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REVIEW

Model-based drug development: application of modeling and simulation in drug development

Tae Hwan Kim[1] · Soyoung Shin[2] · Beom Soo Shin[3]

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Abstract

Despite enormous success in biomedical science and technology, as well as increased research and development spending, pharmaceutical productivity has faced challenges. The success rates in drug development remain low and have shown a declining trend in the last two decades. The US FDA has also recognized the inefficiency in drug development and proposed model-based drug development (MBDD) to improve pharmaceutical productivity and decision making. Modeling and simulation provide a powerful tool to summarize and integrate information from different studies. Application of modeling and simulation can help decision making, design better studies, reduce costs, save time, and ultimately improve success rates. Beyond traditional types of modeling techniques or applications, MBDD is a paradigm that covers the entire spectrum of the drug development process. This review aims to provide an overview of modeling and simulation and their application to various drug development processes, from early discovery to preclinical and clinical stages, as well as formulation optimization. Several types of models will be discussed, and illustrative examples of their applications in the drug development process will be highlighted.

Keywords Model-based drug development · Modeling and simulation · Pharmacokinetics · Pharmacodynamics · Physiologically based pharmacokinetic model · In vitro–in vivo correlation

Introduction

Although the cost and time invested in pharmaceutical research and development (R&D) has been steadily increasing, the number of newly developed medicines continues to decline. It has been reported that around 90% of all potential drugs that enter Phase I clinical trials fail in later phases, and less than 10% ultimately reach the market (Smietana et al. 2016). Moreover, the success rates in drug development have largely declined for more than a decade (Smietana et al. 2016). This means that recent drug development efforts remain costly and inefficient.

To increase the efficiency of pharmaceutical R&D, introduction of a new methodology may be necessary. The need for improved productivity in the pharmaceutical industry has also been recognized by the United States Food and Drug Administration (US FDA). The US FDA has established the "Critical Path Initiative," which proposed the utilization of model-based drug development (MBDD) in 2004 (FDA 2004) and identified innovations in clinical evaluations as a major scientific priority area (Huang et al. 2013).

MBDD is an approach to improve drug development by using pharmacokinetic (PK) and pharmacodynamic (PD) models to describe and predict drug and trial behavior, thereby improving drug development and decision making (FDA 2004). While PK describes the time course of drug concentrations, PD refers the characterization of the drug effect resulting from drug concentrations at the effect site. The relationship between drug dose and plasma concentration and drug effect or side-effects is characterized in the PK and PD model, respectively (FDA 2004). Although they

Tae Hwan Kim and Soyoung Shin have contributed equally to this work.

✉ Beom Soo Shin
bsshin@skku.edu

[1] Department of Pharmaceutics, Center for Pharmacometrics and Systems Pharmacology, College of Pharmacy, University of Florida, 6550 Sanger Road, Orlando, FL 32827, USA

[2] College of Pharmacy, Wonkwang University, 460 Iksan-daero, Iksan, Jeonbuk 54538, South Korea

[3] School of Pharmacy, Sungkyunkwan University, 2066 Seobu-ro, Jangan-gu, Suwon, Gyeonggi 16419, South Korea

have long been used in the critical phases of drug development process, systemic application of the models into the drug development process has the potential to significantly improve it. Decisions taken during a drug development program to improve drug performance include go/no-go decisions, dosing levels, end points, timing of trials, and many more factors, both clinical and nonclinical. Other decisions that affect the chances of success and the commercial feasibility of a drug candidate include trial design considerations, such as country selection, site selection, patient enrollment, drug supply, staffing for monitors, among others. Each of these decisions could benefit from appropriate statistical models and trial simulation technologies (Reeve et al. 2015).

The drug development process is a stepwise process starting with in vitro biochemical and pharmacology studies, followed by in vivo animal studies, small healthy human volunteer studies, and finally large patient efficacy and safety studies (Leil and Bertz 2014). As confidence in the probability of success of a test molecule increases following this process, the investment in further characterizing a candidate molecule is incrementally increased (Leil and Bertz 2014). After a drug is successfully marketed, life cycle management, such as new formulation development, new routes of delivery, new indications, expansion of the indicated population, or development of combination products (Modi 2017; Moon and Oh 2016), also requires investment of time and resources. Modeling and simulation techniques can be utilized from early drug discovery to development, commercialization, and even life cycle management. This review intends to provide an overview of the utility of modeling and simulation across drug development processes. Several examples of the applications of modeling and simulation will be highlighted.

Modeling and simulation

Modeling is the process of interpreting multifactorial data including disease, mechanisms, and compound characteristics, and their interplay in the form of mathematical relationships based on certain assumptions (Zhang et al. 2008; Workgroup et al. 2016). The complexity of a model is determined by its intended use, and the value of the model is determined by how useful it is for its intended purpose.

