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Draft Guidance on Sucralfate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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: Tablet; oral

Strength: 1 g

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 color.
- Acceptable comparative physicochemical characterizations of the Test and RLD formulations.
- Acceptable disintegration time for the Test formulation as compared to the RLD
- 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).

[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.

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

1. Comparative acid neutralizing capacity
2. Comparative aluminum release at pH 1.2

III. Comparative Disintegration Time

Comparative disintegration time of the Test and RLD formulations (e.g., in 600 mL of water)

IV. Bioassays of the Test and RLD Formulations:

Disintegrate the tablet formulation in a small amount of water before conducting the following four bioassays.

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

   The aqueous suspension of disintegrated tablet of Test and RLD products should be treated with acid prior to the equilibrium binding study. At least eight different concentrations of HSA or BSA should be used in the study. Consider performing 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. 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. The aqueous suspension of disintegrated tablet of Test and RLD products should be treated with acid prior to the study. The study should include 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. 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 aqueous suspension of disintegrated tablet of Test and RLD products should be treated with acid prior to the enzyme activity study and at least five different concentrations for the Test and RLD products should be used in the study. Consider performing assays under conditions relevant to the in vivo physiological conditions if

possible. 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 % decrease in pepsin activity.