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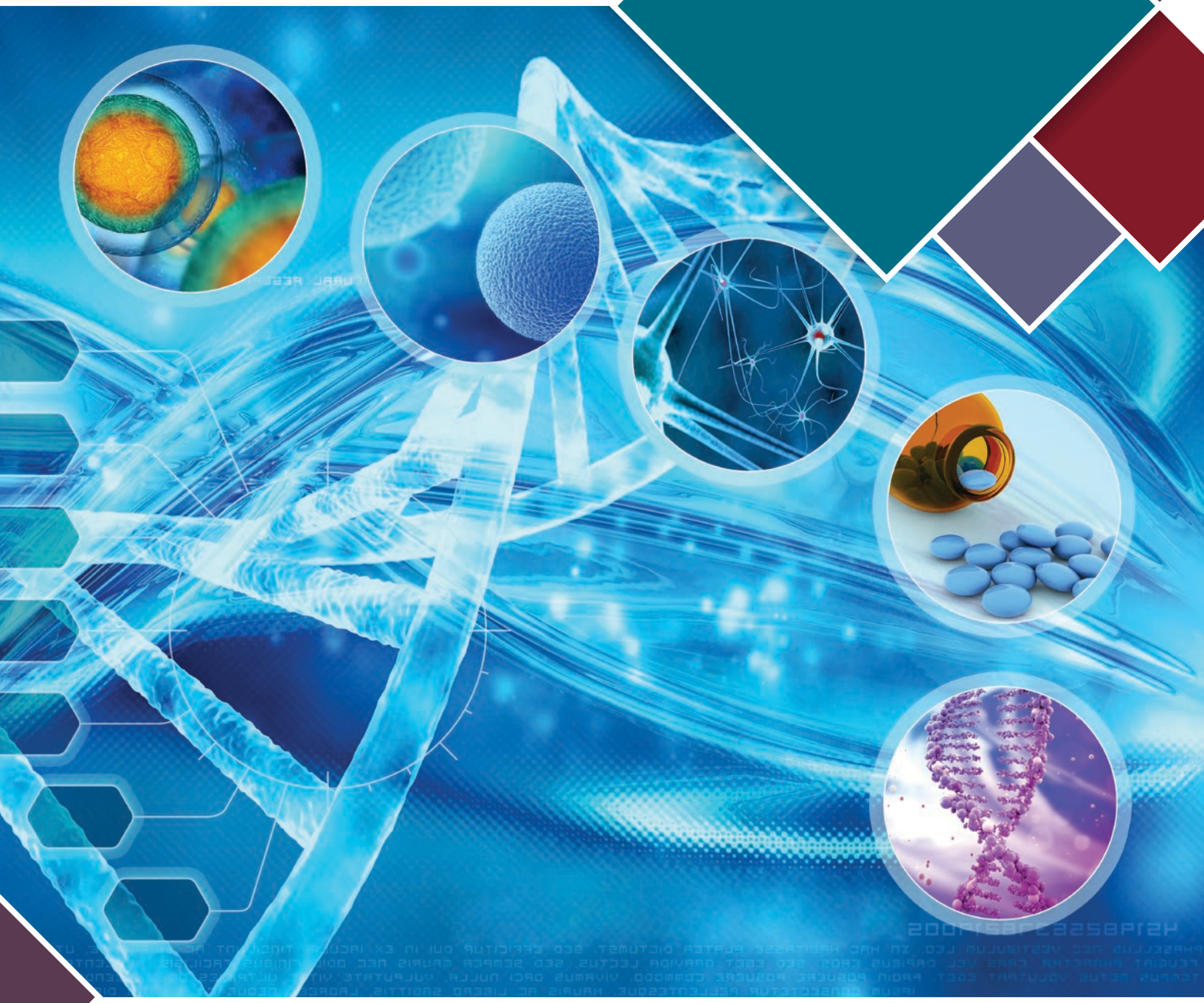

Drug Development and Label Optimization Using Proven Modeling and Simulation Methodology

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Now accepted by regulators, PBPK drives down R&D costs and timelines and allows for greater precision of drug labels

Regulators and sponsors recognize the many benefits of PBPK for informing drug development and labeling:

- Reduce number of required trials
- Expedite trials
- Optimize study design
- Evaluate special populations
- Identify knowledge gaps

The label matters most

The Food and Drug Administration (FDA) or other regulatory body-approved drug label is the official description of a drug product and includes what the drug is used for, who should take it, side effects, instructions for use, and safety information for clinicians and patients. For drug companies, the label is the culmination of years of work and millions, if not billions of dollars. Every element, word, and comma in the label will impact the potential patient population that can benefit from that new drug, while detailing any associated risks, including staying "silent" when information is not available. In other words, what is included or excluded from the label will affect the overall profit potential of the drug.

