Physiologically-Based Pharmacokinetics in Drug Development and Regulatory Science

Malcolm Rowland,[1] Carl Peck,[2] and Geoffrey Tucker[3,4]

[1]Centre for Pharmacokinetic Research, School of Pharmacy and Pharmaceutical Sciences, University of Manchester, Manchester M13 9PT, United Kingdom; email: mrow190539@aol.com

[2]Center for Drug Development Science, Department of Bioengineering and Therapeutic Science, Schools of Medicine and Pharmacy, University of California, San Francisco, San Francisco, California 94143

[3]Clinical Pharmacology, University of Sheffield, The Royal Hallamshire Hospital, Sheffield S10 2JF, United Kingdom

[4]Simcyp Ltd., Sheffield S2 4SU, United Kingdom

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Abstract

The application of physiologically-based pharmacokinetic (PBPK) modeling is coming of age in drug development and regulation, reflecting significant advances over the past 10 years in the predictability of key pharmacokinetic (PK) parameters from human in vitro data and in the availability of dedicated software platforms and associated databases. Specific advances and contemporary challenges with respect to predicting the processes of drug clearance, distribution, and absorption are reviewed, together with the ability to anticipate the quantitative extent of PK-based drug-drug interactions and the impact of age, genetics, disease, and formulation. The value of this capability in selecting and designing appropriate clinical studies, its implications for resource-sparing techniques, and a more holistic view of the application of PK across the preclinical/clinical divide are considered. Finally, some attention is given to the positioning of PBPK within the drug development and approval paradigm and its future application in truly personalized medicine.

INTRODUCTION

PBPK: physiologically-based pharmacokinetic(s)

PK: pharmacokinetic(s)

PD: pharmacodynamic(s)

Although interest in physiological factors that control the uptake, distribution, and elimination of drugs dates back to nineteenth-century publications, particularly in literature that addresses anesthesia, the origins of physiologically-based pharmacokinetics (PBPK), as understood in this review, can be traced to Teorell in 1937 (1). He formally recognized that the body handles a drug as an integrated system: Events that occur in one part influence, and are in turn influenced by, events occurring in other parts through a common convective conduit, the circulating blood (**Figure 1**). However, this holistic, mechanistic, and intellectually appealing view, sometimes referred to as whole-body PBPK, yielded equations describing drug kinetics that were too complex to solve mathematically at the time. Further substantive progress had to await the arrival of enabling computational tools, initially analog computers and subsequently—and now exclusively—digital computers.

Given the complexity of physiologic models, it is perhaps not surprising that simpler empirical models, such as sums of exponentials (and associated half-lives) and compartmental models have predominantly been used to describe or fit measurements of drug and metabolites, generally in plasma. Although pragmatic, such models, typically derived solely from the data, are essentially descriptive. More importantly, they tell us nothing about the rules governing the pharmacokinetic behavior of drugs in blood and tissues. This lack of mechanistic insight limits the usefulness of such empirical models to researchers involved in drug discovery, development, and regulation who encounter (*a*) diversity of chemical structure and mammalian species and (*b*) variability in pharmacokinetics among patients associated with aging, disease, concurrent therapies, and other influences. Here, PBPK models have much greater potential, as illustrated in this review. This potential should be viewed against the backdrop of an industry traditionally reluctant to accept but now increasingly interested in adopting modeling and simulation in pharmacokinetics (PK) and pharmacodynamics (PD) as a knowledge-based decision and management tool in all phases of drug development, from discovery to registration of medicines and beyond (2, 3). This industry also needs to improve its ability to optimize the selection and development of drugs. Furthermore, although considerable progress has been made in limiting the frequency with which unfavorable pharmacokinetics causes failure in clinical development (4), there is still considerable room for improvement.

The first specific use of the term PBPK within the title of a research article appears to be in 1977 (5). Yet, although not labeled specifically as such, PBPK had already seen significant progress throughout the 1960s and early 1970s by researchers in medicine [most notably anesthesiology (6)], in pharmacology (7), and in chemical engineering (8). Moreover, some of the early research in the context of pharmaceutical sciences had already demonstrated the ability to describe accurately and predict the in vivo PK behavior of some drugs from a composite of apparently disparate in vitro (tissue affinity, metabolic stability, plasma binding), physiological, and anatomical data (9), as a foretaste of much of the application of PBPK today.

The growing interest in PBPK is illustrated (**Figure 2**) by an accelerating number of scientific publications, particularly during the past decade, that use the term and offer general reviews on the topic (10–15). The numbers become much greater when all publications devoted to physiological aspects of pharmacokinetics are included, but the trend is similar. Understandably, the majority of these publications deal with issues pertaining to risk assessment of environmental chemicals (16) because PBPK offers the only scientifically sound method of predicting the systemic exposure of such compounds in humans and, thereby, of extrapolating animal to human toxicology. Indeed, much of the scientific framework and application of PBPK has been developed by the environmental risk community (17). In contrast, until the past decade, most research and application of

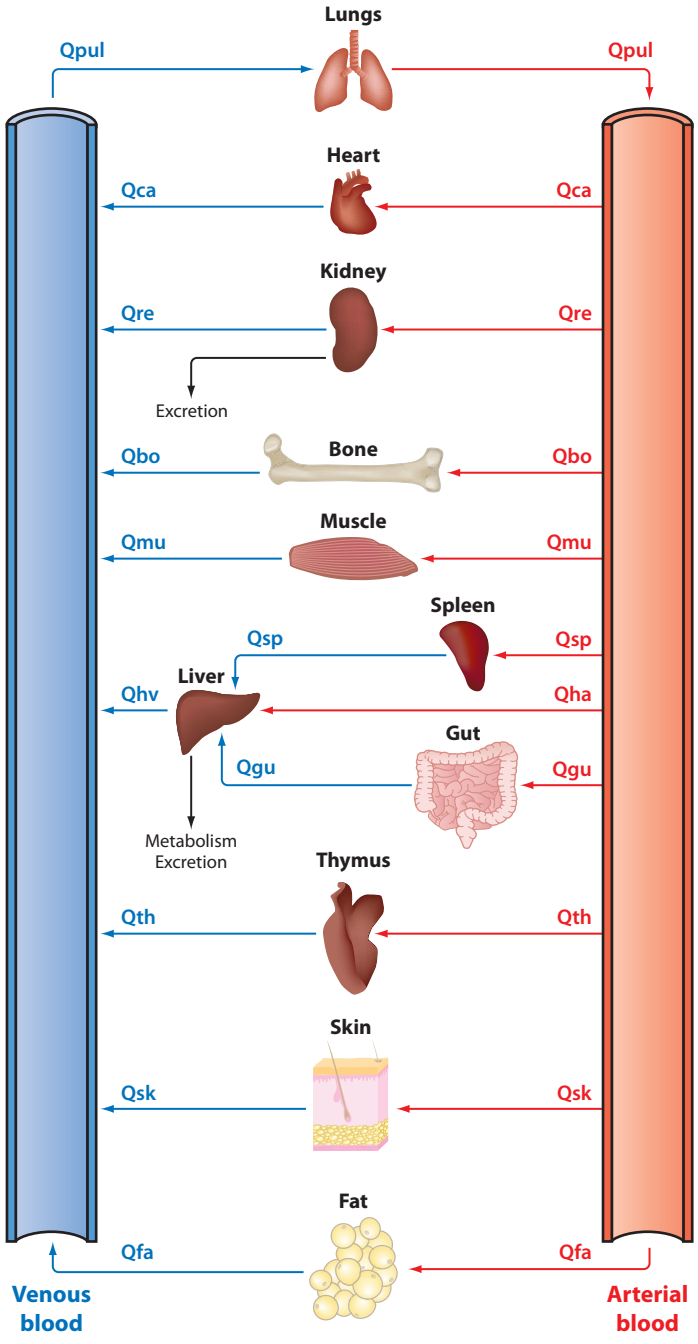


Figure 1

A whole-body physiologically-based pharmacokinetic model. Q refers to blood flow: to the lungs (Qpul), the heart (Qca), the kidneys (Qre), the bones (Qbo), the muscles (Qmu), the spleen (Qsp), the liver (Qha), the hepatic vein (Qhv), the gut (Qgu), the thymus (Qth), the skin (Qsk), and the fat (Qfa). Input can be any site of the body. Elimination is depicted as occurring from only liver and kidneys, whereas it can occur also at other sites for some drugs. Some drugs can undergo enterohepatic cycling. The model can be extended to include a similar model for formed metabolites.

