Research Fueling Approvals: A Case Study of Ferumoxytol

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CDER | US FDA

Pharmaceutical Quality Symposium-SBIA Event
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Learning Objectives

- Gain understanding of Ferumoxytol injection through regulatory research
- Identify critical factors that affect drug product quality

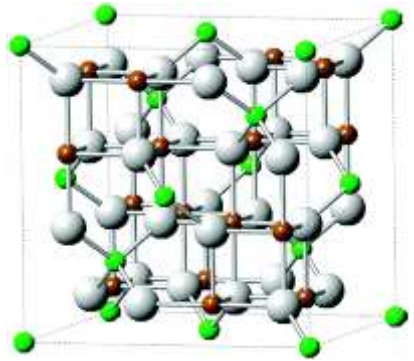
Outline

- Introduction to Ferumoxytol Injection
- Quality Attributes and Challenges in Characterization
- Research Capabilities in DPQR/OTR and CDRH
- Case Studies
- Summary

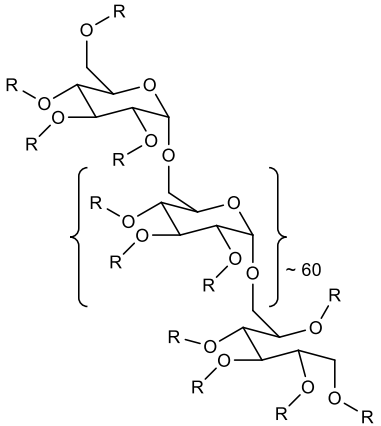
Introduction to Ferumoxytol Injection

- Iron-based injectable drug as a treatment for iron deficiency anemia.
- Consist of a polynuclear iron oxide core and stabilized by a carbohydrate shell.
- Drug product contains 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

Ferumoxytol: Complex Nano Product

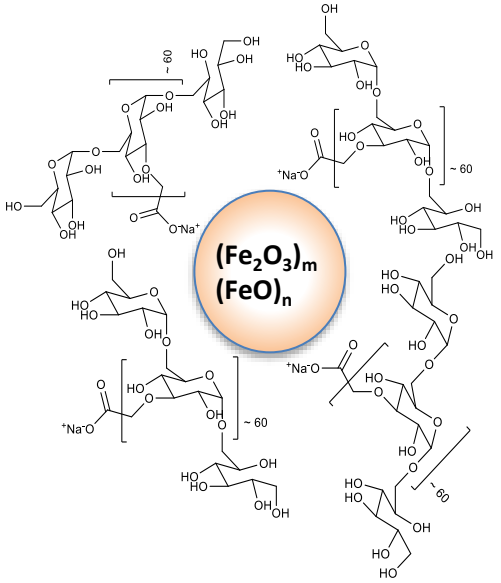


Iron Oxide Magnetite Crystal Structure[1]
Green atoms: Fe^{2+}
Brown atoms: Fe^{3+}
Grey atoms: O^{2-}



R = $-CH_2COO^-Na^+$ / -H, ~14 / 175

Polyglucose sorbitol carboxymethylether (PSC)



- Chemical Name: Polyglucose sorbitol carboxymethylether (PCS) superparamagnetic iron oxide
- Molecular Weight[2]: 275.7 KDa
- Particle Size[2]: 23.6 nm (Iron core: 6 nm)
- Iron oxide core is non-stoichiometric magnetite (Contain both Fe_3O_4 and γ–Fe_2O_3)
- Carbohydrate (PSC) is obtained from dextran 10 via multiple-step synthesis

1: Manoj B. Gawande, Paula S. Branco, and Rajender S. Varma, *Chem. Soc. Rev.* **2013,** *42*, 3371-3393.
2: Jahn MR, et al. *Eur. J. Pharm. Biopharm*. **2011**, 78, 480-491

FDA Daft Product-Specific Guidance

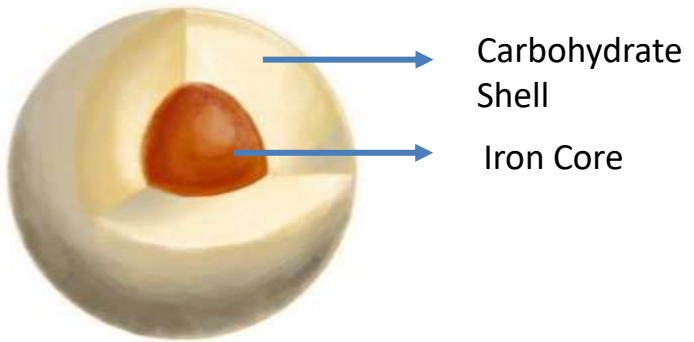
- BE Requirements:
  - Bioequivalence (BE) study with pharmacokinetic (PK) endpoints
  - *In vitro* particle size distribution study
- Special Considerations
  - The proposed drug product should be qualitatively (Q1) and quantitatively (Q2) the same as the reference listed drug (RLD)
  - Sameness in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

Challenges in Establishing Sameness

- Ferumoxytol is a complex nanomaterial containing both inorganic and organic components.
- Sample manipulation is needed when conventional characterization tools are used.
- Specialized analytical tools are adopted and some of them are not used for routine drug product characterization.
- Variability in characterization data are common: sample, instrument, and method difference.
- The assessment team decided to bring in FDA research team early and to understand the drug product.

