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Challenges and opportunities with modelling and simulation in drug discovery and drug development

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Abstract

The benefits of modelling and simulation at the pre-clinical stage of drug development can be realized through formal and realistic integration of data on physicochemical properties, pharmacokinetics, pharmacodynamics, formulation and safety. Such data integration and the powerful combination of physiologically based pharmacokinetic (PBPK) with pharmacokinetic–pharmacodynamic relationship (PK/PD) models provides the basis for quantitative outputs allowing comparisons across compounds and resulting in improved decision-making during the selection process. Such PBPK/PD evaluations provide crucial information on the potency and safety of drug candidates *in vivo* and the bridging of the PK/PD concept established during the pre-clinical phase to clinical studies. Modelling and simulation is required to address a number of key questions at the various stages of the drug-discovery and -development process. Such questions include the following. (1) What is the expected human PK profile for potential clinical candidate(s)? (2) Is this profile and its associated PD adequate for the given indication? (3) What is the optimal dosing schedule with respect to safety and efficacy? (4) Is a food effect expected? (5) How can formulation be improved and what is the potential benefit? (6) What is the expected variability and uncertainty in the predictions?

Keywords: *Modelling and simulation, pharmacokinetics, pharmacodynamics, physiologically based pharmacokinetics, physiologically based pharmacokinetic (PBPK), pharmacokinetic–pharmacodynamic relationship (PK/PD)*

Introduction

In drug discovery and pre-clinical development drug candidates are characterized for physico-chemical properties, absorption, metabolism, distribution and excretion (ADME), efficacy and safety in a variety of animal models and *in vitro* systems (Leahy 2004).

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This vast amount of data is used to drive the decision-making process as compounds move into development.

Biological mechanism-based models allow separation of biological and compound-specific components and are thus, by design, capable of integrating information about various processes, related to pharmacokinetics, pharmacodynamics (both efficacy and toxicity), and formulation. They can be used not only to estimate summary *in vivo* pharmacokinetic parameters, but also to predict the complete drug concentration and effect time-course *in vivo*. Use of such models can have a major impact during all phases of drug discovery and development and may ultimately result in significant cost reductions for the pharmaceutical industry (Table I). Key questions addressed by modelling and simulation

Table I. Modelling and simulation contributions at various stages in pre-clinical and clinical development.

Stage	Key activities	Impact
Lead optimization	Mechanistic/physiological model of absorption	Guide the screening cascade for more focused experimentation
	Predictive PK using PBPK modelling with *in silico* and *in vitro* data as inputs	Preserve resources by determining compounds likely to have good PK before *in vivo* experimentation
Clinical candidate selection	Mechanistic/physiological model of absorption	Identify critical pharmaceutical issues such as active metabolites that may impact development of the compound
	PBPK modelling to predict human PK and efficacious dose	Provide realistic prediction of human PK and dose required to achieve efficacy
	PK/PD modelling for both efficacious and toxic PD effects	Select the compound that has the greatest likelihood of achieving efficacy while avoiding adverse effects
	Use Monte Carlo techniques to simulate PK behaviour of populations (healthy individual and/or disease population)	Provide a basis for understanding risks and likely efficacy in a realistic population instead of in an average person
	Identify key uncertainties	Provide tool for focusing experimentation to obtain critical information
Entry into human	Further refine PBPK/PD models to simulate clinical trial	Use simulation for optimizing the design of clinical trial
	Mechanistic/physiological models of absorption	Provide prediction of food effects and assist with clinical trial design
Clinical development	PBPK/PD modelling	Provide feedback to project team on their methods for predicting human PK and PD behaviour
	Refine modelling of behaviour of population (healthy individual and/or disease population)	Assist in the optimization of therapeutic dose levels
		Use results in from early stages of clinical development to further refine clinical trial design and clinical plan

include the following. (1) What is the expected human PK profile for potential clinical candidate(s)? (2) Is this profile and its associated PD adequate for the given indication? (3) What is the optimal dosing schedule with respect to safety and efficacy? (4) Is a food effect expected? (5) How can formulation be improved and what is the potential benefit? (6) What is the expected variability and uncertainty in the predictions?

This paper describes how we apply modelling and simulation to address these questions at the various stages of the drug-discovery and -development process and covers some methodological aspects mainly related to physiologically based modelling.

Methodological aspects

The need for integration of data from diverse sources including physicochemistry, pharmacokinetics, formulation, pharmacodynamics, and toxicology has led to an increased use of mechanism-based models during drug discovery and the early phases of drug development.

Physiologically based absorption, distribution, metabolism and elimination (ADME) modelling

Physiologically based models for ADME divide the body into anatomically and physiologically meaningful compartments, including the gastrointestinal tract for absorption, the eliminating organs (e.g. kidney and liver), and non-eliminating tissue compartments (such as fat, muscle, brain, etc.) and connects these by the circulatory system (Figure 1).

