“Non-Inferiority” Assessment for Iron-Carbohydrate Complexes

James E. Polli

jpolli@rx.umaryland.edu

October 10, 2016

Outline

- Introduction
- Clinical design
- Bioanalytical methods

TEAM IRON

Sarah Michel, PhD

Maureen Kane, PhD

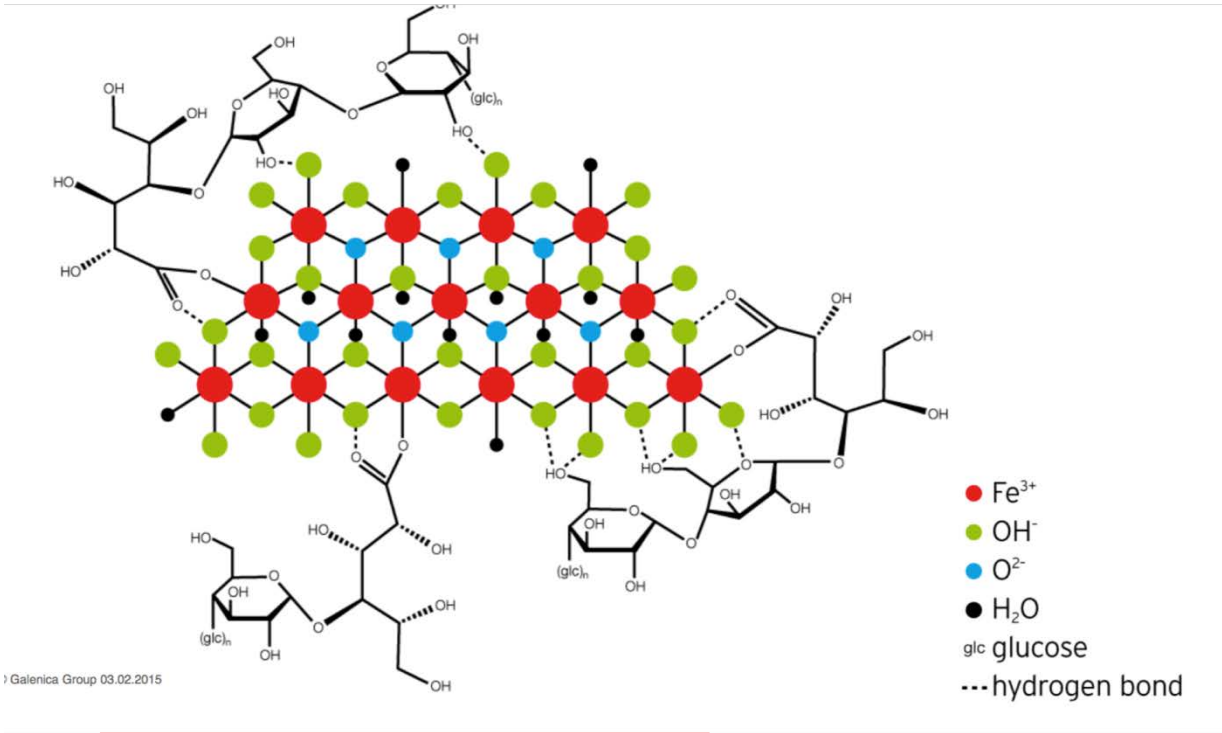
Angela Wilks, PhD

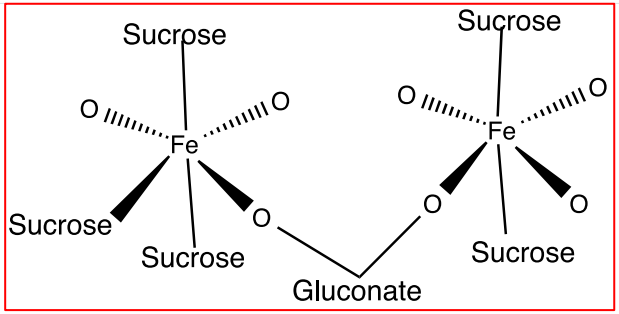
James Polli, PhD

IV Iron

- Polynuclear iron core [iron (III)-oxyhydroxide] stabilised by a carbohydrate complex
  - Nano-sized colloidal structures
- Target tissues
  - Bone marrow
  - Off-target: serum, kidney, liver, lungs, heart
- Endocytosis
  - Reticuloendothelial system (RES): liver macrophages or hepatocytes, spleen
- Physiochemical properties impact
  - Release, trafficking, colloid degradation

