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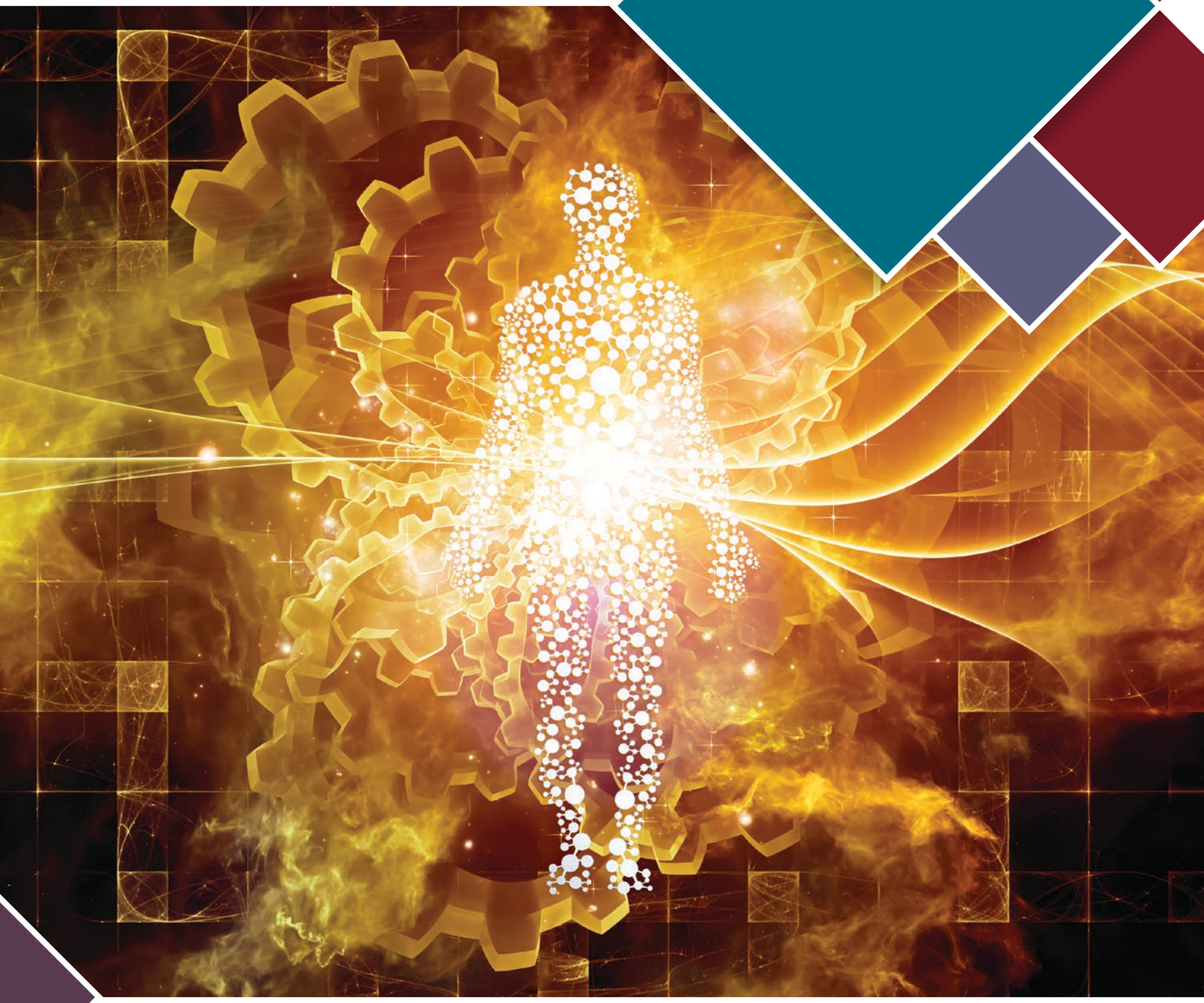

Physiologically-based Modeling Supports Drug Development Decisions, Regulatory Interactions and Drug Labeling

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PBPK modeling has seen a strong increase in regulatory attention and successful applications in recent years.

Modeling and simulation strategies help drug developers learn more about a drug, earlier. By combining diverse information resources, model-based approaches characterize a drug profile and anticipate the full range of clinical outcomes in studied and unstudied scenarios, even before *in vivo* studies begin

Development teams and regulators alike increasingly rely on *in silico* methods to fill knowledge gaps and support decision-making during discovery, development and regulatory review.

