Status of Physiologically Based Pharmacokinetic (PBPK) Modeling and Simulation in Drug Development and Regulatory Sciences

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Disclaimer

• The views expressed in this presentation are those of the speaker and do not reflect the official policy of the FDA. Cases discussed are for illustrative purpose only. No official endorsement by the FDA is intended nor should be inferred.
Outline

• Regulatory efforts in advancing PBPK modeling and current status
• PBPK modeling best practice and quality control
• Case examples
• Summary
What do we do?

OUTREACH

RESEARCH

HARMONIZE

SUPPORT

POLICY

GUIDE

REVIEW

Zhao P. 2015 AAPS
PBPK Submissions to OCP

Cumulative as of June 18, 2014 (n=96)

Cumulative as of Dec. 30, 2017 (n=254)

Sinha, MHRA PBPK Workshop 2014, London, UK

Grimstein et al. 2018 the Journal of Pharmaceutical Sciences
Number of NDA submissions per year containing PBPK analyses

<table>
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<th>Year</th>
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<td>17</td>
</tr>
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<td>2017</td>
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Grimstein et al. 2018, the Journal of Pharmaceutical Sciences
Advisory Committee Meetings and Public Workshops on PBPK Modeling

- **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
Publications cover a wide range of PBPK aspects

Absorption

DDI

Intrinsic factors
PBPK Related Guidance

In Vitro Metabolism- and Transporter-Mediated Drug-Drug Interaction Studies Guidance for Industry

Clinical Drug Interaction Studies — Study Design, Data Analysis, and Clinical Implications Guidance for Industry

Physiologically Based Pharmacokinetic Analyses — Format and Content Guidance for Industry

MIDD Pilot Program

• Model Informed Drug Development (MIDD) Pilot Program provides a process for drug developers and FDA to discuss the application of MIDD approaches, including PBPK modeling and simulation, to a specific drug development program

• Early communication on the PBPK modeling and simulation plan at the investigational new drug (IND) application stage is encouraged

Outline

• Regulatory efforts in advancing PBPK modeling
• PBPK modeling best practice and quality control
• Case examples
• Summary
Factors Affecting Oral 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

Metabolite Info
• Fa, Fg
• In vivo dissolution
• Drug in each cmpt

Parent and metabolite PK
• Fh, BA
• PK profiles
A broad spectrum of issues can be assessed using absorption modeling

• Biopharmaceutics
  o Dissolution
  o Product quality

• Clinical pharmacology
  o Fraction absorbed
  o PK/BE metrics assessment
  o PK in special populations
  o Gastric pH mediated drug-drug interactions
  o P-gp mediated drug-drug interactions
  o Assessing food effects
General process applying PBPK modeling 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 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 in vivo dissolution profile and to identify biorelevant dissolution conditions by comparing with in vitro dissolution profiles; (3) simulate different dosing regimens; (4) conduct virtual BE study; (5) connect the PK model with a PD model; etc.

Fig. 1. The flow diagram shows a general process of using a physiologically based absorption model in QbD-based drug development.
General process applying PBPK modeling 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

Wagner, CPT-PSP, 2015
PBPK modeling borrows prior knowledge

CYP3A Perpetrator Model

CYP3A Sensitive Substrate Model

CYP3A Perpetrator Model

CYP2C9 Sensitive Substrate Model

CYP2C9 Perpetrator Model

CYP2C9 Perpetrator Model

OCT2 Sensitive Substrate Model

OCT2 Perpetrator Model

OCT2 Perpetrator Model

P-gp Sensitive Substrate Model

P-gp Perpetrator Model

P-gp Perpetrator Model

The Primary Drug Model
Outline

• Regulatory efforts in advancing PBPK modeling
• PBPK modeling best practice and quality control
• Case examples
• Summary
Case Examples

• Ibrutinib
  – To assess effect of ibrutinib on oral P-gp substrates

• Ceritinib
  – To explore the role of P-gp in ceritinib absorption, food effect, and the effect of elevated stomach pH on ceritinib PK

• Panobinostat
  – To assess the effect of elevated gastric pH on panobinostat absorption