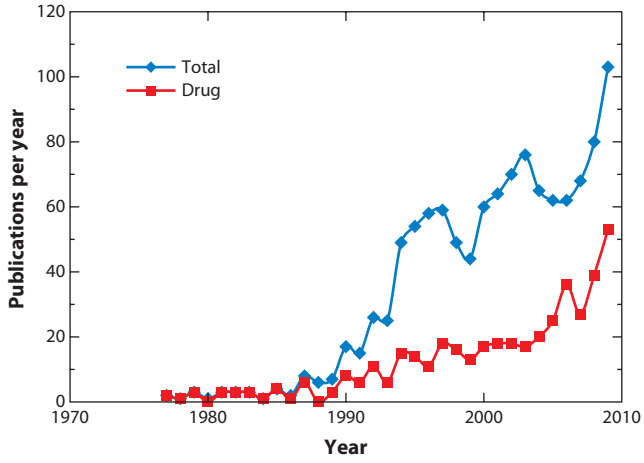


Figure 2

The annual rate of scientific publications whose article titles contain the phrase "physiologically-based pharmacokinetics." Of the total publications, a fraction of the publications relates to drugs, whereas the remainder deals with environmental chemicals. Source: ISI Web of Knowledge, Thomson Reuters.

PBPK in the pharmaceutical arena occurred in academia. The first workshop dedicated to exploring PBPK in drug development and regulation took place in 2002 (18). Acceptance, let alone adoption, by the pharmaceutical industry at that time was minimal, as was interest by regulatory agencies. However, the situation has changed markedly since then, and developments during this period are the major focus of this review. Also, the primary emphasis of this review is on PBPK that involves small-molecule drugs (<1000 g mol^{-1}). Biologics tend to have simpler pharmacokinetics that are almost exclusively characterized with empirical—or at best, semiempirical—models. Even so, some PBPK work has begun in this area (19–21), and it has been argued that PBPK is needed to provide insights into important distributional complexities (22, 23), which impact not only PK but also PK/PD relationships when the target resides in a peripheral tissue. Thus some biologics display complex, target-mediated disposition kinetics, whereby kinetics and dynamics are intimately linked. In addition, contemporary developments in the refinement of physiologically based recirculatory models describe events early after the administration of drugs (24), particularly those used in anesthesia (25–27). However, this review concentrates primarily on compounds in use and in development for the treatment of chronic conditions.

PHILOSOPHY OF PHYSIOLOGICALLY-BASED PHARMACOKINETIC MODELS

PBPK models comprise three major components: system-specific properties, drug properties, and the structural model. System-specific properties include organ mass or volume, blood flow, and tissue composition. Drug properties include tissue affinity, plasma-protein binding affinity, membrane permeability, enzymatic stability, and transporter activities. The structural model comprises the anatomical arrangement of the tissues and organs of the body, linked by perfusing blood. Unlike empirical models, the structures of which are dictated by the observed drug data, a PBPK structural model is independent of the drug and is the same for all mammalian species, although the degree of complexity often varies with the intended application. Commonly, PBPK models, in which all organs and tissues of the body are included as distinct entities, tend to be used when

simulating expectations. This is a "bottom-up" approach in that the interactions of a drug with all components of the body are integrated, with the primary aims of permitting mechanistic insights into the global behavior of the system and of making valid extrapolations. The previous disadvantage of prolonged computational time associated with such complex PK models has been all but eliminated with the ever-increasing power and speed of modern computers. Reduced models, with lumped tissues, are used increasingly when estimating parameters from experimental data. This is more of a "top-down" approach, with a tendency for the complexity of the structural model to be conditioned in part by the data. A key issue is the need for formal methods of model reduction, which preserve global body characteristics such as cardiac output and body weight, place criteria on the lumping of tissues based on their kinetic features, and ensure mass balance of the drug (28, 29).

A critical component of PBPK modeling that allows facile solution of the model equations is the availability of software tools, examples of which are listed in **Table 1** along with their Web sites. Although much of this enabling software, particularly the open access sources, has existed for many years, there has been limited uptake by those involved in drug discovery and development. This reluctance to use the software arises from a lack of relevant associated physiological, biochemical, and drug-related databases and a lack of user-friendly input and output interfaces.

Table 1 Physiologically-based pharmacokinetics (PBPK) software and associated Web sites

Custom physiologically-based pharmacokinetics (PBPK) software: The following is a list of proprietary software systems that are custom designed for PBPK modeling by users in drug discovery, development, and regulation.
Simcyp Simulator, Simcyp Ltd. (157): **http://www.simcyp.com**
GastroPlus, Simulations Plus Inc.: **http://www.simulations-plus.com**
PK-Sim, Bayer Technology Services (196): **http://www.systems-biology.com/products/pk-sim.html**
Cloe Predict, Cyprotex Ltd.: **http://www.cyprotex.com/cloepredict/**
General-purpose high-level scientific computing software: The following packages are high-level programming or matrix languages that provide general tools for scientific computing. Their use for PBPK modeling implies that investigators may need capabilities that more user-friendly software does not provide.
Berkeley Madonna, University of California at Berkeley: **http://www.berkeleymadonna.com/**
MATLAB and Simulink product families, The MathWorks Inc.: **http://www.mathworks.com/**
MLAB, Civilized Software Inc.: **http://www.civilized.com/**
GNU Octave, University of Wisconsin: **http://www.octave.org/**
Biomathematical modeling software: The tools in the following list have been designed explicitly for mathematical modeling of biological systems. Some have a user-friendly (graphical) interface, and their manuals are usually designed to appeal to the biomedical investigator. The degree to which they can be used for PBPK modeling is dictated by the limitations imposed by the graphical interface, speed of computation, and flexibility of the modeling language. Some of these tools also provide mixed-effects (population) capabilities, with which, at least in principle, sparse data sets can be analyzed.
ADAPT 5, Biomedical Simulations Resource, University of Southern California: **http://bmsr.usc.edu/**
ModelMaker, ModelKinetix: **http://www.modelkinetix.com/**
NONMEM, ICON: **http://www.icondevsolutions.com/nonmem.htm**
STELLA, isee systems inc. (formerly High Performance Systems Inc.): **http://www.iseesystems.com/softwares/Education/StellaSoftware.aspx**
WinNonlin, Pharsight, a Certara company: **http://www.pharsight.com**
SAAM II, University of Washington: **http://depts.washington.edu/saam2/**
acslX, The AEgis Technologies Group Inc.: **http://www.acslx.com/products/toolkits.shtml**
PhysioLab, Entelos Inc.: **http://www.entelos.com/**

IVIVE: in vitro–in vivo extrapolation

Several developments over the past decade have addressed these deficiencies, however. These include the availability of dedicated commercial software that meets end-user requirements, a spate of recent commentaries specifically devoted to the application of PBPK in drug discovery and development (10, 11, 30–36), together with a noticeable increase in the application of PBPK modeling by industry with the realization of its value. Important features of any PBPK-based software are the sourcing, verification, and assembly of the large amount of pertinent physiological and related literature required for the optimal application of PBPK, as well as transparency with regard to assumptions and methods.

An aspect of PBPK that receives continual attention is the degree of complexity of individual tissues and organs within the global structural model. The most common representation—which depicts tissues as single, well-stirred, perfusion rate–limited compartments—has served reasonably well when describing and extrapolating the disposition kinetics of many small lipophilic compounds. The latter features are characteristic of many environmental chemicals, but drug candidates, especially modern ones, tend to be much larger molecules that require more complex representations, particularly if they are also relatively polar. In these cases, membrane permeability in some tissues and the role of transporters and their interplay with enzymes need to be accommodated (37–40).

