Journal of Pharmaceutical Sciences xxx (2016) 1–12

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Research Article

Physiologically Based Absorption Modeling to Impact Biopharmaceutics and Formulation Strategies in Drug Development—Industry Case Studies

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ARTICLE INFO

Article history:

Keywords:
pharmacokinetics
physiologically based pharmacokinetic modeling
absorption
food effects
oral absorption
particle size

ABSTRACT

In recent years, there has been a significant increase in use of physiologically based pharmacokinetic models in drug development and regulatory applications. Although most of the published examples have focused on aspects such as first-in-human (FIH) dose predictions or drug–drug interactions, several publications have highlighted the application of these models in the biopharmaceutics field and their use to inform formulation development. In this report, we present 5 case studies of use of such models in this biopharmaceutics/formulation space across different pharmaceutical companies. The case studies cover different aspects of biopharmaceutics or formulation questions including (1) prediction of absorption prior to FIH studies; (2) optimization of formulation and dissolution method post-FIH data; (3) early exploration of a modified-release formulation; (4) addressing bridging questions for late-stage formulation changes; and (5) prediction of pharmacokinetics in the fed state for a Biopharmaceutics Classification System class I drug with fasted state data. The discussion of the case studies focuses on how such models can facilitate decisions and biopharmaceutic understanding of drug candidates and the opportunities for increased use and acceptance of such models in drug development and regulatory interactions.

Introduction

Traditionally, preclinical biopharmaceutical evaluation of formulations in a pharmaceutical development setting has involved the use of *in vitro* dissolution assays and *in vivo* testing in animal models. It is common that the screening is performed in a staged fashion, that is, first formulations are screened in dissolution assays before dosing the most promising ones to animals.[1] Dissolution testing is also still used as the primary means in ensuring the *in vivo* performance and consistency of drug product in manufacturing/release testing environment. However, unless an *in vitro–in vivo* correlation (IVIVC) has been established, the biopharmaceutics inferences out of dissolution tests may be limited to the dissolution performance just being reflective of prior clinical/manufacturing experience. Over the years, significant efforts have been placed in developing dissolution conditions more closely related to physiological conditions and bringing them earlier in the development process to inform with biopharmaceutics questions. Often referred to as biorelevant dissolution, such methodologies involve media or apparatuses that are intended to more closely mimic the intraluminal fluid compositions under the premise that these will be inherently more predictive than traditional quality control type of dissolution testing. The relevant advances in the field have been reviewed recently.[2]

However, the relationship between compound or formulation properties and oral absorption *in vivo* is complex and cannot always be captured solely by dissolution testing. A more mechanistic link is often required to gain biopharmaceutical understanding of the *in vivo* oral absorption process. Oral absorption physiologically based pharmacokinetic (PBPK) models are in principle well positioned to help building this link between experimental data (e.g., solubility, dissolution, permeability, etc.) and *in vivo*

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http://dx.doi.org/10.1016/j.xphs.2015.11.034
0022-3549/

absorption behavior of drug candidate compounds. The principles of oral absorption PBPK models have been reviewed in the literature, and the availability of commercial software such as GastroPlus[3], simCYP[4], PK-Sim,[5] or Intellipharm[6] allows easier access to such models for pharmaceutical scientists.

Reviewing available literature, it quickly becomes apparent that in recent years, there has been a significant increase in use of PBPK models in drug development and regulatory applications. Most of the publications have focused on aspects such as first-in-human (FIH) dose predictions and drug–drug interactions (DDIs).[7-10] The use of PBPK modeling for DDIs is also reflected in recent regulatory guidances by the US Food and Drug Administration (FDA),[11] European Medicines Agency,[12] and the Ministry of Health Labor and Welfare of Japan.[13] On the contrary, the number of publications focusing on formulation and biopharmaceutics issues in a drug development setting is much more limited. Food effect predictions have been relatively well documented.[14-18] More recently, a few publications have also focused on understanding stomach pH-related interactions.[19-22] A few literature reports have demonstrated the potential applicability of PBPK modeling to study active pharmaceutical ingredient (API) properties[22-24] or understand the impact of dissolution differences during manufacturing changes.[22,25-27] In the meantime, publications, primarily by Regulatory Authorities, have clearly indicated the potential utility of such models to support Quality-by-Design arguments and gain biopharmaceutical understanding. [22,28-30]

