvastatin | Transport | Full | Both | In vitro, SF | No | N.S. | C | 1 | ASCLX | (Bosgra et al., 2014) |
| P-gp | Dabigatran | DDI | Full | Both | In vitro | No | N.S. | A, B, E | 1 | PK Sim | (Zhao and Hu, 2014) |
| | Digoxin | Transport | Full | Both | BC | No | A, S | A, B | 4 | Simcyp | (Neuhoff et al., 2013b) |

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| | Digoxin | Pregnancy | Full | Oral | In vivo | No | S | D | 5 | Gastroplus | (Xia et al., 2013b) |
|---|---|---|---|---|---|---|---|---|---|---|---|

[a] BC= back calculated from in vivo data, PE= parameter estimation, SA= sensitivity analysis, SF= scaling factor. [b]Age, sex and genotype are denoted as A, S and G, respectively. N.S.= not specified . [c]Data sets used in model verification included: (A) Single dose PK, (B) alternative dosing regimen, (C) alternative formulation, (D) alternative population, (E) DDI. [d]Validation Criteria fell into 5 categories. (1) Not specified, (2) Ratio of PK parameter(s) must be within 30% of observed, (3) Ratio of PK parameter(s) must be within 2 fold of observed, (4) PK parameters must be within 30% of observed, (5) PK parameters must be within 2 fold of observed. [e] Berkeley M.= Berkeley Madonna.

**Table 6: Summary of the PBPK models published for compounds that are FDA probe substrates, inhibitors, or inducers but the models were developed for a different purpose than the FDA category.**

| Compound | Application | Type | Oral or IV | Simulated genotype specified? | Clearance[a] | Verification[b] | Simulations age, gender matched?[c] | Acceptance Criteria[d] | Software[e] | Citation |
|---|---|---|---|---|---|---|---|---|---|---|
| Alprazolam | DDI | Full | Oral | No | In vitro | E | N.S. | 5 | Winnonlin | (Guo et al., 2013) |
| Clopidogrel | DDI | Minimal | Oral | Yes | In vitro | B, E | S | 1 | Simcyp | (Tornio et al., 2014) |
| Clopidogrel | Genetics | Full | Oral | Yes | In vitro | B, D, E | N.S. | 1 | Simcyp | (Djebli et al., 2015) |
| Lansoprazole | Absorption | Minimal | Oral | No | In vivo | C | N.S. | 1 | Gastroplus | (Wu et al., 2013) |
| Metformin | Other (diabetes) | Full | Oral | No | in vivo | D | N.S. | 3 | Winnonlin | (Li et al., 2015) |
| Metformin | Pregnancy | Full | Oral | No | In vivo | D | S | 5 | Gastroplus | (Xia et al., 2013a) |
| Methadone | Pregnancy | Full | Oral | No | BC | B, D | S | 4 | Simcyp, Matlab | (Ke et al., 2013a) |
| Nisoldipine | Other (diabetes) | Full | Oral | No | In vivo | D | N.S. | 3 | Winnonlin | (Li et al., 2015) |
| Oseltamivir | Pediatrics | Full | Both | No | In vitro, SF | C, D, E | N.S. | 1 | Gastroplus | (Parrott et al., 2011) |
| Oseltamivir | Clinical PK | Full | Oral | Yes | In vitro | D | N.S. | 1 | PK-Sim | (Hu et al., 2014) |
| Oseltamivir | RI | Full | Oral | No | In vivo | B | N.S. | 1 | Simcyp | (Hsu et al., 2014) |
| Phenobarbital | DDI | Full | Oral | No | In vivo | B,E | N.S | 5 | WinNonlin | (Guo et al., 2013) |
| Pravastatin | Clinical PK | Full | IV | No | In vitro, SF | C | N.S. | 1 | Berkeley M. | (Jones et al., 2012) |
| Propranolol | Formulation | Full | Oral | No | In vivo | B, C | N.S. | 1 | Gastroplus | (Wang et al., 2013b) |
| Rosuvastatin | Clinical PK | Full | IV | No | In vitro, SF | C | N.S. | 1 | Berkeley M. | (Jones et al., 2012) |
| Sertraline | DDI | Minimal | Oral | Yes | In vitro | E | N.S. | 1 | Simcyp | (Siccardi et al., 2013) |
| Theophylline | DDI | Minimal | Oral | No | In vivo | B,E | A, S, G | 3 | Simcyp | (Xu et al., 2009) |
| Valsartan | Clinical PK | Full | IV | No | In vitro, SF | C | N.S. | 1 | Berkeley M. | (Jones et al., 2012) |
| Verapamil | DDI | Full | Oral | No | In vitro | E | N.S. | 3 | Winnonlin | (Guo et al., 2013) |
| Voriconazole | Pediatrics | Full | Both | No | In vitro, SF | C, D | N.S. | 1 | Simcyp | (Zane and Thakker, 2014) |
| Voriconazole | DDI | Minimal | Oral | Yes | In vitro | E | S, G | 1 | Simcyp | (Damle et al., 2011) |

