Practical Considerations for Bioequivalence of GI Locally Acting Products

SBIA 2020: Advancing Innovative Science in Generic Drug Development Workshop
Session 4: Practical Considerations in the Study Design and Data Evaluation Recommended in PSGs
Topic 2: In Vitro Feeding Tube Testing and GI Locally-Acting Products

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Outline

- Examples of locally acting drugs
- Role of bioequivalence (BE) testing in generic drug development
- Review of regulatory BE approaches
- Determination of the optimal BE approach for locally acting gastrointestinal (GI) drugs
- Presentation of case studies
- Summary and conclusions

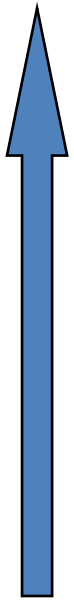
Examples of Locally acting Drugs

- Topical drugs applied to skin
- Nasal spray products
- Inhalation drug products
- Ophthalmic products
- Locally acting GI drugs

Role of BE Studies

- The proposed generic must be shown to be bioequivalent to the reference listed drug to establish that the two are therapeutically equivalent (TE)
- TE products can be substituted for each other without any adjustment in dose or additional therapeutic monitoring

Approaches to Determining Bioequivalence (21 CFR 320.24)



- *In vivo* measurement of active moiety or moieties in biologic fluid
- *In vivo* pharmacodynamic comparison
- *Well-controlled comparative clinical trials*
- *In vitro* comparison
- Any other approach deemed appropriate by FDA

The Challenges of Establishing BE for Locally Acting GI Drug Products

- Not absorbed or poorly absorbed
  - Pharmacokinetic (PK) endpoints are not feasible
  - In vitro BE studies (predictive of in vivo performance)
  - Pharmacodynamics (PD) and/or comparative clinical endpoints
- Systemically absorbed
  - Pharmacologic effects are primarily local
  - Systemic absorption may occur at sites other than site of action
    - PK (may use pAUC) and In vitro studies
    - PK, PD and/or comparative clinical, and in vitro studies

BE Recommendations for Locally Acting GI Drug Products

Method	Drugs (examples)	Comment
In vitro only	Cholestyramine powder, sevelamer HCl tablet	binding agents (Binds bile acids or Phosphate), no detectable PK
In vitro (Q1 and Q2 same), **OR** in vivo (Q1 and Q2 not same)	Acarbose tablet (PD), Vancomycin HCl capsule (clinical)	IR, no detectable PK
In vitro + PK	Mesalamine, balsalazide disodium	PK as in vivo dissolution surrogate, in vitro testing as confirmative study
PK + in vitro (Q1 and Q2 sameness)	Rifaximin tablet	PK studies as in vivo dissolution surrogates
Clinical + PK + in vitro (Q1/Q2 not same)	Rifaximin tablet	IR, minimally absorbed due to the low solubility and permeability.
In vitro (Q1 and Q2 sameness)	Sucralfate Oral Suspension	Not absorbed, bioassays based on mechanism of action

Case 1 – Mesalamine Products

Mesalamine Related Products

- *Pro-drugs*: sulfasalazine tablets and suspension, olsalazine sodium capsules and balsalazide disodium tablets
- *Delayed-release products*: Asacol®, Asacol® HD, Liada®, and Delzicol®
- *Extended-release products*: Pentasa® and Apriso®
- *Topical products*: rectal enema (Rowasa®) and suppository (Canasa®)

BE Approaches for Mesalamine Oral Products

Products	Mesalamine DR Tablets	Mesalamine ER Capsules
In vivo PK (fasting and Fed)	Mesalamine in plasma AUC8-48, AUC0-t, and Cmax	Mesalamine in plasma AUC0-3, AUC3-t, AUC0-t, and Cmax
In vitro dissolution	compare dissolution profiles using f2 values at pHs expected in GI tract between the Test and Reference products	
Guidance	Mesalamine DR Tablets (Asacol, Asacol HD, Liada) https://www.accessdata.fda.gov/drugsatfda_docs/psg/Mesalamine_draft_Oral%20tab%20DR_RLD%2019651_RC10-16.pdf Mesalamine ER Capsules (Pentasa and Apriso) https://www.accessdata.fda.gov/drugsatfda_docs/psg/Mesalamine_draft_Oral%20cap%20ER_RLD%2020049_RC10-17.pdf	

