

Advances in Iron Colloid Products: Product-Specific Guidance Discussion

SBIA 2021: Advancing Generic Drug Development: Translating Science to Approval
Day 1, Session 3: Complex Generics: Complex Injectables, Ophthalmic and Otic Products

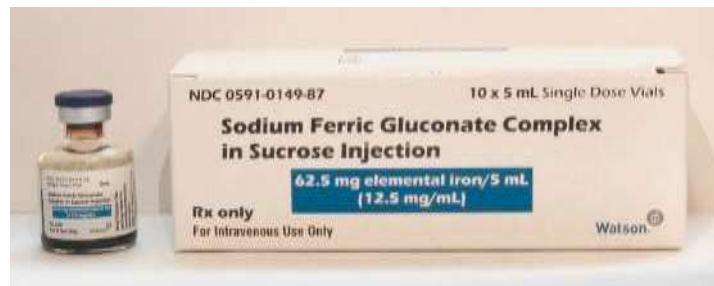
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September 21, 2021

Learning Objectives

- List different iron complex products to treat iron deficiency
- Describe different iron species in vivo after infusion of iron complex products
- Recognize significant contributions of GDUFA research to develop analytical methods for direct measurement of drug-bound iron
- Discuss the major revisions of the product-specific guidance for iron complex products

Iron Complex Products to Treat Iron Deficiency



Human Iron Physiology

- **Blood**

- Red blood cell (RBC) (hemoglobin), >60%
- Serum ferritin (minimal)
- Transferrin-bound (<0.1%)
- Non-transferrin-bound iron (negligible): weakly binding of iron to albumin, citrate, amino acids, and sugars, also termed as labile iron

- **Tissue**

- Ferritin, ~30%
- Myoglobin, ~10%
- RES: iron recycle

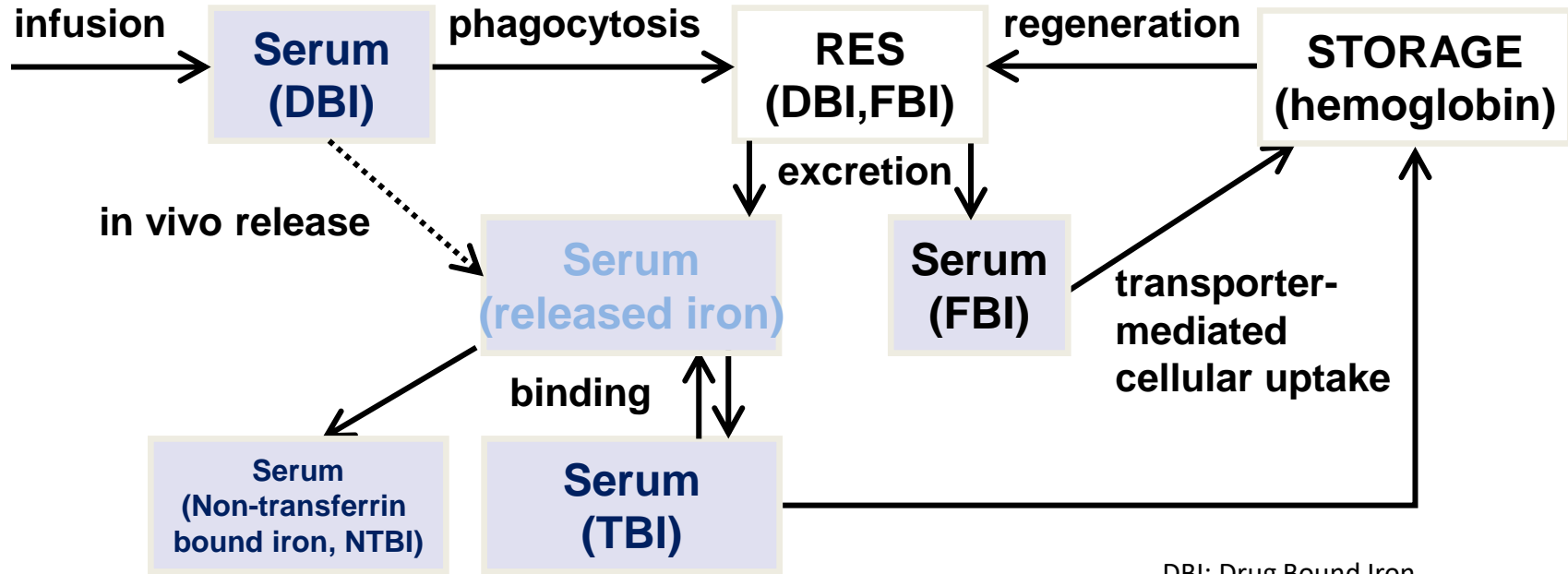
- **Iron test using serum sample**

- Ferritin-bound iron (FBI): 1.5-25 µg/dL
- Non-transferrin-bound iron (NTBI): 0-1 µg/dL
- Transferrin-bound iron (TBI)
 - 100-200 µg/dL (baseline)
 - 250-450 µg/dL (total iron binding capacity (TIBC))
 - Slightly higher TIBC in iron-deficient subjects