Among modeling approaches, physiologically-based pharmacokinetic modeling (PBPK) excels at addressing questions of drug exposure—especially for unstudied and difficult-to-study populations—and has seen a strong increase in regulatory attention and successful applications in recent years.

The utility of model-based drug development

> "Ethical and practical issues may limit the numbers of studies one can conduct to test all clinically relevant scenarios."
>
> – Sinha et al. 2014
> FDA Center for Drug Evaluation and Research
> Office of Compliance

Today's powerful and actively evolving computational tools enable sponsors and regulators to understand potential drug characteristics and subject responses earlier in development, with greater certainty. Model-based approaches support timely, confident decisions across the development and regulatory life cycle by gathering disparate sources of information about a drug, its competitors, target disease and patients into a mathematical knowledge framework. That framework outlines the candidate's risk-benefit profile and quantifies uncertainties at each stage in development.

In model-based drug development (MBDD), scientists apply these models to explore new chemistries, extrapolate from *in vitro* properties to *in vivo* behaviors, and understand sources of variability in dose-exposure and dose-exposure-response relationships—making it possible to predict results for unstudied doses, formulations, populations, concomitant medications, and more. Drug sponsors and regulators use these tools to:

- Speed discovery of safe and effective new compounds
- Identify nonviable candidates earlier in development
- Optimize dosing, sampling schemes and trial designs
- Anticipate drug interactions and subpopulation effects
- Evaluate—and often avoid—the need for additional trials

MBDD uses all available information to better inform development planning and decision-making, while containing costs and minimizing patient exposure to experimental therapies.

In drug discovery, mathematical models relating 3D chemical structure to biological activity—the structure-activity relationship, or SAR—enable medicinal chemists to design molecules for enhanced potency against a biological target while avoiding known toxicities. Systems biological approaches model the complex network of genetic, cellular and tissue interactions in a drug's target environment to assess its therapeutic potential.

Physiologically-based pharmacokinetic (PBPK) modeling predicts the absorption, distribution, metabolism and excretion of a drug. PBPK modeling and simulation enable drug developers to predict drug exposure levels based on patient and drug characteristics, concomitant medication, and more. PBPK aids dose selection and anticipates potential drug interaction from first-time-in-man studies through post-marketing evaluations in new subpopulations. It can fill knowledge gaps, especially where clinical data are scarce.

As clinical data become available, population pharmacokinetic/pharmacodynamic (PK/PD) modeling and simulation can be used to evaluate sources of variability in subject responses. These methods inform trial design, dosing and labeling decisions, as well as post approval evaluations of unstudied dose regimens.[25] Addressing broader questions of value, a clinical utility index, or CUI, combines the drug's probable risk-benefit profile with expert opinion and competitive information to evaluate a candidate's viability in the clinic and on the market.

An efficient informatics infrastructure is required to support MBDD in order for researchers to collate information from these modeling activities across phases of development. Making the growing knowledge-base readily available to scientists across disciplinary boundaries can enhance communication, exploration, discovery, and enable fast, informed decision-making.

The role of physiologically-based PK modeling

Growing understanding of human physiology and drug disposition together with advances in computer science have enabled increasingly sophisticated, biologically grounded models of drug disposition and exposure. Using a mathematical representation of the biological system, PBPK models quantify the behavior of and variability in biological mechanisms influencing drug time-concentration profiles. The models can be created based on *in vitro* and pre-clinical data, with or without supporting clinical data.[5,14,16] The models are based on diverse information sources, including published data on related compounds, drug-independent information about patient and disease characteristics, and *in vitro*, pre-clinical and early clinical data on the compound under study.

Scientists use PBPK models to perform simulations of drug exposure across differences in species (including humans), drug compounds, formulations, and more, making it possible to anticipate the dose-exposure relationship in unstudied situations. PBPK approaches are particularly powerful when there is inadequate *in vivo* data to address a hypothesis of interest but sufficient *in vitro* and pre-clinical data to essentially conduct an *in silico* trial.

PBPK modeling has a broad range of applications from early discovery through late clinical development.[7] These methods are especially valuable to early risk and toxicity assessments, and dose selection for first-in-human trials, new formulations, or new patient populations—for example, translating from adult to pediatric dosing. PBPK modeling is based on biological mechanisms; it enables researchers to anticipate important influences on exposure, such as drug-drug, drug-food, and drug-gene interactions. The resulting models and simulation results provide an evidence-based rationale to support recommendations in the drug label.

