

## EDITORIAL

# American Society for Clinical Pharmacology and Therapeutics 2019 Annual Meeting Pre-Conferences

Jane P.F. Bai<sup>1,\*</sup>, Cynthia J. Musante<sup>2,\*</sup>, Suzana Petanceska<sup>3,\*</sup>, Lei Zhang<sup>4,\*</sup>, Liang Zhao<sup>4</sup> and Ping Zhao<sup>5,\*</sup>

The American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2019 Annual Meeting included two pre-conferences titled “PBPK (Physiologically-Based Pharmacokinetic) Modeling for the Development and Approval of Locally Acting Drug Products” and “Advancing QSP (Quantitative Systems Pharmacology) Toward Predictive Drug Development: From Targets to Treatments.” This special issue of *CPT: Pharmacometrics and Systems Pharmacology* is dedicated to the perspectives, short reviews, and original research articles provided by pre-conference speakers and organizers to inform the community at large of the current status of PBPK and QSP applications in pharmaceutical research and development.

## PBPK PRE-CONFERENCE

The full-day PBPK pre-conference was cosponsored by the ASCPT and the US Food and Drug Administration (FDA) and cochaired by Liang Zhao, PhD, US FDA, and Ping Zhao, PhD, Bill & Melinda Gates Foundation. It was designed to address the challenges associated with developing PBPK models for locally acting drug products and using them during drug development and demonstration of bioequivalence (BE).

For locally acting drug products, measuring drug concentrations at the site of action in humans may not be feasible or ethical. As clinical efficacy and safety data serve as the pivotal information for new drug approval, pharmacodynamic or comparative clinical end-point BE study results can serve as surrogate measures to evaluate drug exposure equivalence for generic drugs. However, pharmacodynamic or comparative clinical end-point BE studies are costly and often are insensitive to formulation or dose differences, especially when the drug exposure and clinical response relationship is flat. PBPK models can help identify the potential correlation between systemic and local drug exposure and determine whether the shape of the systemic pharmacokinetic curve can be used as a surrogate measure of local drug exposure.

This pre-conference covered the following three classes of locally acting drug products: orally inhaled and nasal drug products, topical dermatological drug products,

and ophthalmic drug products. In addition, it had a dedicated session to discuss the method and implementation challenges with speakers and panelists from academia, industry, software developers, and regulatory agencies. This pre-conference offered a poster session on the latest PBPK modeling efforts in this area, which enhanced scientific communication and stimulated knowledge exchange among meeting attendees.

The pre-conference achieved its objectives of demonstrating the critical role of PBPK as not only a viable data integration and analysis tool but also a common platform that allows a product developer to communicate with regulators in a quantitative manner. Participants also identified scientific gaps and new opportunity areas to enhance PBPK toolsets for each route of delivery discussed.

The PBPK-related papers published in this special issue from the FDA reflect current practices and challenges in the field. Given the difficulties associated with establishing BE for orally inhaled drug products, the review examines the utility of different models in this space and discusses how model verification can be achieved<sup>1</sup>. In general, challenges to verify PBPK models stand for locally acting drug products given that the drug concentrations at the site of action are not easily measurable and systemic concentrations may not reflect drug delivery at the site of action or are not detectable. Considerations for model verification, including leveraging clinically relevant *in vitro* and/or *in vivo* data for the product or data from an array of products with relevant formulation properties and use conditions are discussed in a commentary.<sup>2</sup>

## QSP PRE-CONFERENCE

The utilization of QSP has increased following the 2011 publication of the seminal white paper on this topic.<sup>3</sup> A recent survey by the International Consortium for Innovation and Quality in Pharmaceutical Development<sup>4</sup> (IQ Consortium) highlighted disparities and knowledge gaps between large and small pharmaceutical companies in the application of QSP approaches in pharmaceutical research and development. Recognition of the gaps and inconsistencies in QSP modeling practices among scientists