Disclaimer: The models were developed by the Applicants and reviewed by the review team. Refer to Drugs@FDA for details. Cases discussed are for illustrative purpose only.
# Ibrutinib

## Dosage, Indication, General PK

- Immediate release oral capsules or tablets, 70 mg and 140 mg
- Mantle cell lymphoma (MCL) and Marginal zone lymphoma (MZL): 560 mg QD
- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL), Waldenström’s macroglobulinemia (WM), and Chronic graft versus host disease (cGVHD): 420 mg QD
- PK proportionally increases up to 840 mg

### Absorption
- BA: complete absorption, expected low BA due to first pass metabolism
- Tmax ~1-2 hours
- Food increases exposure ~2-fold

### Distribution
- fup: 2.7%
- Vd,ss/F: ~10000 L

### Metabolism
- Primarily by CYP3A, to a minor extent by CYP2D6

### Elimination
- CL/F ~ 1000 L/h, T1/2 = 4-6 hours

## Drug-drug Interaction
- CYP3A substrate
- In vitro, a P-gp inhibitor

[https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/205552s025lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/205552s025lbl.pdf)
Ibrutinib PBPK Modeling Purposes

• The Applicant’s analysis
  – Assess the effect of CYP3A inhibitors or inducers on the PK of ibrutinib
  – Explain potential food effect
  – Predict drug exposure in subjects with hepatic impairment

• FDA’s analysis
  – Predict ibrutinib exposure in GI segments to determine the potential for ibrutinib to inhibit (P-gp)

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205552Orig2s000ClinPharmR.pdf
Pan et al. The Journal of Clinical Pharmacology (2016), 56(S7) S122–S131
Ibrutinib PBPK Model Structures

• Absorption
  – Advanced Dissolution, Absorption and Metabolism (ADAM)
    • Low solubility and higher permeability
    • Solubility increases with decreasing pH

• Distribution
  – Full body PBPK (Vss based on Kp values)

• Metabolism and Excretion
  – CLint + CLrenal (minimal)

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205552Orig2s000ClinPharmR.pdf
PBPK modeling supported dosing recommendation for DDIs

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205552Orig2s000ClinPharmR.pdf
Ibrutinib PBPK Modeling Impact

- Simulation suggested ibrutinib is quickly absorbed in the GI tract, and absorption is generally completed in 2.5 hours. Therefore, assuming ibrutinib can inhibit P-gp along the GI tract in vivo, the inhibitory effect on substrates can be minimized if the substrate is not administered during the absorption phase of ibrutinib.
- Simulation supported dosing recommendations when ibrutinib is co-administered with moderate CYP3A modulators.

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205552Orig2s000ClinPharmR.pdf
# Ceritinib

## Dosage and Indication
- Immediate release capsules 150 mg
- Patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive: 450 mg QD with food
- PK proportionality in the dose range of 50 to 750 mg

<table>
<thead>
<tr>
<th>Absorption</th>
<th>Distribution</th>
</tr>
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<tbody>
<tr>
<td>- Tmax: ~1-2 hours</td>
<td>- fup: 3%</td>
</tr>
<tr>
<td>- High fat meal: ↑AUC 73%, ↑Cmax 41%</td>
<td>- Vd/F = 4230 L</td>
</tr>
<tr>
<td>- Low fat meal: ↑AUC 58%, ↑Cmax 43%</td>
<td></td>
</tr>
</tbody>
</table>

## Absorption
- High fat meal: ↑AUC 73%, ↑Cmax 41%
- Low fat meal: ↑AUC 58%, ↑Cmax 43%

## Distribution
- fup: 3%
- Vd/F = 4230 L

## Metabolism
- CYP3A
- CLss/F = 33.2 L/h, CLsd/F = 88.5 L/h
- T1/2 = 41 hours in patients
- 68% was excreted as unchanged ceritinib in feces

## Drug-drug Interaction
- CYP3A substrate, CYP3A and CYP2C9 inhibitor
- In vitro, P-gp substrate

https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/205755s010lbl.pdf
Ceritinib PBPK Modeling Purposes

• The Applicant’s analysis
  – Assess the effect of CYP3A modulators on ceritinib PK
  – Propose dosing recommendation for DDI scenarios

