Challenges in BCS-based biowaivers

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NIPTI: The National Institute for Pharmaceutical Technology & Education
Improving quality and lowering costs of pharmaceuticals
Biopharmaceutics Classification System (BCS)

Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System Guidance for Industry
BCS Class 3: Research path forward

• Quantify excipient interactions with transporters
• Integrate into PBPK models of oral absorption
• Combine with FDA data warehouse of successful BE studies on products with different excipients
• Test via prospective in vivo studies

• Two or more drugs (FDCs)
• Utility of literature data (e.g. how to assess whether data is “good”)

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BCS Guidance

• BCS class 1
  – In general, ... excipients ... in FDA-approved IR solid oral dosage forms will not affect ...”

• BCS class 3
  – “Unlike for BCS class 1 products, ... BCS class 3 test drug product must contain the same excipients as the reference product. ... The composition of the test product must be qualitatively the same ... and should be quantitatively very similar to the reference product. Quantitatively very similar includes ...”
# Excipients

<table>
<thead>
<tr>
<th><strong>Lamictal</strong></th>
<th><strong>Teva lamotrigine</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>lamotrigine</td>
<td>lamotrigine</td>
</tr>
<tr>
<td>lactose</td>
<td>lactose monohydrate</td>
</tr>
<tr>
<td>magnesium stearate</td>
<td>magnesium stearate</td>
</tr>
<tr>
<td>microcrystalline cellulose</td>
<td>microcrystalline cellulose</td>
</tr>
<tr>
<td>povidone</td>
<td>povidone</td>
</tr>
<tr>
<td>sodium starch glycolate</td>
<td>sodium starch glycolate</td>
</tr>
<tr>
<td>FD&amp;C yellow #6 (100mg), ferric oxide yellow (150mg), and FD&amp;C blue #2 aluminum lake (200mg)</td>
<td>FD&amp;C yellow #6 (100mg), ferric oxide yellow (150mg), and FD&amp;C blue #2 aluminum lake (200mg)</td>
</tr>
<tr>
<td>-</td>
<td>colloidal silicon dioxide; pregelatinized starch</td>
</tr>
</tbody>
</table>
Biowaivers and BCS

• Biowaiver – waiver of need to demonstrate in vivo BE based on in vitro BE

• Apply biowaivers to less risky drugs, but which are those?!?

• Biopharmaceutics Classification System (BCS)
  – Based on solubility and intestinal permeability
  – Class 1 = high solubility and high permeability
  – Class 3 = high solubility and low permeability
    • Class 3 biowaivers: Excipients should not modulate drug absorption
The percent approval of different classes of BCS drugs listed on WHO EML from 2000 to 2011

Excipient Effects

• Class 3 Biowaivers: Excipients should not modulate drug absorption
Study 1

• Cimetidine and acyclovir – BCS class 3 drugs
• 14 common excipients
• Three capsule formulations for each drug
• In vivo evaluation (2 capsules as single dose)
  – Fasted, single-dose, four-way crossover bioequivalence study (n=24) in healthy human volunteers
• Oral liquid used as reference product
• Average BE analysis to determine impact of excipients
Study 1

Two 4 way crossover BE study in healthy subjects

Study 1A

Cimetidine
BCS Class III

3 Test capsules: 3 excipients in each capsule

Reference: commercial oral Solution

Study 1B

Acyclovir
BCS Class III

3 Test capsules: 3 excipients in each capsule

Reference: commercial oral suspension
Study 2

4 way cross over
BE study:
Cimetidine

- CimTest-A: < 45mg HPMC
- CimTest-B: < 40mg Mag Stearate
- Commercial Cimetidine oral solution
- Reference Solution: Oral solution without sorbitol

V-blender

Turbula mixer
<table>
<thead>
<tr>
<th>Excipient</th>
<th>Recommended maximum allowable amount for a class 3 biowaiver (mg)</th>
<th>Maximum excipient amount studied here (mg)</th>
<th>Typical excipient amount (when present) in an IR tablet or capsule with a total weight of 300mg</th>
<th>Maximum amount (mg) in Inactive Ingredient Database</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microcrystalline Cellulose</td>
<td>Qualitatively same and quantitatively very similar</td>
<td>600</td>
<td>100mg (20%-90%)</td>
<td>1385.3</td>
</tr>
<tr>
<td>Hydroxypropyl Methyl Cellulose</td>
<td>Qualitatively same and quantitatively very similar</td>
<td>40</td>
<td>10mg (2%-5%)</td>
<td>444.4</td>
</tr>
<tr>
<td>Sodium Lauryl Sulfate</td>
<td>50</td>
<td>50</td>
<td>4.5mg (0.5%-2.5%)</td>
<td>51.69</td>
</tr>
<tr>
<td>Corn Starch</td>
<td>900</td>
<td>900</td>
<td>150mg (25%-75%)</td>
<td>1135</td>
</tr>
<tr>
<td>Sodium Starch Glycolate</td>
<td>200</td>
<td>200</td>
<td>12mg (4%)</td>
<td>876</td>
</tr>
<tr>
<td>Colloidal Silicon Dioxide</td>
<td>40</td>
<td>40</td>
<td>1.5mg (0.1%-1%)</td>
<td>100</td>
</tr>
<tr>
<td>Dibasic Calcium Phosphate</td>
<td>600</td>
<td>600</td>
<td>150mg (25%-75%)</td>
<td>635.5</td>
</tr>
<tr>
<td>Crospovidone</td>
<td>100</td>
<td>100</td>
<td>10mg (2%-5%)</td>
<td>340</td>
</tr>
<tr>
<td>Lactose</td>
<td>900</td>
<td>900</td>
<td>240mg (80%)</td>
<td>1020</td>
</tr>
<tr>
<td>Povidone</td>
<td>70</td>
<td>70</td>
<td>7.5mg (0.5%-5%)</td>
<td>240</td>
</tr>
<tr>
<td>Stearic Acid</td>
<td>80</td>
<td>80</td>
<td>6mg (1%-3%)</td>
<td>72</td>
</tr>
<tr>
<td>Pregelatinized Starch</td>
<td>200</td>
<td>200</td>
<td>150mg (5%-75%)</td>
<td>435.8</td>
</tr>
<tr>
<td>Croscarmellose Sodium</td>
<td>120</td>
<td>120</td>
<td>37.5mg (0.5%-25%)</td>
<td>180</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>40</td>
<td>40</td>
<td>7.5mg (0.25% to 5%)</td>
<td>400.74</td>
</tr>
</tbody>
</table>
Conclusions and Limitations

• 12 out of 14 were found to be non-problematic: should be no more than quantities studied
• HPMC and microcrystalline cellulose: should be qualitatively the same and quantitatively similar to reference product
• It is possible that other BCS class 3 drugs have properties that differ from cimetidine and acyclovir to render those drugs susceptible to other excipient influences that cause modified drug absorption.
• [T]he greatest concern would appear to be a drug that depends on an uptake transporter that an excipient inhibits by virtue of the excipient having molecular structure similarity to the transporter's pharmacophore or recognition site.
Commentaries

  – results obtained by Vaithianathan et al. should not be extrapolated to other drugs

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