Quality Assessment Driven by FDA Research

- Research capabilities
- Case studies
  - Whole product characterization
  - Carbohydrate shell characterization
  - Iron core characterization
- Drug product stability-case studies



Characterizing Physicochemical Properties

	Examples of Characterization Studies	Examples of Methods
Whole Drug Product	Equivalence in 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 (ICP-MS) SEC, AUC or GPC DLS and AFM AFM
Iron Core	Iron core size and morphology Crystallinity 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 titration VSM, SQUID
Carbohydrate Shell	Carbohydrate composition and carbohydrate-Iron core interaction Surface properties Carbohydrate characterization	FT-IR, thermal analysis, PSD under serial dilution Zeta potential NMR, SEC-MALS

Zou P., Tyner K, Raw A, Lee S, AAPS J. 2017, 1359-1376.

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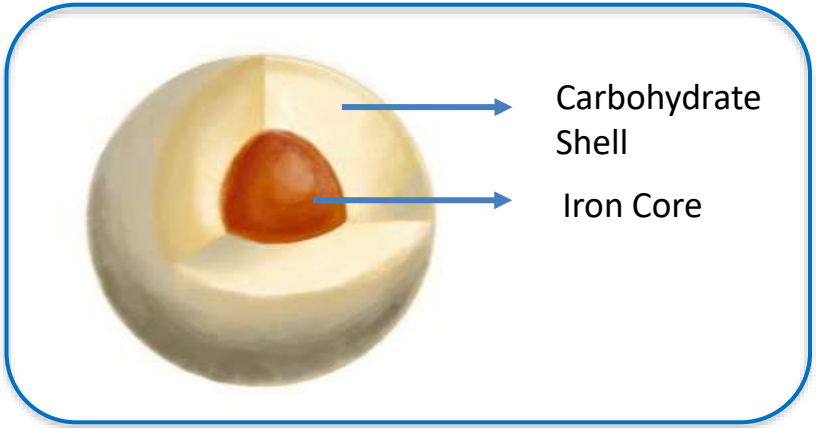


Product Quality Assessment Capabilities

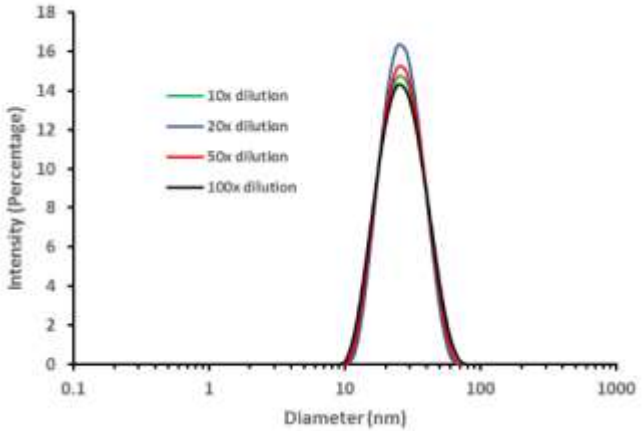
Particle Size Characterization

No.	Instrument Name	Manufacturer	Category	Principle	Size range (µm)	Shape	Charge	Wet/Dry	Resolution (1-5)	Nano Instrument?
1	Zetasizer Nano ZSP	Malvern	Ensemble	Homodyne DLS	0.0003 to 1	N	Y	Wet	2	Y
2	NanoFlowSizer (inline measurement, PAT)	InProcess	Ensemble	Spatially-resolved DLS	0.0003 to 1	N	N	Wet	3	Y
3	DynaPro	Wyatt	Ensemble	Homodyne DLS	0.0003 to 1	N	N	Wet	2	Y
4	NanoFlex	Microtrac	Ensemble	Heterodyne DLS	0.0008 to 1	N	N	Wet	2	Y
5	Field-flow Fraction (FFF) + DLS	Wyatt	Classifying	Separation + ensemble	0.001 to 1	Indirectly	N	Wet	5	Y
6	Zeta-view	Microtrac	Counting	Nanoparticle tracking	0.03 to 1	N	Y	Wet	4	Y
12	Micro-flow imaging (MFI)	ProteinSimple	Counting	Image analysis	1 to 70	Y	N	Wet	4	N
13	Polarized Light Microscopy	Olympus	Counting	Image analysis	>1	Y	N	Wet/Dry	4	N
14	Horizon	Halo Labs	Counting	Image analysis (USP 788 Method 2)	>1	Y	N	Wet (membrane filter)	3	N
15	Sympatec QICPIC	Sympatec	Counting	Image Analysis	1 to 3000	Y	N	Dry	4	N
16	FBRM	Mettler-Toledo	Counting	Focused Beam Reflectance Measurement	1 to 1000	N	N	Wet/Dry	4	N
17	Flow Imaging Microscopy (FlowCAM)	Yokogawa	Counting	Image analysis	1 to 600	Y	N	Wet	4	N

A dedicated lab with 10+ complementary sizing techniques, covering nano- to micron range, including wet and dry samples. Supported over 20 ANDA/NDA assessment.

