PBPK Current Status and Challenges: A Regulatory Perspective

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Development of Best Practices in Physiologically Based Pharmacokinetic Modeling to Support Clinical Pharmacology Regulatory Decision-Making

November 18, 2019
Silver Spring, MD
Outline

• Regulatory efforts in advancing PBPK M&S
  – Submission update
  – PBPK related guidances
  – Model informed drug development (MIDD) and PBPK
    • Workshops and Advisory Committee Meetings

• Challenges and proposals

• Summary
What do we do?

Outreach

Harmonize

Policy

Guide

Research

Support

REVIEW

Modified from Zhao P. 2015 AAPS
Utility of PBPK in Clinical Pharmacology Reviews

Number of NDA/BLA Submissions to OCP Per Year Containing PBPK Analyses (updated 10/19/2019)

Number of NDA submissions containing PBPK analyses (2008-2019/10)

% of new drug approvals containing PBPK

PBPK Submissions to OCP

As of June 18, 2014 (n=96)

As of Dec. 30, 2017 (n=254)

2018-2019 Oct. 31 (n=107)

# Regulatory Application & Predictive Performance

## Drug Interactions
- **CYP450 Drug as Substrate**
  - Inhibitor interaction prediction with higher potency clinical data verification
  - Concern with Rifampin under prediction
  - Dual enzyme time dependent inhibitor and inducer prediction not mature
  - Some experience with Pgp and combined Pgp/CYP3A interaction prediction and negative interaction prediction for basolateral uptake transporters, but knowledge gaps exist
  - Intestinal BCRP, hepatic OATP1B1/3, NTCP, MRP2, OATPs, and renal OATs and OCT2 positive prediction not mature
  - In vitro/in vivo extrapolation for solute carriers complex
- **CYP450 Drug as Perpetrator**
  - Negative interaction prediction
  - Some experience with positive interaction prediction, but knowledge gaps exist
- **Transporter Systems**
  - Some experience with UGT's, but prediction not mature
- **Phase II Metabolism**
  - Some experience with BCS Class I drugs
- **Pediatrics**
  - Some experience, but knowledge gaps exist
  - Greater utility likely in age ≤ 2 years
- **Renal or Hepatic Impairment**
  - Some experience, but prediction not mature
- **Pregnancy, ethnicity, geriatrics, obesity, & disease states**
  - Prediction not mature

## Specific Populations
- **Food, formulation, & tissue concentration**
  - Prediction not mature
  - Some experience, but knowledge gaps exist
  - BCS Class III and IV prediction not mature

## Other Areas
- **BCS Class I drugs**
  - Some experience with BCS Class II, but knowledge gaps exist
  - BCS Class III and IV prediction not mature

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Slide courtesy of J. Grillo*
PBPK Related Guidances

# PBPK Analyses Report Content

<table>
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<tr>
<th>Executive Summary</th>
<th>• Objectives (<strong>intended uses</strong>)&lt;br&gt;• Overview of model development and simulations&lt;br&gt;• Key conclusions</th>
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<tr>
<td>Introduction</td>
<td>• Brief and relevant drug’s physicochemical, PK, PD, and E-R properties&lt;br&gt;• PBPK related regulatory history including cross-referencing to PBPK study reports for different <strong>intended uses</strong></td>
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<tr>
<td>Materials and Methods</td>
<td>• Details about model development, verification/modification (justification), and application&lt;br&gt;• Details and sources of input parameters and key assumptions&lt;br&gt;• Simulation design&lt;br&gt;• Software (version)</td>
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<td>Results</td>
<td>• Results from model verification/validation, and sensitivity analysis&lt;br&gt;• Results from model application</td>
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<td>Discussions</td>
<td>• Discuss the adequacy of PBPK analyses to support <strong>intended uses</strong>&lt;br&gt;• Discuss any recommendation based on PBPK analyses and additional relevant evidence&lt;br&gt;• Discuss model limitation</td>
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<tr>
<td>Appendices</td>
<td>• List of tables, figures, acronyms and abbreviations, references</td>
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https://www.fda.gov/media/101469/download
Model-Informed Drug Development: Current US Regulatory Practice and Future Considerations

Yaning Wang¹, Hao Zhu¹, Rajanikanth Madabushi¹, Qi Liu¹, Shiew-Mei Huang¹ and Issam Zineh¹

Model-informed drug development (MIDD) refers to the application of a wide range of quantitative models in drug development to facilitate the decision-making process. MIDD was formally recognized in Prescription Drug User Fee Act (PDUFA) VI. There have been many regulatory applications of MIDD to address a variety of drug development and regulatory questions. These applications can be broadly classified into four categories: dose optimization, supportive evidence for efficacy, clinical trial design, and informing policy. Case studies, literature papers, and published regulatory documents are reviewed in this article to highlight some common features of these applications in each category. In addition to the further development and investment in these established domains of application, new technology, and areas, such as more mechanistic models, neural network models, and real-world data/evidence, are gaining attention, and more submissions and experiences are being accumulated to expand the application of model-based analysis to a wider scope.
Model-Informed Drug Development

