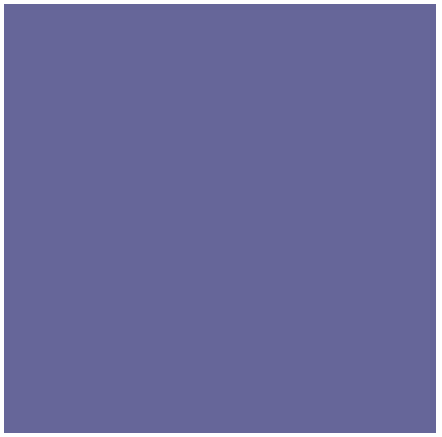
Relevant Challenges in Determination of Bioequivalence of Generic IV Iron Formulations



Amy Barton Pai, Pharm.D., BCPS, FASN, FCCP, FNKF
Professor
Albany College of Pharmacy and Health Sciences
Albany, NY
amy.bartonpai@acphs.edu

Disclosures

- No relevant financial or nonfinancial relationships to disclose

+ Addressing Regulatory Science Initiatives for Generic Drugs

- **Alignment with FY 2016 Priorities: Equivalence of Complex Products**
  - "…scientific research supports the development of guidance and policy that clarifies ANDA pathways for complex drugs including nanomaterials (iron colloids…)"

- Innovative approaches to pre-approval development of generic drugs, including new methodologies for design and conduct *of* ***in vitro, ex vivo****, and clinical studies and* ***identification of scientifically robust strategies for demonstration of bioequivalence for various product classes***

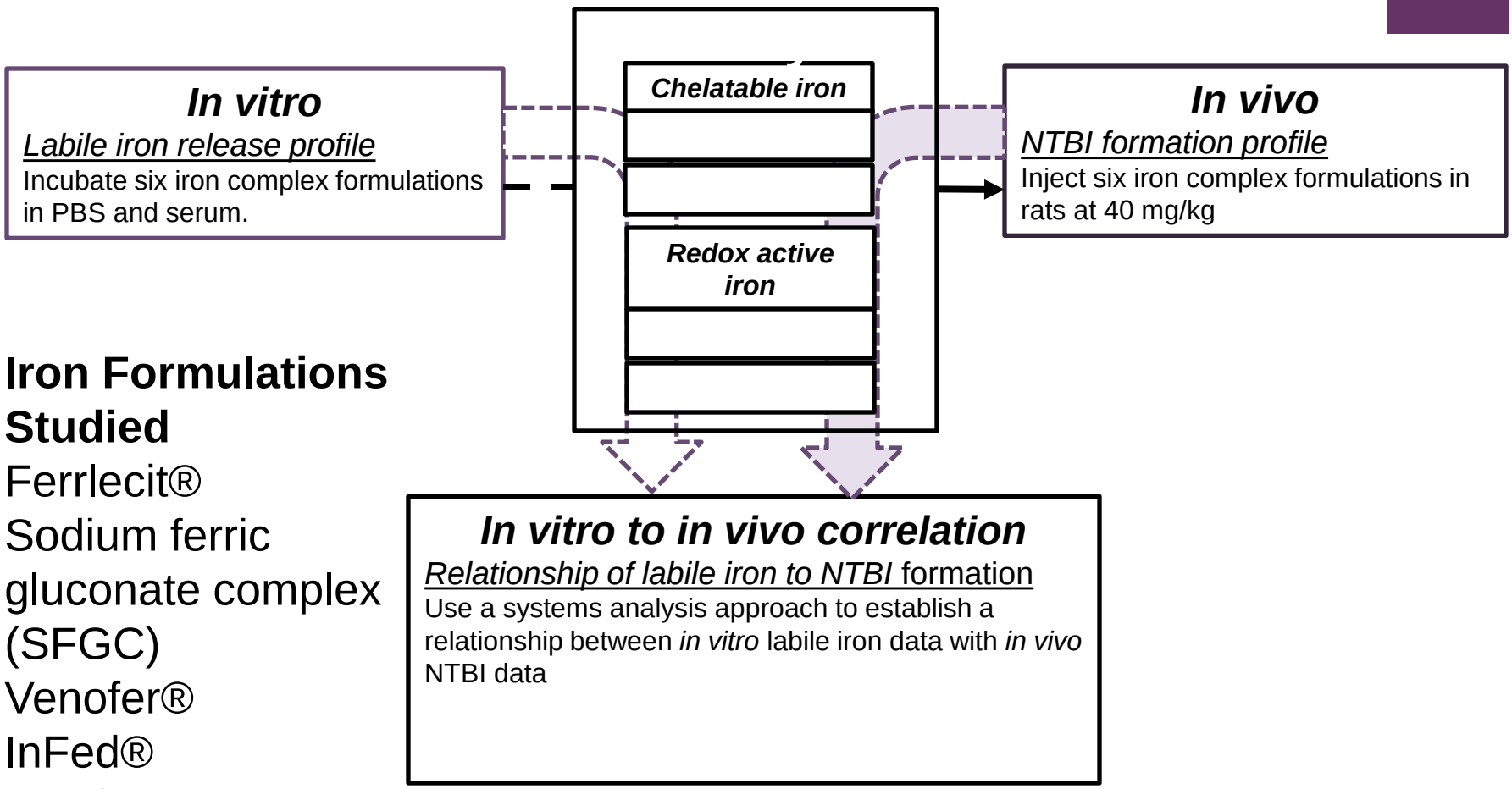
http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM469453.pdf

