PBPK modeling and simulation has value throughout the drug development life cycle.

The Clinical Pharmacology and Translational Research section submitted this article.

PBPK MODELING AND SIMULATION:

YESTERDAY'S SCIENTIFIC ENDEAVOR IS TODAY'S REGULATORY NECESSITY

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While the use of physiologically based pharmacokinetic (PBPK) modeling and simulation (M&S) in drug development was first proposed in 1937 by Torsten Teorell, the applications were mainly confined to environmental science and the fields of animal or human toxicology until the 21st century.[1] It is only in the past five years that its impact has reached the point where it is actively encouraged by global regulators and increasingly leveraged by biopharmaceutical companies. It is now well accepted that throughout a drug's life cycle, PBPK can be used to support decisions on whether, when, and how to conduct certain clinical pharmacology studies and to support dosing recommendations for product labeling. It is used to support strategic decision-making, providing valuable information regarding clinical trial design, and it can be used to help obtain clinical trial waivers. Most important, PBPK helps answer a myriad of "what if" questions that could not be answered without lengthy, expensive, logistically challenging, and sometimes ethically questionable clinical studies. So what caused such a shift between the end of the 20th century and today, when PBPK is considered an industrial necessity?

WHAT IS PBPK?

Traditionally, PBPK was considered a modeling approach used to address the time-course of chemical distribution (including drugs) into various animal and human organs. This was achieved by considering the species-specific blood flows to each organ and drug partitioning across tissues based on the chemical nature of each compound. With the 21st century advent of in vitro-in vivo extrapolation (IVIVE) to attain the rates of whole organ drug metabolism and transport from laboratory experiments involving human tissue or subfractions, PBPK modeling has become a systems biology approach. As with any systems approach, the new PBPK-IVIVE linked model allows separating the parameters pertaining to the animal or human body (the system) from the drug and the study design. PBPK models map drug movements in the body to a physiologically realistic compartment structure using sets of differential equations (as with the classical PBPK). However, they also add the biological elements of each organ which determine the rate of absorption and elimination and are not limited to drug distribution. This approach includes mini-models within models that describe drug disposition in specific organs such as the brain, liver, gut, skin, lung, and kidney.

PBPK models consider drug-dependent biological and physiochemical factors, as well as drug-independent intrinsic and extrinsic factors that impact such system parameters and hence drug disposition. Extrinsic factors include temporal changes such as pregnancy, age, disease, dietary habits, and exposure to environmental conditions or prescribed chemicals and drugs, while genetics, ethnicity, and gender are considered intrinsic factors. PBPK models incorporate all these sources of variability based on prior knowledge of what they

do to the system. Therefore, these models can predict the direction and magnitude of impact from each of these factors on drug exposure.

ENCOURAGEMENT FROM GLOBAL REGULATORS

In a March 2015 paper[2] by scientists at the Food and Drug Administration (FDA), including Janet Woodcock, director of FDA's Center for Drug Evaluation and Research (CDER), the agency states, "modeling and simulation has served as a useful predictive tool in dose selection for pivotal trials, dosing in select populations such as pediatrics, optimization of dose and dosing regimen in a subset patient population, prediction of efficacy and dosing in an unstudied patient population in clinical trials, characterizing exposure and dose-related QT interval prolongation, and using PBPK modeling in predicting drug-drug interactions." Woodcock wrote, "Modeling (PBPK) work performed thus far at CDER has contributed tremendously to overall drug development, in terms of safety and efficacy, which ultimately results in patients' benefits."

In the past two years, FDA has held numerous public and scientific meetings focused on the advances in PBPK to pave the road for its increased use in informing key drug development decisions. To that end, the newly passed FDA Reauthorization Act[3] specifically identifies PBPK as a method for enhancing regulatory science and expediting drug development in both the Prescription Drug User Fee Act and the Generic Drug User Fee Amendments.

The European Medicines Agency (EMA) also recognizes PBPK's potential for advancing drug development and is currently developing additional guidance on the topic. In a paper published earlier this year,[4] EMA states, "PBPK modeling is an approach with broad potential. A variety of different scenarios can be simulated, and models can be refined during the drug development cycle as new clinical data are available. PBPK models are valuable tools for drug developers, and they are taken into consideration by regulators to support decision making and recommendations in the product label."