The models use physiological and species-specific parameters (such as local pH in the gastrointestinal tract, blood flow rates to tissues, tissue volumes, enzyme abundance)

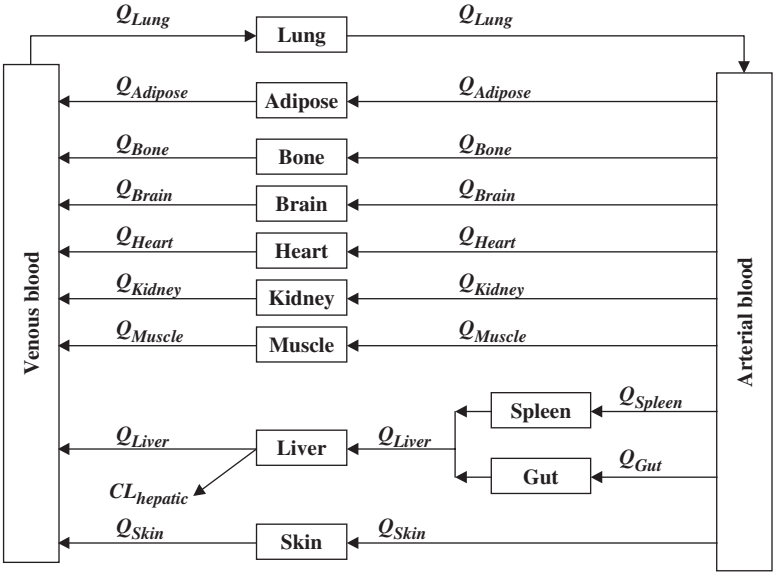

Figure 1. Physiologically based pharmacokinetic model (PBPK).

to describe the ADME processes. These physiological parameters are coupled to compound-specific parameters such as physicochemical and biochemical parameters (e.g. tissue/blood distribution coefficients and metabolic clearance) to predict the plasma and tissue concentration versus time profiles of a compound in an *in vivo* (animal or human) system following intravenous or oral administration.

Excellent reviews of whole-body physiological models have been published recently (Rowland 1985; Andersen 1995a, 1995b; Andersen et al. 1995; Nestorov et al. 1998; Nestorov 2003, 2007; Leahy 2004; Rowland et al. 2004; Clewell et al. 2007).

This approach to ADME modelling should be used whenever possible as an alternative to purely empirical methods such as the widely used non-compartmental analysis or descriptive models such as a sum of exponentials. Empirical methods require prior *in vivo* experiment to measure concentration profiles which can then be described and characterized via derived PK parameters such as clearance, volume, and half-life. In contrast, the physiologically based pharmacokinetic (PBPK) approach simulates and predicts the time-course of drug concentrations based on prior knowledge of the physiology of the test species and the physicochemical and biochemical properties of the drug. This PBPK prediction takes account of, as far as possible, all available knowledge on the compound. Thus, much of the *in vitro* data generated during pre-clinical screening of drug candidates may be incorporated in a meaningful way (e.g. lipophilicity, ionization, protein binding, microsomal clearance, solubility, and permeability) (Clewell et al. 2007). The comparison of PBPK-simulated profiles to actual measurement becomes a confirmatory step used to assess the reliability of the model and the underlying assumptions. A mismatch of simulation and observation may indicate that processes omitted from the current model are significant and need to be better characterized for a full understanding of compound behaviour (e.g. additional clearance routes, active processes, enterohepatic circulation, etc.) and can ultimately lead to an improved understanding of the compound. Clearly, the insight achieved via integration of multiple types of data in a realistic framework is not achievable using empirical approaches. Additionally, the model framework characterized by known physiological parameters for blood flows and tissue volumes provides a rational approach to interspecies scaling. Specific biochemical factors with known species differences measurable *in vitro* are readily incorporated. This mechanistic framework results in significant advantages in predictive power for the first in human study (Jones et al. 2006b).

The integrative nature of the PBPK model also facilitates communication between different drug-discovery team members and between pre-clinical and clinical teams. Thus, the medicinal chemist can relate structural changes to changes in compound properties and via the PBPK model to changes in pharmacokinetics. The formulation scientist can explore the effects of dosage form changes with different release characteristics on overall *in vivo* exposure. The pharmacologist can use the PK model to simulate concentration profiles during PD experiments under different doses or dose regimens and thus better understand the concentration–effect relationship.