Modeling involves cycles of development and validation to find the best model that helps predict how a system will behave without real-life testing. Once initial data are obtained, the first and most critical step of the modeling procedure is designing of a model structure that can describe the obtained data. Next, the structural model is translated into a series of mathematical equations using various modeling software, followed by finding the optimal parameters for the observed data. Once the parameters are estimated, the data predicted by the model are compared with the observed data, which is called "model validation." If the predictions do not properly describe the observed data, the structural model should be modified, and the process repeated until the model is successfully validated. The model can be further validated by evaluating its predictions by simulation compared to data not used in model development. If the model finally passes validation, the model can be utilized for simulation and prediction.

Pharmacokinetic models (compartment model vs. physiologically based PK models)

PK models describe the time-course of drug concentrations. The most commonly employed approach in PK models is to represent the body as a system of compartments. A compartment is a group of tissues or organs in which the drug is well-mixed and kinetically homogenous, and serves as the building block for many PK models. Therefore, compartments are usually conceptual and do not have any physiological or anatomical relevance. Mammillary models generally have a central compartment with one or two peripheral compartments linked by rate constants (Wagner 1975; Mould and Upton 2012). As model parameters are defined by rate constants, they are not directly interpreted for any physiological meaning, but can provide more interpretable PK descriptors such as clearance and volume of distribution (Jones and Rowland-Yeo 2013).

Although compartmental models are pragmatic, they are mainly empirical and descriptive without mechanistic insights. In cases where diversity in chemical structures and species and high inter-individual PK variabilities exist, physiological models have enormous potential. Compared with compartment models, physiologically-based pharmacokinetic (PBPK) models usually consist of a larger number of compartments, which correspond to the different organs or tissues in the body connected by circulating blood flow (Fig. 1). Each compartment is defined by tissue volume (or weight) and tissue blood flow rate, which differ across species.

PBPK models comprise physiological parameters, drug-specific parameters, and the structural model (Rowland et al. 2011). Although physiological parameters represent organ mass or volume, blood flow, and tissue composition, drug-specific parameters represent tissue affinity, protein-binding affinity, membrane permeability, enzymatic stability, and transporter activities. The structural model consists of the anatomical arrangement of the tissues and organs of the body, which is drug-independent and the same for all mammalian species. Thus, the complexity of the PBPK model varies from a whole body PBPK model to a reduced model with lumped tissues for its intended use. Within the global structural model, each tissue or organ is commonly

