

Draft Guidance on Iron Sucrose

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

- Active ingredient:** Iron Sucrose
- Form/Route:** Injectable; Intravenous
- Recommended studies:** 2 studies

1. Type of study: Fasting
Design: Single-dose, randomized, parallel in vivo study
Strength: 100mg/5mL (Dose 100 mg)
Subjects: Healthy males and females, general population
Additional Comments: The products should be administered undiluted as a slow intravenous injection dose of 100 mg over 5 minutes.

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. In addition, there is no need to perform baseline correction of Total Iron and Transferrin-bound Iron.

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2. Type of study: Particle size distribution
Design: In vitro testing on at least three lots of both test and reference products

Parameters to measure: D₁₀, D₅₀, D₉₀

Bioequivalence based on: D50 and SPAN [i.e. (D₉₀-D₁₀)/D₅₀] or polydispersity index using the population bioequivalence statistical approach.

Waiver request of in vivo testing: 50mg/2.5mL, 65mg/3.25mL, and 200mg/10mL, based on (i) acceptable bioequivalence studies on the 100mg/5mL strength; and (ii) proportional similarity of the formulations across all strengths.

Dissolution test method and sampling times: Not Applicable.

Special Considerations:

1. The proposed parenteral drug product should be qualitatively (Q1) and quantitatively (Q2) the same as the RLD. Equivalence in the stoichiometric ratios of iron, sucrose, 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 ANDA and RLD. Attributes that should be included in the characterization are:
 - Iron core characterizations including but not limited to core size determination, iron oxide crystalline structure and iron environment.
 - Composition of carbohydrate shell and surface properties.
 - Particle morphology.
 - Labile iron determination under physiologically relevant conditions. The tests can be performed with in vitro haemodialysis system ¹, the catalytic bleomycin assay of spiked human serum samples ^{1,2}, the spectrophotometric measurement of Fe reduction, 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 \(Draft\)](#).

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 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.