Adaptability is one of the powerful features of PBPK models allowing them to evolve from generic into compound-specific models (Luepfert and Reichel 2005). The process of model adaptation is driven by the hypothesis that triggers an appropriate experimental assay generating additional compound-specific data on the PK process to be incorporated into the model. This way PK processes can be evaluated until the PBPK model contains all relevant factors, i.e. has evolved from a generic to a compound-specific PBPK model. Potential model refinements are illustrated on Figure 2. The process of PBPK model adaptation provides an ideal basis for data and knowledge integration as compounds move through the discovery and development phases and allows the subsequent phase of drug development

	Absorption	Clearance	Distribution
Generic	HT solubility(Thesa) PAMPA orin silico Peff	Liver microsomes Well stirred model LM Binding in silico	Tissue composition Perfusion limited
Refined	Fessif/ fassifsolubility Caco2 perm eability Gut metabolism Efflux / Influx transport GI fluid degradation Formulation effects	Hepatocytes Renal clearance Biliary excretion Transport processes Intestinal metabolism Binding (plasma, liver)	Permeability limited Measured K In vivo Vss Transport

Figure 2. Assumptions for generic physiologically based pharmacokinetic (PBPK) models and potential refinements.

to become much more efficient. Required studies can be rationally designed based on a highly integrated understanding of the compound being prepared for entry into human.

The variability and uncertainty associated with the PBPK simulations require special attention. It is important to distinguish uncertainty from variability. Uncertainty can be defined as the possible error in estimating the 'true' value of a parameter. Variability, on the other hand, represents true inter-individual and inter-occasion differences. Thus, uncertainty is a defect that can typically be reduced by experimentation, and variability is a fact of life (Clewell et al. 2007). In practice, it is often difficult to differentiate the contribution of variability and uncertainty to the observed variation in the reported measurements of a particular parameter (Clewell et al. 2007). As is apparent from the literature and available clinical data (Nestorov 2007, Rostami-Hodjegan and Tucker 2007, Willmann et al. 2007) there is a large degree of variability in the population both in terms of physiology (tissue volumes, blood flows, transit times, etc.) and biochemistry (plasma binding, cytochrome P450 (CYP) expression and activity, etc.). In order to produce predictions that are more representative of the target population, this variability together with any uncertainty (variations due to assumptions, hypotheses, handling of system, etc.) must be accounted for. The incorporation of these factors can be translated into a measure of confidence in the prediction. Several important theoretical and applied contributions focused on estimating, handling, and accounting for uncertainty and variability in PBPK models have recently been reported in the area of sensitivity and uncertainty analysis of PBPK models (Nestorov 2001, 2003, 2007; Gueorguieva et al. 2006b), Monte Carlo PBPK modelling and simulation (Kato et al. 2003), population PBPK models (Meibohm et al. 2005), Bayesian PBPK estimation and modelling (Gueorguieva et al. 2006a), and fuzzy approaches (Gueorguieva et al. 2004). Very simple techniques can also be used as a way to communicate uncertainty effectively. By simply determining the minimum and maximum value of an uncertain but important model parameter, and performing a simulation for a range of values, the impact of that parameter on PK predictions can be illustrated (Clewell et al. 2007). Quantifying key uncertainties and providing a range of possible

Table II. User-friendly software packages for PBPK modelling.

Software	Developer	Website	Description
Simcyp®	Simcyp	http://www.simcyp.com	Clinical trial simulator for PK and DDI studies with PBPK modelling capabilities and algorithms for scaling *in vitro* data
GastroPlus™	Simulations Plus, Inc.	http://www.simulations-plus.com	Software for predicting oral absorption in humans and pre-clinical species that has a module for PBPK modelling
PK-Sim™	Bayer Technology Services	http://www.pksim.com/	Software for oral absorption and PBPK modelling in pre-clinical species and humans that can simulate physiological variability in response
MEDICI-PK™	CiT Computing in Technology GmbH	http://www.cit-wulkow.de/	Software for PBPK modelling of drug and multiple metabolites and interactions in humans and pre-clinical species
Cloe PK™	Cyprotex	http://www.cyprotex.com	Tool aimed at prediction of rat and human PK at the earliest stages of drug discovery based on early pre-clinical data

outcomes that could all be reasonable based on the current knowledge of the PK properties of the compound will allow for more informed decision-making.

Advances in modelling and simulation tools

Several commercially available software packages with generic PBPK models for humans or pre-clinical species and PBPK/PD modelling capabilities are now available (Table II). Many of these tools can be applied through all stages of pre-clinical and clinical development and are designed for use in the pharmaceutical industry. They are user-friendly, fast, flexible, and require reasonable mathematical expertise from the user. To increase the throughput of these tools, information technology specialists can work with the software to facilitate fast and automated import of data and export of results.

These software packages are exceptionally useful tools for understanding, exploration, prediction, and visualization, and are enjoying increasing use in the pharmaceutical industry. Nevertheless, the practical experience shows the importance of a modelling and simulation scientist who can guide scientists in appropriate use, performs validation exercises, follows new developments, and keeps a deep understanding of the underlying mathematical model for a critical understanding of the output. Upon introduction of the software, methodological conservatism, and inertia should not be underestimated.