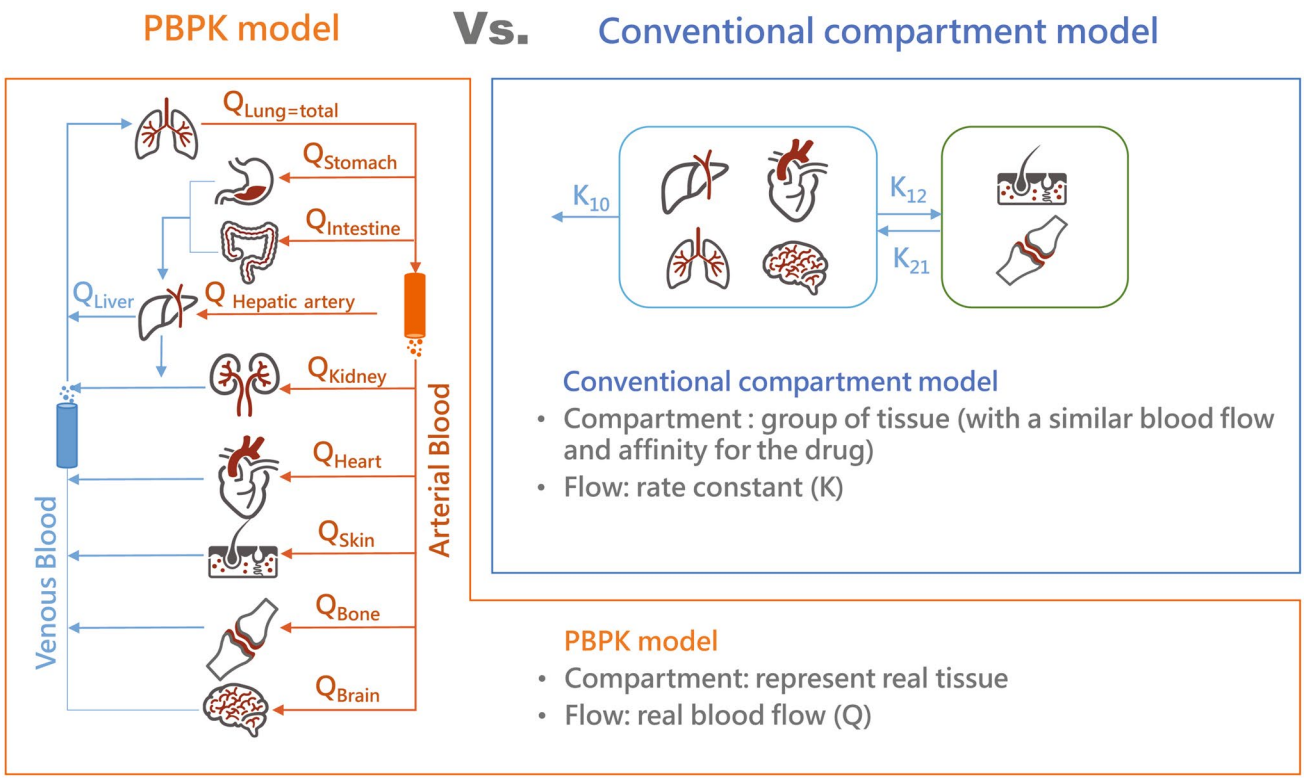

Fig. 1 A conventional compartment model and physiologically-based pharmacokinetic (PBPK) model

represented as a single, well-stirred, or perfusion rate-limited compartment, especially when considering small lipophilic compounds. For many modern drug candidates with large molecular weights, however, more complex representations such as membrane permeability and role of transporters and their interplay with enzymes may need to be included (Watanabe et al. 2009; Poirier et al. 2009).

The major advantage of a PBPK model is its predictive power. By replacing parameters, a PBPK model developed based on one species can be used to model and predict PK for another species of interest. PBPK modeling can provide a better prediction of human PK than empirical approaches (Jones et al. 2006; Luttringer et al. 2003). PBPK modeling could also anticipate the quantitative extent of PK-based drug–drug interactions (DDI) and the impact of age, genetics, disease, and formulation on PK (Rowland et al. 2011). A PBPK model for the all-trans-retinoic acid (ATRA) provides an illustrative example of a successful application of this approach. The model was developed to characterize the PK of ATRA and its metabolites across species and routes of administration, and allowed assessment of the human teratogenic risk from ATRA based on animal data (Clewell et al. 1997). The PBPK model was then used to evaluate potential fetal exposure to ATRA from a topical skin treatment containing ATRA, and facilitated its successful review and subsequent approval by the FDA (Rowland et al. 2004).

Pharmacodynamic models

Pharmacodynamics (PD) encompasses the relationship between drug concentrations and pharmacological effects. The combination of PK models with PD models, i.e., PK/PD modeling, is the mathematical approach that links the time-course of drug concentration (PK) and concentration-effect relationships (PD), and allows a description of the complete time-course of the drug effect to a given dosing regimen (Derendorf and Meibohm 1999; Zhang et al. 2008). Figure 2 illustrates a representative diagram for the relationship between PK and PD (Shin et al. 2008). Most PK/PD models utilize plasma drug concentrations which "drive" the PD. This is especially true for mechanism-based PK/PD modeling, which considers the underlying physiological response, can also help in the identification and evaluation of drug-response determinants, and facilitate predictive simulations for optimizing future development steps (Meibohm and Derendorf 2002).

Binding of drug molecules to target biomolecules such as enzymes, receptors, and DNA initiates pharmacological responses that are generally dependent on the administered dose, with a higher receptor-drug binding typically producing a greater response (Clark 1926). The law of mass action and the relatively low quantity of targets leads to a capacity limitation in most pharmacological responses. Thus, as the

