

## Pharmacokinetics/Pharmacodynamics and the Stages of Drug Development: Role of Modeling and Simulation

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### ABSTRACT

Pharmacokinetic (PK) and pharmacodynamic (PD) modeling and simulation (M&S) are well-recognized powerful tools that enable effective implementation of the learn-and-confirm paradigm in drug development. The impact of PK/PD M&S on decision making and drug development risk management is dependent on the question being asked and on the availability and quality of data accessible at a particular stage of drug development. For instance, M&S methodologies can be used to capture uncertainty and use the expected variability in PK/PD data generated in preclinical species for projection of the plausible range of clinical dose; clinical trial simulation can be used to forecast the probability of achieving a target response in patients based on information obtained in early phases of development. Framing the right question and capturing the key assumptions are critical components of the “learn-and-confirm” paradigm in the drug development process and are essential to delivering high-value PK/PD M&S results. Selected works of PK/PD modeling and simulation from preclinical to phase III are presented as case examples in this article.

**KEYWORDS:** drug development, modeling and simulation, pharmacokinetics/pharmacodynamics, NONMEM, design optimization

### INTRODUCTION

Each phase of the drug development process is designed to accrue the necessary information to assess the probability of technical success for a new chemical entity (NCE). Continually expanding the knowledge base supporting the efficacy and safety attributes of an NCE remains the fundamental pathway to successful drug development. The “learn-and-confirm” paradigm<sup>1</sup> has been proposed as an efficient and rational approach to drug development (Figure 1). Effective implementation of learning and confirming requires timely application of modeling and simu-

lation (M&S) tools. Advancements made in computational tools have greatly facilitated the wider application of M&S in the design of clinical trials.<sup>2</sup>

The integration of pharmacokinetic (PK) and pharmacodynamic (PD) information through M&S in drug development<sup>3,4</sup> has provided opportunities to accelerate the evaluation of NCE in humans.<sup>5</sup> The use of models to describe PK/PD data is a well-established approach.<sup>6</sup> However, a model-based drug development program that uses a drug and disease model for exposure-response analysis<sup>7</sup> and clinical trial simulations<sup>8-10</sup> in an integrated approach to effective knowledge use for decision making and risk management is a novel paradigm. Predictive modeling and focused simulations require explicit framing of the key development questions, understanding of the underlying assumptions, and the iterative refinement of the models during every phase of a drug development program. The number of iterations with actual clinical trials is dependent on the quality of prior knowledge and the cost and risk that a particular drug development program is willing to accept.

The general objectives and the mode, “learn or confirm,” at each phase as outlined in Table 1 are useful as a basis for defining specific M&S tasks. The questions and tasks listed are not intended to be a comprehensive list, but they serve to stimulate thought and guide appropriate use of M&S.

The impact of M&S on NCE development depends on the type and amount of prior information available. Two extreme cases of prior information are outlined in Table 2. Most of the time, development program teams will find themselves in an intermediate scenario. In these cases, it is vital to leverage the existing data and simultaneously manage the risk and uncertainty, because certain critical aspects remain unknown. In every case, robust trial design strategies are needed. Robustness can be achieved by understanding and using prior information, as well as carefully acknowledging and assessing risk and uncertainty.

Reflecting on the possible circumstances described in these tables, 4 examples that highlight specific applications of M&S at various stages of drug development are presented in this article. The first example (case study 1) leverages comparator information to project likely clinical doses for an antihypertension drug in the preclinical phase of development. The second example (case study 2) illustrates the

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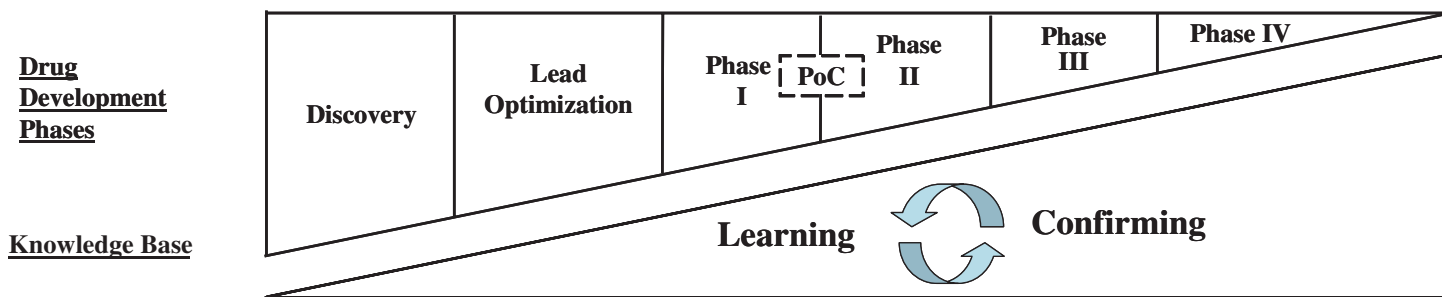


Figure 1. The learn-and-confirm drug development paradigm.

use of mixed-effects modeling of phase I data to support dosing and sampling design in the first patient trial for an antimicrobial agent. The third example (case study 3) exemplifies the use of population PK and biomarker exposure-response modeling to design an optimal dosing regimen for a combination therapy trial in oncology. The last example (case study 4) describes the application of a drug and disease model to support the design of phase II/III trials, thereby supporting registration and commercialization needs.

### The Preclinical Phase: Empirical Dose Projection

Before clinical testing, it is important to compare the PK/PD properties of candidate molecules; model potential relationships among dose, concentration, efficacy, and/or toxicity; and, ultimately, support the selection of the doses chosen for early clinical testing. The utility of PK/PD-based M&S before clinical development is highly dependent on the amount and quality of information available from preclinical studies and literature data on clinical comparator(s). Depending on the availability of prior information for the NCE (Table 2), M&S before clinical development can either provide quantitative predictions of clinical performance or be used in a more limited manner to answer “what if” types of questions. For the “nth-in-class” molecules, there is typically a wealth of information available on comparator or competitor molecules, which can be used to carry out M&S exercises that support planning for the early clinical stages of the program. A combination of M&S approaches, including population analysis of sparse preclinical PK data, allometric scaling to predict human PK, and empirical efficacy scaling, can be used to project the anticipated human dose and/or dosing regimen. The M&S tasks at this stage are primarily designed to “learn” about these properties of the molecule that are then “confirmed” by the data generated in the early clinical development.

#### Case Study 1

A NCE, possessing a high amount of prior information from other drugs in the therapeutic class, was to be eval-

uated as a treatment for hypertension. The main M&S objective was to project the clinical dose range based on the preclinical PK/PD properties of the NCE. The preclinical and clinical PK/PD properties of a comparator drug were well known. Although this example focused on 1 NCE, several NCEs were evaluated previously using M&S to identify the optimal clinical candidate. After identification of the candidate, PK/PD modeling was used to support the dose selection for phase I studies. Among others, the development team posed the following questions: (1) what is the concentration–effect relationship of the NCE relative to the comparator, and (2) what dose range should be evaluated in early clinical trials?

Figure 2 illustrates the steps taken to develop a dose/exposure-response relationship in rats and the compilation of comparator data from literature for building a clinical dose-response relationship. The human PK and PK/PD of the NCE were projected based on data collected in rat, dog, and monkey absolute bioavailability studies, a rat hypertension model study, and the summary basis of approval (SBA) for the comparator molecule. These data were integrated as indicated in Figure 2 to predict a dose-response relationship for NCE for treatment of clinical hypertension. The main assumptions of these analyses were as follows: (1) the relative efficacy and potency observed in the rat hypertension model between the comparator and the NCE were predictive of the relative efficacy and potency in humans, and (2) allometric scaling provided a reasonable estimate of the clearance of the NCE in humans. These assumptions and possible alternative PK/PD methods are additionally discussed.

In preclinical experiments, hypertensive rats were administered daily oral doses of the NCE, the comparator, or the vehicle (control) for a 2-week period. Blood pressure (BP) response to treatment was measured at the end of the 2-week treatment period. Figure 3 illustrates the dose response observed for the comparator and for the NCE in this rat hypertension model. The NCE appeared more potent and more efficacious than the comparator.

