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

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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)**

Refinement of assays/selection of models

Projections
## Current Status of Absorption Modeling

<table>
<thead>
<tr>
<th>Application</th>
<th>Current Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guide FIH formulation/dose</td>
<td><strong>Relatively well established</strong>&lt;br&gt;Supplements formulation decision trees</td>
</tr>
<tr>
<td>Guide formulation development past FIH</td>
<td><strong>Relatively well established</strong>&lt;br&gt;Guide formulation decisions (e.g., API PSD, MR development); helps with replacement/reduction of preclinical studies (3Rs)</td>
</tr>
<tr>
<td>Projection of bioequivalence</td>
<td><strong>Occasional application, mostly for “well-behaved” compounds</strong>&lt;br&gt;Inform bioequivalence POS/“internal” biowaivers</td>
</tr>
<tr>
<td>Food effect projections and projections of DDI with pH-altering agents</td>
<td><strong>Relatively well established</strong>&lt;br&gt;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 (e.g., 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><strong>Starting to gain increased attention</strong></td>
</tr>
</tbody>
</table>
Case Study 1: Guide Early Formulation Development

Fa vs pH/dose

No precipitation during stomach emptying assumed

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

Modeling to Develop a pH-Resistant Formulation

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

<table>
<thead>
<tr>
<th>Formulation</th>
<th>M&amp;S Predicted AUC Impact</th>
<th>Observed AUC Impact Preclinically</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>91% reduction</td>
<td>95% reduction</td>
</tr>
<tr>
<td>F4</td>
<td>6% reduction</td>
<td>5% increase</td>
</tr>
<tr>
<td>F5</td>
<td>90% reduction</td>
<td>85% reduction</td>
</tr>
</tbody>
</table>

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

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

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

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 PN070
MR-4629

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)
0 1 2

Mass (mg)
0 10 20 30 40 50 60 70 80 90 100 110 120

Concentration (µg/mL)
0 1 2 3

Simulation Time (hr)
0 20 40 60 80 100 120
Predictions vs Experimental Data – Identification of Clinically Relevant Dissolution

Dissolution at pH 4.5 and 6.8 overpredicts differences relative to clinical BE study. Dissolution at pH 1.2 most clinically relevant

### M&S projections

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC&lt;sub&gt;0-120hr&lt;/sub&gt; (%CV)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (%CV)</th>
<th>Relative AUC&lt;sub&gt;0-120hr&lt;/sub&gt;</th>
<th>Relative C&lt;sub&gt;max&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dissolution in pH 4.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>120 mg (current site)</td>
<td>34.4 (16.3%)</td>
<td>1.65 (15.3%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>120 mg (new site)</td>
<td>35.8 (15.3%)</td>
<td>1.82 (14.4%)</td>
<td>1.04</td>
<td>1.10</td>
</tr>
<tr>
<td>Dissolution in pH 6.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>120 mg (current site)</td>
<td>30.8 (17.2%)</td>
<td>1.50 (18.6%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>120 mg (new site)</td>
<td>34.1 (15.1%)</td>
<td>1.71 (19.1%)</td>
<td>1.11</td>
<td>1.14</td>
</tr>
</tbody>
</table>

### Clinical BE data

<table>
<thead>
<tr>
<th>PK Parameters</th>
<th>Treatment</th>
<th>Geometric Mean Ratio (A vs B)</th>
<th>90% Confidence Interval (A vs B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;0-∞&lt;/sub&gt; (μg*hr/mL)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>A</td>
<td>32.3 ± 13.1</td>
<td>1.01</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>32.1 ± 14.6</td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (μg/mL)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>A</td>
<td>1.94 ± 0.47</td>
<td>0.97</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>1.98 ± 0.41</td>
<td></td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (hr)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>A</td>
<td>1.25 (0.5 – 2.0)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>1.00 (0.5 – 4.0)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>1</sup> Calculated as the area under the concentration-time curve from time 0 to infinity.

<sup>2</sup> Time to reach the peak concentration.

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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)
• 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

B. Observed vs predicted (fed state)

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 $P_{app}$: ~ $9 \times 10^{-6}$ 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>Compartment</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</td>
<td>1.30</td>
<td>0.25</td>
</tr>
<tr>
<td>Duodenum</td>
<td>0</td>
<td>9.100</td>
<td>6.00</td>
<td>0.26</td>
</tr>
<tr>
<td>Jejunum 1</td>
<td>0</td>
<td>5.200</td>
<td>6.20</td>
<td>0.93</td>
</tr>
<tr>
<td>Jejunum 2</td>
<td>0</td>
<td>2.600</td>
<td>6.40</td>
<td>0.74</td>
</tr>
<tr>
<td>Ileum 1</td>
<td>0</td>
<td>0.600</td>
<td>6.60</td>
<td>0.58</td>
</tr>
<tr>
<td>Ileum 2</td>
<td>0</td>
<td>0.600</td>
<td>6.90</td>
<td>0.42</td>
</tr>
<tr>
<td>Ileum 3</td>
<td>0</td>
<td>0.600</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>
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
Opportunity Areas for Regulatory Guidance

- Modeling acceptance/qualification criteria for IVIVC/B.E. 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 (e.g., food effect biowaivers, acid-reducing agents)
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