Whole Product Characterization-Ferumoxytol

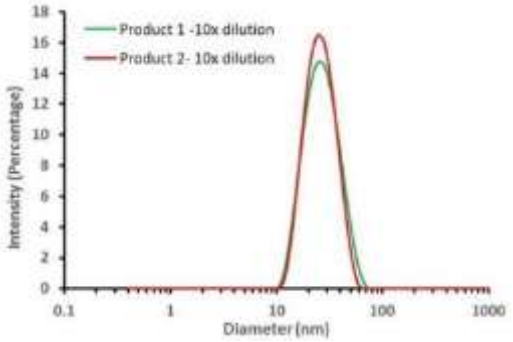
Particle size characterization: Dynamic Light Scattering

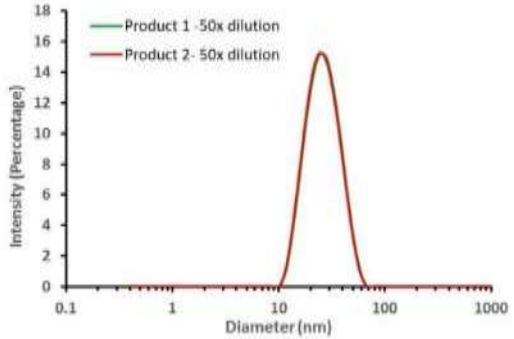


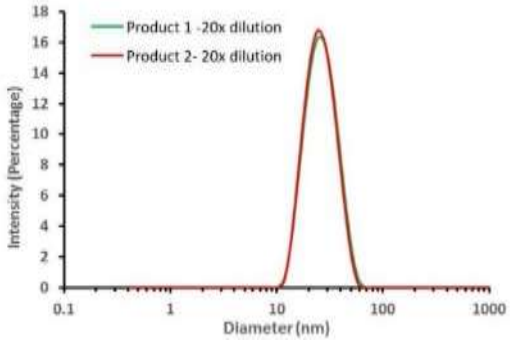
Overlay of intensity-based hydrodynamic size distribution. Effect of dilution on particle size distribution of Ferumoxytol sample.

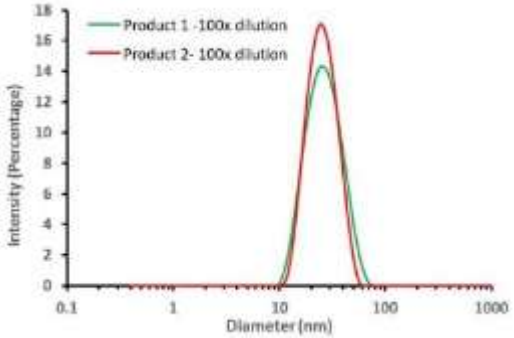
Whole Product Characterization-Ferumoxytol

Effect of dilution on particle size characterization





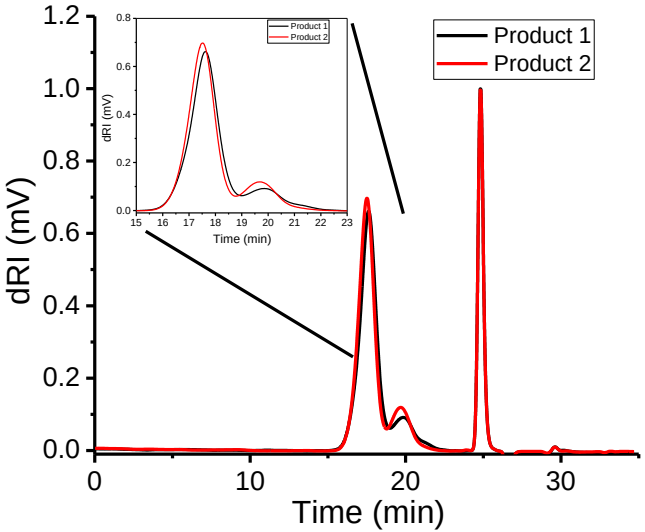




Whole Product Characterization-Ferumoxytol

Molecular weight determination by SEC-RI

Size exclusion chromatography set up with different detectors



Chromatograms of Size exclusion chromatography with refractive index (SEC-RI) signals. Whole particle molecular weight.