While modeling and simulation (M&S) has been an important element in drug development for some time, its impact over the past two years with regard to labeling has been profound. Specifically, FDA's acceptance of physiologically-based pharmacokinetic (PBPK) modeling and simulation has impacted key label elements in more than twenty cases, driving down R&D costs and timelines, and increasing the likelihood of both clinical trial and regulatory success.

MODELING AND SIMULATION is a proven scientific approach used to inform crucial drug development decisions. Accepted by regulators and used across the development cycle, it integrates knowledge and relationships between the disease, drug characteristics, patient populations and clinical trial parameters.

- Potency
- Solubility
- Binding
- IND Support

- Human PK Parameters
- FIH Dosing
- Pediatric Dosing
- Cardiac Safety Risk
- Toxicity

- PK Parameters
- Dose/Exposure
- Safety Profile
- DDI
- Special Populations

- Safety/Efficacy Model
- Exposure-Response
- Trial Simulation
- Phase 2a Meeting Support

- Exposure-Response
- Comparative Effectiveness
- Regulatory Advisory Committee
- Post-marketing AE

KEY RESULTS
range from estimating drug safety and efficacy, to first-in-human dosing, through to clinical trial design.

Modeling and simulation

While M&S (also known as model-based drug discovery and development) has been a growing area of science for more than 30 years, it was FDA's 2004 Critical Path Initiative report that clearly articulated the value of this approach for informing crucial development decisions, including first-in-human dosing, understanding safety and efficacy, linking biomarkers to outcomes, optimizing trial design, and addressing subpopulations such as pediatrics. In support of their acceptance of M&S, both the FDA and European Medicines Agency (EMA) have issued key guidance documents, covering topics such as population pharmacokinetics, drug-drug interactions (DDI), pediatric populations, hepatic- and renally-impaired populations, and pregnancy. In fact, modeling and simulation, using clinical data and iterated throughout the phases, is now expected by the regulatory bodies and was leveraged for drug labeling decisions in more than 90% of 2015 approved drugs. Taken together, the advances in M&S and use in regulatory approvals have delivered unquestionable results, expediting therapies to patients.

> "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."
>
> – Dr. Janet Woodcock, FDA

In a March 2015 paper written by scientists at the FDA, including Janet Woodcock, Director of the FDA's Center for Drug Evaluation, 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."

What is PBPK and when should it be used?

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 set a strategy to 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. The fact that PBPK modeling is being leveraged by all top pharma, key academics and regulators is a testament to the power of this approach. Most important, in the past couple of years, the regulators have been increasingly accepting of PBPK for key label elements such as DDIs and dosing. This methodology can be employed throughout the drug development process from pre-clinical to clinical and post-market, in an iterative manner, delivering tangible value in cost and time savings and precise delineation of potential patient populations.

How can PBPK inform the drug label?

PBPK is a powerful tool for informing drug labels due to its mechanistic approach. It considers multiple intrinsic and extrinsic factors such as genotype, disease state, renal/hepatic impairment, ethnicity and age.

Although dedicated clinical pharmacology studies can quantify the impact of certain intrinsic or extrinsic factors on drug exposure, it is often not feasible (or cost-effective, informative or ethically appropriate) to investigate every possible scenario, especially when there is complex interplay among multiple factors. PBPK models incorporate information about how drug exposure changes with drug-induced enzymatic inhibition. Thus, the models can predict and quantify the magnitude of potential DDIs and sometimes eliminate the need for additional clinical studies.