Serum total iron (TI) = TBI + serum ferritin bound iron (FBI) + NTBI

- Transferrin-iron Saturation Percentage (TS%) = $\frac{\text{TBI}}{\text{TIBC}} \times 100\%$
- TS% normal range: 15-50% (M), 12-45% (F)

Iron Transport after Infusion of Iron Complex Products



DBI: Drug Bound Iron

RES: Reticuloendothelial System

After iv infusion: $TI = DBI + TBI + FBI + NTBI$

Theoretically, NTBI is formed when: 1) The iron preparation is not stable; 2) Labile iron is released when transferrin is saturated

Product-Specific Guidance (PSG) for Iron Sucrose (N021135) (2013 Version)



Active Ingredient: Iron Sucrose

Dosage Form; Route: Injectable; intravenous

Recommended Studies: Two studies

1. Type of study: Fasting

Design: Single-dose, randomized parallel in vivo study

Strength: EQ 100 mg Iron/5 mL (Dose 100 mg)

Subjects: Healthy males and females, general populations

Additional comments: The products should be administered undiluted as a slow intravenous injection dose of 100 mg over 5 minutes.

Analytes to measure: 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

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: D10, D50, D90

Bioequivalence based on: D50 and SPAN [i.e. (D90-D10)/D50] or polydispersity index using the population bioequivalence statistical approach.

Additional Thoughts about 2013 PSG



- Direct measurements of different iron species in vivo
- Feasibility of crossover study design
- NTBI in vivo
 - NTBI may induce toxicity if taken up by liver, heart, ...

Research Project

**Research project:**

Evaluation of Iron Species in Healthy Subjects Treated with Generic and Reference Sodium Ferric Gluconate (U01FD005266)

ClinicalTrials.gov Identifier: NCT02399449

Awardee:

Drs. Sarah Michel and James Polli, University of Maryland

Project durations:

Sept 2014 – Apr 2019

Objective:

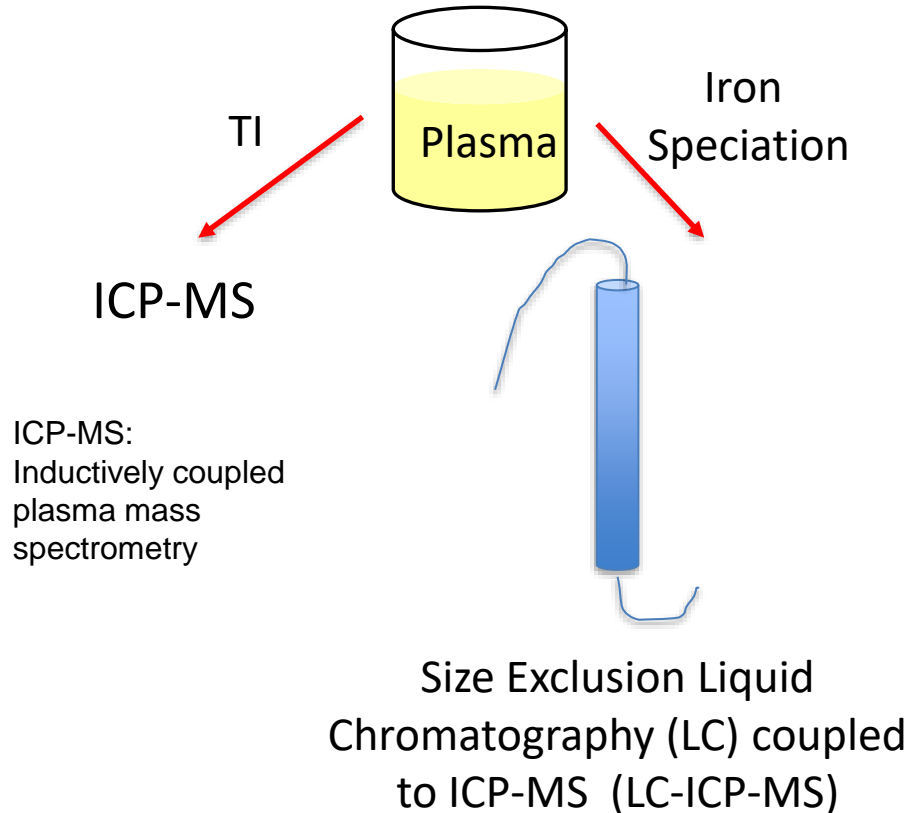
Conduct in vivo studies to compare plasma total iron (TI), transferrin bound iron (TBI), non-transferrin bound iron (NTBI) levels and oxidative stress after i.v. administration of reference listed drug (RLD) and generic sodium ferric gluconate injections in healthy subjects.