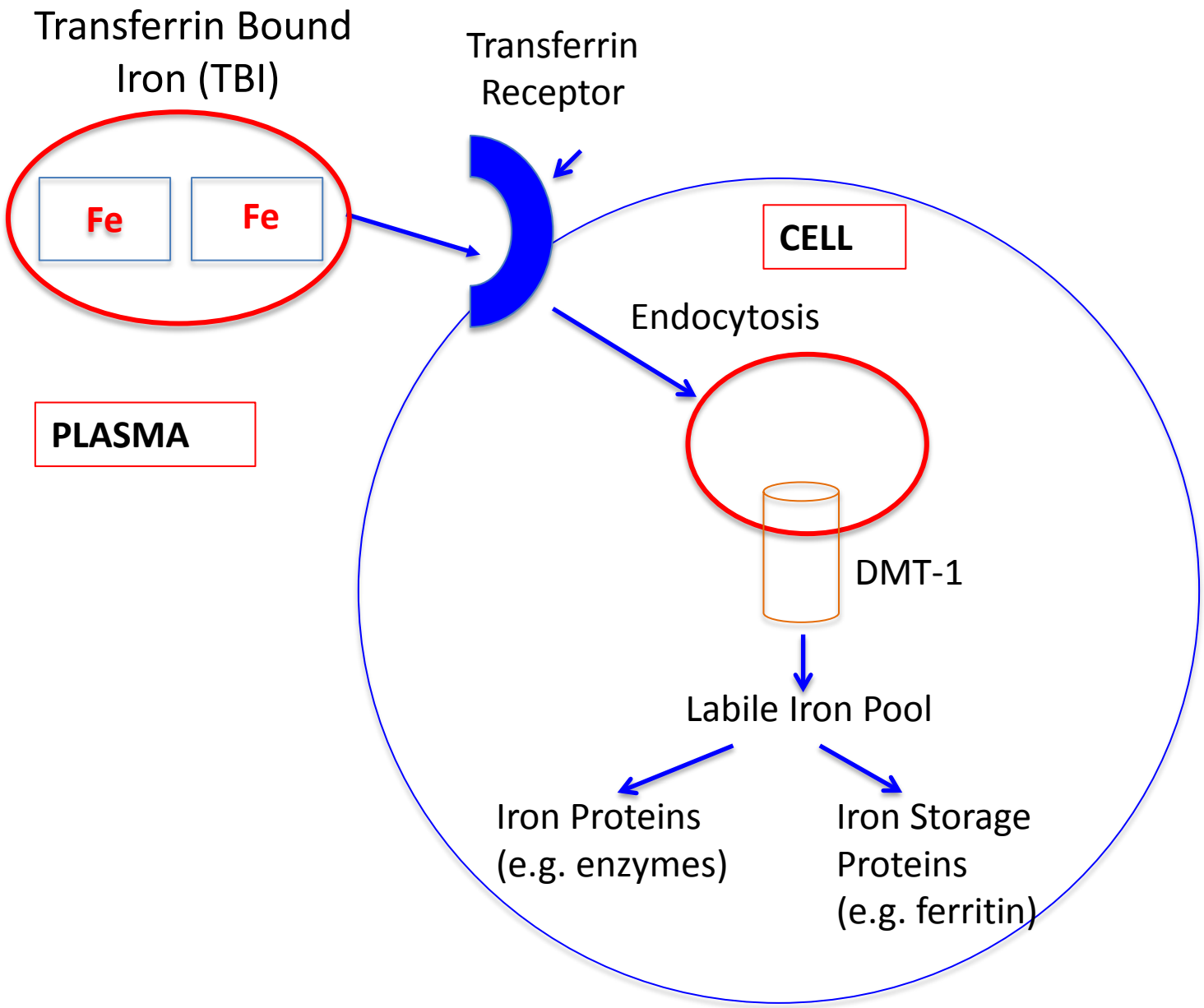
Sodium Ferric Gluconate



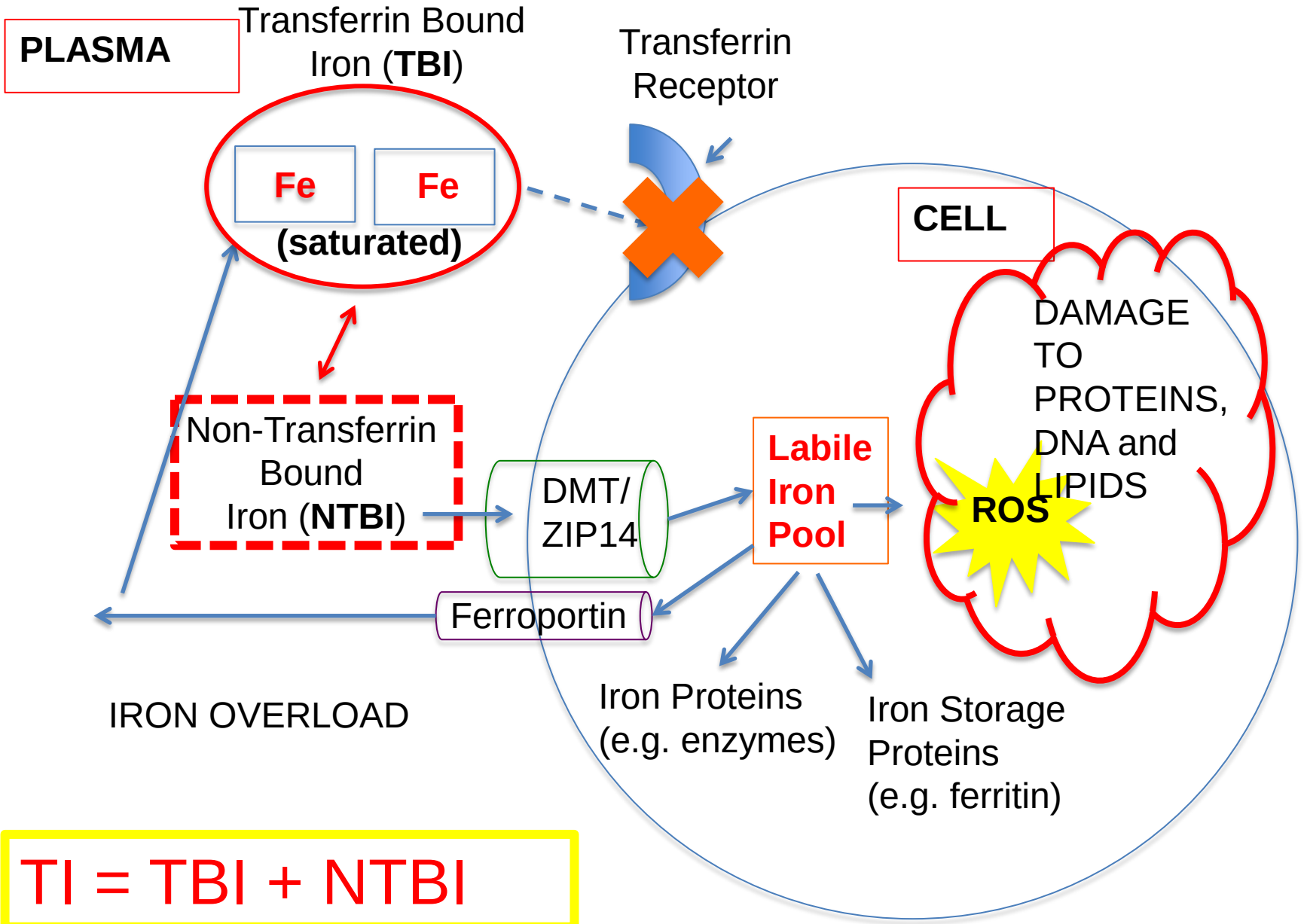


IV iron: iron (III)-oxyhydroxide form stabilized by a carbohydrate complex which leads to nano-sized colloidal structures.