Despite the relatively few publications, the available published drug development examples do clearly demonstrate the potential use of these models to drive biopharmaceutics decisions. [17,18,20-27] Although not always published, biopharmaceutical/absorption modeling is nowadays used within the pharmaceutical industry to make a broad range of development decisions often starting from the pre-FIH phase throughout the different phases of development. The intent of this report is to present case studies of use of such models across different pharmaceutical companies. Five case studies are presented, covering different aspects of biopharmaceutics or formulation questions demonstrating how these models can drive decisions and increase biopharmaceutical understanding of drug candidate compounds and potentially also provide evidence for regulatory interactions similar to what is being done with PBPK modeling for DDI questions.

Application of Absorption PBPK Modeling in Pharmaceutical Development

Increasingly, biopharmaceutical modeling is being adopted to estimate the absorption of orally administered compounds from the gastrointestinal (GI) tract for decision-making. Absorption PBPK modeling can be used during pharmaceutical development to help with formulation questions such a selection of API particle size distribution (PSD), to gain understanding of more general biopharmaceutics questions (e.g., prediction of food effect and providing input into clinical trial design), or to feed into other types of PBPK modeling such as DDI models. Table 1 lists the most common applications of absorption PBPK modeling on the basis of our experience. The model application spans the entire pre-FIH to life-cycle management space. Models in subsequent phases of development build on earlier models, and as more information becomes available, they become more detailed. For example, in pre-FIH stage, often models are based on solubility/API PSD, whereas moving into later stage development, detailed dissolution data are incorporated into the models. We have attempted in Table 1 to also list some of the most commonly available data relevant to development of the absorption PBPK models in each development phase; however, it is worth clarifying that depending on the specific compound activities and development paradigms in each organization, these activities may shift between phases; for example, if dissolution data are generated before FIH, these may be used instead of API PSD based models.

Table 1
Common Applications of Absorption PBPK Modeling in Pharmaceutical Development

Development Stage	Formulation-Related Application	General Biopharmaceutics-Related Application	Common Data Available
Pre-FIH	• Evaluating toxicology dose limitation in preclinical species • Impact of dose, solubility, API PSD for FIH formulation[23] • Understanding of formulation behavior in preclinical studies	• FIH dose prediction [8-10] • Impact of physiological variability (e.g., stomach pH)[20-22] • Food effect assessment[14] • Verify understanding of oral absorption and disposition in different preclinical species • IVIVE evaluation in preclinical species • Estimate of precipitation time *in vivo* from preclinical data[17]	• pKa, LogP/LogD • Solubility data (screening vs. more definitive experiments) • *In vitro* metabolism data • Permeability estimate • Preclinical species IV PK data • Stability in biorelevant fluids • FIH formulation characterization • PSD for FIH formulation
FIH, phase IIB/III	• Impact of changes in dissolution profile, formulation related • Impact of changes in dissolution profile, process and /or stability related • Impact of release rate for MR formulations[22] • Impact of API PSD[22,24] • Physiologically based IVIVC[31]	• Impact of physiological variability (e.g., stomach pH)[20,21] • Food effect assessment[16-18] • Estimate of precipitation time *in vivo* from clinical data • Verification of understanding of oral absorption and disposition in healthy volunteers and patients • PBPK-PD	• *In vitro* dissolution for development formulations • Formulation characterization data • Single ascending dose/multiple ascending dose human PK data • Efficacy data
Phase IIB/III, filing	• Impact of changes in dissolution profile, bioequivalence projections for intended commercial product[25-27] • Physiologically based IVIVC for specifications, biowaivers	• Food effect biowaivers • Absorption-related DDIs • General characterization of absorption (and input in other PBPK applications)	• *In vitro* dissolution for to be marketed formulation • Phase I-III PK data • Absolute bioavailability data (if available)
Postfiling/life-cycle management	• Bioequivalence projections for LCM products or for dissolution differences seen in supply • Assessment of alternative formulations (e.g., MR if first filled product is IR)	• Projections of absorption in alternate populations (e.g., pediatric)[32]	• Dissolution profiles from commercial formulation