Specific Aims

1. Compare brand and generic sodium ferric gluconate quality attributes
2. Develop bio-analytical methods to determine plasma TI, TBI, and NTBI concentrations
3. Conduct a prospective, randomized, 2-way crossover study to compare plasma TI, TBI, NTBI levels in healthy subjects treated with generic and RLD. Monitor TBI, total iron binding capacity and serum ferritin level during washout period to ensure iron storage and transport has returned to baseline.
4. Evaluate the oxidative stress and toxicity caused by generic and RLD using in vitro and in vivo biomarkers
5. Monitor any side effects or adverse reactions during the study period
6. Conduct statistical analysis to determine whether there are any significant differences between generic and RLD in NTBI level and others

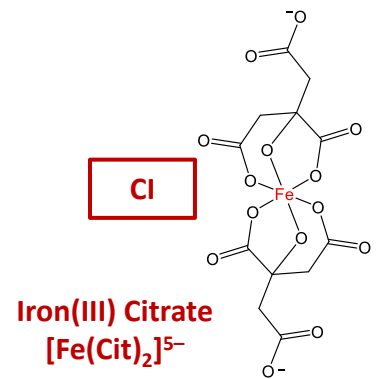
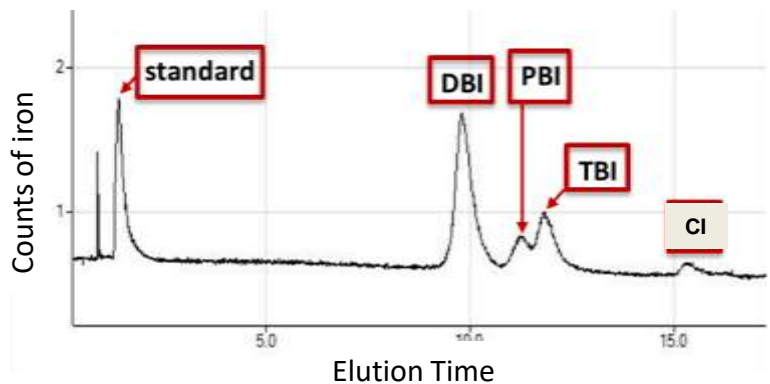
Text highlighted blue: Focus of this presentation

Strategy to Measure Iron Species



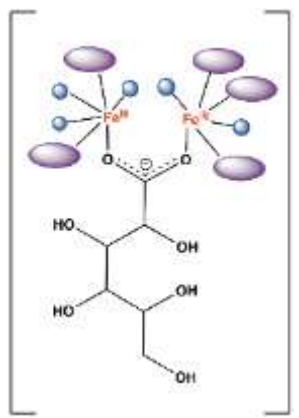
Species	Molecular Weight (kDa)
Transferrin	80
Ferritin	450
Albumin	67
Citrate	0.43
Sodium Ferric Gluconate	289-440

Iron Speciation



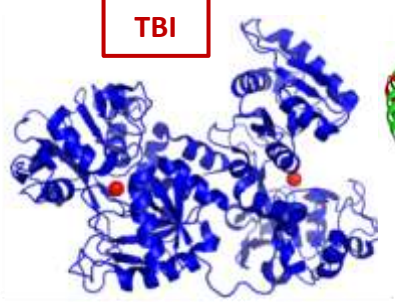
DBI: Drug bound iron
 PBI: Protein bound iron
 TBI: Transferrin bound iron
 CI: Iron citrate
 ABI: Albumin bound iron
 FBI: Ferritin bound iron

