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Draft Guidance on Iron Sucrose

August 2025

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Active Ingredient:	Iron sucrose
Dosage Form:	Injectable
Route:	Intravenous
Strengths:	EQ 50 mg iron/2.5 mL (EQ 20 mg iron/mL), EQ 100 mg iron/5 mL (EQ 20 mg iron/mL), EQ 200 mg iron/10 mL (EQ 20 mg iron/mL), EQ 65 mg iron/3.25 mL (EQ 20 mg iron/mL), EQ 75 mg iron/3.75 mL (EQ 20 mg iron/mL)
Recommended Studies:	One in vivo bioequivalence study with pharmacokinetic endpoints, one in vitro bioequivalence study with particle size distribution, and comparative characterization studies

In vivo bioequivalence study with pharmacokinetic endpoints:

1. Type of study: Fasting
   Design: Single-dose, randomized in vivo study
   Strength: EQ 100 mg iron/5 mL
   Dose: 100 mg iron
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: The products should be administered undiluted as a slow intravenous injection dose of 100 mg over 5 minutes for both the test (T) and reference standard (RS) products at the same rate. The in vivo bioequivalence study may be conducted using either a parallel or a crossover design. A replicate crossover study may be an appropriate alternative to the parallel or nonreplicated crossover studies. Bioequivalence can be demonstrated by following either the approaches in Option 1 or Option 2.

Option 1: **Analytes to measure:** Iron sucrose-associated iron in serum, provided that a direct measurement of the colloidal form is achievable.

Bioequivalence based on (90% CI): Iron sucrose-associated iron in serum

Option 2: **Analytes to measure:** When direct measurement of iron sucrose-associated iron is not possible, 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.

In vitro bioequivalence study with particle size distribution:

2. Type of study: Particle size distribution
Design: In vitro testing on at least three lots of both T and RS products
Strength: EQ 100 mg iron/5 mL
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 T product and RS product batches tested should be submitted as supporting information.

Parameters to measure: Z-average and polydispersity index (PDI) or D_{50} and SPAN 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 T and RS products 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.[1]

[1] The recommendation on collecting data on different life stages is NOT applicable.

Waiver request of in vivo testing: EQ 50 mg iron/2.5 mL, EQ 65 mg iron/3.25 mL, EQ 75 mg iron/3.75 mL and EQ 200 mg iron/10 mL, based on (i) acceptable in vivo bioequivalence study and in vitro particle size distribution testing on the EQ 100 mg iron/5 mL strength; and (ii) evidence supporting identical formulation composition across all strengths

Dissolution test method and sampling times: Not applicable.

Comparative characterization studies:

The proposed T product should be qualitatively (Q1)[2] and quantitatively (Q2)[3] the same as the reference listed drug (RLD). Comparative physicochemical characterization of the T and RS products should be conducted with orthogonal analytical methods.[4] The comparative studies should be performed on a minimum of three batches of the T[5] product and three batches of the RS product and should include:[6]

- Physicochemical properties of the drug product:
  - Particle size and size distribution[7]
  - Particle morphology
  - Zeta potential at pH values spanning the acidic, neutral, and basic ranges
  - Molecular weight determination by size-exclusion chromatography (SEC)[8]
  - Interaction between polynuclear ferric oxyhydroxide core[9] and sucrose
  - Stoichiometric ratios of iron, carbohydrate, and relevant components, before and after dialysis/ultrafiltration
  - Fe(III) to Fe(II) reduction potential and reduction kinetics

- Polynuclear ferric oxyhydroxide core characterization:
  - Core size and morphology
  - Polynuclear ferric oxyhydroxide crystalline structure and environment
  - Magnetic properties

[2] Q1 (Qualitative sameness) means that the T product uses the same inactive ingredient(s) as the RLD product.
[3] Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the T product are within ±5% of those used in the RLD product.
[4] The characterization methods should be suitable for their intended purpose. If small molecular weight components (e.g., unbound sucrose, 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.
[5] The applicant should demonstrate that all T batches are manufactured using a process reflective of the proposed commercial scale manufacturing process. At least one of these T 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.
[6] 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.
[7] 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.
[8] Molecular weight determination by SEC method, as part of identification as recommended in USP Monograph on iron sucrose, may be used.
[9] For the iron core, polynuclear ferric oxyhydroxide (polynuclear iron(III)-oxyhydroxide) is considered synonymous with polynuclear ferric hydroxide (polynuclear iron(III)-hydroxide).

- 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] 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, check 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.