Certara's PBPK platform, the Simcyp Simulator, streamlines drug development through PBPK modeling in virtual patient populations. It incorporates numerous databases containing human physiological, genetic and epidemiological information. By integrating this information with *in vitro* or clinical data, the Simcyp Simulator can predict behavior in 'real-world' populations. It can handle DDIs involving up to four drugs plus three metabolites and accommodates simultaneous competitive enzyme and transporter inhibition, irreversible time-based enzyme inhibition, enzyme induction, and suppression.

The Simcyp Simulator is the result of more than 12 years of collaboration with a consortium that now includes 33 leading pharma companies, academia, and major regulatory bodies in an ongoing development program.

How does PBPK modeling change the conduct of clinical trials?

Given the immense cost of conducting clinical trials, new technologies that have the potential to change the conduct of clinical trials represent a possible sea change in drug development. PBPK modeling and simulation is now routinely used in drug development and regulatory review to assist with clinical trial management.

Substituting actual clinical DDI studies with informative "virtual" trials can save millions of dollars and take years off development time, addressing both the immediate concerns of the regulatory reviewers as well as answering the "what-if" questions designed to test the limits of safety. The proof cases listed later in this paper identify around 100 DDI studies performed virtually using PBPK that were used to inform the drug label.

Sponsors may seek to avoid conducting trials that would have very high cost, duration, and/or pose ethical issues. For example, rivaroxaban (Xarelto®), marketed in the US by Janssen Pharmaceuticals Inc, has been approved for the prevention of deep vein thrombosis which could lead to pulmonary embolism in patients undergoing knee or hip replacement surgery. As increased rivaroxaban exposure is associated with a steep increase in the risk of major bleeding, it became apparent to regulators that they needed to examine the possibility of synergistic effects on exposure that could arise from multiple, combined patient factors. Simulations were performed, which showed the potential for clinically relevant drug-drug-disease interactions when a combined P-gp and moderate CYP3A4 inhibitor is used concurrently with rivaroxaban in patients with mild to moderate renal impairment. As a result, cautionary language was immediately added to the product labeling while further trials to quantify these effects were undertaken (Grillo et al. 2012).

PBPK also provides great benefit in informing study design. Researchers at the US FDA have conducted simulation studies demonstrating the importance of considering the specific PK characteristics of both substrate and inhibitor when designing an *in vivo* DDI study (Zhao et al. 2009). As a result, sponsors are urged to recognize that there is no single optimal design for drug interaction evaluation and that modeling and simulation can be used to determine the best dosing strategy (Huang et al. 2009).

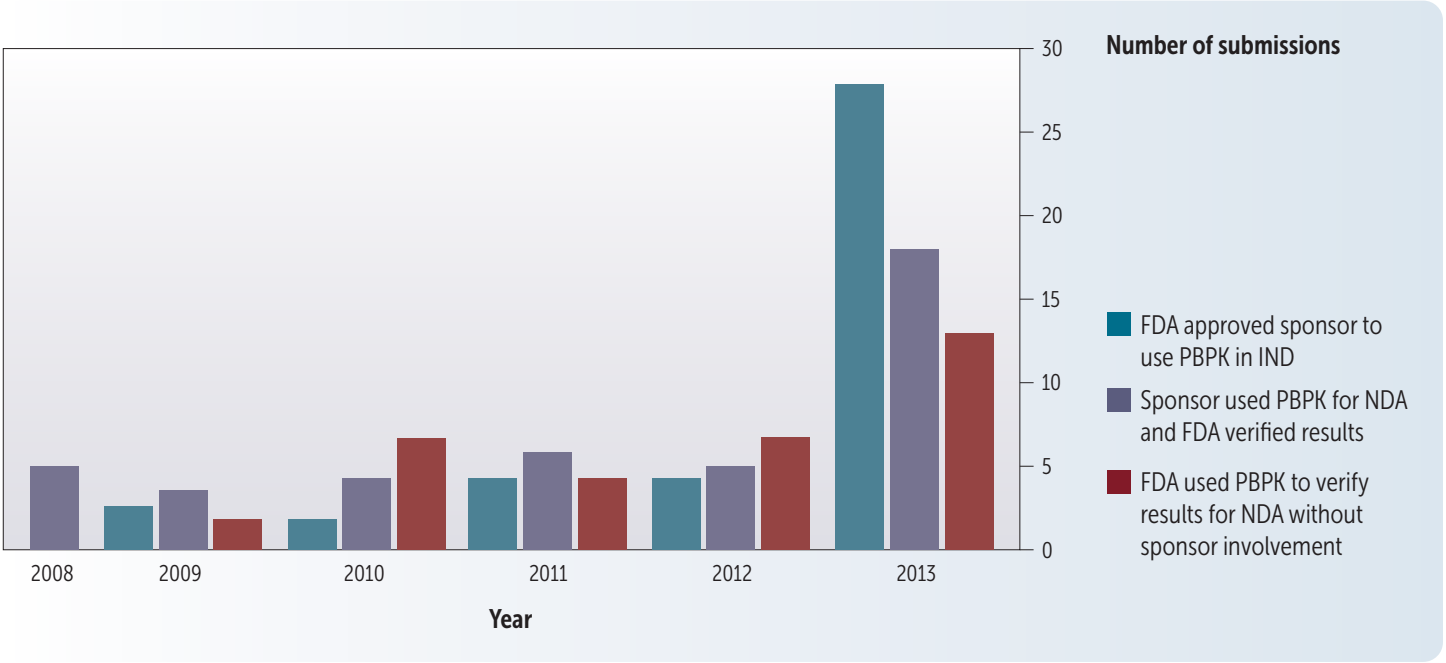
From regulatory science to regulatory policy?