The complexity of PBPK is particularly compounded when confronted with the interplay of phenomena involved in oral drug absorption. This demands modeling the complex processes of dissolution, intestinal permeation, and, for some drugs, metabolism, all of which occur simultaneously within a continuously changing environment as material moves down the gastrointestinal tract (41, 42). Initially, reasonably simple compartmental absorption and transit (CAT) models that divide the gastrointestinal tract into segments were developed (43), but these generally proved inadequate. They have been replaced by more sophisticated advanced models—the advanced compartmental absorption and transit (ACAT) model (31, 44); the advanced dissolution, absorption, and metabolism (ADAM) model (45); and the model embedded in PK-Sim (46)—to accommodate the complex axial heterogeneity of all components that impact intestinal drug absorption (**Figure 3**). Progress has also been made toward more sophisticated PBPK models that accommodate other routes of drug administration such as the skin (47) and lung (48) and models that represent events within specific target tissues such as the brain (49) and solid tumors (50).

The need for more complex organ models is also evident when predicting the hepatic uptake and clearance of drugs. Whereas the simple, well-stirred model of hepatic clearance, which assumes passive distributional processes, is still widely employed, it will benefit from expansion to accommodate specific uptake and efflux transporters, in addition to metabolism (51).

Realization of the benefits of PBPK has served as an impetus for identifying and improving methods that obtain the requisite drug input parameter values of the structural model. To varying degrees, these models use in vitro data as inputs, and the process is commonly referred to as in vitro–in vivo extrapolation (IVIVE) (32). In some organizations, the requirement for in vitro input data at the appropriate time during drug development has had a significant impact on the organization of preclinical ADME (absorption, distribution, metabolism, excretion) programs. Much of the validation of in vitro methods is undertaken in animals, primarily the rat, allowing a critical evaluation of the individual components that comprise IVIVE. Ultimately, however, the utility of PBPK-based IVIVE is its ability to predict PK quantitatively in humans. A particular strength of PBPK modeling is the capability, with the use of Monte Carlo methods, to predict variability in PK beyond observed limits and to anticipate individuals whose attributes combine to give extreme PK risk (32, 52–55).

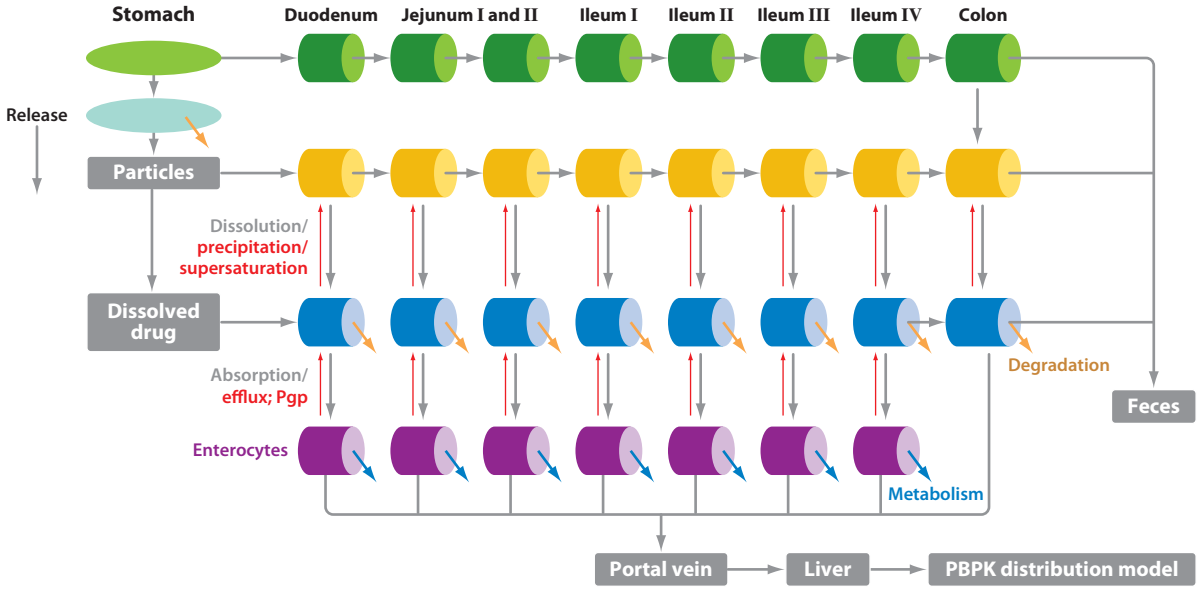


Figure 3

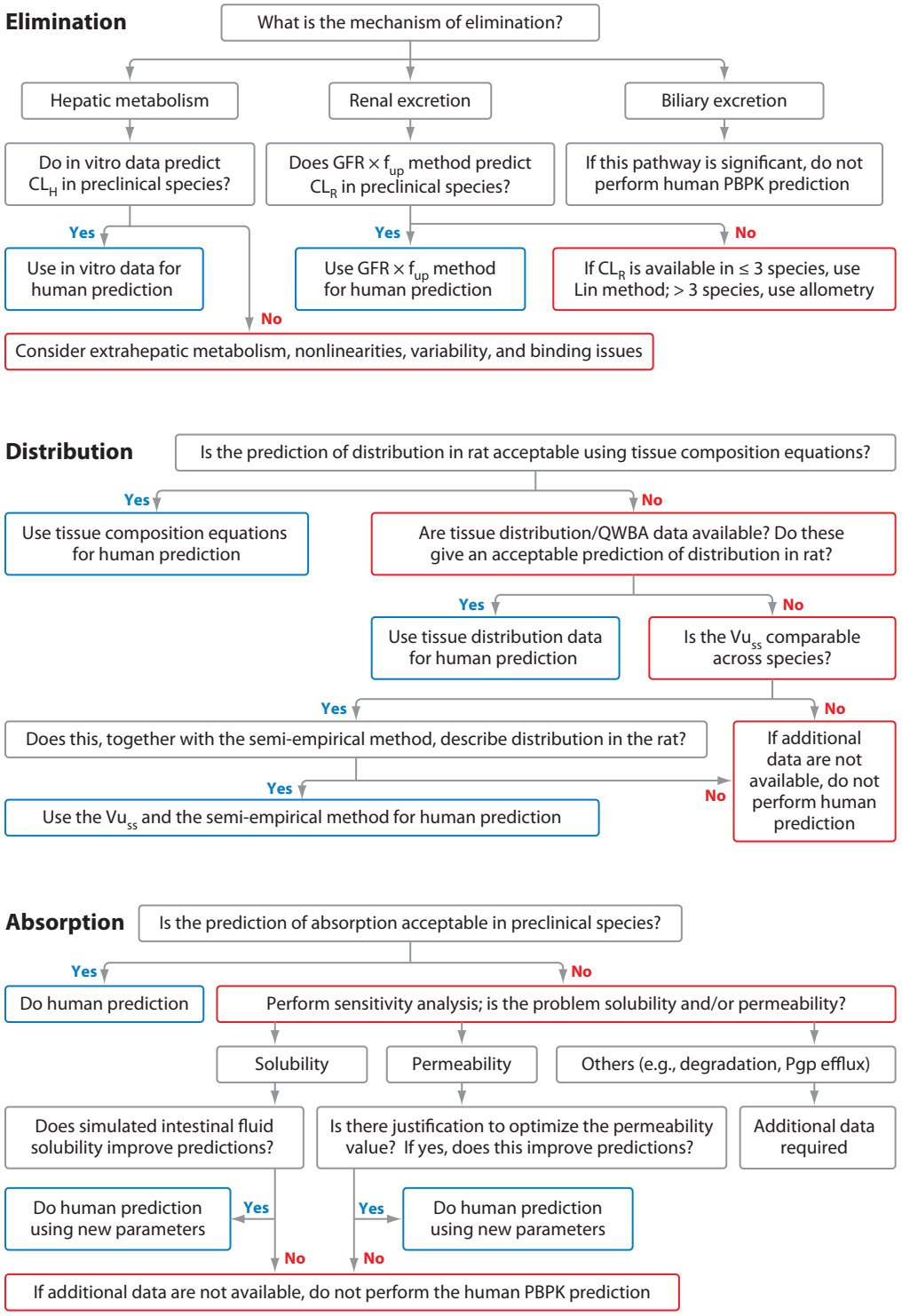
The advanced dissolution, absorption, and metabolism (ADAM) model of events in the gastrointestinal tract. The intestine is divided into segments, each comprising four compartments to account for luminal solid (*green*), particulate (*yellow*), dissolved drug (*blue*), and drug passing through the enterocytes (*purple*), where it may be subject to metabolism and transport (45). Abbreviations: PBPK, physiologically-based pharmacokinetic; Pgp, P-glycoprotein.

