Contains Nonbinding Recommendations

Draft Guidance on Sucralfate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Sucralfate

Dosage Form; Route: Suspension; oral

Strength: 1 g/10 mL

Recommended Study: In vitro studies

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)[1] and quantitatively (Q2)[2] the same except the flavor/color.
- Acceptable comparative physicochemical characterizations of the Test and RLD formulations.
- Acceptable bioassays of the Test and RLD formulations.

I. Sameness of Active Pharmaceutical Ingredient:

Generic applicant should characterize the proposed API (Test), and demonstrate that its composition and molecular formula are consistent to the structural information in the labeling. At least three batches of the Test API should be characterized to assess API sameness. The recommended characterizations include but not limited 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 Fourier transformation Infrared spectroscopy (FT-IR), ultraviolet spectroscopy (UV), solid state ^{27}Al NMR, differential scanning calorimetry (DSC), thermogravimetric analysis (TGA) and powder X-ray diffraction (PXRD).

II. Comparative Physicochemical Characterizations of the Test and RLD Formulations:

[1] Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the reference product.
[2] Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within ±5% of those used in the reference product.

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 (time required to re-disperse, sedimentation time and volume)
6. Comparative acid neutralizing capacity
7. Comparative aluminum release at pH 1.2

III. Bioassays of the Test and RLD Formulations:

1. In vitro equilibrium binding study with human serum albumin (HSA) or bovine serum albumin (BSA)

   The acid pre-treated Test and RLD formulations should be used in the equilibrium binding study. At least eight different concentrations of HSA or BSA should be used in the study. Please consider to perform assays under conditions relevant to the in vivo physiological conditions if possible. The equivalence is based on the 90% CI of Langmuir binding constant k2 from the equilibrium binding study. Additional details on an equilibrium binding study and data analysis are available in the Guidance on Cholestyramine oral powder[3]. Please provide optimization report for the selection of all the assay conditions.

2. In vitro equilibrium binding study with bile salts

   See above for comments on the study design and data analysis.

3. In vitro kinetic binding study with bile salts

   See above for comments on the study design. This study should be conducted by incubating the acid pre-treated Test and RLD formulations for at least eight different lengths of time, with two different constant bile salt concentrations. Additional details on a kinetic binding study and data analysis are available in the Guidance on Cholestyramine oral powder. Please provide optimization report for the selection of all the assay conditions. The equivalence is based on the qualitative comparison between the Test and RLD formulations with respect to the % binding of bile salts to sucralfate.

4. In vitro enzyme (pepsin) activity study

   The acid pre-treated Test and RLD formulations should be used in the enzyme activity study and at least five different concentrations of the Test and RLD formulations should be used in the study. Please consider to perform assays under conditions relevant to the in vivo physiological conditions if possible. Please provide optimization report for the selection of all the assay conditions. The equivalence is based on the qualitative

[3] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM273910.pdf

comparison between the Test and RLD formulations with respect to the % decrease in pepsin activity.