Plasma Iron Acquisition Pathway



Iron Overload



TI = TBI + NTBI

IV iron products

- iron sucrose (Venofer)
- sodium ferric gluconate (Ferrlecit) and one generic
  - sodium ferric gluconate complex in sucrose injection
- iron dextran (CosmoFer) and other BP-rated products
- ferumoxytol (Feraheme)
- ferric carboxymaltose (Ferinject; Injectafe)
- iron isomaltoside (Monofer)
- ferric pyrophosphate citrate (Triferic) [packet for solution]

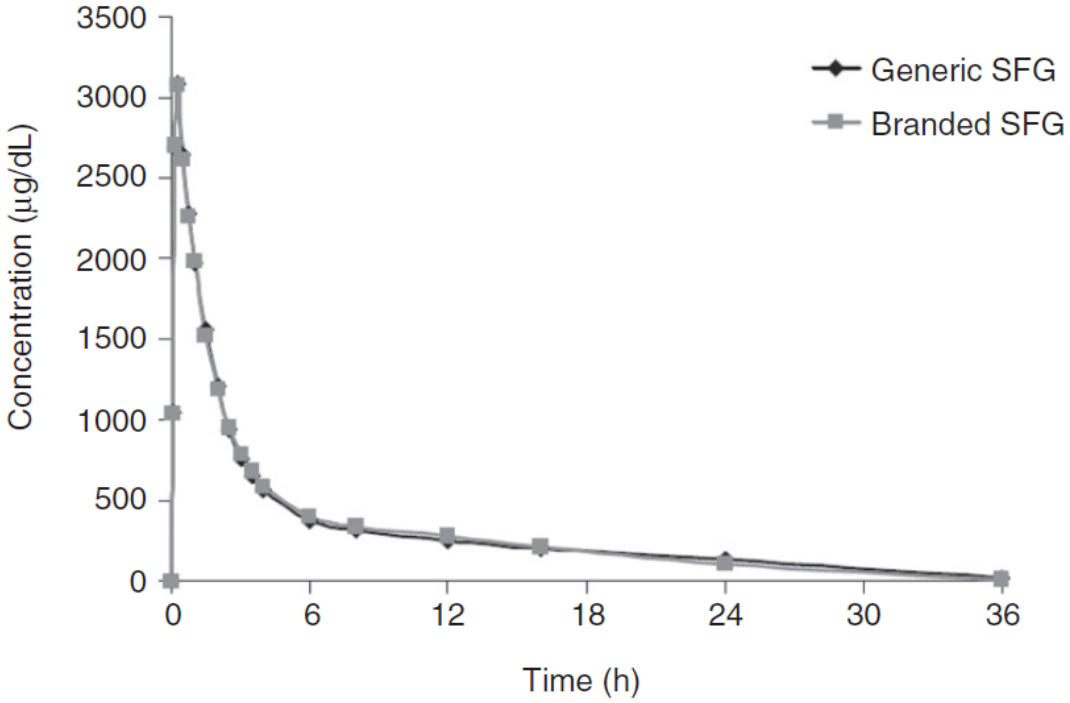
Sodium ferric gluconate complex in sucrose injection

Sodium ferric gluconate complex in sucrose injection

- Ferrlecit (Sanofi-Aventis) and generic (EuroHealth International SARL)
  - Generic approved Mar 31, 2011; AB-rated
- To treat iron deficiency anemia in with chronic kidney disease receiving hemodialysis who are receiving supplemental epoetin therapy
- Hypersensitivity reactions; benzyl alcohol toxicity
- 62.5 mg of elemental iron in 5 mL
- Ferrlecit
  - 195 mg/mL sucrose; 9mg/ml benzyl alcohol; pH 7.7 (generic product pH 7.7-9.7)

Baribeault

- Uncorrected and baseline-corrected mean serum concentrations of total serum iron were similar.

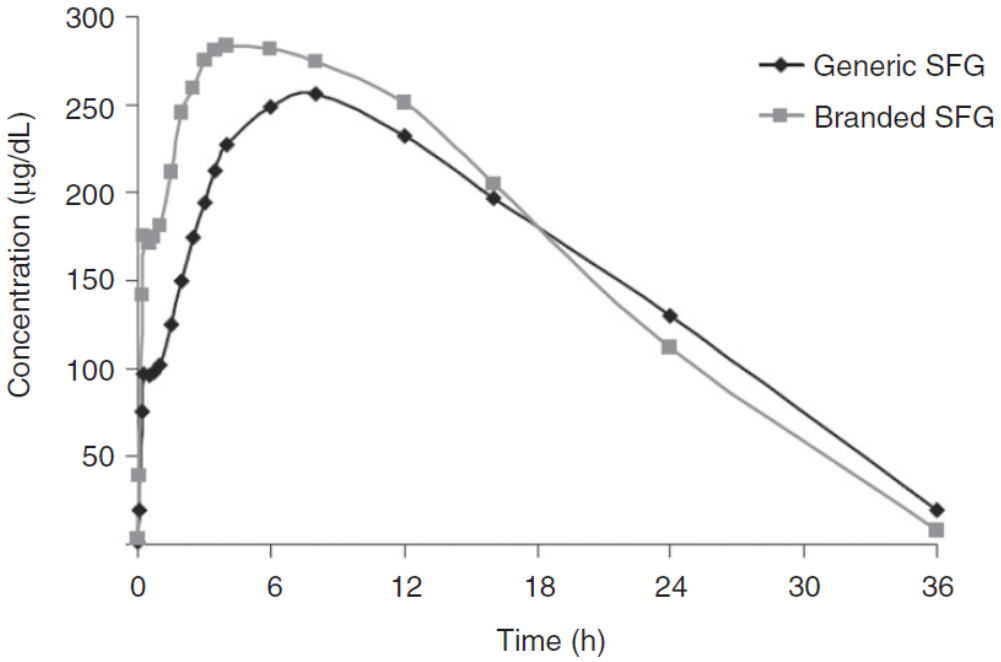


Baseline-corrected mean serum concentrations of total serum iron.

Baribeault D. Sodium ferric gluconate (SFG) in complex with sucrose for IV infusion: bioequivalence of a new generic product with the branded product in healthy volunteers. Current Medical Research & Opinion. 27(8):1653-7, 2011.

Baribeault

- For transferrin-bound iron (TBI), Cmax ratio and AUC ratios were 87% and 92%, respectively.



Baseline-corrected mean serum concentrations of TBI.

EMA 2015

- Reflection paper on the data requirements for intravenous iron-based nano-colloidal products developed with reference to an innovator medicinal product
- “Weight of evidence approach” involving quality, non-clinical, and clinical

2015 EMA

- “difficulty to fully characterise and define iron complex based particles using quality methods alone”
- “conventional bioequivalence studies in humans, would not be sufficient for the assurance of comparability ”
- “The extent of supplementary non-clinical and clinical data required is discussed in the sections below and depends on how accurately the physicochemical and non-clinical characterisation can be used to predict differences that could influence the efficacy and safety of the product.”