To address the concentration-effect relationship question, sparse blood samples were collected after the last dose for

**Table 1.** Effective Application of Modeling and Simulation by Stage of Drug Development

Phase	Overall Objectives	Mode*	Questions	Modeling and Simulation Tasks
Phase 0: Preclinical	<ul style="list-style-type: none"> <li>■ Demonstration of biologic activity in experimental animal models of disease.</li> <li>■ Accrual of toxicology data to support initial dosing in humans.</li> <li>■ Identify a lead candidate(s) based on desired attributes.</li> </ul>	Learn	<ul style="list-style-type: none"> <li>➤ What are the “efficacy” and “safety” characteristics of the NCE in animal models?†</li> <li>➤ What dose range should be studied in early clinical trials given the uncertainty in the predicted dose required for efficacy and safety?</li> </ul>	<ul style="list-style-type: none"> <li>➤ Guide the developmental strategy with an integrated decision-making criteria.</li> <li>➤ Begin evaluation of biomarker performance relative to decision criteria.</li> <li>➤ Understand the mechanism(s) of action.</li> <li>➤ Design PK/PD experiments and analyze PK/PD data.</li> <li>➤ Predict human clearance based on in vivo/in vitro data.</li> <li>➤ Predict efficacy estimates (potency, EC<sub>50</sub>) based on preclinical exposure-response and comparator data.</li> <li>➤ Integrate clearance, potency, and bioavailability estimates for dose projection incorporating uncertainty and expected variability.</li> <li>➤ Assess the margin of safety based on target “efficacy” concentration and exposure data from toxicology studies.</li> </ul>
Phase I	<ul style="list-style-type: none"> <li>■ Assess tolerable dose limit.</li> <li>■ Assess pharmacokinetic and pharmacodynamic characteristics.</li> </ul>	Learn	<ul style="list-style-type: none"> <li>➤ What is the maximum tolerable dose?</li> <li>➤ What are the PK attributes of the NCE in initial human studies? Are they linear and/or predictable?</li> <li>➤ What are the PD effects of the NCE in initial human studies?</li> <li>➤ What is the shape of the dose/concentration—response curve ?</li> </ul>	<ul style="list-style-type: none"> <li>➤ Develop or update the PK and PD models.</li> <li>➤ Simulate exposure and response for intended dosing regimens, incorporating variability.</li> <li>➤ Quantify the variability in PK and PD (if applicable).</li> <li>➤ Assess if parameters are likely to change in the target population and subpopulations.</li> </ul>
Phase IIA (PoC)	<ul style="list-style-type: none"> <li>■ Demonstrate efficacy in the intended population (per indication).</li> </ul>	Confirm	<ul style="list-style-type: none"> <li>➤ What are the attributes of the drug in target population compared to the existing therapy?</li> </ul>	<ul style="list-style-type: none"> <li>➤ Develop a drug-disease model to understand time course of disease progression and dose-response to interventions.</li> </ul>
Phase IIB	<ul style="list-style-type: none"> <li>■ Optimal use in target population (per indication).</li> </ul>	Learn	<ul style="list-style-type: none"> <li>➤ What trial design for a PoC/Phase IIB study will unequivocally demonstrate efficacy in the target population?</li> <li>a) Patient population (inclusion/exclusion criteria)</li> <li>b) Number and strength(s) of doses</li> </ul>	<ul style="list-style-type: none"> <li>➤ Simulate outcome given assumptions and study design considerations.</li> <li>➤ Use simulations or optimization tools to design dosing and sampling schemes.</li> <li>➤ Assess the probability of success given a study design.</li> </ul>

(Continued)

Table 1. (Continued)

Phase	Overall Objectives	Mode*	Questions	Modeling and Simulation Tasks
	<ul style="list-style-type: none"> <li>▪ Establish doses to be evaluated in Phase III.</li> </ul>		<ul style="list-style-type: none"> <li>➤ What are the critical aspects reflecting the value of a PoC study vs. larger Phase 2 study?               <ul style="list-style-type: none"> <li>a) What should be the duration of the study?</li> <li>b) What are the optimal sample collection schemes</li> <li>c) What types of biomarkers, surrogates or endpoints, responses should be measured?</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>➤ Analyze dose-exposure-response data using a model based approach</li> <li>➤ Assess the impact of covariates using a population PK/PD model.</li> <li>➤ Stress test and validate the population PK/PD model.</li> <li>➤ Assess efficacy/toxicity profile of NCE relative to standard of care or comparator(s).</li> </ul>
Phase III	<ul style="list-style-type: none"> <li>▪ Demonstrate safety and efficacy for clinical use.</li> </ul>	Confirm	<ul style="list-style-type: none"> <li>➤ Do the intended dose(s) demonstrate the desired safety and efficacy in the population?</li> <li>➤ Is the dose likely to change in a given subpopulation or special population? If so, by how much?</li> </ul>	<ul style="list-style-type: none"> <li>➤ Validate the population PK/PD model.</li> <li>➤ Assess the impact of applicable covariates.</li> <li>➤ Establish/confirm dose/exposure-response relationship in target population/subpopulations.</li> <li>➤ Assess need for dose adjustment in special populations.</li> </ul>

\*Learn vs. confirm phase I.

†Efficacy and safety characteristics in animal models may be biomarker responses associated with pharmacological activity that may be predictive of clinical safety and efficacy. Clinical safety and efficacy may be a biomarker response, a surrogate end point, or a clinical outcome.

**Table 2.** Prior Information and the Goals of M&S

Amount of Prior Information	Scenario	Modeling and Simulation Goals
High	<ul style="list-style-type: none"> <li>➤ Nth in class/crowded competitive landscape</li> <li>➤ Few assumptions and low uncertainty in predictions</li> </ul>	Leverage existing data and model to shorten and focus development
Low	<ul style="list-style-type: none"> <li>➤ First in class/unknown mechanism(s) of action</li> <li>➤ Many assumptions and high uncertainty in predictions</li> </ul>	Manage risk and uncertainty

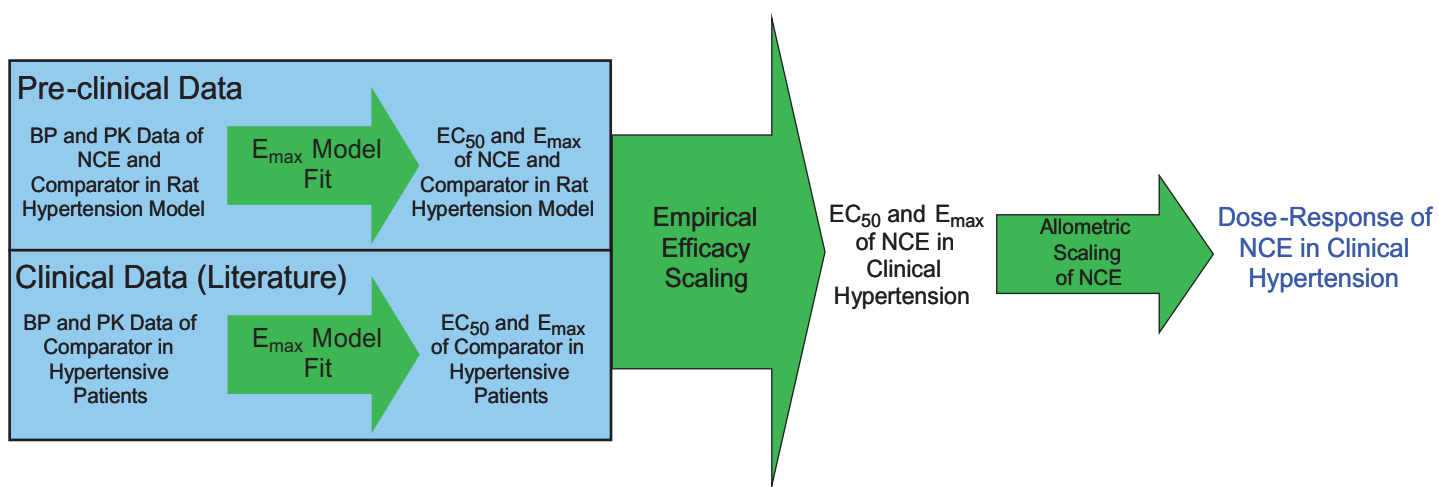
PK assessment, and these concentration data were analyzed using a population PK approach separately for the NCE and the comparator. The resulting individual animal exposure values were then combined with the individual animal BP data and analyzed using a maximal effect ( $E_{max}$ ) model of the form shown in equation 1 in Figure 4, where C is the average steady-state concentration ( $C_{ss}$ ), and  $E_0$  is the baseline percent reduction in BP, which was fixed to zero. The  $E_{max}$  model fit of individual animal exposure-response data and the 90% confidence interval (CI) of the predicted mean concentration-response curves are shown in Figure 3.