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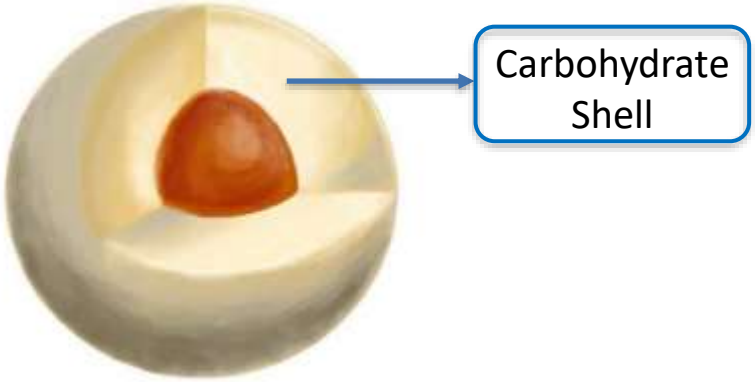
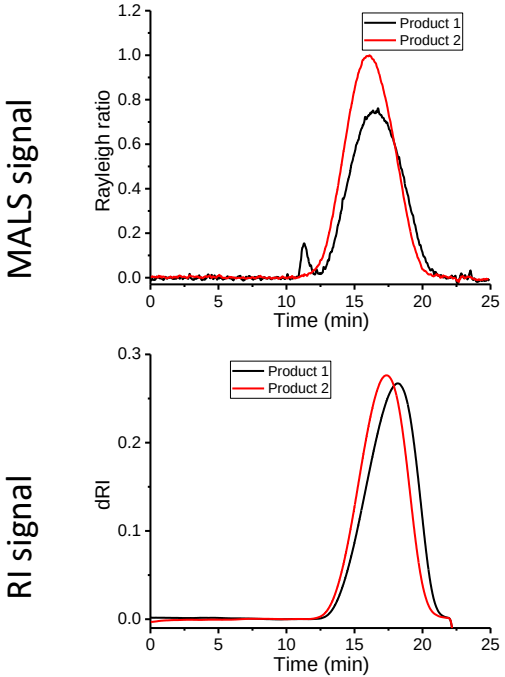
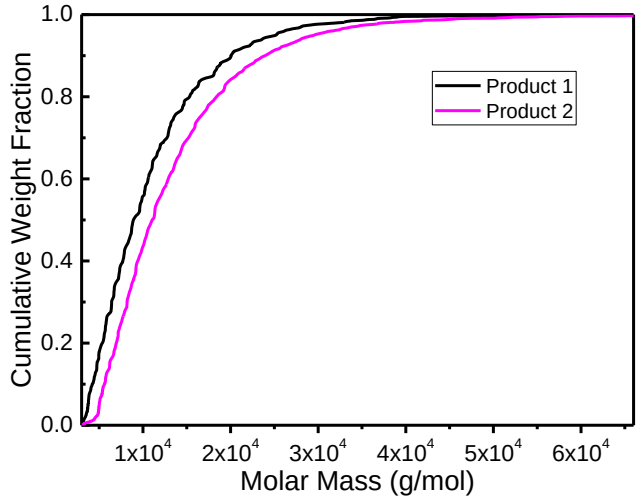


Carbohydrate Shell Characterization-Ferumoxytol

Molar mass distribution of carbohydrate shell



Chromatograms of Size Exclusion Chromatography-Multi Angle Light Scattering- Refractive Index signals (SEC-MALS-RI)



Molar mass distribution of carbohydrate shell from Ferumoxytol samples

Quality Assessment Driven by FDA Research

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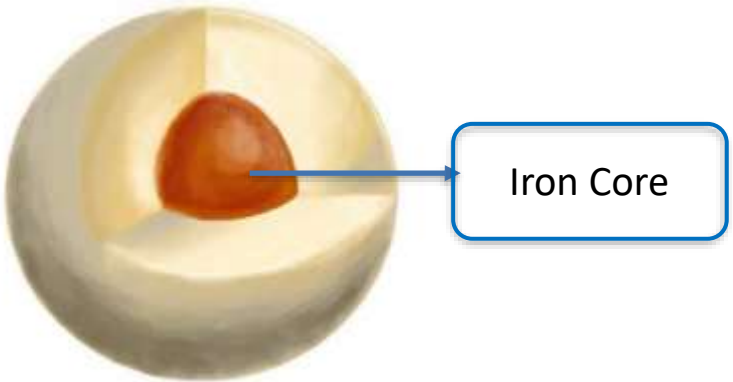
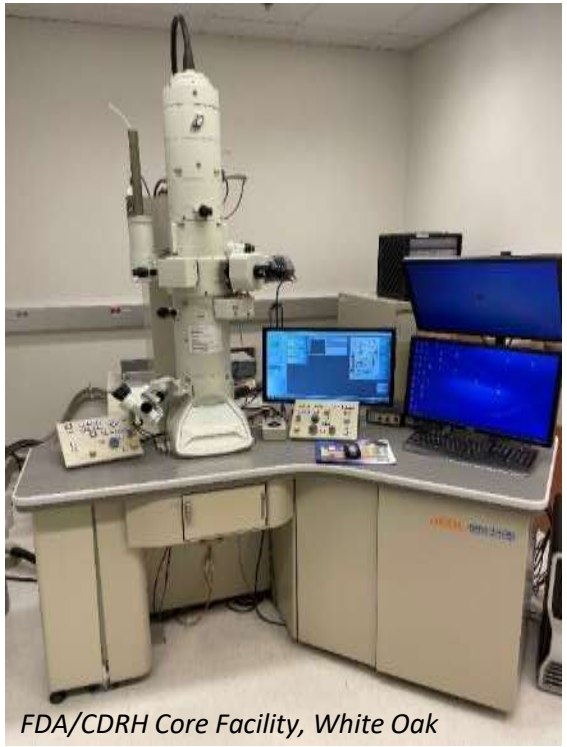


Iron Core Characterization- Ferumoxytol

Transmission Electron Microscopy (TEM)



