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Draft Guidance on Ferumoxytol

November 2024

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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, and supportive comparative characterization studies

To demonstrate bioequivalence by the studies recommended in this guidance, the test product should be qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the reference listed drug (RLD).

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

[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.

Additional comments:

a. The test[3] and reference standard (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 (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.

Option 1: **Analytes to measure:** Ferumoxytol-associated iron in plasma or serum

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

OR

Option 2: **Analytes to measure:** Measure each of the following

1. Total iron in plasma or serum
2. Transferrin-bound iron in plasma or 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.

[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.

One in vitro bioequivalence study with particle size distribution endpoints:

1. Type of study: Particle size distribution
   Design: In vitro testing on at least three batches of both test[3] and RS products
   Strength: EQ 510 mg iron/17 mL (EQ 30 mg iron/mL)
   Additional comments: The sample preparation method and selected particle sizing methodology should be adequately optimized and validated to demonstrate the adequacy of the selected method in accurately and reliably identifying and 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 test product and RS product batches tested should be submitted as supporting information.

Parameters to measure: Z-average size and polydispersity index (PDI) or D_{50} and SPAN $[(D_{90}-D_{10})/D_{50}]$, 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 test 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.[a]

Comparative characterization studies:

Comparable physicochemical characterization of the test product and the RS product should be performed on a minimum of three batches of the test product[3] and three batches of the RS product using orthogonal analytical methods, and should include, but are not limited to the following:

a. Iron core characterizations: core size and morphology, iron oxide crystalline structure, iron environment, magnetic properties.
b. Carbohydrate shell characterization: composition of carbohydrate shell.
c. Physicochemical properties of the drug product: particle size and morphology, surface properties, colloid molecular size,[4] interactions between iron core and the carbohydrate shell, stoichiometric ratios of iron, polyglucose sorbitol carboxymethylether, and other relevant components.

[4] The colloid molecular size can be evaluated by size exclusion chromatography (SEC).

d. Labile iron determination under physiologically relevant conditions. The tests can be performed with ultra-filtration,[5] in vitro hemodialysis system,[5] the catalytic bleomycin assay of spiked human serum samples[5,6] the spectrophotometric measurement of Fe reduction, chelatable iron assay[7] or other methods that are validated for accuracy and precision.

Waiver request of in vivo testing: Not applicable

Dissolution test method and sampling times: Not applicable

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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.

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

[6] 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.

[7] 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.