Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Ferric Derisomaltose

February 2024

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredient:	Ferric derisomaltose
Dosage Form:	Solution
Route:	Intravenous
Strengths:	100 mg/mL (100 mg/mL), 500 mg/5 mL (100 mg/mL), 1 gm/10 mL (100 mg/mL)
Recommended Studies:	One in vivo bioequivalence study with pharmacokinetic endpoints, one in vitro bioequivalence study, and supportive comparative characterization studies

To demonstrate bioequivalence by the studies recommended in this guidance, the test product should be qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the reference listed drug (RLD).

One in vivo bioequivalence study with pharmacokinetic endpoints:

1. Type of study: Fasting
   Design: Single-dose parallel
   Strength: 1 gm/10 mL (100 mg/mL)
   Subjects: Adult patients with iron deficiency anemia who have intolerance or had unsatisfactory response to oral iron and/or non-hemodialysis dependent chronic kidney disease

[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 concentrations of the inactive ingredient(s) used in the test product are within ±5% of those used in the RLD product.

Additional comments:

a. The products should be diluted with 0.9% Sodium Chloride Injection, USP and administered via intravenous infusion over 20 minutes. The RLD labeling instructions on preparation and administration should be followed in pharmacokinetic bioequivalence studies and the same method should be utilized for all patients within the study to reduce pharmacokinetic variability.
b. Study subjects should have prescriptions for treatment with ferric derisomaltose injections. Inclusion criteria should include at least: (1) males and non-pregnant females weighting 50 kg or more; (2) Hemoglobin ≤11 g/dL and either of the following: (a) transferrin saturation (TSAT) <20%, and s-ferritin <100 ng/mL for those with intolerance or unsatisfactory response to oral iron or (b) s-ferritin ≤100ng/mL (or ≤300 ng/mL if TSAT ≤30%) for those with non-hemodialysis dependent chronic kidney disease. Exclusion criteria should include at least: Patients with significant comorbidities or expected changes in concomitant medications that can potentially affect the pharmacokinetics of ferric derisomaltose.
c. Monitor for signs and symptoms of hypersensitivity during and after ferric derisomaltose administration for at least 30 minutes and until clinically stable following completion of the infusion.
d. Applicants may select either option below on analyte(s) to measure and criterion for assessing bioequivalence of the pharmacokinetic study.

Option 1: **Analytes to measure:** Ferric derisomaltose-associated iron in serum

Bioequivalence based on (90% CI): Ferric derisomaltose-associated iron in serum

OR

Option 2: **Analytes to measure:** Measure each of the following:

1. Total iron in serum
2. Transferrin-bound iron in serum

Bioequivalence based on (90% CI):

1. Maximum value of the difference in concentration between Total iron and Transferrin-bound iron over all time points measured; and
2. Difference in AUC between Total iron and Transferrin-bound iron*

*AUC of Total iron and AUC of Transferrin-bound iron should be calculated separately to maximize the number of data points used in cases of missing data in the transferrin-bound iron and total iron concentration-time profiles. In addition, baseline correction of Total iron and Transferrin-bound iron is unnecessary.

One in vitro bioequivalence study with particle size distribution endpoints:

1. Type of study: Particle size distribution
   Design: In vitro testing on at least three batches of both test[3] and reference standard (RS) products
   Strength: 1 gm/10 mL (100 mg/mL)[3]
   Additional comments: The sample preparation method and selected particle sizing methodology should be adequately optimized and validated to demonstrate the adequacy of the selected method in accurately and reliably identifying and measuring the size of the drug particles. Applicant should perform size characterization at different dilution conditions as part of method development to demonstrate the impact of dilution. Full particle size distribution profiles representative of all test product and RS product batches tested should be submitted as supporting information.

Parameters to measure: Z-average size and polydispersity index (PDI) or D_{50} and SPAN $[(D_{90}-D_{10})/D_{50}]$, as appropriate

Bioequivalence based on (95% upper confidence bound): Z-average and PDI or D_{50} and SPAN using the population bioequivalence (PBE) statistical approach. Applicants should provide no less than 10 datasets from three batches each of the test and RS products to be used in the PBE analysis. For additional information on PBE statistical analysis, refer to the most recent version of the FDA product-specific guidance on *Budesonide Inhalation Suspension* (NDA 020929).[a]

Comparative characterization studies:

Comparative physicochemical characterization of the test product and the RS product should be performed on a minimum of three batches of the test product[4] and three batches of the RS product using orthogonal analytical methods, and should include, but not limited to, the following:

a. Iron core characterization: core size and morphology, crystalline structure, iron environment, magnetic properties, Fe(III) to Fe(II) reduction potential, reduction kinetic and Fe(II) content.
b. Carbohydrate shell characterization: composition of carbohydrate shell.
c. Physicochemical properties of the drug product: particle size and morphology, surface properties, colloid molecular size,[5] interactions between iron core and the carbohydrate shell, stoichiometric ratios of iron, derisomaltose, citrate, and other relevant components.

[3] Testing of a strength(s) other than the designated RS strength, or a portion of the strength (i.e., part of a vial), and waiving of other strengths may be acceptable. Justification may include, but is not limited to, why testing of another strength(s), or portion of a, is representative of the designated RS strength.
[4] The applicant should demonstrate that all test batches used for in vitro characterizations and bioequivalence studies are manufactured using a process reflective of the proposed commercial scale manufacturing process. At least one of these test batches should be produced by the commercial scale process and used in the in vitro comparative characterization studies and in vitro and in vivo bioequivalence studies.
[5] The colloid molecular size can be evaluated by size exclusion chromatography (SEC).

d. Labile iron determination under physiologically relevant conditions: The tests can be performed with in vitro haemodialysis system,[6] the catalytic bleomycin assay of spiked human serum samples,[6,7] the spectrophotometric measurement of Fe reduction, chelatable iron assay[8] or other methods that are validated for accuracy and precision.

Waiver request of in vivo testing: Waiver request of 100 mg/mL and 500 mg/5 mL strengths based on (i) acceptable in vivo and in vitro bioequivalence studies on the 1 gm/10 mL strength and (ii) proportionally similar formulations of the 100 mg/mL and 500 mg/5 mL to the 1 gm/10 mL strength

Dissolution test method and sampling times: Not applicable

Document History: Recommended February 2024

Unique Agency Identifier: PSG_208171

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

[6] Balakrishnan VS, *et al*. Physicochemical properties of ferumoxytol, a new intravenous iron preparation. *Eur J Clin Invest.* 2009 Jun; 39(6):489-96.

[7] Burkitt MJ, *et al*. A simple, highly sensitive and improved method for the measurement of bleomycin-detectable iron: the 'catalytic iron index' and its value in the assessment of iron status in haemochromatosis. *Clin Sci (Lond).* 2001 Mar; 100(3):239-47.

[8] Tesoro A, et al. Validated HPLC Assay for Iron Determination in Biological Matrices Based on Ferrioxamine Formation. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2005 Sep 5;823(2):177-83.