Pharmacokinetic–pharmacodynamic relationship (PK/PD) modelling

Drug discovery and early clinical development can benefit in many ways from integration of PK/PD concepts. Understanding the concentration–effect relationship as early as possible

during drug discovery is crucial as the optimal pharmacokinetic properties of compounds need to be defined in the context of their relationship to the efficacy profile. At these discovery and early development stages a wide range of doses and exposures are tested allowing a complete evaluation of the dose concentration–effect relationship for therapeutic and toxic effects. PK/PD evaluations provide crucial information on the potency and tolerability of the drug *in vivo* and the bridging of the PK/PD concept established during the pre-clinical phase to clinical studies. PK/PD analysis is a multilayered process starting with plotting the right data in the right way (include/exclude protein binding, assuming minimal/maximal effect, assuming direct effect/hysteresis, etc.), getting more elaborate with building simple empirical (data-driven) models (direct effect/indirect effect, etc.), comparisons with calculated receptor occupancy based on exposures and *in vitro* binding measurements to more mechanistically or physiologically based models typically combining data from very heterogeneous sources (e.g. in-house concentration time-course, *in vitro* parameters, and literature data from competitors).

The time-course of drug effects is the result of many factors including formulation, pharmacokinetic, and pharmacodynamic properties as well as physiological factors such as circadian rhythms, homeostatic mechanisms, and disease progression. Given this complexity, the analysis of the time-course of drug response using PK/PD models represents a much more efficient way to deal with pharmacological effects than the use of simple methods based upon single parameters such as onset time, peak effects, or integrated effects such as the area under time versus effect curves. By fitting models reflecting the drug (biopharmaceutics, pharmacokinetics, and pharmacodynamics) and system properties to the data, a description of the entire response versus time profile is obtained. There are a number of potential complexities in the time-course of drug action: delayed distribution from plasma to the effect site, indirect mechanisms of action, irreversible binding to receptor, development of tolerance, rebound, metabolite interactions, changes in protein binding, and irreversible effects. However, different models have been developed to describe each of these situations. Current methods of integrating various system complexities into these models have been reviewed recently (Mager et al. 2003; Danhof et al. 2007). PK/PD models are useful not only to describe data, but also to predict behaviours under different dose regimens, to plan new experiments, and eventually to predict clinical effects. PK/PD concepts are currently being implemented as early as possible in drug development to integrate the current knowledge about mechanism of drug action and disease or system progression, and feedback knowledge from the clinic to research.

Impact of modelling and simulation during drug discovery and non-clinical development

This section provides examples of how modelling and simulation can add value during lead identification and lead optimization where very limited data are available, during clinical candidate selection where more data are available, and during early drug development where a rich data set is available before and after entry into humans. The impact of an appropriate use of modelling and simulation during these phases include support for definition of target profile at the start of lead optimization; simulation of *in vivo* PK/PD profiles during lead optimization and before *in vivo* experiment; prioritization and selection of clinical candidates; rational prediction of PK/PD in man; support for safety assessment; assessment of formulation/food effects; and quantitative prediction of drug–drug interactions in man based on *in vitro* data.

Lead identification and lead optimization stages: definition of target profile

During these phases high-throughput chemistry generates numerous compounds and the physicochemical, pharmacokinetic, and pharmacological properties targeted within a particular project need to be defined. Since PBPK/PD models integrate all properties in a single framework (Figure 3), they can be extremely useful to define the range of properties needed to achieve a desired clinical outcome in terms of extent and duration of effect.

Lead optimization stage: simulation of in vivo PK/PD profiles before any in vivo experiments based on high-throughout data

Efforts to reduce, refine and replace animal experiments within the industry are a current focus. Also determination of *in vivo* PK is considerably more costly and slower than *in vitro* screening, and so whenever possible there is interest in using simulation to optimize use of experimental resources. PBPK can be used at this stage to prioritize compounds for *in vivo* experimentation, giving an estimate of the expected PK profile of new drug candidates in man and providing some mechanistic understanding of the compound's properties and of the relevance of the assays used in the screening strategy.

PBPK modelling allows determination of the mechanisms consistent with the observed *in vivo* data and when simulation does not adequately describe animal PK data this may indicate that a biological phenomenon affecting PK has not been included in the model or is not represented by the assays used to screen the compounds. The emerging technology of generic PBPK modelling has been shown in recent studies to have potential as a tool for assessing the PK of compounds in the early stages of drug development. For example, recent papers reported studies applying generic PBPK modelling to predict rat PK and human PK (Brightman et al. 2006a, 2006b) following intravenous administration of test compound. Also Parrott et al. (2005b) studied generic PBPK modelling to predict rat PK following both intravenous and oral administration of test compound and showed that generic simulation may be applicable for typical drug-like compounds to predict differences in PK parameters of more than twofold based upon minimal measured input data. However, the results indicated that some caution is required since certain chemical classes were poorly predicted