> "Modeling and simulation have been important scientific investment areas for US FDA's OCP [Office of Clinical Pharmacology], and will continue to be a major area of growth."
>
> – Huang et al. 2013
> FDA Center for Drug Evaluation and Research
> Office of Clinical Pharmacology

> "As a model using system- and drug-specific information, PBPK is increasingly being applied during drug discovery and development, and is informing regulatory review including drug labeling."
>
> – Sinha et al. 2014
> FDA Office of Clinical Pharmacology

> In parallel with the increasing number of submissions containing PBPK, the agency has increasingly utilized de novo (ie, US FDA initiated) PBPK in its reviews to help characterize PK in a variety of complex clinical scenarios.
>
> – Huang et al. 2013
> FDA Office of Clinical Pharmacology

> The use of PBPK modeling and simulation facilitated the following types of [FDA IND and NDA] decisions: the need to conduct specific clinical pharmacology studies, specific study designs, and appropriate labeling language.
>
> – Zhao et al. 2011
> FDA CDER OCP

Reflecting their utility in drug development, PBPK analyses are taking on increasing importance in regulatory submissions and review. From 2008 to 2012, PBPK modeling appeared in 33 IND/NDA submissions to the FDA.[5] In 2013, an estimated 50 submissions included PBPK analyses or requested advice on PBPK approaches.[16] Beyond looking to a drug sponsor's PBPK analyses to inform decisions, scientists in the FDA Office of Clinical Pharmacology (OCP) increasingly develop their own models and simulations to better understand a drug candidate's PK profile and dosing.

Suboptimal dose selection accounts for about 16% percent of FDA rejections for first-round submissions.[15] In efforts to address the situation, the FDA conducted workshops in March 2014 to discuss PBPK for dose optimization and solicit comments on a draft concept paper.[20] The meeting output and working group white paper are available online at www.regulations.gov.[7]

In addition, recent publications from the FDA encourage the introduction of model-based approaches early in development and provide examples of PBPK's utility in regulatory interactions.

Successful applications of PBPK

Long held as an important tool to estimate environmental chemical exposure in man, PBPK is now seeing greatly expanded applications across development phases, from lead optimization[13] to dose adjustments for special populations.[9,22] PBPK analyses have been used to project first-time-in-man exposure and dosing based on *in vitro* data.[24] With addition of the relevant factors to the models, these mechanism-informed methods are particularly useful in evaluating the potential for drug-drug, gene-drug and drug-food interactions. In later development, scientists use PBPK methods to project dosing in new populations such as children or organ compromised patients.

In regulatory interactions, PBPK analyses can provide an evidence-based rationale to support dosing recommendations, claims of bioequivalence, and labeling. By using existing data to extrapolate dosing and exposure levels to new scenarios, PBPK also provides a powerful tool to evaluate and even avoid the need for additional studies.

Optimizing first-in-humans dosing

PBPK can help predict human exposure levels even when data from animal and *in vitro* studies tell conflicting stories. For example, in a 2012 study, rat, dog and *in vitro* data gave an unusably wide range for predicted drug clearance in man.[4] A retrospective analysis demonstrated that population-based PBPK analysis based on physicochemical properties and *in vitro* human intrinsic clearance could predict the observed human exposure levels.

Predicting exposure for a new formulation

Physiologically relevant PK modeling provided clarity for a new formulation that exhibited unexpectedly complex PK.[11] The new formulation had failed to prove bioequivalent to its predecessor in terms of plasma concentrations at mole-equivalent dosing. Modeling and dose simulations helped to uncover an extensive first-pass metabolism that explained the unexpectedly low systemic exposure, and supported the recommended dose regimen.

Anticipating PK Interactions

Recent guidance from the FDA and European Medicines Agency highly recommend PBPK approaches early in a development program to predict the likelihood and severity drug-drug

interactions (DDIs),[3,21] particularly those arising from time-dependent inhibitors and mixed inhibitors/inducers of drug metabolizing enzymes. Both discuss the incorporation of *in vitro* enzyme and transporter studies, and emphasize the preference for PBPK over other modeling approaches in this area.