Experience in the Global Market with Generic IV Iron Formulations

- Many generic iron sucrose products available globally
  - Regulatory oversight for development variable
  - Mandated generic switches common
- Animal data show increased oxidative stress induction and higher tissue iron deposition with generic products compared to reference listed drug (RLD)
- Clinical observational studies have demonstrated reduced efficacy and increased adverse event profiles with generic products vs. the RLD
- Differential safety and adverse event profiles have been mechanistically linked to direct release of labile iron from the formulations

Toblli JE. Biometals. 2015 Apr;28(2):279-92; Kuo KL. et al J Am Soc Nephrol. 2014 Nov;25(11):2596-606;, Stein et al. Curr Med Res Opin. 2012 Feb;28(2):241-3. Lee ES. Curr Med Res Opin. 2013 Feb;29(2):141-7., Aquera ML et al. PLoS ONE 2015;10(8), Pai AB Biometals

Systematic Approach to Predict Serum Non-transferrin Bound Iron (NTBI) from IV iron Formulations

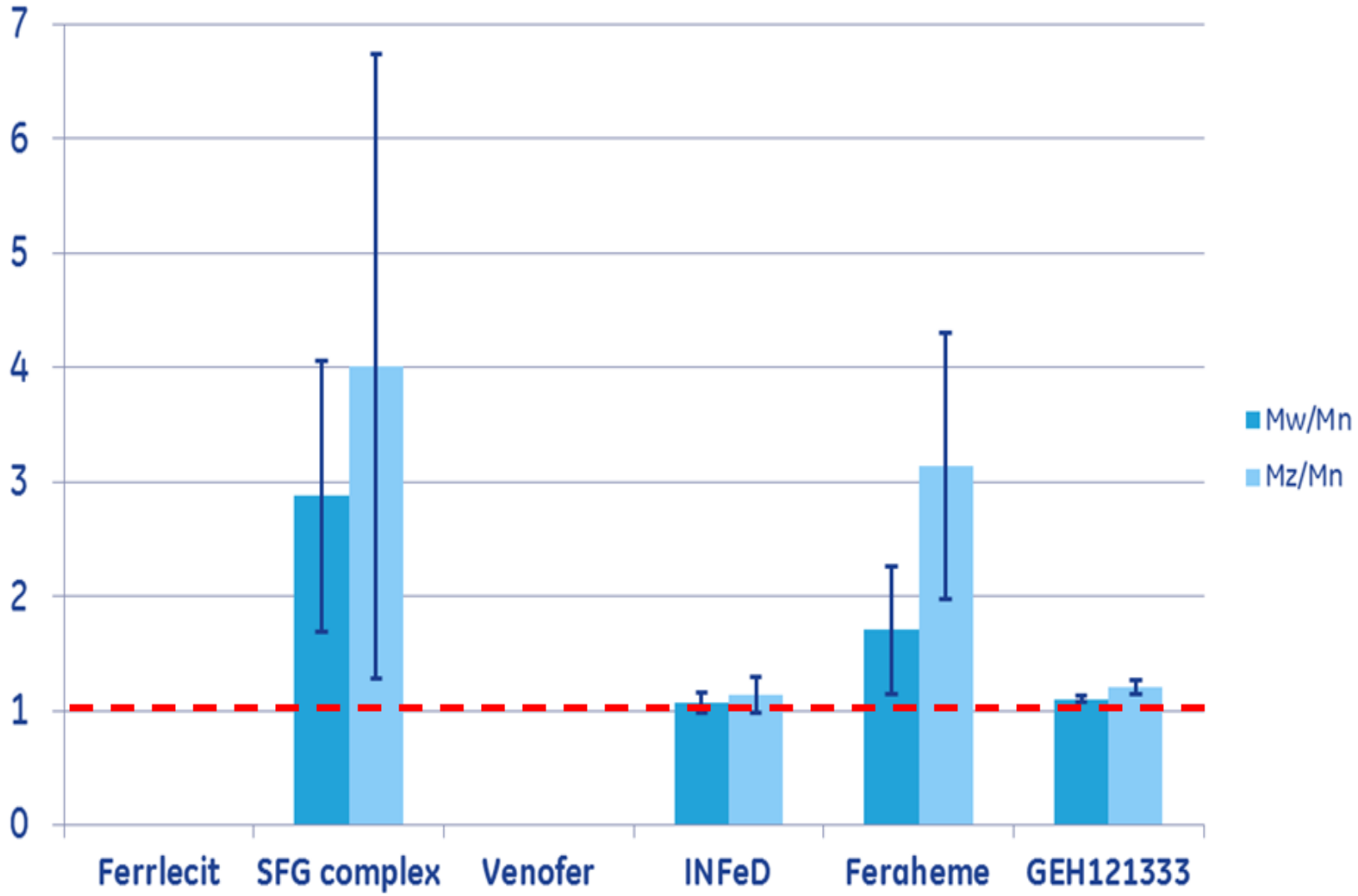


Iron Formulations Studied

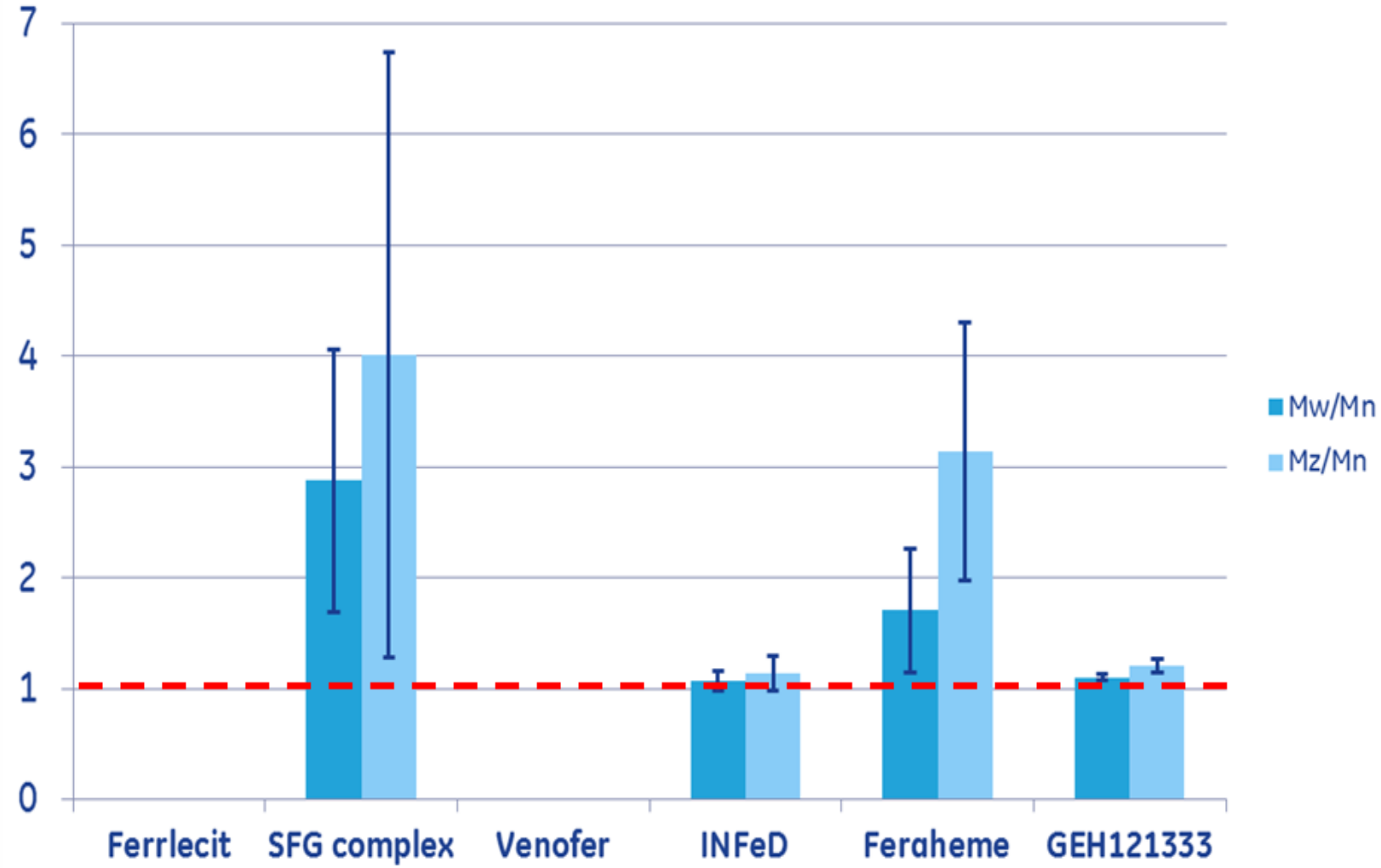
Ferrlecit®
Sodium ferric gluconate complex (SFGC)
Venofer®
InFed®
Feraheme®
GEH121333

