Biowaivers and Harmonization Guidelines for Class I and 3 Drugs: Biowaiver Case Studies

- Barbara M. Davit, Merck & Co., Inc.
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I am an employee and shareholder of Merck & Co., Inc.

The comments presented are my own and not intended to represent those of Merck & Co., Inc.
Agenda

- Introduction – initiating BCS evaluation
- Navigating regulatory guidelines
- Case studies
- Summary and conclusions
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Drug teams determine BCS classification of all preclinical candidate (PCC) drugs
Presently, drug teams do not evaluate BDDCS
Early in development, in vitro solubility and in vitro permeability studies are conducted to obtain preliminary BCS classification.

Class I
- High solubility
- High intestinal permeability

Class II
- Low solubility
- High intestinal permeability

Class III
- High solubility
- Low intestinal permeability

Class IV
- Low solubility
- Low intestinal permeability
A two-staged approach

A preliminary classification is undertaken based on predicted clinical efficacious dose

In vitro solubility studies are conducted

Permeability is assessed in vitro
  – LLC-PK1 cells

BCS classification guides further development
Impact of BCS classification in further drug development

Class I
- Consider conducting pivotal permeability studies
- Conduct multimedia in vitro dissolution studies
- Consider BCS biowaiver application(s)

Class II
- Conduct in vitro dissolution studies
- If weak base with pH-sensitive solubility, may consider developing enabled formulation

Class III
- Consider conducting pivotal permeability studies
- Conduct multimedia in vitro dissolution studies
- Consider BCS biowaiver application(s)

Class IV
- Conduct in vitro dissolution studies
- If weak base with pH-sensitive solubility, may consider developing enabled formulation
Pivotal in vitro permeability studies

- Conducted later in development, if
  - Clinical dose established
  - Likely to
    - Initiate Phase III
    - File for marketing approval in US and/or EU

- Preclinical options
  - Caco-2 cells; rat intestinal perfusion

- Clinical options
  - Oral bioavailability; mass balance
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Differences between US, EMA BCS biowaiver criteria until 2015

<table>
<thead>
<tr>
<th>BCS application</th>
<th>US-FDA</th>
<th>EMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCS Class I biowaivers permitted</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>BCS Class III biowaivers permitted</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>BCS biowaivers permitted for pharmaceutical alternatives (e.g., capsule vs tablet)</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Criteria for high in vivo permeability</td>
<td>≥ 90% oral bioavailability</td>
<td>≥ 85% oral bioavailability</td>
</tr>
<tr>
<td>pH range for in vitro solubility studies</td>
<td>pH 1 – 7.5</td>
<td>pH 1.2 – 6.8</td>
</tr>
<tr>
<td>Paddle speed for dissolution studies</td>
<td>50 rpm; no exceptions</td>
<td>50 rpm; will consider 75 rpm with justification</td>
</tr>
</tbody>
</table>
Can request a BCS biowaiver for pharmaceutical alternatives

BCS Class III biowaivers may be granted if criteria are met

In vivo evidence of high permeability demonstrated by oral BA of ≥ 85%

pH range for in vitro solubility studies is now 1.2 to 6.8

Paddle speed of 75 rpm may be acceptable with justification

Changes to FDA criteria for BCS biowaivers implemented in 2015
Some major differences between US, EMA BCS biowaiver criteria

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</thead>
<tbody>
<tr>
<td>Strength for solubility studies</td>
<td>Highest strength</td>
<td>Highest single therapeutic dose</td>
</tr>
<tr>
<td>Method for determining high intestinal permeability</td>
<td>In vitro and preclinical methods acceptable</td>
<td>Only a clinical absolute BA or mass balance study</td>
</tr>
<tr>
<td>In vitro dissolution testing for BCS classification</td>
<td>500 mL media</td>
<td>900 mL media</td>
</tr>
</tbody>
</table>
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Drug A

- Drug approved worldwide
- Absolute BA = 87% (as per labeling)
- Designated as Class III under original FDA BCS guidance posted in 2000
- Will seek Class I designation from FDA, as per 2015 draft guidance criteria
  - Investigating development of Drug A in an immediate-release (IR) fixed-dose combination doublet with a second Class I drug
Drug B

- Drug is highly soluble
- Initially developed as an IR capsule; changed formulation to an IR tablet; both rapidly dissolving
- High intestinal permeability shown in vitro
- FDA rejected BCS biowaiver request in support of change from capsule to tablet
May resubmit BCS biowaiver request to FDA, considering revisions in 2015 draft guidance

Under draft guidance, sponsors may request BCS biowaiver for capsule v tablet BA comparison
Drug C

- Drug is highly soluble, and tablets are rapidly dissolving

- Stability study results necessitated change to a different API morphic form during Phase III

- BCS Class I biowaiver designation will be requested from both US-FDA and EMA

- Conducted an in vitro permeability study with Caco-2 cells, and an in vivo clinical mass balance study showing > 85% absorption
Drug C (con’t)

- In vitro permeability study results will be used to support BCS Class I biowaiver request for US-FDA filing
- In vivo mass balance study results will be used to support BCS Class I biowaiver request for EMA filing
- US-FDA and EMA requirements for showing high permeability not harmonized
- Fortunately, both in vitro and clinical studies were conducted
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Summary and conclusions

- Preliminary BCS classification can be conducted early to guide drug development
- Pivotal studies to confirm BCS Class I or III are conducted later in development
- Attempts to harmonize US-FDA and EMA BCS guidance benefit worldwide filings
- Challenges still exist due to several differences between US and EMA criteria for Class I/III designation
Acknowledgements

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- Paul Fackler
- Dave Storey
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