

*Contains Nonbinding Recommendations*  
**Draft Guidance on Sucroferric Oxyhydroxide**

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

**Active Ingredient:** Sucroferric oxyhydroxide

**Form Form; Route:** Tablet, chewable; oral

**Recommended Studies:** Two in vitro studies

1. Type of study: In vitro equilibrium binding study  
Design: At pH 1.2, 3.0, and 7.5  
Strength: 500 mg  
Subjects: Not applicable (N/A)  
Additional comments: The equilibrium binding study is considered the pivotal bioequivalence (BE) study. The equilibrium binding study should be conducted on whole tablets. This study should be conducted by incubating the test and reference products with at least eight different concentrations of phosphate, at pH 1.2, 3.0, and 7.5. The maximum phosphate binding region (attainment of plateau) should be clearly demonstrated prior to selecting these eight phosphate concentrations for the study. Phosphate concentrations should be spaced along the spectrum until the maximum binding is clearly established. All incubations should be conducted at 37°C. Wait at least one hour until equilibrium pH has been reached. The pH should be monitored and adjusted every 15 minutes if needed. Each binding study should be repeated at least 12 times. In addition, data should be provided demonstrating that the length of time selected for incubation with the phosphate-containing medium yields maximum binding.

For additional details on a similar equilibrium binding study design, see the lanthanum carbonate tablet/oral and chewable tablets/oral and sevelamer hydrochloride tablet/oral draft guidances. Also see Swearingen, et al., "Determination of the Binding Parameter Constants for Renagel® Using the Langmuir Approximation at Various pH Values by Ion Chromatography," *J. Pharm. Biomedical Anal.*, 29 (2002), pp. 195-201.

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2. Type of study: In vitro kinetic binding study  
Design: At pH 1.2, 3.0, and 7.5  
Strength: 500 mg  
Subjects: N/A  
Additional comments: The kinetic binding study should be used to support the pivotal equilibrium binding study. For the kinetic study, the three following phosphate concentrations should be used to incubate whole tablets: the lowest and highest concentrations used in the corresponding equilibrium binding study, and the mid

concentration of approximately 50% of the highest concentration used. Furthermore, the study should be conducted at pH 1.2, 3.0, and 7.5. Sucroferric oxyhydroxide-phosphate binding should be monitored as a function of time. At least 8 time points should be chosen up to 24 hours that adequately address binding under each condition. All incubations should be conducted at 37°C under constant gentle shaking, and each binding study should be repeated at least 12 times.

For additional details on a similar equilibrium binding study design, see the lanthanum carbonate tablet/oral and chewable tablets/oral and sevelamer hydrochloride tablet/oral draft guidances. Also see Swearingen, et al., "Determination of the Binding Parameter Constants for Renagel® Using the Langmuir Approximation at Various pH Values by Ion Chromatography," *J. Pharm. Biomedical Anal.*, 29 (2002), pp. 195-201.

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**Analytes to measure (in appropriate biological fluid):** Unbound phosphate in filtrate (to calculate phosphate bound to sucroferric oxyhydroxide).

For the in vitro equilibrium binding study, the Langmuir binding constants  $k_1$  and  $k_2$  should be determined in the equilibrium binding study. The test/reference ratio should be calculated for  $k_1$ . The 90% confidence interval (CI) should be calculated for  $k_2$  with the acceptance criteria of 80% to 120%.

For the in vitro kinetic binding study, the test/reference bound phosphate ratios at the various times should be compared but not subjected to the 90% CI criteria.

**Bioequivalence based on (90% CI):** The Langmuir binding constant  $k_2$  from the equilibrium binding study.

**Waiver request of in vivo testing:** N/A

**Dissolution test method and sampling times:** The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods website available to the public at the following location: <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).