

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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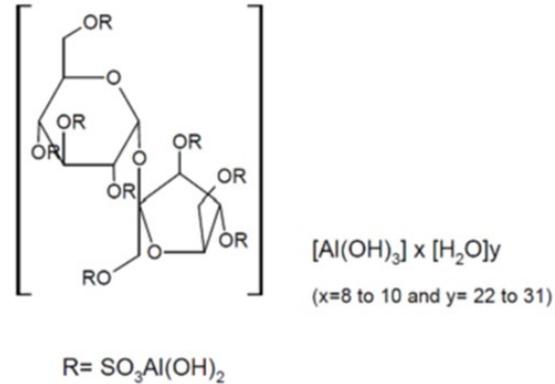


Learning Objectives

- ❑ 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

Sucralfate Oral Suspension

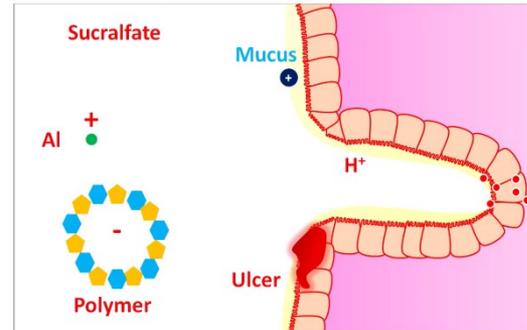
- Reference Listed Drug (RLD): Carafate® (sucralfate) Oral Suspension, 1 g/10 mL approved in 1993



- 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**

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

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 statutory 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
 - Mucoadhesion (duodenum) assay
 - Delay in acid diffusion
 - Delay in bile salt diffusion
 - Binding with human fibrinogen
 - 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

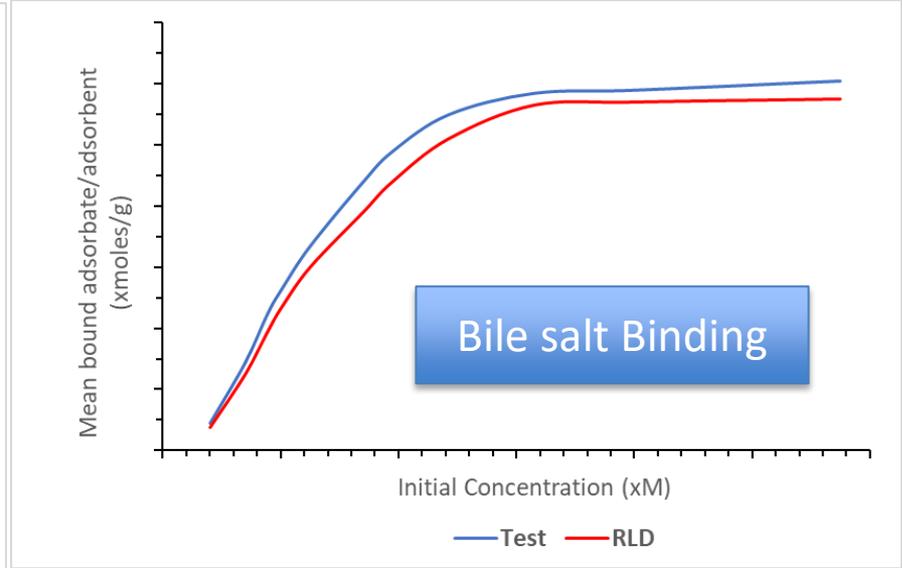
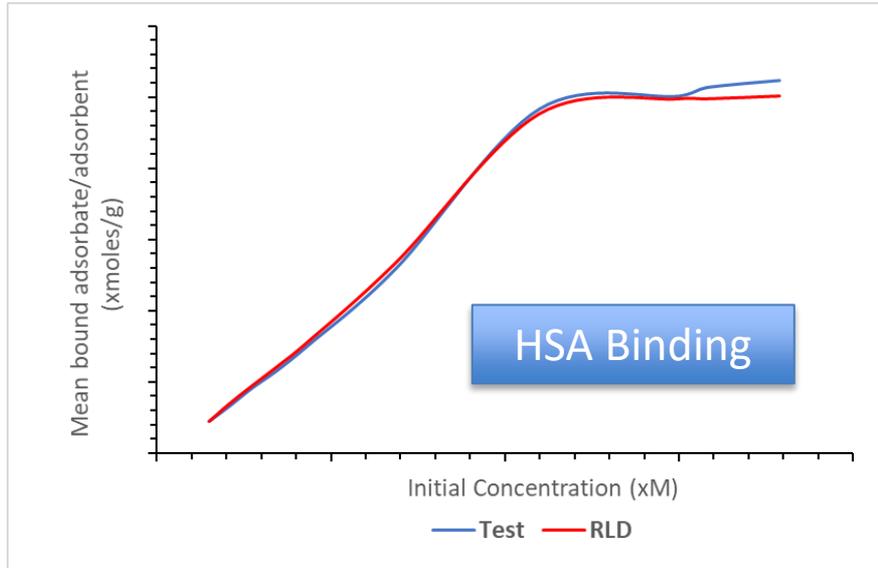
Binding constants: K_d vs k_1/k_2