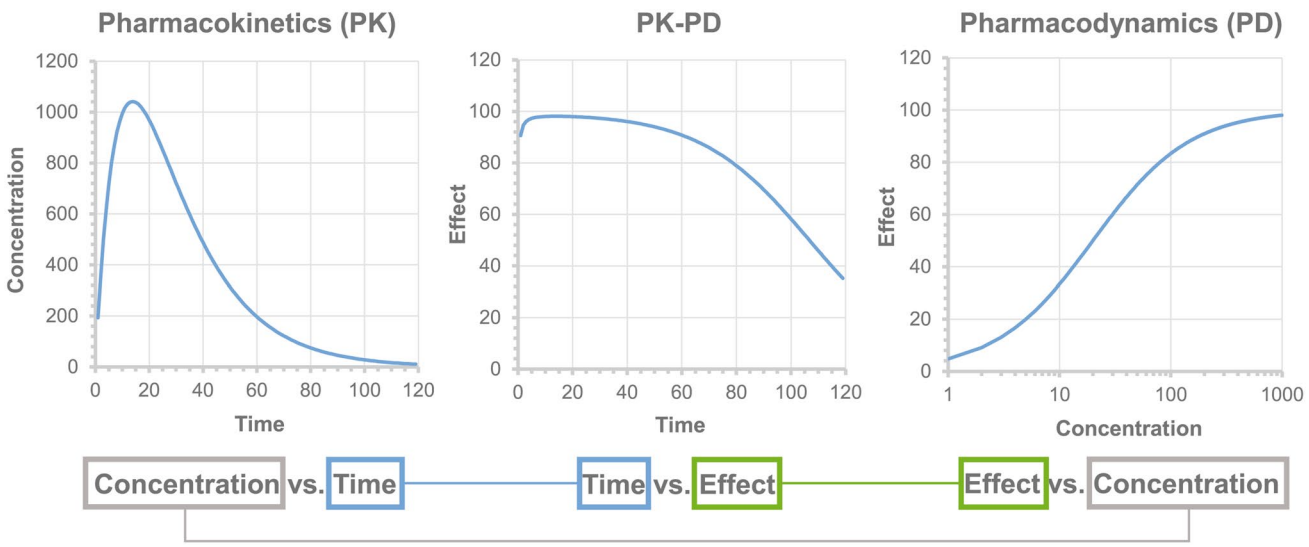

Fig. 2 Representative diagram for relationship between pharmacokinetics (PK) and pharmacodynamics (PD). Pharmacokinetic-pharmacodynamic (PK/PD) modeling combines PK and PD and allows characterization and prediction of the time-course of drug effects

dose increases over a certain point, the response may be saturated and the relationship between drug concentration and response becomes nonlinear. At steady state, following long-term intravenous infusion, drug concentrations in all parts of the body remain constant with time. Thus, the relationship between steady-state concentrations and the magnitude of drug effects can be obtained, which is time-invariant or static. Several mathematical models to describe static drug concentration–response relationships are available, including the maximum effect (E_{max}) model, log-linear E_{max} model, and the sigmoid E_{max} model. These static models are highly useful, but they are limited to equilibrium or steady-state conditions and unable to describe the time-course of pharmacological effects following acute dosing, which may provide better understanding of the mechanisms of drug action.

Kinetic models relate the time-course of drug concentration to that of drug response, and provide more complete characterization of PD and better insight into the underlying mechanisms of the effects (Shin et al. 2008). The simplest kinetic models, the direct effect models, assume a direct relationship between plasma drug concentration and response. Several models have also been developed to describe mechanisms responsible for the delay between the time-courses of plasma concentration and drug effects. For example, the biophase model assumes that a delay is associated with drug distribution into the active site, i.e., biophase. Indirect response models assume that the delay is related to the production or elimination of endogenous substances related to the observed drug effect. Transduction models attempt to describe a cascade of signaling events that act as intermediates between drug-receptor binding and drug response. Models to characterize irreversible drug responses and complexities such as tolerance and sensitization are also available.

Allometric scaling

Although PBPK modeling has a unique advantage in interspecies scaling, extrapolation from animals to humans is primarily based on classical allometric relationships. Unlike PBPK models, which tend to be resource-demanding and costly, allometric scaling uses data that are routinely obtained during drug development and relatively simple calculations (Ings 1990). Thus, allometric scaling has been practically used for the estimation of first-in-human (FIH) doses in clinical trials. It is generally observed that PK and biological turnover parameters are predicted by using allometric principles and pharmacological capacity (E_{max}) and sensitivity (EC_{50}) parameters are mostly similar across species (Mager and Jusko 2008).

Allometric scaling is an empirical relationship among size, time, and its consequences such as PK, without mechanistic understanding. Similarities in structural, physiological, and biochemical properties among species allow allometric equations that characterize the dependence of biological variables (θ) on body weight (W) (Dedrick 1973; Mordenti 1986):

$$\theta = a \times W^{b}$$

where a and b are drug/process coefficients. A regression of the logarithm of the equation produces a linear relationship and allows estimation of PK parameters in any animal species. The allometric exponent, b, is approximately 0.75

for clearances, 1.0 for organ sizes or volumes, and 0.25 for physiological times (Boxenbaum 1982). These relationships seem to be reasonably uniform across animal species (Boxenbaum 1982; Ritschel et al. 1992; Lin 1995) and provide a useful tool in predicting human PK parameters. Simple allometry is useful for drugs that generally exhibit low protein-binding, are eliminated via renal excretion or blood flow-limited hepatic metabolism, and do not involve transporter mechanisms (Huang and Riviere 2014). Figure 3 illustrates an interspecies correlation between a PK parameter and body weights based on the data obtained from four animal species, and the prediction of a human parameter.

