Bioequivalence and Pharmaceutical Equivalence Criteria for Drugs Acting Locally Within GI Tract: Mesalamine, Sevelamer, Acarbose, Vancomycin

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The following represents the personal opinions of the presenter and not necessarily those of the US-FDA or Merck Research Laboratories.
Agenda

• How regulatory agencies (focus on US-FDA) define bioequivalence (BE) and pharmaceutical equivalence (PE)

• Factors considered by FDA in recommending BE approaches for drugs that act locally within the gastrointestinal (GI) tract

• Description of mesalamine, sevelamer, acarbose, vancomycin BE approaches

• Summary and conclusions
How is bioequivalence (BE) and pharmaceutical equivalence (PE) defined (by US-FDA)?
What factors are considered in determining if two products are therapeutically equivalent?

Two therapeutically equivalent products can be switched in patients and provide the same safety and efficacy.

The reference should already be approved with established safety and efficacy.

The test should have acceptable CMC.

Test and reference product should:

- Be bioequivalent
- Be pharmaceutical equivalents
- Have the same labeling
How is bioequivalence (BE) defined?

• Two products are bioequivalent when there is no significant difference in the rate and extent of availability at the site of action when products are given at the same molar dose under the same experimental conditions.

• For systemically-active drugs, BE is determined by comparing rate and extent of drug absorption in a pharmacokinetic (PK) study:
  – Peak plasma concentration ($C_{\text{max}}$) represents rate of absorption
  – Area under drug plasma concentration versus time profile (AUC) represents extent of absorption

• For locally acting drugs, FDA will consider approaches other than PK to determine rate and extent of availability at site of action.
How does the US-FDA define pharmaceutical equivalence (PE)?

Drug products in identical dosage forms

Meet identical compendial or other applicable standards

Contain identical amounts of identical active ingredient

Do not necessarily contain the same inactive ingredients

Contain the same salt or ester of the same therapeutic moiety

If, MR deliver the identical amount of active ingredient over same dosing interval
Acceptable regulatory approaches for BE

In decreasing order of:
- Reproducibility
- Accuracy
- Sensitivity
What factors does FDA consider in recommending BE approaches for locally-acting GI drugs?
Considerations in selecting BE approach for a locally-acting drug

Choice of BE study design depends on ability to compare drug delivered by test and reference at site of action.
### Some definitions of terminology applied to BE evaluation

<table>
<thead>
<tr>
<th>Terminology</th>
<th>Abbr.</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Qualitatively the same</td>
<td>Q1</td>
<td>Test and reference products have the same active and inactive ingredients</td>
</tr>
<tr>
<td>Quantitatively the same</td>
<td>Q2</td>
<td>Test and reference products contain the same amounts of active and inactive ingredients</td>
</tr>
<tr>
<td>Physicochemical attributes of a topical dosage form</td>
<td>Q3</td>
<td>Test and reference products have the same physicochemical composition</td>
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</table>
Sevelamer tablets
FDA recommends an *in vitro* approach for sevelamer tablets

- Sevelamer is insoluble in aqueous media and not absorbed, therefore, it cannot be measured in plasma
- Sevelamer binds phosphate ions *in vitro* and *in vivo* via the same mechanism
- If there is no significant difference in the manner in which test and reference bind phosphate ions *in vitro*, then it can be concluded that test and reference availability do not differ significantly at the site of action *in vivo*
- FDA recommends conducting *in vitro* binding studies with the following endpoints
  - *In vitro* equilibrium binding study (the pivotal BE study)
  - *In vitro* kinetic binding study (supportive evidence of BE)
Rationale for using an *in vitro* approach for sevelamer tablet BE studies

<table>
<thead>
<tr>
<th>Drug substance</th>
<th>Indication</th>
<th>Mechanism of action</th>
</tr>
</thead>
</table>
| • A polymeric amine that binds phosphate | • A phosphate binder  
• Indicated for control of serum phosphorus in dialysis patients with chronic kidney disease | • Binds to phosphate ions in the GI tract  
• Lowers phosphate absorption  
• This results in lowering of serum phosphate levels |
Rationale for using an *in vitro* approach for sevelamer tablet BE studies