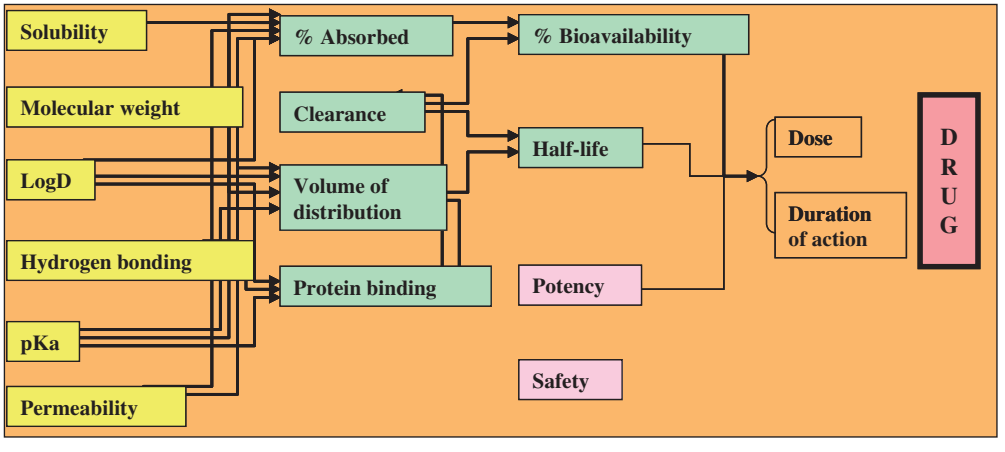

Figure 3. PBPK/PD models integrate all properties in a single framework.

and it was recommended that generic PBPK models should only be applied for prioritization after verification of the simulations with *in vivo* pharmacokinetics for a few compounds of a given chemical class.

Clinical candidate selection: simulation

PBPK has a great potential to assist clinical candidate selection where numerous factors must be considered and data related to the PK and PD of a compound need to be combined and compared in a rational way. This potential was illustrated by Parrott et al. (2005a) who demonstrated the use of PBPK modelling to select the best clinical lead from among five candidates. The pre-clinical data for the five candidates was integrated and the efficacious human doses and associated exposures were estimated. The PBPK models were linked to a PD model so that the dose resulting in a 90% effect could be identified. This example showed that the PBPK approach facilitates a sound decision on the selection of the optimal molecule to be progressed by integrating the available information and focusing the attention onto the expected properties in human. Importantly, the method can include estimates of variability and uncertainty in the predictions to allow decisions to be based on significant differences between the compounds.

Entry into human: empirical versus physiologically based approaches for predictions of human PK

Recently, empirical and PBPK approaches were compared for the prediction of human pharmacokinetics using 19 diverse compounds taken from recent clinical development projects at Roche (Jones et al. 2006b). As a result of this evaluation a strategy for predicting human PK was proposed whereby the ability of PBPK modelling to predict PK is verified as a first step in pre-clinical species, and the human PK is only predicted if the model could predict PK in pre-clinical species (Figure 4). In addition, algorithms were proposed

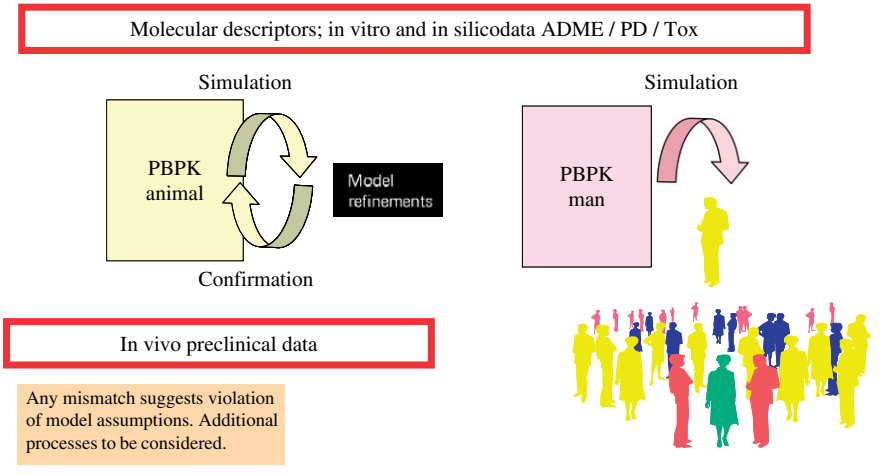

Figure 4. Strategy for predicting human PK.

for model development and data gathering for a better understanding of absorption, distribution, elimination and of the likely human PK behaviour.