In one case study recently published by the FDA OCP,[5] *in vitro* data had raised concern that a candidate oncology therapy might affect patient exposure to co-administered drugs through its inhibition of the enzyme CYP3A. A PBPK analysis showed that due to its short plasma half life and other factors, the candidate therapy would have negligible effects on CYP3A substrates even if the new drug proved an order of magnitude more potent than expected. The results prevented the need for additional clinical study to test DDIs.

PBPK is similarly successful in evaluations of drug-gene, drug-disease and other interactions altering PK. For example, one recent study applied PBPK to predict changes in drug exposure with a rare mutation in the cytochrome P450 CYP2 gene family.[23] Another group of researchers developed a PBPK model to help evaluate possible alterations in PK in cancer patients.[2]

> "The knowledge gained from predict-learn-confirm exercises will contribute to regulatory decision making, and collaboration among stakeholders—industry, global regulatory agencies, academia, and others will be important."
>
> – Huang et al. 2013
> FDA Office of Clinical Pharmacology

Minimizing experimental exposure in children and other special populations

Regulators have recommended similar use of PBPK to individualize dosing based on patient characteristics, and to improve understanding of PK in difficult-to-study groups such as pediatric, pregnant, geriatric, and organ compromised patients.[5,6,10,16]

In another FDA example,[5] a PBPK model was used to establish pediatric dosing that would match drug exposures studied in adults, for a trial in children ages 12 to 18. Using data from that trial, the model was then refined to optimize dosing in younger children.

Supporting the drug label

Three recent drug labels highlight the application of PBPK modeling in FDA market approval.[1] These three recently approved drugs were developed by members in the Simcyp Consortium, a community of users and stakeholders in the PBPK modeling product, the Simcyp Simulator.

The sponsor of Olysio® (simeprevir), a new therapy to treat chronic hepatitis C virus infection, applied population-based PBPK modeling for clinical dose selection and DDI study design. Simulations of co-administration of either a strong or moderate CYP3A inducer highlighted the requirement for dose-response assessment for two drugs: Imbruvica® (ibrutinib) for mantle cell lymphoma, and Opsumit® (macitentan) for long-term treatment of pulmonary arterial hypertension. The full label for Imbruvica describes the PBPK results in some detail.[8]

Answering the FDA's call

PBPK methods supply a platform for exploring and discussing drug actions under varied clinical scenarios, as well as an evidence-based rationale for dose recommendations in trial designs, regulatory submissions and drug labels. These biologically informed models gather relevant information from not only the study drug, but related compounds and indications. The collected knowledge enables your team to maximize learning from early development stages, improving certainty in decision-making from discovery through all stages of development.

> “We seek early engagement with drug developers who intend to use PBPK and other integrative approaches to maximize learning from early-phase clinical trials.”
>
> – Sinha et al. 2014
> FDA Office of Clinical Pharmacology

The models and analyses provide a knowledge platform to support development decisions, and a more complete picture of drug disposition and dosing as input to regulatory discussions, submissions and reviews. These approaches are an important tool in answering the FDA's call for early and close communication with sponsors.

Enhancing your development program with Certara

Certara provides scientific expertise and advice to facilitate critical decision-making in pre-clinical and clinical drug development. This is done through the continual development of modeling tools including the Simcyp Simulator, the world's leading PBPK/PD-based modeling platform, in association with expert advice from a team of highly experienced scientists.

We construct extensive demographic, physiological, biochemical and genetic databases (including known variability), and combine them with drug-specific information to predict PK outcome in virtual populations. This can then be linked to PD outcome. With the potential for optimally informed early clinical decisions to trim development costs by tens of percentage points,[12] we believe the Certara PBPK Model and Simulation approach presents an attractive option.

Examples of questions we have helped answer for our clients

- Which candidate should we take forward?
- Should we license this compound?
- What should the first-in-human dose be?
- What will be the impact of genetic polymorphism on exposure?
- Should we change the dosage form?
- How will food affect bioavailability?
- To what extent will the compound cross the blood-brain barrier?
- How will disease (hepatic, renal, obesity) affect exposure?
- Which drug interaction studies (DDI—as perpetrator/victim) should we perform?
- Can we get a waiver for specific DDI studies?
- What are the likely differences in exposure between Chinese and Caucasians?
- What dose should be recommended in neonates, infants and children?
- How will pregnancy affect exposure?
- Will exposure be significantly greater in geriatric patients?
- What is the likelihood of clinical success in an upcoming trial?
- What is the likelihood of financial success for a drug post-regulatory approval?

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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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