DBI

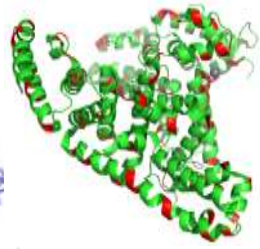


PBI = ABI + FBI

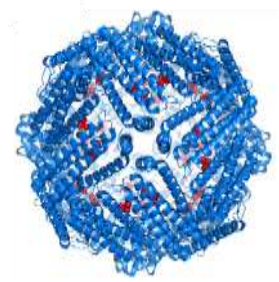
TBI



Albumin



Ferritin

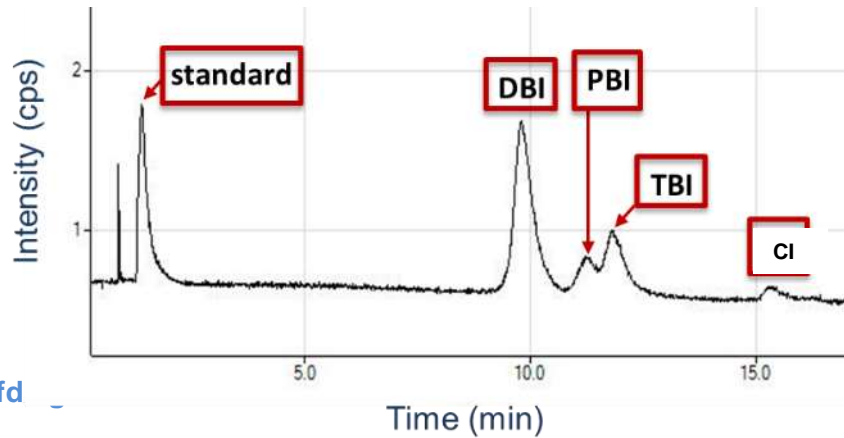


Independent Confirmation of LC Peaks



Species	Molecular Mass (kDa)	Peak Elution (min)	Characterization
Ferritin	450	10 – 10.5	SDS-PAGE Gel
Transferrin	79.6	11.5 – 13.5	SDS-PAGE Gel, MALDI-MS (m/z = 79.5 kDa)
Albumin*	66.5	10.5 – 11.5	SDS-PAGE Gel, MALDI-MS (m/z = 66.8 and 133.6 kDa)
Citrate	0.43	15 – 16.5	ESI-MS (m/z = 191.0, 366.4, 488.9, 733.8 Da)

*monomer and dimer detected



- FBI and ABI peaks cannot be separated well
- ABI level is estimated to be very low as albumin preferably binds to copper and zinc
- NTBI \approx CI

Snapshots of Iron Speciation: Tracking the Fate of Iron Nanoparticle Drugs via a Liquid Chromatography–Inductively Coupled Plasma–Mass Spectrometric Approach


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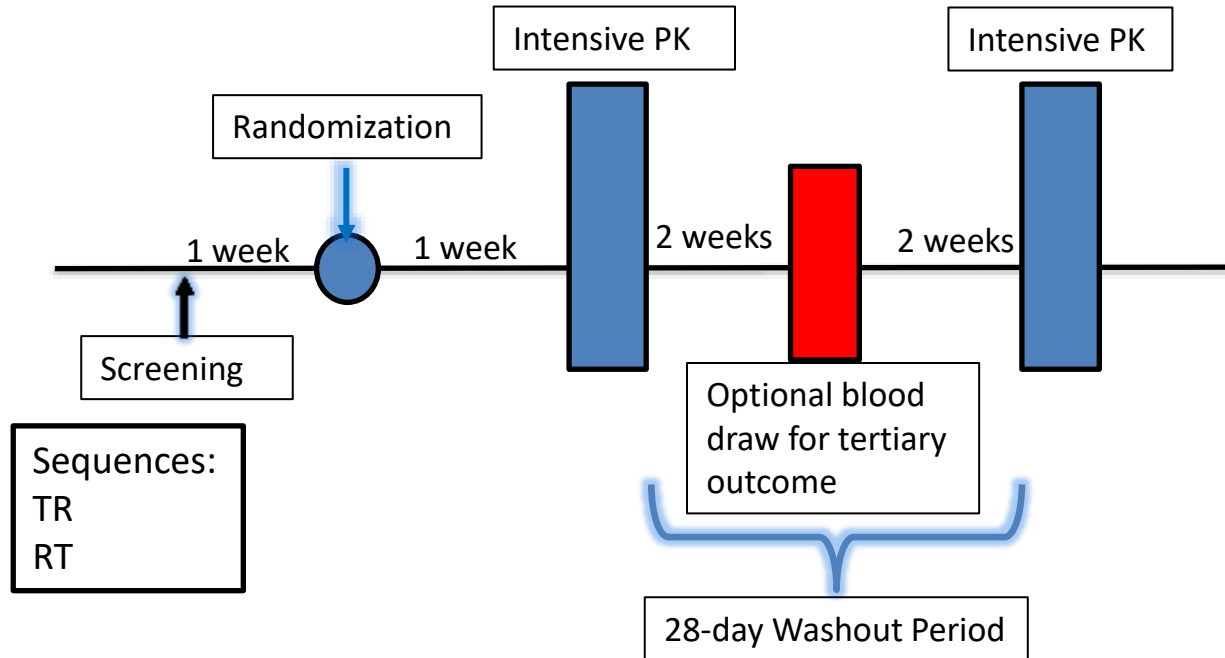
^{||}Department of Medicine, University of Maryland School of Medicine, Baltimore, Maryland 21201, United States