Based on this strategy proposed, a human PK prediction could be made for 70% of compounds studied. Furthermore, the prediction accuracy for these compounds in terms of the percentage of compounds with an average fold error of less than twofold was 83, 50, 75, 67, 92 and 100% for apparent oral clearance (CL/*F*), apparent volume of distribution during terminal phase after oral administration (V_z/F), terminal elimination half-life ($t_{½}$), peak plasma concentration (C_{max}), area under the plasma concentration–time curve (AUC), and t_{max}, respectively. Simulated plasma concentrations and PK parameters were compared with human data so that the accuracy of the prediction methods could be assessed. The human PK data were more accurately predicted by the PBPK modelling approach than by the empirical approach (Jones et al. 2006b).

Poor predictions with PBPK models are often a result of incomplete knowledge resulting in processes omitted from the model (e.g. for biliary clearance and enterohepatic recirculation there are limited options for quantitatively predicting the effects on human PK). For such situations, an alternative method of performing the human PK extrapolation (e.g. allometric scaling) might seem attractive. However, based on the Roche data set, there is no reason to believe that allometric scaling or other empirical methods will work if PBPK modelling does not appear to be a good method for predicting the human PK for a compound.

The strategy for prediction to man is now being applied prospectively at Roche and the accuracy of the predictions using PBPK as well as its superiority over more empirical approaches has been confirmed. Predicted versus observed profiles are illustrated in Figure 5 for the lowest and highest doses tested in phase 1 for four projects. The predicted data were in good agreement with the observed data at high doses. At low doses, the levels for project 4 were significantly overestimated. This was most likely the result of binding to the target which was not accounted for in the model. The impact of such specific binding on the plasma concentration versus time profile became negligible as the dose and exposures were increased. At the expected therapeutic dose, the plasma levels were consistent with the expectations so that the prediction was still considered useful in the project.

Physiologically based approaches to simulate the impact of food and formulation effects on human PK

The use of physiologically based models has recently been extended to the simulation of food and formulation effects (Jones et al. 2006a). Thus, it was shown that biorelevant solubility tests can be used together with physiologically based absorption models to predict clinical food effects caused by solubility and/or dissolution rate limitations and by degradation in the gastrointestinal tract (Jones et al. 2006). For six Roche compounds, the simulations captured well the magnitude of the food effect and for the majority of compounds correctly predicted the observed plasma exposure in fasted, fed and high fat diet conditions. In this latter study, the suitability of the dog as a model for human absorption was also explored as this model is often used to investigate the potential for absorption related food effects in human. For compounds where absorption is enhanced in the presence of food, the relevance of this animal model is doubtful due to the differences in gastrointestinal physiology and composition of intestinal fluids between dog and human (Dressman 1986); Paulson et al. (2001) observed that the food effect of celecoxib was threefold greater in the dog than in human. As reported by Jones et al. (2006a) the food

