

Advances in Iron Colloid Products: Quality Considerations When Conducting Comparability Studies

SBIA 2021: Advancing Generic Drug Development: Translating Science to Approval
Day 1, Session III: (Complex Injectables, Ophthalmic, and Otic Products)

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Learning Objectives

- Use comparative studies to establish and demonstrate sameness in physicochemical properties between generic and reference iron colloid drug products
- Apply quality considerations when conducting comparative studies

Outline

- Introduction to Iron Colloid Drug Products
- FDA Product-Specific Draft Guidance
- Quality Considerations When Conducting Comparability Studies
- Summary

Iron Colloid Drug Products

- Iron-based injectable drug as a treatment for iron deficiency anemia, with reference to an innovator product
- Consist of a polynuclear iron core, presented in ferric oxyhydroxide or iron oxide form, and stabilized by a carbohydrate shell
- Colloidal iron drug products contain nano-sized particles
- Mode of Action (MOA): uptake of nano-sized particles via the endocytic route (e.g. internalize via cells of the mononuclear phagocyte system (MPS)) has been suggested
- Adverse effects:
 - Hypersensitivity reactions such as anaphylaxis
 - Oxidative stress caused by low molecular weight (MW) iron species

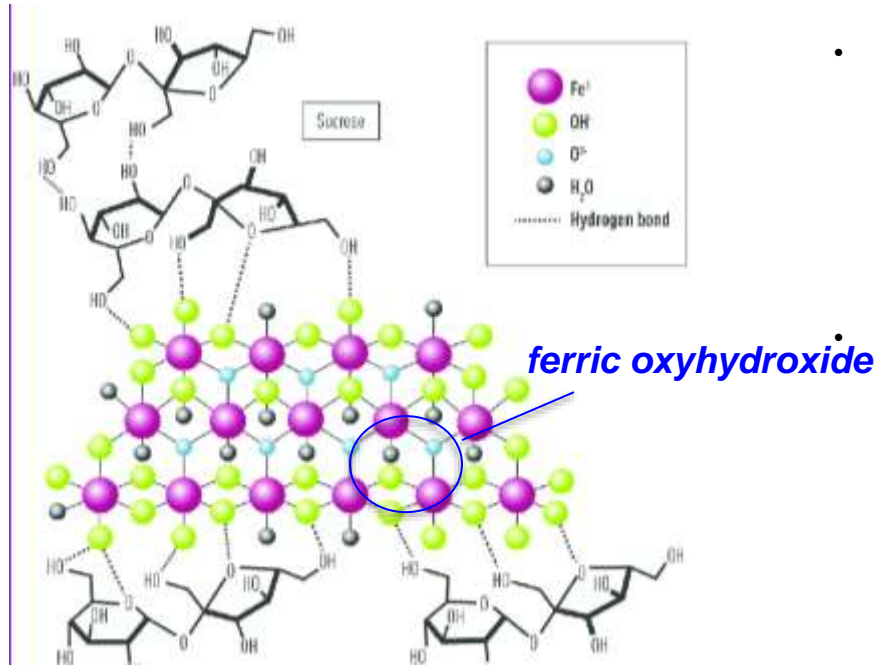
US Approved Iron Colloid Drugs

Trade Name	Pre-June 2021 Labeled non-proprietary Name	Current Applicant	Approval Date	Particle Size (DLS/TEM) ^{1, 2}
INFeD	Iron dextran	Allergan Sales	04/29/1974	12.2 nm
Dexferrum	Iron dextran	Luitpold	02/23/1996	20 nm ²
Ferrlecit	Sodium ferric gluconate	Sanofi Aventis	02/18/1999	8.6 nm
Venofer	Iron Sucrose	Luitpold	11/06/2000	8.3 nm
Feraheme	Ferumoxytol	AMAG Pharma. Inc.	06/30/2009	23.6 nm
Injectafer	Ferric carboxymaltose	Luitpold	07/25/2013	23.1nm
Monoferic	Ferric derisomaltose	Pharmacosmos	01/16/2020	9.9 nm

Generic approval: Sodium ferric gluconate Injection, 03/31/2011,
Ferumoxytol Injection, 01/15/2021

Ferric Oxyhydroxide As Active Ingredient

FDA's May 26, 2021, response to Citizen Petition Docket No. FDA-2016-P-1163:



- “We conclude instead that **ferric oxyhydroxide** is responsible for the pharmacological activity of both Velporo and Venofer, **and is thus the active ingredient** in both drug products under the regulatory definition of “active ingredient.” **Sucrose and starches are merely excipients** providing stability and processing functions, while the purported differences in certain physicochemical properties of the polynuclear ferric oxyhydroxide cores in Velporo and Venofer are a result of the manner in which ferric oxyhydroxide is formulated.” - [pg 40]