<sup>1</sup>Office of Clinical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland, USA; <sup>2</sup>Quantitative Systems Pharmacology, Early Clinical Development, Pfizer Inc, Cambridge, Massachusetts, USA; <sup>3</sup>Division of Neuroscience, National Institute on Aging at the National Institutes of Health, Bethesda, Maryland, USA; <sup>4</sup>Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland, USA; <sup>5</sup>Bill & Melinda Gates Foundation, Seattle, Washington, USA. \*Correspondence: All authors (Jane.Bai@fda.hhs.gov; Cynthia.J.Musante@pfizer.com; petanceskas@nia.nih.gov; LeiK.Zhang@fda.hhs.gov; Liang.Zhao@fda.hhs.gov; ping.zhao@gatesfoundation.org)

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galvanized academic, industry, and regulatory scientists to co-organize this meeting, which was cosponsored by the ASCPT, the IQ Consortium, the International Society of Pharmacometrics, and the FDA in collaboration with the National Institute on Aging at the National Institutes of Health (NIA-NIH).

This full-day pre-conference focused on applications of QSP in drug discovery, development, and regulatory reviews. Through presentations and panel discussions, the objectives were to engage researchers and decision-makers across academia, industries, regulators, and funding agencies on the following:

- Current status of QSP applications in drug discovery, development, and review
- Real and perceived technical and operational challenges to implementing a QSP approach in pharmaceutical research and development
- Roadblocks and opportunities for more successful applications

The QSP-related papers from the FDA, members of the International Consortium for Innovation and Quality in Pharmaceutical Development, and the NIA-NIH published in this special issue reflect current practices and challenges in the field. We are encouraged to find that the number of regulatory QSP submissions has steadily increased every year during the past 7 years.<sup>5</sup> Furthermore, the funding agencies are playing an important role in the development of broad QSP capabilities in the academic sector and in enabling multistakeholder partnerships. Implementation of the Comprehensive *In-Vitro* Proarrhythmia Assay initiative exemplifies a private-public partnership for the goal of advancing QSP in drug development.<sup>6</sup>

QSP has facilitated key decisions and transitions in drug discovery and development. Systems biology and systems pharmacology approaches of integrating big data across genetics, RNAs, transcription factors, proteomics, metabolomics, and chemicals (perturbagens) are the foundations for QSP. This aspect of QSP is increasingly being enabled by the NIH across many disease areas, including Alzheimer's disease, through large-scale team efforts, the development of new translational infrastructure, and the promotion of open science practices. Not unlike other modeling and simulation approaches,<sup>7</sup> one key to advancing QSP success is the development of strategies to assess QSP models, thus quantitatively and deterministically linking a drug's mode of action in mechanistic detail but with minimal uncertainty in the context of human biology and drug interactions. Conducting virtual clinical trials with cohorts of virtual patients derived from QSP models has enabled applications of QSP to late-stage drug development, such as the development of immune-oncology combination therapy; however, several challenges remain. One challenge, for instance, is modeling placebo responses by way of parameterizing a virtual placebo group with a QSP model,<sup>8</sup> whereas another challenge is reducing model uncertainty in the context of capturing complex human biology.

Assessing QSP models in the context of use with the involvement of a multidisciplinary team may offer flexibility while increasing confidence in their predictive power.<sup>9</sup> The stakeholders from pharmaceutical industry, the NIA-NIH, and the FDA, though appreciating the increasing utility of QSP in drug discovery and development, face the challenges of defining QSP best practices as well as qualifying and validating QSP models within an acceptable range of quantitative and statistical certainty. As described by contributing authors to this special issue, QSP has a role in drug discovery and development; however, these challenges must be overcome before routine integration into pharmaceutical research and development processes can be realized.

## SUMMARY

The perspectives, reviews, and articles contained in this special issue of *CPT: Pharmacometrics and Systems Pharmacology* are representative of current opinions and the state of the art of PBPK and QSP in model-informed drug discovery and development and regulatory science. Although much progress has been made in each of these fields, many challenges and knowledge gaps remain to be addressed. However, we believe that through continuous open dialogues and scientific exchanges among stakeholders, such as occurred at these two pre-conferences, we can come together to identify solutions to key challenges and find new opportunities to apply these approaches in drug discovery and development.

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