Physiology Based Pharmacokinetic Absorption Modeling in Generic Drug Product Development and Regulatory Decisions- **Opportunities and Challenges**

**GastroPlus User Group webinar**
Maitri Sanghavi,
Biopharmaceutics & Pharmacokinetics
PTC, Zydus Cadila
30th April, 2019
Disclosure Statement

The views expressed in this talk represent my personal opinions and do not necessarily represent the views of any organizations.
Abstract

Physiology based pharmacokinetic (PBPK) modeling is widely used within the pharmaceutical industry to predict oral drug absorption. The potential utility of PBPK absorption modeling in the regulatory setting has been highlighted by both industries and regulators. A recent survey of the pharmaceutical industry highlighted that in silico PBPK absorption modeling is widely used during development to address a variety of biopharmaceutics issues. Application of PBPK modeling to support clinically relevant specifications has been encouraged by various regulatory agencies. A sequential process of implementing PBPK modelling and simulation at various steps of generic drug product development is discussed. Various quintessential points are explained with relevant examples, and how PBPK modeling can accelerate the drug development process is highlighted. Further, challenges and ‘keep in mind’ points are discussed with regulatory filing perspectives.
Outline of the presentation:

- Introduction
- Generic drug product development
- Application of modeling & simulation
- Regulatory impact of PBPK
- Simulation methodology & case studies
- Challenges & summary
Introduction: Mechanistic vs Conventional deconvolution

ACAT [Advanced Compartmental Absorption & Transit] Model

Mechanistic Absorption Modeling (MAM)

- Unreleased
- Undissolved
- Dissolved

Lumenal Degradation
Gut Wall Metabolism

Portal Vein
Liver
Gallbladder

Systemic Circulation
Hepatic Artery

Brain
Adipose
Muscle
Skin

Physiologically based Pharmacokinetics (PBPK)
Generic Drug Product Development

Early Stage Development

- Selection of drug product - literature review
- Reference product characterization
- QbD based formulation & process development

6-12 months

Late Stage Development

- Pilot BE-studies
- Scale up & exhibit Pivotal BE-studies
- ANDA filing & review

18-24 months

Life Cycle Management

- Market approval
- Commercialization
- Post approval changes

24 months

Time Scale
Applications of PBPK in drug product development

Early and late development phase – Reduce trial & error

- For formulation optimization
- Understand the mechanisms that affect the absorption
- Dissolution method and acceptance criteria:
- Clinically relevant limits for CMAs and CPPs
- Food effect assessment
- Biowaiver

Post approval changes

- To justify post approval CMC changes
- To justify manufacturing site transfer
## Regulatory impact of PBPK - USFDA - 2016

<table>
<thead>
<tr>
<th>Type</th>
<th>No.</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANDA Reviews &amp; Citizen petitions</td>
<td>22</td>
<td>✤ Implement clinical relevant PK metrics for BE assessment</td>
</tr>
<tr>
<td>Pre-ANDA interactions (including CC)</td>
<td>26</td>
<td>✤ Development of BE criteria for analgesics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>✤ Assessment of BE standards for GI locally acting products</td>
</tr>
<tr>
<td></td>
<td></td>
<td>✤ Simulation of in vivo alcohol dose dumping studies</td>
</tr>
<tr>
<td>BE Guidances</td>
<td>31</td>
<td>✤ Simulations for the development of BE criteria for HVDs and NTI drugs</td>
</tr>
<tr>
<td>Regulatory Research Studies</td>
<td>30</td>
<td>✤ Pharmacokinetic(PK)/Pharmacodynamic (PD) modeling and simulation to determine the appropriate study design and evaluate clinical endpoint sensitivity for BE assessment</td>
</tr>
</tbody>
</table>

ANDA: abbreviated new drug application; BE: bioequivalence; CP: citizen petition; CC: controlled correspondence; GI: gastrointestinal; HVD: highly variable drugs; NTI: narrow therapeutic index.
Regulatory scientists trained on GastroPlus™ PBPK modeling
Rate of acceptance of PBPK analyses by FDA & EMA
Tour of the policy development in PBPK area

- 2010: WHO guidance
- 2012: FDA & EMEA workshops
- 2014: FDA & EMEA Draft guidance
- 2016: FDA & EMEA Guidelines
- 2018: FDA final guidance & EMEA Guidelines
Regulatory guidelines

Physiologically Based Pharmacokinetic Analyses — Format and Content
Guidance for Industry

Flow diagram of mechanistic modeling

*Optimum blend of human intelligence and artificial intelligence is must..!!*
Developed PK model using preferably intravenous data. IR can be used in the absence of IV data.