2015 EMA

- “An extensive comparability exercise with a single reference medicinal product will be required to demonstrate that the iron-based nano-colloidal product has a highly similar quality profile when compared to the reference medicinal product.”

- “A list of tests to be applied routinely to the iron-based product should be defined, taking relevant pharmacopoeial monographs into account.”
- “[E]xtensive investigations using state of the art characterisation methods should be applied …”

2015 EMA

- “There is insufficient regulatory experience with comparative non-clinical bio-distribution studies to demonstrate similarity of iron-based nano-colloidal products at present.”
- “Single-dose parallel or crossover design is recommended. The primary variables are the AUCt and Cmax of total- and transferrin-bound iron. Baseline correction is recommended to decrease interindividual variability.”

FDA Draft Guidance on Sodium Ferric Gluconate Complex

- Fasting, single-dose 125mg, randomized, parallel in vivo study
  - Healthy males and females
  - Measure: Total iron in serum and transferrin-bound iron (TBI) in serum
  - BE based on: 90% CI of a) maximum value of the difference in concentration between total iron and TBI over all time points measured; and b) difference in AUC between total iron and TBI
  - Particle size distribution
- Requires Q1/Q2
- Requires sameness in physicochemical properties
- Iron core characterizations (e.g. iron oxide crystalline structure), composition of carbohydrate shell, particle morphology, labile iron determinations (e.g. in vitro haemodialysis system)

FDA Draft Guidance on Ferric Carboxymaltose

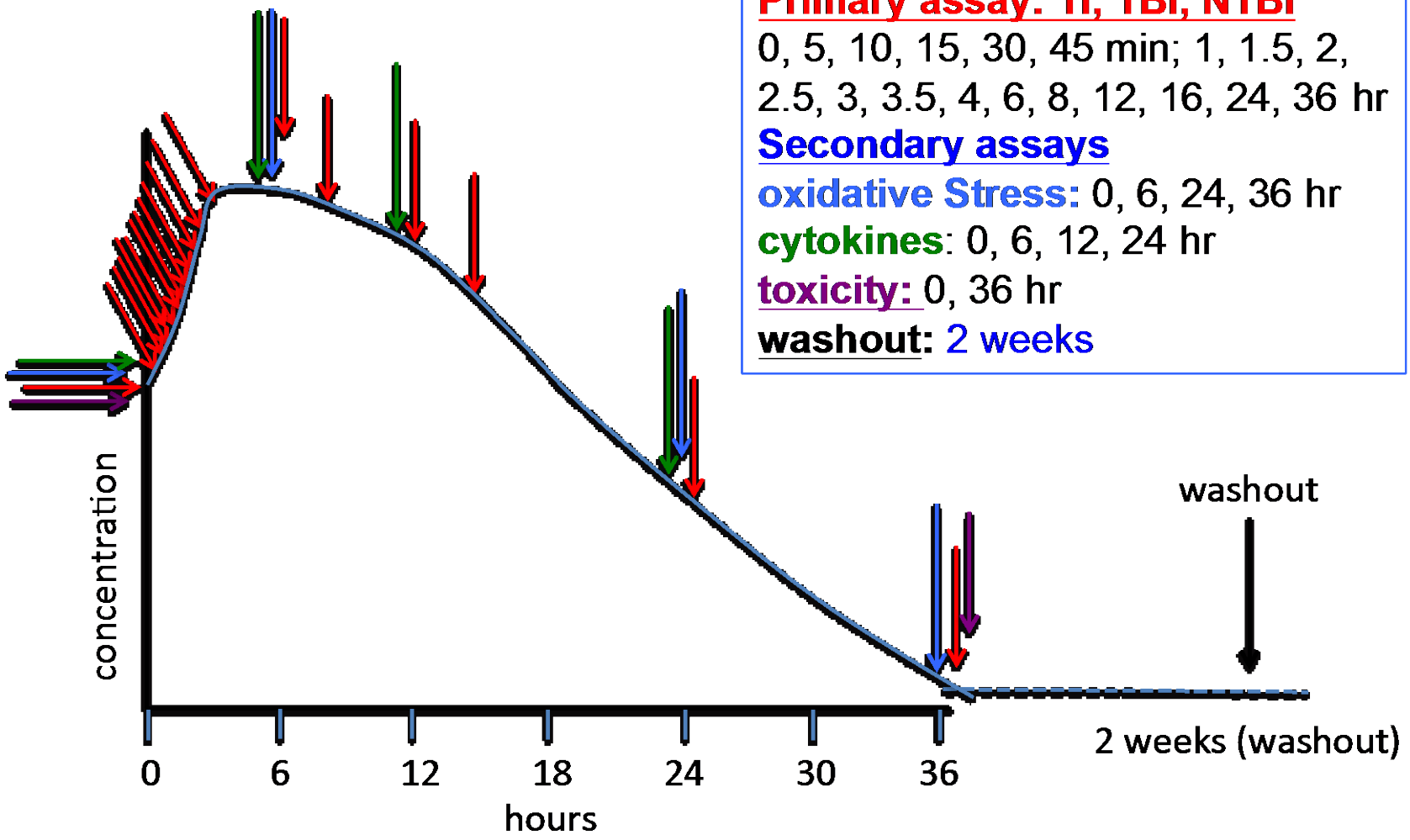
- Fasting, single-dose 750mg, randomized, parallel in vivo study
  - Adult patients with iron deficiency anemia … and/or patients with non-dialysis dependent chronic renal disease
  - Measure: Total iron in serum and TBI in serum
  - BE based on: 90% CI of total iron
- Particle size distribution
- Requires Q1/Q2
- Requires sameness in physicochemical properties
- Iron core characterizations (e.g. iron oxide crystalline structure), composition of carbohydrate shell and surface properties, particle morphology, labile iron determinations (e.g. in vitro haemodialysis system)