Parameters estimated resulting from the M&S analyses are shown in Table 3. The clearance of the comparator was higher than that of the NCE. Although not shown, both compounds displayed nonlinear PK across the dose range studied, and PK in the animal model was also moderately different from PK in normal animals. This situation emphasizes the importance of collecting exposure measurements in the same preclinical model used to obtain efficacy measurements. The comparator molecule appears to be more potent than the NCE (lower  $EC_{50}$ ); however, the  $E_{max}$  for the NCE was predicted to be higher than the comparator. Therefore, these results suggest that at high concentrations,

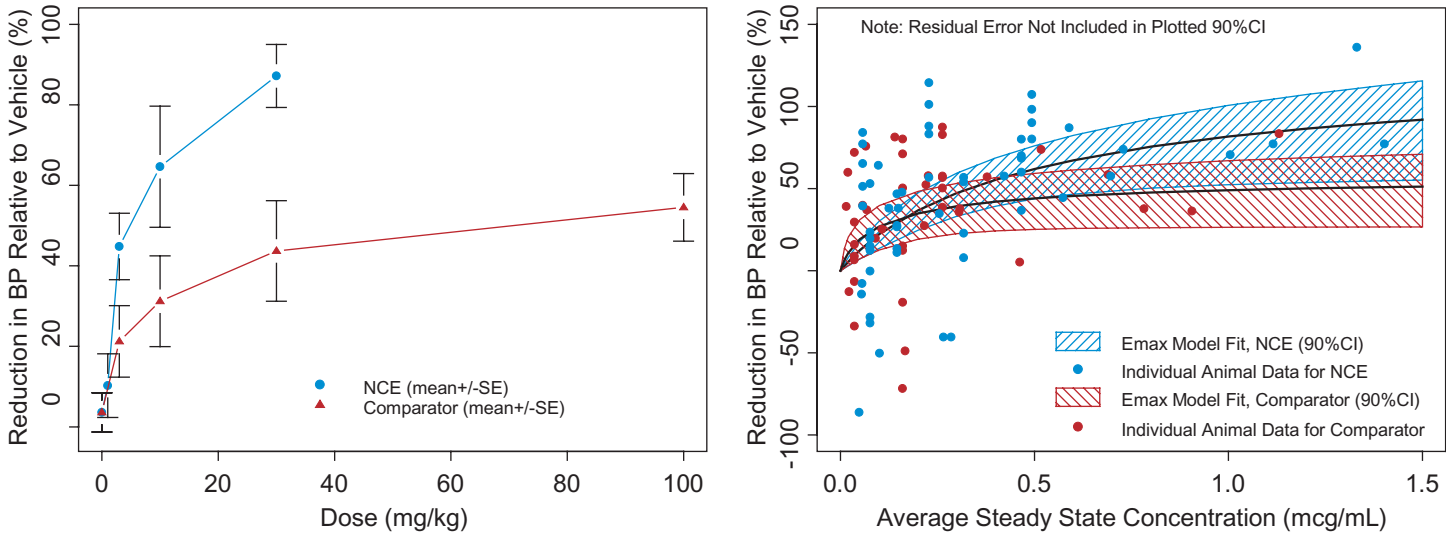
the NCE may produce superior BP reduction relative to the comparator molecule, whereas at low concentrations the BP response of the 2 molecules is expected to be comparable.

The SBA for the comparator compound contained mean BP response data from 2 dose-response studies in hypertensive patients and mean oral clearance values from healthy subjects. The SBA stated that clearance values in healthy subjects and hypertensive patients were similar. The oral clearance values were used to establish the average  $C_{ss}$  at the dose levels used in the 2 dose-response studies. Thereby, a dataset was established and used to relate BP reduction to  $C_{ss}$ . An  $E_{max}$  model of the form shown in equation 1 was fit to these data.

The concentration-response parameters for the NCE in clinical hypertension were calculated using an empirical scaling approach by combining the results of the rat hypertension  $E_{max}$  model parameters and the clinical  $E_{max}$  model parameters of the comparator as shown in Figure 4 (equations 1-3). The empirical efficacy-scaling model assumed that the relative  $EC_{50}$  (concentration at 50% of maximum effect) and  $E_{max}$  (NCE to the comparator) in hypertensive patients were equal to the relative  $EC_{50}$  and  $E_{max}$  in the rat hypertension model. The parameter values



**Figure 2.** PK/PD analysis flowscheme. Information from several sources was integrated to predict the dose response for the NCE in humans.



**Figure 3.** Dose and concentration response of the comparator and NCE in rat hypertension model.

used in equations 2 and 3 in Figure 4 were not single point estimates but rather a distribution of parameter values generated from the uncertainty in the parameters estimated from the preclinical and clinical data. Correspondingly, the clinical estimates of  $E_{max}$  and  $EC_{50}$  for the NCE were propagated as distributions that reflect the uncertainty in the model parameters.  $E_0$  was defined as the response to placebo; it was assumed that the NCE trial would have the same placebo response as the comparator trial. The model equation for  $EC_{50}$  included additional terms to improve

accuracy and minimize potential assumptions. These terms accounted for the difference in protein binding ( $f_u$ ) between the NCE and comparator and the difference in receptor binding affinity ( $K_b$ ) between the NCE and comparator, because the ratio of human-to-animal binding affinity of the NCE may not be the same as that for the comparator. The need for adjusting the empirical scaling based on binding affinity is explained based on a hypothetical case where a NCE is able to bind with high affinity to the receptor in the animal model and has a low  $EC_{50}$  value

$$Effect = E_0 + \frac{E_{max} \times C}{EC_{50} + C} \tag{1}$$

$$EC_{50, NCE, human} = EC_{50, Competitor, human} \times \left( \frac{EC_{50, NCE}}{EC_{50, Competitor}} \right)_{rat} \tag{2}$$

$$\times \left( \frac{f_{u_{rat}}}{f_{u_{human}}} \right)_{NCE} \times \left( \frac{f_{u_{human}}}{f_{u_{rat}}} \right)_{Competitor} \left. \vphantom{\frac{EC_{50, NCE}}{EC_{50, Competitor}}} \right\} \begin{array}{l} \text{Adjust for differences} \\ \text{in protein binding} \\ =0.67 \end{array}$$

$$\times \left( \frac{K_{b_{human}}}{K_{b_{rat}}} \right)_{NCE} \times \left( \frac{K_{b_{rat}}}{K_{b_{human}}} \right)_{Competitor} \left. \vphantom{\frac{EC_{50, NCE}}{EC_{50, Competitor}}} \right\} \begin{array}{l} \text{Adjust for differences in} \\ \text{binding to receptor} \\ =1.83 \end{array}$$

$f_u$  = Fraction Unbound (Plasma Protein Binding)

$$Emax_{NCE, human} = Emax_{Competitor, human} \times \left( \frac{Emax_{NCE}}{Emax_{Competitor}} \right) \tag{3}$$

$$E_{0, NCE, clinical} = E_{0, Competitor, clinical} \tag{4}$$

**Figure 4.** Equations for case study 1.

**Table 3.** Estimated CL, E<sub>max</sub> and EC<sub>50</sub> for NCE and Comparator in Rat Hypertension Model\*

Drug	Mean (90% CI) PK Parameter Estimate CL (L/hr)	Mean (90% CI) PD Parameter Estimate	
		EC <sub>50</sub> (µg/ml)	E <sub>max</sub> (% Reduction in BP Relative to Vehicle)
Comparator	1.8 (1.3–2.2)	0.085 (0.016–0.42)	57 (27–86)
NCE	0.25 (0.18–0.32)	0.44 (0.15–1.1)	130 (60–190)

\*CL indicates clearance. The PK and PD parameters were estimated as separate steps, first determining the individual animal clearance values and then combining these values with individual blood pressure response data and fitting these with an E<sub>max</sub> model.

in animals but binds to the human receptor with much lower affinity. Without correcting for a difference in binding affinity, the empirical scaling approach would estimate a human EC<sub>50</sub> that is influenced only by the low EC<sub>50</sub> value in animals when, in reality, the EC<sub>50</sub> value for humans could be much higher than predicted or may result in lack of efficacy in humans. The predicted E<sub>max</sub> model parameters for the NCE in clinical hypertension generated using empirical efficacy scaling are shown in Table 4 relative to the comparator values.

Empirical efficacy scaling is an effective approach to estimate clinical efficacy using preclinical data. It leverages the information obtained from comparator molecules of the same class and implicitly takes into account biological mechanisms that relate the concentration of the drug in the plasma to the observed effect, which are not specifically accounted for in the modeling or may not be known. If this approach cannot be used because of a lack of comparator data, then alternative approaches that require additional assumptions may be used. Such alternative approaches would likely include some form of mechanistic modeling that attempts to account for the factors that are implicit in the empirical approach, such as drug distribution between plasma and target organs, interaction of molecules with the target receptor, and downstream response processes.

