Non-Quantitative (Q2) Sucralfate Oral Suspension Approval

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

- Describe the FDA's considerations in developing the product specific guidance for Sucralfate Oral Suspension

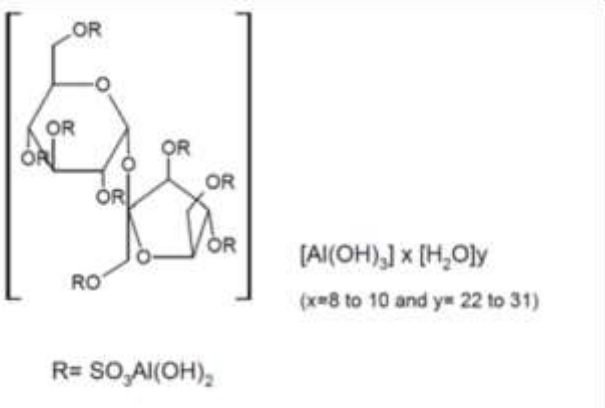
- Explain the FDA's rationale for recommending qualitative (Q1) and quantitative (Q2) sameness between the test and reference formulations when developing a generic version for Sucralfate Oral Suspension products*

- Describe potential alternative bioequivalence (BE) approaches for generic Sucralfate Oral Suspension products

* Product-Specific Guidance (PSG): https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_019183.pdf

Sucralfate Oral Suspension

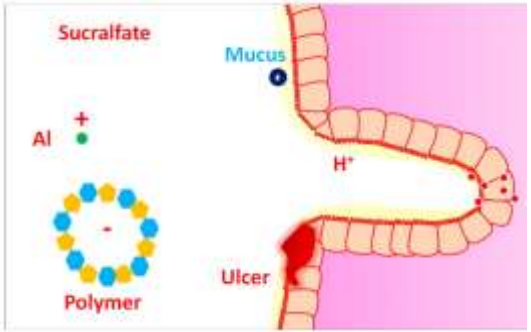
- Reference Listed Drug (RLD): Carafate® (sucralfate) Oral Suspension, 1 g/10 mL approved in 1993



- Indication: In the short-term treatment of active duodenal ulcer
- Administration: Should be taken on empty stomach
- Locally acting agent, with minimal absorption from gastrointestinal tract

Sucralfate - Mechanism of Action

- In the acidic environment dissociated into sulfated sucrose and aluminum salt
- Negatively charged sucrose sulfate binds to positively charged protein on the ulcers
- Forms protective barrier- inhibits diffusion of acid
- Binds pepsin and bile salts



- Stimulates mucosal prostaglandin and bicarbonate secretion

Current BE Recommendations for Sucralfate Oral Suspension in PSG*

Test and RLD formulations -

- Same Active Pharmaceutical Ingredient (API)
- **Qualitatively (Q1) and quantitatively (Q2) the same**
- Acceptable comparative physicochemical characterization
- **Acceptable bioassays**

* PSG for Sucralfate Oral Suspension: https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_019183.pdf

Bioassays Recommended in PSG

Based on postulated mechanism of action for sucralfate

- In vitro equilibrium binding – Human or Bovine Serum Albumin (HSA/BSA)

  Bioequivalence: 90% CI of Langmuir binding constant (K2)

- In vitro equilibrium and kinetic binding - Bile Salts

  Bioequivalence: 90% CI of K2

- In vitro enzyme activity – Pepsin

  Equivalence: Quantitative comparability of percent decrease in pepsin activity

* PSG for Sucralfate Oral Suspension: https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_019183.pdf

Optimization of Bioassays

- Study conditions should be sensitive enough to detect the relevant differences between test product and reference standard
- Physiologically relevant conditions should be taken into consideration in designing and conducting the in vitro binding studies
- Study condition for each bioassay should be optimized and justification should be provided for the parameters such as:
  - Negatively charged complex formation process
  - Reactants adsorbate-adsorbent concentration such as sucralfate, serum albumin, total bile acid, pepsin, pepsin substrate
  - Assay duration and pH conditions

Case Study: Non Q2 Test Formulation

- Test formulation is Q1 the same, but not Q2
- The PSG is viewed only as recommendations unless specific regulatory or statuary requirements are cited
- There is no regulatory requirement of Q1/Q2 sameness for oral suspension products
- Potential Q2 differences may be justified with multiple meaningful measures of sameness or provide comprehensive scientific rationale regarding the lack of formulation function impact of difference
- Alternate BE approaches can be utilized for bioequivalence demonstration

