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Draft Guidance on Ferumoxytol

November 2023

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Active Ingredient:	Ferumoxytol
Dosage Form:	Solution
Route:	Intravenous
Strength:	EQ 510 mg iron/17 mL (EQ 30 mg iron/mL)
Recommended Studies:	One in vivo bioequivalence study with pharmacokinetic endpoints, one in vitro bioequivalence study with particle size distribution endpoints, and supportive comparative characterization studies on physicochemical properties

To be eligible for the bioequivalence studies recommended in this guidance, the test product should meet the following criteria:

1. Qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the reference listed drug (RLD). Equivalence in the stoichiometric ratios of polyglucose sorbitol carboxymethyl ether, iron, and other relevant components need to be established.

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

2. Comparable physicochemical properties should be established with orthogonal analytical methods. These in vitro characterizations should be conducted on at least three batches of the test product[3] and three batches of designated reference standard (RS) product. The attributes to be characterized should include, but are not limited to the following:
    a. Iron core characterizations including but not limited to core size determination, iron oxide crystalline structure and iron environment
    b. Composition of carbohydrate shell
    c. Magnetic properties
    d. Particle morphology
    e. Labile iron determination under physiologically relevant conditions. The test can be performed with ultra-filtration[4], in vitro hemodialysis system,[4] the catalytic bleomycin assay of spiked human serum samples[4,5] the spectrophotometric measurement of Fe reduction, or other methods that are validated for accuracy and precision.

One in vivo bioequivalence study with pharmacokinetic endpoints:

1. Type of study: Fasting
   Design: Single-dose, parallel
   Strength: EQ 510 mg iron/17 mL (EQ 30 mg iron/mL)
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments:
    a. The test[3] and RS products each should be administered as an intravenous infusion in 50-200 mL 0.9% sodium chloride injection, USP or 5% dextrose injection, USP over at least 15 minutes.
    b. 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 Abbreviated New Drug Application 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.

Analytes to measure: Ferumoxytol-associated iron in plasma; Transferrin-bound iron in plasma

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

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[3] The applicant should demonstrate that all test batches used for in vitro characterizations and bioequivalence studies are manufactured using a process reflective of the proposed commercial scale manufacturing process. At least one of these test batches should be produced by the commercial scale process and used in the in vitro comparative characterization studies and in vitro and in vivo bioequivalence studies.

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

[5] 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.

One in vitro bioequivalence study:

1. Type of study: Comparative particle size distribution
   Strength: EQ 510 mg iron/17 mL (EQ 30 mg iron/mL)
   Design: In vitro testing on at least three batches of both test[3] and RS products

Parameters to measure: Z-average size 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

Applicant should perform size characterization at different dilution conditions as part of method development to demonstrate the impact of dilution. Applicants should provide no less than 10 datasets from 3 batches each of the test and RS products to be used in the PBE analysis. For additional information on PBE statistical analysis, refer to the most recent version of the FDA product-specific guidance on *Budesonide Inhalation Suspension* (NDA 020929).[a]

Waiver request of in vivo testing: Not applicable

Dissolution test method and sampling times: Not applicable

Document History: Recommended December 2012; Revised November 2023

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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.