Bioequivalence for Oral Locally Acting Gastrointestinal Drug Products

SBIA 2023—Advancing Generic Drug Development: Translating Science to Approval

Day 2, Session 6: Noteworthy Complex Generic Drug Approvals: Oral Locally Acting & Oral Suspension Drug Products

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Learning Objectives

- Identify bioequivalence (BE) approaches for oral locally acting gastrointestinal (GI) drug products
- Provide examples of drug products to establish BE
- Explain the rationales of BE recommendations

BE of Oral Locally Acting GI Drugs

- BE recommendation is based on drug product properties and the products' mechanism of action
  - Systemic absorption
    - ✓ In vivo studies: Pharmacokinetic (PK) studies; pharmacodynamic (PD) studies; comparative clinical endpoint BE studies
    - ✓ In vitro studies
  - No or poor systemic absorption
    - ✓ In vivo studies: PD studies; comparative clinical endpoint BE studies
    - ✓ In vitro studies

Establishing BE for Oral Locally Acting GI Drugs

	Drug Examples
In vitro	• Cholestyramine (binding) • Sevelamer (binding + API sameness)
In vitro or in vivo	• Vancomycin [(1) If Q1/Q2 the same: dissolution; or (2) If not Q1/Q2 the same: comparative clinical endpoint BE study]
In vitro and in vivo	• Mesalamine (PK studies+ dissolution) • Rifaximin [(1) If Q1/Q2 the same: PK studies + dissolution; or (2) If not Q1/Q2 the same: Comparative clinical endpoint BE study + PK studies + dissolution)]
In vivo	• Mebendazole (PK studies + comparative clinical endpoint BE study) • Metronidazole (PK studies) • Orlistat (PD study)

API: Active pharmaceutical ingredient; Q1: Qualitatively; Q2: Quantitatively;

Challenge Question #1

If a drug product is not systemically absorbed, which of the following is NOT an adequate method to establish BE?

A. PD study

B. In vitro study

C. PK study

D. Comparative clinical endpoint BE study

Examples of BE Establishment for Drug Products

- Case 1: Sevelamer drug products
  - In vitro studies (i.e., API sameness and binding)
- Case 2: Mesalamine drug products
  - PK studies + In vitro study (i.e., comparative dissolution)
- Case 3: Vancomycin HCl capsules
  - (1) Comparative clinical endpoint BE study, or (2) In vitro study (i.e., comparative dissolution)
- Case 4: Fidaxomicin drug products
  - (1) Comparative clinical endpoint BE study, or (2) PK studies + in vitro study (i.e., comparative dissolution)

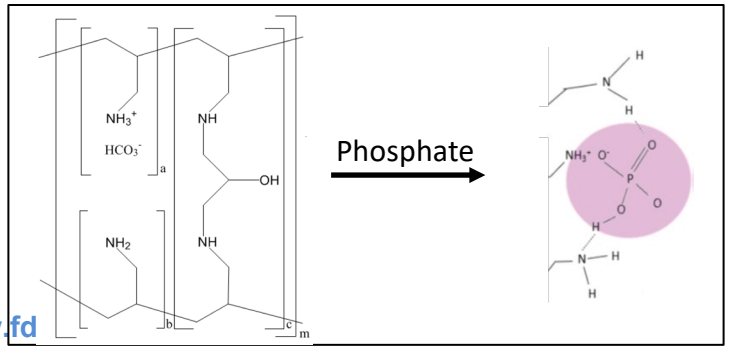
Case 1: Sevelamer Drug Products

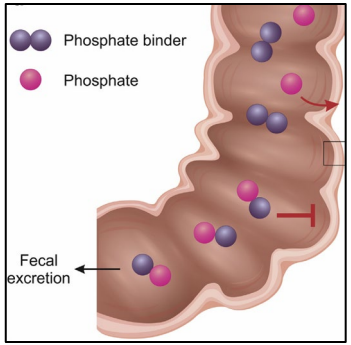
Sevelamer Carbonate Drug Products

- Dosage forms and approved ANDAs:

Dosage forms	Tablet	For suspension
Approved ANDAs	10	5

- Indication: For the control of serum phosphorus
- Mechanism: Sevelamer carbonate contains multiple amines to bind to phosphate molecules.





BE Approaches for Sevelamer Carbonate Drug Products

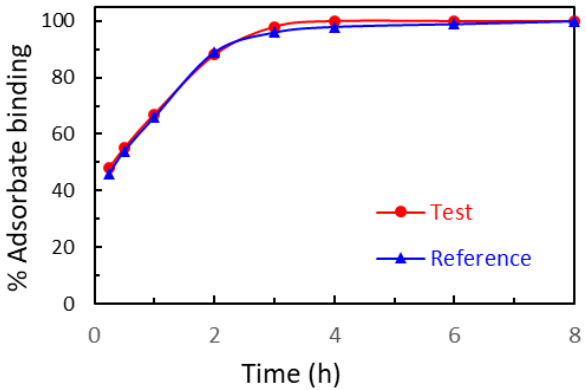
- API sameness
- In vitro kinetic binding study
- In vitro equilibrium binding study

API Sameness

- Sevelamer is a complex API.
- API sameness determination is based on the totality-of-the-evidence approach, e.g., API synthetic route + comparative physico-chemical characterizations.
- API characterization: Degree of crosslinking, degree of protonation, particle size, elemental analysis, swelling index, etc.