Regulatory agencies around the globe are embracing the use of model-based approaches to drug development, including PBPK models. Scientists from the FDA Office of Clinical Pharmacology have affirmed the utility of PBPK for optimizing trial designs, predicting the impact of intrinsic and extrinsic factors on PK, and developing dosing recommendations for special populations. Indeed, approximately 50 submissions to the FDA in 2013 either requested advice on using PBPK or incor-

porated this approach in their approval filings (Sinha et al. 2014). The majority of these submissions used PBPK for predicting DDIs and drug exposure in pediatric and organ-impaired patients.

In 2012, the FDA Center for Drug Evaluation and Research (CDER) issued a draft guidance for industry with recommendations for performing drug interaction studies, study design, implications for dosing, and labeling recommendations. In this document, they advocate the use of PBPK models to evaluate complex DDIs. Information gleaned from this approach includes quantifying the magnitude of DDIs in various clinical situations. These situations include multiple patient factors such as renal impairment or genetic deficiency in certain drug metabolizing enzymes. Indeed, PBPK models can be used to compliment or, sometimes even, bypass clinical trials.

Increasing use of PBPK in FDA submissions



In the same year, the EMA also published guidelines on the investigation of drug interactions. Like the FDA, they are also seeing more frequent inclusion of PBPK in marketing authorization applications. They indicate that PBPK simulations may serve as the basis for clinical treatment recommendations such as dose adjustments and contraindications. The agency also cited this approach for helping predict the biological mechanisms of drug metabolism such as determining the relative contribution of enzymes to drug clearance. Finally, they propose the use of PBPK for informing study protocols at different stages of drug development.

Both the FDA and EMA held workshops on PBPK in 2014 to further the discussion resulting in a published papers in 2015. In his opening remarks, Dr. Sinha reported increased PBPK submissions to the FDA in recent years as well as the evolving landscape of using PBPK to answer dose-selection questions within different areas. For example, the majority of the applications to date are for the prediction of DDIs, followed by the drug exposure predictions in pediatrics and in organ-impaired subjects, and the effect of other patient factors. And from EMA, PBPK is viewed as of great potential value to support benefit–risk evaluations, providing a mechanistic basis for extrapolation beyond the clinical trial population, reducing uncertainty, and enabling better labeling around DDIs and in special populations (eg, elderly, pediatric, etc).

PBPK and the Drug Label

By the end of 2015, we identified 20 cases where PBPK was clearly used to inform the final drug label.