PHYSIOLOGICALLY-BASED PHARMACOKINETIC MODELS IN DRUG DEVELOPMENT

In keeping with their data requirements, PBPK models are most readily applied during the final stages of candidate selection, and particularly in clinical drug development, rather than during discovery and compound screening. The earlier processes evaluate large numbers of compounds and must depend primarily on relatively coarse PK and toxicology screens to divide the undesirable drug candidates, according to predefined criteria, from the promising ones. Nevertheless, the early investment in measurement of molecular descriptors and in silico predictions of physicochemical properties—log P (n-octanol/buffer partition coefficient), pKa, and polar surface area—can be informative in estimating some of the compound-specific parameters utilized in a PBPK model [e.g., membrane permeability (56), tissue affinity (57), and nonspecific microsomal binding (58–60)]. Subsequently, as the number of candidate compounds is reduced and as further in vitro information on metabolism and transport accumulates, the confidence in the accuracy of the prediction via PBPK should increase. **Figure 4** illustrates a preclinical approach to the prediction of human PK based on PBPK.

Physiologically-Based Pharmacokinetics Versus Allometry

Knowing the PK of a compound helps calculate not only the first in-human dose but also the drug's ultimate clinical utility. Historically (and still, to a considerable extent, today), a popular approach to the prediction of human PK has been allometry (61), which assumes that the only difference between man and other mammals is size. However, the issue is not that simple. Other mammals invariably differ from humans with regard to the activity and specificity of drug metabolic and



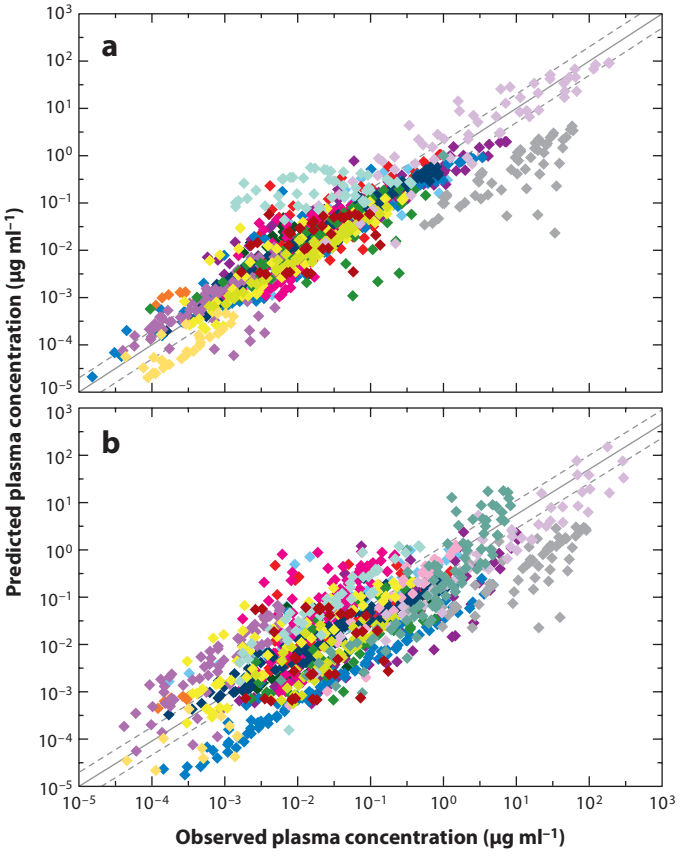


Figure 5

Comparison of observed mean plasma concentrations of 19 compounds with those predicted by (*a*) physiologically-based pharmacokinetic (PBPK) modeling and (*b*) allometry, using the PBPK strategy described in **Figure 4**. Allometry involved the use of pharmacokinetic data from at least three of the following species: mouse, rat, dog, pig, or monkey. Each color represents the data set for a specific compound. Clinical data were available for these compounds at a range of doses after intravenous infusion or oral administration [T. Lave (Roche), personal communication of individual concentration-time data summarized in Jones et al. (197)].

transport processes; gastrointestinal absorption is also quite different. Therefore, the significant imprecision in allometric prediction of the human PK of drugs is not surprising, especially those extensively and slowly metabolized drugs when given orally (61). These are the very compounds that industry has predominantly been developing in recent decades as part of an attempt to produce stable drugs with relatively long exposure times, thereby allowing once-daily dosing. **Figure 5** illustrates an example of improvement of PBPK over allometry.

←

Figure 4

Example of an industrial decision tree for applying physiologically-based pharmacokinetic (PBPK) modeling to predict human pharmacokinetics (PK) before first-in-human studies. Abbreviations: CL_H, hepatic clearance; CL_R, renal clearance; f_{up}, unbound fraction in plasma; GFR, glomerular filtration rate; QWBA, quantitative whole-body autoradiography; Vu_{ss}, steady-state volume of distribution of unbound drug. Adapted from schema in References 197 and 198.

A major requirement of any methodology is accurate prediction of the concentration at any time after drug administration, a key consideration in addressing questions such as whether the intended dosage regimen yields a sufficient concentration at the end of the planned dosing interval to ensure exposure above a critical value, such as the unbound IC_{50} against the target. As commonly applied, allometry often fails in this regard because clearance is combined with a single value for distribution, the volume of distribution, which yields a monoexponential elimination; in practice, on the other hand, PK curves are invariably polyphasic. Although attempts have been made to overcome this problem based on allometric prediction of mean residence time (e.g., Reference 62), the approach still retains many of the deficiencies inherent in allometry.

In contrast to allometry, PBPK can be used to predict the full disposition-time profile, the likely intersubject variability in PK, and the complexities of oral drug absorption as more and more data become available during drug development. Furthermore, apart from human renal clearance, which is predicted reasonably accurately from rat data through allometry, the only drug-related information needed initially are human in vitro metabolic and transporter data coupled with physicochemical and material properties of the compound. Moreover, for highly lipophilic drugs, renal and biliary clearances are predictably low and contribute minimally to total clearance. Consequently, from a research resource point of view, the PBPK approach is both compound and animal sparing. On the other hand, the PBPK approach can be compromised by an inability of in vitro systems to measure accurately the rate of metabolism of slowly cleared drugs, and by problems with obtaining reliable estimates of plasma and nonspecific microsomal binding when this value is very high (<0.1% unbound). The former problem may be overcome by the development of more stable and viable metabolic systems (63), whereas the latter problem may be offset by developments in competitive binding assays (64) and by prediction based on physicochemical properties (65). Alternatively, in problematic areas, the use of microdosing to humans may well help predict the likely PK at pharmacologic doses before full-blown Phase 1 development (66).

Prediction of Drug Clearance

Intense research has been directed toward accurately predicting drug clearance, the global metric that quantifies systemic exposure within the body for a given bioavailable dose or dosing rate (32, 67, 68). Within the context of PBPK modeling, the strategy employed is first to partition clearance into the contributions by individual organs, primarily the liver and kidneys, and then to partition it into individual processes, metabolism and excretion, with further finer stratification as appropriate. The method to predict hepatic metabolic clearance is long standing (69) and comprises three steps (70). The first step is determination of in vitro intrinsic clearance using hepatocytes, microsomes, or recombinant enzymes. The second step involves scaling of intrinsic clearance measured in vitro to a value for the whole liver using a combination of scaling factors (hepatocellularity, milligrams of microsomal protein per gram of liver, specific enzyme abundance, relative enzyme activity, and liver weight). The third and last step involves conversion of the estimated in vivo intrinsic metabolic clearance to net hepatic metabolic clearance using a model of hepatic clearance that incorporates external factors such as hepatic blood flow, plasma-protein binding, and blood cell partitioning. The main liver models used, in decreasing frequency, are the venous equilibrium (well-stirred) model, the dispersion model, and the undistributed sinusoidal (parallel-tube) model. A major difference in outcome among these models is in the predicted fraction of compound escaping the liver, and hence oral bioavailability, for a given intrinsic clearance of high extraction-ratio compounds (71).