However, the simple allometric scaling for the prediction of PK parameters can be misleading for some drugs. There is poor prediction for humans with simple allometric scaling for drugs that are highly protein-bound, have significant biliary excretion, extensive active renal secretion, active metabolism, and other transport processes, or have species-specific binding or distribution (Huang and Riviere 2014). Alternative approaches to improve the predictive performance of allometry have been reported, especially for clearance. Despite no physiological significance, the prediction of clearance can be improved by including brain weight or maximum life-span potential terms into the allometric equation for drugs undergoing extensive hepatic metabolism and renal elimination (Mahmood and Balian 1996). Various innovative approaches have also been reported by incorporating the rule of exponents, protein binding, in vitro data, etc. (Huang and Riviere 2014). Several species-invariant time methods, such as Dedrick plots, which correct species differences in physiological time, are also available to estimate clearance (Shin et al. 2003).

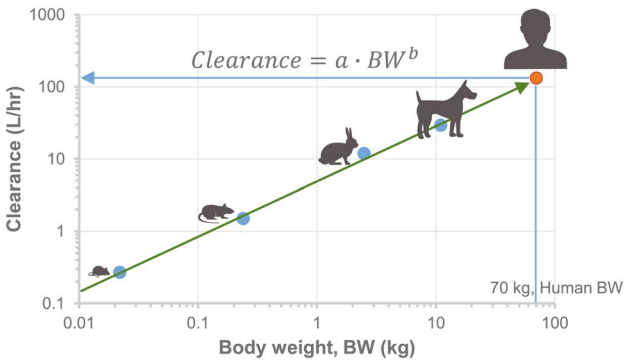

Fig. 3 Interspecies correlation between pharmacokinetic parameters and the body weights

In vitro and in vivo correlation

According to the FDA, in vitro and in vivo correlation (IVIVC) has been defined as "a predictive mathematical model describing the relationship between an in vitro property of an extended-release (ER) dosage form and a relevant in vivo response" (FDA 1997). Once IVIVC is established during formulation development, the in vitro dissolution properties can serve as a surrogate for the in vivo PK study, which can accelerate the formulation development process (Cardot and Davit 2012).

There are four levels of IVIVC defined by the FDA (FDA 1997). The level A IVIVC is the most preferred, correlating entire in vitro dissolution and in vivo input profiles, whereas levels B, C, and multiple-level C designations describe relationships based on the summary statistics derived from in vitro and in vivo data (Table 1) (FDA 1997; Dunne et al. 2005).

In establishment of level A IVIVC, characterization of appropriate in vivo input profiles is one of the most challenging steps. Several conventional deconvolution approaches such as Wagner-Nelson, Loo-Riegelman, and numerical deconvolution have been widely employed to extract in vivo absorption profiles from blood drug concentration–time profiles. Wagner-Nelson and Loo-Riegelman methods are both model dependent approaches, assuming one-compartment and multi-compartment systemic disposition models, respectively (Wagner and Nelson 1963; Loo and Riegelman 1968). Numerical deconvolution is a model-independent method not implementing pharmacokinetic model assumptions (Cutler 1978). However, these approaches rely on the assumption that the rate-limiting step in the in vivo input is the drug dissolution process, and that absorption is rapid and complete. Once the in vitro dissolution and in vivo input profiles are obtained, the relationship between in vitro and in vivo data needs to be further determined to develop IVIVC (FDA 1997; Pharmacopoeia 2004). Unlike these two-stage deconvolution approaches, single-stage convolution methods

Table 1 Four levels of IVIVC defined by the US FDA (FDA 1997)

Level	In vitro	In vivo
A	Dissolution profile	Input profile
B	Mean dissolution time (MDT)	Mean residence time (MRT) Mean absorption time (MAT)
C	Dissolution parameter ($t_{50\%}$, $t_{90\%}$, etc.)	Pharmacokinetic parameter (AUC, T_{max}, or C_{max})
Multiple C	Amount of drug dissolved at several time points (at least three dissolution time points)	One or more pharmacokinetic parameters of interest (C_{max}, AUC, etc.)

have also been proposed. Using the convolution model, the in vivo input data is simultaneously described with systemic PK, which allows the prediction of blood concentration–time profiles from in vitro dissolution profiles (O'Hara et al. 2001). Although the conventional IVIVC approaches have limited applications to highly permeable drugs such as biopharmaceutical classification system (BCS) class I and II drugs, recent approaches have shown their potential to establish IVIVC for drugs with complex physiological absorption processes (Abuhelwa et al. 2016; Kim et al. 2017).

