

## **Draft Guidance on Ferric Citrate**

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

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

This draft guidance provides recommendations for the development of a generic drug product, ferric citrate tablets, using ferric citrate as the active pharmaceutical ingredient (API). First, FDA provides recommendations for demonstrating API sameness. Second, FDA provides recommendations for demonstrating bioequivalence of this product.

### **Recommendations for demonstrating API sameness:**

The API, ferric citrate, is a relatively complex drug substance. Sameness of ferric citrate can be established based on comparative physico-chemical characterizations. The sponsor is advised to perform side-by-side comparative testing using the Test API and the API from the RLD product. At least three batches of the Test API and at least three batches of the extracted RLD (Reference) API should be characterized to assess API sameness. Based on the data generated from the characterization, the sponsor should define and prove the chemical structure and molecular formula of the Test API in comparison to the Reference API.

### **Recommendations for demonstrating bioequivalence:**

**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: Eq 210 mg iron  
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, chewable tablet/oral, and the 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: Eq 210 mg iron  
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. Ferric citrate-phosphate binding should be monitored as a function of time. At least eight 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, 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 ferric citrate).

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 should be calculated for  $k_2$ , with 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% confidence interval 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 Web site, 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 flavors of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).