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PERSPECTIVE

Application of Physiologically Based Pharmacokinetic (PBPK) Modeling to Support Dose Selection: Report of an FDA Public Workshop on PBPK

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The US Food and Drug Administration (FDA) public workshop, entitled ''Application of Physiologically-based Pharmacokinetic (PBPK) Modeling to Support Dose Selection'' focused on the role of PBPK in drug development and regulation. Representatives from industry, academia, and regulatory agencies discussed the issues within plenary and panel discussions. This report summarizes the discussions and provides current perspectives on the application of PBPK in different areas, including its utility, predictive performance, and reporting for regulatory submissions.
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A workshop entitled "Application of Physiologically-based Pharmacokinetic (PBPK) Modeling to Support Dose Selection" was hosted on March 10, 2014 by the US Food and Drug Administration (FDA) at its White Oak Campus in Silver Spring, MD.[1] The workshop endeavored to (i) assess the current state of knowledge in the application of PBPK in regulatory decision-making, and (ii) share and discuss best practices in the use of PBPK modeling to inform dose selection in specific patient populations. The conference benefited from strong and diverse participation from the FDA Center for Drug Evaluation and Research (CDER) leaders, European Medicine Agency (EMA) delegates, and pharmaceutical industry and academia representatives. The workshop commenced with plenary presentations by speakers from the FDA, industry, and academia. In the two panel sessions, detailed questions on the current status and future applications of PBPK in drug development and regulatory decisions were discussed. An important focus of the dialog was the need to better define what constitutes a credible physiological system and the evidentiary standards needed for using such a system in making regulatory decisions. This report provides a content summary of the workshop, based on plenary presentations and panel session transcripts posted on the FDA's website.[2]

In her opening remarks, Dr. Janet Woodcock, Director of CDER, highlighted the importance of using innovative approaches in drug development to overcome challenges in characterizing drug safety and efficacy under the current drug development paradigm. The challenge for pharmaceutical industry, regulators, and academic researchers is to design more efficient and economical clinical development programs to ensure safe and effective medical products. For example, modeling may be used for the following: evaluation and/or optimization of clinical trial designs, recommendation of dosing in specific populations, understanding the often high degree of uncertainty and interindividual variability observed in clinical trials, and ultimately even the prediction of drug exposure in clinically untested scenarios. Understanding the properties of both the drug and the prediction tool is, however, a vital prerequisite for achieving reliable predictions and for developing general principles about the robustness, predictability, and reliability of the model, rather than looking at each case individually. This will allow the FDA, industry, and other stakeholders to be on the same level in terms of what needs to be done to increase confidence in model predictions. In this context, Dr. Woodcock encouraged the Office of Clinical Pharmacology (OCP) to publish a PBPK Guidance, and stated that the modeling work performed thus far at CDER has contributed tremendously to overall drug development, in terms of safety and efficacy, which ultimately result in patient benefits.

The workshop was chaired by Dr. Vikram Sinha, Director of the FDA's Division of Pharmacometrics. In his introduction, he asked a key regulatory question: "Since dose–response information for efficacy and safety in special populations is often lacking, what are the options for getting the dose 'right' for these groups?" and indicated that PBPK is a viable option given the distinctive separation of physiology and drug-dependent information in the model. He reported increased PBPK submissions to the FDA in recent years as well as the evolving landscape of using PBPK to answer dose-selection questions within different areas. For example, the majority of the applications to date are for the prediction of drug–drug interactions, followed by the drug exposure predictions in pediatrics and in organ-impaired subjects, and the effect of other patient factors. He emphasized the importance of integrating all available information gathered throughout the drug development process to arrive at clinically meaningful, reliable predictions.

