Q1 and Q2 Recommendations: Sucralfate Oral Suspension

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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Disclaimer

- This presentation reflects the views of the authors and should not be construed to represent FDA's views or policies.

Learning Objectives

You will learn to:

- ❑Define qualitative (Q1) and quantitative (Q2) sameness and employ best practices in determining Q1/Q2 sameness
- ❑Recognize the different scenarios where Q1/Q2 sameness is recommended for locally acting gastrointestinal (GI) drugs
- ❑Describe key case study of Q1/Q2 recommendations for locally acting GI drugs: sucralfate
- ❑Describe the rationale behind bioequvlence (BE) recommendations of sucralfate suspension

Definition of Q1 and Q2 Sameness

- Q1/Q2 is an assessment of the inactive ingredients in the proposed generic drug product compared to the inactive ingredients in the reference listed drug (RLD) where:

  Q1: the inactive ingredients are the same (qualitative sameness)

  Q2: the concentrations of the inactive ingredient are the same* (quantitative sameness)

*FDA's practice generally accept ±5% difference

Rationale of Q1 and Q2 Sameness in Oral Drug Products

- Generic oral drug products are not expected to be Q1/Q2 the same as their RLD
- In certain cases, inactive ingredients may impact either the availability of the drug at the site of action or the product performance or both

  e.g., bile salt or a surfactant that acts as an absorption enhancer in products of low permeability drugs

Determination of Q1 and Q2 Sameness

While developing an oral drug product for an abbreviated new drug application (ANDA), a firm can ensure that the product is Q1/Q2 the same as the RLD by:

- Checking the product qualitative composition in the approved labeling of the RLD
- Submitting a controlled correspondence requesting whether the proposed formulation(s) are suitable for BE approach if the product-specific guidance (PSG) includes a Q1/Q2 recommendation

Draft guidance for industry: Controlled Correspondence Related to Generic Drug Development (December 2022)

Locally Acting GI Drugs and Q1/Q2 Sameness

- Several PSGs of locally acting GI drugs products include Q1/Q2 recommendations
- The Q1/Q2 sameness in the PSGs is either:

1. Prerequisite to waive in vivo with pharmacokinetic endpoints
2. Prerequisite to waive in vivo studies with clinical endpoint
3. Combined with in vitro studies for BE determination (only BE option)

Locally acting GI Drugs Products whose PSGs Included Q1/Q2 Sameness *

Acarbose tablet	Linaclotide capsule	Rifaximin tablet
Barium sulfate suspension	Lubiprostone capsule	Sodium phosphate dibasic anhydrous & sodium phosphate monobasic monohydrate tablet
Barium sulfate paste	Miglitol tablet	
Ferric citrate tablet	Nitazoxanide tablet	Sucralfate tablet
Fidaxomicin tablet	Nitazoxanide suspension	Sucralfate suspension
Fidaxomicin for suspension	Plecanatide tablet	Vancomycin hydrochloride capsule

*As of Aug 2023

Challenge Question #1

One reason a PSG of an oral drug product to recommend Q1/Q2 sameness is :

A. As a prerequisite to waive in vivo BE studies

B. To ensure the particle size of the excipients is the same

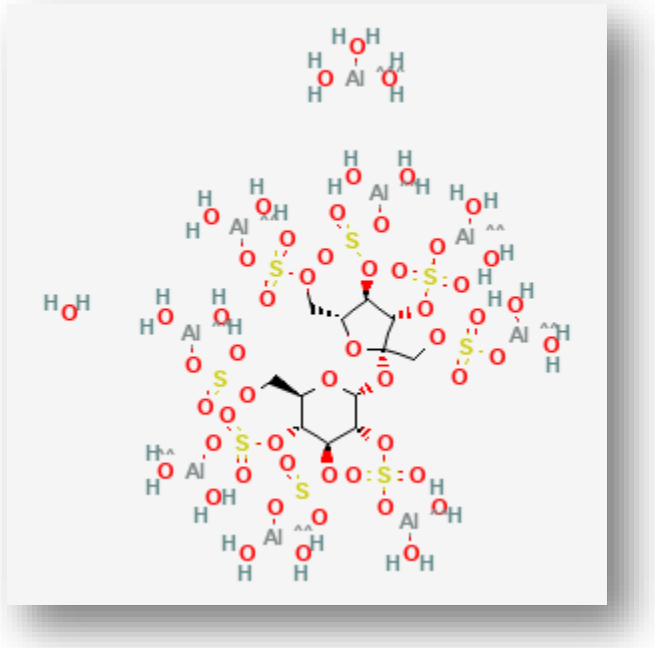
C. To encourage developing generic drug products that are the same as the RLD

Case study

Sucralfate Oral Suspension

Sucralfate

- A locally acting agent indicated in the short-term treatment of active duodenal ulcer
- Minimally absorbed from the GI tract
- Aluminum (Al) salt of sucrose octasulphate
- Available as tablet and suspension



