Physiologically Based Pharmacokinetic Modeling and Simulation in Drug Product Development and Review

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May 23, 2018

Disclaimer: The views expressed in this presentation are that of the speaker and do not reflect the official policy of the FDA. No official endorsement by the FDA is intended nor should be inferred.
Why PBPK?

Prediction!
Outline

• Introduction: PBPK / mechanism - based PK modeling
• Regulatory efforts in advancing PBPK modeling
• Case examples
• Summary
PBPK (mechanism-based PK) Models for Absorption

Zhang X. et al. (2014) CPT
Inputs and Outputs

**Drug substance and product information:**
- Dose and dose volume
- Solubility vs. pH profiles
- logP, pKa
- Dissolution: MR: dissolution profiles; IR: particle size and density
- Diffusion coefficient
- Permeability
- Metabolic kinetics

**Physiological parameters**
- GI transit time
- GI geometry
- GI fluid properties
- Enzymes/transporters distribution
- Blood flow

**PK parameters**
- Clearance, Vd
- Tissue/organ parameters for physiologically based distribution and elimination models

\[
\int \frac{dy}{dx} +, -, \times, \div, etc.
\]

- Fa, Fg
- In vivo dissolution
- Drug in each cmpt

- Fh, BA
- PK profiles
PBPK (mechanism-based PK) Models for Distribution

Fig. 1. A schematic of a PBPK model ($Q$ blood flow, $CL_{int}$ intrinsic clearance)

PBPK (mechanism-based PK) Models for Metabolism and Excretion


Outline

• Introduction: PBPK / mechanism - based PK modeling
• Regulatory efforts in advancing PBPK modeling
• Case examples
• Summary
Regulatory efforts in advancing mechanistic modeling and simulation

Zhao P. 2015 AAPS
Advisory Committee Meetings and Public Workshops

- **2012**: Meeting of the Pharmaceutical Science and Clinical Pharmacology Advisory Committee Topic 4: applications of PBPK modeling in pediatric studies

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

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

- **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
PBPK Related Guidance

In Vitro Metabolism and Transporter-Mediated Drug-Drug Interaction Studies — Study Design, Data Analysis and Clinical Implications
Guidance for Industry

Clinical Drug Interaction Studies — Format and Content Guidance for Industry

Physiologically Based Pharmacokinetic Analyses — Format and Content Guidance for Industry

# PBPK Reviews in 2014-2017 New Drug Approvals

<table>
<thead>
<tr>
<th>Year</th>
<th>Count</th>
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</thead>
<tbody>
<tr>
<td>2014</td>
<td>6</td>
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<td>2015</td>
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<td>2016</td>
<td>1</td>
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<td>2017</td>
<td>8</td>
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<table>
<thead>
<tr>
<th>Year</th>
<th>% in new drug approvals</th>
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<tbody>
<tr>
<td>2014</td>
<td>15%</td>
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<td>2015</td>
<td>16%</td>
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<td>2016</td>
<td>5%</td>
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<tr>
<td>2017</td>
<td>17%</td>
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Drugs@FDA: [https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm](https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm)

Supplement new drug reviews are not included.
Publications cover a wide range of PBPK aspects

**Physiologically Based Pharmacokinetic Modeling for Predicting the Effect of Intrinsic and Extrinsic Factors on Darunavir or Lopinavir Exposure Coadministered With Ritonavir**

Christian Wagner, PhD¹*, Ping Zhao, PhD², Vikram Arya, PhD, FCP¹, Charu Mullick, MD³, Kimberly Struble, PharmD³, and Stanley Au, PharmD, BCPS¹*

**Regulatory Experience With Physiologically Based Pharmacokinetic Modeling for Pediatric Drug Trials**

R Leong¹, MLT Vieira¹, P Zhao¹, Y Mulugeta¹, CS Lee², S-M Huang¹ and GJ Burckart¹

K. Sandy Pang⁴, Atiqr Rahman⁵, Lei Zhang⁵, Lawrence J. Lesko⁶, and Shiew-Mei Huang⁴

**Pharmacokinetic Models for the Effect of Food on Oral Physiologically Based Pharmacokinetic Prediction of Linezolid and Emtricitabine in Neonates and Infants**

Peng Duan¹ · Jeffrey W. Fisher² · Kenta Yoshida³ · Lei Zhang³ · Gilbert J. Burckart³ · Jian Wang³
Outline

• Introduction: PBPK / mechanism - based PK modeling
• Regulatory efforts in advancing PBPK modeling
• Case examples
• Summary
Case 1: Letermovir (approved in 2017)

- To explain the greater-than-dose-proportional PK of letermovir after IV and PO dosing
- To explain the difference in letermovir exposure observed in White and Japanese healthy volunteers
- To evaluate effect of letermovir on CYP3A and CYP2C8 substrates

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209939Orig1s000,209940Orig1s000ClinPharmR.pdf
General process applying PBPK to predict CYP modulation