Development and application of exposure-based, biological, and statistical models derived from preclinical and clinical data sources to address drug development or regulatory issues*

QSAR: Quantitative structure–activity relationship
QSPR: Quantitative structure–property relationship

* From PDUFA 6; Excludes statistical designs involving complex adaptations, Bayesian methods, or other features requiring computer simulations to determine the operating characteristics of a confirmatory clinical trial.
Advisory Committee Meetings and Public Workshops on PBPK Modeling


- 2019: Regulatory Education for Industry (REdI) and CERSI Workshop: Current State and Future Expectations of Translational Modeling Strategies to Support Drug Product Development, Manufacturing Changes and Controls

- 2017: Meeting of the Pharmaceutical Science and Clinical Pharmacology Advisory Committee Session I: Role for physiologically based pharmacokinetic (PBPK) modeling and simulation in drug development and regulation

- 2016: Public workshop: Oral Absorption Modeling and Simulation for Formulation Development and Bioequivalence Evaluation Workshop

- 2014: Public workshop: Application of Physiologically Based Pharmacokinetic Modeling to Support Dose Selection

- 2012: Meeting of the Pharmaceutical Science and Clinical Pharmacology Advisory Committee Topic 4: applications of PBPK modeling in pediatric studies
Needs for PBPK Modeling Best Practices

FDA perspective paper

- Applications of Physiologically Based Pharmacokinetic (PBPK) Modeling and Simulation During Regulatory Review (CPT 2011, PMID: 21191381)
- Best practice in the use of physiologically based pharmacokinetic modeling and simulation to address clinical pharmacology regulatory questions (CPT 2012, PMID: 22713733)
- Physiologically Based Pharmacokinetic Modeling in Regulatory Science: An Update From the U.S. Food and Drug Administration’s Office of Clinical Pharmacology (JPharmSci 2019, PMID: 30385284)

Industries/academic comments

- Physiologically based pharmacokinetic modeling in drug discovery and development: A pharmaceutical industry perspective (CPT 2015, PMID: 25670209)
- Physiologically Based Pharmacokinetic (PBPK) Modeling and Simulation Approaches: A Systematic Review of Published Models, Applications, and Model Verification (DMD 2015, PMID: 26296709)
- Physiologically Based Pharmacokinetic Model Qualification and Reporting Procedures for Regulatory Submissions: A Consortium Perspective (CPT 2018, PMID: 29315504)

Selected examples only
# Challenges and Proposals

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<thead>
<tr>
<th>Challenges</th>
<th>Proposals</th>
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<td><strong>System parameters:</strong></td>
<td>Methodology development</td>
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<tr>
<td>• Lack of understanding in transporter</td>
<td></td>
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<td>expression/activity</td>
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<td>• Lack of understanding in ontogeny</td>
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<td><strong>Drug parameters:</strong></td>
<td>Methodology development</td>
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<td>• Limited confidence in IVIVE in certain</td>
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<td>scenarios</td>
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<td>• Lack of characterization of drug disposition</td>
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<td><strong>Limited review timelines for complex models</strong></td>
<td>Process: early communication with relevant</td>
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<td>review divisions</td>
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<td>Resource: knowledge management</td>
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Collaboration Opportunities

- **Academic Institutions**
  - Collaborative Agreements (e.g., MOU, CRADA)
  - CDER Network of Experts (NoE) Program

- **Academic Faculty**
  - Faculty Sabbatical/Scientific Visit Program
  - Advisory Committees (AC)/Special Government Employee (SGE)

- **Professional & Graduate Students**
  - Doctor of Pharmacy APPE Rotations
    - Clinical Pharmacology
    - Drug Labeling
  - Student Summer Internships (Salaried)
    - Professional and Graduate Students
  - ORISE Fellows

- **Industry**
  - IQ consortium

- **Platform developers**

**MOU:** https://go.usa.gov/xQxVa; **NoE:** https://go.usa.gov/xQxyu; **AC:** https://go.usa.gov/xQxVk; **APPE:** https://go.usa.gov/xQxV5; **ORISE:** https://go.usa.gov/xQxVN
• PBPK submission becomes routine at FDA
• Accumulating experience in non-DDI scenarios
• Active research is ongoing to support future guidance development and review activity
Acknowledgements

- FDA fellows:
  - Yu Jiang
  - Hechuan Wang
  - Shaun S. Kumar
  - Jieon Lee

- FDA OCP/DPM
  - Hao Zhu

- FDA OCP/DPM/PBPK team:
  - Jianghong Fan
  - Manuela Grimstein
  - Xinyuan Zhang
  - Yuching Yang

- FDA OCP IO
  - Joe Grillo
  - Shiew-Mei Huang
  - Issam Zineh
  - EPPM staff