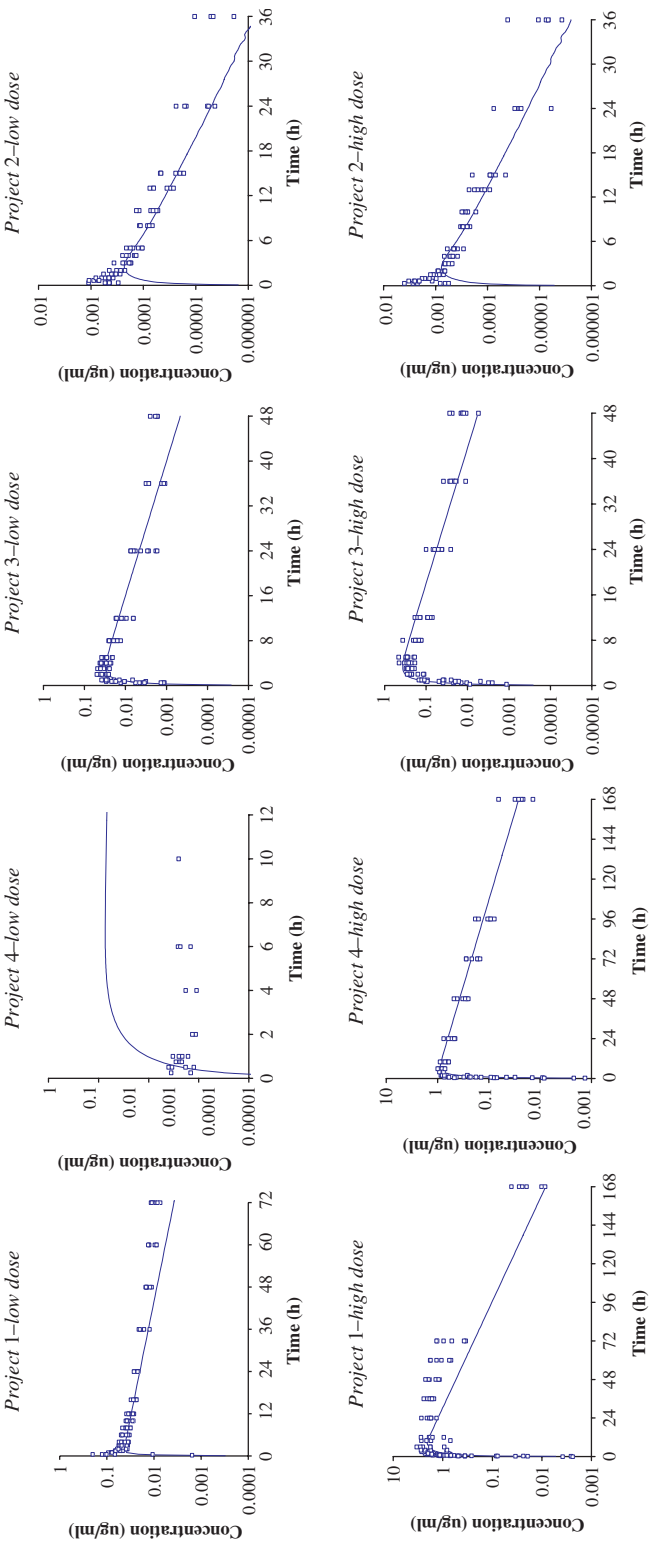

Figure 5. Prospective predictions of human plasma concentration–time profiles made for four Roche compounds. Predicted (line) and observed (boxed data points) data are shown for the lowest and highest doses of the phase 1 studies.

effect observed in the dog (9.3, fed vs. fasted) for one compound was also much greater than that actually seen in human (1.5–2.4, fed versus fasted). A more appropriate use of *in vivo* dog food effect data may be for the purposes of understanding the mechanism of food effect. By using *in vitro* biorelevant solubility data from the dog to simulate *in vivo* food effects in the dog, a solubility/dissolution mechanism can be confirmed before performing human *in vitro* to *in vivo* extrapolations/simulations (Jones et al. 2006a).

Quantitative predictions of drug–drug interactions

The use of *in vitro* technologies to evaluate the potential for metabolic drug–drug interactions has become routine in the drug development process. However, the quantitative interpretation of these *in vitro* data and their relevance for the *in vivo* situation in man remain a challenge. Various simulation software, such as Simcyp®, offering a framework for the quantitative integration of these data became recently available (Proctor et al. 2004; Rostami-Hodjegan and Tucker 2004; Howgate et al. 2006; Inoue et al. 2006; Rostami-Hodjegan and Tucker 2007). Simcyp utilizes fundamental scaling procedures described by Houston (1994a, 1994b) and Houston and Carlile (1997) for the prediction of *in vivo* hepatic clearance (CL_H) from *in vitro* metabolism data. These *in vitro* metabolism data can be obtained from individual cytochrome P450s (CYP) in human-expressed recombinant systems. These are used for predicting not only the behaviour in average individuals, but also in whole populations or in special subpopulations. In order to predict drug–drug interactions involving CYP, Simcyp utilizes the relationship between the inhibitor concentration at the active site *in vivo* and the inhibition constant (K_i) determined *in vitro*. Competitive inhibition, induction, and/or mechanism-based inactivation mechanisms can be investigated within this software, according to the principles described by Ito et al. (1998a, 1998b) and Tucker et al. (2001). Simcyp not only predicts the mean value, but also simulates the extremes in the population by applying a Monte Carlo approach.

A Simcyp model for Tarceva™ was recently developed using *in vitro* data from individual cytochrome P450s (CYP) in human-expressed recombinant systems (Jones et al. 2005). The objective was to investigate the relative contribution of different enzymes to Tarceva clearance and the potential impact of inhibition of the primary enzyme on exposure. Tarceva is an orally active antitumour agent developed for the treatment of advanced or metastatic solid tumours such as non-small cell lung cancer (NSCLC) and pancreatic cancer. The metabolism of Tarceva was first investigated *in vitro* using human liver microsomes (HLM) and human recombinant enzymes. Tarceva was found to be metabolized primarily by CYP3A4 with a secondary contribution from CYP1A2. Using various *in vitro* metabolic parameters and literature data, Simcyp predicted a relative contribution of approximately 70% vs. approximately 30% of these two enzymes to metabolic elimination. A drug–drug interaction study was conducted in the presence of a potent CYP3A4 inhibitor, ketoconazole in healthy male volunteers. Ketoconazole caused an 86% increase in Tarceva plasma area under the concentration curve (AUC) and almost a twofold increase in maximum plasma concentration (C_{max}). This increase was consistent with a Simcyp prediction of a twofold increase in AUC; validating a primary (approximately 70%) role of CYP3A4 enzyme in the elimination of Tarceva.