Pai AB NIH 1U01FD004889-01

Physicochemical Characterization



Polydispersity Assessment: Field Flow Fraction-Quasi-elastic Light Scattering

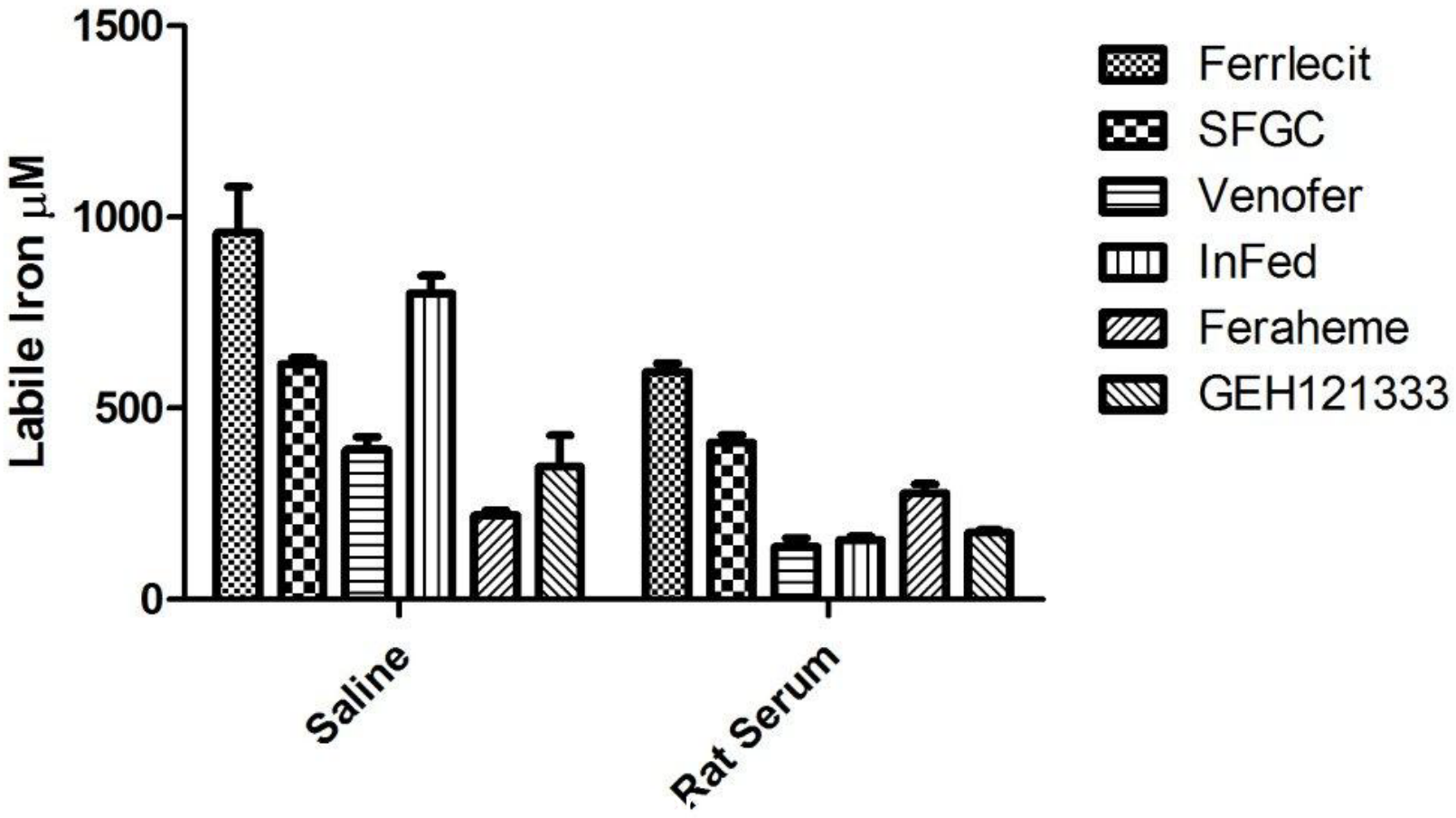


Assessment of Labile Iron Release *In Vitro*

Labile Iron Assay	Assay Method	Approximate LOD	Practical limitations	*In vitro* limitations
Bleomycin detectable iron (BDI)	Redox active iron	10 µM Fe	Narrow assay dynamic range (10-100µM). Non-linear calibration response curve.	Apparent interference in the presence of agent complex.
Rhodamine fluorescence conversion	Redox active iron	30 µM Fe	Reaction product is very sensitive in ambient conditions and degrades rapidly.	No detectable signal in the presence of agents.
Directly chelatable iron: FL-DFO	Chelatable iron	2 µM Fe	Narrow assay dynamic range (~2-~60µM). Non-linear calibration response curve.	Reduced or abolished fluorescence in the presence of agents
HPLC-DFO	Chelatable iron	20 µM Fe	None	Kinetic effect of DFO binding to labile iron

