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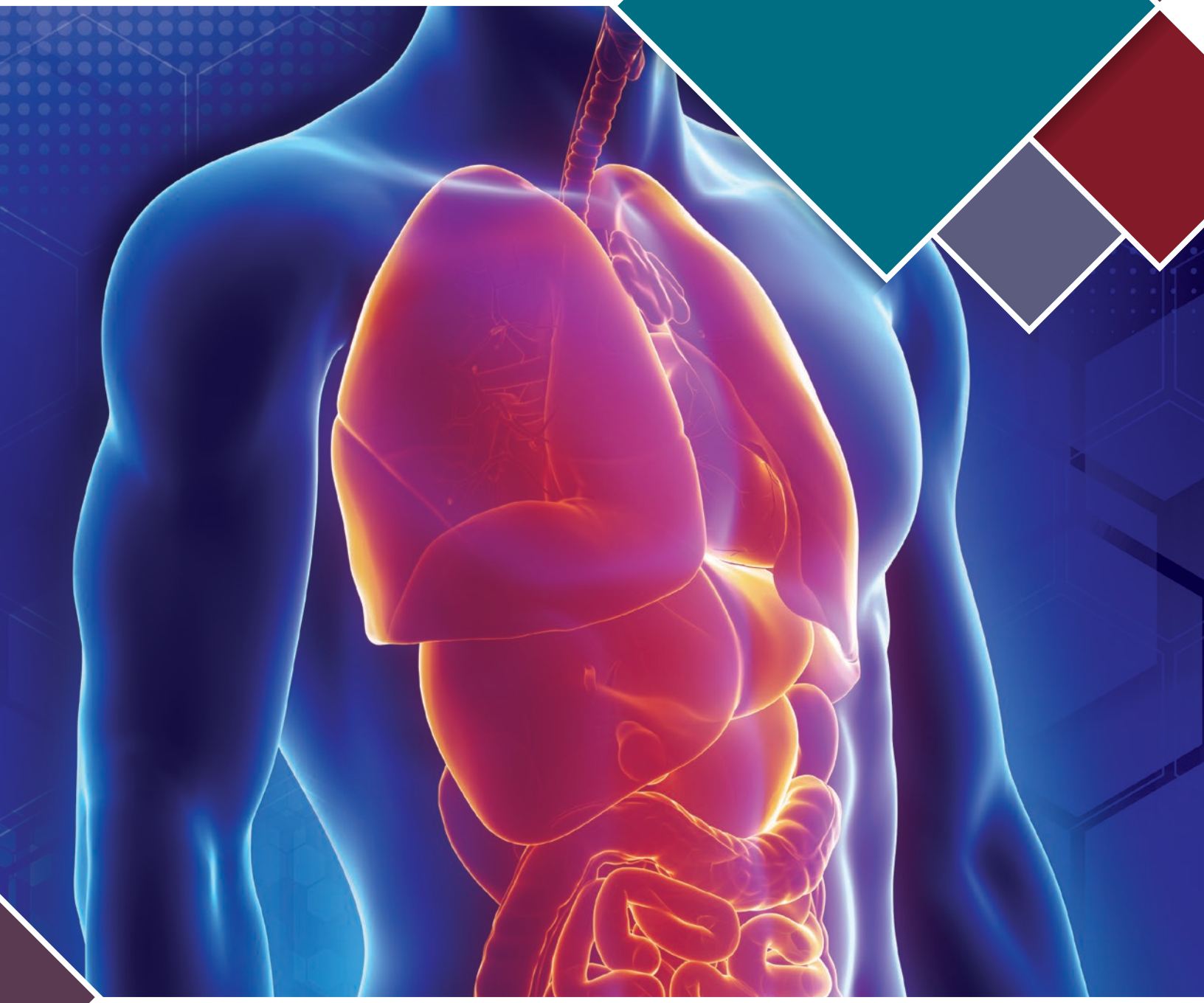

PBPK Modeling in Regulatory Review, Product Labeling and Safety Monitoring

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Modeling and simulation strategies help drug developers learn more about a drug, earlier

The FDA Office of Clinical Pharmacology (OCP) has recently described its efforts in development of model-based regulatory science and resultant application to regulatory review of therapeutic products. One such area of active development is physiologically-based pharmacokinetic (PBPK) modeling. 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.

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.