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...

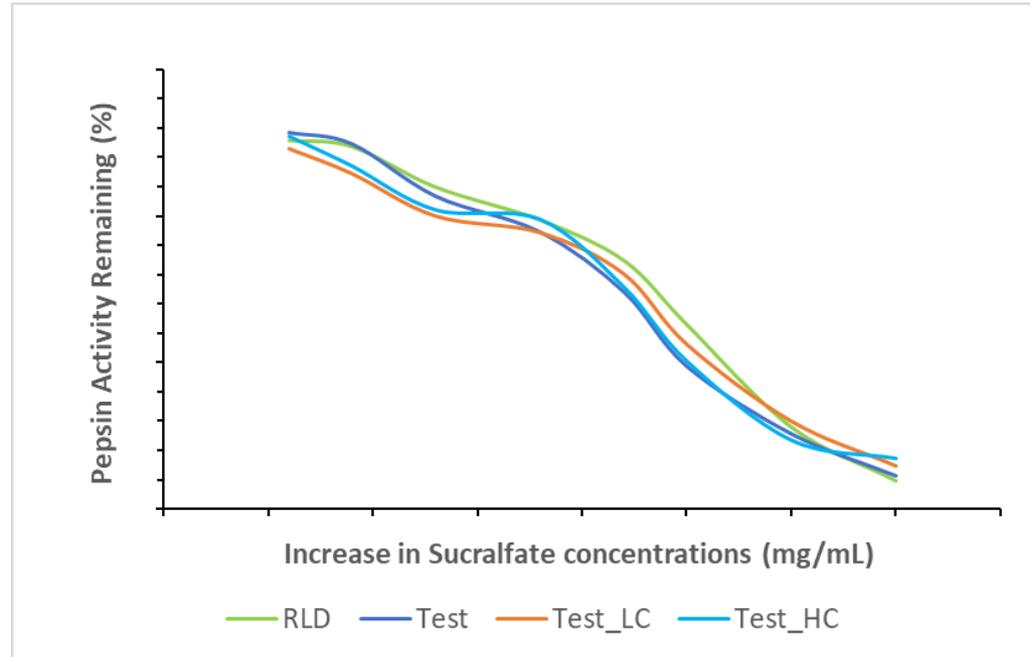


90% CI of K_2 are within 80%-120%

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



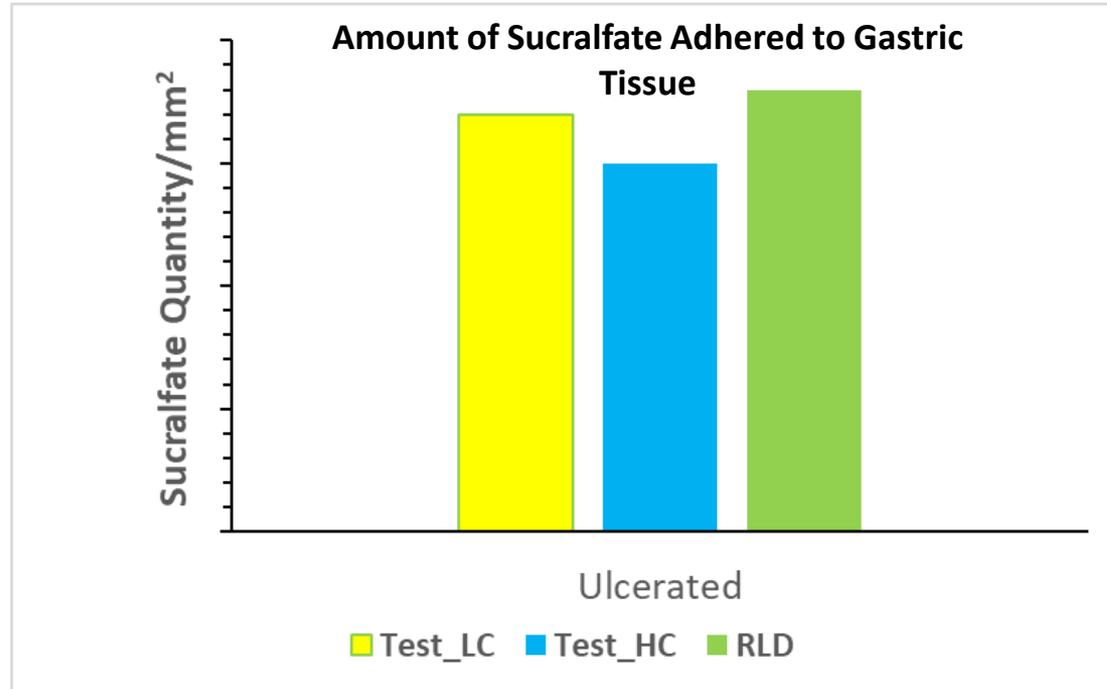
- Pepsin Activity Study



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



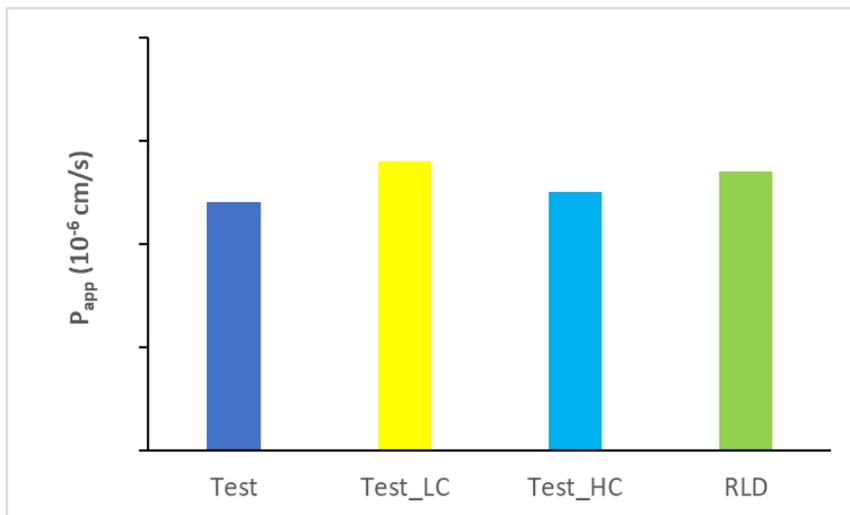
- Mucoadhesion Study



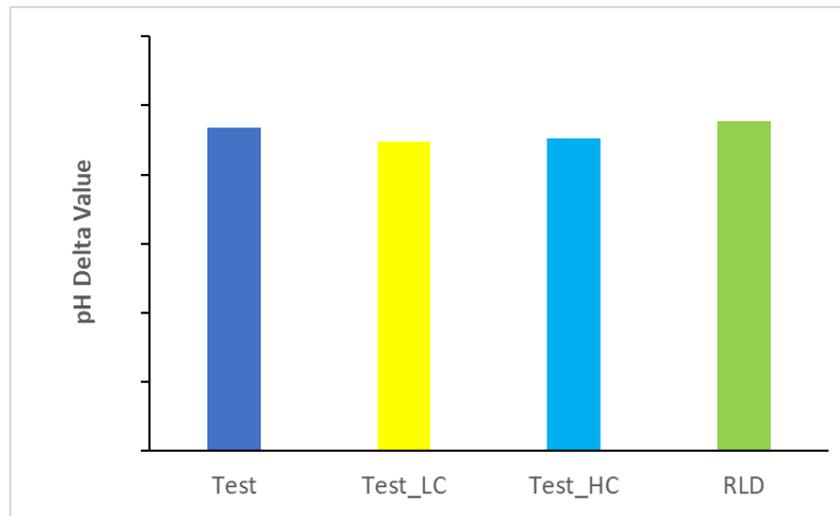
Evidence to Demonstrate BE for non Q2 Test Formulation cont'd...



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

Acknowledgements



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We Are OGD

Ask me why...

“We **monitor** the **safety** of **generic** drugs for as long as they are in the market.”

“When I reach for the medicine cabinet, I know I am safe, I am a patient, too!”





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