Oral Absorption Modeling and Simulation for Formulation Development and Bioequivalence Evaluation
An Industry Perspective

Filippos Kesisoglou, PhD
Biopharmaceutics,
Pharmaceutical Sciences and Clinical Supply
Merck Research Laboratories
Merck & Co., Inc., Kenilworth, NJ, USA
Outline

• Introduction and current status of absorption modeling in formulation development

• Case studies
  – Formulation development and achlorhydric simulations
  – Dissolution impact on PK and BE projections
  – Multimedia dissolution and BE projections
  – Projection of API form change and population simulations
  – Food effect projection for a BCS I compound
  – Absorption modeling-based IVIVC for IR tablet

• Conclusions and future directions
Quality by Design and Biopharmaceutics

- Understanding of the formulation dissolution/release in vivo (and the factors affecting that) that ensures the anticipated dose response

- Link the in vivo dissolution/release to an in vitro assay to ensure consistency of product administered to patients

Biopharmaceutics Risk Assessment Roadmap
Integrate Knowledge to Optimize Outcome – Adopt Model to Question at Hand

IN VITRO
(Formulation characterization, solubility/pchem properties, dissolution studies, metabolic assays, permeability assays, etc)

IN SILICO
(QSAR, absorption, and PK/PBPK models)

IN VIVO (preclinical)

IN VIVO (clinic)
<table>
<thead>
<tr>
<th>Application</th>
<th>Current Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guide FIH formulation/dose</td>
<td>Relatively well established</td>
</tr>
<tr>
<td></td>
<td>Supplements formulation decision trees</td>
</tr>
<tr>
<td>Guide formulation development past FIH</td>
<td>Relatively well established</td>
</tr>
<tr>
<td></td>
<td>Guide formulation decisions (eg, API PSD, MR development); helps with replacement/reduction of preclinical studies (3Rs)</td>
</tr>
<tr>
<td>Projection of bioequivalence</td>
<td>Occasional application, mostly for “well-behaved” compounds</td>
</tr>
<tr>
<td></td>
<td>Inform bioequivalence POS/“internal” biowaivers</td>
</tr>
<tr>
<td>Food effect projections and projections of DDI with pH-altering agents</td>
<td>Relatively well established</td>
</tr>
<tr>
<td></td>
<td>More for risk assessment and to inform formulation direction. Relatively small impact on clinical practice as studies typically conducted</td>
</tr>
<tr>
<td>Input to other models (eg, DDIs)</td>
<td>Potential for impact if DDI is at gut level and sensitive to formulation (not very common scenario)</td>
</tr>
<tr>
<td>Link dissolution and PK to drive IVIVCs and clinically relevant specifications</td>
<td>Starting to gain increased attention</td>
</tr>
</tbody>
</table>
Case Study 1: Guide Early Formulation Development

Fa vs pH/dose

No precipitation during stomach emptying assumed

<table>
<thead>
<tr>
<th>Stomach pH</th>
<th>Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>200</td>
</tr>
<tr>
<td>2</td>
<td>400</td>
</tr>
<tr>
<td>3</td>
<td>600</td>
</tr>
<tr>
<td>4</td>
<td>800</td>
</tr>
<tr>
<td>5</td>
<td>1000</td>
</tr>
</tbody>
</table>

Adequate bioavailability under normal fasted conditions

FIH formulation decision; free base – defer antacid mitigation post-FIH (decision may differ for other programs)

Parameter sensitivity analysis is a common tool in early formulation stage

Adequate exposures obtained in Phase I PK – Formulation development to mitigate acid-reducing interactions as a follow-up

Model-based steady-state predicted exposures

Comparison of F1 formulation in pentagastrin- and famotidine-pretreated dogs
Translate Dissolution Data to Clinical Exposures

Dissolution at “PPI-simulating” pH 3.0 media, USP II

Conclusion: Formulation 4 high POS to mitigate stomach pH sensitivity (confirmed in subsequent clinical study)
Case Study 2: Mechanistic Modeling of Dissolution Data

- BCS I compound
- Enteric-coated beads to protect from stomach acid instability
- Standard USP 2-stage acid-challenge dissolution method

\[- \frac{dX_s}{dt} = \frac{DS}{h} \left( C_s - \frac{X_d}{V} \right) \quad \Rightarrow \quad - \frac{dX_s}{dt} = \frac{3DX_0}{pfh(r_0^3 - rc^3)} \left[ \frac{X_s}{X_0} \left( r_0^3 - rc^3 \right) + rc^3 \right]^{2/3} \left( C_s - \frac{X_d}{V} \right)\]

Parameter sensitivity analysis indicated that even a T80 of ~2 hours would result in no impact on AUC and minimal impact on $C_{max}$.
Case Study 3: Multimedia Dissolution and BE

Etoricoxib

BCS II
Log D = 2.28 (pH 7.0)
pKa = 4.5
Caco-2 Permeability = $5.23 \times 10^{-5}$ cm/sec

pH 2.0 (0.01N hydrochloric acid) = 25.1 mg/mL
pH 3.07 (0.1M glycine buffer) = 2.01 mg/mL
pH 4.01 (0.1M sodium acetate buffer) = 0.3 mg/mL
pH 5.03 (0.1M sodium acetate buffer) = 0.09 mg/mL
pH 6.9 (water) = 0.05 mg/mL