Japan's Pharmaceuticals and Medical Devices Agency (PMDA) is also using PBPK for regulatory approval. From 2014 to 2016, it approved 17 new drug applications for new molecular entities that leveraged PBPK. PMDA stated, "PBPK M&S results have been utilized in Japan to explain dose adjustments and to provide information about the proper use of the drug."[5]

INFORMING THE DRUG LABEL

PBPK modeling uses virtual populations to predict the absorption, distribution, metabolism, and excretion (ADME) of a drug. Models based on in vitro data are developed and confirmed with early clinical data to enable the drug development team to make crucial go/no-go decisions and guide label development. PBPK enables drug developers to predict drug exposure levels based on patient and drug characteristics and concomitant medications. It can fill knowledge gaps, especially where clinical data are scarce. Most important, PBPK has been used to inform key label elements regarding drug-drug interactions (DDI) and dosing. This methodology can be employed throughout the drug development process from preclinical to clinical and postmarket, in an iterative manner, delivering tangible value in cost and time savings and precise delineation of potential patient populations.[6]

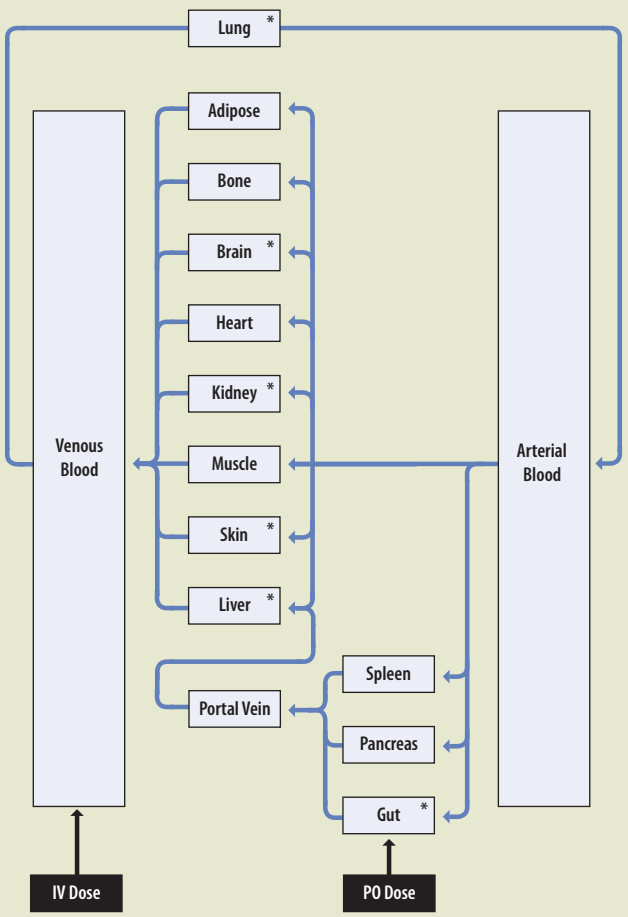
While PBPK is often used during the R&D phases of drug development, there are now more than 30 FDA-approved drugs where the use of PBPK is acknowledged in the drug label. Those drugs represent more than 200 individual label claims that were provided without the need for clinical trials, demonstrating the confidence in the data obtained from PBPK M&S. About 60 percent of those claims are for DDIs, but PBPK has also been used for oral absorption, pediatric, hepatic impairment, and renal impairment dosing recommendations in the label.

Perhaps the greatest impact for PBPK in drug labeling thus far has been in the oncology space, and by extension oncology rare diseases. A recent paper on this topic surmises that the rationale is based on the shortage of appropriate patient populations and/or ethical and safety concerns in this population. This analysis demonstrated that PBPK successfully informed the labels of 18 new oncology drugs as both a victim of DDIs or genetic variation and as a perpetrator of DDIs.[7] It also provided drug absorption information and dosing for organ-impaired populations.

