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EDITORIAL

Physiologically Based Pharmacokinetics Is Impacting Drug Development and Regulatory Decision Making

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It is no coincidence that the reports of two meetings, one organized by the US Food and Drug Administration (FDA), in March 2014, and the other by the UK Medicines and Healthcare Products Regulatory (MHRA), in collaboration with ABPI (the Association of British Pharmaceutical Industry), in June 2014, have been published in tandem in *CPT-PSP*.[1,2] Both reports deal with the same topic, namely, the impact of physiologically based pharmacokinetics (PBPK) in clinical drug development and the best practices for such applications. This reflects the transition of PBPK from academic curiosity to industrial norm, manifested by the regulatory agencies encouraging its use and receiving an increasing number of submissions containing PBPK models. The goal of both meetings was to help determine the need and facilitate the development of regulatory guidances on this subject within the conceptual framework of model informed drug development and regulatory decision-making. A further reflection of this intent is the publication by the European Medicines Agency of a Concept Paper on PBPK.[3] One is reminded of a similar train of events surrounding the introduction of population PK/PD and nonlinear mixed effects modeling in the early-late 1990s, again with encouragement and receptivity of regulatory agencies leading to FDA guidance on the topic.[4] Indeed, the intention of PBPK modeling and simulation is to complement other approaches, such as compartmental modeling, or, in some cases, replace them with a more mechanistic approach. PBPK models represent an important class of models that characterize absorption, distribution, metabolism, excretion (ADME) processes and their underlying biological and physiological drivers. An increased understanding of these drivers and their unique interactions with drug substance and formulation factors provides critical insights into how drugs will behave in healthy volunteers and patients with disease.
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A key feature of both meetings was the desire on the part of the regulatory agencies to discuss with scientists from industry and academia current practices and issues in PBPK with the aim of improving a common understanding of its utility and limitations, as well as facilitating consensus on best practice in the development, qualification, application, and reporting of PBPK modeling activities. Irrespective of the intended application, the two common components of PBPK are: physiological and biological information (system properties assumed to be independent of drugs), and drug-specific information, which starts with physicochemical and human *in vitro* data. While the body of systems property data together with reference data on many commonly prescribed drugs is steadily increasing, and is found incorporated in commercial PBPK software platforms, there are still important gaps that need filling. These include the distribution, frequency, and functional activity of many enzymes, beyond the CYPs, and transporters, as well as components of tissues affecting drug distribution, beyond the established ones of lipids, phospholipids, and plasma proteins. An important distinction also needs to be made between scaling from *in vitro* to *in vivo* (IVIV) of biological data compared to drug data. In the case of much biological data there is high confidence in the IVIV scaling factor, such as the ratio of the number of hepatocytes in an *in vitro* system to that in an adult liver. In contrast, confidence is often poorer that an *in vitro* estimate of a drug-specific parameter, such as intrinsic clearance, applies to the *in vivo* situation, as reflected by the need to adjust the *in vitro* value (sometimes considerably) to best fit the human *in vivo* data. Here attention to the quality and reproducibility of the *in vitro* drug data is crucial, as a great discrepancy between the *in vitro* and adjusted values can raise doubts in the mind of the regulator that the company fully understands all the mechanisms responsible for the *in vivo* handling of the drug. Notwithstanding this issue, the advantage of PBPK models over empirical models of PK is the ability to constantly integrate new information, whether system or drug properties, to improve the predictive ability of the model or to provide greater insights in the absorption, distribution, metabolism, excretion (ADME) drivers and processes responsible for PK. As such, the PBPK model should be viewed as an accumulating knowledge repository of system and drug attributes intended to reduce uncertainty and risk. Therefore, the qualification of the models to do various predictions and the confidence associated with such predictions change over time in parallel with the accumulation and consolidation of the information that goes into the model.

There is a danger, as with all computer models, to use PBPK models thoughtlessly. PBPK models are highly dimensional and several combinations of parameter values of the model may equally and plausibly predict a limited set of

