Regulatory Product Research: *Oral Systemic Drug Products*

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BE Science Needs

- Cmax and AUC Predictors
- BE is Different Products **Same** Drug (API)
- ‘DME’ of ‘ADME’-PK is the Same
- Mechanistic Analysis at Absorption Site (The ‘A’ of ADME)
- Extending BCS, oral (IR & MR) and other routes
Extending The Science of ‘Biowaivers’

Immediate Release (IR)
• BCS Class I: Slower Dissolution?
• BCS Class III: Quantative same, Qualitative Similar
• BCSa Class II & IV: SubClasses A,B, C

Modified Release (MR)
• Dynamic and changing luminal environment
• Transport (& transporters) and metabolism along the GIT
Key Science for Oral is *in vivo* Dissolution

- *In Vivo* Predictive *in Vitro* methods (iPD)
- Media and Method
- Not a QC Method
- Needed for Product Development & Regulatory Decisions
  - Product Changes (SUPAC)
  - Dose scaling (biowaivers)
  - QbD
  - PAT
Setting & Evolving Regulatory Standards in the 21st Century

• Innovative New Delivery Technologies

• Modernizing Manufacturing and Production Methods
  – QbD & PAT Initiatives
  – What do we target short of expensive human studies

• Drug Product Focused Research
  – Both Brand (innovator) and Generic

• Pharmaceutical Product Regulatory Research Institute (P2R2)
BE Gold Standard: Systemically Active Drugs

- Cmax and AUC
- BE is Relative BA
- Same Drug (API)
- DME of ADME is the Same
- BE is science of ‘A’
The Science of Relative BA (BE) is the Absorption at the Site of Application

\[ M_{abs} (t) = \int_0^t \int \int (P_{eff} \cdot C) dA dt \]
Evaluation of BE as Relative BA adds Complexity (Cmax & AUC)

- Is First-Pass Metabolism linear?
- Vd kinetics vs. elimination kinetics?
- Is Clearance linear?
- Affect the ‘DME’ not the ‘A’.
BE Science is at the Absorption Site

- Product differences (Same Drug)
- Product altering Site (Permeability, Peff)
- Product changes with Time at Site, (C at absorbing surface)
  - Evaporation of solvent (vehicle)
  - API solid state changes

\[ M_{abs}(t) = \int_0^t \int_A (P_{eff} \cdot C) dA dt \]
Oral Products

Movement of Drug Through GI Tract:

Flux = j = P_{eff} \cdot C
Measure Gastrointestinal Variables During Drug Absorption

- Gastric Emptying & duodenal appearance
- Intestinal transit & segmental absorption
- Gastrointestinal motility: fasted and fed
- GI Variables: pH, buffer capacity, viscosity luminal solubilization
- Physical-chemical product changes: Solid state, pKa(*in vivo*)
Oral IR and MR

• Oral IR Absorption from Upper Small Intestine
  – Solubilization, buffering, Volume under BE conditions

• Oral MR: Entire GI Tract
  – Changing luminal environment
  – Transit and release in GIT
  – Absorption ‘windows’
  – Fasted vs. Fed dosing and transit
  – Dosage form factors: Size, Disintegrating vs. Non-Disintegrating
    • Shear rate and hydrodynamic variables
Mean GI Fluid Volume*

Stomach

Small Intestine

* Marciani L, et.al., Mole. Pharmaceutics,
Dissolution of Clinical Dosage form
(800 mg Dr. Reddy’s Reference Listed Drug(RLD))

800mg intact tablet dissolution in pH 6.5, 10 mM HCO₃ buffer (15% CO₂ & total buffer concentration of 14 mM). USP 2 apparatus, 50 rpm & 37 °C

<table>
<thead>
<tr>
<th>Bulk Volume, ml</th>
<th>Extent of dissolution</th>
<th>Time to dissolve 50% dose, min</th>
<th>Time to 100%, min</th>
</tr>
</thead>
<tbody>
<tr>
<td>500</td>
<td>105%</td>
<td>13</td>
<td>80</td>
</tr>
<tr>
<td>900</td>
<td>102%</td>
<td>10</td>
<td>60</td>
</tr>
</tbody>
</table>

USP Test: pH = 7.2 50mM Phosphate
50 RPM paddle (Apparatus 2)
Not Less Than 80% dissolved in 60 min

100% dissolved ≈ 10 min
BCS Subclass: Absorption Profile

API

- A= Acid
- B=Base
- C=Neutral
## BCS SubClasses * Dissolution (iPD)

<table>
<thead>
<tr>
<th>BCS Class</th>
<th>0.1 N HCl</th>
<th>pH 6.5</th>
<th>Permeability</th>
<th>Media*</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>PIB**</td>
</tr>
<tr>
<td>IIa</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>15 and 30 min in PGB**, then PIB**</td>
</tr>
<tr>
<td>IIb***</td>
<td>High</td>
<td>Low</td>
<td>High</td>
<td>15 or 30 min in PGB**, then PIB**</td>
</tr>
<tr>
<td>IIc</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>Dissolution 15 and 30 min in PGB**, Then PIB** + surfactant to match in vivo solubilization</td>
</tr>
<tr>
<td>III</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>Same as I</td>
</tr>
<tr>
<td>IVa</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>Same as IIa</td>
</tr>
<tr>
<td>IVb**</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>Same as IIb**</td>
</tr>
<tr>
<td>IVc</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Same as IIc</td>
</tr>
</tbody>
</table>
Transition to *in vivo* relevant Dissolution