For the purposes of estimating doses in humans, the human intravenous clearance of the NCE was projected with uncertainty based on allometric scaling of the intravenous clearance values obtained in rat, dog, and monkey studies. In some cases, the accuracy of clearance projection may be

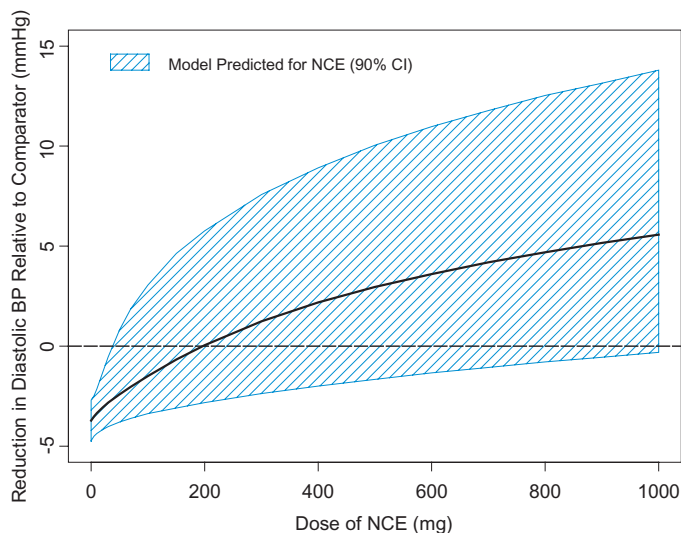
improved if differences in the intrinsic clearance between species are accounted for in the allometric equation. The intrinsic clearance rate based on results from in vitro studies was found to be similar across species for this NCE; therefore, no adjustments to the allometric equation were applied. It was assumed that optimization of the formulation would lead to a bioavailability of 25% in humans, with an uncertainty of 50% coefficient of variation. Combining the estimated oral clearance with the E<sub>max</sub> concentration-response parameters resulted in a predicted dose response for the NCE in clinical hypertension (Figure 5). Note that Figure 5 does not show the absolute diastolic BP reduction but rather the BP reduction relative to the BP reduction produced by the marketed dose of the comparator. This relative efficacy prediction thereby begins to address the questions posed by the team initially.

The M&S results suggest that a median dose of 200 mg (90% CI, 40 to 1,100 mg) would produce the same BP reduction as the marketed dose of the comparator. The 90% CI of 40 to 1,100 mg revealed a very high level of uncertainty and may infer low informational value of this result in guiding clinical plans and dose selection. At the preclinical stage of development, the uncertainty in the clinical dose will be the greatest. As the compound progresses through development, this uncertainty will be reduced as clinical data accrue. However, a significant portion of this uncertainty is because of how the question was posed, that is, a dose to produce a specific effect. It is not often well recognized that at the time of compound registration, there may still be marked uncertainty in the dose that produces a

**Table 4.** Estimated E<sub>max</sub> and EC<sub>50</sub> for NCE and Comparator in Clinical Hypertension

Drug	Mean (90% CI) Parameter Estimate		
	E <sub>0</sub> * (Reduction in DBP relative to baseline, mmHg)	EC <sub>50</sub> (µg/ml)	E <sub>max</sub> (Reduction in DBP <sup>1</sup> Relative to Baseline, mmHg)
Comparator	1.6 (0.63–2.6)	0.43 (0.15–1.3)	9.0 (4.8–13)
NCE	1.6 (0.63–2.6)	2.7 (0.28–24)	20.0 (6.9–53)

\*Response to placebo for NCE assumed to be the same as comparator.



**Figure 5.** Predicted dose response for the NCE in clinical hypertension relative to observed response for the marketed dose of the comparator.

certain effect. For this example, the comparator, at the time of registration, had a 90% CI range (upper/lower) of 6 for the predicted dose that would produce the same efficacy as the final registered dose. For the NCE, the 90% CI range was markedly larger, as is typically expected at this stage of development. Part of the uncertainty is also the result of the asymptotic nature of the  $E_{max}$  dose-response relationship combined with the shallow dose-response curve for this NCE. If the target effect of a compound is close to the  $E_{max}$ , the upper bound of the uncertainty in the dose required to produce the target effect will be infinite even if the uncertainty in the dose-response relationship is very small.

For this NCE, the goal of the phase I program was to study the tolerability, safety, and PKs of the NCE over the entire range of potential clinical doses. At the end of the phase I program, the uncertainty in dose selection for subsequent studies would be markedly reduced simply by learning and confirming from the knowledge gained about the PKs of the NCE in humans. In some cases, it may not be possible to study the complete range of dose uncertainty in a phase I program. In these cases, the M&S task can be helpful to determine the probability of not achieving the efficacy exposure within a more limited range of doses, given the current understanding of the uncertainty distribution describing efficacious exposure. Another consideration that can be incorporated into the M&S task would be the inclusion of exposure data from toxicology studies (ie, NOAEL, no observable adverse effect level). These data may provide the probability of achieving efficacious exposure at an exposure below a putative toxicity limit. It is obvious from this case example that an M&S exercise can also be used as a tool to understand the sources of the

uncertainty in dose selection and as a means to justify the potential need for additional preclinical studies to reduce the level of uncertainty in predicting human exposure and efficacy.

It is important to emphasize that it is intended that the results from early clinical studies are to be used to confirm the predictions from this preclinical M&S work. After the completion of phase I studies, the model can be updated to reflect the better understanding about the uncertainty in the human PK and possibly to incorporate biomarker data that provide information about the NCE exposure-response relationships. Thus, this example illustrates the importance of collecting exposure data in preclinical pharmacology models to allow a rigorous evaluation of the PK/PD properties of NCEs. The preclinical PK/PD information was shown to have predictive value when integrated with clinical PK/PD information from comparator molecules to project clinical doses for the NCE.

### **Phase I: Preliminary PK Modeling**

Initial studies in humans offer the first opportunity to characterize the basic PK characteristics of the NCE and, if feasible, the shape of the concentration-response curves. The PK or PK/PD models developed from the data of the phase I studies can be used to optimize dosing regimens in the initial efficacy-safety trials in patients, as well as for designing subsequent phase I studies, such as for the evaluation of alternative formulations or drug delivery systems.

### **Case Study 2**

This example illustrates the use of a population PK model to answer key questions during the development of a new antimicrobial agent in early clinical development. What is the expected variability in PK? What dosing regimen will provide the desired target exposure? What is the “optimal” sampling design in a phase II or proof-of-concept (PoC) study?

Serial concentration-time data were available from 19 healthy, male and female subjects administered NCE in doses ranging from 1 to 200 mg in the first single-dose—multiple-dose study in humans. A 2-compartmental population PK model best described the data. Table 5 lists the PK parameter estimates and between-subject variability of the parameters.

For the first efficacy trial in patients, the target concentration was defined based on the concentration required to kill 90% of the susceptible bacterial strains, or  $IC_{90}$ , determined from an  $E_{max}$  model fit of in vitro exposure-kill data (equation 1, Figure 4; results not shown). The clinical target concentration was 1.7 mcg (microgram)/mL (calculated by dividing in vitro  $IC_{90}$ , or 0.05 mcg/mL, by plasma

**Table 5.** NCE Population Pharmacokinetic Parameters in Healthy Subjects\*

Parameter	Population Mean(% SEE)	Intersubject Variation (% SEE)
CL (L/h)	0.34 (14.3)	0.096 (15.1)
V <sub>1</sub> (L)	4.47 (16.1)	0.008 (19.1)
Q (L/h)	0.503 (28.9)	NE
V <sub>2</sub> (L)	8.5 (16.5)	0.11 (24.0)
Residual error (proportional)		0.2 (12.8)

\*SEE indicates SE of the estimate; CL, clearance; Q, intercompartmental clearance; V<sub>1</sub> and V<sub>2</sub>, central and peripheral volume of distribution; NE, not estimated.

unbound fraction of 0.03). Given the target exposure, the population PK model, and margin of safety based on preliminary preclinical safety information, the objective of M&S for the first efficacy trial was to select one dose level to be studied as a once-a-day regimen that would maintain concentrations >1.7 mcg/mL for the entire dosing period in ≥85% of the patients.