FDA/CDRH Core Facility, White Oak

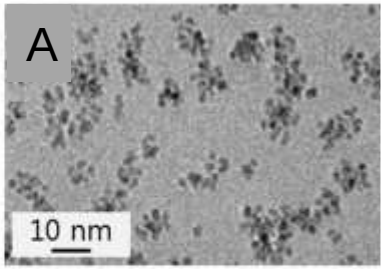
Literature Reports on
Intravenous Ferumoxytol DP Characterization

Iron agent class.	Core size (nm)	Method	Particle size (nm)	Method	Core structure	Ref
Ferumoxytol	10	XRD			maghemite	Neiser et al. (2015)
	5–10	Mössbauer			maghemite	
	6.2 ± 1.4	TEM	26.3	GPC	magnetite/ maghemite	Jahn et al. (2011)
	6.4	XRD	23.6	DLS		
	3.25	TEM			maghemite	Bullivant et al. (2013)
	6.4	TEM	17–31	DLS		Chen, (2010)
	9 ± 2	TEM	60 ± 4	NTA		Graczyk et al. (2015)
			21 ± 5	LS		

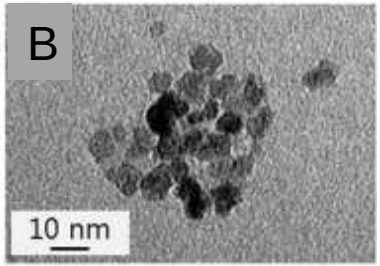
Y. Wu et al. / International Journal of Pharmaceutics 505 (2016) 167–174

Iron Core Characterization- Ferumoxytol

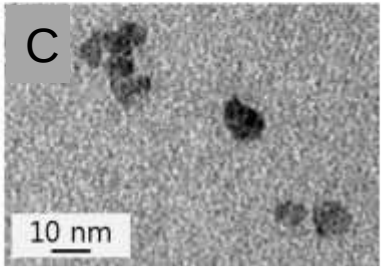
Transmission Electron Microscopy (TEM)



Cryo-TEM



RT-TEM (Silica)

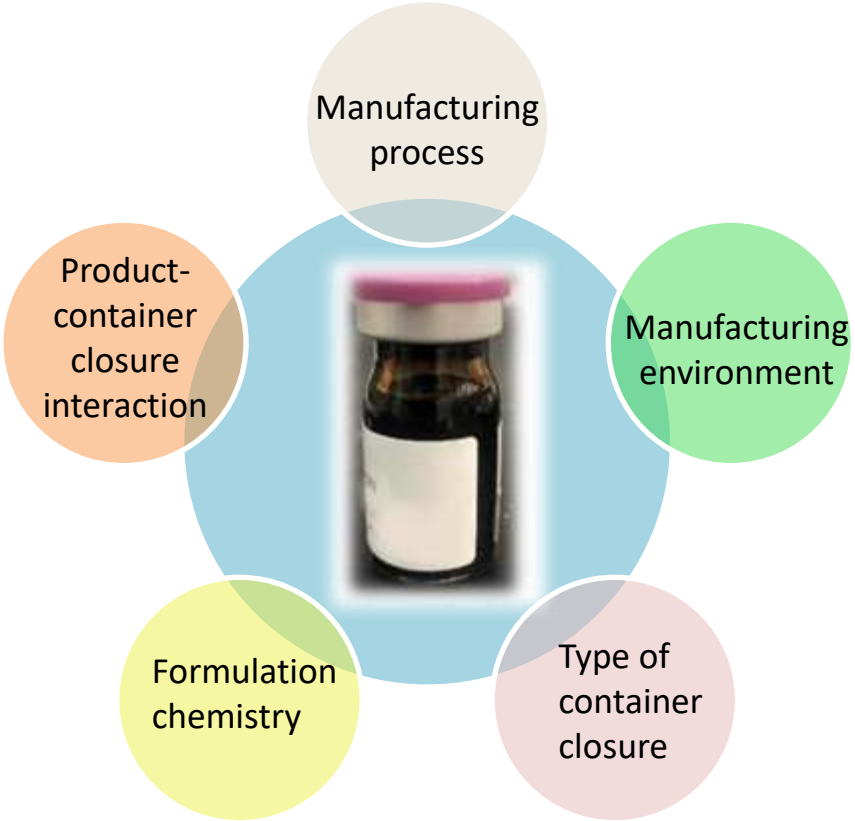


RT-TEM (Carbon)

Sample	Cryo-TEM core size (nm)	DLS Z-Average Diameter (nm)	PdI (DLS)	Zeta Potential (mV)	pH	Fe concentration, ICP-MS (mg/mL)
Ferumoxytol	2.1±0.3	24.8±1.5	0.08	-25	7.1	29.5±3.1

