Impact of Excipients

BCS Class 3 Drug Product Dissolution and Permeability

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Chief Operating Officer
BCS Class 3 drugs

The value to the generic industry in expanding BCS class 3 waivers to non-Q1/Q2 formulations

- BCS Class 3 drugs constitute 25% of drugs marketed in the United States
- Almost 40% of orally administered drugs on the WHO Model List of Essential Medicines are BCS Class 3 drugs.

Impact of Biopharmaceutics Classification System-Based Biowaivers
Jack A. Cook, Barbara M. Davit, and James E. Polli
Absorptive Flux (J)  

\[ J = C_{\text{int}} \cdot P_{\text{wall}} \]

Where:
- \( P_{\text{wall}} \) = effective or BCS permeability
- \( C_{\text{int}} \) = concentration in lumen

Which implies...

“...If two drug products, containing the same drug, have the same concentration time profile at the intestinal membrane surface then they will have the same rate and extent of absorption”

Absorptive Flux (J)  

\[ J = C_{int} \times P_{wall} \]

- \( P_{wall} \): effective or BCS permeability
- \( C_{int} \): concentration in lumen

Which further implies...

When *in vitro* testing can demonstrate the same GI concentration time profile under all luminal conditions...it can serve as a reliable surrogate for judging **therapeutic equivalence** of pharmaceutically equivalent drug products.
BCS 3 Biowaiver Eligibility

- The drug substance is **highly soluble**
  - The highest strength is soluble in 250 mL or less of aqueous media within the pH range of 1 - 6.8 at 37 ± 1°C.

- The drug product is very **rapidly dissolving**
  - A mean of 85 percent or more of the labeled amount of the drug substance dissolves within 15 minutes using USP Apparatus 1 at 100 rpm or Apparatus 2 at 50 rpm in 500 mL or less in -
    1. 0.1 N HCl or Simulated Gastric Fluid USP without enzymes;
    2. a pH 4.5 buffer; and
    3. a pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes.

- The test product formulation is **qualitatively the same and quantitatively very similar** to the RLD
(ii) BCS class 3 drug products: Unlike for BCS class 1 products, for a biowaiver to be scientifically justified, BCS class 3 test drug product must contain the same excipients as the reference product. This is due to the concern that excipients can have a greater impact on absorption of low permeability drugs. The composition of the test product must be qualitatively the same (except for a different color, flavor, or preservative that could not affect the BA) and should be quantitatively very similar to the reference product. Quantitatively very similar includes the following allowable differences:

- Changes in the technical grade of an excipient
- Changes in excipients, expressed as percent (w/w) of the total formulation less than or equal to the following percent ranges:
  - Filler (± 10%)
  - Disintegrant, Starch (± 6%)
  - Disintegrant, Other (± 2%)
  - Binder (± 1%)
  - Lubricant, Calcium or Magnesium Stearate (± 0.5%)
  - Lubricant, Other (± 2%)
  - Glidant, Talc (± 2%)
  - Glidant, Other (± 0.2%)
  - Film Coat (± 2%)

The total additive effect of all excipient changes should not be more than 10 percent.

*FDA Final Guidance December 2017*

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**Diagram**

- Are there excipients in the formulation with known or suspected effects on drug absorption?
  - Yes
  - Are excipients which may affect absorption with ±10% of the amount of the excipient in the reference product?
    - Yes
    - Are all excipients qualitatively the same and quantitatively similar?
      - Yes
      - Biowaiver possible, provided that dissolution similarity is demonstrated between the test and reference formulations
      - No
      - Biowaiver cannot be granted
    - No
  - No
Challenges

- **Legal - Potential Patents**

- **Will we receive feedback***?**
  - “Consistent with the Agency’s past and current practices, FDA does not intend to review proposed formulations that are neither required by regulation nor recommended in guidance to be Q1/Q2 to the RLD”

- **Logistics - Cycle time for Q1/Q2 response**

- **Deformation techniques -** Multiple cycles may be required

- **Can we create excipient exception categories?**
  - Insoluble excipients
  - Excipients that are food constituents

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*Controlled Correspondence Related to Generic Drug Development Guidance for Industry, Draft Guidance, November 2017*
How Excipients May Impact Absorption?

Release rate/amount of drug in solution
- Altered disintegration time
- Altered dissolution rate
- Altered local pH
- Complexation (excipient-drug complexes)

Transit and luminal volumes
- Faster gastric emptying
- Increased luminal volume (osmotic effect)
- Altered small intestinal transit time

Altered effective permeability
- Damage to intestinal surface/ tight junction modulation
- Inhibition of efflux
- Inhibition or enhancement of active uptake

Altered metabolism
- Inhibition of gut wall metabolism

Ref. Dr. Talia Flanagan
Conventional Techniques

Dissolution

- Using USP Apparatus 1 or Apparatus 2
- In a volume of 500 mL to 900 mL
- Representative media:
  - 0.1 N HCl or Simulated Gastric Fluid USP without enzymes;
  - pH 4.5 buffer
  - pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes.
Limitations with Conventional Techniques

- Dissolution testing - **insensitive** to excipient-drug complexation and impact of altered local pH

- Over-sensitivity of the cell monolayers to excipient effects – **model configuration?**

- Sensitivity to excipients such as SLS at concentrations known to be safe and widely used – **deviation from “real world” correlation**
  Rege, et al. (J Pharm Sci. 2001;90(11):1776-1786

- Same excipients tested in in situ rat intestinal perfusion model, with no obvious excipient-related effects outside the inherent variability of that model – **in vitro model over-discrimination or variability of in situ perfusion**

