Iron Colloid Drug Products: Characterization and Impurity Considerations

Yiwei Li, Ph. D.
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

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Outline

- Introduction to Iron Colloid Drug Products
- FDA Recommendations
- Physicochemical Characterization and Impurity Considerations
- Case Study
- Conclusions

Iron Colloid Drug Products on US market

Trade Name	Labeled non-proprietary Name	Current Applicant	Approval Date	Particle Size by DLS
Venofer	Iron Sucrose	Luitpold	11/06/2000	8.3 nm
Dexferrum	Iron dextran	Luitpold	02/23/1996	30 nm
INFeD	Iron dextran	Allergan Sales	04/29/1974 and 1957	22-45 nm
Ferrlecit	Sodium ferric gluconate	Sanofi Aventis	02/18/1999	8.6 nm
Feraheme	Ferumoxytol	AMAG Pharma. Inc.	06/30/2009	31-53 nm
Injectafer	Ferric carboxymaltose	Luitpold	07/25/2013	23.1nm

Iron Colloid Drug Products

- Iron replacement product for the treatment of iron deficiency anemia
- Composed of an iron oxide core and a carbohydrate shell
- Presence of free carbohydrate component
- Mode of Action (MOA) of delivery: the internalization of Iron Colloid by macrophages and the incorporation of iron
- Adverse effects:
  - Hypersensitivity reactions such as anaphylaxis
  - Oxidative stress caused by low molecular iron species

FDA Recommendations for Characterization of Ferumoxytol

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.

FDA Draft Guidance on Ferumoxytol, Recommended Dec 2012

Iron Colloid Drug Product ANDA Applications

- ANDAs are reviewed on a product-by-product basis
- Physicochemical characterization is critical for establishing pharmaceutical equivalence between an innovator iron colloid product and a generic version
- Physicochemical properties under consideration should be those likely affecting the safety and efficacy of the iron carbohydrate drug products.
- Physicochemical Characterization of Iron Carbohydrate Colloid Drug Products. Zou, P., Tyner, K., Raw, A., Lee, S., *The AAPS Journal.* **2017**, 19(5), 1559 – 1376

Physicochemical Characterization

	Properties	Common Tests
Whole particle	Stoichiometric ratios of iron, free and bound carbohydrate and other relevant components Molecular weight distribution (Mw, Mn, and Mw/Mn) Particle size Distribution Particle Morphology	Iron and carbohydrate assay, elemental analysis SEC, AUC or GPC DLS and AFM AFM
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 Mossbauer, EPR, 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 Zeta potential NMR, SEC

Impurity Considerations

	Possible Impurities	Common Tests
Whole particle	Low molecular weight iron and free iron species Labile iron Other DS and DP manufacturing process related substances (Cl^-, Na^+, NH_4^+, etc.)	Dialysis or Ultrafiltration assay, elemental analysis Bleomycin assay or Iron chelation assays
Iron core	Limit or content of Fe (II) Elemental impurity	Ferene® derivatization/UV ICP
Carbohydrate shell	Total organic carbon Manufacturing process related impurities Potential degradation products	TOC NMR, MS, HPLC, GC NMR, MS, HPLC, GC

Considerations on Physicochemical Characterization

- Sameness in certain physicochemical properties between RLD and the test product should be established
- A comprehensive approach is preferred
- Interfering species should be removed
- Critical in-use/dilution studies should be considered
- Selection of the appropriate analytical technologies and method procedures
- Variability in characterization data has been reported in literature[1,2]

[1] Balakrishnan, V.S., et. al., Euro. J. Clinical Investigation, 2009, 39(6), 489-496.
[2] Bhavesh, S., et. al., J. Pharmaceutical Investigation, 2015, 45, 35-49.

Minimizing Variability

- Characterization of multiple batches
- Adoption of the same sample preparation procedures, experiment conditions, and data analysis
- Orthogonal approaches and complementary techniques
- Critical in-use/dilution studies should be considered
- Sufficient sampling size for proper statistical analysis
- Method validation, and selection of suitable reference standards

Case Study One

The firm proposed to conduct comparative Total Fe content testing between the test product and RLD.

Assessment:

Total Fe content may include Colloidal Fe and low molecular weight Fe and free Fe species.

Recommendation:

The firm is recommended to measure Colloidal Fe Content and control Low molecular weight Fe and Free Fe as impurities. Comparative studies should be designed to report the above as separate properties.

Case Study Two

The firm proposed to dilute the Iron Sucrose test product 1000 times prior to conducting particle size measurement via DLS.

