

Draft Guidance on Ferumoxytol

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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: Ferumoxytol

Form/Route: Injectable; Injection

Recommended studies: 2 studies

1. Type of study: Fasting
Design: Single-dose, randomized, parallel in vivo study
Strength: 510 mg iron/17 mL (Dose: 510 mg)
Subjects: Healthy males and non-pregnant females, general population
Additional Comments: The products should be administered undiluted at a rate up to 1 mL/sec.

Analytes to measure (in appropriate biological fluid):

Ferumoxytol-associated iron in plasma or serum
Transferrin-bound iron in serum

Bioequivalence based on (90% CI): Ferumoxytol-associated iron in plasma or serum

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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: Not Applicable.

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 to the RLD. Equivalence in the stoichiometric ratios of polyglucose sorbitol carboxymethylether, iron, 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.
 - Magnetic properties.
 - Particle morphology.
 - Labile iron determination under physiologically relevant conditions. The test can be performed with ultra-filtration ¹, in vitro hemodialysis 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 \(Draft\)*](#).
4. A parallel study is recommended because the effect of the drug on baseline ferritin level may be long-lasting at the recommended dose level and such change may alter the physiological response to subsequent ferumoxytol doses. A crossover study can be an option if the ANDA applicant demonstrates that iron storage and transport has returned to baseline, i.e. transferrin-bound iron, total iron binding capacity and serum ferritin should return to baseline. Prior to using alternative study designs (e.g. crossover), the applicant should submit the study protocols for review by the Division of Bioequivalence.

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.