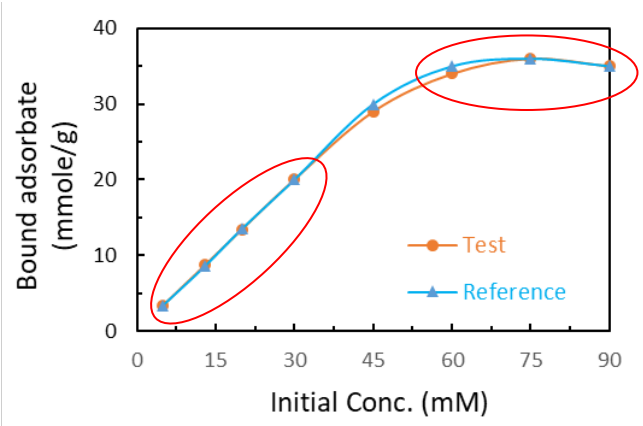
In Vitro Kinetic Binding Study

- The binding study is recommended due to the mechanism of action.
- Assess the rate of binding and the time to reach the binding equilibrium.
- Support in vitro equilibrium binding study.
- Test/Reference bound adsorbate ratios at the various time should be compared but not subjected to 90% confidence interval.



In Vitro Equilibrium Binding Study

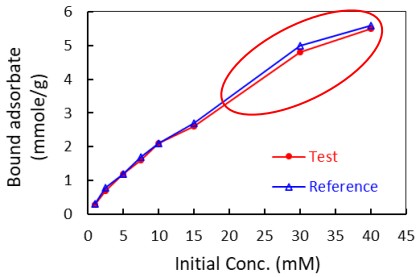
- Evaluate affinity and capacity binding constants
- Consider as the **pivotal BE study**
- Conduct under conditions of constant time and varying adsorbate concentration
  - The concentration should be selected to ensure the binding curve is well defined and captures the maximum binding.
  - Different concentration may be applied to different pH conditions.



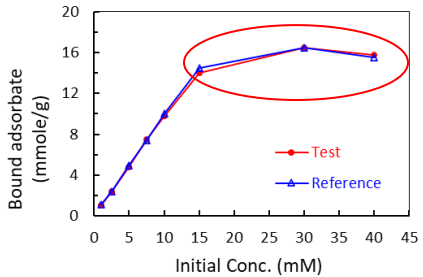
Case Example for ANDA Review: Binding Study

- The PSG recommends binding studying under pH 4 and pH 7 conditions.
- Applicant selected the same adsorbate (i.e., phosphate) concentration range for both pH 4 and pH 7
  - Problem: At pH 4, it did not reach to equilibrium

pH 4 (without acid pretreatment)



pH 7 (without acid pretreatment)



- Different phosphate concentration ranges may be used under different conditions because phosphate has higher affinity to sevelamer under pH 7.

Case 2: Mesalamine Drug Products

Mesalamine Drug Products

- Dosage forms and approved ANDAs:

Dosage forms	DR Capsule	DR Tablet		ER Capsule	
RLD	NDA204412	NDA021830	NDA022000	NDA022301	NDA020049
Approved ANDAs	1	1	4	6	1

- Indication: For the treatment of active ulcerative colitis
- Mechanism: A topical anti-inflammatory effect on colonic epithelial cells
- Bioavailability: 20% - 35% (depend on drug products)

BE Approaches for Mesalamine Drug Products

	DR Products	ER Products
In vivo Study	PK studies – Fasting and fed conditions – Cmax and AUC_{8-48}, AUC_{0-t}	PK studies – Fasting and fed conditions – Cmax and AUC_{0-3}, AUC_{3-t}, AUC_{0-t}
In vitro Study	Comparative dissolution testing under various pH conditions (e.g., pH 4.5 – 7.5) – Use dissolution similarity factor (f2) to compare test vs. reference – 24 dosage units of the test product and at least 2 lots of the reference standards	Comparative dissolution testing under various pH conditions (e.g., pH 4.5 – 7.5) – Use f2 to compare test vs. reference

Review of Comparative Dissolution Testing

- High variability of dissolution data:
  - Bootstrapping method
  - f2 evaluation: mean and lower bound of 90% confidence interval

Test vs. Reference
[e.g., T vs. (R1+R2); T vs. R1; T vs. R2]

(Test vs. Reference)
vs.
(Reference 1 vs. Reference 2)

  - Methods other than bootstrapping method with sufficient justification are also acceptable.