[a] BC= back calculated from in vivo data, SF= scaling factor. [b] Data sets used in model verification included: (A) Single dose PK, (B) alternative dosing regimen, (C) alternative formulation, (D) alternative population, (E) DDI. [c] Age, sex and genotype are denoted as A, S and G, respectively. N.S.= not specified. [d] Validation Criteria fell into 5 categories. (1) Not specified, (2) Ratio of PK parameter(s) must be within 30% of observed, (3) Ratio of PK parameter(s) must be within 2 fold of observed, (4) PK parameters must be within 30% of observed, (5) PK parameters must be within 2 fold of observed. [e] Berkeley M= Berkeley Madonna

**Table 7: List of compounds for which Full PBPK models were used to address pharmacological and toxicological questions**

| Compound | Model purpose | A priori criteria? | Model Quality Assessment | Conclusions | Citation |
|---|---|---|---|---|---|
| Acetaminophen | Assessing various calibration strategies for linking PBPK models to toxicodynamic models of hepatotoxicity | No | Qualitative discussion of the agreement between simulated and observed PK ($C_{max}$, metabolite ratios) | Predicted liver toxicity in agreement with observed | (Péry et al., 2013) |
| Cyclosporine | Simulation of receptor occupancy in accute graft-versus-host organs and kidneys after intermittent or continuous infusion | No | Mann-Whitney test to compare means, chi-square test to compare proportions, bias and precision, number of simulations within 2-fold of the observed, weighted residuals | A greater therapeutic index was predicted following continuous infusion | (Gérard et al., 2010) |
| Cyclosporine | To establish a connection between the likelihood and severity of graft-versus-host disease and cyclosporine exposures in circulation, graft-versus-host target organs and lymphoid tissues | No | Student's t-test to compare means, chi-square test to compare proportions, AIC for model selection | Blood cyclosporine levels can be used as an indicator of therapeutic efficacy | (Gérard et al., 2011) |
| Efalizumab | Develop a PD linked PBPK model to predict efficacy of efalizumab | Yes | Observed data within the predicted 5th and 95th centile | The model predicted the efficacy of efalizumab in treatment of psoriasis | (Chetty et al., 2015) |
| Formamide | Develop a PBPK model to evaluate the relationship between dose and hepatic exposure | No | | 40mg/day dose was proposed bases on a safety index | (Yan et al., 2012) |
| Levofloxacin | Exploratory study to predict the extent of tissue exposure of levofloxacin in humans as a basis for future PK/PD work. | Yes | Fold error in PK parameters less than 2 | Levofloxacin penetrated well into tissues, including the liver kidneys and spleen | (Zhu et al., 2015a) |
| Moxifloxacin | Simulate tissue concentrations versus time in patients with intra-abdominal infections | Yes | Fold error in PK parameters less than 2 | Concentrations in intra-abdominal tissues were predicted to be higher than in vitro MIC for common pathogens | (Zhu et al., 2015b) |
| Moxifoxacin | Using PBPK modeling to evaluate the effect of macrophages on tissue concentrations of moxifloxacin to enhance understanding of the effects of disease on PK/PD | No | Simulated concentration versus time profiles were evaluated for bias and precision | Macrophage concentrations are predicted to effect tissue concentration of moxifloxacin | (Edginton et al., 2009) |
| Nicotine | Develop a PBPK model to describe nicotine exposure and receptor binding in the brain | No | Qualitative discussion of the agreement of the predicted and observed data | PK/PD modeling allowed for prediction of nicotine receptor occupancy in the brain | (Teeguarden et al., 2013) |
| "S1" | Predicting brain extracellular fluid concentrations as a starting point for PK-PD modeling | No | - | Unclear whether the PBPK model would accurately predict PD | (Ball et al., 2014) |
| Temozolomide | PD linked PBPK model for simulating the brain concentration of temozolomide and the levels DNA brain adducts | No | | Predictions were in close agreement with observed data and parameter estimates had low coefficients of variation | (Ballesta et al., 2014) |