Structure of Sucralfate

Drugs@FDA, NDA 018333 and NDA 019183, Labeling-Package insert
Sucralfate | C12H54Al9O55S - PubChem (nih.gov)

Approved Sucralfate Products in the United States

Product	Strength	Proprietary name	NDA	Approval date	Generic	Product-specific guidance
Sucralfate tablet	1 gm	Carafate	018333	10/30/1981	A070848* A074415 A215576 A215705	Recommended in 07/2014; withdrawn 12/2015, Revised 9/2019, 02/2023
Sucralfate suspension	1 gm/ 10 mL	Carafate	019183	12/16/1993	A209356* A211884 A212913	Recommended in 07/2014; withdrawn 12/2015, Revised 10/2017, 02/2023

*First generic approved for tablet was 1996 and the suspension was approved in 2019

History of BE Recommendations

Recommended in 07/2014; withdrawn 12/2015

Active ingredient: Sucralfate

Form/Route: Suspension/Oral

Recommended studies: 1 study

Type of study: Bioequivalence (BE) Study with Clinical Endpoint
Design: Randomized, double blind, parallel, three-arm, placebo-controlled in vivo
Strength: 1 gm/10 mL
Subjects: Healthy males and nonpregnant females with dyspepsia symptoms and active duodenal ulcer disease, verified at screening endoscopy.
Additional comments: Specific recommendations are provided below.

The PSGs of sucralfate products were withdrawn because:

- It was considered unethical to enroll patients who are H. pylori positive without providing standard therapy (in the placebo arm)
- The recommendation to recruit patients who are H. pylori negative would significantly limit the enrollment

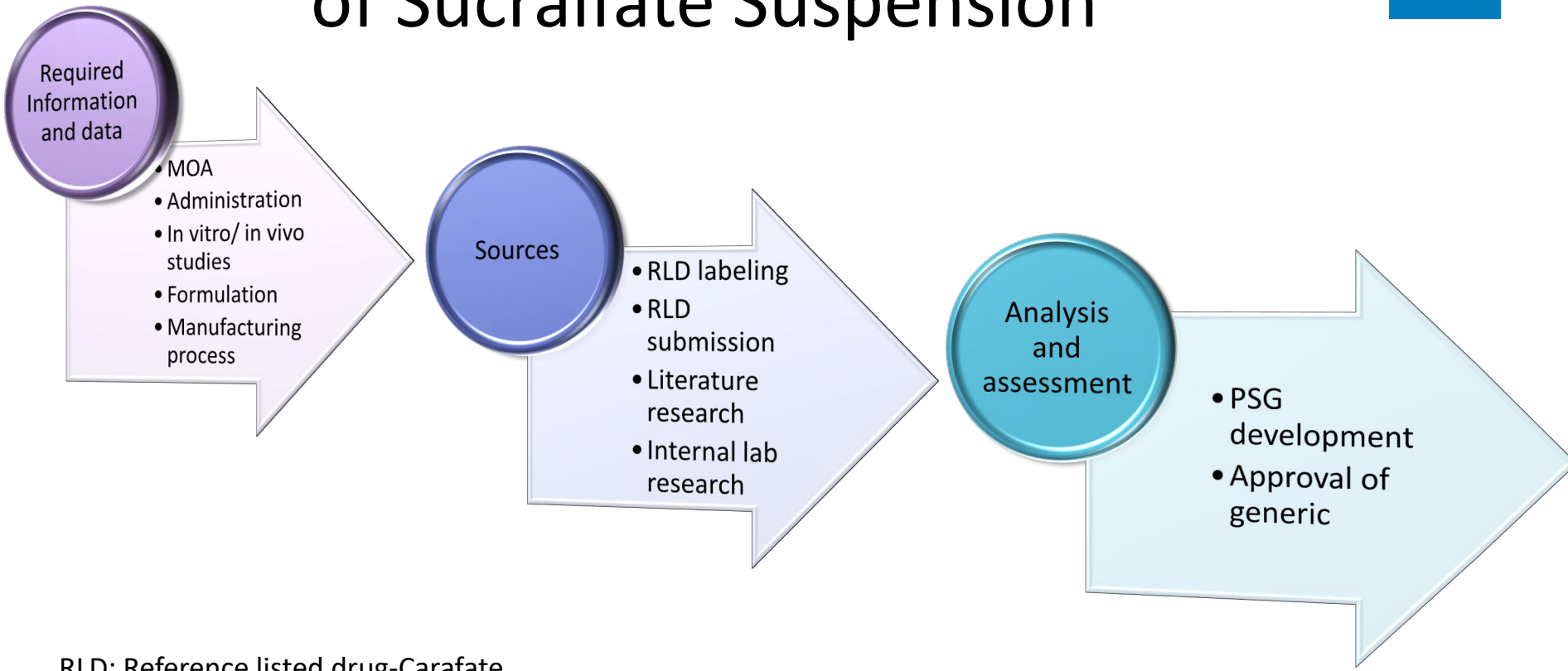
Resulted in need for development of an alternative approach for BE evaluation

Alternative In Vitro Approach

- The selection of the in vitro bioequivalence method for a locally acting drug is based on product-specific factors and a scientific understanding of the product's mechanism of action (MOA).

