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Draft Guidance on Ferric Derisomaltose

February 2026

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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 with particle size distribution, and 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:

In vivo bioequivalence study may be conducted in either adult patients with iron deficiency anemia (Option 1) or healthy subjects (Option 2).

[1] Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the RLD.
[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.

I. Option 1: In vivo bioequivalence study conducted in adult patients with iron deficiency anemia

Type of study: In vivo bioequivalence study with pharmacokinetic endpoints
Design: Single-dose, randomized, parallel in vivo study
Strength: 1 gm/10 mL (100 mg/mL)
Dose: 1 gm
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
Additional comments:

a. The products should be diluted with 0.9% Sodium Chloride Injection, USP and administered via intravenous infusion over at least 20 minutes. The RLD labeling instructions on preparation and administration should be followed in a bioequivalence study 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, non-lactating females weighing 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 ≤100 ng/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. Applicant may select either Option A or Option B on analyte(s) to measure and criterion for assessing bioequivalence of the pharmacokinetic study.

Option A: **Analyte to measure:** Ferric derisomaltose-associated iron in serum

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

OR

Option B: **Analytes to measure:** Total iron and 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 total iron and transferrin-bound iron concentration-time profiles. Baseline correction of total iron and transferrin-bound iron is unnecessary.

II. Option 2: In vivo bioequivalence study conducted in healthy subjects

Type of study: In vivo bioequivalence study with pharmacokinetic endpoints
Design: Single-dose, randomized, in vivo study
Strength: 1 gm/10 mL (100 mg/mL)
Dose: 100 mg
Subjects: Healthy males and non-pregnant, non-lactating females
Additional comments:

a. Exclude subjects with previous hypersensitivity reaction or intolerance to iron infusion.
b. Exclude subjects with drug-induced allergic reaction, significant allergies, or past or present history of dermatologic disorder (e.g., eczema).
c. The products should be diluted with 0.9% Sodium Chloride Injection, USP and administered via intravenous infusion over at least 20 minutes. The RLD labeling instructions on preparation and administration should be followed in a bioequivalence study.
d. Subjects should be monitored for signs and symptoms of hypersensitivity during and after administration for at least 30 minutes and until clinically stable following completion of administration.
e. Applicant may select either Option A or Option B as shown in Option 1 above on analyte(s) to measure and criterion for assessing bioequivalence of the pharmacokinetic study.

One in vitro bioequivalence study with particle size distribution:

1. Type of study: Particle size distribution
Design: In vitro testing on at least three batches of both test[3] product and reference standard (RS)
Strength: 1 gm/10 mL (100 mg/mL)[3]
Additional comments: The sample preparation method and selected particle sizing methodology should be optimized and validated to demonstrate the adequacy of the selected method in 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.

[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.

Parameters to measure: Z-average 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 product and RS to be used in the PBE analysis. Refer to the section of "Recommendation Related to the PBE Statistical Analysis Procedure" in the most recent version of the FDA product-specific guidance on *Budesonide Inhalation Suspension* (NDA 020929)[a] for additional information regarding PBE computation.[4]

Waiver request of in vivo testing: Waiver request of strengths other than the tested strength based on (i) acceptable in vivo and in vitro bioequivalence studies on the tested strength and (ii) proportionally similar formulations across all the strengths.

Dissolution test method and sampling times: Not applicable

Comparative characterization studies:

Comparative physicochemical characterization of the test product and RS should be conducted with orthogonal analytical methods[5]. The comparative studies should be performed on a minimum of three batches of the test[6] product and three batches of the RS and should include[7]:

- Polynuclear ferric oxyhydroxide structure[8] characterization:
    - Size and morphology
    - Polynuclear ferric oxyhydroxide crystalline structure and environment
    - Magnetic properties

- Carbohydrate characterization:
    - Structure and composition of carbohydrate component

- Physicochemical properties of the drug product:
    - Particle size and size distribution[9]
    - Particle morphology
    - Zeta potential at pH values spanning the acidic, neutral, and basic ranges

[4] The recommendation on collecting data on different life stages is not applicable.
[5] The characterization methods should be suitable for their intended purpose. If small molecular weight components (e.g., unbound carbohydrates, free iron) interfere with the method, they should be removed. However, sample manipulation may impact colloidal properties. Therefore, characterization methods with minimal sample manipulation are recommended.
[6] The applicant should demonstrate that all test batches are manufactured using a process reflective of the proposed commercial scale manufacturing process. At least one of these test batches should be produced at the commercial scale and used in the in vitro comparative characterization studies and in vitro and in vivo bioequivalence studies.
[7] For further information on the characterization of iron carbohydrate parenteral products, see: Zou P, et al. Physicochemical characterization of iron carbohydrate colloid drug products. AAPS J. 2017 Sep; 19(5): 1359-1376.
[8] Polynuclear ferric oxyhydroxide (polynuclear iron(III)-oxyhydroxide) is considered synonymous with polynuclear ferric hydroxide (polynuclear iron(III)-hydroxide).
[9] Orthogonal analytical methods should be employed to characterize the particle size and size distribution in addition to the primary method used for the particle size distribution in the in vitro bioequivalence study.

- Molecular weight determination by size-exclusion chromatography (SEC)
- Interactions between polynuclear ferric oxyhydroxide, citrate and carbohydrate
- Stoichiometric ratios of iron, derisomaltose, citrate, sodium, chloride and relevant components before and after dialysis/ultrafiltration
- Fe(III) to Fe(II) reduction potential and reduction kinetics

- Labile iron determination under physiologically relevant conditions. The tests may be conducted using an in vitro hemodialysis system,[10] the catalytic bleomycin assay of spiked human serum samples,[10,11] the spectrophotometric measurement of Fe reduction, chelatable iron assay[12] or other methods that are adequately validated.

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

[10] Balakrishnan VS, *et al*. Physicochemical properties of ferumoxytol, a new intravenous iron preparation. *Eur J Clin Invest.* 2009 Jun; 39(6):489-96.
[11] 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.
[12] 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.