PLENARY SESSIONS

The plenary sessions offered three perspectives: FDA (presented by Dr. Ping Zhao, Division of Pharmacometrics,

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Table 1 Current status on the use and predictive performance of PBPK in various clinical pharmacology applications, as concluded from the Workshop

Scenario	Application	FDA's opinion on the current status	Additional points from industry
Drug–drug interactions	Drug as enzyme substrate	• Substrate/inhibitor models verified with key clinical data may be used to simulate untested scenarios and support labeling (especially for CYP3A and CYP2D6 substrates) • Predictive performance for predicting the effect of enzyme inducer on investigational drug has not been established	• Challenges in predicting non-CYP pathways; expression levels and scaling factors unclear
	Drug as enzyme perpetrator	• Use to determine the lack of enzyme inhibition • Additional evidence needed to demonstrate predictive performance for positive interactions by comparing observed interaction magnitude and prospectively simulated magnitude from multiple examples	• Challenges in predicting combined TDI and induction • Challenges in predicting intestinal CYP metabolism
	Transporter-mediated interactions	• *In vitro - in vivo* extrapolation not mature due to inadequate body of information • Complicated by transporter-enzyme interplay • Predictive performance yet to be adequately demonstrated	• Challenges in predicting intracellular concentrations • Scaling factors poorly understood
Specific patient populations	Hepatic and renal impairment	• Predictive performance yet to be adequately demonstrated, particularly in severe impairment subjects • System component(s) needs additional research	
	Pediatrics	• Allometry is reasonable for PK down to age 2 years old • Less than 2 years old, ontogeny and maturation need to be considered	
Additional specific populations and situations	Pregnancy, ethnicity, geriatrics, obesity, disease states, food, formulation, and pH effects, and tissue concentration	• Limited experience to draw conclusions	• For drug absorption, there is high confidence in predicting the effects for BCS Class I drugs; for BCS Class II drugs, additional work in scaling of solubility, dissolution, and precipitation data is needed (Roles of BCS Classes III and IV were not discussed)

For more detailed information, see refs. 2 and 6. BCS, Biopharmaceutics Classification System.

CDER), industry (presented by Dr. Neil Parrott, Hoffman-La Roche, representing industry PBPK working group), and academia (Dr. Malcolm Rowland, University of Manchester, UK). Dr. Zhao's and Dr. Parrott's presentations focused on the current status of the use and predictive performance of PBPK in different clinical pharmacology applications, whereas Dr. Rowland's presentation was well reflected by the title "PBPK: Where are we now and where might we be in the future?"

The FDA's views on the predictive performance of PBPK in different application areas are summarized in **Table 1**. Based on regulatory research and review experiences, predictive performance was considered well established for evaluating the drug–drug interaction potential of an investigational drug as a substrate of metabolizing enzymes, specifically those metabolized by cytochrome P450 (CYP) 3A and 2D6 enzymes.[3,4] Dr. Zhao proposed a step-wise workflow to predict the effect of CYP inhibitors on drug exposure under clinically untested situations (**Supplemental Figure 1**). He discussed the New Drug Application (NDA) review of ibrutinib to illustrate, as an example, a successful application of PBPK in which the FDA used PBPK predictions to fill in unknown clinical gaps during the evaluation of a breakthrough therapy drug.[5] For applications in which predictive performances of PBPK are either less or not as well established, Dr. Zhao provided examples of the utility of PBPK to support regulatory decision-making and suggested future directions that are needed to overcome current limitations and to enhance predictability in these areas (**Table 1**).

Dr. Parrott's presentation on "Industry PBPK Working Group White Paper" summarized the current industry views, as collected among experts from 10 major pharmaceutical companies of the PBPK working group of International Consortium on Innovation and Quality (IQ).[6] He outlined PBPK modeling strategies and approaches used in industry across the drug development continuum, and underscored the role of PBPK in applications specific to