- BE studies in humans showed lack of excipient effect with two model BCS Class 3 compounds and 12 commonly used excipients – **Lack of in vivo correlation but in vivo can be difficult to deconvolute and/or scale**
Basis for Innovation: Biopharmaceutics

“The study of the chemical and physical properties of drugs and the biological effects they produce”

Using this principle:
- Develop tools that are more bio-relevant
- Link API and formulation to their effect

Applications
- Infer pharmaceutical and bioequivalence
- Performance testing of dosage forms
  - Predict and control BA & BE
  - Accelerate product development

Adapted from Robert Lionberger, “Biopharmaceutics of Non-Orally Administered Drugs”
Innovation: IDAS

**In Vitro Dissolution Absorption System** combines traditional dissolution testing with a means to **determine and quantify** interactions with a bio-relevant membrane.

Biopharmaceutics Dissolution with Better *In Vivo* Correlation
Why IDAS?

Batch Release Data for Product A- Q value was similar for different manufacturers

Dissolution for Compound B [BCS III]

- The test product failed bioequivalence. for C_{max} and AUC
- IDAS – dual gated process

IDAS Achieves Discrimination

Data using IDAS shows marked differences in AUC and % permeated for different manufacturers

<table>
<thead>
<tr>
<th>Product</th>
<th>AUC (0-2 hours)</th>
<th>% Permeation (0-2 hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FF15-025</td>
<td>7304.8 ± 407.1</td>
<td>2.33 ± 0.52</td>
</tr>
<tr>
<td>FF15-027</td>
<td>4001.3 ± 590.1*</td>
<td>0.25 ± 0.13*</td>
</tr>
<tr>
<td>FF15-028</td>
<td>2166.1 ± 756.8*</td>
<td>0.51 ± 0.16*</td>
</tr>
<tr>
<td>FF15-029</td>
<td>5043.8 ± 1157.7*</td>
<td>0.55 ± 0.35*</td>
</tr>
<tr>
<td>FF15-030</td>
<td>6477.0 ± 1031.9</td>
<td>0.51 ± 0.16*</td>
</tr>
</tbody>
</table>

*: p < 0.05
Why IDAS?

- Dissolution, solubility and permeability are routinely measured independently and under conditions that may have less physiologic relevance.
- Poor discrimination, which impacts the link between *in vitro* drug product release characteristics and *in vivo* performance.
- Concomitant evaluation of bio-relevant processes.
IDAS Achieves Improved Dose Discrimination:
Dissolution vs. permeability in fasted simulated intestinal fluid for a tablet with different strengths

**Amount Dissolved vs. Time**

**Amount Permeated vs. Time**

**AUC Normalized to Dose**

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IDAS Resource Library

- **Posters**
  - **In Vivo Correlation:** Assessment of Drug Gastrointestinal Supersaturation Using a Two-Stage In Vitro Dissolution Absorption System 2 (CRS 2018)
  - **Supersaturation:** Assessment of drug gastrointestinal supersaturation using In Vitro Dissolution - Absorption System 2 (AAPS 2018)
  - **Food Effects:** Study of the Effect of Simulated Fast vs Fed State on the Dissolution and Permeation of BCS Class 1-4 Drugs Using the In-vitro Dissolution Absorption System 2 (AAPS 2018)
  - **In Vivo Correlation:** Evaluation of the In Vitro Dissolution and Absorption (IDAS2) as a potential surrogate for in vivo performance of drug formulations (AAPS 2018)
  - **Biowaivers:** Applications of the In vitro Dissolution and Absorption System 2 as a Bioequivalence Biowaiver Tool (AAPS 2018)

- **Publications**
  - **Supersaturation:** In Vitro and In Vivo Assessment of the Potential of Supersaturation to Enhance the Absorption of Poorly Soluble Basic Drugs (in progress, 2019)
  - **PSD:** Simultaneous Analysis of Dissolution and Permeation Profiles of Nanosized and Microsized Formulations of Indomethacin Using the In Vitro Dissolution Absorption System 2 (Li, et al., J Pharm Sci. 2019, in press)
Proposed Experimentation

- Use IDAS to evaluate excipients at 3 levels:


<table>
<thead>
<tr>
<th>Excipient</th>
<th>Concentration (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HBSSg, pH 6.5 (control)</strong></td>
<td>Low</td>
</tr>
<tr>
<td>Lactose monohydrate</td>
<td>0.5</td>
</tr>
<tr>
<td>Povidone K30</td>
<td>0.05</td>
</tr>
<tr>
<td>Hypromellose 2910 (4000 mPa·s)</td>
<td>0.5</td>
</tr>
<tr>
<td>SLS</td>
<td>0.025</td>
</tr>
<tr>
<td>PEG-400</td>
<td>0.075</td>
</tr>
</tbody>
</table>

# Consistent with the Inactive Ingredients Database;
Expanded Utility of BCS Class 3 Biowaivers

(ii) BCS class 3 drug products: Unlike for BCS class 1 products, for a biowaiver to be scientifically justified, BCS class 3 test drug product must contain the same excipients as the reference product. This is due to the concern that excipients can have a greater impact on absorption of low permeability drugs. The composition of the test product must be qualitatively the same (except for a different color, flavor, or preservative that could not affect the BA) and should be quantitatively very similar to the reference product. Quantitatively very similar includes the following allowable differences:

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*FDA Final Guidance December 2017*

To work towards – Exception categories, alternative pathways for evaluation, expanded tolerance ranges