“[...] the Agency has approved numerous iron carbohydrate drug products containing ferric oxyhydroxide and one or more carbohydrates.... These drugs include INFeD (iron dextran, NDA 017441 approved on April 29, 1974); Dexferrum (iron dextran injection, NDA 040024 approved on February 23, 1996); Ferrlecit (sodium ferric gluconate complex in sucrose injection, NDA 020955 approved on February 18, 1999); and Venofer (iron sucrose, NDA 021135 approved on November 6, 2000). These products can generally be described as consisting of a ferric oxyhydroxide core, stabilized by a sugar moiety (dextran in the case of INFeD and Dexferrum, sucrose in the case of Ferrlecit and Venofer).” [pgs 7-8]

Active Ingredient Name Change for Iron Complex Products Post-June 2021



Old Name	Active Ingredient	Proprietary Name	Application No.	Market Status	Manufacturer
Sodium ferric gluconate	FERRIC OXYHYDROXIDE	FERRLECIT	<u>N020955</u>	Rx	SANOFI AVENTIS US LLC
Iron dextran	FERRIC OXYHYDROXIDE	INFED	<u>N017441</u>	Rx	ALLERGAN SALES LLC
Sodium ferric gluconate	FERRIC OXYHYDROXIDE	SODIUM FERRIC GLUCONATE COMPLEX IN SUCROSE	<u>A078215</u>	Rx	WEST-WARD PHARMACEUTICALS INTERNATIONAL LTD
Iron sucrose	FERRIC OXYHYDROXIDE	VENOFER	<u>N021135</u>	Rx	AMERICAN REGENT INC
Iron dextran	FERRIC OXYHYDROXIDE	DEXFERRUM	<u>N040024</u>	DISCN	AMERICAN REGENT INC
Iron dextran	FERRIC OXYHYDROXIDE	IRON DEXTRAN	<u>N010787</u>	DISCN	SANOFI AVENTIS US LLC
Iron dextran	FERRIC OXYHYDROXIDE	PROFERDEX	<u>N017807</u>	DISCN	NEW RIVER PHARMACEUTICALS INC

FDA Product-Specific Draft Guidance



- Two BE studies:
 - Bioequivalence (BE) study with pharmacokinetic (PK) endpoints
 - *In vitro* particle size distribution study
- Special Considerations
 - The proposed drug product should be qualitatively (Q1) and quantitatively (Q2) the same as the reference listed drug (RLD)
 - Sameness in physicochemical properties of the drug product, polynuclear iron core characterization, carbohydrate characterization, and labile iron determination

Comparability Studies Are Required



- Pharmaceutical characterization data are needed as evidence of product sameness between test and RLD to support comparative safety and efficacy
- Comprehensive side-by-side studies need to be performed on drug product, iron core, carbohydrate, and labile iron determination under physiological relevant conditions
- Differences between the products must be thoroughly investigated and appropriately justified. It may be challenging to claim sameness to the reference product if the differences are significant and detected in multiple properties
- Analytical methods need to be established and validated to determine not only similarities, but also potential differences in physicochemical properties and quality attributes
- Well-defined and controlled drug substance and drug product manufacturing process must be established to ensure consistent quality of the proposed drug product

Type of Comparability Studies

	Example of Comparability Studies	Example of Methods
Drug Product	Stoichiometric ratios of iron, free and bound carbohydrate and other relevant components Molecular weight distribution (Mw, Mn, and Mw/Mn) Particle size Labile iron	Iron and carbohydrate assay, elemental analysis (ICP-MS) SEC or GPC DLS and AFM Bleomycin or iron chelation assays
Iron core	Iron core size and morphology Crystallinity (iron crystalline structure) Iron environment Fe^{3+} to Fe^{2+} reduction potential and Fe (II) content Magnetic properties	TEM, XRD, SAXS Mossbauer, Raman, XRD, XANES Mossbauer, EPR, Raman, UV-Vis Polarography, Cerimetric VSM, SQUID
Carbohydrate shell	Carbohydrate composition and carbohydrate-Iron core interaction Surface properties Characterization of carbohydrate	FT-IR, NMR, thermal analysis, PSD under serial dilution Zeta potential, potentiometric NMR, SEC-MALS

Comparability Studies of Drug Product



- Demonstrate that all relevant critical quality attributes (CQAs) found in the proposed drug product are comparable to that of the RLD
- Quality considerations:
 - Extensive characterization of drug substance (performed either by DMF holder or in-house) is needed to ensure high quality and consistency in drug substance manufacturing process
 - For stoichiometric characterization, consider all relevant components of the drug product including C, H, Fe, Cl, Na, carbohydrate, and other organic components
 - Given the presence of potential interfering species such as unbound carbohydrate and other impurities, consider characterizing product prior and after the removal of interfering species
 - Consider comparability studies under in-use conditions per RLD labeling information (including after dilution with appropriate diluents)