Application of PK/PD modelling during drug discovery and non-clinical development

Development of a model that will accurately simulate the pharmacokinetic system of a drug candidate is an achievement in its own right. With the addition of simple assumptions

about therapeutic concentrations at the site of action such models can be used to give a first approximation of the dose–therapeutic response relationship. However, as the drug concentration–effect relationship is most frequently highly non-linear, inclusion of pharmacodynamic models is often necessary to characterize truly the dose–response relationship. This is of particular importance when trying to make comparisons between drug candidates in order to select the most suitable candidate for further development.

In the early stages of lead optimization when compounds are being tested for potency, ADME and physico-chemical properties and *in vitro* potency data (e.g. IC_{50} from a binding assay study) can be used as first approximation to define a pharmacodynamic relationship. If such a model is combined with a PBPK model, quantified using the ADME and physico-chemical screening data, the likely dose–response, in terms of target (e.g. receptor or enzyme) inhibition or agonism, can be estimated. Thus, modelling and simulation can serve as an *in silico* screen utilizing the available data. Normally, as the number of suitable drug candidates is reduced the remaining candidates are screened using *in vivo* animal pharmacology models. Often it is possible to establish pharmacodynamic relationships and models from the data obtained in these *in vivo* studies. Data can range from a simple *in vivo* confirmation of *in vitro* potency data, e.g. plasma enzyme inhibition, and more complex biomarkers of disease such as changes in hormone levels to complex behavioural changes in nervous system function. Models based on these data can be used in combination with PBPK models to approximate the animal data before attempting to extrapolate to humans.

The main uncertainty in such a combined PK/PD approach is scaling the pharmacodynamic model from the animal pharmacology model to the human situation. For drug targets that are situated in the blood, this can be relatively straightforward. Although one cannot usually make predictions about final clinical endpoints, one can often extrapolate simple drug effects or biomarkers of clinical response. This becomes increasingly difficult when the target is not easily measurable even in animal models. It is also difficult when the link between responses in animal models and changes in disease state are not well understood. These uncertainties will decrease as more experience is obtained in the use of animal disease models, as our knowledge of human disease increases and as our current knowledge is applied quantitatively in an effort to predict human disease states and the therapeutic effects of drugs. A good example is the company Entelos, Inc. (Michelson 2003, 2006; Bangs 2005; Kansal and Trimmer 2005; Stokes 2005), who have developed sophisticated, mechanistic computer models of human physiology and disease. Models of this type can be used at many stages of the drug development process including drug discovery. When used in combination with predictive pharmacokinetic models, such as PBPK models, the dose–clinical therapeutic response of drug candidates can be estimated long before the drug reaches the clinic.

Summary and conclusions

Overall, the examples presented in this paper illustrate how modelling and simulation can add value at various stages of the research and development process, can help to create a continuous feedback loop between pre-clinical and clinical stages, and can contribute to scientifically and rationally guided drug discovery and development.

The benefits of modelling and simulation at the pre-clinical stage can be realized through formal and realistic integration of data obtained from the various functions supporting

project teams, namely physicochemical properties, pharmacokinetics, pharmacodynamics, formulation, and safety. Such data integration into PBPK combined with PK/PD models provides the basis for quantitative outputs allowing comparisons across compounds and resulting in improved decision-making during the selection process. In addition, mechanistically based models are valuable tools for hypothesis testing and to obtain mechanistic understanding on the compound's properties. In addition, models provide the opportunity to make uncertainty and variability more transparent. With the availability of human (PBPK) models at the pre-clinical stage, early estimates of the PK/PD profiles in the relevant target (human) population can be obtained reducing uncertainty and improving decision-making.

The power and utility of PBPK modelling is further increased when linked with mechanistically based pharmacodynamic models. This powerful combination of predictive physiology-based pharmacokinetic models with a pharmacodynamic effect — either in a phenomenological way or by means of more advanced pharmacodynamic models — is shifting the endpoint of a simulation from a concentration versus time curve towards the time-course of a pharmacodynamic outcome. Such PBPK/PD evaluations provide crucial information on the potency and safety of drug candidates *in vivo* and the bridging of the PK/PD concept established during the pre-clinical phase to clinical studies.

Obstacles to the wider use of modelling approaches such as PBPK in the pharmaceutical industry have been attributed to several factors (Rowland et al. 2004): uninformed management attitudes, suboptimal organizational structures, lack of user-friendly modelling software, lack of appropriate and easily accessible relevant physiological and related databases, and, of importance, lack of adequately trained researchers in PBPK modelling. Another rate-limiting step for a wider use of modelling is often obtaining and gaining familiarity with the critical data. One strategy employed by the pharmaceutical industry to avoid this rate-limiting step is to train the people involved in obtaining and interpreting data in performing routine modelling and simulation analyses. The modelling and simulation specialist can then focus their time on training colleagues, guiding application of modelling, developing new methods, and addressing the more challenging issues that arise. This strategy is assisted by user-friendly PBPK modelling software that can be used by scientists not formally trained as modellers.

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