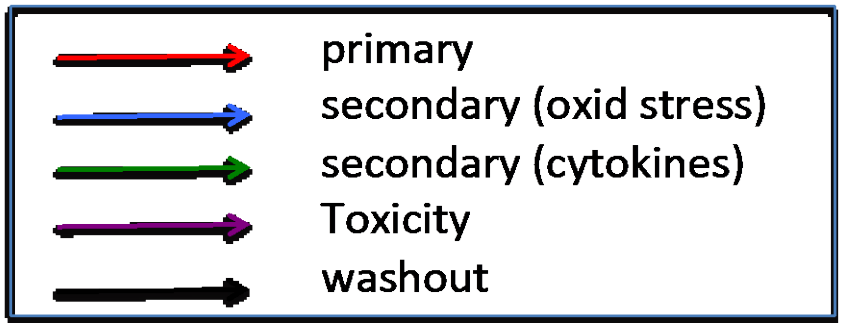
Outline

- Introduction
- Clinical design
- Bioanalytical methods

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

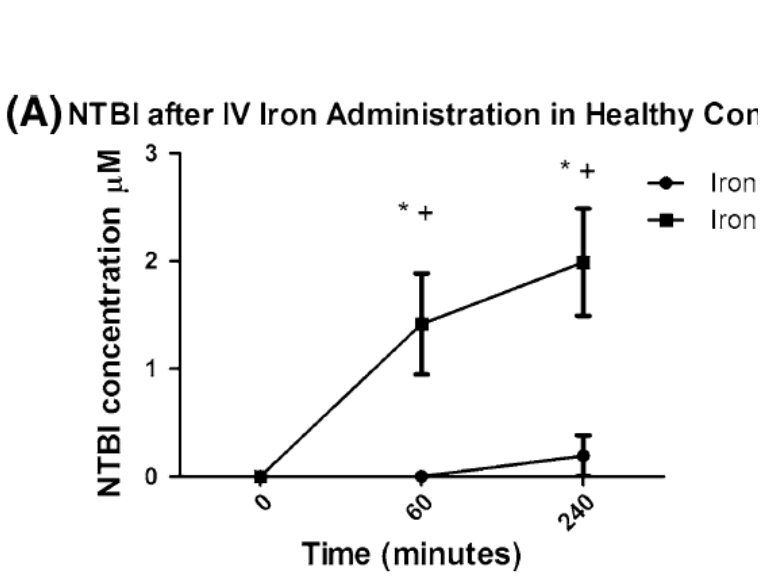
- Primary outcome: non-inferiority of generic against brand with respect to NTBI
  - H0: NTBI exposure from generic is over 1.25-fold greater than brand
- Secondary outcomes: Providing scientific evidence for consideration of any possible additional safety measures
  - Over 34 measures (e.g. total iron, clinical iron measures, glutathione, F2-isprostanes, cytokine panel, liver panel)
- Randomized, open-label, 2-way, cross-over, two period, fasted single-dose study in n=44 healthy subjects
- ICP-MS as read-out for all iron measures: Total iron, TBI, and NTBI

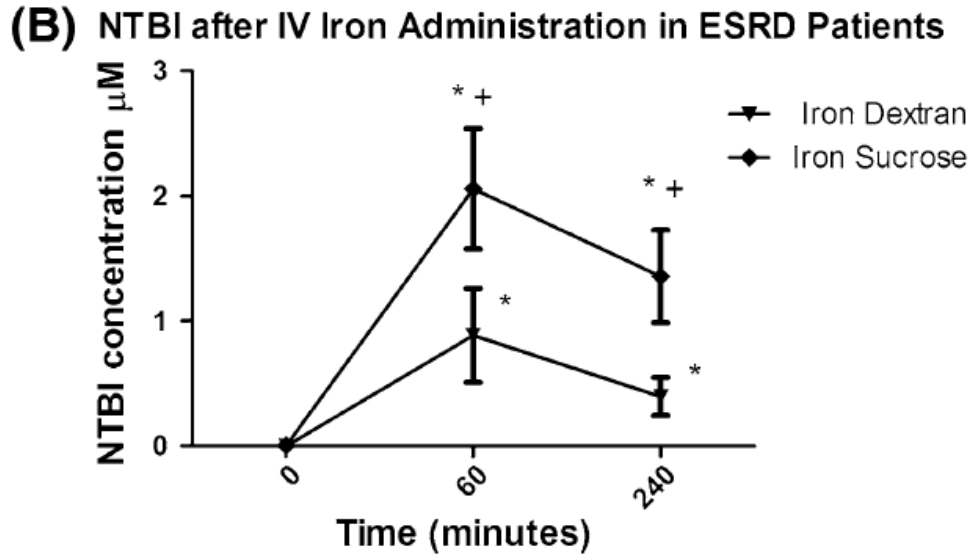

Primary assay: TI, TBI, NTBI
0, 5, 10, 15, 30, 45 min; 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 16, 24, 36 hr
Secondary assays
oxidative Stress: 0, 6, 24, 36 hr
cytokines: 0, 6, 12, 24 hr
toxicity: 0, 36 hr
washout: 2 weeks
concentration
washout
2 weeks (washout)
0
6
12
18
24
30
36
hours


primary
secondary (oxid stress)
secondary (cytokines)
Toxicity
washout

NTBI

- Intro





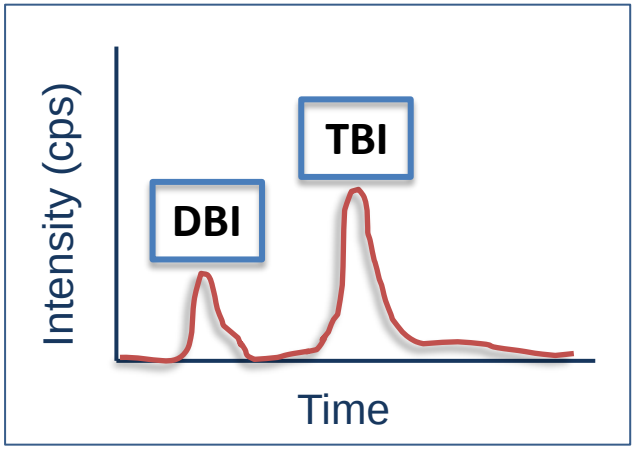
Pai AB; Conner T; McQuade CR; Olp J; Hicks P. Non-transferrin bound iron, cytokine activation and intracellular reactive oxygen species generation in hemodialysis patients receiving intravenous iron dextran or iron sucrose. BioMetals. 24(4):603-13, 2011.

