Application of PBPK Models in Assessment of Bioequivalence

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Novel Gut Absorption Models and Physiologically-Based IVIVC
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Disclaimer

The views expressed in this presentation are those of the speaker and not necessarily those of the Food and Drug Administration (FDA).
New Office of Research and Standards within OGD

• Division of Therapeutic Performance (DTP)
  - Facilitates pre-ANDA development of generic drugs
  - Conducts and promotes regulatory science research to establish standards to ensure therapeutic equivalence of generic versions of drug products.
  - Evaluates post-approval safety, product use and bioequivalence issues with approved generic drugs.

• Division of Quantitative Methods And Modeling (DQMM) –
  - Establishes predictive and physiological models of drug product performance, drug absorption, drug pharmacology, and other quantitative methods to ensure generic drug equivalence.
  - Develops new tools to analyze in vitro, pharmacokinetic, pharmacodynamics and clinical bioequivalence studies.
M&S in Generic Drug Evaluation

- New Division of Quantitative Methods and Modeling under OGD/ORS
- Support generic drug policy development and regulatory decisions
  - BE guidance development
    - pAUC, e.g. zopidem, …. (all consideration of pAUC include simulation evaluation)
    - Complex Drugs: BE for iron colloids
    - Narrow Therapeutic Index drugs (NTID) classification
      - nonlinear PK properties (refer to phenytoin & carbamazepine posters)
    - Clinical endpoint bioequivalence trial simulations
  - Post-marketing efficacy & safety evaluation of generic drugs
    - Evaluate risks of potential failure mechanisms
    - Methylphenidate, Warfarin, Nifidipine
- GDUFA Regulatory Science Grants awarded in Sept 2014
  - PBPK for non-oral delivery routes (7)
  - PK/PD and pharmacometrics for generic drugs (4)
Office of Research and Standards Scientific Leaders

Transforming Research into Standards

• Lucy Fang
  – PK/PD models, NTI drugs

• Susie Zhang
  – Absorption models

• Jeff Jiang
  – Peptides and complex mixtures

• Sam Raney
  – Topical and transdermal products

• Bavna Saluja
  – Inhalation and nasal products, Abuse deterrent formulations

• Stephanie Choi
  – Complex drug products, Ophthalmic products

• Yih Chain Huang
  – Bioequivalence guidance development
Technology and Platforms

• Mechanistic Models
  – PBPK / absorption
  – mechanistic IVIVC/R
  – Mechanism based diffusion models
  – Computational Fluid Dynamics (CFD) models
  – Molecular modeling for complex drug substances

• Empirical Models
  – PK/PD modeling
  – Clinical trial simulation
  – Statistical regression models

• Simulation
  – Virtual BE simulations
  – Clinical trial simulations
Modeling and Simulation Examples

• The context for biopharmaceutic modeling and simulations in the generic drug framework is different than from modeling and simulation in drug discovery and development
  – Much more knowledge about drug and human PK data often available
• Solid Oral Examples
• Complex Drug Example
Factors Affecting Oral Absorption

- Unreleased
- Transit
- Undissolved
- Transit
- Dissolved
- Precipitation
- Degradation
- Solubility
- Lipophilicity
- Controlled releasing rate
- Particle size distribution
- GI transit time
- GI fluid hydrodynamics
- GI fluid composition
- GI fluid pH
- GI fluid volume
- Permeability
- Etc.

Liver

Distribution and Elimination PK models

PD models

Influx

Efflux

D

M

E

Portal Vein

Enterocyte

GI Lumen

Enterocyte

Portal Vein
Mechanistic Oral Absorption Models

\[ \text{dissolution rate} = \frac{dM}{dt} = \frac{DS}{h} (C_s - C_t) \]

\[ \text{absorption rate} = \frac{dM}{dt} = \iint_A J_w dA = \iint_A P_w C_w dA \]

- Quasi-equilibrium models
- Steady-state models
- Dynamic models
  - Compartment models
    - Mass balance
    - First-order transit along the GIT
    - Passive and active transport through enterocytes
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**
- Fh, BA
- PK profiles

**Parent and metabolite PK**
- Fa, Fg
- In vivo dissolution
- Drug in each cmpt
Whether the GI local concentration/exposure correlates with the plasma concentration/exposure

- Modeling and simulation of mesalamine absorption supported FDA’s responses to citizen petitions on mesalamine bioequivalence.

- pH dependent solubility
- Short half life
- Metabolized by N-Acetyltransferases
- Targets lower GIT and acts topically
- Modified release dosage form
Approaches

Model was developed based on i.v., suspension, and suppository PK data.

Fit pH dependent dissolution profiles as model input for in vitro dissolution.

