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PERSPECTIVE

Where Do PBPK Models Stand in Pharmacometrics and Systems Pharmacology?

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Modern population-based physiologically-based pharmacokinetic models have contributed to the advancement of model-informed drug development and regulatory decision making. These models are developed based on principles of "systems pharmacology," which covers a range of modeling approaches, including "quantitative systems pharmacology." To integrate pharmacometric and systems pharmacology approaches a profound understanding of the objectives and remits of each technique is required and new definitions, algorithms, model assessment criteria, and tools are urgently needed.

BACKGROUND

Dr. France Mentre, in her Editorial titled CPT: PSP 2.0, shared her vision at the start of her role as Editor-in-Chief. The commentary was centered around two major topics, namely pharmacometrics and quantitative systems pharmacology (QSP). With her encouragement, I try outlining where physiologically-based pharmacokinetic (PBPK) models stand in relation to pharmacometrics and systems pharmacology approaches. This perspective is divided into two parts, the first briefly addresses the status of PBPK and QSP and the second focuses on potential integration of pharmacometric techniques and PBPK/QSP models.

Status of PBPK and QSP

The origins of PBPK models can be traced back to the work of Teorell in 1937.[1] For many decades, PBPK models have been used by environmental toxicologists. Typically, these models shared some specific characteristics, for example, the models were drug-specific, the majority of compartments were well-stirred, and the models were parameterized using *in vivo* observations, they could not incorporate *in vitro* data as inputs, and variability was incorporated using Monte Carlo techniques. The development of methods to predict tissue to plasma partition ratios[2] alleviated a significant hurdle in the use of PBPK models. Advancement and integration of *in vitro in vivo* extrapolation (IVIVE) techniques have significantly contributed to the recent resurgence of modern PBPK models. IVIVE-linked PBPK models allowed bottom-up simulations and predictions of plasma and tissue concentrations. Further, IVIVE techniques facilitated separation of the compound and species (system) parameters, which is a major paradigm shift allowing the development of generic PBPK models, as opposed to compound-specific models. The population-based PBPK models are capable of predicting intersubject and intrasubject variability using 'correlated' Monte Carlo methods. These models can be fairly simple with a few differential equations and a handful of parameters or very sophisticated with hundreds of differential equations and thousands of parameters. Over the last decade, PBPK models have been extensively used by the pharmaceutical industry for internal decision making and regulatory interactions as well as informing drug labels.[3] There are already more than 70 publications in CPT:PSP that contain PBPK in their title.

Although PBPK models were initially developed to determine the drug concentrations in plasma and various tissues, their areas of application have expanded to handle drug effects (or side effects) too. Obvious examples are enzymes and transporters induction or inhibition where the drugs affect enzymes and transporters' expression/function and these subsequently affect the drug PK. A major advantage of the modern population-based PBPK models is their ability to predict and extrapolate beyond the initial data used to develop the models, which is a general limitation of data-driven models (see next section). This is a paradigm shift from the conventional "learn-confirm" to a "predict-learn-confirm-apply" cycle. This change is largely due to combining IVIVE approaches with PBPK models and a similar strategy has also been advocated for the QSP models. IVIVE-PBPK models have also been applied in the biopharmaceutical area to enhance and expand the extrapolation capability of mechanistic absorption models.[4]

Bradshaw and co-workers have recently argued that well-defined terminology provides direction, focus, and branding for a scientific discipline such as QSP.[5] From a semantic viewpoint, QSP includes any modeling approach that is quantitative and deals with systems pharmacology, however, the QSP model-specific definition and scope are as they are described in the National Institutes of Health (NIH) white paper.[6] In broader terms, PBPK and other emerging disciplines, like physiologically-based biopharmaceutics modeling and Quantitative Systems Toxicology and Safety, all fall under the umbrella of QSP approaches. Perhaps, as suggested by Bradshaw and co-workers, we should use the term "quantitative systems pharmacokinetic" models instead of PBPK to better encompass their broad range of application.[5] Examples of combining quantitative systems pharmacokinetic models with classic QSP models have been published and the integration of these complementary approaches can considerably expand their individual scope as suggested recently.[7]

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Integration of pharmacometric and systems pharmacology

Integration of pharmacometric and system pharmacology disciplines requires collaboration and the ability of individuals in the different disciplines to relate to one another's needs and objectives. Commonly, pharmacometric models are data-driven and developed relying on robust statistical models/algorithms derived to describe data and rigorously assess the ability of the developed models to reproduce the observed data. In contrast, systems pharmacology-based models are developed to quantitatively understand a biological, toxicological, or disease process in response to therapeutic modulation with less emphasis on describing specific observations, if they are available at all. As a result, there have been debates, including in this journal, around developing new terminologies and criteria for assessing the performance of systems pharmacology-based models.[8] Although sometimes it is acceptable for PBPK or QSP model predictions to miss some of clinical observations, pharmacometric approaches are less forgiving in this regard because the objective is to best describe the observed data. Identification of population covariates of drug exposure and response is a major application of population PK analysis. However, often covariates are already incorporated in the PBPK and QSP models. It is essential to develop robust and rigorous model assessment criteria for any type of models; however, these criteria should be applied appreciating conceptual differences between the models and use appropriate techniques for the different models; "horses for courses." In PBPK best practice, model "qualification" and "verification" terms are used and recently a "credibility" assessment framework is proposed.[9] Qualification generally refers to the process of establishing confidence in a PBPK model to handle and simulate the intended use and verification concerns with the predictive performance of the model for previously unseen scenarios.[10] Nonetheless, in the pharmacometric field, model assessment mainly focuses on goodness-of-fit between the model and the observed data and there is less or no emphasis on predicting unseen scenarios.

There are well-established and robust tools that pharmacometricians use for population pharmacokinetic analysis and model assessment. However, often these tools are not designed to handle the larger and more complex PBPK or QSP models. Therefore, using pharmacometric-specific tools for fitting PBPK or QSP models to observe data becomes challenging. Perhaps, currently, the only technical solution to apply pharmacometric algorithms and tools to PBPK and QSP models is to use a model reduction approach; however, this results in the loss of detail incorporated in the PBPK and QSP models. Therefore, the ultimate solution should be developing methods, algorithms, and tools that can handle PBPK and QSP models and appreciate their differences and requirements from those of the data-driven top-down models. Modern PBPK platforms are already capable of fitting model parameters to observed clinical data (e.g., the Reverse Translational tool and the Parameter Estimation module in the Simcyp Simulator, Certara UK). A major advantage of PBPK and QSP models is their ability to integrate data from various sources, with different degrees of variability and uncertainty, sometimes in different scales. In such circumstances, the Bayesian-based approaches might be more suitable to inform, refine, and optimize PBPK and QSP models.

Application of advanced Bayesian approaches, development of new algorithms, tools, and model assessment criteria to facilitate analysis and characterization of QSP/PBPK models require close collaboration between the pharmacometric and QSP communities to enhance the synergies between these disciplines while appreciating the inherent differences in these approaches.

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