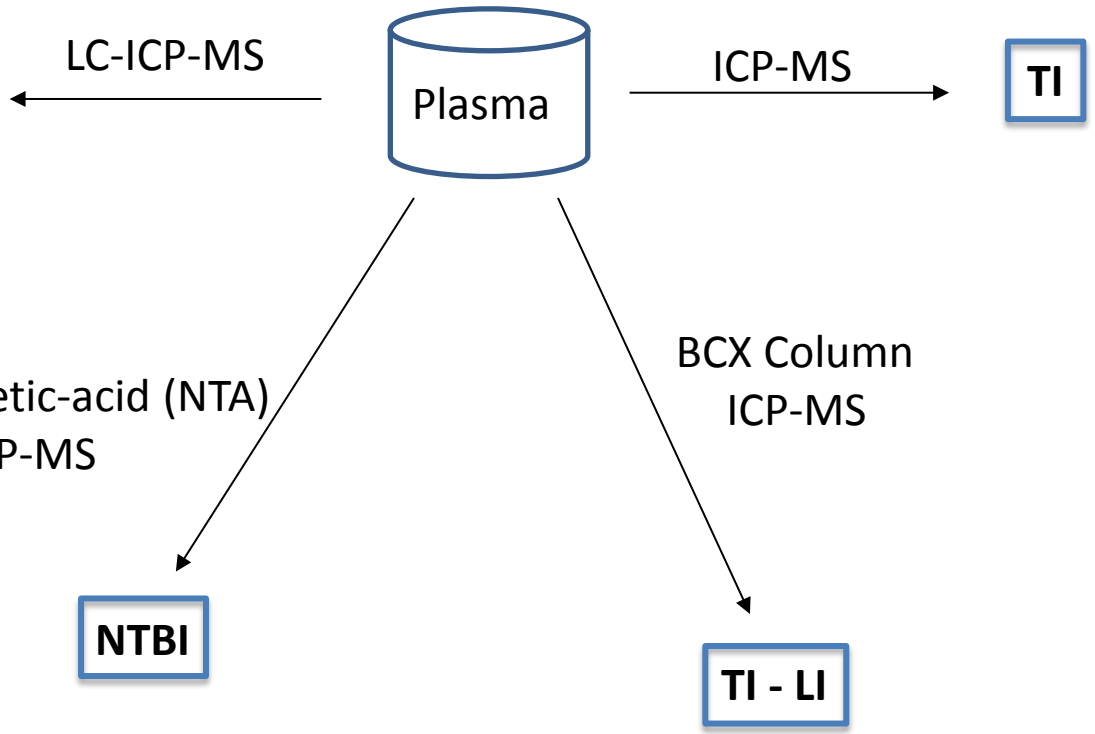
Type of iron	Level before infusion	Level after infusion
TI	Male: 0.49-1.81 ppm Female: 0.37-1.70 ppm	Approx. 30 ppm
TBI	Approx. same as above	Approx. 3.5 ppm
Labile iron	Perhaps 0.05 ppm	Perhaps 0.1 ppm
Drug bound iron	0	125mg/5L = 2500 mcg/dL = 25 ppm

Outline

- Introduction
- Clinical design
- Bioanalytical methods

Our strategy:





TI = TBI + NTBI

NTBI = DBI + LI

Terms:

TI = Total Iron in Plasma

TBI = Transferrin Bound Iron

NTBI = Non-transferrin Bound Iron

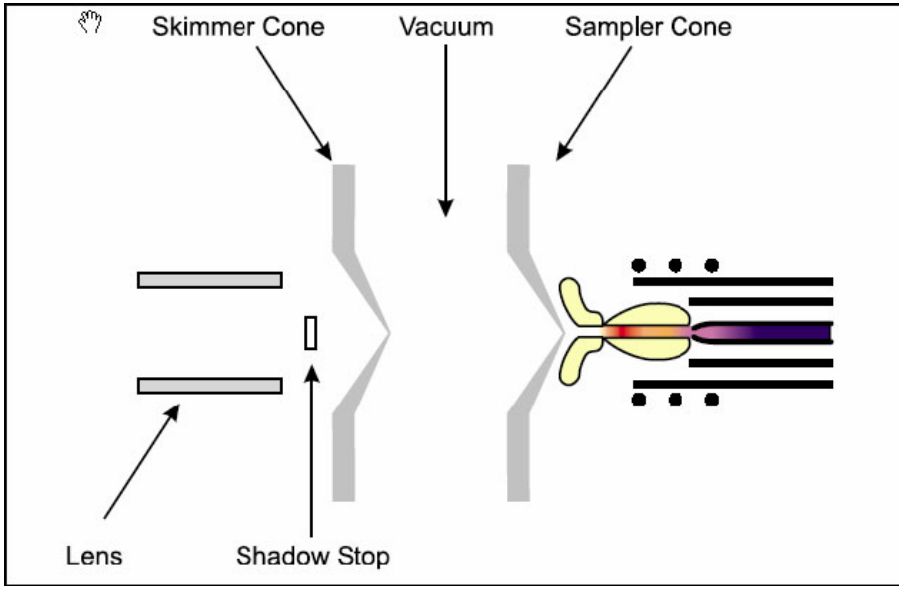
DBI = Drug Bound Iron

LI = Labile Iron (Fe-Albumin, Fe-Citrate, “free” Fe)

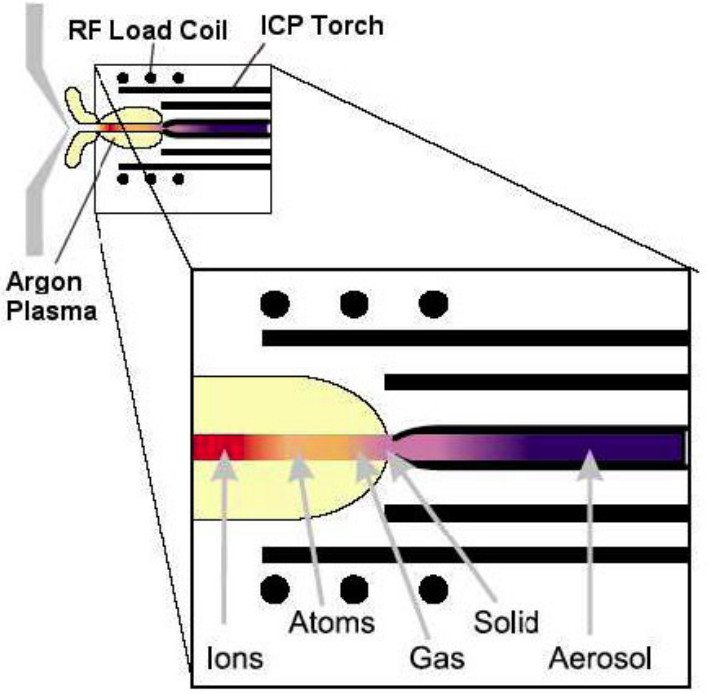
Inductively coupled plasma mass spectrometry (ICP-MS)