Applications of modeling and simulation in drug development

Modeling and simulation can be applied to all aspects of drug development from drug discovery to preclinical, clinical, and life cycle management (Fig. 4). Various purposes and benefits of the modeling and simulations applied in the drug development process are introduced with several examples (Table 2).

Drug discovery

At the discovery stage, modeling and simulation can be used in identifying new targets and characterizing target mechanisms (Workgroup et al. 2016). Systems approaches have been used in pharmacology to understand drug actions at the organ level (Zhao and Iyengar 2012). Quantitative systems pharmacology modeling is now more broadly intended to quantitatively characterize biological systems, disease processes, and the effects of drug actions on the system, leading to identification of drug targets and mechanisms of action. Physiologically based absorption and PK modeling and simulations have also provided useful tools to screen potential drug combinations by quantitative assessment on PK interactions for fixed dose combination products (Moon and Oh 2016). These modeling approaches could be applied to enable decision making not only at the stage of early discovery, but also at later stages of drug development.

For example, the use of mathematical models to identify key factors in disease has been reported for hepatic steatosis (Wallstab et al. 2017). The model captures the triglyceride metabolism of animal cells and a multitude of molecular processes driving cellular lipid droplet dynamics. Model simulations evaluate how variations in the lipid load of hepatocytes, and in the abundance of enzymes and proteins, may affect the size distribution of lipid droplets, and finally, identify key molecular players in the development of hepatic steatosis (Wallstab et al. 2017).

Dwivedi et al. demonstrated the potential utility of mechanistic models of disease biology to study drug-system interactions (Dwivedi et al. 2014). A multiscale systems model of interleukin (IL)-6-mediated immune