Develop oral absorption model and internal validation.

Validate model
External validation
Sensitivity analysis

Use model to predict in vivo performance of batches

Population simulation
Virtual bioequivalence

In silico dissolution safe place
Simulate BE trails for theoretical target batches

In vivo oral fasting data of test formulation

With maximum available different clinical datasets

Target in vitro data/ intended model application

Model application

Model validation

Model Set up

Biopharmaceutical property set up
Formulation set up
Physiological set up
Compartmental PK
Example 1: BCS class 2 drug formulated as MR tablet

Case:
- Matrix based formulation in multiple strengths having low ISCV
- pH dependent solubility, lower solubility at acidic pH
- No food effect and linear PK
- Available data: Fasting, fed BE data for highest strength and one fed study data for lower strength, IR BE data.

Intended purpose of the simulation:
- Formulation composition was different for lower strength to match $f_2$ in dissolution. Agency requested to conduct additional BE studies for lower strength
- To assess the risk of not conducting additional BE study for the lower strength
Model development

<table>
<thead>
<tr>
<th>Physiochemical Properties</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight (g/mol)</td>
<td>Around 300</td>
</tr>
<tr>
<td>pKa</td>
<td>5.8 (basic)</td>
</tr>
<tr>
<td>$P_{\text{eff}}$ (cm/sec)</td>
<td>$3.3 \times 10^{-4}$</td>
</tr>
<tr>
<td>log P</td>
<td>1.7</td>
</tr>
<tr>
<td>Dosage form</td>
<td>CR Integral Tablet</td>
</tr>
<tr>
<td>Dose volume (ml)</td>
<td>250</td>
</tr>
<tr>
<td>Aqueous solubility (mg/mL @ pH 6.8)</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Model building with formulation AA, x mg, fasting

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Observed</th>
<th>Predicted</th>
<th>% PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>1.88</td>
<td>1.91</td>
<td>-1.77</td>
</tr>
<tr>
<td>$T_{\text{max}}$</td>
<td>8</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>$AUC_{0-1}$ (ng-h/ml)</td>
<td>53.45</td>
<td>56.40</td>
<td>-5.23</td>
</tr>
<tr>
<td>$AUC_{0-\text{inf}}$ (ug-h/mL)</td>
<td>54.79</td>
<td>56.62</td>
<td>-3.23</td>
</tr>
</tbody>
</table>
Model verification

Model verification with formulation AB x mg, fasting state

Model verification with Formulation AA, x mg, fed state

slower in vitro and in vivo release than the batch used in model building,
Model verification

Formulation A, 0.5 X mg, Fed

Formulation B, 0.5 X mg, Fed

Additional Verification of the model with different strength studies
Model application

Virtual BE of formulation A vs formulation B, 0.5xmg under fasting state

Population Simulation: Parent

<table>
<thead>
<tr>
<th>Result</th>
<th>Cmax</th>
<th>AUC</th>
<th>AUCt</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(GeomMeanT/GeomMeanR) *100</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>96.28</td>
<td>93.35</td>
<td>94.09</td>
</tr>
</tbody>
</table>

90% CI (GeomMeanT/GeomMeanR)

| 90.618 | 105.29 |
| 82.974 | 105.02 |
| 84.121 | 105.25 |
Example 1 Case conclusion

✓ The developed mechanistic absorption PK models described the key features in the PK curves under fasting and fed condition for both the strengths

✓ Mechanistic absorption modeling coupled with virtual BE was successfully employed to simulate PK profiles for lower strength having different composition under fasting state
Example 2: Evaluation of target particle size

**Case:** Compound was a weak base, BCS Class II, IR formulation, having pH dependent low solubility, Tmax-4h

**Absorption Modeling Strategy:** Simulation was used to predict the upper boundaries of the drug substance particle size distribution on *in vivo* performance of the drug product. Parameter sensitivity analysis was also done to identify the boundaries in which PSD will fail the BE and PSD which gives satisfactory results.