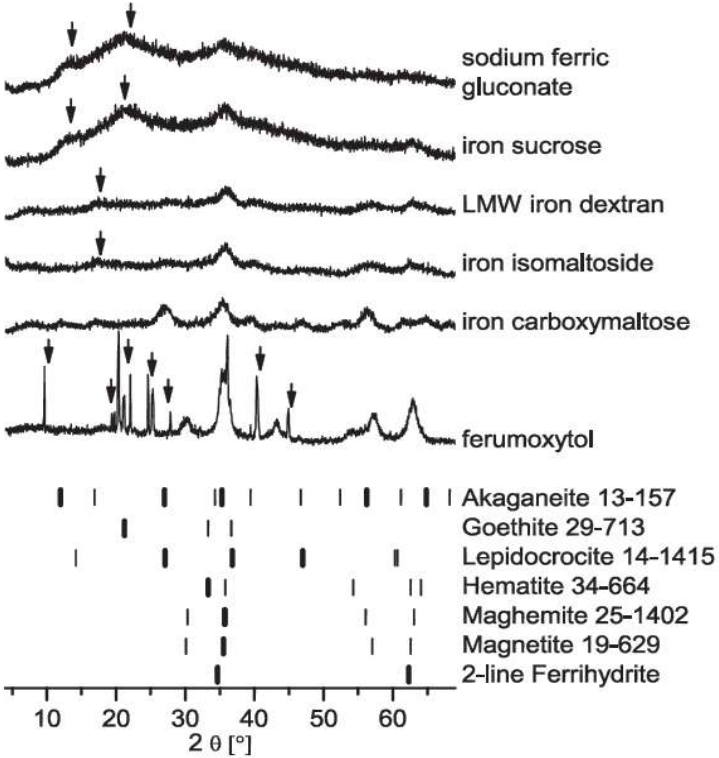
Assessment:

The proposed dilution may impact the particle size measurement.

Recommendation:

The firm is recommended to conduct sequential dilution studies and assess the effects of dilution on the particle size of the drug products.

Case Study Three



Jahn, M.R., et al., Eur J Pharm Biopharm, 2011. 78(3): p. 480-91

The firm proposed to use XRD to determine crystallinity and PSD of Iron sucrose iron core.

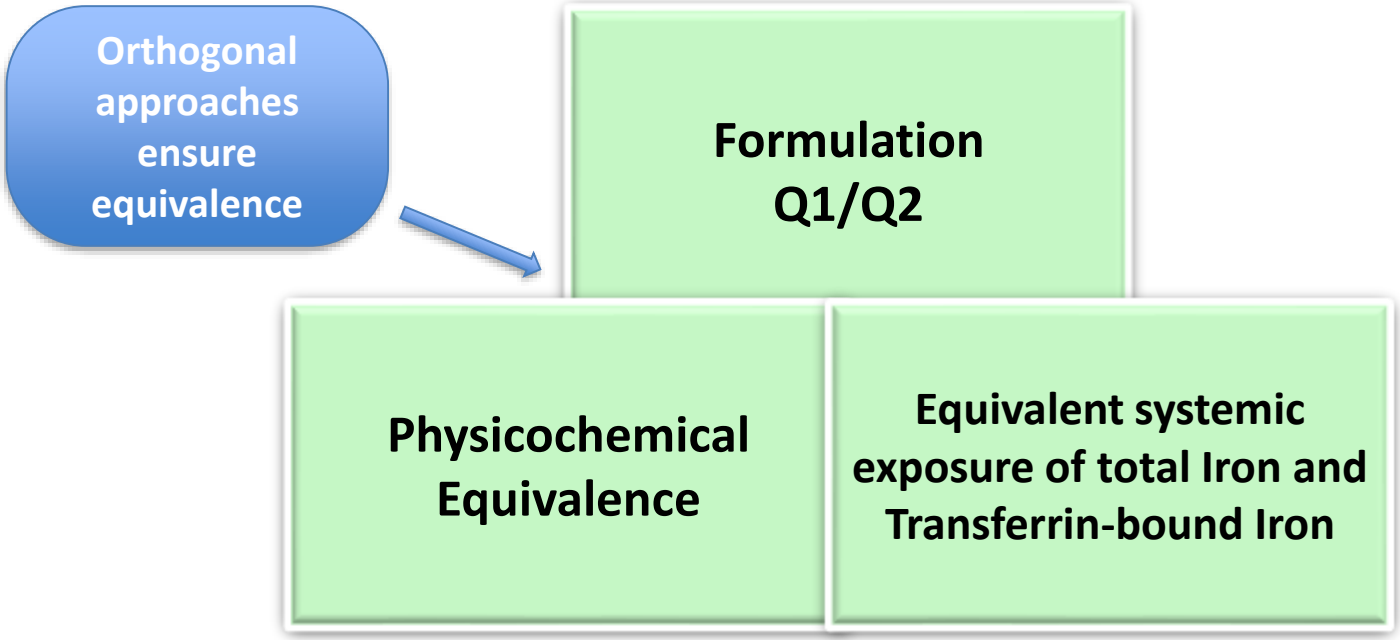
Assessment:

Weak and broad diffraction peaks may not be suitable for crystallinity ID and PSD determination.

Recommendation:

Orthogonal techniques are recommended to corroborate the XRD findings.

Achieving Equivalence



Physicochemical comparability, including control on particle size distribution, considered in combination with Q1/Q2 sameness, as well as pharmacokinetic together ensure the bioequivalence of Iron colloid drug products.

Conclusions

- ANDAs for Iron colloid drug products are reviewed on a product-by-product basis
- Sameness in physicochemical characterization is one of the key components for establishing equivalence
- A comprehensive approach, risk-based design of experiment, and proper validation/calibration are required to reduce data variability

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