Based on historical information on comparator compounds, it is known that disease and protein binding can contribute to differences in PK properties of an NCE between healthy subjects and patients. To minimize the risk of underpredicting the dose, a 20% higher clearance (lower exposure) was assumed, and an additional 10% variability was added to the between-subject variability in clearance and volume for patients. Concentration-time data were simulated for 500 patients administered daily doses ranging from 100 to 300 mg for 14 days. Eighty-five percent of patients maintained the 24-hour trough concentrations above the target at doses >200 mg. The percentages of patient population that failed to achieve target concentration after the first dose are shown in Table 6. The 200-mg dose, therefore, met the criteria as the lowest dose, which maintains persistent drug exposure for the entire dosing interval in 85% of the patient population.

The 90% confidence prediction band from the population model and observed phase I plasma concentration data for the NCE after a single 200-mg dose are shown in Figure 6. The histogram depicts the distribution of model-predicted trough concentrations at 24 hours.

Population PK modeling based on phase I data should ideally be pooled across multiple studies. This modeling is vital as the first-step to learn about the PK characteristics and quantify the variability of the NCE in human subjects. Nonetheless, the expected PK variability inpatient population and important covariates cannot be reliably identified in such phase I studies. Population PK modeling of larger phase II or phase III are necessary to provide robust PK

characteristics that reliably estimate variability and identify the critical covariates. Yet the informational contribution that is attained using such preliminary population PK model of phase I data, in conjunction with protein binding and in vitro efficacy data, is vital to efficient drug development and is needed to facilitate the selection of the most likely clinically efficacious dosing regimen for phase II/III efficacy studies in patients.

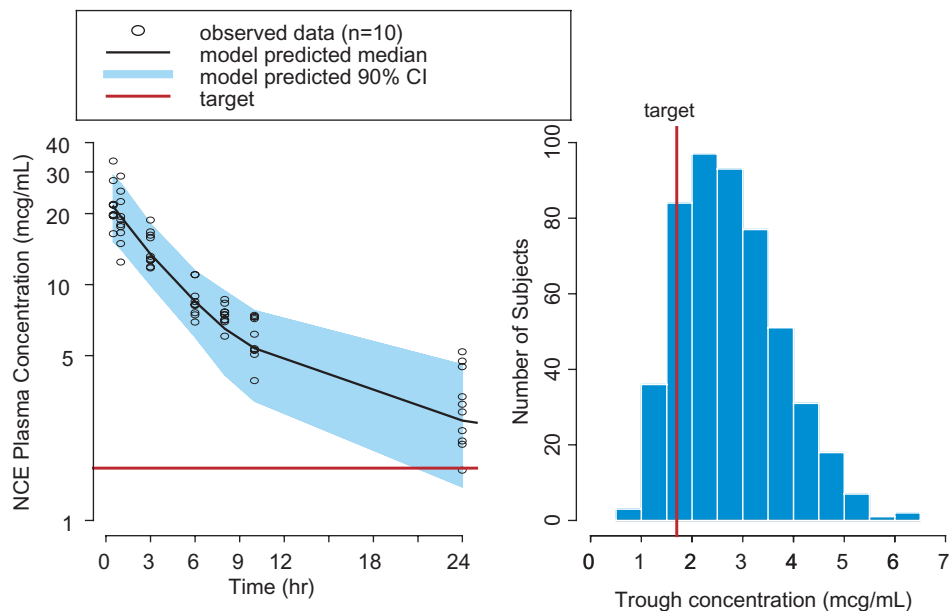
#### Case Example for Optimization of PK Sampling Design

The preliminary model can also be useful for designing the PK sampling scheme to be incorporated in subsequent phase II/III studies. Using simulations and bootstrapping, it is possible to optimize the analyses of sparse PK data from phase II/III using the mixed-effects modeling approach.<sup>11</sup> For example, a clinical study was planned with the same NCE to critically evaluate a new oral formulation being introduced in phase II. The objective of this M&S project was to leverage the existing population PK model to design the most efficient and cost-effective sampling scheme for this study, including the number of samples and the placement of sampling times. This example illustrates the use of the population model to optimize a PK sampling design using Population Fisher Information Matrix (PFIM) using the PFIM/PFIM\_OPT program<sup>12</sup> developed by Retout and Mentre.<sup>13</sup>

The degree of accuracy and precision in the estimation of parameters for a PK or PK/PD model can be highly influenced by the sampling design. Simulations are commonly used to compare and choose optimal design alternatives.<sup>14,15</sup> A design is considered optimal if it minimizes the bias and maximizes the precision of key parameter estimates. Because of the variety of possible factors, simulations are labor intensive and time consuming, and simulation intricacy is often the reason that design optimization is not widely practiced in the early phase of drug development. The software program, PFIM/PFIM\_OPT, developed by Retout and Mentre,<sup>13</sup> is a highly efficient tool that applies the Fisher Information Matrix to nonlinear mixed-effects models. The theoretical discussion and application of D-optimality have been published extensively

**Table 6.** Percent of Patients With 24-Hour Concentrations Failing Target Concentration Versus Daily Administered Dose

Daily Dose (mg)	Percent Patients Failing Target (%)
100	55
150	29
200	13
250	6
300	3



**Figure 6.** Observed (symbol) and model-predicted plasma concentration-time profile. Median (solid lines) and 90% prediction band (shaded) of 500 simulated subjects after a 200 mg dose; solid red line is the in vitro determined  $IC_{90}$ ; histogram is model-predicted distribution of plasma concentration at 24 hours.

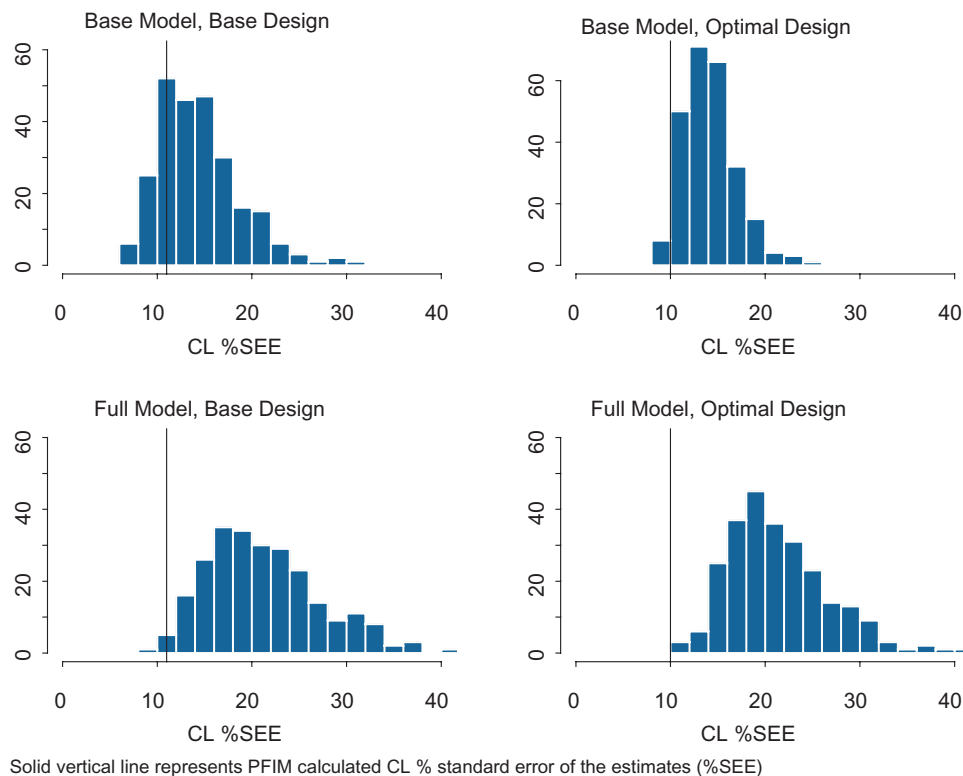
elsewhere.<sup>12,13</sup> The PFIM approach is certainly a more efficient way to evaluate the information content properties of alternative study designs compared with brute force simulations. Given a preexisting model, the D-optimality criteria for a particular design can be calculated, along with the best-case SEs of all of the parameter estimates.