**Site of action**
- Sevelamer binds phosphate in the GI tract

**Reference formulation**
- Film-coated tablets containing sevelamer and several excipients

**Sensitivity, feasibility**
- Sevelamer binds phosphate *in vitro*
- *In vitro* binding is via the same mechanism as *in vivo* binding
Vancomycin capsules
FDA recommends an *in vitro* approach for vancomycin capsules

- The test and reference product should contain the same inactive ingredients in the same amounts (Q1, Q2 sameness)
- The endpoints compared are dissolution rates in media of varying pH (1.2, 4.5, 6.8)
- The media of varying pH represent conditions in the gastrointestinal (GI) tract
- Dissolution profiles are compared using the f2 (similarity factor) metric
- Two dissolution profiles are considered similar if $f2 \geq 50$
Rationale for using an *in vitro* approach for BE studies of vancomycin capsules

**Drug substance**
- A tricyclic glycopeptide antibiotic derived from *Amycolatopsis orientalis*
- Vancomycin is highly soluble at conditions expected throughout the GI tract

**Indication**
- Treatment of severe diarrhea caused by *Clostridium difficile* infection

**Mechanism of action**
- Inhibits cell wall biosynthesis in gram-positive bacteria
## Rationale for using an *in vitro* approach for vancomycin capsule BE studies

### Site of action
- Vancomycin is poorly absorbed and acts locally within the GI tract.
- As the vancomycin drug substance is highly soluble, it is expected to be completely dissolved by the time it reaches the site of action (the colon).

### Reference formulation
- Gelatin capsule containing vancomycin and polyethylene glycol.

### Sensitivity, feasibility
- If test and reference dissolution rates at the conditions recommended by FDA do not differ significantly, then should provide same rate and extent of availability at site of action.
- In this case the *in vitro* approach is more sensitive than a clinical endpoint approach.
Acarbose tablets
An in vitro BE approach is suitable for acarbose tablets, if certain criteria are met

- The test and reference product should contain the same inactive ingredients in the same amounts (Q1, Q2 sameness)
- The endpoints compared are dissolution rates in buffered media of varying pH (pH 1.2, 4.5, 6,8)
- The media of varying pH represent conditions in the gastrointestinal (GI) tract
- Dissolution profiles are compared using the f2 (similarity factor) metric
- Two dissolution profiles are considered similar if f2 ≥ 50
- If test not Q1/Q2 to reference, must use in vivo pharmacodynamic (PD) approach for BE
Rationale for using *in vitro* approach for BE studies of acarbose tablet that is Q1/Q2 to reference

<table>
<thead>
<tr>
<th>Drug substance</th>
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<tbody>
<tr>
<td>An oligosaccharide</td>
</tr>
<tr>
<td>Soluble in water</td>
</tr>
<tr>
<td>Less than 2% of an oral dose is absorbed</td>
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<table>
<thead>
<tr>
<th>Indication</th>
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<tr>
<td>To improve glycemic control in Type 2 diabetes patients (as adjunct to diet, exercise)</td>
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<thead>
<tr>
<th>Mechanism of action</th>
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</thead>
<tbody>
<tr>
<td>Inhibits alpha-glucosidase in the GI tract</td>
</tr>
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</table>
Rationale for using *in vitro* approach for BE studies of acarbose tablet that is Q1/Q2 to reference

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<tr>
<th>Site of action</th>
<th>Reference formulation</th>
<th>Sensitivity, feasibility</th>
</tr>
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</table>
| • Delays digestion of ingested carbohydrates in GI tract  
  • This results in a smaller rise in blood glucose concentration following meals | • An immediate-release tablet | • Acarbose is highly soluble and tablets dissolve rapidly  
  • If test and reference dissolution rates at the conditions recommended by FDA do not differ significantly, then should provide same rate and extent of availability at site of action |
Rationale for using *in vivo* approach for BE studies of acarbose tablet that is not Q1/Q2 to reference

- Dissolution testing would not be adequate to ensure that there is no unique interaction between an excipient and the mechanism of action of the active ingredient
- An *in vivo* BE study is recommended for acarbose tablet formulations that are not Q1/Q2 to the reference
- The *in vivo* study should use the PD endpoint of changes in blood glucose concentrations (using $C_{\text{max}}$, AUEC)
- A pilot study should be conducted first in order to
  - Determine the appropriate dose for the pivotal BE study;
  - Assure that the glucose-lowering response is not on the plateau of the dose-response curve
Mesalamine Delayed-Release (DR) Oral Dosage Forms
A combination *in vivo* and *in vitro* approach for BE studies of mesalamine DR products

- Objective is to show that there is no significant differences in the way in which test and reference release mesalamine.