Scientific Rationales

- Mesalamine oral products are absorbed throughout GI tract, not just at site of action
- PK profiles can be analyzed over defined time intervals using partial AUC to determine the fraction of absorption at the site of action and best discriminate the formulation difference.
- The in vitro dissolution testing over a range of pH serves as a surrogate of in vivo drug release in the GI tract

BE Approaches for Mesalamine Rectal Products

Brand Name/Generic name	BE Recommendation					Guidance posting date
	In vivo PK studies using healthy subjects	**Analytes to be measured**	**BE based on 90% of AUC and Cmax**	**In vitro Dissolution (BE)**	**In vitro physicochemical characterization**	
Rowasa (mesalamine rectal enema)	Fasting	mesalamine	mesalamine	0.1N HCl; pH 4.5 buffer; pH 6.8 buffer; pH 7.2 using paddle at 25 and 50 rpm	NA	Jan 2008
Canasa (mesalamine rectal suppository)	Fasting	mesalamine	mesalamine	NA	differential scanning calorimetry: viscosity; melting point; and density.	Mar. 2013

Scientific Rationales

- Drug product is administered at the intended site of action; Drug is absorbed at site of activity; no pAUC.
- For rectal enema, in vitro dissolution testing is well established and used for formulation comparison.
- For rectal suppositories, the drug release from a suppository depends upon physicochemical properties not dissolution.
- To ensure BE for rectal absorption, Q1 and Q2 criteria was added for mesalamine rectal enema and suppositories.

Case 2 – Acarbose Tablets

Acarbose Tablets

Indication	Improve glycemic control in patients with Type 2 diabetes
Mechanism of action	Inhibits activity of alpha-glucosidase within GI tract
Site of absorption	Some absorption (<2%); site(s) unknown
In vitro dissolution	Ensure equivalent release of formulations in multi-media

Acarbose Tablets: BE Approach

Study type	Subjects	Endpoint	BE based on
In vitro (If Q1/Q2 same)	N/A	Dissolution rate	T & R tablet dissolution profiles at pHs expected in GI tract
In vivo (If Q1/Q2 not same)	Healthy	PD	Amount by which serum glucose declines after sucrose load
Guidance	Acarbose Tablets (PRECOSE) https://www.accessdata.fda.gov/drugsatfda_docs/psg/Acarbose_oral%20tablet_NDA%2020482_final%2008-17.pdf		

Acarbose Tablets: Rationale for BE Approach

- Plasma concentrations do not reflect acarbose availability at the site of drug action
- Reduction in blood glucose levels is a suitable and readily measurable PD endpoints
- Acarbose is highly soluble and tablet in vitro dissolution performance is highly predictive of in vivo release, thus
- If T and R tablets are qualitatively (Q1) and quantitatively (Q2) the same, not necessary to conduct the PD study

Case 3 – Rifaximin Tablets

Rifaximin Tablets

Indication	Treatment of travelers' diarrhea (TD) caused by noninvasive strains of Escherichia coli; irritable bowel syndrome with diarrhea (IBS-D)
Mechanism of action	An antibacterial drug within GI tract
Site of absorption	Minimally absorbed upper GI tract due to the low solubility and permeability
In vitro dissolution	Discriminate any potential differences that cannot be detected by PK

Rifaximin Tablets: BE Approach

Study type	Subjects	Endpoint	BE based on
In vitro+ In vivo (Q1 and Q2 same)	Healthy	PK	• Rifaximin in plasma • T & R table dissolution profiles at pHs expected in GI tract
in vitro + in vivo (Q1 and Q2 not same)	Healthy and Patients with diarrhea	PK and Clinical	• Rifaximin in plasma • Comparative clinical endpoint • T & R tablet dissolution profiles at pHs expected in GI tract
Guidance	Rifaximin Tablets (XIFAXAN) https://www.accessdata.fda.gov/drugsatfda_docs/psg/Rifaximin_oral%20tablet_NDA%20022554%20and%20021361_RV03-17.pdf		

Rifaximin Tablets: Rationale for BE Approach

- The difference of In vivo performance are minimized due to Q1/Q2 sameness.
- BE studies with PK endpoints studies serve as approximate surrogates for in vivo dissolution.
- PK study is recommended for the 200 mg strength because rifaximin does not exhibit dose-proportional pharmacokinetics.
- In vitro dissolution test is recommended to discriminate any potential differences that cannot be detected by PK.
- Differences in product in vivo performance caused by excipients are unknown for non-Q1/Q2 formulations. Therefore, comparative clinical endpoints BE study is recommended.