In this example, the population PK model was updated based on additional data from multiple phase I studies. The final model included interoccasion variability on clearance and volume, body weight, gender, and age as covariates on clearance and peripheral volume. Because the PFIM approach is limited in its handling of off-diagonal elements, interoccasion variability, or covariate effects, the covariance matrix was simplified, and mean values of influential covariates, (ie, body weight and age) were used. For comparisons, the extensive PK sampling design in phase I was chosen as the base case. The optimization process produced a design with 2 sampling times per visit over 2 visits (a total of 4 samples per subject from 60 subjects) selected from the following time points: 0.5, 2, 6, 8, 12, 18, and 36 hours from the administration of the dose. The D-optimality criteria (efficiency and expected bias) were similar between the rich (base) design and the final (optimal) design. The SEs of the parameter estimates were comparable between the base and the optimized study design, suggesting that the sparse design would yield meaningful PK parameter estimates with adequate precision using a population model. In essence, the use of PFIM led to a more practical and cost-effective phase II study with fewer samples being collected from each patient.

Currently, the implementation of PFIM precludes the inclusion of covariance among random effects, interoccasion variability, or covariate effects. In addition, the D-optimality operation is limited in that it is “nonselective” and optimizes the composite aspects of an entire model. There is a need to develop alternative methodology that would allow optimization based on the relative importance of specific parameters; for example, clearance may be more a more critical parameter than distributional volumes. Because of these limitations, the evaluation of optimal study designs for covariate and period effects requires the use of the more laborious simulation approach. However, even in that case, D-optimization can be conducted initially to minimize the design space, followed by simulations performed within a more limited scope to complete the evaluation.

To evaluate these properties of simulation and D-optimality, simulations of the phase II study (optimal sparse sampling scheme) were conducted (500 replicates) to compare the robustness of the design selected by PFIM to the base design (extensive sampling scheme), using the base and the full model. The simulated datasets were evaluated using both base and full models and the FOCE (first order conditional estimation) method in NONMEM. The precision of the clearance estimate for both designs and both models are shown in Figure 7. For the base model, the optimal design gave more precise SE estimates than the base design (smaller median and range of SE estimates).

However, when the full model was used, the optimal design did not make a significant improvement over the



**Figure 7.** Distributions of % SE of clearance estimates for the base and the optimal designs using the base and the full (including covariates) models. SE (%) of clearance was estimates based on 250 replicates of simulated data sets.

base design, with larger SEs being estimated on all of the covariate effects using the optimal design (results not shown). This was expected, because it was not possible to incorporate the effects of covariates at this stage of development. The simulations and predictions, however, can evolve and improve. For example, simulations can again be used to increase the ability to confirm covariate effects in phase III studies by using the additional data generated in phase II trial(s). These additional evaluations also increase the robustness of parameter estimation, as can be seen by the increase in the number of successful NONMEM runs (Table 7).

**Proof of Concept Study:  
Confirming Biologic Activity**

Phase I oncology studies are typically conducted in patients with metastatic cancer. Because of the stage of their disease, these patients are often being treated with a combination of therapeutic agents. Given the patient population and the complexity of the disease and treatment regimens, the design and analysis of oncology studies are particularly well suited to a population-based approach. Beyond the normal objectives in phase I drug research, oncology phase I studies need to characterize potential PK/PD interaction, as well as assess interindividual and interoccasion variability.

The recognition of the role of membrane transporters in drug disposition and disease has made transporters a new therapeutic target of interest. Cancer cells have the ability to develop resistance to chemotherapeutic agents because of overexpression of membrane efflux transporter proteins, such as P-glycoproteins (P-gp). The limitation of many clinical P-gp inhibitors has been excessive toxicity when coadministered with chemotherapy at therapeutic doses. Toxicity may result not only from the PD effects but also from very profound PK interactions. Because of these complications, many P-gp inhibitors have failed when used in combination with other oncolytic drugs because of an inadequate mechanistic understanding of the contribution of P-gp inhibition, as well as cytotoxic chemotherapy to the overall therapeutic effect. Using mechanistic PK/PD models, it is possible to appropriately assess both the impact on PK interaction (potential toxicity), as well as the PD effects

**Table 7.** NONMEM Evaluation of Full Model Fit to Simulated Datasets for Base and Optimal Designs

"Unsuccessful"		
NONMEM runs	Base	Optimal
"Terminated"	51 of 500	123 of 500
"Minimization successful; covariance step aborted"	114 of 449	187 of 377

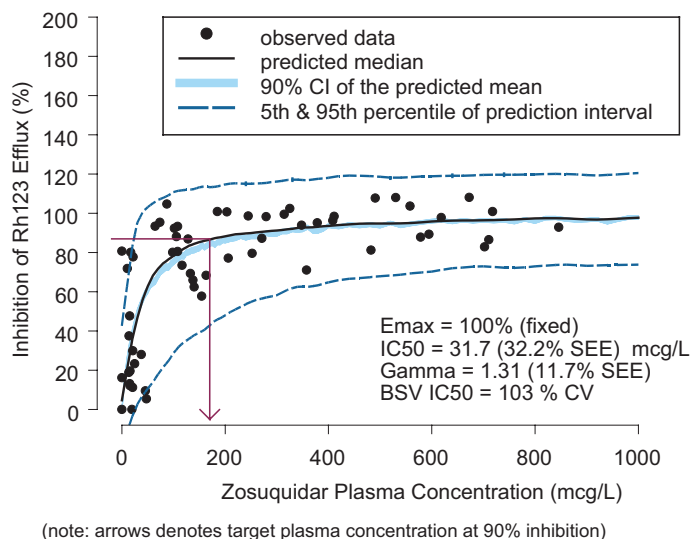
(potential efficacy) of the combination.<sup>16</sup> Toxicity can result either from the inhibition of the metabolism of the parent oncolytic drug or by the excessive accumulation of metabolites, which are toxic. A clear example of the impact of a transport inhibitor on toxicity is illustrated by the metabolism of doxorubicin to doxorubicinol. Doxorubicinol is transported by P-gp. Coadministration of a P-gp inhibitor with doxorubicin caused a 10-fold increase in doxorubicinol area under the curve (AUC).<sup>17</sup> An increase in toxicity was related to the impact of the P-gp inhibitor on doxorubicinol AUC.<sup>18</sup>

### Case Study 3

Zosuquidar is a potent and highly selective inhibitor of P-gp being investigated as a noncytotoxic multidrug-resistance modulator. Coadministration of zosuquidar increases the tumor cell exposure to chemotherapy, whereas potentially reducing dose-related toxicity. The development team posed the following question: What dosing regimen of zosuquidar should be used in combination with chemotherapeutic agents?

In this example, population PK/PD models were developed separately for zosuquidar and the cytotoxic agent. These models were applied to identify the potentially optimal combination-dosing regimen. The IC<sub>90</sub> (90% of maximum P-gp inhibition) of zosuquidar was determined to be 170 ng/mL by modeling both the zosuquidar exposure and a biomarker of the percentage of inhibition of P-gp activity in vivo (Figure 8). The inhibition of P-gp was determined in patients using a surrogate assay of P-gp function, which measured rhodamine 123 (a fluorescent substrate of P-gp) uptake in CD56 cells. Identification of this PK/PD relationship supported the use of a clinically feasible short-duration infusion ( $\leq 6$  hours, as opposed to 24 hours) to be investigated in a subsequent combination phase I trial with daunorubicin.<sup>19</sup>

In a phase I clinical trial, zosuquidar and doxorubicin were administered separately and concomitantly to 40 cancer patients on 2 occasions (cycles of treatment). Zosuquidar was given as a 48-hour continuous intravenous infusion, and doxorubicin was administered as a 30-minute intravenous infusion, 24 hours after the start of zosuquidar infusion. Plasma samples were collected to characterize the PK of doxorubicin and doxorubicinol in the presence and absence of zosuquidar. The PK model building and selection process have been published elsewhere.<sup>19,20</sup> The final model consisted of a 3-compartment model for doxorubicin, a 2-compartment model for doxorubicinol, and interindividual and interoccasion variability on key PK parameters. The effect of zosuquidar on doxorubicin and doxorubicinol clearance and volume of distribution was assessed as a categorical covariate (dose  $\geq 500$  mg or  $< 500$  mg). The model