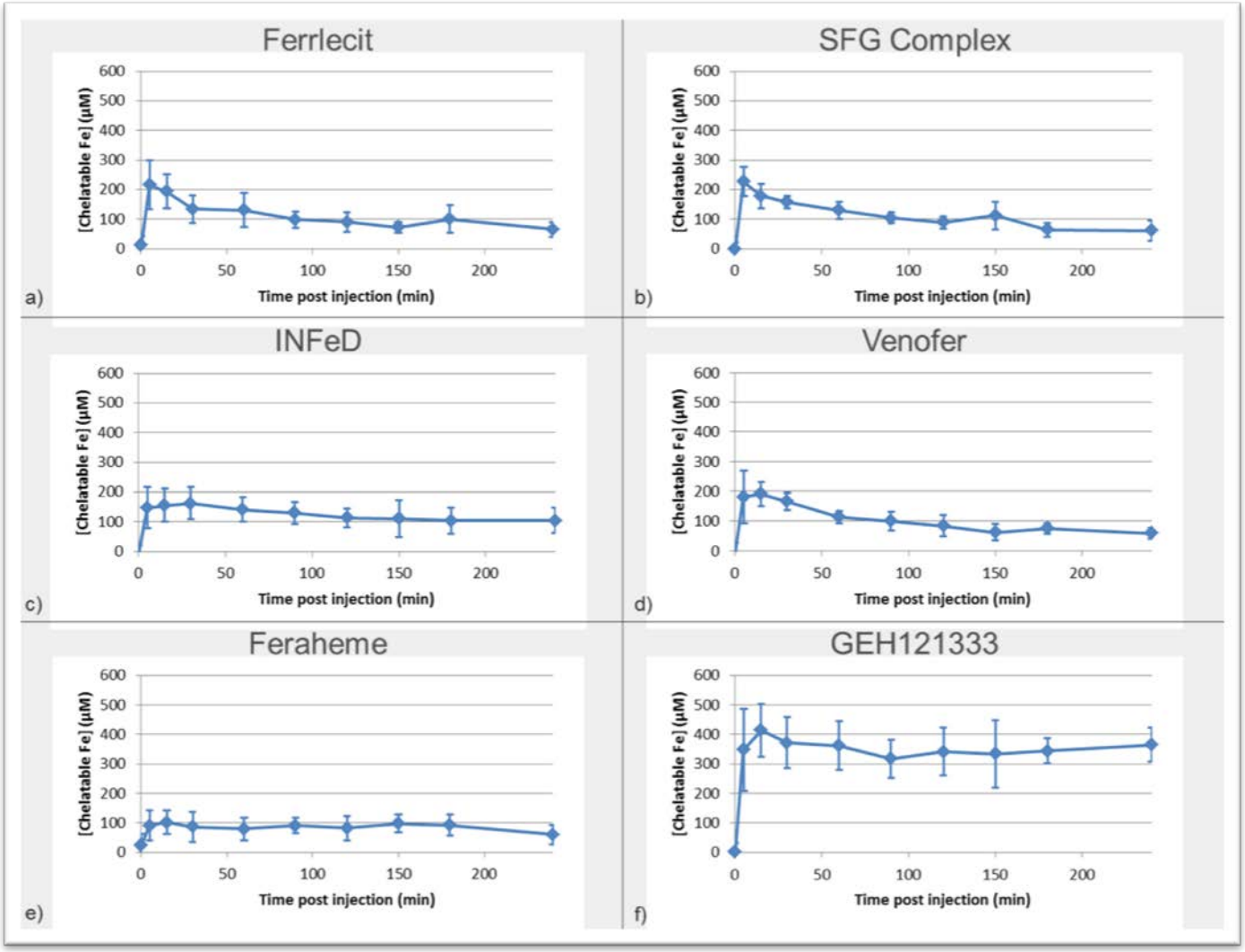
LOD=limit of detection, DFO=desferroximine

Labile Iron Release from IV Iron-Complexes *in vitro*



All IV iron formulation final concentrations = 0.952 mg/mL

Labile Iron Release Profiles *In Vivo**



3 Stage Process

1. Dose Finding
2. Initial PK
3. Final PK

* Male Sprague-Dawley rats receiving single doses of 40 mg/kg

PK Analysis of Labile Iron *In Vivo*

Formulation	CLt/F (mL/min)	Vc/F (mL)	K_r (min^{-1})	Half-life (min)
Venofer	6.49 (39.9)	1041 (17.1)	**2.22 (24.1)**	129 (37.5)
Ferrlecit	5.43 (40.3)	1075 (33.4)	**2.02 (33.9)**	163 (50.6)
SFGC	4.86 (36.6)	987 (20.2)	**2.07 (41.8)**	192 (72.8)
InFeD	3.41 (47.0)	1245 (19.7)	**1.07 (30.2)**	360 (50.1)
Feraheme	3.59 (69.7)	1972 (35.6)	**0.701 (66.1)**	565 (48.7)
GEH121333	0.774 (46.2)	506 (21.1)	**0.972 (28.7)**	623 (33.4)

Mean (%CV) system parameter estimates, No fixed parameters, Kr (min^{-1}) represents the rate of direct release of labile iron from the iron-carbohydrate complex

Summary

Requests from FDA OGD to promote generic IV iron ANDA efficiency enhancement

- Further evaluation of PCC limitations for inter-product comparison
- Study additional formulations *in vitro* and *in vivo*
- Evaluate lot-to-lot variations
- More clearly define the optimal assay for labile iron measurement both *in vitro* and *in vivo*
- Conduct further analyses to evaluate viable *in vitro* to *in vivo* correlation models for labile iron release for potential inclusion in guidance
- Post-marketing surveillance of generic IV iron usage patterns and adverse events
- Clinician awareness of bioequivalence challenges

http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM282505.pdf

Questions?