Application of the IVIVE approach for predicting drug clearance has been successful, particularly for conventional drug molecules (lipid-soluble molecules with a molecular weight less

than ~300–500 g mol^{-1}). However, this approach is associated with a systematic trend to underprediction for drugs metabolized by cytochrome P450 (CYP) and UDP-glucuronosyltransferase (UGT), particularly when human liver microsomes and hepatocytes are used (e.g., References 72–74). Predictions based on expressed enzymes tend to be more accurate (75). To reach accurate conclusions, the following are essential: attention to the quality of the in vitro data (and the in vivo data, which can be highly variable and limited), use of appropriate scaling factors (76), correction for nonspecific binding in the in vitro preparations (74), and, in specific cases, allowance for active uptake (68). Underprediction can arise from the release of membrane-bound, long-chain unsaturated fatty acids, which act as potent competitive inhibitors of several UGT enzymes and CYP2C9 (77, 78). Thus considerable improvement in prediction may be achieved by addition of albumin or serum to the incubate in order to bind the fatty acids that inhibit some enzymes (77). A body of information on the prediction of clearance by metabolic enzymes other than CYPs and UGTs, particularly involving conjugation reactions mediated by amidases and sulfatases, is currently lacking. Prediction of the role of transporters in hepatic uptake and biliary secretion within the frame of PBPK is advancing and showing promise (38, 79–85). Progress on the determination of scaling factors for individual transporters for IVIVE is being made, but more needs to be done with regard to measurement of their absolute tissue abundance and functionality. Particular difficulties arise in extrapolation with solute carriers, where activity is influenced by the concentration of counter ions. In some PBPK applications, researchers attempt multiple fitting of transport and other parameters rather than using a pure bottom-up approach (86).

Some success has been achieved in predicting first-pass metabolic clearance in the gut wall through use of a minimal physiologically-based model that incorporates a hybrid function of permeability and enterocytic blood flow (87–90). The theoretical basis of this Q_{gut} model has recently been extended with the promise of even greater utility (91).

Few attempts to develop PBPK-based IVIVE of renal clearance have been made (92), which, in part, may be explained by the relatively high success of predicting human values empirically through allometric scaling of animal data (primarily rat data).

Prediction of Drug Distribution

A major limitation of PBPK has been an inability to predict individual tissue distribution in humans. Until recently, the only approach was to administer drug to an animal, measure its distribution in the tissues, and extrapolate tissue partition coefficients to humans. Because this is clearly a long and tedious process with great demands on analytical resources, it was rarely done in the industrial setting. This limitation has largely been overcome by studies linking tissue affinity to tissue composition and physicochemical drug properties. This approach started in the context of environmental chemicals (93) and was successfully extended into the pharmaceutical arena. Initially, investigators considered neutral and weakly acidic lipophilic compounds (94) and showed that tissue affinity depended substantially on neutral and phospholipid tissue content. Although the approach was subsequently refined (95), it performed poorly for moderately strong bases (predominantly ionized at physiological pH). With the recognition that these compounds bind strongly through ion pairing to acid phospholipids, inclusion of these elements along with pH gradients into the model allowed its successful extension to basic drugs (96). Erythrocytes also contain known quantities of acidic phospholipids, thereby helping the prediction process by offering a simple in vitro method of assessing the affinity of drugs for these lipids. Further work has extended the application to acidic drugs and zwitterions (57). A limitation of the approach is that, whereas tissue composition is well defined for the rat, detailed human data are relatively

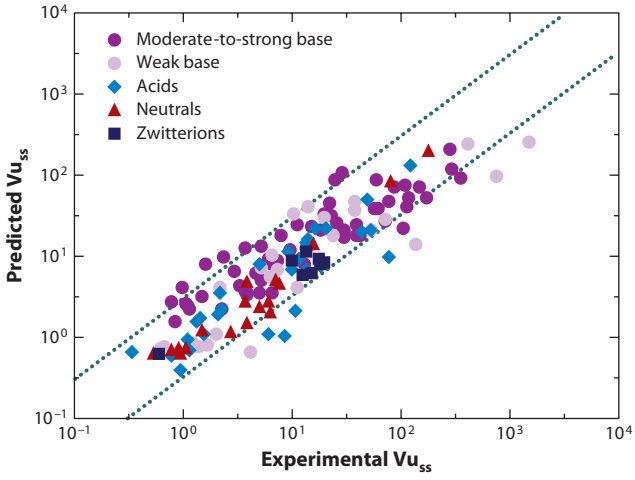


Figure 6

Correlation between observed and physiologically-based pharmacokinetic (PBPK) model–predicted unbound volume of distribution at steady state (Vu_{ss}) for 142 compounds in humans. The lines are threefold on either side of the line of identity (96).

deficient. Although there are similarities, there are also some important differences in the acidic phospholipid content of some tissues that should be taken into account (97, 98).

Although not the primary distributional parameter for PBPK modeling, the only global human measure of tissue affinity is the volume of distribution at steady state, estimated from plasma data obtained following intravenous drug administration. Tested against this global parameter, the in vitro tissue model predicted observations in humans reasonably well (98, 99) (**Figure 6**), although some clear outliers indicate the need for further research. Transporters are not included in the general PBPK tissue model, which also assumes a simple perfusion-rate limitation. Thus further modification is indicated to accommodate the distribution of drugs into specific tissues (e.g., the brain), where permeability or active transport often limits accessibility.

Prediction of Drug Absorption

Inasmuch as the rate and extent of oral bioavailability is an amalgam of pharmaceutical, physiological, and metabolic/transport determinants, the modeling of this process draws on many areas of drug discovery and development that have not always been integrated optimally. The development of comprehensive software is changing this, and the PBPK approach is now applied more frequently in drug candidate selection and formulation development and in the support of regulatory submissions. For example, these applications have addressed the following:

- The impact on oral bioavailability in humans of basic formulation factors (solubility, particle size, and distribution) (100, 101)
- IVIVE of dissolution (102, 103)
- Food effects (104–106)
- Selection of optimal modified-release profiles (45, 107)
- The impact on absorption of regional variability along the gut of enzymes and transporters (e.g., on midazolam, digoxin, and talinolol) (44, 45, 86, 108, 109)
- The extent of interindividual variability in drug absorption (45, 110)
- The justification of biowaivers for poorly soluble/highly permeable compounds (111–113)

Limitations of some of the commercially available PBPK software for the simulation of oral drug absorption are discussed by Sugano (42).

DDI: drug-drug interaction(s)

Prediction of Plasma Drug Concentration: Time Profile

The use of PBPK models to combine predictions of absorption, distribution, and clearance, like no other methodology, allows the full time-course of systemic drug and metabolite exposure to be evaluated realistically under all the conditions and situations likely to be encountered during clinical development and beyond. Linking this ability with preclinical estimates of effective drug concentration (e.g., from receptor binding affinity and animal PK/PD studies) enables the possibility of a priori selection of a safe and informative first-in-human dose. Although commercial PBPK software is increasingly being used within the industry for this latter purpose, there are as yet relatively few published examples based on compounds in development (114, 115).

Prediction of Drug-Drug Interactions

A noteworthy number of drugs have been withdrawn from the market over the past 15 years because of serious and unmanageable drug-drug interactions (DDIs). In many of these cases, the withdrawal has arisen from the inhibition of an enzyme—particularly of CYP3A4—involved in the metabolism of a coadministered drug. The resultant excessive exposure to the drug has in many of the cases precipitated pronounced QT prolongation and torsades de pointes (terfenadine, astemizole, cisapride, levacetylmethadol, dofetilide), rhabdomyolysis (cerivastatin), or both (mibefradil) (116). Arguably, all these interactions could have been predicted from an appreciation of in vitro metabolism. This is further underlined by contemporary examples involving inhibition of the formation of an active metabolite and serious loss of efficacy. For example, epidemiological findings of increased risk of death from breast cancer in patients taking paroxetine with tamoxifen may be explainable by inhibition of CYP2D6 (117). A decrease in the antiplatelet effect of clopidogrel in patients taking omeprazole can be explained by inhibition of CYP2C19, the enzyme responsible for formation of clopidogrel's active metabolite; this DDI has implications for risk of myocardial reinfarction (118).