- In all sponsor-submitted cases, the regulators approved the use of PBPK in lieu of performing clinical studies. All included the substitution of PBPK for at least one DDI studies; in several cases there were more than 10 for a single drug. Increasingly, the use of PBPK has been accepted in lieu of other studies beyond DDI, such as for the hepatically impaired and for absorption (food impact for example).
- Dosing and dosing regimen were informed by PBPK and translated into the label for each drug.
- While most of the cases were for new molecular entities, in the Revatio example, PBPK was used for a post-marketing approval.
- Additional special populations can be evaluated using PBPK. In the Olysio® (simeprevir) example, the FDA reviewer states, "The model can be used to predict other untested drug-interaction situations and to evaluate the effect of various intrinsic factors (eg, ethnicity, liver disease)."
- In some cases, the FDA reviewer recommended using PBPK in post-marketing to confirm safety issues. In the Jevtana® (cabazitaxel) example, the FDA reviewer eliminated the need for a post-marketing study based solely on the PBPK results.

> "'PBPK-thinking' in drug development is encouraged as it leads to a mechanistic understanding of the processes involved in the disposition of a drug, helps to identify gaps in understanding of ADME (ie, when profiles cannot be predicted), leads to design of more informative studies, reduces the number of uninformative studies, is complementary to other modeling and simulation (M&S) approaches (eg, to inform dose selection, optimal study design, etc). This continued development is key to facilitating greater confidence for extrapolation (eg, pediatric, elderly, DDI, etc), thereby reducing the data requirements in these populations and supporting better drug labeling."
>
> – Dr. Terry Shepard, The Medicines and Healthcare Products Regulatory Agency

These 20 novel drugs all used PBPK to inform the drug label; almost 100 label claims using PBPK were accepted without the need for in vivo clinical studies; 50% of these drugs leveraged fast track, breakthrough, accelerated, or priority review regulatory paths.

PFIZER **Revatio (sildenafil)** Pulmonary Arterial Hypertension	**JOHNSON & JOHNSON** **Xarelto (rivaroxaban)** Deep Vein Thrombosis and Pulmonary Embolism	**TIBOTEC** **Edurant (rilpivirine)** HIV Infection	**ARIAD** **Iclusig (ponatinib)** Chronic Myeloid Leukemia FDA Review
JANSSEN **Olysio (simeprevir)** Hepatitis C	**ACTELION** **Opsumit (macitentan)** Pulmonary Arterial Hypertension	**PHARMACYCLICS** **Imbruvica (ibrutinib)** Mantle Cell Lymphoma and Chronic Lymphocytic Leukemia	**ASTRAZENECA** **Movantik (naloxegol)** Opioid Induced Constipation
GENZYME **Cerdelga (eliglustat)** Gaucher Disease	**SANOFI** **Jevtana (cabazitaxel)** Prostate Cancer	**NOVARTIS** **Zykadia (ceritinib)** Metastatic Non-Small Cell Lung Cancer	**PFIZER** **Bosulif (bosutinib)** Chronic Myelogenous Leukemia FDA Review
ASTRAZENECA **Lynparza (olaparib)** Advanced Ovarian Cancer	**NOVARTIS** **Farydak (panobinostat)** Multiple Myeloma	**EISAI** **Lenvima (lenvatinib)** Thyroid Cancer	**NOVARTIS** **Odomzo (sonidegib)** Basal Cell Carcinoma
GENENTECH **Cotellic (cobimetinib)** Metastatic Melanoma	**ASTRAZENECA** **Tagrisso (osimertinib)** Metastatic Non-small Cell Lung Cancer	**ALKERMES** **Aristada (aripiprazolel)** Schizophrenia	**GENENTECH** **Alecensa (alectinib)** Non-small Cell Lung Cancer

Imbruvica: An example of the power of the Simcyp approach

Pharmacyclic's Imbruvica® (ibrutinib) illustrates the power of PBPK modeling to inform both the drug label as well as dosing optimization strategy. Imbruvica is an orally administered inhibitor of the enzyme Bruton's tyrosine kinase. It has received FDA approval and designation as a breakthrough therapy for the treatment of mantle cell lymphoma, chronic lymphocytic leukemia, and Waldenström's macroglobulinemia.

