Assessing API "Sameness"

SBIA 2022: Advancing Generic Drug Development: Translating Science to Approval

Day 2, Session 5: In Vitro Binding Study for Locally Acting GI Drug Products

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Learning Objectives

- ❑ Identify the need for demonstrating active pharmaceutical ingredient (API) sameness recommended in product specific guidances (PSGs) for complex products with complex APIs

- ❑Understand and rationalize the assessment for API sameness studies

Generic Drugs and API Sameness

Pharmaceutical Equivalence

Have the **same active ingredient**, same dosage form, strength, same route of administration under the same conditions of use

Bioequivalence

Same clinical effect and safety profile

Therapeutic Equivalence

(to RLD)

Locally Acting Gastrointestinal (GI) Drugs

➢ Complex drug products

- Due to **complex routes of delivery (locally acting)**
- Some contain **complex APIs or drug substances**:

such as polymer, heterogenous mixtures of small molecules, macromolecular complexes…

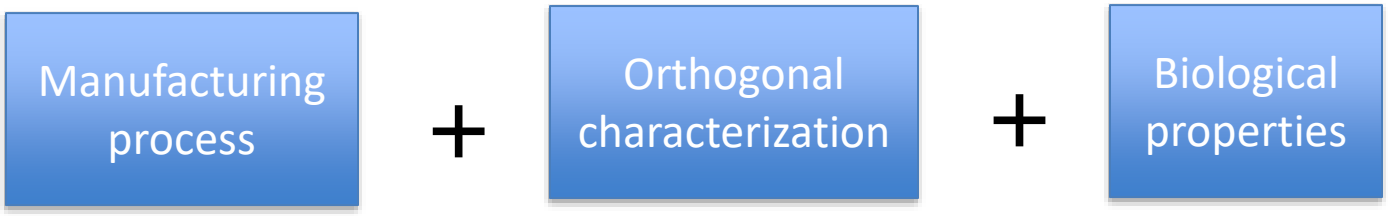
*FDA **Product-Specific Guidances** for Generic Drug Development (https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm)*

Examples of PSGs with API Sameness Recommendations for Complex APIs

PSGs for selected locally acting GI drugs	Demonstrating API Sameness	Bioequivalence recommendation
Ferric citrate tablet	Ferric citrate	Option 1 (Q1/Q2+IVRT) or option 2 (in vitro and in vivo)
Sevelamer Carbonate for oral suspension	Sevelamer Carbonate	Two in vitro studies
Sevelamer HCl tablet	Sevelamer hydrochloride	Two in vitro studies
Colesevelam hydrochloride for oral suspension	Colesevelam hydrochloride	Four in vitro binding studies
Sodium zirconium cyclosilicate suspension	sodium zirconium cyclosilicate	In vitro equilibrium/kinetic binding studies
Sucralfate tablet/suspension	Sucralfate	In vitro binding studies + Q1/Q2/Q3

Consideration in Demonstrating Complex API Sameness

The totality-of-the-evidence approach



Starting material, critical intermediates and steps, CQAs and CPPs

Composition and structure signature analysis, Physicochemical properties, impurity profile et al

Comparative biological activity analysis if needed

FDA takes these factors into consideration when developing product specific guidances (PSGs) and reviewing ANDA products with complex API

Ref: "Regulatory considerations in demonstrating complex API sameness" FDA workshop, March 2021

Challenge Question #1

Which of the following statements is NOT true?

A. FDA Approved generic drugs are therapeutically equivalent to RLD drugs.

B. ICH develops and issues new and revised product specific guidances to foster generic drug product development, submission and approval.

C. Demonstrating API sameness is often recommended in PSGs for complex products with complex APIs

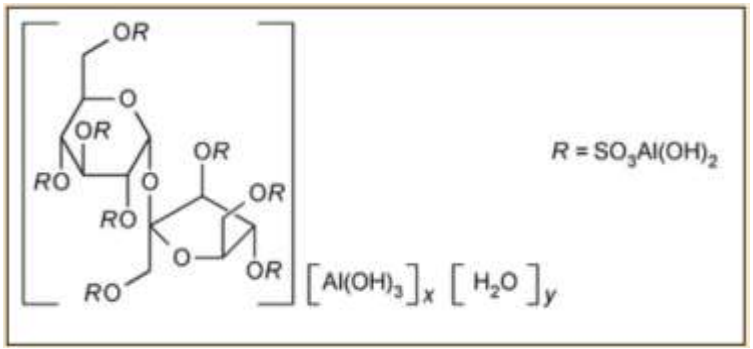
D. Totality-of-evidence approach is used in developing PSGs and reviewing ANDAs with complex API.