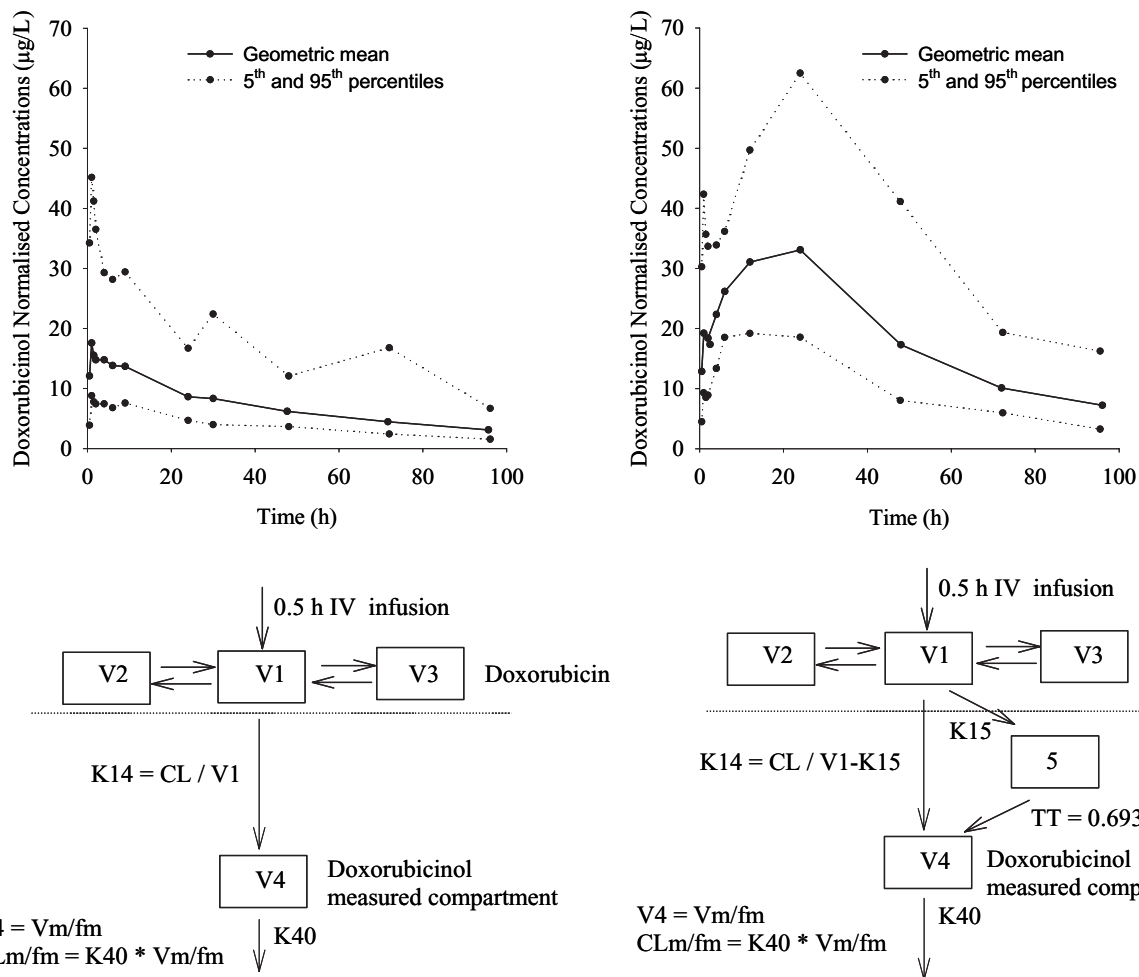


**Figure 8.** Percentage inhibition of rhodamine 123 P-gp-mediated efflux versus zosuquidar steady-state plasma concentration. The solid line is the model predicted median, the blue-shaded band is the 95% CI of the mean, and the dashed lines are 95% population prediction limits.

identified a significant PK effect of zosuquidar at doses  $\geq 500$  mg on doxorubicin and doxorubicinol. Doxorubicin clearance, peripheral volume of distribution, doxorubicinol apparent clearance, and apparent volume of distribution in the presence of high doses of zosuquidar ( $\geq 500$  mg) decreased by 25%, 26%, 48%, and 73%, respectively.

Doxorubicinol concentration versus time profiles showed differences (increase in AUC and delayed time to maximum concentration, or  $t_{\max}$ ) when the total dose of zosuquidar was  $> 500$  mg (Figure 9, top). A model with 5 compartments best accounted for these differences (Figure 9, bottom). The doxorubicin PK model was the input function for the doxorubicinol PK model; a fourth compartment was linked to the central compartment (assuming all of the doxorubicin is converted to doxorubicinol). This model adequately predicted the doxorubicinol PK profile, in the absence or presence of low doses ( $< 500$  mg) of zosuquidar. The fifth compartment (2 additional parameters) helped to characterize the later  $t_{\max}$  (24 hours versus 4 hours, median  $t_{\max}$  in cycle 1) observed in the doxorubicinol PK profile with zosuquidar (dose  $\geq 500$  mg).

Although the model is empirical, there is an underlying mechanistic rationale: the fifth compartment allows a delay to occur between doxorubicinol input and output. In effect, this acts as a “depot” compartment and mimics the hypothesis that P-gp inhibition prevents the doxorubicinol clearance. Hence, doxorubicinol plasma concentrations increase toward an equilibrium state until P-gp inhibition is terminated. The short distribution half life of zosuquidar (0.4 hours) and the direct PK/PD relationship (Figure 8) support the hypothesis that the decrease in doxorubicinol



**Figure 9.** Doxorubicinol pharmacokinetic profiles at 0 to < 500 mg of zosuquidar (top left), at ≥ 500 mg of zosuquidar (top right), and the corresponding models (bottom).

concentration after 24 hours occurs because, at the end of P-gp inhibition, zosuquidar concentrations declined rapidly, removing the P-gp inhibition and allowing the fractional clearance of doxorubicinol mediated by P-gp transport to resume. The 500-mg cutoff was consistent with the mean plasma IC<sub>90</sub> (90% of maximum P-gp inhibition, or 170 ng/mL) of zosuquidar determined from the modeling of zosuquidar exposure-percent P-gp inhibition-response relationships.

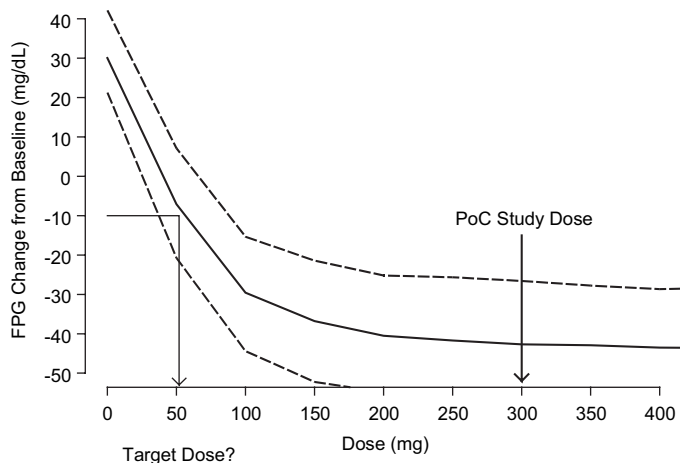
Results from M&S suggest that a shorter (more convenient and economical) zosuquidar intravenous infusion schedule (6 hours) was feasible. The shorter length of infusion produces maximal P-gp inhibition while minimizing the PK interaction. A flexible infusion schedule can be designed to optimize the duration of maximal P-gp inhibition with minimal impact on elimination of the oncolytic and, hence, toxicity. Understanding and quantifying the degree of the PK interactions with a coadministered cytotoxic agent using a population modeling approach permitted the combination of the NCE with standard doses of chemotherapy in subsequent trials.

### Phase II/III: Drug-Disease Modeling and Study Designs

In late-stage drug development, the goal is to leverage the information obtained from previous clinical trials and design phase III studies that will most efficiently generate conclusive and confirmatory information about the safety and efficacy of the drug. In this pursuit, the objectives of PK/PD-based M&S can be divided into the design of clinical trials and the efficient analyses of data that will adequately support the regulatory filing. Clearly, the overarching aim is to understand the attributes of a NCE versus existing therapy and facilitate the benefit-risk assessments.

### Case Study

A NCE was being developed for the treatment of hyperglycemia in type 2 diabetes. To meet regulatory objectives, the desirable clinical outcome was to demonstrate a meaningful decrease in fasting blood/plasma glucose (FPG) and hemoglobin A1c (HbA1c). Both of these measurements can be considered “causal path” biomarkers and are well accepted by regulatory agencies.<sup>21</sup> The initial M&S



**Figure 10.** Change in FPG at 12 weeks. Solid curve is median glucose response; dashed lines are 5% and 95% of response. Vertical and horizontal lines with arrows indicate target dose(s) at target response.

