

*Contains Nonbinding Recommendations*

*Draft – Not for Implementation*

## **Draft Guidance on Ferric Oxyhydroxide**

**September 2021**

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This guidance, which interprets the Agency’s regulations on bioequivalence at 21 CFR part 320, provides product-specific recommendations on, among other things, the design of bioequivalence studies to support abbreviated new drug applications (ANDAs) for the referenced drug product. FDA is publishing this guidance to further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval for generic versions of this product.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in FDA guidances means that something is suggested or recommended, but not required.

In March 2015, FDA issued a draft product-specific guidance for industry on generic ferric oxyhydroxide oral chewable tablet (previously titled “Draft Guidance for Sucroferric Oxyhydroxide”). We are now issuing revised draft guidance for industry that replaces the previously issued guidance.

**Active Ingredient:** Ferric oxyhydroxide

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

**Recommended Studies:** Two in vitro studies

1. Type of study: In vitro equilibrium binding study  
Design: At pH 3.0 and 7.5  
Strength: EQ 500 mg Iron  
Subjects: Not applicable  
Additional comments: The equilibrium binding study is considered the pivotal bioequivalence (BE) study. The equilibrium binding study should be conducted on whole tablets. The tablets should be used directly without any acid pre-treatment. This study should be conducted by incubating the test and reference products with at least eight different concentrations of phosphate, at pH 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 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 3.0 and 7.5

Strength: EQ 500 mg Iron

Subjects: Not applicable

Additional comments: The kinetic binding study should be used to support the pivotal equilibrium binding study. The kinetic binding study should be conducted on whole tablets. The tablets should be used directly without any acid pre-treatment. 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 3.0 and 7.5. Ferric 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 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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**Analyte to measure:** Unbound phosphate in filtrate (to calculate phosphate bound to ferric 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 to 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 to 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:** Not applicable.

**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 each of all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application.

**Revision History:** Recommended March 2015; Revised September 2021

**Unique Agency Identifier:** PSG\_205109