EDITORIAL

Clinical Studies for the Sake of Negative Data: The Proof Is in the Pudding

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MODEL-INFORMED DRUG DEVELOPMENT (MIDD)

Over the past 20 years, the chorus of voices advocating for greater use of model-informed drug development (MIDD) and trumpeting its success has grown in volume, as regulatory agencies and the pharmaceutical industry have improved collaboration and aligned on a shared goal of greater efficiency and smarter decision making to improve attrition rates. A review of the literature reveals numerous examples of the successful use of modeling and simulation in all stages of drug development, from the selection of starting doses for first-in-human studies to exposure–response analyses and Bayesian adaptive designs for selecting phase III doses, to clinical trial simulation and lifecycle management.[1–3] Recently, the US Food and Drug Administration (FDA) initiated a pilot program to facilitate the application of MIDD approaches with the goal of improving clinical trial efficiency, increasing the probability of regulatory success, and optimizing individualization of therapy.[4]

Opportunities for MIDD include the use of physiologically based pharmacokinetic (PBPK) modeling to address the risk of drug–drug interactions (DDIs), inform dose selection for special populations and pediatrics, and to predict the impact of changes in formulation or the effect of food on drug absorption. PBPK modeling and its application have grown rapidly in recent years, with greater acceptance by both the pharmaceutical industry and regulators for decision making, as well as to inform clinical dosing recommendations. As the FDA's Office of Clinical Pharmacology (OCP) has reported, the most extensive experience in the application of PBPK is in the prediction of cytochrome P450 (CYP)-mediated DDIs, with many examples of recommendations in product labels reflective of PBPK modeling in lieu of clinical data.[5]

PBPK AND CLINICAL DDI STUDIES

Given the apparent acceptability of PBPK approaches to inform of DDI risk and potentially even for labeling purposes, why are certain clinical DDI studies still conducted, when on face value the results of such studies seem reasonably predicted? In the current issue of *Clinical and Translational Science*, the results of two DDI assessments are published for the hepatitis C virus (HCV) NS5A inhibitor and NS3/4A protease inhibitor combination elbasvir and grazoprevir.[6,7] The potential for clinically relevant DDIs between the antiviral combination and buprenorphine/naloxone or morphine were assessed. In describing the rationale for the clinical DDI studies, the authors cite the relative importance of opioid addiction therapy to HCV-infected patients, the theoretical DDI risk based on drug disposition and elimination pathways, and the consequences of unintentional opioid intoxication or withdrawal. In the case of methadone, the authors state that the results of the DDI studies informed the inclusion of study participants on opioid agonist therapy in the phase III clinical studies for elbasvir and grazoprevir.

At first blush, the description of the theoretical basis for a potential interaction with buprenorphine, naloxone, or methadone may call into question the need for clinical DDI studies, as negative results would have been reasonably predicted. Indeed, the results of the studies indicate no evidence of clinically significant interactions. Might this have been a reasonable case for using PBPK modeling in lieu of clinical studies? The case for modeling is often pressed upon drug developers and regulators in our zeal to further PBPK and model-informed drug development. However, it is important to recognize the many forces and aspects at play when assessing the value of clinical data in drug development.

NEGATIVE CLINICAL STUDIES IN DRUG DEVELOPMENT

During my tenure as a former reviewer in the FDA's OCP, I did not always appreciate why decisions were made by drug developers, including the decision to conduct certain DDI studies. Now working in industry, my perspective has changed. Although I continue to be an advocate for MIDD, seeking opportunities to use model-based or innovative approaches to improve efficiency and decision making in drug development, I have also come to appreciate the value of generating clinical data in some circumstances, even when a negative study result is predicted. There is of course consideration for the role of drug transporters in drug disposition, the impact of which is difficult to predict in many cases. In addition, it is a challenge to predict the magnitude of a DDI effect with precision, which may limit the value of PBPK predictions and necessitate clinical data in some cases. However, there are many other considerations that impact when and why DDI studies are conducted, beyond the basics of drug disposition and confidence in a PBPK model prediction. Some of the questions we may ask ourselves include:

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What are the consequences of an unexpected DDI in this case? What is the value of allowing a particular comedication in phase III with respect to enrollment or interpretation of results? How will ethics committees react to our plans to allow a particular comedication in phase III? What are the implications for the pivotal trial if there is an unexpected finding? How will regulatory authorities in different regions respond to a PBPK approach to addressing DDI risk? How will reimbursement authorities globally interpret the data and consider it in their assessments? How will our patient population and the prescribing community understand the data and recommendations in the label?

Sometimes the answers to these questions lead us down the route of PBPK modeling alone to address a DDI. In other cases we may use PBPK modeling along with clinical data, such as population-PK analysis. And yet in other cases we may choose to conduct a phase I DDI study in healthy subjects, but use PBPK modeling to design the study or select doses. In all of these cases PBPK modeling is valued, but it is utilized in different ways. Sometimes a clinical DDI study is conducted with the intention that the results will improve models or predictions for other potential DDIs. The point is, negative DDI study results may be as valuable as positive results; negative DDI studies should not be dismissed as a waste of development time or resources. In the end, clinical data may be extremely valuable for strategic or other purposes, even when they are negative.

Conflict of Interest. The author is an employee of Vertex Pharmaceuticals Incorporated. The views expressed in this editorial are those of the author only and do not reflect those of Vertex Pharmaceuticals Incorporated.

1. Kimko, H. & Pinhelro, J. Model-based clinical drug development in the past, present and future: a commentary. *Br. J. Clin. Pharmcol.* **79**, 108–116 (2014).
2. Nayak, S. *et al.* Getting innovative therapies faster to patients at the right dose: impact of quantitative pharmacology towards first registration and expanding therapeutic use. *Clin. Pharmacol. Ther.* **103**, 378–383 (2018).
3. EFPIA MID3 Workgroup, *et al.* Good practices in model-informed drug discovery and development: practice, application, and documentation. *CPT Pharmacometrics Syst. Pharmacol.* **5**, 93–122 (2016).
4. U.S. Food & Drug Administration. Model-Informed Drug Development Pilot Program. https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm 600311.htm (accessed 2 May 2018).
5. Sinha, V., Zhao, P., Huang, S.M. & Zineh, I. Physiologically based pharmacokinetic modeling: from regulatory science to regulatory policy. *Clin. Pharmacol. Ther.* **95**, 478–480 (2014).
6. Feng, H-P. *et al.* No pharmacokinetic interactions between elbasvir or grazoprevir and buprenorphine/naloxone in healthy participants and participants receiving stable opioid agonist therapy. *Clin. Transl. Sci.* **11**, 562–572.
7. Feng, H-P. *et al.* No pharmacokinetic interactions between elbasvir or grazoprevir and methadone in participants receiving maintenance opioid agonist therapy. *Clin. Transl. Sci.* **11**, 553–561.