Validation of Model Against Clinical Data for the Reference Formulation

A. Protocol 43
Etoricoxib 120 mg PN043

B. Protocol 48
Etoricoxib 120 mg PN048

C. Protocol 70
Etoricoxib 120 mg PN070 MR-4312

Etoricoxib 120 mg PN048 Absorption and dissolution

- Red: Result-AmtDiss-1
- Blue: Result-AmtAbs-1
- Purple: Result-AmtPV-1
- Green: Total SC-1

Time (hr)
Dissolution at pH 4.5 and 6.8 overpredicts differences relative to clinical BE study. Dissolution at pH 1.2 most clinically relevant.
Case Study 4: Impact of API Form

- Weak base/BCS II
- **Dosed as HCl salt**
  - SGF solubility (pH 1.2) = 2.4 mg/mL
  - FaSSIF solubility (pH 6.5) <1 µg/mL
  - HCl salt dissolves fast and provides high bioavailability regardless of stomach pH

**Simulation approach**

**Goal:** Assess potential risks from conversion of HCl salt to free base in the formulation (eg, due to excipient interaction)

Simulated exposures in virtual HV population

HCl salt was simulated as nonprecipitating solution and free base absorption simulated based on pH solubility curve

At 20% free base, a small effect on total exposure is predicted (GMR to HCl salt is predicted at 0.95)
At 50% free base, the predicted mean relative Fa is 85%
In a simulated Japanese population (larger percentage of patients with stomach pH >4), more differentiation of the formulations due to 20% free base (although GMR still 0.90)
Beyond Formulation BE – Case Study 5: Food Effect Projections for BCS I

- Weak base
- pKa 7.9, LogD (7.4) -0.5
- Highly soluble (~ 4 mg/mL)
- Highly permeable
- Small first-pass effect

Successful Prediction of Food Effect

A. FE sensitivity to dose

Food effect for well-behaved BCS I compounds where fasted-state model is established can be predicted via M&S in lieu of a clinical study
Case Study 6: Absorption Modeling-Based IVIVC

BCS III
Dose: 4 mg
pKa: 1.75 (base), 10.95 (acid)
Solubility: ~ 0.8 – 2 mg/mL (pH 1 – 10)
LLC-PK1 $P_{\text{app}}$: ~ 9 x 10^{-6} cm/sec
Regiodependent absorption (~30% colonic bioavailability)

Incorporation of Regional Absorption in PBPK Model Allows for Successful Predictions

Regional absorption incorporated in model

<table>
<thead>
<tr>
<th>Compartments</th>
<th>Peff</th>
<th>ASF</th>
<th>pH</th>
<th>Transit Time (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>0</td>
<td>0.0</td>
<td>1.30</td>
<td>0.25</td>
</tr>
<tr>
<td>Duodenum</td>
<td>0</td>
<td>9.10</td>
<td>6.00</td>
<td>0.26</td>
</tr>
<tr>
<td>Jejunum 1</td>
<td>0</td>
<td>5.20</td>
<td>6.20</td>
<td>0.93</td>
</tr>
<tr>
<td>Jejunum 2</td>
<td>0</td>
<td>2.60</td>
<td>6.40</td>
<td>0.74</td>
</tr>
<tr>
<td>Ileum 1</td>
<td>0</td>
<td>0.60</td>
<td>6.60</td>
<td>0.58</td>
</tr>
<tr>
<td>Ileum 2</td>
<td>0</td>
<td>0.60</td>
<td>6.90</td>
<td>0.42</td>
</tr>
<tr>
<td>Ileum 3</td>
<td>0</td>
<td>0.60</td>
<td>7.40</td>
<td>0.29</td>
</tr>
<tr>
<td>Caecum</td>
<td>0</td>
<td>0.026</td>
<td>6.40</td>
<td>4.19</td>
</tr>
<tr>
<td>Asc Colon</td>
<td>0</td>
<td>0.026</td>
<td>6.80</td>
<td>12.57</td>
</tr>
</tbody>
</table>

Absorption modeling IVIVC projected vs observed
Looking Forward

• Increased application of absorption models to understand fundamental biopharmaceutics questions (eg, food effect, stomach pH) and inform clinical study designs

• Increased utilization of absorption modeling in CMC filing sections
  – Supportive arguments for formulation development and Quality by Design, when relevant to final market image

• Increased utilization of absorption modeling and IVIVC to inform specifications (clinically relevant specifications)
Informing Clinically Relevant Specifications

Current focus is mostly in this space for IR formulations

Area of future focus for IR – currently mostly applied to MR formulations

Biorelevant dissolution data
Release method dissolution data

“Deconvolute” in vitro data
“Deconvolute” in vitro data

“Inherent” formulation behavior (dissolution method independent)

PBPK modeling
IVIVC

Clinical performance

Translate back to dissolution specifications
Opportunity Areas for Regulatory Guidance

• Modeling acceptance/qualification criteria for IVIVC/BE questions

• Regulatory framework for clinically relevant specifications and absorption modeling/IVIVC for IR products
  – Including global harmonization

• Use of absorption modeling as surrogate for clinical studies (eg, food effect biowaivers, acid-reducing agents)
Acknowledgements

• PQRI BTC
• AAPS Quality by Design and Product Performance Focus Group
• Amitava Mitra, Binfeng Xia, and other Merck colleagues