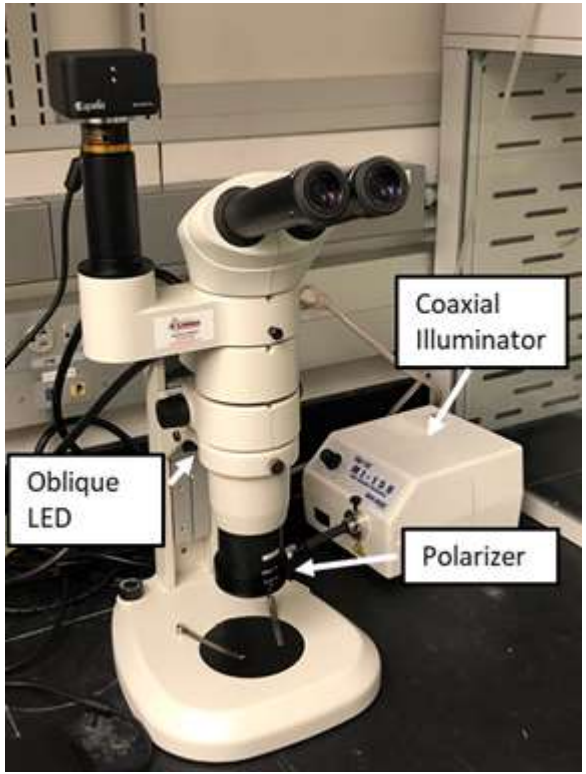
Y. Wu et al. / International Journal of Pharmaceutics 505 (2016) 167–174

Potential Sources of Particulates in Injectables

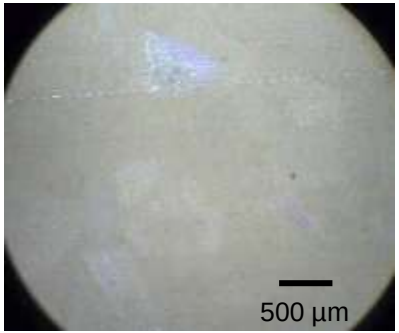


Product Quality Assessment Capabilities

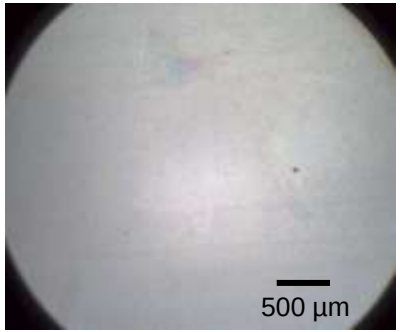
Particulate Characterization: Stereomicroscopy



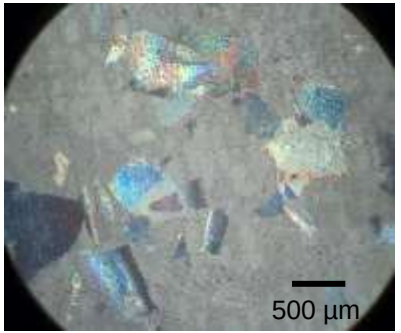
Stereomicroscope



Oblique



Coaxial

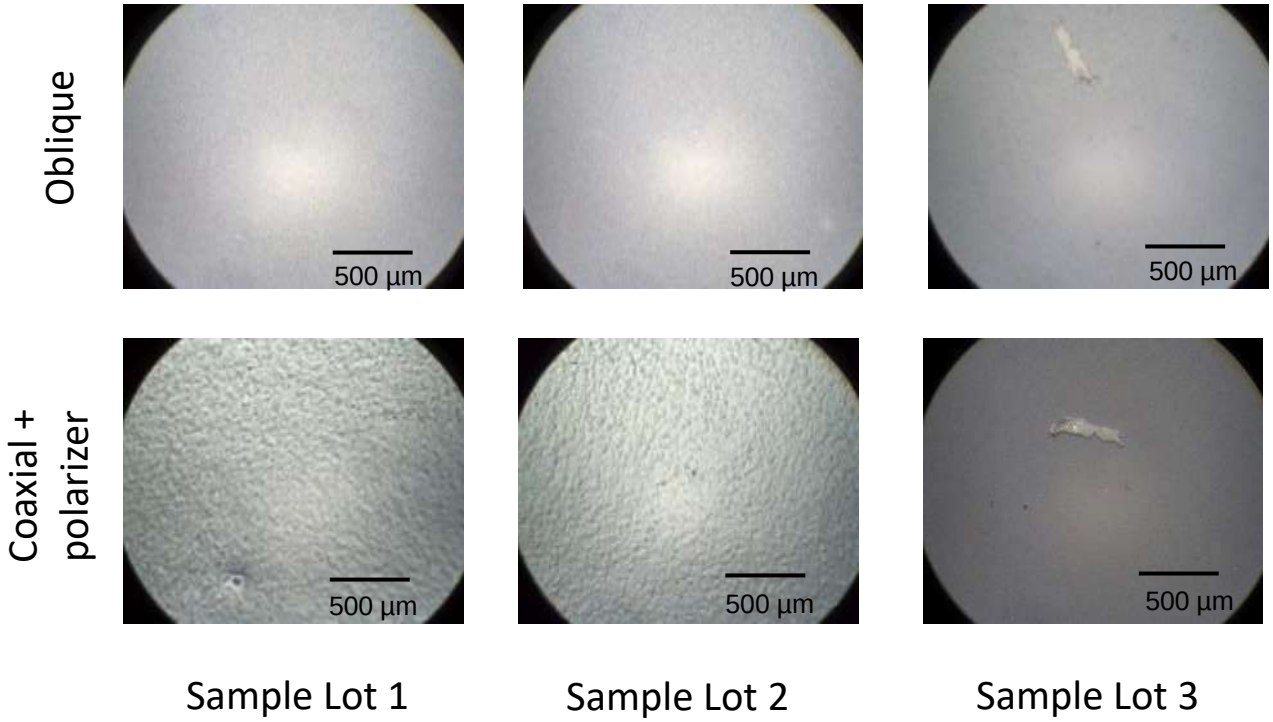


Coaxial + polarizer

Utility of Stereomicroscopy for particulate characterization in a drug product solution