Lionberger, R.A. FDA Critical Path Initiatives: Opportunities for Generic Drug Development. AAPS J 10, 103–109 (2008) doi:10.1208/s12248-008-9010-2

Development of BE Recommendations of Sucralfate Suspension



RLD: Reference listed drug-Carafate

BE Recommendations of Sucralfate Suspension

1. Sameness of active pharmaceutical ingredient (API)

   Sucralfate is a complex API

2. Comparative physicochemical characterization of products

   Product attributes that impact its quality, physical stability~~,~~ and performance

3. Bioassays of products include binding studies

   In vitro studies based on the MOA of sucralfate

Q1 and Q2 sameness of Sucralfate

- In addition to sameness assessment of API and comparative in vitro testing of both the proposed test and the reference standard, the test product should be Q1 and Q2 the same as RLD.
- The recommendation of Q1/Q2 sameness with RLD applies to all inactive ingredients except for flavor or color

Challenge Question #2

Which of the following is FALSE regarding sucralfate suspension:

A. Contains a complex active pharmaceutical ingredient

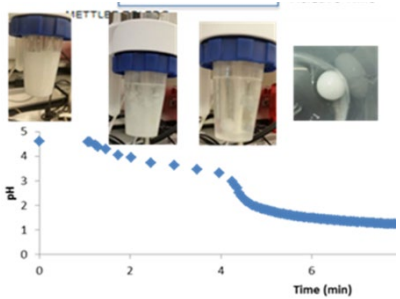
B. Is considered complex due to its route of administration

C. Its current BE recommendations include BE studies with pharmacokinetic endpoints

D. Its current BE recommendations include in vitro binding study

Evidence of the Impact of Inactive Ingredients: API

- In acidic media, sucralfate becomes charged and thus binds to proteins in the ulcer area



Acid Titration of Sucralfate API

- Sucralfate (API) aggregates and forms a paste with adhesive properties with acid

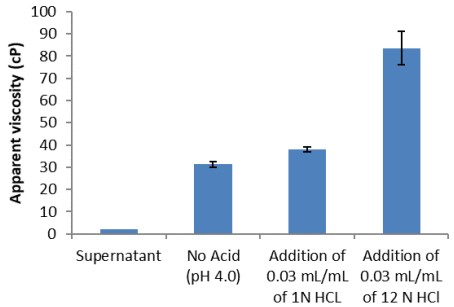
Role of the adhesive paste is not fully understood

Al-Ghabeish, et al.. In Vitro Evaluation of the Performance of a Locally Acting Gastrointestinal Drug, Sucralfate.(Poster).AAPS Annual Meeting, San Diego, CA, Nov 11-15, 2017

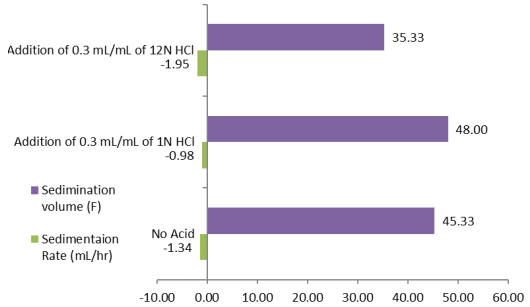
Evidence of the Impact of Inactive Ingredients: Suspension

- Sucralfate suspension doesn't form the adhesive paste in acidic media

Viscosity and sedimentation rate increase with acid addition (aggregation)



Apparent Viscosity of Sucralfate Suspension



The Sedimentation of Sucralfate Suspension

Al-Ghabeish, et al.. In Vitro Evaluation of the Performance of a Locally Acting Gastrointestinal Drug, Sucralfate.(Poster).AAPS Annual Meeting, San Diego, CA, Nov 11-15, 2017

Rationale of Q1/Q2 for Sucralfate Suspension

Both the mechanism of action of sucralfate and the impact of the excipients on the performance of sucralfate are not fully understood

Rationale of Q1/Q2 for Sucralfate Suspension

The BE determination is based on a totality of evidence approach, which involves characterizations on both the drug substance and the formulation of a proposed generic product that has the same active and inactive ingredients

Summary

- Q1/Q2 recommendation for oral drug products is considered when the inactive ingredients may impact the availability of the drug either at the site of action or the product performance or both
- For BE determination of some locally acting GI drugs, Q1/Q2 sameness can be used as a prerequisite to waive in vivo studies
- The current BE in vitro recommendations of sucralfate suspension, case study, are based on the product attributes and the mechanism of action of sucralfate
- Demonstrating BE for sucralfate suspension is based on a totality of evidence approach of a proposed generic product is Q1/Q2 same as the RLD

Questions?

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