Application of Physiologically Based Biopharmaceutics Modeling in Support of Drug Product Quality

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This presentation reflects the views of the presenter and should not be construed to represent the FDA's views or policies.
Outline

• Overview of review tasks at Division of Biopharmaceutics in FDA
• Physiologically-Based Biopharmaceutics Modeling (PBBM) in support of drug product quality
  – Common applications
  – Common deficiencies
  – Model workflow - general strategy
  – Case study
• Summary/Take Home Message
Overview of review tasks at FDA’s Division of Biopharmaceutics

Clinically relevant specifications

- Dissolution/In vitro Release
- ER claim
- IVIVC
- IVIVR
- Mechanistic modeling
- Patient-centric product quality
- QbD Risk Assessment
- Design space verification
- Biowaivers (BCS, CFR, Safe Space based)
- RTRT dissolution models
Common regulatory applications of PBBM in support of drug product quality

Dissolution method, Acceptance criteria (AC)
  • Bio-predictive ability of dissolution method
  • Clinically relevant dissolution AC/wider AC

Clinically relevant specifications of CMAs and CPPs
  CMAs (e.g., particle size, polymorphic form)
  CPPs (e.g., milling, compression force/hardness process evaluation)

Quality related Bio-waiver
  • Waiver request based on physiologically based IVIVC/IVIVR

Formulation impacts
  Formulation-related food effect
  API form change or formulation change on PPI interactions
  Prediction of product performance by looking at GI local drug concentration and regional absorption
Number of NDA submissions containing PBBM in support of drug product quality (2008-2018)
Number of ANDA submissions containing PBBM in support of drug product quality (since 2016)
Common PBBM deficiencies observed in FDA submissions

• Model is not mechanistically sound,
  – Lack of parameter plausibility
  – API driven or formulation driven dissolution/absorption misinterpreted
  – In vitro dissolution not bio-predictive or not reflecting the in vivo dissolution
  – Assumption of 100% bioavailability, while incomplete absorption was indicated by in vivo study

• Verification data is insufficient,
  – Not objective oriented model verification
  – Inappropriate data selection for model verification
  – Additional verification needed for the intended purpose

• Model structure information is insufficient,
  – No formulation information
  – No mechanistic framework accounting for impact of quality attributes on absorption
  – No justification for input parameter values selected in drug, PK, formulation, physiology
  – Insufficient data/program files

• Reliability of simulation results is questionable,
  – Uncertainty of subject variability
How to develop PBBM?
Physiologically-Based Biopharmaceutics Modeling workflow

Model Objective(s)

Model Development

Parameters, Structure, Assumptions

Model verification

Acceptable?

Yes ➔ Model application

No ➔ Acceptable?

"Learn and Confirm"

Model refinement
Case study:

- Objective: To establish clinically relevant API particle size specification/formulation design space for a BCS class IV immediate release oral dosage formulation

- Oncology drug for treatment of leukemia
- Immediate release capsule
- 2 strengths: low and high compositionally proportional
- BCS class 4
- High strength used in model development
- Wide particle size range used in pivotal clinical trials
# Drug parameters:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MW</td>
<td>417</td>
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<tr>
<td>pKa</td>
<td>3.9</td>
</tr>
<tr>
<td>logP</td>
<td>2.6</td>
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<tr>
<td>Solubility</td>
<td>![Solubility Graph]</td>
</tr>
<tr>
<td>Peff_</td>
<td>0.14 x 10^-4 cm/sec (human)</td>
</tr>
<tr>
<td>Density</td>
<td>1.37 g/mL</td>
</tr>
<tr>
<td>Dissolution</td>
<td>Rapid dissolution in acidic medium</td>
</tr>
</tbody>
</table>
Modeling workflow

Base model development using IV and PO data

Model modification/refinement using clinical data at 6 different doses

Model verification/validation using 5 sets of independent clinical data

Parameter sensitivity analysis (PSA)

Model application

Virtual bioequivalence (BE) to define clinically relevant PSD limits

Regulatory decision

"Learn and Confirm"
Modeling input and output

**API and product formulation input:**
- Solubility vs. pH profiles
- logP, pKa
- Dose and dose volume
- Diffusion coefficient
- Permeability
- Metabolic/transport kinetics
- Dissolution:
  - IR: particle size and density; MR: dissolution profiles

**Physiology input:**
- pH in GI
- GI transit time
- GI fluid volume
- Bile salt
- Enzymes/transporters distribution
- Blood flow

**PK input:**
- Clearance
- Vd
- Inter-compartment rate constant
- Protein binding
- Tissue/organ parameters for drug distribution and elimination

**Model output:**
- PK profiles
- Cmax
- AUC
- Tmax
- In vivo dissolution
- Fa, Fg
- F
- Drug in regional GI

*Input determines your output!*
PSA showing the effect of particle size on systemic exposure

Conduct PSA for your parameters of uncertainty!
Virtual BE supporting regulatory decision

Setting clinically relevant particle size within the specification vs. (T): upper bounds of particle size vs. (R): lower bounds

Conduct virtual BE to take into consideration variability of individual parameters!
Summary

The use of Physiologically-Based Biopharmaceutics Modeling contributes to:

– Enhanced drug product understanding, in conjunction with quality by design (QbD) approach
– Patient-centric product quality
– Establishment of *in vitro and in vivo* link, a key element in setting clinically relevant drug product specifications
– Potential reduction in the number of in vivo BA/BE studies (e.g., due to formulation or manufacturing process changes) prior to approval process or post-approval changes.
Take home messages (1): A few questions to raise before developing a model

• What is the proposed model purpose or intended regulatory use?
• Are there sufficient data for model development and verification to justify the intended purpose?
• Are the data robust?
• What is the appropriate model strategy?
• Early communication with Division of Biopharmaceutics is encouraged!
Take home messages (2): Document checklist for FDA submission (not limited to)

- Model report (stating model objective and your “thought” process)
- Modeling workflow
- Drug product/formulation information and process understanding
- Solubility data
- Relevant dissolution information and dissolution profile data
- PK data and study design
- Sources of parameters
- Coding or mathematical equations
- Hypothesis
- Datasets (allowing executing independent analysis)
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