Studies Submitted in Support of Non Q2 Test Formulation

- Test formulation is Q1 the same, but not Q2

	RLD	Test	% Difference between Test and RLD
Excipient A	x%	y%	> 5%

- Additional In vitro bioassays were conducted which included
  - Mucoadhesion (Gastric) assay
  - Delay in acid diffusion
  - Binding with human fibrinogen
  - Mucoadhesion (duodenum) assay
  - Delay in bile salt diffusion
  - Cytoprotection (Gastric) Study

Studies Submitted in Support of Non Q2 Test Formulation cont'd…

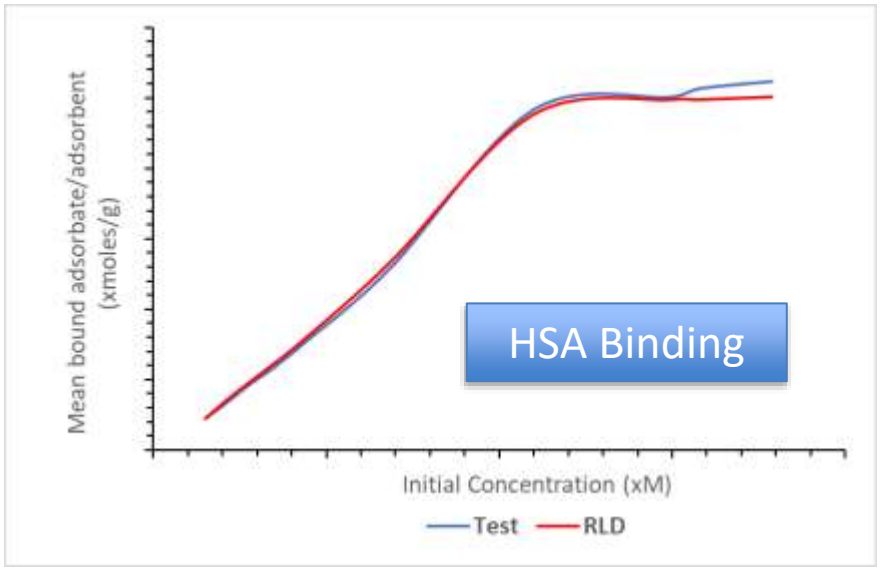
- Study Design Concern:
  - Conducted bioassays on different test formulation variants that included changes in multiple excipients
  - HSA Binding Assay - Inadequate Sucralfate/HSA concentrations

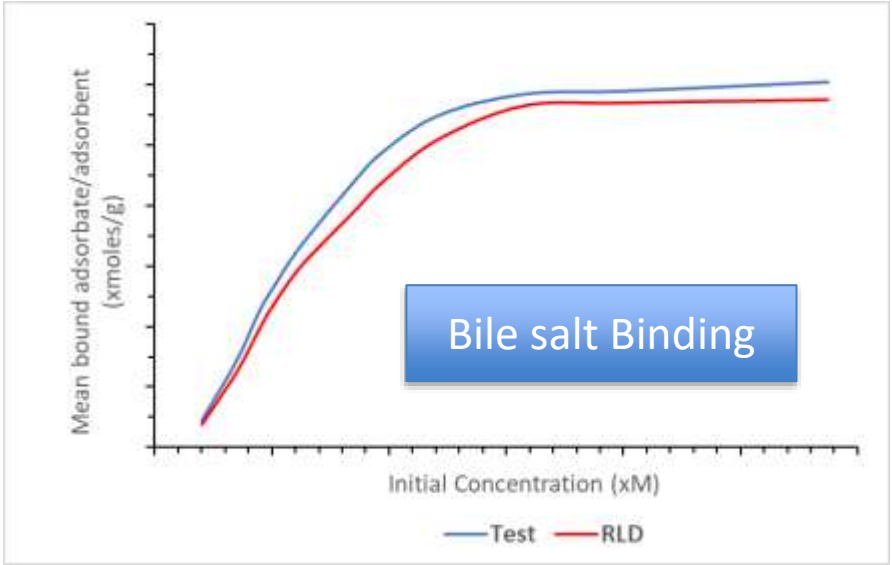
Binding constants: K_d vs k_1/k_2

Evidence to Demonstrate BE for non Q2 Test Formulation

- Altered test formulations with specific changes to only excipient A (bracketing concentrations covering proposed test and RLD amounts)
  - Test_LC
  - Test_HC
- Re-performed all the bioassays
  - PSG Recommended Studies
  - Additional Studies: Mucoadhesion (gastric) assay, Delay in bile salt diffusion, Delay in acid diffusion
- Repeated HSA binding study design as per the PSG recommendation

