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Draft Guidance on Ferric Oxyhydroxide

September 2021

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

This guidance, which interprets the Agency's regulations on bioequivalence at 21 CFR part 320, provides product-specific recommendations on, among other things, the design of bioequivalence studies to support abbreviated new drug applications (ANDAs) for the referenced drug product. FDA is publishing this guidance to further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval for generic versions of this product.

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In November 2013, FDA issued a draft product-specific guidance for industry on generic ferric oxyhydroxide intravenous injectable (previously titled "Draft Guidance for Iron Sucrose"). We are now issuing revised draft guidance for industry that replaces the previously issued guidance.

Active Ingredient: Ferric oxyhydroxide

Dosage Form; Route: Injectable; intravenous

Recommended Studies: Two studies

1. Type of study: Bioequivalence (BE) study with pharmacokinetic (PK) endpoints
   Design: Single-dose, randomized in vivo study
   Strength: EQ 100 mg Iron/5 mL (Dose 100 mg)
   Subjects: Healthy males and females
   Additional comments: The products should be administered undiluted as a slow intravenous injection dose of 100 mg over 5 minutes for both the test and reference products at the same rate. The in vivo BE study may be parallel or crossover design. A replicate crossover study may be an appropriate alternative to the parallel or nonreplicated crossover study. BE can be demonstrated using method in either option 1 or option 2.

Analyte to measure (option 1): Iron in the form of colloidal ferric oxyhydroxide in serum when a direct measurement of the colloidal form is achievable

Bioequivalence based on (90% CI): Iron in ferric oxyhydroxide colloid in serum

Analytes to measure (option 2): When direct measurement of iron in the form of colloidal ferric oxyhydroxide is not possible, 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, baseline correction of Total iron and Transferrin-bound iron is unnecessary.

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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: 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 statistical approach.

Applicant should perform size characterization at different dilution conditions as part of method development to demonstrate the impact of dilution. For additional information on population bioequivalence statistical analysis, refer to the draft Guidance on Budesonide (NDA 020929).

Waiver request of in vivo testing: EQ 50 mg Iron/2.5 mL, EQ 65 mg Iron/3.25 mL, EQ 75 mg Iron/3.75 mL and EQ 200 mg Iron/10 mL, based on (i) acceptable in vivo bioequivalence study and in vitro particle size distribution testing on the EQ 100 mg Iron/5 mL 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)[1] and quantitatively (Q2)[2] the same as the reference listed drug (RLD).

2. Comparable physicochemical properties need to be established with orthogonal analytical methods. Both the drug product as is and the ferric oxyhydroxide colloid[3] particles should be characterized. These in vitro characterizations should be conducted on at least three batches of the test[4] and reference products. At least one test batch should be produced by the commercial scale process and used in the in vitro and in vivo bioequivalence study. The attributes to be characterized should include, but are not limited to the following:
    - Physicochemical properties of the drug product: particle size, surface charge (zeta-potential), colloid identification test with size-exclusion chromatography (SEC),[5] interaction between ferric oxyhydroxide and sucrose, stoichiometric ratios of iron and other excipients.
    - Ferric oxyhydroxide colloid characterization: ferric oxyhydroxide crystalline structure and environment, magnetic properties, particle morphology, Fe(III) to Fe(II) reduction potential, reduction kinetic and Fe(II) content.
    - Labile iron determination under physiologically relevant conditions. The tests can be performed with an in vitro haemodialysis system,[6] the catalytic bleomycin assay of spiked human serum samples,[6,7] the spectrophotometric measurement of Fe reduction, chelatable iron assay[8] or other methods that are validated for accuracy and precision.

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[1] Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the RLD 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 RLD product.
[3] The drug substance ferric oxyhydroxide exists as colloid. When characterizing ferric oxyhydroxide colloid, applicant should remove sucrose (the stabilizer) as much as possible to minimize its potential interference.
[4] The applicant should demonstrate that all test batches used for in vitro characterizations are manufactured using a process reflective of the proposed commercial scale manufacturing process.
[5] Identification by SEC as recommended in USP Monograph on ferric oxyhydroxide ("iron sucrose") may be used.
[6] Balakrishnan VS, et al. Physicochemical properties of ferumoxytol, a new intravenous iron preparation. *Eur J Clin Invest.* 2009 Jun;39(6):489-96.
[7] 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.
[8] 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.