- Combines a high-temperature ICP (Inductively Coupled Plasma) source with MS
  - ICP is different than thermal ionization
    - ICP is a plasma source where energy is obtained by electric currents (which are produced by electromagnetic induction, i.e. magnetic fields)
  - Plasma is one of the four states of matter
    - Most abundant matter in universe (and in neon signs!)
    - Unlike gas, plasma forms structures under a magnetic field
  - High temperature of ICP helps minimizes matrix interferences (e.g. destroys molecular bonds) and preferentially yield M+
  - ICP ionizes the atoms the sample elements

Inductively coupled plasma mass spectrometry (ICP-MS)

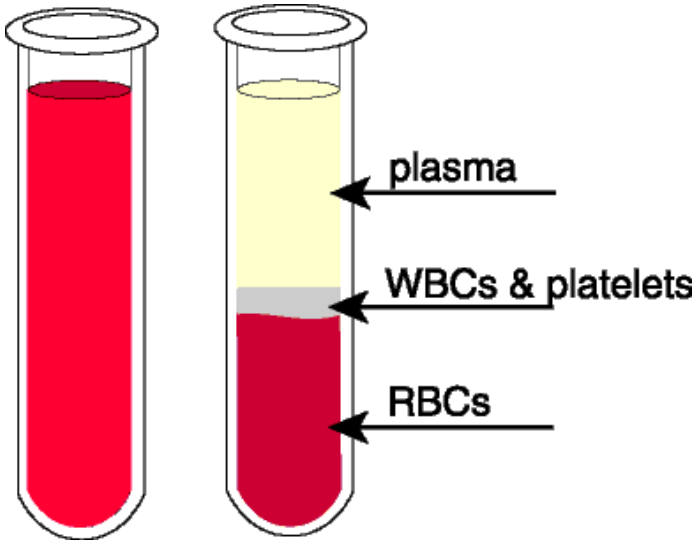


The interface region of an ICP-MS.



Sample subjected to ionization by ICP.

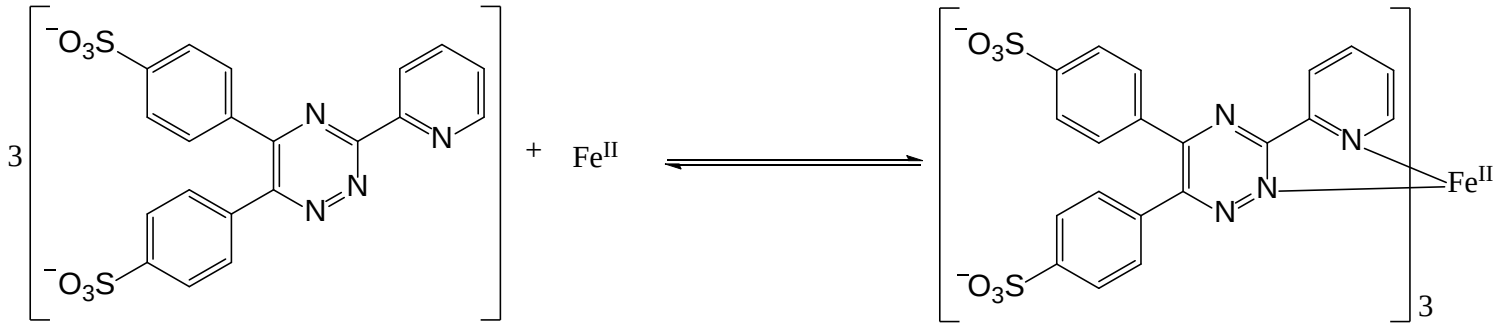
Total Iron (TI)