**Outcome:** This information and exploring these boundaries really helped with the future developments which reduced time and cost by waiving pilot studies.
Example 3: Evaluation of clinically relevant specifications for BCS class III compound with non linear PK- ER formulation

**Case:** BCS III compound, ER formulation and pH independent high solubility across the pH
- Dose dependent bioavailability due to saturation of Pgp
- Very long half life & negative food effect
- Intended objective of simulation was widening of dissolution specifications

**Absorption Modeling Strategy:** The ACAT model was proposed to mechanistically predict drug dissolution and intestinal absorption including gut metabolism and active transport processes after oral administration.
- $V_{\text{max}}$ and $K_{m}$ values of the Pgp have been incorporated.
- Safe space determination
- Sensitivity analysis
- Virtual bioequivalence

**Outcome:** Mechanistic absorption model allowed IVIVR of the compound having non-linear PK
Proposed dissolution specification was found to produce bioequivalence between the pivotal test and reference formulations when simulated using crossover virtual trials in GastroPlus
Example 4: Evaluation of in vivo impact of slowing down dissolution with time

**Case:** To justify slow down of in vitro release observed over a time for BCS II drug having pH dependent solubility and long half life. Multimedia dissolution was performed. Slower release rate was observed at one of the conventional media.  

**Objective:** Is it relevant to the product in vivo performance???

**Absorption Modeling Strategy:**
- Two compartment PK model fitted to IV data and validated using different set of available in vivo data.
- Z factor was fitted to slower (non-f2 matching) and normal dissolution profiles
- PSA and virtual BE trial

**Outcome:** Slower batch was found to produce bioequivalence between the pivotal test and reference formulations when simulated using crossover virtual trials in GastroPlus. In vivo study was conducted as a back up to evaluate in vivo impact. The results were inline with the simulated results.
Example 5: Evaluation of clinically relevant specifications for BCS class II compound - ER formulation

**Case: To support wider dissolution specifications**
BCS class II compound having pH dependent low solubility & high permeability, relatively high ISCV (30-35%) and short half-life (5-7 h)

**Absorption Modeling Strategy:** Same standard modeling practice has been followed which was explained earlier. Model was validated by 2 available different datasets. Model was also validated by published literature dataset. Virtual BE and PSA were then conducted to evaluate safe space.

**Outcome:** Proposed dissolution specification was found to produce bioequivalence between the pivotal test and reference formulations when simulated using crossover virtual trials in GastroPlus
Challenges

✓ Appropriate selection of input parameters
✓ Assumptions and optimization
✓ Model verification
✓ Lack of biorelevant *in vitro* methods
✓ Biopharmaceutics knowledge
✓ Excipient effects-better understanding of formulation performance *in vivo*
✓ Inclusion of CMA & CPP parameters in the commercially available software
✓ Identification and transparent communication of knowledge gaps
✓ Clarity on regulatory expectations
Models that guide formulation selections or subsequent formulation modifications, such as API particle size or release rates for modified-release formulations, are routinely applied in early development.

Establishing confidence in physiological model is crucial for effective use of PBPK.

A well qualified model with high confidence can be used to aid regulatory decision-making.

Mechanistic Absorption/PK/PBPK in generic drug product development is still underutilized tool in the industry.
Looking to the future

✓ Development and refinement of guidelines and recommendations for more efficient reporting of model results for regulatory submissions is mandatory.

✓ The adoption of these harmonized practices will result in better decision-making, ultimately will lead to improved patient outcomes with the development of safe and efficacious drugs.
Thank you