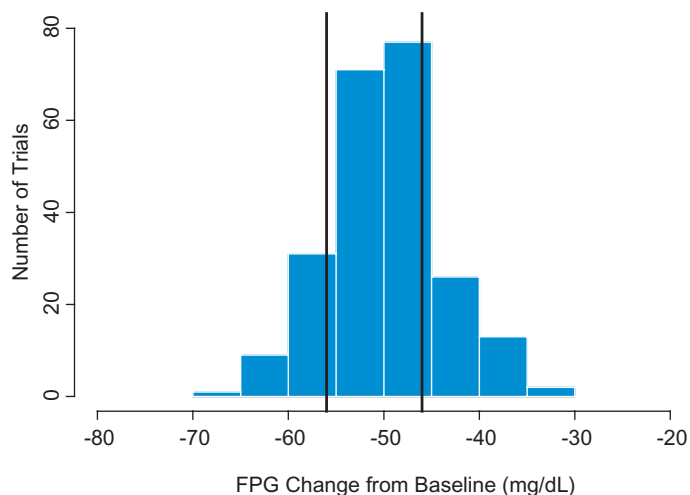
approach required the development of a drug-and-disease model based on comparator data in published literature. This model allowed an evaluation of the benefits that could accrue by conducting a PoC study for a NCE with high prior information. Once the PoC was established for the NCE, the focus of drug development shifted to understanding the optimal use of a NCE (Table 1). The PoC study demonstrated lowering of blood glucose in a 4-week study at a dose near the maximum tolerated dose. Because the mechanism of action was novel, a clear benefit over existing therapy is not known. Furthermore, nonclinical safety and early clinical data indicated a risk of QT/QTc (heart-rate corrected QT) interval prolongation. Therefore, in addition to the drug-disease model for glucose (and HbA1c), a model describing the time course of change in QT and its relationship to concentration was also developed based on proprietary and literature information.<sup>22,23</sup> A 12-week phase IIB study is being designed that will lead into a large phase III study. Among others, the development team posed the following questions: (1) what are the efficacy attributes of the NCE relative to a comparator or existing therapy; (2) how many doses (and/or dose strengths) should be studied in phase II and III; (3) what are the impact of study design considerations, such as the use of other hypoglycemic agents, washout duration in the lead-in phase, and dropout rates? (4) what is the value of using a comparator (positive) in these studies, which comparator should be used, and at what dose; and (5) what are the characteristics of the study population (eg, body weight, baseline FPG/HbA1c, renal function, and concomitant medications) and how will they contribute to the overall variability in response?

These questions can be categorized into those evaluating the attributes of the NCE and those that address specific trial-design considerations. The drug-and-disease model

was updated based on the additional information attained from the PoC study. The first application of the model was to explore the likely dose-response relationship for the NCE. The goal was to choose a dose range for the phase II trial that would maximize the probability of achieving a target response. Figure 10 illustrates the distribution of the response (change from baseline FPG) from 200 replications of a trial at 12 weeks. The simulation results provide insight into the choice of doses that could be included in the phase II dose-ranging trial. The results can be used to evaluate the probability of achieving a target response at a selected dose or, conversely, to evaluate the probability that a certain dose will achieve a target response. At 12 weeks, a 50-mg dose was predicted to yield a 10-mg/dL decrease in FBG from baseline. Based on the model, this effect translated to a 50-mg/dL improvement in FBG compared with placebo, a clinically significant effect on glucose. The model predicts that there is a 90% chance that the median response will fall between 4 mg/dL and -26 mg/dL at the 50-mg dose; the corresponding doses at these percentiles can also be identified. Based on the analyses of simulations, appropriate doses to be included in a dose finding study were determined.

Once developed, models should be “validated.” A simplified predictive check is illustrated in Figure 11, whereby observed mean glucose response for a comparator is captured within the distribution of simulated outcomes. More extensive validation methods, such as posterior predictive check, can be used;<sup>24</sup> the scope and extent of validation testing will depend on the use of the model.

Inherent assumptions necessary for the projection of dose-response curves are the properties of the dose-response relationships (eg, potency, maximal effect, and steepness



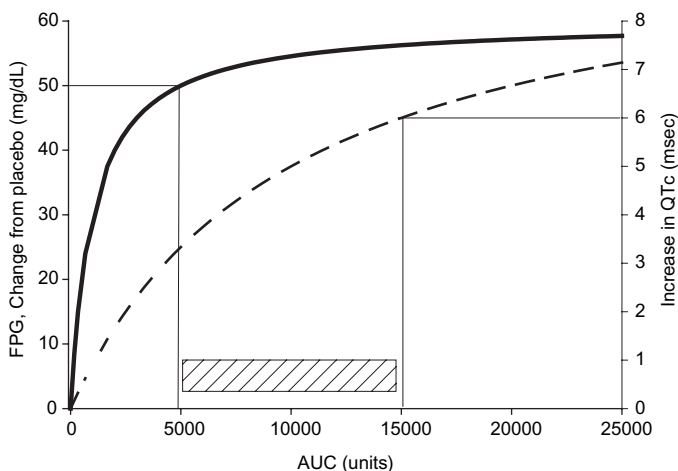
**Figure 11.** Distribution of median response from 200 simulated trials. The histogram describes the median response from 200 trials at 12 weeks. The horizontal lines are observed data from 2 separate clinical trials of the comparator.

**Table 8.** Power to Determine a Dose Response

Design	Dose Groups (mg)	Sample Size per Arm	Power
1	0, 50, 100, 300	50	0.89
2	0, 50, 300	50	0.92
3	0, 100, 300	50	0.58
4	0, 50, 100, 300	10	0.68
5	0, 50, 100, 200, 300	40	1.0

of the dose-response). Once the desired target effect (eg, a 50-mg/dL decrease in FPG) was identified, the focus could shift to the optimization of the study design to robustly demonstrate that effect. A specific trial design was chosen to provide the highest probability of demonstrating a particular effect given the assumptions and uncertainties. The power to detect a dose response of a NCE that can be achieved through alternative trial strategies or by varying dose groups and number of subjects is illustrated in Table 8. Briefly, for each replication of a trial design, the mean response data (change from baseline as a function of dose) were fit to 2 basic models for statistical assessment of dose-response. The first model assumed that all of the doses were equivalent (namely, flat dose-response); the second assumed that there was a basic  $E_{max}$  dose response. A difference in the objective functions of  $>3.84$  was considered significant at the  $p < 0.05$  level for 1 additional parameter; thus, a dose response was declared for that trial. The percentage of 200 trial replications that positively identified a dose response was considered the power of the trial design to determine a dose response.

On the completion of the phase IIB trial, analyses of data can be accomplished in the following 2 parts: (1) population PK analyses to explain the variability,<sup>24</sup> and (2) population PD analyses to describe the time course of glucose



**Figure 12.** Top. median exposure-response relationship: FPG and QTc prolongation.

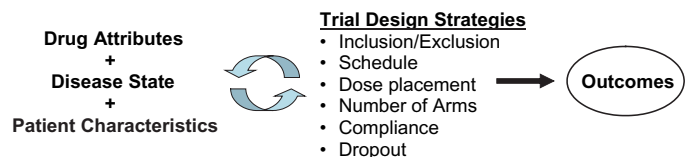
response across the dose groups. The results from the phase IIB study should be used to update the drug and disease model so that this model can be more informative for additional predictions. In this example, selection of doses for a phase III trial needed to take into consideration the decrease in FPG (efficacy), as well as the prolongation in QT (safety).

Figure 12 illustrates the model-predicted median exposure-response relationship for the 2 end points, change in FPG and QTc prolongation. Thus, if the desired median effect on FBG is a decrease of 50 mg/dL from placebo, and the QTc prolongation should not exceed 6 ms, then a therapeutic concentration range and corresponding dose range can be identified. Thus, understanding these exposure-response relationships<sup>25</sup> can be used to define a therapeutic index of a drug.<sup>26</sup> Understanding the associated PK and PD variability will allow for appropriate dosage adjustment in special populations.

### CONCLUSION

Model-based drug development programs (Figure 13) that integrate knowledge of the disease state, drug attributes, and patient characteristics to predict the range of possible outcomes have been proposed as an approach more-effective use of knowledge and development decision making.<sup>27</sup>

Simulation is an important tool that has the ability to capture the variability and uncertainty that is implicitly inherent in drug development programs. The prerequisite to conducting meaningful simulations is the availability of an appropriate drug and disease progression model. These models can be built using data from the literature and from information in the public domain; and they can be structured to explore the current understanding of the drug characteristics. Timing is critical; the development of models should begin well in advance of a drug entering clinical development so that the model can be used and refined by each decision-making process. In each of the example M&S projects, model development was prospectively planned, and focused simulations were performed well in advance of the clinical trial. Each model was updated during the development process based on results of new trial data. PK/PD M&S are increasingly being used to accelerate and streamline the drug development process.<sup>28</sup>



**Figure 13.** Drug and disease model.

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