Advocacy of the use of in vitro studies to predict the extent of inhibition of metabolism in vivo dates back to the early 1990s (119–121). At that time, the risk of metabolically-based DDIs was evaluated in healthy subjects primarily through the use of model substrates such as antipyrine and model inhibitors such as cimetidine, without regard for their enzymology. With advances in understanding of the different isoforms of cytochrome P450 involved in drug metabolism, it became apparent that studies using hepatic microsomes, hepatocytes, and recombinant enzymes could rationalize and focus the selection and design of subsequent in vivo studies with selective substrates and inhibitors. A quantitative paradigm for this IVIVE was outlined (119) based on the change in the area under the plasma drug concentration–time curve (AUC) caused by competitive enzyme inhibition (122). The important determinants of this change were identified as the ratio of the inhibitor concentration (I) at the enzyme site to its inhibition constant (K_i) and the fraction of the dose of the victim drug metabolized by the inhibited enzyme. (The I value is approximated by its unbound plasma concentration in the systemic circulation and, to allow for inhibition on first pass through the liver after oral administration, that estimated in the portal vein; K_i is determined in vitro and corrected for nonspecific binding. Subsequent elaborations of the basic algorithm have incorporated enzyme inhibition in the gut wall on first pass (123–125), the inhibition of glucuronidases as well as CYPs (45), irreversible mechanism-based inhibition (124, 126), and enzyme induction (127–131). Predictions of the extent of the last two of these phenomena require

FDA: U.S. Food and Drug Administration

a knowledge of the degradation rate constant of the affected enzyme(s) [current estimates for CYP3A4 are widely variable (132)] and careful attention to the design of the in vitro experiments to derive the extra parameters needed for extrapolation [k_{inact} and K_I, the rate constant defining the maximal rate of enzyme inactivation and the inhibitor concentration associated with half maximal inactivation, respectively; Ind_{max} and $IndCu_{50}$, the maximal increase in the level of induced enzyme and the unbound inducer concentration associated with half maximal induction, respectively (132–134)].

The equations necessary to predict change in the AUC represent "static" models, and this approach has been reasonably successful in recovering the in vivo extent of CYP-mediated inhibition (competitive and, to a lesser extent, mechanism based), as indicated by many reports from industrial scientists (e.g., References 135–143). In general, when using the more comprehensive equations and appropriate in vitro data, it is possible to make predictions within twofold of observed extent of inhibition in ~80% of cases in which hepatic permeability and transport are not significant issues. Experience in predicting the extent of enzyme induction is more limited but is also encouraging (128–131, 144). The incorporation of DDIs involving transporters remains a continuing challenge (145, 146), and interactions involving the modulation of CYP-mediated metabolism of drugs by cytokines released by therapeutic proteins also require consideration (147).

Nesting interaction with enzymes in the liver and gut within semi- and full PBPK models has allowed a "dynamic" evaluation of the impact of a DDI with respect to the full concentration–time profiles of the interacting compounds (146, 148–150). These dynamic models are more accurate in recovering the extent of metabolic interactions, especially those involving time-dependent changes in enzyme abundance (142, 143, 151, 152). In addition, they have been used to evaluate aspects of experimental design including dosage, choice of dosage form, and the timing of dosage of interacting compounds (153, 154). These models also have been used to assess more complex scenarios involving simultaneous dose-dependent inhibition and induction (124, 155) as well as competition for plasma binding, the inhibitory effects of both parent drug and metabolites (149, 156, 157) (**Figure 7**), the lack of adherence, and multiple DDIs. The latter are a particular regulatory concern and impose prohibitive limitations on in vivo studies to cover the various permutations of combinations. When outcomes are simulated, the worst-case combination(s) can be selected for in vivo evaluation. The latter are most likely to involve the combination of drugs that inhibit different enzymes such that the effects are more than additive, whereas in the case of drugs competing for the same enzyme, the net effect tends to default to that of the more potent compound (124). The most advanced software can accommodate up to three inhibitors and two metabolic profiles (one for substrate and one for an inhibitor), creating a multiplex of autoinhibition, autoinduction, and all permutations of mutual interactions (52).

In evaluation of the risk associated with a particular DDI, PBPK prediction and assessment should not be based solely on what might happen in the mythical average subject; it should also encompass possible extremes in a population (124, 158, 159). For example, renal impairment or the genetic absence of a functional enzyme other than the one being inhibited can markedly amplify the extent of an interaction (124). Unless specific in vivo studies are undertaken to address such issues, the chances of including individuals with the relevant attributes in a typical Phase 1 investigation in healthy subjects are small. Simulating outcomes in virtual populations can provide an early warning of extreme cases before late-phase studies in patients are begun. That an original academic-based perspective (160) has been followed by updates from the pharmaceutical industry (161–163) and the U.S. Food and Drug Administration (FDA) (164–166) is a sign of the maturing of the application of IVIVE and PBPK modeling for the quantitative prediction of DDIs.