Case 4 – Sucralfate Oral Suspension

Sucralfate Oral Suspension

Indication	The short-term (up to 8 weeks) treatment of active duodenal ulcer
Mechanism of action	The antiulcer activity is the result of formation of an ulcer-adherent complex that covers the ulcer site and protects it against further attack by acid, pepsin, and bile salts (local not systemic)
Site of absorption	Minimally absorbed from GI tract
In vitro	Sensitive enough to detect the relevant product difference
Guidance	Sucralfate Oral Suspension (CARAFATE) https://www.accessdata.fda.gov/drugsatfda_docs/psg/Sucralfate_oral%20suspension_NDA%20019183_RV08-17.pdf

Sucralfate Oral Suspension: BE Approach

Study type	Endpoint	BE based on
Formulation* comparison	N/A	Q1/Q2 sameness
In vitro Bioassays	Binding to human serum albumin (HSA) or bovine serum albumin (BSA)	In vitro equilibrium binding study; the 90% CI of Langmuir binding constant k2 from the equilibrium binding study
In vitro Bioassays	Binding to bile acids	• In vitro equilibrium binding study; the 90% CI of Langmuir binding constant k2 from the equilibrium binding study
In vitro Bioassays	Binding to bile acids	Kinetic binding: Compare T/R with respect to the % binding of bile salts to sucralfate
In vitro Bioassays	Enzyme (pepsin) activity study	The qualitative comparison between the Test and Reference formulations with respect to the % decrease in pepsin activity.

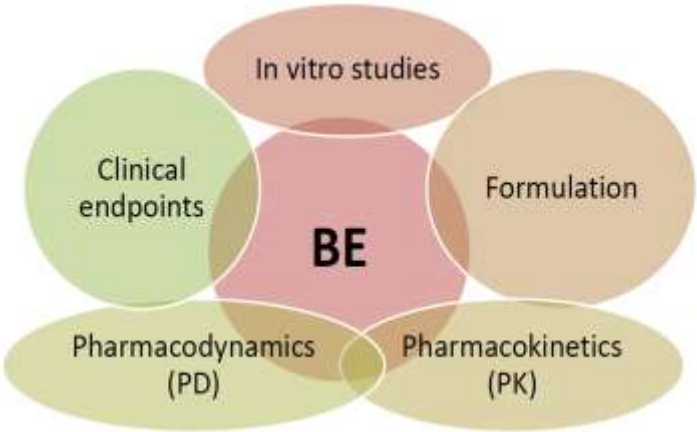
*Active Pharmaceutical Ingredient sameness and acceptable comparative physicochemical characterizations of the Test and RLD formulations are not discussed in this presentation.

Sucralfate Oral Suspension: Rationale for BE Approach

- With Q1/Q2 sameness, bioassays are identified based on postulated mechanisms of action and used to establish BE.
- Sucralfate releases aluminum ions when it is exposed to acid, and produces negatively charged complex which binds tightly to positively charged protein on the ulcer site.
  - absorption activity of protein can be measured using HSA or BSA
- Insoluble complex forms a barrier that prevents back diffusion of hydrogen ions, inactivates pepsin, and absorbs bile acids refluxed from the duodenum.
  - In vitro equilibrium/Kinetic binding study with bile salts
  - In vitro enzyme (pepsin) activity study

Summary and Conclusion

- Despite difference in BE approaches for locally acting GI drugs, each approach is carefully thought out and designed based on the unique properties of the drug substance and drug product



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Challenge Question

Considerations when developing bioequivalence recommendations for locally acting GI products include which of the following?

a. Whether the particular drug product is systemically absorbed.

b. Whether the drug product is Q1/Q2 the same as the reference product.

c. Whether the drug is highly soluble.

d. All of the above