Contains Nonbinding Recommendations

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Draft Guidance on Sucralfate

February 2023

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Active Ingredient: Sucralfate

Dosage Form; Route: Tablet; oral

Strength: 1 gm

Recommended Studies: One sameness of API study, one comparative physicochemical characterization study, and four bioassay studies

The proposed test drug product should be qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the Reference Listed Drug (RLD). Bioequivalence may be established based on sameness assessment of active pharmaceutical ingredient (API) and comparative in vitro testing of both the test and reference products include:

1. Sameness of API:

   Applicants should characterize the API of test product and demonstrate that its composition and molecular formula are consistent to the structural information in the RLD labeling. At least three batches of the API should be characterized to assess API sameness. The recommended characterizations include but are not limited to:

   a. API composition: sucrose octasulfate and aluminum content
   b. Elemental analysis for carbon, hydrogen, sulfur, and aluminum on test API including assessment of carbon/sulfur and carbon/Al ratios
   c. Acid neutralizing capacity
   d. Spectroscopic characterizations, such as Fourier transformation infrared spectroscopy, ultraviolet spectroscopy, solid state ^{27}aluminum nuclear magnetic

[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.

resonance, differential scanning calorimetry, thermogravimetric analysis and powder X-ray diffraction

2. Comparative Physicochemical Characterizations of the Test and Reference Products:
    a. Comparative acid neutralizing capacity
    b. Comparative disintegration time of the test and reference products (e.g., in 600 mL of water)
    c. Comparative aluminum release at pH 1.2 (Refer to the **Dissolution test method and sampling times** below)

3. Bioassays of the Test and Reference Products:

Disintegrate the tablet formulation of test and reference products in a small amount of water and treat the aqueous dispersion of disintegrated tablet with acid before conducting the following four bioassays. If possible, perform the bioassay studies under conditions relevant to the in vivo physiological conditions. Provide the method development and validation report for the studies.

a. In vitro equilibrium binding study with bile salts:
The equilibrium binding study is considered as the pivotal bioequivalence study. This study should be conducted by incubating the acid pretreated dispersion of each test and reference product with at least eight different concentrations of bile salts. The eight concentrations should be spaced along the spectrum until the maximum binding is clearly established. Each binding study should be repeated at least 12 times. In addition, data should demonstrate that the length of time selected for incubation with bile salt-containing medium yields maximum binding.

Bioequivalence based on (90% CI): Langmuir binding constant (k2) from the equilibrium binding study

b. In vitro kinetic binding study with bile salts:
The kinetic binding study should be used to support the pivotal equilibrium binding study. The kinetic binding study should be conducted by incubating the test and reference products for at least eight different lengths of time, with two different constant bile salt concentrations. Times should be selected along the spectrum until the maximum binding is clearly established. Each binding study should be repeated at least 12 times.

Equivalence based on: The quantitative comparison between the test and reference formulations with respect to the percent binding of bile salts to sucralfate

Additional details on the study design of equilibrium and kinetic binding study with bile salts are available in the most recent version of the FDA product-specific guidance on *Cholestyramine Oral Powder* (NDAs 016640; 019669).[a]

c. In vitro equilibrium binding study with human serum albumin or bovine serum albumin:
See in vitro equilibrium binding study with bile salts for comments on the study design and data analysis.

d. In vitro enzyme (pepsin) activity study:
The study should include at least five different concentrations of acid pretreated dispersion of each test and reference product in the study.

Equivalence based on: The quantitative comparison between the test and reference products with respect to the percent decrease in pepsin activity

Dissolution test method and sampling times: The dissolution information for this drug product can be found in the FDA's Dissolution Methods database, http://www.accessdata.fda.gov/scripts/cder/dissolution/. Conduct comparative dissolution testing on 12 dosage units for each of the test and reference products. Specifications will be determined upon evaluation of the Abbreviated New Drug Application (ANDA).

Revision History: Recommended July 2014; Withdrawn December 2015; Revised September 2019, February 2023

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[a] For the most recent version of a product-specific guidance, check the FDA product-specific guidance web page at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.