Table 2 Summary of the most important points discussed at the panel discussions

Panel questions	Summary
Panel Session 1: Applications of PBPK	
The goal of this session was to discuss potential applications of PBPK in drug evaluation, and to determine which areas relevant to drug development and review are currently amenable to the use of PBPK.	
General	Use of PBPK should be appropriately weighed with the complexity of the question. Its utility becomes more significant in situations (e.g., products under accelerated approval process) or populations where it is difficult or not ethical to conduct clinical trials. PBPK provides a more mechanistic understanding of the various factors influencing pharmacokinetics (e.g., nonlinearity) and helps drug developers understand their molecule better. It provides a learning platform where knowledge can be accumulated and turned into information to assess dosing recommendations in patient populations.
A. Drug–drug interactions 1. Under what circumstances can and should PBPK models be used to predict the effect of concomitant medications on the pharmacokinetics of an investigational drug via modulation of CYP-mediated metabolism? How should we use such models to design studies and inform drug labeling?	For the prediction of the effect of enzyme modulators on the pharmacokinetics of substrate ("victim" DDI), the substrate's fractional metabolism via the pathway(s) of interest (f_m) is central, and the early availability of mass balance data (typically conducted with radiolabeling the substrate) are useful. In cases where a healthy subject phenotype does not represent target population or explain the variability, a PBPK model may be used to inform design to obtain additional sparse PK data from efficacy/safety trials, which can supplement existing data. This comment also applies to applications beyond DDIs.
2. What are current knowledge (data, model) and confidence in using PBPK to predict the effect of an investigational drug on CYP-mediated metabolism? How should we use such models to design studies and inform drug labeling?	Two areas that need additional research are predicting DDIs in the gut and predicting time dependent inhibition (current PBPK systems tend to over-predict the extent of inhibition).
3. What is the current knowledge (data, model) and confidence in using PBPK to predict drug–drug interactions related to drug transporters systems? How should we use such models to design studies and inform drug labeling?	Transporter biology, tissue expression, and predicting intracellular drug concentration are areas that require more research to improve predictive performance of PBPK. Confidence in model prediction varies for different transporters. PBPK as a platform should be used to evaluate the role of transporters and to design studies.
B. Pharmacokinetic prediction in humans: first-in-human (FIH) Under what circumstances should PBPK be used to predict PK prior to a FIH? Comment on its utility vs. other methods (e.g., allometry) and predicting PK for biologics.	Primarily for drug developers, FIH prediction using PBPK is important for decision-making and allows additional learning of the molecule and coping with situations when other methods may not be adequate.
C. Other specific populations and scenarios 1. Is there sufficient knowledge to use PBPK to predict pharmacokinetics for the following: a. Organ impairment (hepatic or renal) b. Age (pediatric or geriatric) For pediatrics, what is the utility of using a PBPK approach in humans older than 2 years? c. Different ethnicity/race groups d. Pregnancy e. Concomitant food intake and new formulations f. Intracellular concentrations	Organ impairment Disease progression and underlying co-morbidities should be considered when predicting the effect of organ impairment. Data-sharing especially from longitudinal studies and at the subject level may be useful. Pediatrics Effect on elimination pathways should be better defined across the entire age spectrum. PBPK and allometry are complementary methods, and it will be important to know when they do not agree. PBPK adds value when age-dependent drug absorption plays a role. To this end, effect of formulation in pediatric patients needs to be considered. Other patient populations/scenarios were not discussed.
Panel Session 2: PBPK Model Verification and Reporting in Regulatory Submissions	
The goal of this session was to discuss assessment of model fidelity and best practices in reporting. There is heterogeneity in the level of detail on PBPK models included in submissions to the FDA. The FDA would like to establish basic requirements for a PBPK-related regulatory submission to ensure completeness, consistency, and efficiency in the review process.	
1. What would be the critical elements for each of the following categories within a PBPK study report? Comment on the following: • Purpose • Summary input parameters and assumptions • Necessary sensitivity analysis • Model verification process • Model application • Simulation results • Discussion/conclusion	PBPK modeling should remain more iterative than conventional PK/PD modeling, because new findings help improve the model and overall understanding. Although level of details in PBPK submissions may vary, purpose and parameters considered critical by the sponsors should be clearly presented. • Variability assessment is often missing in regulatory submissions. • Adequacy of a submitted PBPK work should be assessed in conjunction with known therapeutic index of the drug and modeling purpose. • Model optimization may lead to a more predictive model. However the process should be transparent, consider other data (e.g., emerging

Table 2. *cont.*

Panel questions	Summary
2. How should model fidelity be assessed? For example, given the significant inter-study variability of PK across various studies of a given drug, should model verification focus on the ability of the model to reasonably describe the PK data from all available clinical studies in the target populations? 2a. What other approaches should be used? 2b. When data from multiple studies are available, what external verification approaches should be utilized?	*in vitro*, clinical interaction, urine, human mass-balance data) in addition to plasma PK data, be purpose driven, and be discussed with regard to model plausibility. • A reasonable range for sensitivity analysis should be provided and justified. Standardization on the general utility of system model and inclusion of database for other drugs are needed. Model parameters with known certainty can be pre-specified, allowing more informed determination of candidate parameters for sensitivity analysis. At FDA-sponsor meetings, attendance of individuals knowledgeable of the modeling work is preferred from both sides.