• FDA’s analysis to explore
  – Sensitivity of ceritinib exposure to changes in effective permeability (Peff)
  – Food effect
  – Sensitivity of ceritinib exposure to changes in gastric pH

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205755Orig1s000ClinPharmR.pdf
Pan et al. The Journal of Clinical Pharmacology (2016), 56(S7) S122–S131
Ceritinib PBPK Model Structures

- Absorption
  - First order
  - Advanced Dissolution, Absorption and Metabolism (ADAM)
    - Low solubility
- Distribution
- Metabolism and Excretion

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205755Orig1s000ClinPharmR.pdf
Pan et al. The Journal of Clinical Pharmacology (2016), 56(S7) S122–S131
Ceritinib PBPK Modeling Impact

- Sensitivity analysis of apparent permeability (Peff) suggested P-gp played minimal role in ceritinib absorption. An in vivo DDI study with an P-gp inhibitor was not necessary.

- Model predicted 10% decrease in Cmax and AUC when gastric pH was increased to 7.
  - In healthy subjects taking PPIs: AUC ↓ by 76% (66%, 83%) and Cmax ↓ by 79% (70%, 86%).
  - In a patient group taking PPIs: AUC ↓ by 30% (0%, 52%) and Cmax ↓ by 25% (5%, 41%)

- Model predicted Cmax and AUC increased by 38 and 34%, respectively under fed condition
  - High fat meal: ↑AUC 73%, ↑Cmax 41%
  - Low fat meal: ↑AUC 58%, ↑ Cmax 43%

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205755Orig1s000ClinPharmR.pdf
https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/205755s010lbl.pdf
# Panobinostat

## Dosage and Indication
- Capsules: 10, 15, and 20 mg
- In combination with bortezomib and dexamethasone, is indicated for the treatment of patients with multiple myeloma
- 20 mg, taken orally once every other day for 3 doses per week

## Absorption
- BA ~ 21%
- Tmax ~ 2 hours
- High fat meal: ↓Cmax and AUC_{0-48} by ~ 44% and 16%, respectively

## Distribution
- fup: 10%

## Metabolism
- Extensively metabolized
- CYP3A accounts for 40% of total hepatic elimination

## Elimination
- CL/F ~160 L/hr, T1/2 ~37 hours
- <2.5% of the dose in urine and <3.5% of the dose in feces were unchanged

## Drug-drug Interaction
- CYP3A substrate
- CYP2D6 inhibitor

[https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205353s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205353s000lbl.pdf)
Panobinostat PBPK Modeling Purposes

• To evaluate the effect of CYP3A modulators 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
Panobinostat PBPK Model Structures

- Absorption
  - advanced compartmental and transit model (ACAT)
    - Solubility decreases with increasing pH
- Distribution
  - Compartment model
- Metabolism and Excretion

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

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>
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</thead>
<tbody>
<tr>
<td>Delayed T_{max} (hr)</td>
<td>0.5</td>
<td>1.3</td>
</tr>
<tr>
<td>% decrease in C_{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>

**Observed compared to fasted condition**

<table>
<thead>
<tr>
<th>Normal Breakfast</th>
<th>High-fat Breakfast</th>
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<tbody>
<tr>
<td>Delayed median T_{max} (hr)</td>
<td>1.5</td>
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<tr>
<td>% decrease in GMR C_{max}</td>
<td>36%</td>
</tr>
<tr>
<td>% change in GMR AUC_{0-inf}</td>
<td>-14%</td>
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Summary

- Physiologically based PK and absorption modeling can be a tool to address many clinical pharmacology questions, such as:
  - PK in special populations
  - Gastric pH mediated drug-drug interactions
  - P-gp mediated drug-drug interactions
  - Assessing food effects
- Confidence level in PBPK predictive performance varies.
- Discussions on best practice in modeling are encouraged.
- Early engagement with the FDA on PBPK modeling and simulation plan is encouraged.
Acknowledgement

• Yuching Yang, Manuela Grimstein, Jieon Lee, Jianghong Fan, Joseph A. Grillo, Hao Zhu, Yaning Wang, Shiew-Mei Huang, Issam Zineh
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