Evidence to Demonstrate BE for non Q2 Test Formulation cont'd…

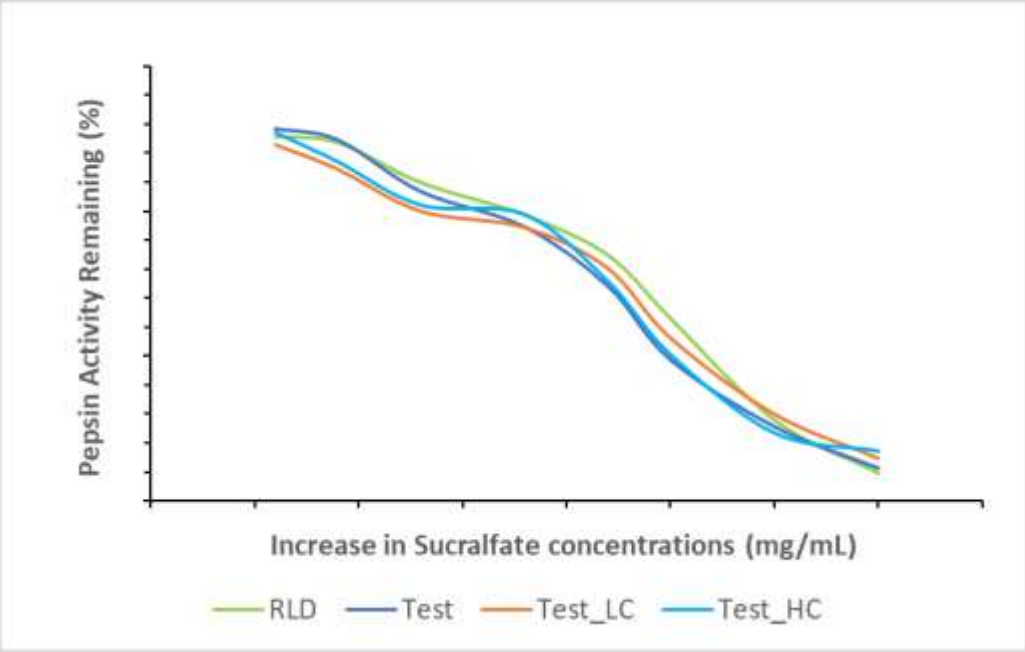




90% CI of K_2 are within 80%-120%

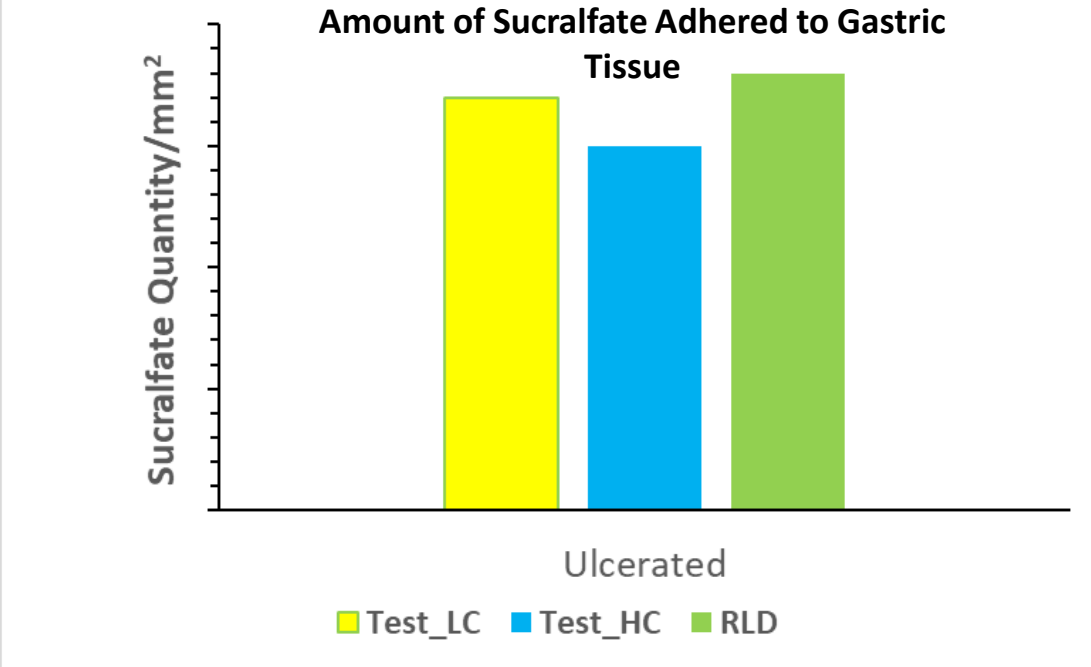
Evidence to Demonstrate BE for non Q2 Test Formulation cont'd…