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plasma drug profiles, recognizing that such profiles are global reflections of the many interactions of drugs with body components. Hence, to derive the most value from PBPK it is critical to ask the right questions, be clear on any assumptions, and to design appropriate experiments with appropriate statistical rigor that have the best chance of providing data and information to enable discriminating between possible models. Unlike population PK, where model verification often involves demonstrating that a model developed with a subset of the pool of PK data accurately predicts the PK in the remaining pool or an independent PK dataset, PBPK data are too often limited and verification comes more in accurately extrapolating outcomes to a previously unexplored scenario, such as PK profiles from healthy subjects to patients with poor renal function for a drug whose hepatic clearance is uptake rate-limited. Even so, no model can be expected to accurately predict situations about which some critical unknown mechanism or component is missing. Nonetheless, a discrepancy between prediction and observation can often suggest, through interrogation of the PBPK model and sensitivity analysis, future experiments to better understand the missing gaps related to the PK of the compound. In PBPK model building, as with empirical models, many companies have applied the model directly to oral data, and while this is successful in some cases, often there is a confounding identifiability issue with little or no ability to separate absorption from tissue distribution or clearance processes. Here intravenous data, which is increasingly gained from an i.v. tracer dose superimposed on an oral dose (normally for absolute bioavailability determination), can offer an intermediate step in model building of the disposition kinetics of a drug, prior to application of the model to the oral data. In addition, improved confidence in pathophysiological model parameter values may be gained by modeling simultaneously, rather than individually, the PK of several compounds that have been studied under the same clinical condition, be it a disease state, pregnancy, or comedication. In this situation, drugs are being used as probes to reflect and quantify the underlying properties of the system.

Currently, in clinical development, PBPK predictions are most commonly applied to drug–drug interactions (DDIs) and when robust this approach offers the possibility of reducing the need to undertake an extensive number of interaction studies. In essence, PBPK facilitates extrapolating to scenarios that have not, nor need to be, explored experimentally in humans; in fact, labels of some recently approved drugs contain an increasing amount of *in silico* information of DDIs based on PBPK. However, more work needs to be done on complex interactions involving multiple CYPs, some with genetic polymorphisms, and transporter processes. The next most common category of PBPK applications is as an aid in the design of pediatric studies (and indeed, beyond pediatrics to other understudied populations), although there is still much that needs to be understood in children below 2 years, and especially in neonates, where ontogeny plays such an important role in both system and drug parameters. Another area of interest is pharmacogenomics and race, where the relative distribution of the various less-than-fully functional alleles and their activities can be incorporated into the model. Other areas of needed further study include pregnancy, interaction between food and solid oral dosage forms, especially modified release formulations, diseases beyond renal and hepatic impairment, although there is still much to learn about these diseases, and routes of administration beyond the oral route. While listed here separately, the power of PBPK is its ability to predict realistically complex scenarios that often arise in clinical practice, such as patients with multiple pathologies and comorbidities who may be receiving several interacting drugs, some of which exhibit genetic polymorphism in one or more metabolic or transporter processes.

The MHRA and FDA workshops clearly looked towards the future in terms of what needs to be done to ensure *best practice* in model building, content, and format of PBPK submissions to regulatory agencies, integration of transporters, germline mutations in CYPs and transporters, complex active pharmaceutical ingredients (APIs) such as non-mAb biological drugs, and system properties as a function of age or diet. While skepticism of the utility of PBPK models exists to some degree, because of lack of understanding of some aspects of the system properties, necessitating various assumptions and judgments, future efforts in PBPK modeling and simulation should focus on improving the "facts" or evidence, that is the science of presenting mathematical and mechanistic "truths." As with the critical success factors of the FDA Animal Rule, which enables marketing approval for a new drug product based on animal efficacy studies, regulatory authorities may someday similarly rely on the sponsor's choice of an *in silico* PBPK model, adequately validated with *in vitro* and *in vivo* studies and with due regard to variability, to allow some important decisions to be made, such as selection of an effective dose in a given clinical scenario, when there is a reasonably well-understood pathophysiological mechanism of drug effects, and sufficient prior clinical dose, PK, and PD information. The significance of this approach becomes even more apparent given that many conditions involving a combination of effects (special populations), or orphan drugs for rare diseases, are infrequently studied during drug development and recommendations at the time of first approval may be difficult without PBPK or other generalizable prediction approaches.

Finally, although it makes sense to create generalizable rules that govern, and hence predict, the impact of various factors, such as comorbidities on ADME processes of drugs, in reality this requires a more in-depth understanding of not only the pathophysiological changes associated with the comorbidity status but also a detailed description and understanding of the ADME processes involved for the drug under development. The investment in gaining such information needs to be made early in the development program, which may necessitate some changes in practice. However, the benefits gained in being able to better rationalize the subsequent early drug development and clinical pharmacology programs should more than outweigh the early costs.

Conflict of Interest. M.R. is the Chair of the Scientific Advisory Board of Certara, A.R.-H. is an employee of the

University of Manchester and part-time secondee to Certara. L.J.L. declares no conflict of interest.

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