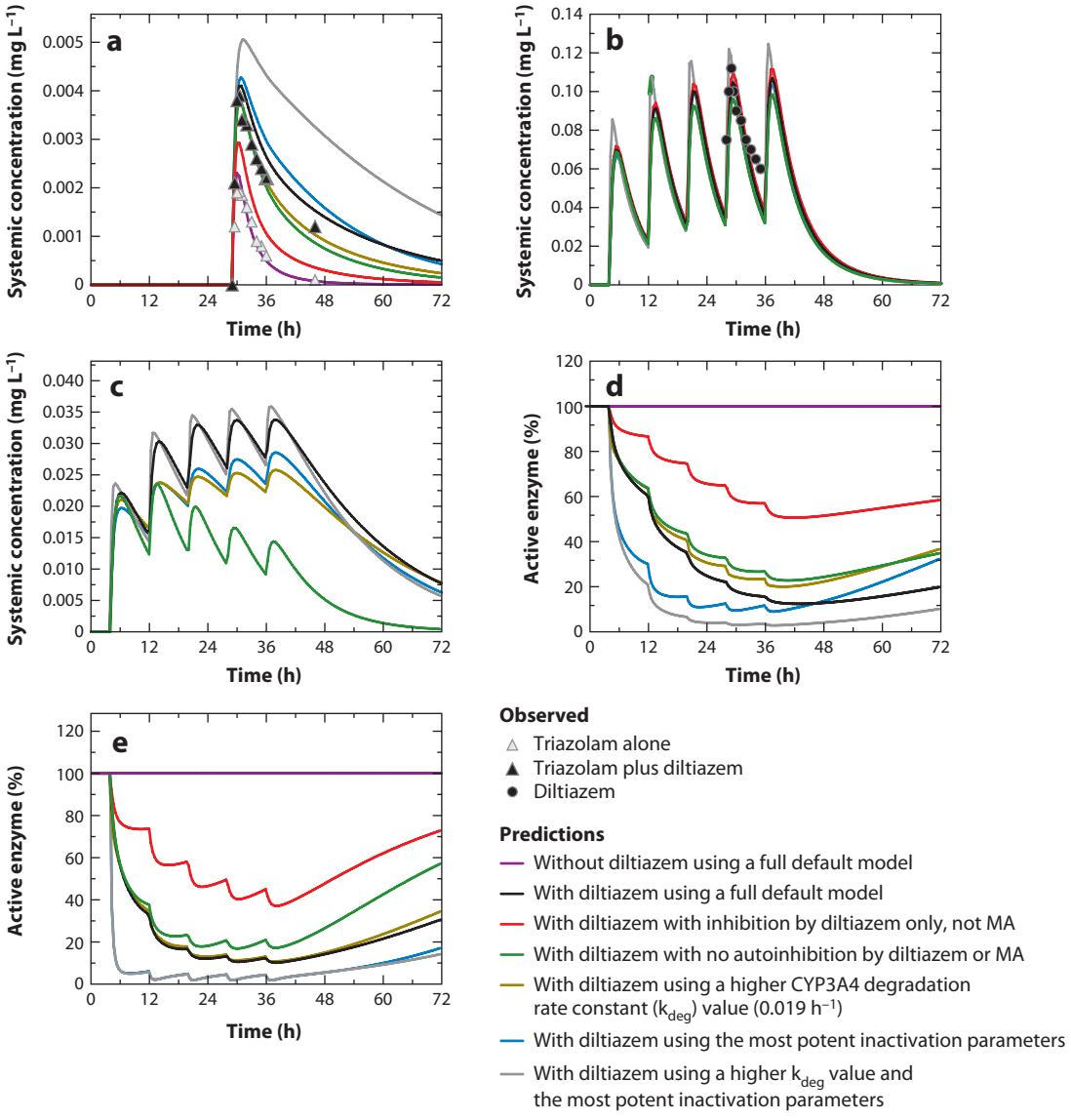


Figure 7

Prediction of the triazolam-diltiazem interaction using physiologically-based pharmacokinetic (PBPK) modeling. Inhibition, both competitive and mechanism-based, and induction are explored. Shown are observed and model-predicted plasma concentration–time profiles of (*a*) triazolam and (*c*) its N-desmethyl metabolite (MA) after a single 0.25-mg oral dose of triazolam, in the absence and presence of diltiazem (60 mg t.i.d.), together with those of diltiazem (*b*). Light gray triangles indicate observed triazolam concentrations when it is administered alone; black triangles indicate coadministration of diltiazem. Black circles correspond to observed diltiazem concentrations. The colored lines indicate predictions based on different assumptions. The predicted changes in hepatic and gut CYP3A content as a result of diltiazem administration are shown in panels *d* and *e*, respectively, under the different assumptions defined above (157).

Prediction of the Effects of Age

With recent regulation requiring studies of new drugs in children and the ethical need for minimizing the burden of such studies, IVIVE and PBPK modeling have the potential to anticipate pharmacokinetic differences in pediatric patients relative to adult patients (167) and to assist in the selection and optimal design of in vivo investigations (168). The value of PK data from juvenile animals is limited, and although allometric scaling of human drug clearance based on body weight raised to the $^3/_4$ power (169) is supported by data on the age dependency of liver volume (170), it does not account for the ontogeny of drug-metabolizing enzymes or transporters. Thus in humans younger than ~2 years of age, a more drug-specific approach is needed to accommodate the differential rates of maturation of drug-metabolizing enzymes; beyond 2 years of age, allometry generally works well. From prior knowledge of the many physiological and enzymatic changes that occur during development, coupled with in vitro information on metabolism by adult enzymes, the IVIVE method has enabled prediction of drug clearance and its variability in neonates, infants, and children with acceptable accuracy (171, 172, 173). These efforts are being extended to the prediction of full concentration–time profiles using PBPK models (174). This extension is relatively tractable for drugs administered intravenously. However, given prior knowledge of changes in organ size, composition, and blood flow, the complexities and variability of the developing gastrointestinal tract pose a considerable challenge in predicting full PK profiles after oral dosing in infants.

Decreases in renal and hepatic clearance of drugs occur with advancing age in adults. The decreases in hepatic clearance largely reflect progressive reduction in liver mass (170), microsomal protein, and hepatocellularity (76), whereas the intrinsic activity of metabolizing enzymes per gram of liver is generally maintained (175). These and other features relating to change in body weight are readily incorporated in existing PBPK models.

Prediction of the Effects of Genetics

To the extent that genetic polymorphisms in drug-metabolizing enzymes and their frequencies across various ethnic groups are well documented, this information has been used to evaluate their impact on drug exposure through the use of simulators that allow stochastic modeling of virtual populations. For example, variability imposed by allelic variants of CYP2C9 with decreased catalytic activity can be addressed in both Caucasian and Asian populations based on successful IVIVE (32, 176). By linking the PK model that incorporates genetic variability in CYP2C9 to an indirect pharmacodynamic model of the anticoagulant effect of S-warfarin, Dickinson et al. (177) were able to assess the power of published pharmacogenetic studies to show differences between the genotypes in both kinetics and clinical response. Jornil et al. (178) report the use of a population-based simulator to assess the impact of polymorphism in CYP2D6 on the PK of paroxetine, including the influence of irreversible autoinhibition of the enzyme. Such simulations clearly can help guide future study designs.

Prediction of the Effects of Disease

In principle, it is possible to incorporate pathological features in PBPK models to predict pharmacokinetics in specific disease states defined by etiology and severity. This has been done outside PBPK modeling through measures of renal function, such as creatinine clearance, to predict changes in renal drug clearance. However, although there is a diverse body of literature documenting changes in relevant parameters in other diseases, systematic attempts to assimilate the

information into PBPK models are only now beginning. As a start, some progress has been made in predicting the effect of liver cirrhosis and its severity as defined by the Child-Pugh classification. Incorporating known changes in hepatic blood flow, CYPs, liver volume, hematocrit, and renal function enabled reasonably accurate prediction of the intravenous kinetics of alfentanil, lidocaine, and levetiracetam (179); the intravenous clearances of midazolam, theophylline, metoprolol, and omeprazole (180); and the oral clearances of midazolam, caffeine, theophylline, metoprolol, nifedipine, quinidine, diclofenac, sildenafil, and omeprazole (180). Current regulatory guidelines on pharmacokinetics in patients with impaired hepatic function recommend the development of PBPK models (181). Accordingly, further refinement of existing models may promote the use of simulations to minimize actual studies. For example, data from a study in Child-Pugh B patients could be combined with a PBPK model to obviate the need for further studies in Child-Pugh A and C patients. A lower risk would be defined in the former, and the difficulties in patient recruitment would be avoided in the latter.

Apart from hepatic disease, in which changes in the gene regulation, expression, and activity of specific drug-metabolizing enzymes are reasonably well established, this kind of information is also beginning to emerge for renal (182) and inflammatory disease (183); it thus will be a vital element of extended PBPK models. Similarly, the documentation of changes in body size, tissue composition, and cardiovascular function associated with obesity offers promise for the development of useful PBPK models that capture pharmacokinetic changes and altered dosage requirements for this condition (184).

REGULATORY SCIENCE

The first known application of PBPK by the FDA was in the 1990s' review and approval of tretinoin, a highly teratogenic active ingredient of topical anti-wrinkle cream (185). In consideration of the potential risk of fetal exposure and birth defects, the FDA requested a PBPK simulation, from which it concluded that the risk is de minimis. The FDA reviewer wrote:

> The data obtained in the clinical studies, and those discussed in the nonclinical pharmacokinetic section [of this FDA review] were used to develop a physiologically-based pharmacokinetic model. The model was used to estimate maternal and fetal plasma concentrations of tretinoin and its metabolites in a theoretical abuse situation, i.e., after excessive application to face, lower arms, chest and neck and assuming exaggerated absorption of 10%. This model demonstrated that the systemic concentrations of tretinoin and potentially toxic metabolites achieved under such conditions remained several orders of magnitude below endogenous concentration and minimally teratogenic dose of retinoic acid. (186, p. 19)

Although the 2002 workshop on PBPK in drug development and regulation (18) revealed little active regulatory use of this technique, since that time the FDA has increasingly employed PBPK modeling and simulation for policy development and product review of both new and generic drugs. For example, to clarify guidance for the appropriate dosing regimen of the CYP3A4 inhibitor ketoconazole in DDI studies, PBPK was employed to evaluate the extent of CYP3A4 inhibition applied to the expected range of substrate bioavailability and half-life values (154). FDA scientists concluded that "there is not a single optimal design for drug interaction evaluation: one must consider the pharmacokinetic characteristics of both substrates and inhibitors when designing in vivo drug interaction studies. We encourage the study sponsors to use [PBPK] modeling and simulation to determine the best dosing strategy" (187). FDA application of PBPK has also

been applied to other complexities of drug metabolism and drug interactions, including simultaneous effects of multiple CYP enzyme inhibitors, inducers, and transporters; drug interactions in patients with renal and hepatic impairment as well as those at the extremes of relevant genetic polymorphisms; and the impact of inhibitory metabolites (116, 147, 154, 164–166, 188, 189). PBPK models have also been identified as an approach to predicting the impact of transporters on various PK processes and drug interactions (190).

