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The role of predictive biopharmaceutical modeling and simulation in drug development and regulatory evaluation☆

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ABSTRACT

Advances in predicting *in vivo* performance of drug products has the potential to change how drug products are developed and reviewed. Modeling and simulation methods are now more commonly used in drug product development and regulatory drug review. These applications include, but are not limited to: the development of biorelevant specifications, the determination of bioequivalence metrics for modified release products with rapid therapeutic onset, the design of *in vitro–in vivo* correlations in a mechanistic framework, and prediction of food effect. As new regulatory concepts such as quality by design require better application of biopharmaceutical modeling in drug product development, regulatory challenges in bioequivalence demonstration of complex drug products also present exciting opportunities for creative modeling and simulation approaches. A collaborative effort among academia, government and industry in modeling and simulation will result in improved safe and effective new/generic drugs to the American public.

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1. Introduction

The FDA encourages the implementation of quality by design (QbD) in the development of all pharmaceutical products, including generic drugs (Yu, 2008). The QbD paradigm is based on building quality into the final product by understanding and controlling formulation and manufacturing variables. Since formulation attributes and manufacturing processes can affect the bioavailability of the drug substance, application of QbD principles can help drug applicants ensure that the new formulation and manufacturing process will produce a bioequivalent product.

Formulation strategies are often based on trial and error and formulator experience. Modeling and simulation methods that predict the *in vivo* performance of drug products can greatly improve formulation strategy by aiding scientists in designing a rational approach to formulation development. FDA's "Critical Path Opportunities for Generic Drugs" recognized that the designing of better absorption models and the developing of *in vitro–in vivo* correlations (IVIVC) were critical modeling and simulation research areas. Predictive models of drug release profiles and the relationship between dissolution and bioavailability/bioequivalence can help guide drug applicants in the implementation of QbD (FDA, 2007; Lionberger, 2008).

One such modeling approach useful in predicting *in vivo* performance of formulations is physiologically based pharmacokinetic (PBPK) modeling. PBPK models have a broad scope and comprise three major components: system-specific properties, drug properties, and the structure model (Rowland et al., 2011). In this article we define PBPK models as the models having physiologically based structures for distribution and clearance that predict pharmacokinetics. Models with physiologically based structure for absorption but connected with an empirical distribution and clearance model were defined as physiologically based absorption models. Biopharmaceutical modeling includes physiologically based absorption models, but has a broader range that includes any models that study/evaluate/predict drug product performance from the physicochemical properties of the drug and the formulation properties of the formulation. Mechanism-based models generally indicate models derived following theoretical laws, such as Fick's laws of diffusion and mass balance. PBPK models, physiologically based absorption models, and some biopharmaceutical models are all different types of mechanism-based models. Mechanism-based models that integrate anatomical and physiological parameters, as well as the physicochemical properties of the drug substance, have been used to predict absorption (Willmann et al., 2003, 2004; Yu and Amidon, 1999), clearance (Watanabe et al., 2009), volume of distribution (Rodgers and Rowland, 2007), tissue distribution

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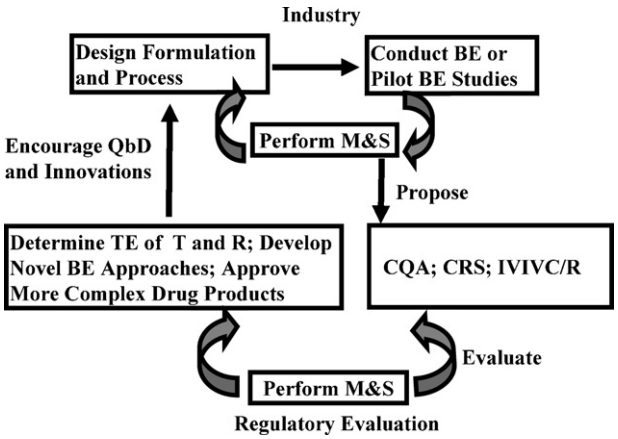

Fig. 1. Advances in predicting *in vivo* performance of drug products has the potential to change how drug products are developed and reviewed. Modeling and simulation can impact drug product development, and the implementation of regulatory concepts such as quality by design also requires advances in biopharmaceutical modeling. *Abbreviations*: M&S, modeling and simulation; BE, bioequivalence; QbD, quality by design; TE, therapeutic equivalence; T, test formulation; R, reference product; CQA, critical quality attributes; CRS, clinically relevant specifications; IVIVC/R, *in vitro* and *in vivo* correlation/relation.