Product Quality Assessment

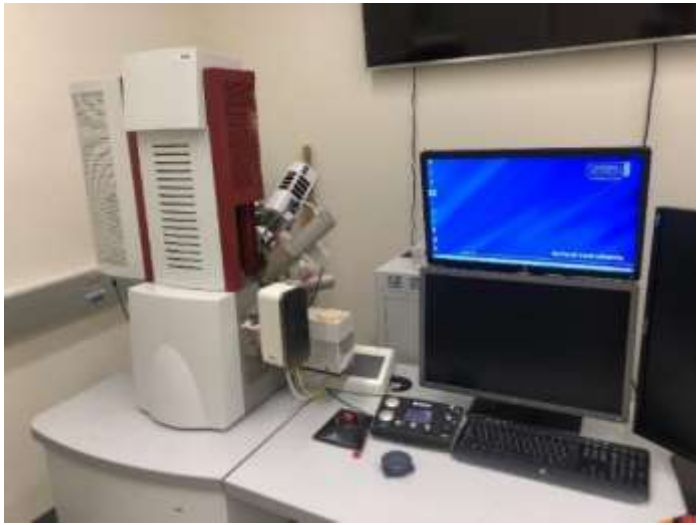
Particulate Characterization: Stereomicroscopy



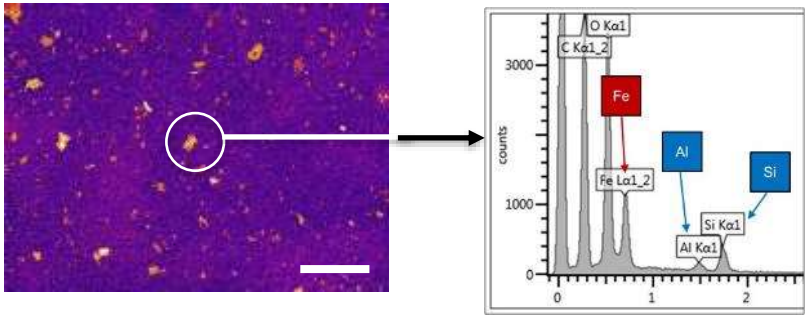
Stereomicroscopy images of membrane filtered Ferumoxytol samples

Product Quality Assessment Capabilities

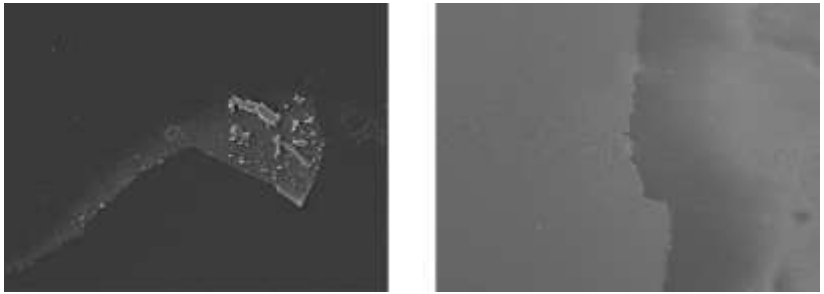
Particulate Characterization: Scanning Electron Microscopy



Field emission scanning electron microscope (SEM) equipped with energy dispersive spectroscope (EDS) at *FDA/CDRH Core facility, White Oak.*



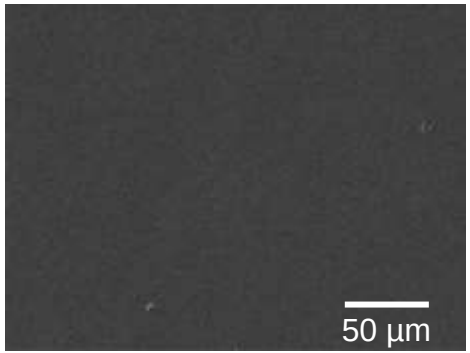
Example of SEM micrograph of membrane filtered product sample (left). SEM-EDS analysis of a particulate (right).



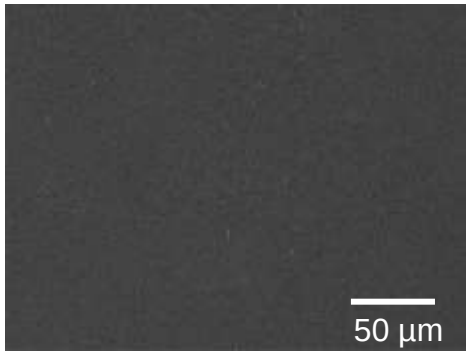
Examples of SEM micrographs of vial inner surface of product samples.