In addition, PBPK approaches have been included in the FDA lactation guidance (191) and encouraged by both the FDA and European Medicines Agency for application in pediatric medicine development (167, 168). PBPK is also emerging as an important regulatory tool for the development of generic drug policy and standards (41). For example, in the generics drug review section of the FDA, the following challenging policy issues are being investigated through the use of PBPK techniques: biowaivers for Biopharmaceutical Classification System Class II and III drugs; assessment of the equivalence of products containing drugs that exhibit multiple concentration peaks; assessment of locally acting gastrointestinal drugs and those administered by topical and pulmonary routes; methods for characterizing complex products; drug release profile criteria; improved in vitro–in vivo correlation (IVIVC); prediction of alcohol-induced dose-dumping; and the evaluation of formulations involving liposomes, nanotechnology, and multiple-component mixtures (192).

THE FUTURE

In the near future, we expect continued improvement in the ability to apply existing PBPK models to predict the effects of transporters in specific organs, alongside the increased application of imaging technology to assess the in vivo roles of these proteins. There will also be an expansion of the ability of PBPK to simulate the impact of specific diseases (in individuals, clinical trials, and entire populations), a linking of PBPK with improved in silico tools for prediction of physicochemical and functional properties of drug molecules, and further linking of PBPK to pharmacodynamic models and models of systems biology. PBPK will diminish the need for studies in animals to predict human PK and enable much, if not all, of the learning of the clinical PK of a drug to be complete by Phase II. An alternative philosophical approach to classical PBPK modeling is synthetic modeling, which seeks to understand complex systems based on the simulation of discrete events that involve spatial interaction between drug molecules and specific cellular components (e.g., enzymes and transporters) (193). However, although synthetic modeling promises to be useful for hypothesis generation, its general applicability in drug development is further in the future.

A major development in PK modeling is likely to be the merging of the bottom-up and top-down approaches with the incorporation of powerful parameter-estimation methods (including sparse data methods such as mixed effects and Bayesian maximum-likelihood procedures) within PBPK software to integrate the experimental data gained during clinical development. PBPK, through simulation of outcomes in virtual populations, will increasingly be used to inform the design of classical population PK (POPPK) studies (188) and to assess the studies' statistical power to identify covariates (194). Prior recognition of significant covariates from the bottom-up approach, which can then be incorporated into the process of POPPK modeling, could improve the utility of this approach to data analysis. For example, whereas Fanta et al. (195) used the POPPK approach to identify hematocrit as a significant covariate of the PK of cyclosporine in children, this result could also be predicted by applying prior knowledge of blood binding and the impact of red cell volume on circulating concentrations of the drug (52). Although PBPK is primarily a tool of the preclinical scientist, there is a clear need to eliminate the distinction

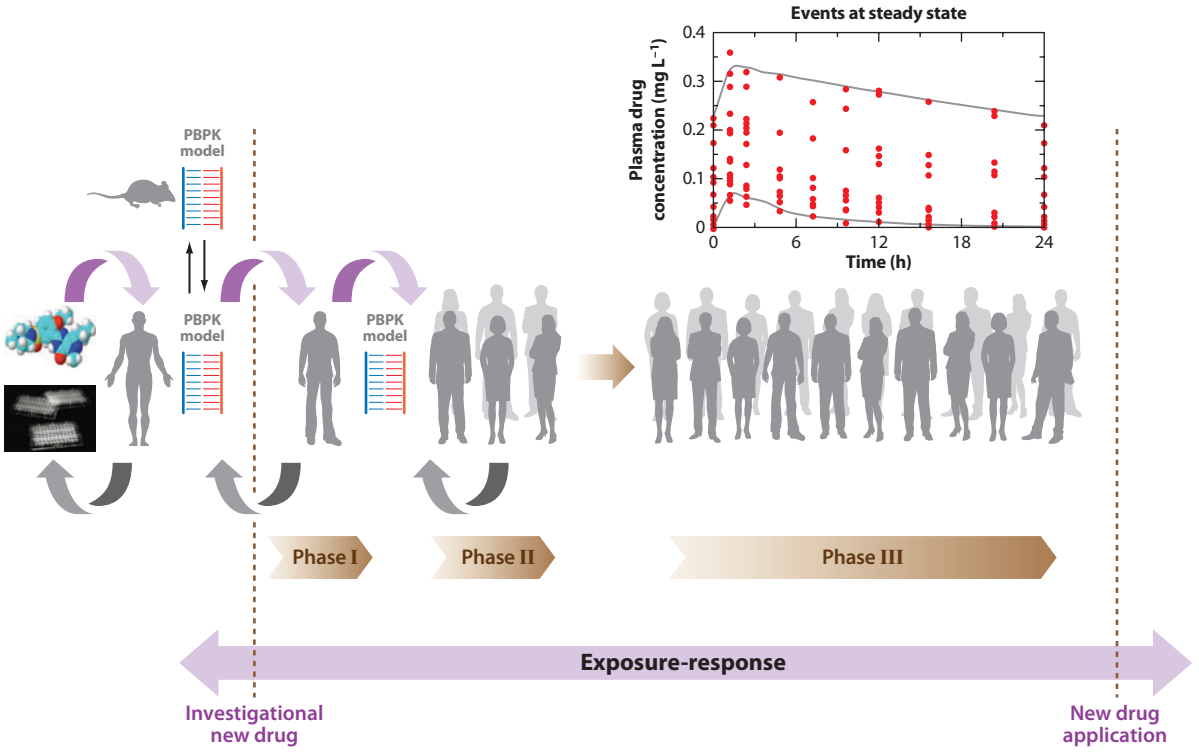


Figure 8

A vision of how physiologically-based pharmacokinetic (PBPK) models will be used in candidate selection and drug development. Compounds within a target pharmacokinetic (PK) profile are predicted through the use of a PBPK model that incorporates a combination of physicochemical and material properties together with in vitro human data. Other important selection criteria, such as limited propensity for drug-drug interactions and expected variability within the target patient population, will also be evaluated at this stage through the PBPK model. Apart from safety and efficacy assessments, animal PK studies of the selected compounds will be undertaken only to critically evaluate less certain aspects of the model, if necessary. For the compounds selected to go forward, predictions of the required first-dose range in humans—based on both PK and pharmacodynamic (PD) considerations—will then be made. Experimental human data collected during Phases I and II will be used to further inform and refine the retained PBPK model through feedback, such that all the learning of the PK of the compound will be completed by the end of Phase II. The model will then be used to help plan Phase III studies and beyond. Sparse PK data will be collected in Phase III (*red circles in top-right graph*) and checked to determine whether the observations are within the expected prediction envelope for the drug (5–95% window shown). Experimental PK data in Phases II and III will also be used to establish exposure-response relationships and associated PK/PD models, which will, in turn, be used to support the claims for, and the labeling of, the drug. The forward and backward curved arrows represent the continuous learning and confirming nature of the process from candidate selection through Phase III clinical development.

between the preclinical and clinical modeler, which would make PBPK software a universal tool within the industry (**Figure 8**).

The cultural resistance to PBPK within industry and regulatory agencies, which is already beginning to decline, will decrease further as the benefits in decision making and cost-effectiveness are more widely recognized. Education in PBPK within academia will increase, as will training of staff within industry to meet the increasing need for the appropriate skills. The application of PBPK is fueling a radical paradigm shift that supplants the contemporary empirical R&D sequence of observation-intensive animal and human studies, with a resource-sparing, predictive approach that emphasizes limited human trials to confirm PBPK-based predictions.

Finally, whereas PBPK is coming of age in drug development and is now being recognized as a useful tool in regulatory assessment, its potential use in the health care arena as an educational tool and for the provision of advice on personalized drug dosage will begin to emerge. One day, when sufficient information is available in a patient, clinicians will be able to link that person to his or her virtual twin within a PBPK model to provide safe, effective, individualized dosage and to avoid undesired drug-drug interactions.

DISCLOSURE STATEMENT

M.R. and C.P. are members of the Scientific Advisory Board of Simcyp Ltd. (Sheffield S2 4SU, United Kingdom). They hold no shares in the company. G.T. is chairman of Simcyp Ltd. and a shareholder in the company. The company, in association with a consortium of international pharmaceutical companies, has a platform for the simulation and prediction of the pharmacokinetics of drugs based on in vitro data and physiologically-based pharmacokinetic modeling.

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