Rationales of BE Recommendations

- About 20% - 35% of mesalamine is systemically absorbed.
- Partial AUC reflects the absorption in the GI tract and can discriminate the formulation differences.
- The in vitro dissolution testing over a range of pH serves as a surrogate of in vivo drug release in the GI tract.
- High dissolution variability is observed in DR dosage forms. More units of products help to perform bootstrapping f2 analysis.

Case 3: Vancomycin HCl Capsules

Vancomycin HCl Capsules

- RLD: NDA 050606; Approved ANDAs: 5
- Indication: Treatment of *C. difficile*-associated diarrhea and staphylococcal enterocolitis.
- Mechanism: Inhibit cell-wall biosynthesis of *Staphylococcus aureus and Clostridioides difficile.*
- Absorption:
  - Poorly absorbed after oral administration.
  - The measurement of vancomycin concentration in plasma is limited.

BE Approaches for Vancomycin HCl Capsule

Options	BE Approaches
Option 1: Q1/Q2 the same	In vitro study: – Comparative dissolution testing under various pH conditions, i.e., 0.1N HCl, pH 4.5 and pH 6.8 o Calculate f2 to compare test and reference standard
Option 2: Not Q1/Q2 the same	In vivo study: – Comparative clinical endpoint BE study (patients)

Rationales of BE Recommendations

- Limited vancomycin enters the systemic circulation.
- Vancomycin is highly soluble at 0.1N HCl, pH 4.5, and pH 6.8. In vitro dissolution testing can predict in vivo release behavior.
- If test product and RLD are Q1/Q2 the same, the differences of in vivo performance are minimized.
- For non-Q1/Q2 formulations, the comparative clinical endpoint BE study is recommended because the impact of certain excipients on in vivo performance is unknown.

Case 4: Fidaxomicin Drug Products

Fidaxomicin Drug Products

- Dosage forms and approved ANDAs:

Dosage forms	Tablet	Suspension
Approved ANDAs	0	0

- Indication: Treatment of *C. difficile*-associated diarrhea
- Mechanism: Fidaxomicin is an antibacterial drug and acts locally in the GI tract on *C. difficile*
- Absorption:
  - Poor permeability and absorption.
  - Systemic absorption is minimal following oral administration.

BE Approaches for Fidaxomicin Drug Products

Options	BE Approaches
Option 1: Q1/Q2 the same	(1) Comparative dissolution under multiple media covering physiologically relevant pH range. – Perform f2 to compare test and reference standard 2) PK studies: Fasting and fed conditions (healthy subjects)
Option 2: Not Q1/Q2 the same	Comparative clinical endpoint BE study (patients)

Rationales of BE Recommendations

- The Q1/Q2 sameness minimizes the differences of in vivo performance between the test product and RLD.
- Bioanalytical methods can characterize drug concentrations adequately.
- Because of instability of fidaxomicin during GI transit, PK studies serve as a confirmatory measure.
- The comparative dissolution study ensures comparable drug release in different portions of the GI tract.
- For non-Q1/Q2 formulations, different type and amount of excipients may have different impact on in vivo performance at the site of action. Therefore, the comparative clinical endpoint BE study is recommended.

Challenge Question #2

Which of the following is a consideration to develop BE recommendations for oral locally acting GI drugs?

A. Mechanism of drug products

B. Systemic or non-systemic absorption of drug products

C. Physical properties of drug products

D. All of the above

Ongoing Research under the Generic Drug User Fee Amendments

Alternative approaches may be utilized to demonstrate BE between test product and RLD. The following ongoing projects intend to develop biopredictive dissolution methods and establish modeling to support BE demonstration for generic locally acting GI drug products.

1) Title: *Development of Physiologically Based Biopharmaceutics Modeling (PBBM) Framework to Support an Assessment of Bioequivalence for Locally-Acting Drugs in the Gastrointestinal Tract in Healthy Subjects and Patients*
   - Model drug: Budesonide, dexamethasone, sulfasalazine, and mesalamine drug products
   - Grant #1U01FD007660-01; University of Bath

2) Title: *Development and Verification of In Vitro Integrated Mechanistic Population-Based PBPK Model Framework Towards Virtual Bioequivalence Assessment of Locally Acting Drug Products in the GI Tract*
   - Model drug: Sulfasalazine, and mesalamine drug products
   - Grant # 1U01FD007662; University of Florida

Summary

- For locally acting GI drugs, systemic exposure may not reflect drug concentrations at the site of action. In addition, drug plasma concentrations may be limited.

- BE recommendations of oral locally acting GI drug products are based on drug product properties and mechanism of action.

- The research effort on improving in vitro dissolution methods and developing predictive in silico model could be a supporting evidence for BE determination.

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