Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Ferric Citrate

August 2021

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

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 June 2020, FDA issued a draft product-specific guidance for industry on generic ferric citrate. We are now issuing revised draft guidance for industry that replaces the previously issued guidance.

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This draft guidance provides recommendations for the development of a generic drug product, ferric citrate tablets, using ferric citrate as the active pharmaceutical ingredient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 (BE) of this product.

Recommendations for demonstrating API sameness:

Sameness of ferric citrate can be established based on comparative physico-chemical characterizations including, but not limited to, (i) oxidation state of the iron in API, (ii) the ratio of ferric iron to citrate, (iii) elemental analysis data, and (iv) spectroscopic data such as high resolution mass spectroscopy, Mössbauer spectroscopy and x-ray powder diffraction. The

sponsor is advised to perform side-by-side comparative testing using the test API and the API from the reference listed drug (RLD) product. A minimum of three batches of the test API and three batches of the extracted RLD (reference) API should be characterized to assess API sameness. Based on the data generated from the characterization, the applicant 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 options: Option 1 or Option 2

I. Option 1:

If the test product formulations are qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the reference listed drug (RLD) in terms of inactive ingredients, then bioequivalence (BE) of the test product with respect to the reference product may be established using an in vitro drug release testing based BE approach.

Bioequivalence based on: Acceptable comparative in vitro drug release tests should be provided for 12 tablets each of the test and reference standard (RS) products. The tests should be performed in the following media: 0.1N HCl, pH 4.5 buffer and pH 6.8 buffer. An f2 test should be performed using mean profiles to assure comparable test and reference product drug release under a range of pH conditions. The f2 test comparing test vs reference in each media should be 50 or greater. Note that the f2 test is not necessary when both test and reference dissolve 85% or more in 15 minutes or less. The methodology used for in vitro drug release testing should be able to discriminate the effect of formulation and manufacturing process variability in the production of the test formulation[3].

II. Option 2:

Recommended Studies: Two in vitro phosphate binding studies and one in vivo BE study with clinical endpoint

1. Type of study: In vitro equilibrium binding study
   Design: At pH 3.0 and 7.5
   Strength: EQ 210 mg iron
   Subjects: Not applicable
   Additional comments:

[1] Q1 (qualitative sameness) means that the test product uses the same inactive ingredient(s) as the RLD product.
[2] Q2 (quantitative sameness) means that the concentrations of the inactive ingredient(s) used in the test product are within ±5% of those used in the RLD product.
[3] Please note that, an in vitro release test (IVRT) method used as part of the quality control specifications may and/or can ultimately be different than the IVRT method developed to support bioequivalence determination and will be assessed at the time of review of the ANDA.

1) 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 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.

2) 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.

2. Type of study: In vitro kinetic binding study
Design: At pH 3.0 and 7.5
Strength: EQ 210 mg iron
Subjects: Not applicable
Additional comments:

1) The kinetic binding study should be used to support the 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 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.

3. Type of study: In vivo BE study with clinical endpoint
Design: Randomized, double blind, parallel, three arm, placebo-controlled in vivo
Strength: EQ 210 mg iron
Subjects: Male and female (nonpregnant and nonlactating) subjects with chronic kidney disease not on dialysis (CKD-NDD)
Additional comments:

1) After a pre-treatment screening period, subjects are randomized to receive test reference (RLD), or placebo products one tablet orally three times a day with meals for 28 days. To establish bioequivalence, the 90% confidence interval of the test/reference ratio of the proportion of subjects with an increase in Hgb of ≥

1.0 g/dL from baseline to week 4 should be contained within [0.80, 1.25], using the per protocol (PP) population. A placebo control arm is recommended to demonstrate that the test product and RLD are active and as a parameter that the study is sufficiently sensitive to detect differences between products using the modified intent to treat (MITT) population. MITT population includes all randomized subjects who use at least one dose of product.

2) Primary Endpoint: Proportion of subjects with treatment success (where success is defined as an increase in Hgb of ≥ 1.0 g/dL from baseline at week 4). Mean changes in iron parameters such as TSAT and ferritin should be compared between products at baseline and at week 4.

3) Screening: A screening period (up to 14 days prior to randomization) is recommended to assess study eligibility and baseline measures.

4) Inclusion Criteria:
   a. Male and non-pregnant (negative serum pregnancy test for women of child-bearing potential), not-lactating female aged > 18 and < 65 years with a Stage 3-5 CKD-NDD with eGFR < 60 mL/min at screening.
   b. Hgb ≥ 9.0 g/dL and <12 g/dL at screening.
   c. Serum ferritin ≤ 300 ng/mL and TSAT ≤ 30% at screening.
   d. Willing and able to give written informed consent.

5) Exclusion Criteria:
   a. Serum phosphorus level at screening < 3.5 mg/dL.
   b. Symptomatic gastrointestinal bleeding or inflammatory bowel disease within 12 weeks prior to screening.
   c. Acute renal insufficiency or requirement for dialysis within 12 weeks prior to randomization.
   d. Blood transfusion or IV iron administration or ESA administration within 4 weeks prior to screening.
   e. Infection requires oral or IV antibiotic use within 2 weeks.
   f. Anemia other than iron deficiency or CKD.
   g. Known allergic reactions to oral or IV iron treatment or any of the excipients.
   h. Liver enzymes (aspartate aminotransferase [AST] or alanine aminotransferase [ALT]) >3 times upper limit of normal (ULN) at Screening.
   i. History of iron overload syndromes, such as hemochromatosis.
   j. Active drug or alcohol dependence or abuse within the 12 months prior to Screening.
   k. Malignancy.
   l. Previous intolerance to oral ferric citrate.
   m. Psychiatric disorder that interferes with the subject's ability to comply with the study protocol.

n. Planned surgery or hospitalization (anticipated to last > 72 hours) during the study.
o. Any other medical condition that, in the opinion of the Investigator, renders the subject unable to or unlikely to complete the study or that would interfere with optimal participation in the study or produce significant risk to the subject.
p. Inability to cooperate with study personnel.

6) Blood Tests: at baseline and weekly
   a. A complete blood count: Hgb, Hct, RBC, WBC and platelet counts.
   b. Complete chemistry profile including liver function tests and serum albumin.
   c. Iron parameters: ferritin, serum iron, TIBC, TSAT, UIBC.
   d. Phosphorus level.
   e. Pregnancy test at screening and the end of study.

7) Restricted Medications and Treatments: Use of other oral or IV iron, ESAs, blood transfusion or phosphate binders will not be permitted during the study.

8) Concomitant Medications Use: Separate concomitant administration of this product and other drugs by at least 2 hours to minimize any potential drug interactions.

9) Discontinuation from Study:
   a. Other illness, medical event or hospitalization necessitating study drug discontinuation.
   b. Investigator's discretion for the best interest of the patient.
   c. Serum phosphorus < 2.0 mg/dL.
   d. Rapid increase in iron storage parameters (i.e., TSAT ≥ 70% or ferritin ≥ 700 ng/mL).
   e. Hgb < 9 g/dL for two consecutive visits at least 7 days apart. For those subjects discontinued due to lack of treatment effect should be identified and included for the bioequivalence evaluation.

Subjects should be advised of the risks to children due to accidental ingestion and to keep the product out of the reach of children.

Analyte to measure: 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 and clinical endpoint of the in vivo BE study.

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 September 2015; Revised June 2020, August 2021

Unique Agency Identifier: PSG_205874