 Supporting Information

Study design



- Primary and secondary outcomes from intensive pharmacokinetic (PK) days
 - Determine if there is higher NTBI levels from generic sodium ferric gluconate than the brand
 - Provide evidence for consideration of possible additional safety measures (not discussed here)
- Tertiary outcome from optional blood draws day during washout period
 - Provide evidence for reasonable washout period



Study performance

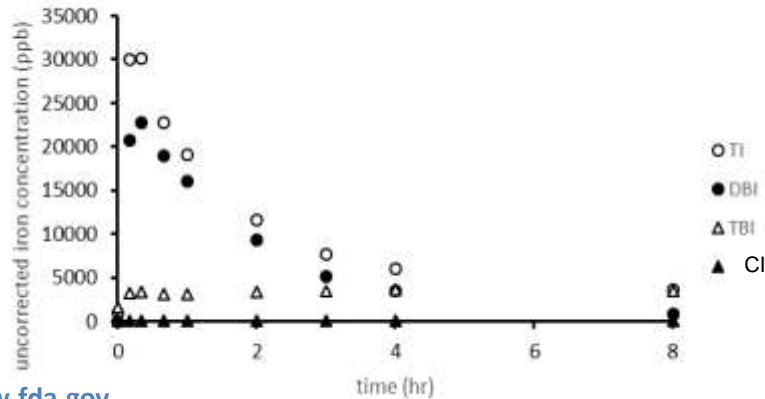
- N=44 subjects completed
- N=35 subjects completed with usable cross-over data
 - Two dropped due to dosing rate
 - Two had t=0 samples hemolyzed
 - Five dropped due to t>0 hemolyzed samples

	Female (n=16)	Male (n=19)	Total (n=35)
Age range (mean)	22-54 (31.6)	22-56 (36.9)	22-56 (34.5)

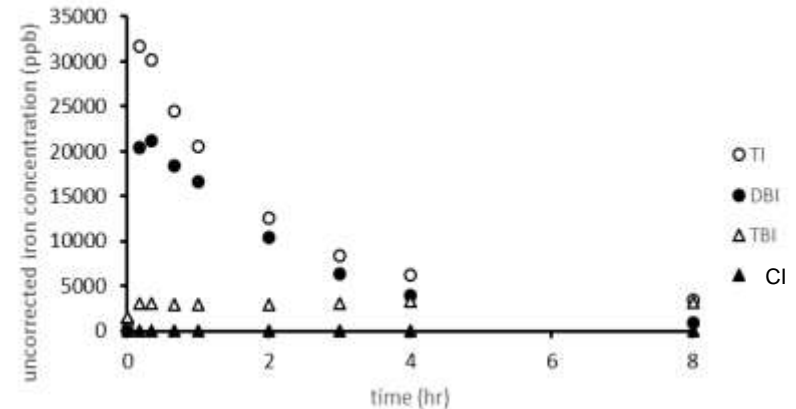
Pharmacokinetic Profiles of Iron Species

Iron species	LLOQ (units)
DBI	300 ppb
TI	200 ppb
TBI	10 ppb
CI (NTBI)	10 ppb

Average of brand



Average of generic



Statistical Analysis of Different Iron Species between Generic and Brand Sodium Ferric Gluconate