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| | | | | | |
|---|---|---|---|---|---|
| Zidovudine | Model intra-cellular concentrations of zidovudine in peripheral blood mononuclear cells and establish efficacy and toxicity following various dosing regimens | No | PK features are well represented by the predictions | 100mg 4 times daily is predicted to be the safest and most efficacious dosing scheme | (von Kleist and Huisinga, 2009) |
| Theoretical Compounds | Proof of concept study to evaluate mechanisms for differences in unbound plasma and tissue concentrations | N/A | N/A | This approach can be used to predict free tissue concentrations of various classes of drugs | (Poulin, 2015) |

**Table 8: List of relevant details to report for publication of PBPK models based on the literature review.**

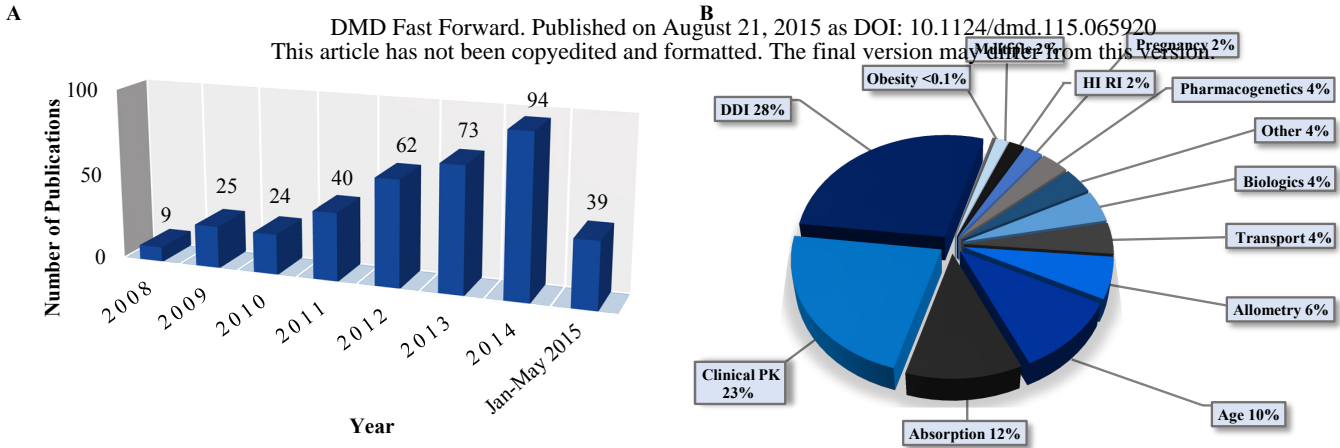| Objectives | • What is the purpose of the model? |
|---|---|
| **Model Acceptance Criteria** | • What criteria are being used to determine if a model is "fit-for-purpose"?<br>• What is the clinical relevance of this criteria?<br>• What independent data sets are used for model testing? |
| **Model development** | • Was the model built using a PBPK software package?<br>    o If not, information regarding the model structure, the source of parameters and their physiological context should be reported<br>• Input parameters (See Zhao et al 2012 for recommended parameters to include)<br>• What parameters, if any, were estimated using parameter estimation or sensitivity analysis?<br>    o Are the estimated parameters physiologically plausible?<br>    o Are the parameters within the range of previously reported values (if applicable)?<br>• Population demographics (Do the simulated and observed populations and study sizes match?) |
| **Model Outcomes** | • Comparison of the predicted and observed PK<br>• Do the predictions meet the predetermined model specification criteria? |
| **Model Performance** | • Was sensitivity analysis performed to assess whether model output parameters are sensitive to specific input parameters? (Yes/No)<br>• What are the verified applications of the model? What is the level of uncertainty in model components? |

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**Figure 1.**

**A**

**B**

**Figure 2.**

**A**



**B**



**C**