- For the *in vivo* BE studies (fasted and fed), mesalamine plasma concentrations are measured, and the metrics $AUC_{8-48h}$, $AUC_{0-t}$, $C_{max}$ must meet BE limits.

- For the *in vitro* BE study, test and reference mesalamine dissolution profiles should be similar (as per f2 metric) in all media tested (pH varying from 4.5 to 7.5).

- Using both approaches provides assurance that test and reference rate and extent of availability at site of action do not differ significantly.

- No need for Q1/Q2 sameness, but test and reference must be PE.
Rationale for using *in vivo* and *in vitro* approaches for BE studies of mesalamine DR products

- **Drug substance**
  - 5-aminosalicylic acid (5-ASA)
  - About 28% of an oral dose is absorbed

- **Indication**
  - Treatment of mild to moderately active ulcerative colitis
  - Maintenance of remission of ulcerative colitis

- **Mechanism of action**
  - May diminish inflammation by blocking cyclo-oxygenase and inhibiting prosta glandin production in the colon
Rationale for using *in vivo* and *in vitro* approaches for BE studies of mesalamine DR products

<table>
<thead>
<tr>
<th>Site of action</th>
<th>Reference formulation</th>
<th>Sensitivity, feasibility</th>
</tr>
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<tbody>
<tr>
<td>Colon, rectum</td>
<td>Delayed-release capsule</td>
<td>In vitro dissolution rates can be compared at pH conditions expected along GI tract</td>
</tr>
<tr>
<td>Data suggest that mesalamine acts locally rather than systemically</td>
<td>Delayed-release tablet</td>
<td>Systemic mesalamine concentrations can be compared over specified time intervals to determine rate and extent of absorption at colon and rectum</td>
</tr>
<tr>
<td>Oral mesalamine is absorbed throughout the GI tract</td>
<td>The proposed generic must be PE to the reference</td>
<td></td>
</tr>
<tr>
<td>BE metrics AUC and $C_{\text{max}}$ reflect all mesalamine absorption, not just at sites of action</td>
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Summary and Conclusions
Summary and conclusions

- The FDA applies sound scientific principles in selecting the optimal BE and PE approach for a locally-acting drug indicated to treat GI disease.
- The objective is to apply the most sensitive, accurate, and reproducible approach to compare test and reference rate and extent of availability at the site of action.
- The examples above show that FDA may recommend a PK, PD, clinical, or in vitro approach, or a combination of approaches.
- In selecting the approach, factors considered include drug site of action, mechanism of action, drug substance properties, nature of reference formulation, and sensitivity/feasibility of approach.
References

• www.regulations.gov – FDA responses to Citizen Petitions on vancomycin, acarbose, mesalamine

• www.fda.gov
  – Drugs@FDA – approved labeling for vancomycin capsules, acarbose tablets, mesalamine DR capsules, sevelamer tablets
  – The Electronic Orange Book
  – CDER Guidance for Industry: BE Recommendations for Specific Products – vancomycin capsules, acarbose tablets, mesalamine DR capsules/tablets, sevelamer tablets

• 21 CFR Part 300 (BA/BE Regulations)
Thanks

- The Office of Generic Drugs locally-acting GI drugs working group
- FDA’s vancomycin capsule Citizen Petition response team
- FDA’s acarbose tablet Citizen Petition response team
- FDA’s mesalamine DR tablet Citizen Petition response team
- FDA’s cholestyramine guidance working group
- The Office of Generic Drugs Bioequivalence Divisions (for the sevelamer guidance)
THANK YOU FOR YOUR ATTENTION!