**Substrate Model**
Build: in vitro + human single dose PK
Verify: other PK; Consider nonlinearity

**Inhibitor/inducer Model**
Build: DDI mechanisms
Verify: DDI with probes

- Predict interactions
  - Prioritize, plan and design the critical study

- Verify and modify (if necessary) substrate model

- Predict untested scenarios
  - Support dose recommendations

_ Zhao P. March 15, 2017 Meeting of the Pharmaceutical Science and Clinical Pharmacology (PSCP) Advisory Committee_
Effect of intrinsic factors on letemovir PK

*Role of OATP:* Letemovir was found to have greater than dose-proportional PK in human studies. One model assumption was that OATP1B1 and 1B3 are responsible for active hepatic uptake and that active uptake is saturable. This was consistent with simulations where turning off UGT Km and Vmax did not affect the ability to recover nonlinear letemovir PK, while turning off OATP1B1 Jmax and Km resulted in simulated linear PK (Figure 15).

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209939Orig1s000,209940Orig1s000ClinPharmR.pdf
Effect of ethnicity on lettermovir PK

QD, simulated vs. observed Cmax and AUC ratios were 0.99 and 0.56, respectively. It has been reported that OATP activity/abundance ratio between Japanese and whites is 0.58. When a factor of 0.58 was used, simulated vs. observed Cmax and AUC ratios were 1.46 and 0.69, respectively. Using an OATP activity/abundance factor of 0.58 in Japanese improved the prediction of Cmax and AUC ratios in Japanese vs. white healthy volunteers (Table 22).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Observed Japanese/Whites GMR</th>
<th>Simulated Japanese/Whites GMR&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Simulated Japanese/Whites GMR&lt;sup&gt;2&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>480 mg</td>
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<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>1.6</td>
<td>1.3</td>
<td>1.6</td>
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<tr>
<td>$\text{AUC}_{0-24}$ (ng·hr/mL)</td>
<td>1.9</td>
<td>1.3</td>
<td>2.1</td>
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<sup>1</sup>OATP activity/abundance = 1 in Japanese; <sup>2</sup>OATP activity/abundance = 0.58 in Japanese.

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209939Orig1s000,209940Orig1s000ClinPharmR.pdf
Effect of letermovir on CYP2C8

(see Section 3.3.4 for more details). A limitation to the modeling was that it is unknown whether letermovir is a CYP2C8 inducer. Coadministration with letermovir was predicted to increase repaglinide AUC by 2-3.5-fold and to increase rosiglitazone AUC by 30-55%. We agree with the applicant’s labeling

<table>
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<tr>
<th>In vitro measurement</th>
<th>Fold Changes in Inhibition Parameters Relative to Measured Values</th>
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<tr>
<td>OATP1B Kᵢ = 1.45 μM</td>
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<td>CYP2C8 Kᵢ = 0.22 μM</td>
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Following co-administration with oral letermovir

<table>
<thead>
<tr>
<th>Predicted REP AUC₀-ₐₖₜ</th>
<th>GMR (90% CI)</th>
<th>Predicted REP Cₘₚₓ</th>
<th>GMR (90% CI)</th>
<th>Predicted REP Cₘₚₓ</th>
<th>GMR (90% CI)</th>
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Following co-administration with i.v. letermovir

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<tr>
<th>Predicted REP AUC₀-ₐₖₜ</th>
<th>GMR (90% CI)</th>
<th>Predicted REP Cₘₚₓ</th>
<th>GMR (90% CI)</th>
<th>Predicted REP Cₘₚₓ</th>
<th>GMR (90% CI)</th>
<th>Predicted REP Cₘₚₓ</th>
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GMR = geometric mean ratio, CI = confidence interval

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209939Orig1s000,209940Orig1s000ClinPharmR.pdf
Case 2: Panobinostat (approved in 2015)

• To evaluate the effect of rifampin (a strong CYP3A) inducer on panobinostat (PAN) exposure
• To evaluate the effect of PAN on CYP3A substrate, midazolam
• To describe the effect of food on Tmax and Cmax of PAN
• To assess the effect of elevated gastric pH on PAN absorption

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/205353Orig1s000ClinPharmR.pdf
General process applying PBPK to predict oral absorption

Construct the PK model: (1). If human PK data are available, deconvolute PK data from i.v. administration (ideally) and/or p.o. administration of the fastest dissolving formulation to obtain disposition model; (2). If no human data, predicted from \textit{in vitro} or animal data.

Collect drug information: formulation information, physicochemical properties, gut and liver extraction ratio, and etc.

Fix the parameters with high confidence in the ACAT model and optimize the parameters with high uncertainty to fit PK data obtained from another formulation.

Validate the model with different PK data set(s): different dosing regimens, different formulations, and different food conditions, etc.

Does the model predict the trend? Do we have enough confidence about the model?

No

Yes

Model exploration: (1) perform PSA to identify the key parameters in the formulation under different conditions to guide the next formulation design to achieve the target PK profile; (2) deconvolution of PK data to obtain \textit{in vivo} dissolution profile and to identify biorelevant dissolution conditions by comparing with \textit{in vitro} dissolution profiles; (3) simulate different dosing regimens; (4) conduct virtual BE study; (5) connect the PK model with a PD model; etc.