For more detailed information, see ref. 2.

decision-making in industry, including lead optimization and candidate selection, prediction of first-in-human PK, and its supportive role in enabling decision-making in later phases of clinical development. Predictive performance for major applications was scored by confidence level (low to high). In applications of common interest to the FDA and industry, consensus for these categories appeared high on predictive performance (**Table 1**, column captioned "FDA's opinion on the current status"), and additional industry views are captured in **Table 1** (last column). Industry also expressed interest to understand the review process, acceptability of model files in specific software, and the key elements and other considerations needed for PBPK report submissions to the FDA.

Dr. Rowland's presentation outlined future directions of PBPK, including the emergence of PBPK-pharmacodynamics (PD), development of biological drug models, establishment of system models for disease populations, and prediction of doses in the geriatric population. His presentation consisted of four main highlights. First, predicting PK in tissue is critical in linking drug exposure to a mechanistic understanding of PD. Second, PK data of a drug "are made more useful by 'borrowing' information from biology and other drugs," and additional tissue/organ data can help enhance biologic plausibility. Third, intravenous PK data are highly valuable in updating a disposition model for subsequent application in an oral model. Finally, one can use a large PK dataset of a probe drug to characterize the variability contributed by various patient factors when covariate correlations are taken into account. He also called to attention to the need for evaluating multiple dosage strengths to allow practical implementation of model-based recommendations for dose modification.

HIGHLIGHTS OF THE PANEL DISCUSSION SESSIONS

The two panel sessions were moderated by Dr. Sinha, and included the following participants:

- FDA: Julie Bullock, Joseph Grillo, Shiew-Mei Huang, Robert Lionberger, Rajnikanth Madabushi, Vikram Patel, Yi Tsong, Yaning Wang, Ping Zhao.
- Other regulatory agencies: Eva Gil Berglund and Anna Nordmark (Medical Products Agency, Sweden); Susan Cole and Theresa Shepard (Medicines and Healthcare Products Regulatory Agency, UK).
- Industry and academia: Jeffrey Barrett (Sanofi Aventis, USA), Stephen Hall (Lilly, USA), Scott Obach (Pfizer, USA), Malcolm Rowland (University of Manchester, UK).

Topics and questions prepared by the FDA for discussion at the workshop, as well as a brief summary provided for each topic/question, are outlined in **Table 2**. In Session 1, panelists reflected on the plenary presentations regarding the utility of PBPK modeling in addressing different clinical pharmacology issues, and their views were generally in agreement with the current status and challenges. Session 2 focused on best practice and reporting of PBPK modeling and simulation for regulatory submission. Dr. Zhao (FDA) gave a presentation entitled "Requirement for Regulatory Submissions of PBPK Modeling and Simulations." Built primarily on a recent publication regarding PBPK best practice,[7] the talk included the following additional considerations: (i) predictive performance should be reflected by the ability of a model to reasonably describe all available data; (ii) biological plausibility of the model components should be demonstrated; (iii) verification against an external dataset likely only confirms assumptions made to a certain aspect of the model; (iv) predictive performance of a system component should be demonstrated through modeling of multiple, relevant drugs; and (v) the predictability of a PBPK model should be seen in the context of its intended use and should not be overinterpreted (e.g., a PBPK model deemed adequate to predict drug interaction potential may not be sufficient to predict the effect of other patient factors such as organ impairment).

CONCLUSION

The workshop concluded with closing remarks from Dr. Issam Zineh, Director of the FDA's Office of Clinical Pharmacology. He summarized that the workshop focused mainly on the comfort of using an emerging science such as PBPK. Analogous to Dr. Woodcock's description of drug development as "progressive reduction of uncertainty," Dr. Zineh used the term "progressive increase in comfort," and stated that work needed to be done to enhance accessibility of PBPK to all stakeholders, as well as to demystify the science to the public. This was accomplished in the areas of population pharmacokinetics, exposure–response relationships, and pharmacogenomics when they were first introduced in drug evaluation and regulatory review. In this context, Dr.

Zineh explicitly mentioned the need for methodological best practices and evidentiary considerations in the use of a new science to leverage decision-making.

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

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