(Baxter et al., 1995; Luttringer et al., 2003; Rodgers et al., 2005; Rodgers and Rowland, 2006; von Kleist and Huisinga, 2007), and drug–drug interaction in humans (Chenel et al., 2008a,b; Kato et al., 2008; Poirier et al., 2007; Vossen et al., 2007). PBPK models are increasingly used as important tools in drug development and regulatory review. FDA's first application of PBPK modeling was in the assessment of the risk of fetal exposure to tretinonin, the active ingredient of a highly teratogenic topical "wrinkle cream". From FDA's analysis, it was concluded that the risk of teratogenicity was minimal and the drug product (Renova®) was approved (Rowland et al., 2011). Today, FDA uses PBPK modeling and simulation in deciding upon the need to conduct specific clinical pharmacology studies, recommendations for specific study designs, and appropriate labeling language (Zhao et al., 2010).

In the context of formulation development, mechanism-based models that have integrated formulation properties as input parameters should yield lower costs and greater time savings. Much effort has been allocated to developing predictive models for oral absorption in various species since oral administration is still the major administration route (Willmann et al., 2003, 2004, 2007, 2010; Yu, 1999; Yu and Amidon, 1999; Yu et al., 1996). As many review articles have already summarized and presented detailed descriptions about how these models were developed and the features of each model (Agoram et al., 2001; Grass, 1997; Huang et al., 2009; Jamei et al., 2009; Norris et al., 2000; Parrott and Lave, 2002), we present here case studies of modeling and simulation-guided oral formulation development based on literature review, as well as drug review areas in which predictive models have been and can be applied.

Fig. 1 graphically illustrates the role of modeling and simulation in drug development and the regulatory review. The pharmaceutical industry and regulatory agency both benefit from incorporating modeling and simulation in the drug development and application review process. For drug companies, modeling and simulation can be helpful in the proper design and formulation of drug products and to propose critical quality attributes, clinically relevant specifications, and IVIVCs. A regulatory agency can employ a variety of modeling and simulation methods to evaluate the above-mentioned, with the objective of confirming the therapeutic equivalence of potential products to the reference product. In addition, modeling and simulation may aid in developing novel approaches to demonstrate bioequivalence, especially for complex drug products. Modeling and simulation efforts foster QbD practices and encourage innovation in drug development and regulatory policy.

In this review, we present examples of regulatory applications of biopharmaceutical modeling in drug review including the development of biorelevant specifications, the determination of bioequivalence (BE) metrics for modified release (MR) products with rapid therapeutic onset, the design of IVIVCs in a mechanistic framework, and the assessment of bioequivalence recommendations for drugs with safety concerns under fasting or fed conditions. Future challenges in drug development with the increasing number of complex drug products will continue to expand the role of modeling and simulation in regulatory science.

2. Modeling and simulation to guide formulation development and abbreviated new drug application (ANDA) review

Over the last two decades, there has been increased emphasis on applying physiologically based absorption models to drug development (Agoram et al., 2001; Parrott and Lave, 2002; Yu, 1999; Yu and Amidon, 1999; Yu et al., 1996). Some pharmaceutical companies use these tools routinely in the drug development chain for drug candidate selection (Brandl et al., 2008), to guide clinical formulation development (Dannenfelser et al., 2004; Kesisoglou and Wu, 2008; Kuentz, 2008; Kuentz et al., 2006), and to reduce the number of trial formulations to decrease development time and cost. Table 1 gives an overview of studies that investigated the impact of formulation properties on pharmacokinetics through physiologically based modeling.

2.1. Formulation development

One of the most frequently used applications of physiologically based absorption models is formulation design and optimization in drug development. This is because physiologically based absorption models integrate formulation properties as input parameters such as particle size distribution, solubility, solubility–pH profiles, and dissolution profiles.

The clinical dosage form development of LAB687 from Novartis is an example of using physiologically based absorption modeling in drug development (Dannenfelser et al., 2004). LAB687 is a poorly soluble and highly permeable compound with minimal first pass metabolism and active transport mechanisms. It has an aqueous solubility of 0.17 μg/mL. Its solubility increases 10-fold in the presence of 40 mM sodium glycocholate with 4 mM lecithin. Three formulations were developed for a dog study: a dry blend consisting of micronized drug, a solid dispersion, and an oral cosolvent–surfactant solution. All formulations were encapsulated and a dose of 50 mg was given to each dog. Before conducting an *in vivo* study, a dog absorption model was developed in GastroPlus™. The model predicted that the change in fraction absorbed is sensitive to changes in *in vivo* solubility and particle size. This suggested that modifying the formulation to improve solubility could increase bioavailability. In this case, modeling and simulation were useful in understanding relationships between absorption and its associated parameters and provided insight into the formulation development process and foresight regarding potential issues prior to formulation investment (Dannenfelser et al., 2004).

Another example of applying physiologically based absorption models in formulation development was published by Roche for R1315 (pK_a = 5.9), which is a poorly soluble (aqueous solubility < 1 μg/mL at pH values higher than 5) and highly permeable