Product Quality Assessment

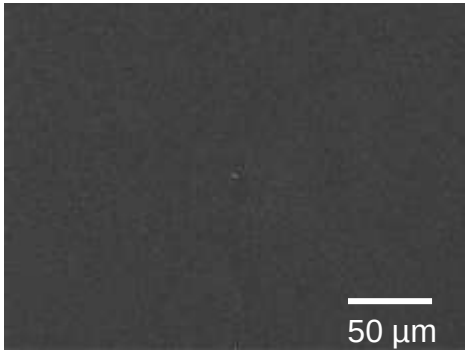
Particulate Characterization: SEM-EDS



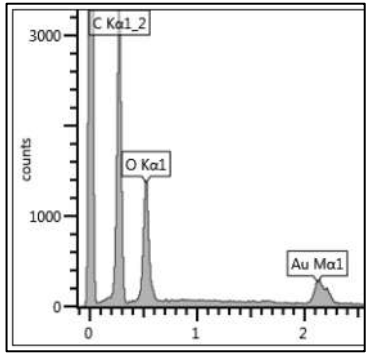
Sample Lot 1



Sample Lot 2



Sample Lot 3



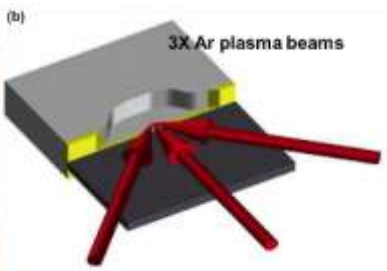
EDS Spectra

SEM-EDS micrographs of membrane filtered Ferumoxytol samples

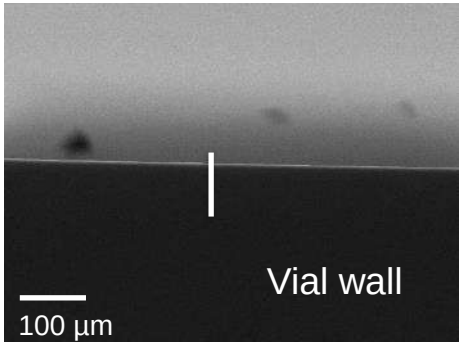
Product Quality Assessment Capabilities

Particulate Source Characterization: SEM-Broad Ion Beam (BIB) Milling System

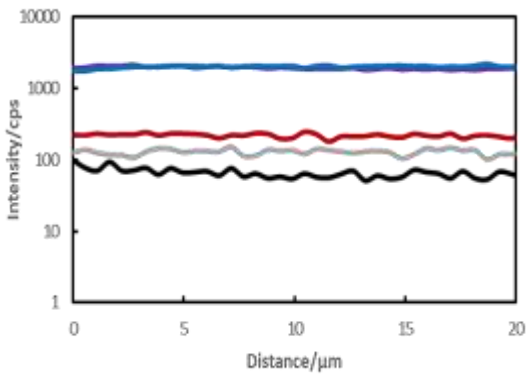
Broad ion beam (BIB) milling system with cryo-stage.



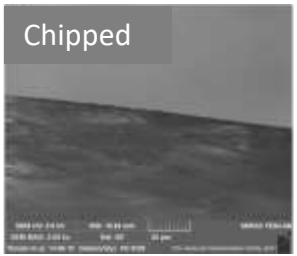
Schematic of BIB setup to create a smooth cross-sectional surface.

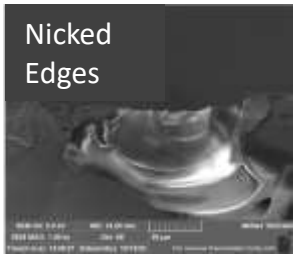


SEM-BIB milled cross-section micrograph of Ferumoxytol product vial



SEM-EDS spectra of the cross-section at the white line indicated in the micrograph





Examples of SEM-non-ion milled sample micrographs showing artifacts in vials with random breaks.

Summary

- Regulatory research facilitates the understanding of critical factors impacting drug product quality and regulatory approval
- Complementary techniques are beneficial to evaluate the product quality attributes and characterization of complex drug products
- Suitability of the techniques is critical for comparative evaluation
- The regulatory assessment supported by product quality research leads to knowledge-based regulatory decisions
- The first generic Ferumoxytol Injection was approved in 01/2021

Acknowledgments

CDER/OPQ/OTR/DPQR

- Youlong Ma, Haiou Qu, Deval Patel, Adil Mohammad
- Xiaoming Xu
- Muhammad Ashraf

CDRH

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- Jiwen Zheng

CDER/OPQ/OLDP/OPMA

- Temitope Oriola
- Pahala Simamora
- Bing Cai
- Andre Raw
- Cassandra Abellard
- Derek Smith
- Samata Tiwari
- Nandini Bhattacharya

Challenge Question #1

Which of the following statements is True?

A. Ferumoxytol is a liposomal product

B. Ferumoxytol is a simple injection product

C. Ferumoxytol is a complex drug product composed of iron oxide core and a carbohydrate shell

D. Ferumoxytol is a liquid based oral product

Challenge Question #2

Which of the following studies are critical for Ferumoxytol characterization?

A. Physicochemical characterization of whole particle
B. Physicochemical characterization of iron core
C. Physicochemical characterization of carbohydrate shell
D. Particle morphology
E. All of the above


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ADMINISTRATION