Comparability Studies of Labile Iron



- Demonstrate that the fraction of labile iron found in the proposed drug product is comparable to that of the RLD
- Quality considerations:
 - Consider assessing labile iron under physiologically relevant conditions^{1, 2}
 - Justifications as how the study is designed to assess the fraction of labile iron released upon administration is needed
 - Consider using stability samples as well as samples under in-use conditions per RLD labeling information (including after dilution with appropriate diluents)

1. References provided in the FDA Guidance on Ferric Oxyhydroxide

2. Pai, A.; Meyer, D.; Bales, B.; Coterio, V.; Pai, M.; Zheng, N.; Jiang, W. Clin. Transl. Sci. **2017**, 10, 194–200.

Comparability Studies of Iron Core

- Demonstrate that iron core characteristics in the proposed drug product are comparable to that of the RLD
- Quality considerations:
 - To attain a high level of assurance that the characteristics are comparable, consider using two or more complementary analytical methods based on different (orthogonal) principles
 - Integrity and stability of iron core (structure, size, and morphology) should be maintained during testing. Consider using analytical techniques that require minimum sample manipulation
 - Consider probes such as Iron-57 Mossbauer spectroscopy and Transmission electron microscopy (TEM) to establish sameness in iron environment, core morphology, and particle size

Comparability Studies of Carbohydrate

- Demonstrate that carbohydrate component in the proposed drug product are comparable to that of the RLD.
- Quality considerations:

The structure and chemical composition of the carbohydrate must be clearly defined and compared to RLD. Difference in the structure and composition of the carbohydrate matrix may increase data requirement to justify sameness

- If carbohydrate shell is chemically modified, sameness in term of the location, degree, and pattern of modification (e.g., carboxymethylation of alcohol groups) should be demonstrated between test and reference products
- If carbohydrate shell is a polysaccharide-based polymer, then the sameness in carbohydrate backbone structure and branching information should be provided
- If carbohydrate shell is a mixture, the different species and the levels that are present in the drug product should be thoroughly characterized, and comparability between test and RLD product should be established

Comparative Stress Test Studies



- The stability of the iron colloid particles may have major impact on efficacy and safety of the product. Demonstrating sameness between test and RLD product under stressed conditions is an integral part of the sameness assessment
- Example of stress tests:
 - Drug product molecular weight (Mw, Mn, Mw/Mn) under accelerated storage conditions or stressed conditions
 - Particle size distribution (PSD) under serial dilution
 - *In vitro* reductive Iron release (time course study)
 - Iron splitting pattern (Mossbauer spectroscopy) at various temperature in the region of the blocking temperature (T_B)

Additional Considerations for Comparability Studies



- Consider providing detailed information regarding the analytical procedures including sample treatment procedures such as dilution, lyophilization, and/or dialysis. Use identical sample treatment procedure for test and RLD and provide the concentration of samples in each test. Whenever applicable, detailed analytical method validation information, instrument calibration information as well as reference standard information should be provided. Sample age should be provided for all studies
- To minimize variability, sufficient sampling size for proper statistical analysis should be part of the study design. For example, statistically meaningful approach should be considered for particle size distribution, and particle morphology assessment
- Justification should be provided if it is not feasible to conduct a study on the finished drug product. For studies designed to characterize the properties of drug product, sample manipulation should be minimized
- Each study should be conducted on a statistically meaningful number of batches of both test and RLD product, after aging under conditions consistent with the label storage conditions. All test batches used for in vitro characterizations should be manufactured using a process reflective of the proposed commercial manufacturing process, and at least one test batch should be produced at the commercial scale

Summary

- Comparability studies need to be conducted in order to establish sameness between test and RLD Iron colloid drug products
- Assessments need to be performed on drug product, iron core, carbohydrate, and labile iron determination
- In addition to the characterization studies conducted under normal conditions, stress test studies of test and RLD products can be used to further demonstrate sameness



Challenge Question #1

How many generic Iron colloid drug products have been approved for the treatment of iron deficiency anemia?

- A. 0
- B. 1
- C. 2
- D. 3

Challenge Question #2

Which of the following statement is NOT true?

- A. Iron colloid drug products contain nano-sized colloidal particles.
- B. The proposed parenteral drug product should be qualitatively (Q1) and quantitatively (Q2) the same as the reference listed drug (RLD).
- C. Comprehensive side-by-side studies need to be performed on drug product, iron core, carbohydrate, and labile iron determination.
- D. For one-time physicochemical characterization studies, detailed analytical method validation information, instrument calibration information as well as reference standard information are not needed.

Questions?

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