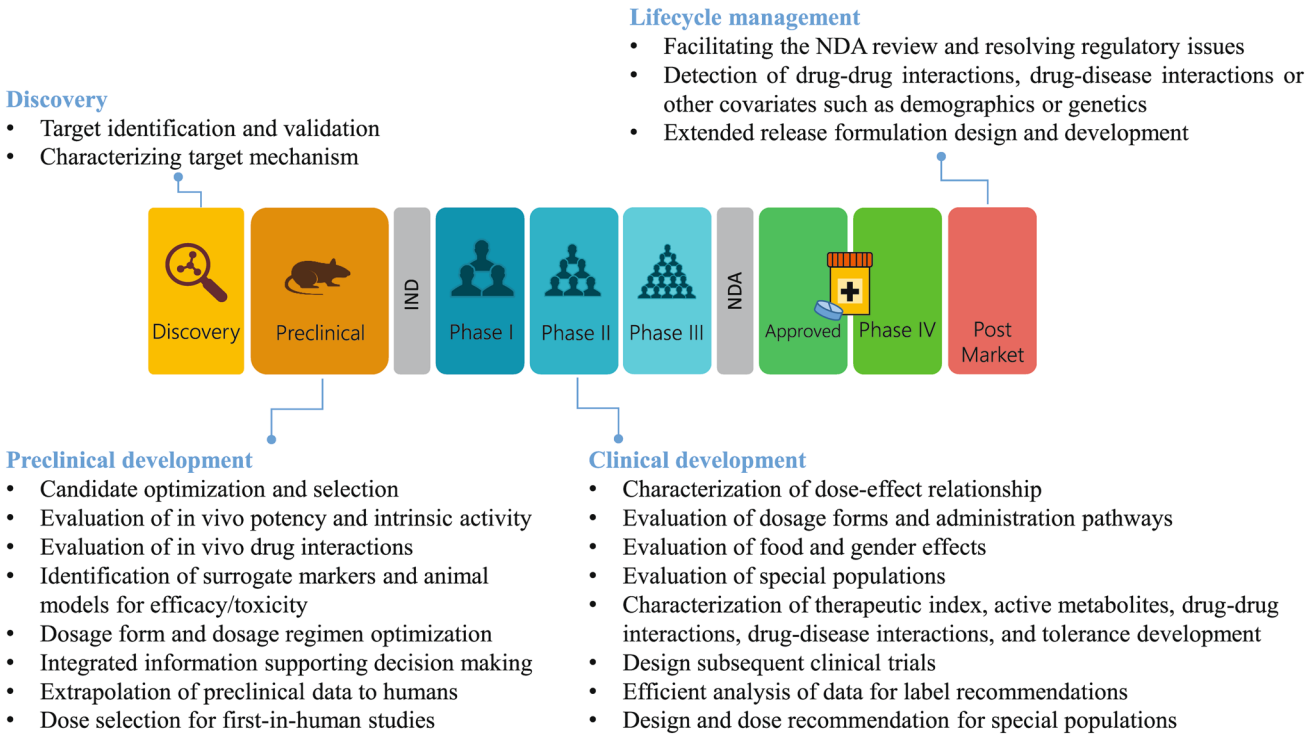

Fig. 4 Modeling and simulation during drug development

Table 2 Application of modeling and simulation in the drug development process

Phase	Types of model	Applications	Examples
Discovery	Systems pharmacology PK model PK/PD model	• Target identification and validation • Characterizing target mechanism	Wallstab et al. (2017), Dwivedi et al. (2014), Kirouac et al. (2013)
Preclinical development	PK model PK/PD model PBPK model Allometric scaling	• Candidate optimization and selection • Evaluation of in vivo potency and intrinsic ativity • Evaluation of in vivo drug interactions • Identification of surrogate markers and animal models for efficacy/toxicity • Dosage form and dosage regimen optimization • Integrated information supporting decision making • Extrapolation of preclinical data to humans • Dose selection for first-in-human studies	Yu et al. (2011), Wong et al. (2013), Chien et al. (2005), Sinha et al. (2012)
Clinical development	PK model PK/PD model PBPK model Population model	• Characterization of dose–effect relationship • Evaluation of dosage forms and administration pathways • Evaluation of food and gender effects • Evaluation of special populations • Characterization of therapeutic index, active metabolites, drug-drug interactions, drug-disease interactions, and tolerance development • Design subsequent clinical trials • Efficient analysis of data for label recommendations • Design and dose recommendation for special populations	Kretsos et al. (2014), Callies et al. (2004), Chien et al. (2005), Johnson et al. (2014), Girgis et al. (2010), Almukainzi et al. (2017)
Lifecycle management	PK model PK/PD model IVIVC	• Facilitating the NDA review process and resolving regulatory issues • Detection of drug-drug interactions, drug-disease interactions or other covariates such as demographics or genetics • Extended release formulation design and development	Guentert et al. (1995), Kovacevic et al. (2009), Abuhelwa et al. (2016), Kim et al. (2017)

regulation in Crohn's disease was developed and combined with a general pharmacokinetic model for monoclonal antibodies. By comparing various biotherapeutic strategies targeting IL-6-mediated signaling in Crohn's disease, the model indicated that targeting IL-6, IL-6Rα, or the IL-6/sIL-6Rα complex are less effective than dual targeting of the IL-6/sIL-6Rα complex in addition to IL-6 or IL-6Rα (Dwivedi et al. 2014).

Similarly, a multiscale systems model of signaling networks in ERBB2-amplified breast cancer was developed to design treatment regimens. This model demonstrated that combined ErbB2/3 blockade is superior to the combination of MEK and AKT inhibitors. Model simulations were used to design optimal drug combination regimens, and identify predictive biomarkers of drug sensitivity and resistance (Kirouac et al. 2013).

Preclinical development

In the preclinical development stage, drug candidates are characterized for physicochemical properties, absorption, metabolism, distribution, and excretion (ADME), and efficacy and safety. Various modeling approaches including PK, PK/PD, and allometric scaling are widely utilized for candidate optimization, selection, and human dose predictions. The modeling and simulation at this stage are primarily designed to "learn" about the properties of the molecule that are then "confirmed" by the data generated in early clinical development (Sheiner 1997; Chien et al. 2005). Major aims of the modeling approaches at this stage include candidate optimization and selection, evaluation of in vivo potency, intrinsic activity, drug interactions, identification of surrogate markers and animal models for efficacy/toxicity,

optimization of dosage forms and regimens, integration of information supporting decision making, extrapolation of preclinical data to humans, and dose selection for FIH studies.

For example, a mechanism-based PK/PD binding modeling approach could be applied to candidate comparisons and human dose selection. The modeling approach was used to estimate the minimum acceptable biological effect level (MABEL) for a FIH study based on PK, receptor occupancy, and cell dynamics in cynomolgus monkeys for a novel monoclonal antibody (Yu et al. 2011).

In the case of a new chemical entity (NCE) with a large amount of prior information from other drugs in its therapeutic class, modeling and simulation allow evaluation of several NCEs and identify the optimal clinical candidate. Then, PK/PD modeling could support the dose selection for phase I studies. Wong et al. described how modeling and simulation techniques could be implemented into the integrated preclinical assessment of a drug candidate (Wong et al. 2013). Preclinical PK of GDC-0917, a new inhibitor of apoptosis protein antagonists, for the treatment of various cancers was characterized, and a PK/PD model informed by prior knowledge of the prototype molecule was developed. The model predicted human PK for GDC-0917, and aided clinical study design, i.e., efficacious doses in humans and the required number of subjects. In addition, leveraging comparator information to project likely clinical doses for an antihypertensive drug in the preclinical phase has been illustrated (Chien et al. 2005).