Understanding a drug's PK profile is essential to developing safe and efficacious dosing recommendations. Imbruvica is a CYP3A substrate. Because of its very high clearance rate, it is particularly susceptible to DDIs. To evaluate the DDI liability, a PBPK approach was utilized (US FDA 2013). The model was developed using *in vitro* and clinical PK data. Then, the model was verified with two clinical DDI studies with ketoconazole (a strong CYP3A inhibitor) and rifampin (a strong CYP3A inducer). Since the model robustly predicted the observed change in C_{max} ratios and AUC (area under the curve) ratios for ketoconazole and rifampin, it was then applied to untested clinical DDI scenarios – moderate and weak CYP3A inhibitors and inducers. The knowledge gained from PBPK simulations informed the labels for Imbruvica as such:

- Moderate CYP3A inhibitors may increase the AUC of Imbruvica by 6 to 9-fold
- Moderate CYP3A inducers may decrease the AUC of Imbruvica by up to 3-fold

While the modeling affected Imbruvica's label, the full impact of PBPK was in providing a dose optimization strategy. The ideal dose of a drug successfully balances efficacy with safety. Co-administration of a CYP3A substrate and CYP3A inhibitors often can cause safety issues as the plasma concentration of the CYP3A rises to potentially toxic levels.

The recommended dose for Imbruvica is 560 mg per day. The highest recommended doses for Imbruvica are 840-1400 mg; doses higher than this present safety issues. Likewise, the lowest recommended dose of Imbruvica is 140 mg; doses below this are unlikely to be effective. Thus, in the case that a moderate CYP3A inhibitor must be used, it is recommended that the Imbruvica dose be reduced to 140 mg to stay within the established safety limits.

The opposite situation is seen in the case of co-administration of CYP3A inducers. Now, the concern is that the CYP induction will result in an increase in drug clearance. Thus, patients need to be given a higher dose than usual to maintain drug efficacy. PBPK models suggested that doubling the Imbruvica dose could still maintain an efficacious level of drug exposure in the case of a moderate CYP3A inducer. However, in the case of a strong CYP3A inducer (rifampin), even doubling the dosage of Imbruvica was not able to maintain an efficacious level of drug exposure. Thus, the 2013 FDA clinical pharmacology review of Imbruvica states that clinicians should "avoid concomitant use of strong CYP3A inducers." Clearly, PBPK is going beyond just providing mere knowledge about drug mechanisms. This powerful tool is guiding and supporting clinicians in providing the most effective and safest treatment to patients.

This breakthrough drug was specifically identified during the workshop entitled "Application of Physiologically-based Pharmacokinetic (PBPK) Modeling to Support Dose Selection" hosted on March 10, 2014 by the US FDA. Dr. Zhao discussed the New Drug Application review of ibrutinib (Imbruvica) to illustrate a successful application of PBPK in which the FDA used PBPK predictions to fill in unknown clinical gaps during the evaluation of a breakthrough therapy drug. PBPK is now used in many fast track, breakthrough, accelerated and/or priority reviews.

PBPK: The benefits abound

Clearly, there are many reasons to integrate PBPK into drug development programs. Saving time and money on avoided trials is an obvious benefit. There is additional value to this approach in the opportunity to expand the potential market for a drug. For example, a drug may be approved to treat adults; PBPK modeling can help expand the usage for that drug into pediatric populations. This methodology can also help sponsors avoid the risk of unexpected toxicities. Perhaps a drug that is safe for healthy adults might cause toxicity in patients with organ impairment. PBPK modeling can help predict these potential risks so that sponsors can write labels that warn against the use of the drug in certain subpopulations. The additional insight gleaned from PBPK into a drug's mechanisms of action places sponsors in a stronger position during interactions with regulatory agencies. Finally, PBPK modeling in virtual populations can help avoid unnecessary duplication of clinical studies as well as provide critical information to optimize trial design and improve safety for participants. PBPK is a growing discipline, with greater uses and benefits still to come. Wider adoption of PBPK methods will accelerate the regulatory review process in different global regions, bring new medicines to patients faster, and provide considerable financial benefits for pharmaceutical companies.

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About Certara

Certara is a leading provider of decision support technology and consulting services for optimizing drug development and improving health outcomes. Certara's solutions, which span the drug development and patient care lifecycle, help increase the probability of regulatory and commercial success by using the most scientifically advanced modeling and simulation technologies and regulatory strategies. Its clients include hundreds of global biopharmaceutical companies, leading academic institutions and key regulatory agencies.

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