\textbf{Fig. 1.} The flow diagram shows a general process of using a physiologically based absorption model in QbD-based drug development
Effect of rifampin on PAN

upon the simulations (Table 20). The simulation results suggest there is no practical FARYDAK dose that will provide exposure matching when given concomitantly with strong CYP3A4 inducers. It is unlikely that a dedicated clinical trial will change this conclusion and is not recommended at this time.

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Mean AUC_{0-24}</th>
<th>Mean AUC_{0-inf}</th>
<th>GM AUC_{0-inf}</th>
<th>Mean C_{max}</th>
<th>GM C_{max}</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAN alone</td>
<td>100</td>
<td>104 (103%)</td>
<td>256 (47%)</td>
<td>231</td>
<td>19.4 (146%)</td>
<td>9.67</td>
</tr>
<tr>
<td>PAN + rifampin (Day 7)</td>
<td>100</td>
<td>42.9 (109%)</td>
<td>97.4 (63%)</td>
<td>80.1</td>
<td>8.34 (149%)</td>
<td>4.34</td>
</tr>
<tr>
<td>GM ratio (90% CI)</td>
<td></td>
<td></td>
<td></td>
<td>0.35 (0.32-0.38)</td>
<td>0.45 (0.41-0.49)</td>
<td></td>
</tr>
</tbody>
</table>

GM = Geometric mean
Source: Applicant's final report for trial 1400354

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/205353Orig1s000ClinPharmR.pdf
Effect of PAN on CYP3A Substrate

(midazolam AUC ratio <1.25). The Agency reviewed this PBPK model, relevant simulations, and conducted additional sensitivity analyses (see Section 4.2.2) and finds that the potential for the concurrent use of FARYDAK with sensitive CYP3A4 substrates to result in a change in the CYP3A substrate exposure that requires intervention is unlikely, but not conclusive (Table 23).

Table 23: Prediction of the drug interaction of LBH589 (20 mg MWF weekly) and midazolam (5 mg single dose on day 15)

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Mean AUC₀-inf</th>
<th>GM AUC₀-inf</th>
<th>Mean C_max</th>
<th>GM C_max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam alone</td>
<td>100</td>
<td>70.0 (64%)</td>
<td>56.2</td>
<td>17.1 (57%)</td>
<td>14.5</td>
</tr>
<tr>
<td>Midazolam + PAN</td>
<td>100</td>
<td>73.2 (64%)</td>
<td>58.7</td>
<td>17.8 (56%)</td>
<td>15.1</td>
</tr>
<tr>
<td>GM ratio (90% CI)</td>
<td></td>
<td>1.04 (1.04-1.05)</td>
<td>1.04 (1.03-1.04)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GM = Geometric mean
Source: Applicant's final report for trial 1400354

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/205353Orig1s000ClinPharmR.pdf
Effect of food and elevated gastric PH on PAN PK

During the review of sponsor’s prediction of drug-drug interaction potential using PBPK approach, the FDA reviewer conducted a similar evaluation of the effect of food and increase in gastric pH using another PBPK platform [8]. Preliminary simulations also show that panobinostat absorption and PK were not affected by elevation in gastric pH, and food delayed panobinostat Tmax and decreased Cmax without changing AUC.

Table 3. FDA’s simulations using sponsor’s PBPK model to evaluate the effect of food on panobinostat PK and oral absorption (GMR: geometric mean ratio; data see Appendix Table 3)

<table>
<thead>
<tr>
<th>Simulated compared to fasted condition (simulation Condition 1)</th>
<th>Default fed condition (gastric transit time 1 hr, Condition 2)</th>
<th>Modified fed condition (gastric transit time 3 hr, Condition 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed T\textsubscript{max} (hr)</td>
<td>0.5</td>
<td>1.3</td>
</tr>
<tr>
<td>% decrease in C\textsubscript{max}</td>
<td>31%</td>
<td>62%</td>
</tr>
<tr>
<td>% change in AUC (0-48hr)</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Observed compared to fasted condition</th>
<th>Normal Breakfast</th>
<th>High-fat Breakfast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed median T\textsubscript{max} (hr)</td>
<td>1.5</td>
<td>2.5</td>
</tr>
<tr>
<td>% decrease in GMR C\textsubscript{max}</td>
<td>36%</td>
<td>44%</td>
</tr>
<tr>
<td>% change in GMR AUC\textsubscript{0-inf}</td>
<td>-14%</td>
<td>-16%</td>
</tr>
</tbody>
</table>
Summary

• PBPK is a tool for drug product development and has been used in regulatory decision making.

• Confidence level in PBPK predictive performance varies.
Acknowledgement

• Yuching Yang, Manuela Grimstein, Jieon Lee, Yaning Wang, Shiew-Mei Huang, Issam Zineh

• Review teams

• Ping Zhao (Bill & Melinda Gates Foundation)