UNDERSTANDING SPECIAL POPULATIONS

The instructions on a drug label are geared to a typical patient population, excluding special

SIMPLIFIED PBPK MODEL



* Organ-specific models within Simcyp Simulator

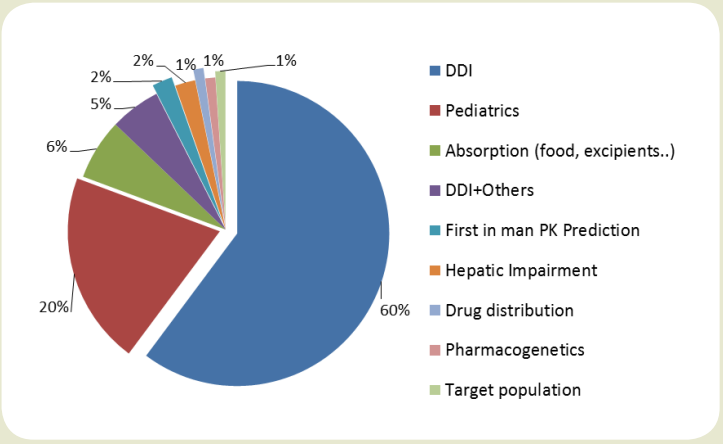
populations such as pediatric and geriatric patients, pregnant women, the obese, and patients with impaired liver or kidney function. Those populations are typically omitted from standard clinical trials.

For example, with less than 10 percent of all medications approved for pregnant women, the lack of dosing guidance represents a significant unmet medical need. Analysis requires consideration of the drug risks to both mother and fetus and needs to incorporate the woman's physiology and ADME, which vary by trimester. These changes can produce a higher or lower dose effect, which could prove to be toxic or decrease efficacy.

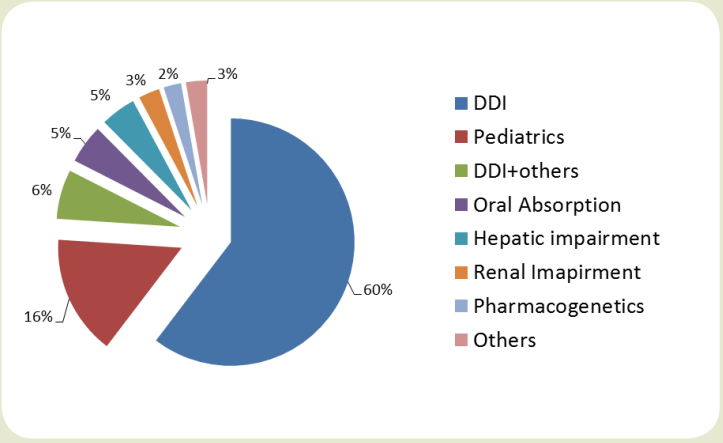
The study of children under age 2 is complicated because their absorption rates and enzyme levels change as their bodies mature. Geriatric patients are often being treated for multiple conditions simultaneously, making it harder to track the impact of an individual drug. Similar challenges exist for other patients with comorbidities or medical conditions that cause deviation from the standard patient cohorts found in clinical trials.

One of PBPK's greatest benefits is its ability to determine the most appropriate drug dose for special populations. The Simcyp PBPK Simulator software has more than 20 virtual subpopulations and more than 70 drug files against which to test virtual drugs. Example subpopulations with published successes include pediatric, geriatric, obese, and renal-impaired patients; pregnant women; and for ethnic bridging.

BY SPONSORS, HOW IS PBPK BEING UTILIZED?



Cumulative as of June 18, 2014 (n=96)
Sinha, MHRA PBPK Workshop, 2014, London, U.K.



Cumulative as of Aug 1, 2016 (n=217)
Aug 1, 2016: 145 cases for DDI and DDI+Others

Courtesy of Ping Zhao, Ph.D., FDA; presented at American College of Clinical Pharmacy 2016

VIRTUAL BIOEQUIVALENCE: THE ROLE OF PBPK IN BIOPHARMACEUTICS

Biopharmaceutics examines the interrelationship of the physical/chemical properties of the drug, the dosage form (drug product) in which the drug is given, and the administration route on the rate and extent of systemic drug absorption.[8] The importance of the drug substance and formulation on absorption and in vivo distribution of the drug to the site of action are described as a sequence of events that precede eliciting a drug's therapeutic effect.

Developing and optimizing a new drug formulation may involve changes in the drug composition, manufacturing process, use and type of equipment, or batch size. These changes, which can occur often, trigger the need to conduct bioequivalence studies to demonstrate "equivalence" between the original accepted formulation and the new one. M&S, specifically in vitro in vivo correlation (IVIVC), is a biopharmaceutical tool used in drug development and formulation optimization to demonstrate that bioequivalence.