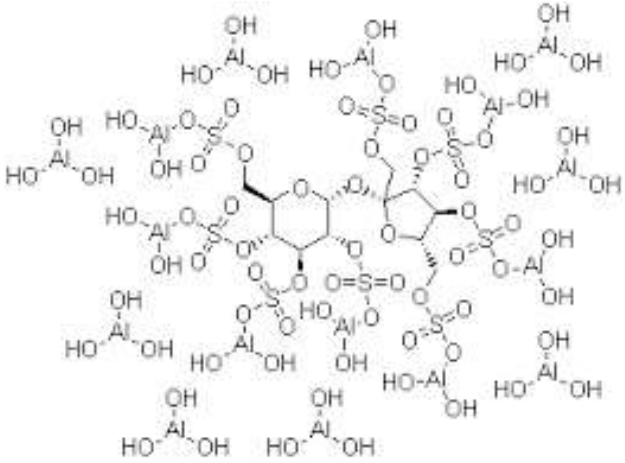
Sucralfate Oral Suspension, 1 g/ 10 mL
Considerations in Assessment of API sameness

Sucralfate Suspension

RLD: NDA 019183, CARAFATE® (sucralfate) Suspension (1g/10mL), (1993)
Indication: short-term (up to 8 weeks) treatment of active duodenal ulcer.
Mechanism of action: locally acting

DS Sucralfate USP





$Al_8(OH)_{16}(C_{12}H_{14}O_{35}S_8)[Al(OH)_3]x[H_2O]y$
in which ***x*= 8 to 10, and *y*= 22 to 31.**

PSG on Sucralfate Suspension

Recommended Jul 2014; Revised Oct 2017

Prior to Revision in Oct 2017 – In vivo BE study with clinical endpoints

Due to challenges such as enrollment of patients into in vivo BE studies, the PSG was revised on Oct 2017 to in vitro BE binding studies

Revised PSG on Sucralfate Suspension

Revised Oct 2017

To qualify for the **in vitro option** for this drug product all of the following criteria should be met:

- The Test and reference listed drug (RLD) formulations have the same active pharmaceutical ingredient (API)
- The Test and RLD formulations are qualitatively (Q1) and quantitatively (Q2) the same except the flavor/color
- Acceptable comparative physicochemical characterizations of the Test and RLD formulations
- Acceptable bioassays of the Test and RLD formulations

Note: PSG for sucralfate tablet was revised Sept 2019

PSG Recommended Characterizations for Demonstrating API Sameness

At least three batches of the Test API should be characterized to assess API sameness. The recommended characterization included but not limit to:

1) **API composition**: sucrose octasulfate and aluminum content

2) Data for C, H, S, Al by **elemental analysis** on Test API, data on C/S ratio and C/Al ratio

3) **Acid neutralizing capacity**

4) **Spectroscopic characterizations**, such as FT-IR, UV, solid state ^{27}Al NMR, DSC, TGA and PXRD.

Conducting API Sameness Studies

1) At least three batches of the **test API** should be characterized (PSG)

2) Test API vs the **extracted RLD API-** *Not feasible due to multiple insoluble components in the formulation*

3) Extracted API from test product vs extracted API from RLD product

4) Comparative analysis of test products vs RLD products (Q3 characterization)

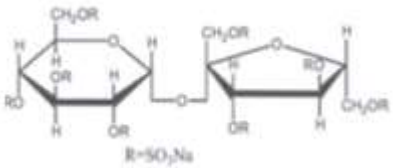
Assessing API “Sameness”

- Molecular formula are consistent to the structural information in the **labeling**

- Physicochemical properties (API composition, acid neutralizing capacity, impurity) meets **USP** tests

- Various spectroscopic analysis- Orthogonal characterization
  - **Encourage to explore other characterization techniques in addition to PSG**

Understanding Critical Manufacturing Process

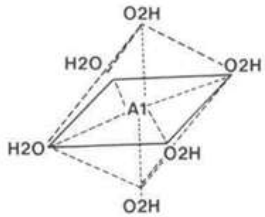


Sodium sucrose sulfate

Aluminization

Basic poly(aluminum chloride)
$[Al(OH)_2Cl]_n$

Crude sucralfate



- Aluminum species is complex in solution, depending on the basicity value ($[OH^-]$ /[Al] molar ratio);
- Aluminization reagent and step can affect the physicochemical properties of the sucralfate complex which in turn affect the protein adsorption activity (by 20-30% reported in literature).
- **Adequately characterize Al reagent and intermediate, identify critical process parameters and in-process controls**

Product Specific Guidance

Comparative Physicochemical Characterizations of the Test and RLD Formulations:

1. Comparative pH
2. Comparative specific gravity
3. Comparative viscosity profile of untreated formulation
4. Comparative change in apparent viscosity with addition of acid
5. Comparative re-dispersibility
6. Comparative acid neutralizing capacity
7. Comparative aluminum release at pH 1.2

PSG on Sucralfate Suspension

I. API "sameness"

II. Q1 and Q2 formulation

III. Comparative Physicochemical Characterizations of the Test and RLD products (Q3)

IV. Bioassays of the Test and RLD products

The totality-of-the-evidence approach

Challenge Question #2

Which of the following studies is NOT recommended in product specific guidance for Sucralfate Oral Suspension revised on Oct 2017:

A. Demonstrating API sameness

B. Comparative physicochemical characterizations of test product and RLD product

C. In vivo BE study with clinical endpoints

D. In vitro BE bioassay binding studies

Summary

- Demonstrating API sameness is often recommended in PSGs for complex drug products with complex APIs
- Other characterization techniques may be explored in addition to the PSG recommendations to ensure adequate characterization of the complex API
- Totality-of-evidence approach is generally used in demonstrating and assessing API sameness and bioequivalence studies

Closing Thought

Advocate close communications with *FDA via various channels (controlled correspondence, Pre-ANDA meetings et al)*

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