- Pepsin Activity Study



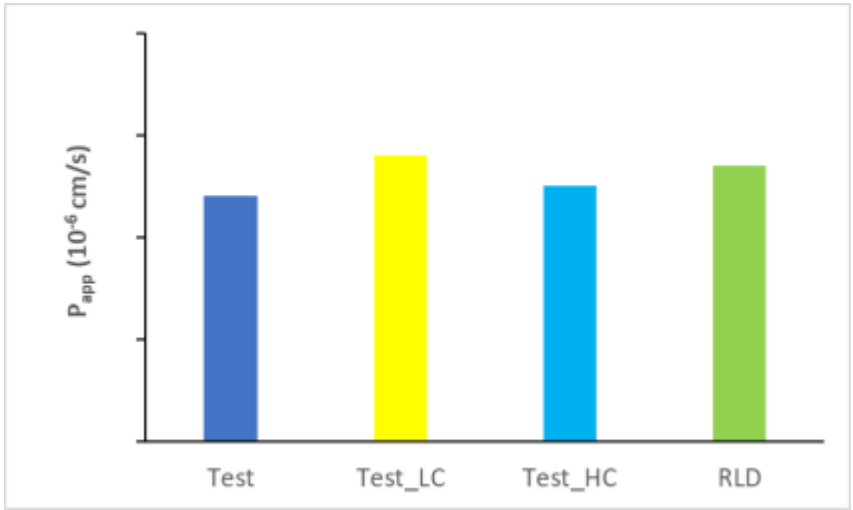
Evidence to Demonstrate BE for non Q2 Test Formulation cont'd…

- Mucoadhesion Study

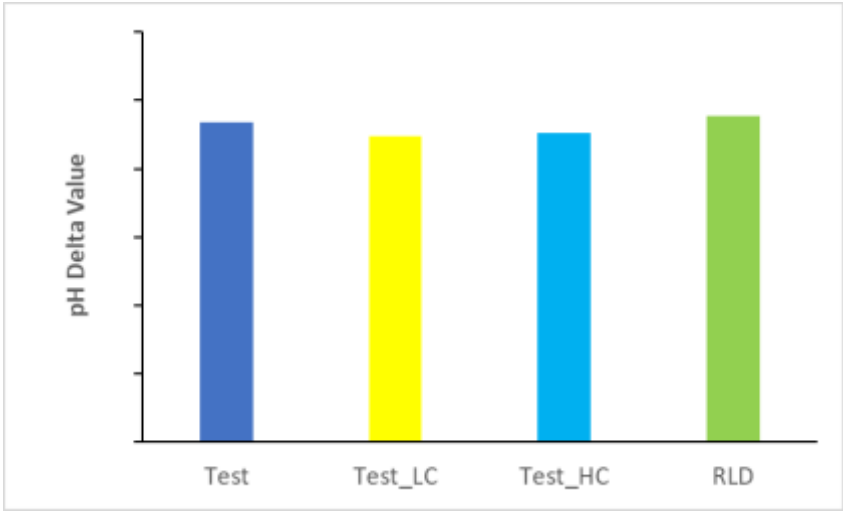


Evidence to Demonstrate BE for non Q2 Test Formulation cont'd…

Delay in Bile Salt Diffusion Study



Delay in Acid Diffusion Study



90% CI of T/R are within 80%-120%

Challenge Question #1

Which statements is NOT true:

A. In vitro bioassay recommendations are based on the mechanism of action of the drug

B. The PSG recommendations for demonstration of BE for Sucralfate Oral Suspension include in vitro and in vivo PK studies

C. Physiologically relevant conditions should be taken into consideration in designing and conducting the in vitro binding studies

D. The totality-of-evidence approach to assess demonstration of bioequivalence

Challenge Question #2

Which statement is NOT true?

A. Sucralfate binds to potassium

B. An in vitro binding study with bile salts is recommended in the PSG for Sucralfate Oral Suspension

C. The BE assessment for the in vitro binding study is based on the 90% CI of Langmuir constant (K_2)

D. API sameness is recommended in the PSG for Sucralfate Oral Suspension

Summary

- The product-specific guidance recommendations for bioequivalence demonstration of Sucralfate Oral Suspension products is based on totality-of-evidence approach
- Alternate approaches with sufficient scientific evidence can be submitted for demonstration of bioequivalence
- In the case study presented, the combined findings from all in vitro bioassays provided totality of evidence for the bioequivalence of non Q2 generic drug product to the RLD product
- Applicants can seek Agency's feedback through multiple communication channels (such as controlled correspondences, product-development meetings, pre-submission meetings, mid-cycle review meetings, post-complete response letter meetings) at various stages for any proposed alternate BE approaches

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