Background

Physiologically-based pharmacokinetic (PBPK) modeling can address various questions raised in drug development and regulatory review, and is used most extensively to predict and quantify the extent of drug-drug interactions (DDIs) from both *in vitro* and clinical data. This assists with dose selection and the design of clinical studies as well as informing decisions relating to product labeling. Here we present some recent examples of the role of PBPK modeling and how the Simcyp Simulator has been used in the regulatory approvals process.

Investigating DDIs due to CYP inhibition or induction

Modeling and simulation was used extensively by Janssen Pharmaceuticals Inc, and Food and Drug Administration (FDA) reviewers in the development of ibrutinib (Imbruvica®)—indicated for the treatment of patients with mantle cell lymphoma. Models built using *in vitro* data were validated using clinical data on the observed effects of both a strong CYP3A4 inhibitor and a strong inducer on ibrutinib exposure. Simulations then predicted the effects of a moderate CYP3A4 inducer and other CYP3A4 inhibitors (strong, moderate and weak) on ibrutinib exposure, as well as investigating the impact of dose staggering and dose adjustment.[2]

Data from PBPK modeling was also included in Actelion's application for regulatory approval of macitentan (Opsumit®), a drug that can delay disease progression in patients with pulmonary arterial hypertension. FDA reviewers performed further simulations to investigate a worst case scenario to assess the drug-drug interaction (DDI) potential of macitentan on repeat dosing with strong CYP3A4 inhibitors ketoconazole and the HIV drug, ritonavir. The results contributed to the reviewer's decision to make recommendations for product labeling.[3]

Labeling recommendations in lieu of clinical data

Ariad Pharmaceuticals performed clinical trials to investigate the impact of CYP inhibition on its chronic myeloid leukemia therapy, ponatinib (Iclusig®). Clinical studies to evaluate the effects of strong inducers were not carried out during development, but had been recognized as a post-marketing requirement. In the interim, FDA reviewers developed a PBPK model using the Simcyp

Simulator to simulate the effect of a strong CYP3A4 inducer on the pharmacokinetic (PK) of ponatinib, using the results to recommend that the product labeling should carry the warning that "co-administration of strong CYP3A4 inducers should be avoided unless the benefit outweighs the possible risk of ponatinib underexposure."[4]

Quantifying the impact of pharmacogenetic status on DDIs

Eliglustat (Cerdelga®, Genzyme) has recently been approved by the FDA for the long-term treatment of adults with Gaucher disease (type 1) who are extensive, intermediate or poor metabolizers of CYP2D6. Ultra rapid metabolizers are unlikely to achieve adequate concentrations for a therapeutic effect.

Metabolized primarily by CYP2D6, and to a lesser extent by CYP3A4, eliglustat is also an inhibitor of CYP2D6 and is both a substrate and inhibitor of P-gp. PBPK modeling and simulation was used extensively to understand and quantify the impact of metabolizer status and concomitant medication on eliglustat exposure—as well as the effect that eliglustat has on other drugs—and guide the specific dose adjustment recommendations and labeling language.[5]

PBPK modeling can be an attractive complement to the conduct and interpretation of studies in patients with organ impairment (eg, hepatic or renal), a logistically and clinically challenging population to study.

Understanding DDI risk in special populations

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 that showed the potential for clinically relevant DDIs 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.[6]

Assessing DDIs for different routes of administration

In the recent filing for regulatory approval of intravenous sildenafil (Revatio® for pulmonary arterial hypertension, Pfizer used simulations to predict differences in the extent of CYP3A inhibition between two different routes of administration. A lower magnitude DDI for intravenously administered sildenafil was reported compared with oral doses.[7]

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.[8] 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 when determining the best dosing strategy.[9]

Simulation of various study designs has recently been demonstrated in the FDA Clinical Pharmacology and Biopharmaceutics Review for ceritinib (Zykadia™)—a drug developed by Novartis for a subgroup of patients with metastatic non-small cell lung cancer. Virtual trials were conducted to investigate various dosing strategies with co-administered strong or moderate CYP3A4 inhibitors, strong or moderate inducers, as well as the effects that ceritinib has on the PK of midazolam. Virtual patients with mild, moderate or severe hepatic impairment were included in simulations. The

sensitivity to changes in gastric pH and the effects of food on the oral absorption of ceritinib were also investigated. The results supported a dosing strategy for the combined use of ceritinib with specific CYP3A inhibitors or inducers.[10]

Impact of PBPK modeling in regulatory review

PBPK modeling and simulation is now routinely used in drug development and regulatory review to assist with clinical trial management and critical decisions related to product labeling. 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.

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