While statistical IVIVC has long been leveraged to demonstrate bioequivalence, its overall regulatory success rate is about 40 percent.[9] To improve on that rate, we are increasingly turning to mechanistic models such as PBPK. PBPK is used to estimate IVIVC by considering separately the various mechanisms involved in drug absorption, such as transit time, gut wall permeability, gut wall metabolism, and hepatic first-pass metabolism from dissolution rate. By integrating the anatomical and physiological parameters of the gastrointestinal (GI) tract with the physicochemical properties of drug substances, PBPK provides a detailed understanding of the mechanisms involved in absorption and how critical they are for formulation.

As with clinical development, FDA has described the great potential it sees for using PBPK in biopharmaceutics applications and for expediting generic drug development.[10] Recent case studies demonstrate that potential by informing a range of formulation questions, such as prediction of absorption prior to and post first-in-human studies, exploration of modified-release formulations, and addressing bridging questions for late-stage formulations. With regard to virtual bioequivalence, FDA's recent award to Simcyp for the study of PBPK for supersaturating orally dosed drug products in the human GI tract, along with

the successful investigation of ketoconazole and posaconazole, classical representatives of Biopharmaceutics Classification System Class 2 drugs, indicate a strong future for PBPK in biopharmaceutics science.

PBPK AND PRECISION DOSING

Precision dosing, a subset of precision medicine, is defined as providing the right drug dose to deliver maximum therapeutic benefit, while reducing risk for each individual patient. The emerging precision dosing field harnesses the explosion of genomic data and various markers of bodily functions using mathematical modeling to ensure that individuals get the best possible treatment.

As discussed earlier, special populations are not typically included in clinical trials, requiring either the use of M&S or postmarketing studies to properly determine dosing. Precision dosing takes this concept a step further to determine a therapeutic recommendation for individual patients based on their characteristics and specific needs (e.g., finer diagnoses and subcategorization of the disease, age, body size, organ function, genetics of drug receptors and enzymes and transporters), and drug interactions. Since we now have a greater understanding of the sources of variability—the individual characteristics of each patient, the mechanisms of action for that disease, and the therapeutic index of the drug—we can use PBPK and other methods to drive personalized dosing decisions.

In 2016, Certara and the University of Manchester cohosted the Inaugural Model-based Personalized Drug Dosing in Healthcare Conference. The conference showcased a range of successful applications of model-informed precision dosing in a clinical setting and outlined opportunities and challenges to institutionalizing that concept. Speakers from eight countries—representing research institutions, academia, pharmaceutical companies, former regulators, and legal authorities—spoke at the summit. Sessions were organized around personalized dosing for special populations, including oncology, HIV+, pediatric, obese, renal-impaired, cell transplant, adolescent psychiatric patients, and pregnant women. In addition to demonstrating how M&S facilitated individualized dosing, the conference focused on linking personalized dosing and its impact on public health. A paper based on the conference was recently published in *Clinical Pharmacology and Therapeutics*.[11]

THE SWISS ARMY KNIFE OF M&S?

Scientists from Astra Zeneca (AZ) recently shared the breadth to which they use PBPK in their development portfolio.[12] Between 2014 and 2016, the company used PBPK in 68 projects across three therapeutic areas (oncology; cardiovascular metabolic diseases; and respiratory, inflammation, and autoimmunity). While the largest number of projects were for determining DDI, other uses were compound ranking, increasing the understanding of a compound's PK, impacting go/no-go decisions, clinical study design and dosing schedule, increasing scientific understanding ("what if" type questions), and pediatric dosing.

The five case studies AZ delivered showed how PBPK has been used to answer regulatory questions; inform dose adjustments pertaining to strong, medium, and weak CYP3A inducers; provide dosing regimen recommendations; predict DDI in early-phase development; and provide bridging between adult and pediatric dosing. The literature adds to these cases in the areas of ethnic bridging, medication use in pregnancy, postbariatric surgery patients, elderly patients with comorbidities, patients with renal failure, understanding food effect, and determining alternative formulations.

In short, PBPK has demonstrated its wide breadth of capabilities in R&D, clinical study, biopharmaceutics, formulation, and precision dosing. It is the Swiss Army knife of M&S.

DISCUSSION POINT

We want to know your opinion!
Please discuss this article on the AAPS Communities at https://community.aaps.org.

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