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LETTER TO THE EDITOR

Response to "Quantitative Prediction of Drug-Drug Interactions Involving Inhibitory Metabolites by Physiologically Based Pharmacokinetic Models: Is It Worth?"

IE Templeton[1]*, Y Chen[1], J Mao[1], J Lin[2], H Yu[3], S Peters[4], M Shebley[5] and MV Varma[2]

To the Editor:

In our recently published article,[1] we demonstrated that physiologically based pharmacokinetic (PBPK) modeling provides mechanistic understanding for the observed clinical drug–drug interactions (DDIs) caused by inhibitory metabolite(s). However, we recommended a step-wise approach (i.e., flow chart) to predict DDIs involving inhibitory metabolites based on the development stage and available data. It should be noted that we recommend the use of static models prior to considering PBPK approaches for achieving quantitative predictions. Additionally, when modeling and simulations are used, a fit-for-purpose strategy based on questions to be addressed should be applied to support decision making. At early stages, when limited preclinical and *in vitro* data are available, static models are advised. However, PBPK models applied after verifying the clinical data allows a "what-if" scenario analysis and aids decision-making regarding study timing and design, dose selection, labeling, and justification of delay/waiver of clinical DDI studies.

In their letter, Tod *et al.*[2] recommended application of their In Vivo Mechanistic Static Model (IMSM) for predicting DDIs involving metabolites. Given that the two key parameters (fraction of oral clearance and inhibition potency) are derived from clinical DDI studies, and, additionally, the derived *in vivo* inhibition potency cannot discern the contribution of parent and metabolite(s) to the observed clinical DDIs, we believe this approach has limited utility in drug discovery and early development. However, the IMSM method could be helpful in clinical practice where clinicians may have to prescribe different drug combinations based on the existing clinical DDI dataset for those drugs. Nevertheless, similar static models informed with *in vitro* inhibition potency of parent and metabolite(s) could facilitate DDI predictions involving inhibitory metabolites.

The application of static models, based on steady-state assumptions, is a well-documented approach. This approach is often applied in the absence of the data typically required for PBPK modeling and simulation.[3] Modifications in the static equations can allow for incorporation of components including: multiple absorption, distribution, metabolism, and excretion (ADME) mechanisms, transporter-enzyme interplay, and multiple inhibitory species including metabolites. Effort should be put into implementing static models with a high degree of mechanistic information relevant to the substrate–inhibitor pair to address the question in hand, and limitations of such models should be considered as needed. For example, static models do not capture the time-dependent concentrations of inhibitor species (parent and metabolite), complex scenarios in which both parent and metabolite exposures are affected by each other, etc.

As outlined in our position paper,[1] static models are useful in predicting DDIs when data are limited or early DDI risk assessment is needed in compound progression. However, mechanistic PBPK models will be more informative for quantitative assessment and simulation of complex DDIs involving inhibitory metabolites.

Conflict of Interest. The authors declare no conflicts of interest.

1. Templeton, I.E. *et al.* Quantitative prediction of drug-drug interactions involving inhibitory metabolites in drug development: how can physiologically based pharmacokinetic modeling help? *CPT Pharmacometrics Syst. Pharmacol.* **5**, 505–515 (2016).
2. Tod, M. *et al.* Quantitative prediction of drug-drug interactions involving inhibitory metabolites by physiologically based pharmacokinetic models: is it worth? *CPT Pharmacometrics Syst. Pharmacol.* 2016 [Epub ahead of print].
3. FDA. Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations. Draft Guidance. In: Center for Drug Evaluation and Research CP, editor. February 2012 ed. druginfo@fda.hhs.gov; 2012.

[1]Genentech, South San Francisco, California, USA; [2]Pfizer Inc., Groton, Connecticut, USA; [3]Boehringer Ingelheim Pharmaceuticals, Ridgefield, Connecticut, USA; [4]Merck Serono, Darmstadt, Hessen, Germany; [5]AbbVie Inc., North Chicago, Illinois, USA. *Correspondence: IE Templeton (templeti@gene.com)
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