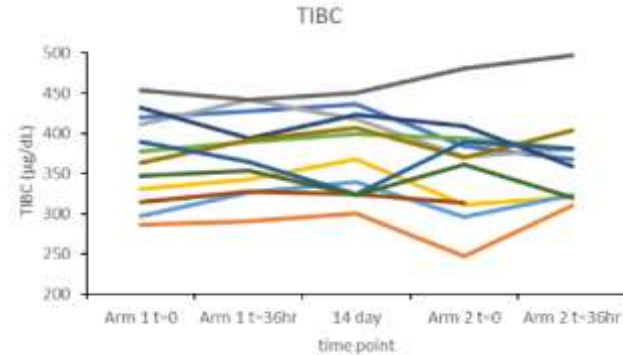
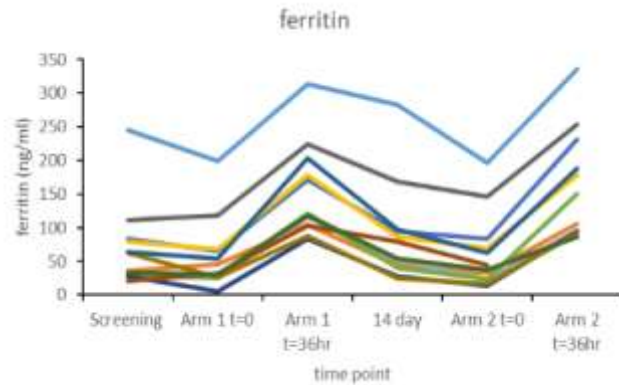
PK metric	Geometric Mean ratio (90% CI)	CV%
DBI AUC	1.083 (1.042-1.126)	9.6
DBI Cmax	0.956 (0.920-0.992)	9.3
TBI AUC,u	0.937 (0.905-0.971)	8.7
TBI Cmax,u	0.931 (0.895-0.968)	9.8
TI AUC,u	1.011 (0.979-1.045)	8.1
TI Cmax,u	1.026 (0.982-1.072)	10.8
CI (NTBI) AUC,u	1.032 (0.861-1.237)	47.3
CI (NTBI) Cmax,u	1.096 (1.011-1.189)	20.3

u = uncorrected (i.e., not baseline-corrected)

Adverse events (AEs)

- 108 AEs that ranged from definitely associated to the study drug and/or study procedures to not associated to the study drug and/or study procedures
 - 71 temporally associated with brand study arm
 - 32 temporally associated with generic study arm
 - 5 occurred before any study drug administration

Ferritin and TIBC Levels



14-28 day seems to be a reasonable washout period in a crossover BE study.

Research Project Summary

- An LC-ICP-MS method was developed for the first time to directly measure the drug-bound iron.
- No significant differences were observed between generic and brand sodium ferric gluconate in TI, TBI, DBI, and NTBI levels.
- 14-28 day seems to be a reasonable washout period in a crossover BE study for iron complex products based on observed ferritin and TIBC levels.



Additional options for bioequivalence study of iron complex products

Active Ingredient Name Change for Iron Complex Products



FDA's May 26, 2021 response to Citizen Petition Docket No. FDA-2016-P-1163: ***Ferric oxyhydroxide*** is responsible for the pharmacological activity ***and is thus the active ingredient***. Sucrose and starches are merely excipients providing stability and processing functions.

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

PSG for Ferric Oxyhydroxide Injection (N021135) (2021 Version)

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.

www.fda.gov

Analytes 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

Summary

- There are multiple innovator iron complex products on the market but with limited generics available.
- There were significant challenges to establish bioequivalence of iron complex products.
- Significant advancements were made in bioanalytical method development and bioequivalence study design of iron complex products:
 - An LC-ICP-MS method was developed for the first time to directly measure the drug-bound iron.
 - No significant differences were observed between generic and RLD in TI, TBI, DBI, and NTBI levels.
 - 14-28 day seems to be a reasonable washout period in a crossover BE study for iron complex products based on observed ferritin and TIBC levels.
- Based on research findings, the PSG for ferric oxyhydroxide injection was updated to include the following:
 - Adding a new option: Direct measurement of iron in the form of colloidal ferric oxyhydroxide is recommended if achievable.
 - The in vivo BE study may be parallel or crossover design.

Acknowledgement

University of Maryland

- Dr. Sarah Michel
- Dr. James Polli

UO1FD005266



Challenge Question #1

Iron in the form of colloidal ferric oxyhydroxide in serum cannot be directly measured.

- A. True
- B. False

Challenge Question #2

Which of the following statements is true?

- A. The in vivo BE study design of ferric oxyhydroxide may be parallel or crossover.
- B. The in vivo BE study design of ferric oxyhydroxide can only be parallel.

Questions?

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