

Draft Guidance on Iron Dextran

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Injectable; injection

Recommended Studies: Two studies

1. Type of study: Fasting
Design: Single-dose, randomized, parallel, in vivo
Strength: 100 mg per vial (Eq 50 mg/mL iron)
Subjects: Male or female patients with iron deficiency anemia who are indicated for their initial treatment with parenteral iron dextran (who have not received parenteral iron supplementation in the past)

Additional comments: (1) Iron dextran may be administered either intravenously or intramuscularly. The sponsor should choose a route of administration and use the same route of administration for all subjects. (2) The total treatment dose of iron dextran should be given over the course of multiple days. However, only PK samples acquired after the first dose should be included in the statistical analysis. The Day 1 dose should include the same fixed-dose of iron dextran for all patients and subsequent doses (if needed) would include the remainder of the total dose calculated for each individual to achieve their total dose.

The total dose of iron dextran for each subject should be calculated according to the RLD label. All subjects should receive the same dose (maximum of 2 mL) on the first day of treatment (Day 1). The second dose (if any) should be given no earlier than 5 days after the first dose. PK sampling should be performed starting on Day 1 until the second dose is given. A sufficient number of samples should be acquired to adequately characterize the PK profile of iron dextran before the second dose is administered. No sampling is required following administration of the second dose or subsequent doses.

The sponsor should propose the Day 1 dose, along with appropriate justification for their selection, as part of the study protocol. The Day 1 dose should be divided to include a test dose (0.5 mL) of the product to be administered at a gradual rate over at least 30 seconds according to the product label and the subjects should be monitored for at least an hour. The remainder of the Day 1 dose can be administered if no adverse reactions are observed.

Analytes to measure (in appropriate biological fluid): Measure each of the following:

1. [Total Iron] in serum
2. [Transferrin-bound Iron] in serum

Bioequivalence based on (90% CI):

- Maximum value of the difference in concentration between Total Iron and Transferrin-bound Iron over all time points measured, and
- 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. There is no need to perform baseline correction of Total Iron and Transferrin-bound Iron.

2. Type of study: Particle size distribution

Design: In vitro testing on at least three batches of both test and RLD products. The three batches of the test product should be manufactured using three different lots of API. In addition, at least one of the three batches of the test product should be produced by the commercial scale process and used in the in vivo bioequivalence study.

Parameters to measure: Harmonic intensity-weighted average particle diameter and polydispersity index (PDI)

Bioequivalence based on (95% upper confidence bound): Harmonic intensity-weighted average particle diameter and PDI using the population bioequivalence statistical approach.

Applicants should perform size characterization at different dilution conditions, and use a sufficiently diluted sample to ensure that the viscosity of the measurement sample is similar to that of the dispersant.

Special considerations:

1. The proposed parenteral drug product should be qualitatively (Q1) and quantitatively (Q2) the same as the RLD. Equivalence of stoichiometric ratios of iron, dextran, sodium chloride and other relevant components need to be established.
2. Sameness in physicochemical properties needs to be established. These in vitro characterizations should be conducted on at least three batches of the test and reference products. The three batches of the test product should be manufactured using three different lots of API. In addition, at least one of the three batches of the test product should be produced by the commercial scale process and used in the in vivo bioequivalence study.

The following attributes should be included in the characterization, but sponsors are not limited to these characterization tests:

- Iron core characterizations including, but not limited to, core size determination, core morphology, ferric oxyhydroxide crystalline structure, iron core environment and Fe(II) content
- Carbohydrate shell characterization including composition of carbohydrate shell, carbohydrate-iron core interactions, and surface charge
- Comparative characterization of dextran isolated from test and reference products including average molecular weight and molecular weight distribution, degree of branching, and percentage of difference glycosidic linkages
- Physicochemical properties of iron colloid particles including stoichiometric ratios of iron, free and bound dextran and other excipients, and average molecular weight and molecular weight distribution
- Labile iron determination under physiologically relevant conditions. The tests can be performed with an in vitro hemodialysis system,¹ chelatable iron assay² or other methods that are validated for accuracy and precision.

3. For additional information regarding statistical analysis of in-vitro data, please refer to *Bioequivalence Recommendations for Specific Products: Budesonide Suspension* .

¹ Balakrishnan VS, *et al.* Physicochemical Properties of Ferumoxytol, a New Intravenous Iron Preparation. *Eur J Clin Invest.* 2009 Jun; 39(6):489-96.

² 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.