+

Measure total iron via ICP-MS

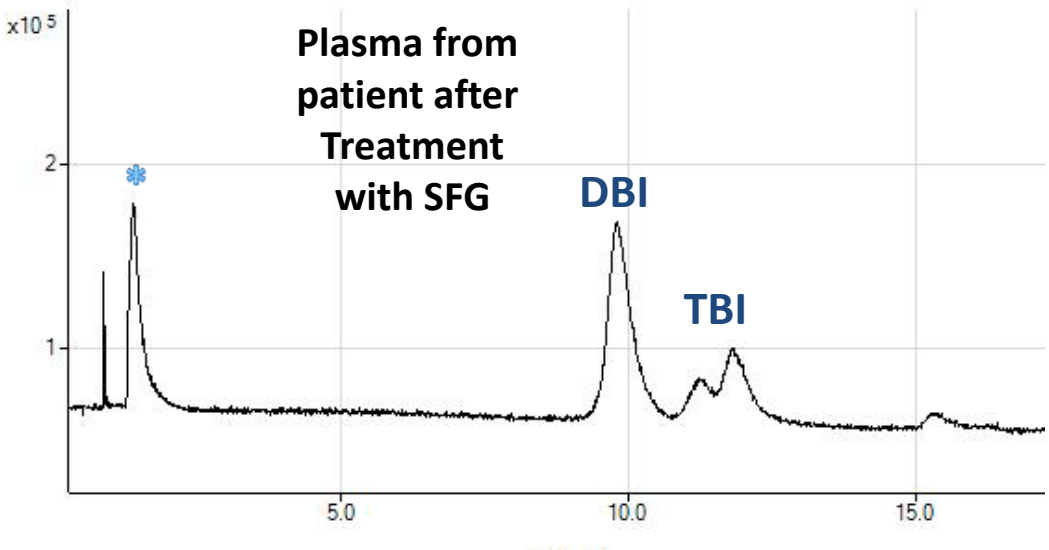
Control: ferrozine assay



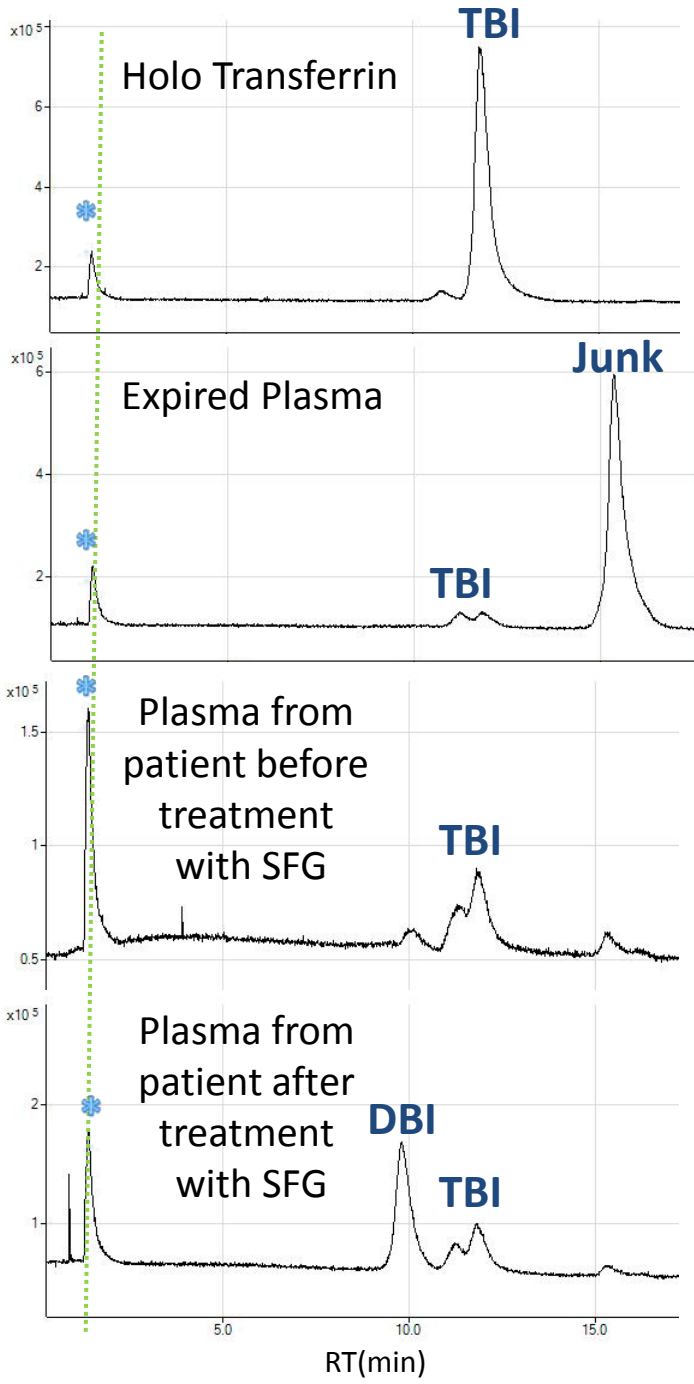
(λ_{max} = 600 nm)

Riemer J, Hoepken HH, Czerwinska H, Robinson SR, & Dringen R (2004) Colorimetric ferrozine-based assay for the quantitation of iron in cultured cells. *Anal Biochem* 331(2):370-375.

LC-ICP-MS to measure TBI and DBI

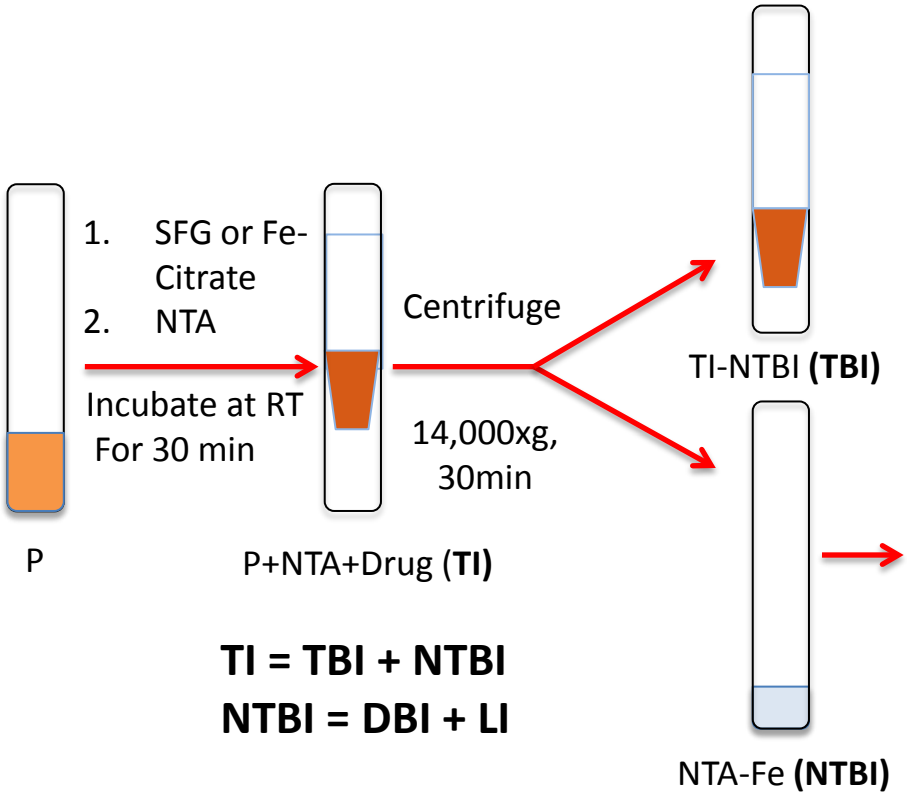


size exclusion chromotography



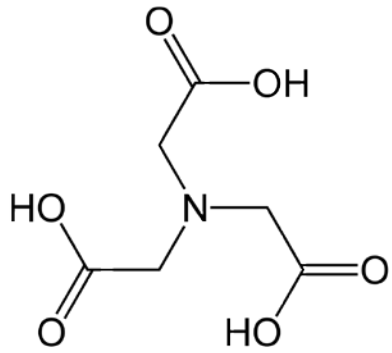
❄ = Post column iron standard

Non-Transferrin Bound Iron (NTBI)



TI = TBI + NTBI

NTBI = DBI + LI



Nitrilotriacetic-acid (NTA)

Terms:
TI = Total Iron in Plasma
TBI = Transferrin Bound Iron
NTBI = Non-transferrin Bound Iron
FC= Ammonium Fe(III) Citrate
P= Plasma
SFG = Sodium Ferric Gluconate

Method adopted and modified from Gosriwatana, I., Loreal, O., Lu, S., Brissot, P., Porter, J., & Hider, R. C. (1999). Quantification of non-transferrin-bound iron in the presence of unsaturated transferrin. Analytical biochemistry, 273(2), 212-220.

Outline

- Introduction
- Clinical design
- Bioanalytical methods