A PBPK model was developed to describe the absorption of a lipophilic BCS Class II investigational compound predominantly metabolized by CYP3A4 when administered as a nanosuspension formulation (Sinha et al. 2012). After optimization, the preclinical rat model was combined with bile micelle solubilization and colonic absorption. The sensitivity analysis also identified that the absorption parameter, fu_{gut} as an important parameter in human PK and DDI.

Clinical development

In clinical development, modeling and simulation can be used to optimize dosing regimens, design subsequent clinical trials, and efficiently analyze data to aid label recommendations. Moreover, it can play a significant role in the design and dose recommendations for special populations, such as pediatric, elderly, and obese patients. Additional applications of modeling and simulation include evaluation of dosage forms and routes of administration, evaluation of food effects, sex effects, and special populations, and characterization of therapeutic index, active metabolites, DDI, drug–disease interactions, and tolerance development.

For example, the first-in-patient study for olokizumab, a humanized monoclonal antibody for the treatment of rheumatoid arthritis, employed model-based, optimal design and adaptive execution (Kretsos et al. 2014). With integration of PK/PD modeling and exploratory statistics expertise, precise and full PK/PD profiles of olokizumab were predicted in a disease-relevant population with a minimal number of patients. The approach resulted in a re-estimation of the study size to half the original number, leading to a faster, cheaper, and more informative clinical study.

Population PK/PD models for zosuquidar, a P-gp inhibitor, suggested a shorter zosuquidar intravenous infusion schedule of 6 h as opposed to 24 h to be investigated in subsequent combination trials with daunorubicin (Callies et al. 2004). The shorter length of infusion produces maximal P-gp inhibition while minimizing the PK interaction and toxicity. A flexible infusion schedule can be designed to optimize the duration of maximal P-gp inhibition with minimal PK interaction and toxicity (Callies et al. 2004; Chien et al. 2005).

Furthermore, the use of modeling and simulation approaches may replace special population studies. The PK of the ER formulation of quetiapine in children and adolescents were quantitatively predicted by PBPK modeling based on PK profiles of immediate-release (IR) formulations in children and adults, and the PK profile of ER formulation in adults (Johnson et al. 2014). These results were accepted by the FDA as a substitute for additional clinical studies, and helped to inform dosing regimens in pediatrics. The PK/PD model of topiramate also demonstrated an efficacious monotherapy dosing regimen in children aged 2–10 years with newly diagnosed epilepsy without further trials (Girgis et al. 2010).

The ability of the PBPK model to characterize and elucidate mechanistic changes contributing to drug absorption and disposition in different organs and tissues in renal dysfunction has been reported as well (Almukainzi et al. 2017).

Lifecycle management

After preclinical and clinical drug development phases, application of modeling and simulation may also be helpful during the life cycle of a drug, i.e., during the NDA submission and review, post-marketing surveillance, as well as during new formulation development.

Modeling approaches integrate information from preclinical as well as clinical studies, including various subpopulations. Thus, modeling allows comparisons of the dose–concentration–effect relationship across species and subpopulations during the review process. Well-defined PK/PD models would further enable simulations for various scenarios, leading to deeper understanding of the compound, and provide justification for dose selection to the reviewer. Thus, modeling approaches can facilitate the New Drug

Application (NDA) review process and help resolve regulatory issues.

PK/PD analysis and modeling approaches also can be useful in post-marketing surveillance. Specifically, population PK/PD modeling within a structured surveillance may be beneficial to detect DDI, drug-disease interactions, or other covariates such as demographics or genetics that interfere with the effect or toxicity of a drug (DeVane et al. 1993). For example, a population PK approach showed that the occurrence of adverse events during moclobemide therapy was associated with average plasma concentrations and was sex dependent (Guentert et al. 1995).

Development of new formulations such as an ER formulation is generally considered a time-consuming and costly process. Since an IVIVC allows prediction of a formulation/manufacturing change in clinical performance of the product, it is known to be the best option in formulation development (Kesisoglou et al. 2015; Eaga et al. 2014; Jadhav et al. 2015; Jun et al. 2017). The utility of IVIVC and gastrointestinal simulation for justification of biowaivers has been shown for carbamazepine in solid dosage forms (Kovacevic et al. 2009).

Conclusions

In summary, the collated examples demonstrate the value of modeling and simulation across various stages of drug discovery, development, and life cycle management. Modeling approaches can increase confidence in the compound, mechanism, or disease rationales and provide support for rational decision making, dose determinations and adjustments for patient subgroups, support labelling, benefit-risk analysis, and increasing confidence in next-stage investment. In general, the additional information offered via these approaches provides an "evidence base" to help decision making informed and efficient.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Research involving human and animal rights This article does not contain any studies with human or animal subjects performed by any of the authors.

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