Adjust pH in the GI lumen against observed PK profiles for each subject...

\[ \frac{dM}{dt} = zM_{u,0} \left( \frac{M_{u,t}}{M_{u,0}} \right)^{\frac{2}{3}} (C_s - C) \]

Simulation to answer specific questions.
Model Development and Validation

Graphs showing the concentration of 5-ASA and Ac-5-ASA over time for different dosages.
Total Colon Exposure Correlates with Plasma Exposure

\[ \text{AUC}_{\text{colon}} (\text{ng*hr/mL}) \]

\[ \text{AUC}_p (\text{ng*hr/mL}) \]

p-value = 0.00011096
What are the formulation parameters that affect PK bioequivalence conclusions?

- Modeling and simulation to understand if formulation design difference could be expected to impact bioequivalence
Example Use in Formulation Evaluation

**pH 1.1**

**pH 6.8**
Gaps for Oral Absorption

• There is a linkage between challenges in absorption modeling and simulation and IVP dissolution.
  – Both need more data about in vivo physiology
  – You want IVP dissolution to be the input that closes gaps in the models

• Gap: Improving the modeling and simulation for colon absorption to fully account for the performance of modified release dosage forms.

• Gap: Improving knowledge of in vivo hydrodynamics is needed to improve the models and IVP dissolution
Gaps for Oral Absorption

- **Variability**: For the generic drug program, simulation of a cross-over bioequivalence study is an important modeling and simulation application but current data sets and models of within subject variability for GI parameters lag the understanding of between subject variability.

- **Formulation**: The interaction of formulation variables with physiological factors is important to the design of bioequivalent formulations. This includes improved prediction of food effect, prediction of bioavailability for complex formulations and solid dispersions, and prediction of bioavailability for nano-size formulations.
What are the best bioequivalence metrics for injectable iron nano-complexes?

• Modeling and simulation help identify improved bioequivalence
Iron Colloid Model

• Physiology

Sodium Ferric gluconate → SFG → Labile Iron → RES → Ferritin → TBI

SI (total serum iron)

• Model

infusion

Plasma, DBI (V_P)

k_pr

RES (V_RES)

k_sr

STORAGE (V_S)

blood loss

Plasma, TBI (V_TBI)

k_ts

Kon/Koff

TIBC
Transferin Saturatiuon and Impact on BE

![Histogram of Transferrin Saturation (%)](image)

- Count
- Transferrin Saturation (%)
- 50 60 70 80 90 100 110 120
- 0 5 10 15 20 25 30 35
Comparison of Bioequivalence Metrics
## M&S Impact in OGD

<table>
<thead>
<tr>
<th>Type</th>
<th>N</th>
<th>Examples</th>
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<tbody>
<tr>
<td>ANDA Reviews</td>
<td>6+</td>
<td>PD modeling and simulation for budesonide nasal spray to support the selected dose for BE study.</td>
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<tr>
<td>CP and Other Consult</td>
<td>19+</td>
<td>Development of BE criteria for zolpidem tartrate ER tablets</td>
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<tr>
<td>Response</td>
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<td>Steady state simulations for risperidone long acting injection</td>
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<td>Simulation of in vivo alcohol dose dumping studies</td>
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<tr>
<td>BE Guidances</td>
<td>20+</td>
<td>Simulations for the development of BE criteria for complex drugs, HVDs and NTI drugs</td>
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<tr>
<td>Regulatory Research</td>
<td>7+</td>
<td>PK/PD modeling and simulation to determine the appropriate study design and evaluate BE between generic anti-epilepsy drugs and immunosuppressant drugs in patients.</td>
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M&S (PBPK) Submissions

- NDA PBPK
- ANDA
  - Little attempt to use in submission
  - Use in development?
  - Two dispute resolution requests
    - Nasal
    - GI locally acting
FY 2014 GDUFA Research Awards

• FDA is engaging with leading pharmaceutical and clinical scientists from across the world to ensure that the regulatory review of generic drugs is based on the best available science.

• Over 100 GDUFA related proposals were submitted and reviewed this summer
Key Areas for FY 2014 Awards

• DQMM: Modeling and simulation tools for the evaluation of generic drug equivalence
  – 7 grants on PBPK for non-oral delivery routes
  – 4 grants on pharmacometrics for generic drugs

• DTP: Advancing in vitro equivalence methods for complex formulations
  – 7 grants on topical/ocular/semi-solid
  – 6 grants on liposomes/sustained release implants
Innovation Model for Future ANDA

Industry

Design Formulation and Process → Conduct BE or Pilot BE Studies

Perform M&S

Propose

Critical Quality Attributes (CQA); Clinically Relevant Specifications (CRS); IVIVC/R

Evaluate

Regulatory Evaluation

Determine TE of T and R; Develop Novel BE Approaches; Approve More Complex Drug Products

Encourage QbD and Innovations
Shared Vision of Regulatory Science Success for Complex Drugs

• Both FDA and Generic Industry Have a Common Customer
  – Patients who want high quality generic products in all product categories
• Pre-ANDA Discussion Can Advance Regulatory Science
• Pre-ANDA Discussion Should Lead to Better ANDA Submissions