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Gaps In Bioequivalence Evaluation (BE) of Complex Drugs How Can Global Experience with IV Iron Generics Advance BE?

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Iron Sucrose in the Global Market

- Iron sucrose (RLD Venofer®) is widely used and is the most frequently administered product in dialysis patients
  - More than 30% of US dialysis patients receive up to 4.8 grams of elemental iron from IV iron formulations annually
  - The average healthy person absorbs 1-2 mg of iron per day
- Many iron sucrose “similars” (ISS) available in Europe, Asia, South America
- Switches often mandated
- Emerging published data on these products across the translational research continuum

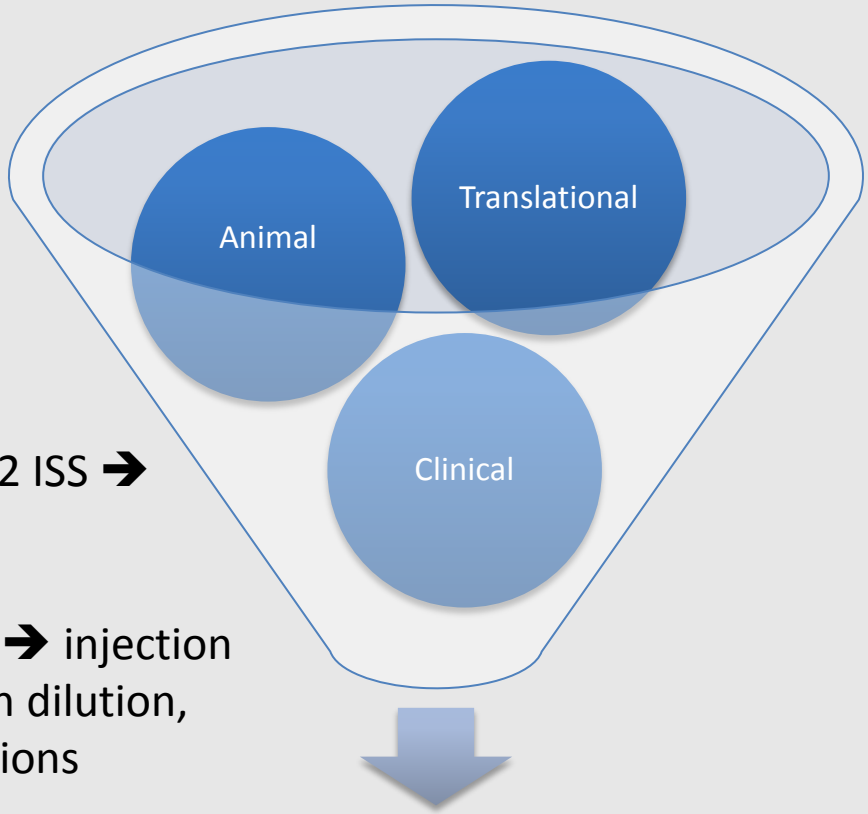
Aster, A., Pai AB, Bissig M., Ann NY Acad Sc, 2017 (in press), Bailie GR., Kidney Int. 2015

Data Across the Translational Research Continuum Implicates Labile Iron-Associated Adverse Effects

Toblli et al. 2011, 2012
ISS vs RLD ➔ increase oxidative stress, cytokine activation, tissue deposition

Stein et al, 2012 ISS ➔ hypotension

Lee et al. 2013 ➔ injection reactions > with dilution, lot-to-lot variations observed



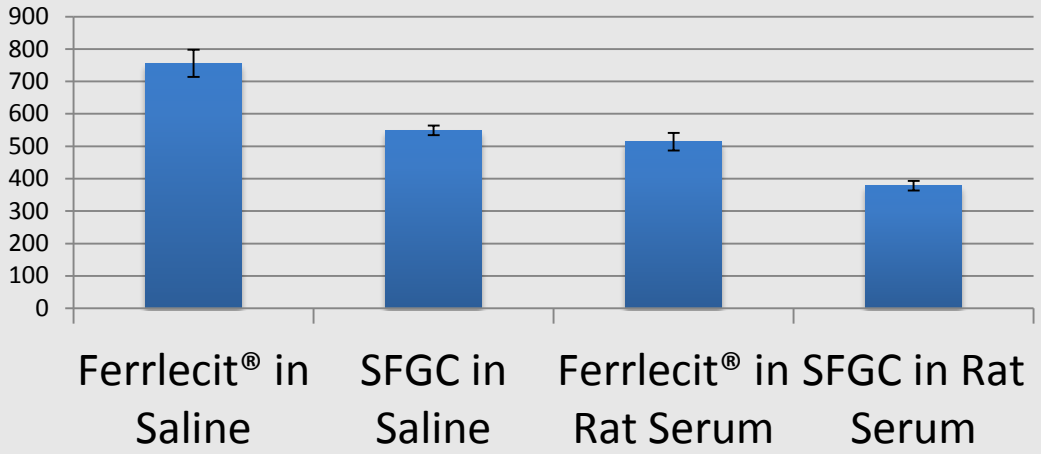
Differences in Formulation-Based Labile Iron (LI) Release

Kuo et al. 2014 ISS vs control➔ oxidative stress, vascular reactivity and damage

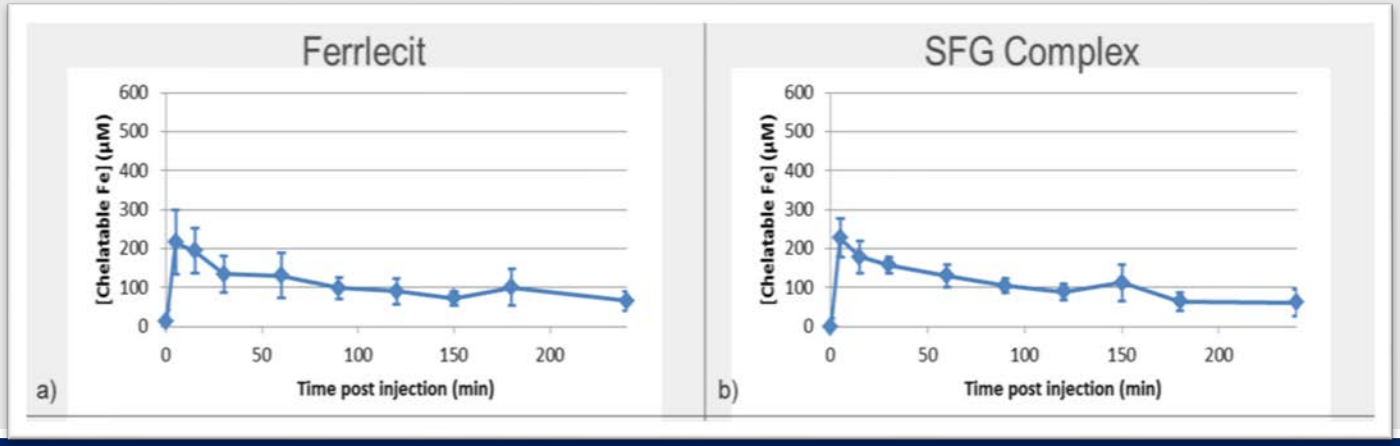
Martin-Malo et al, 2012
ISS vs RLD➔ ISS increase oxidative stress, vascular damage, cell death

LI Release Profile of SFGC vs. RLD Ferrlecit®

Mean (95% CI) *in vitro* LI Concentration (0.95 mg/mL)*



Mean (SD) *in vivo* LI Concentration after 40 mgFe/kg IV in healthy male rats



*Pai AB et al. Clin Transl Sci, 2017

Labile Iron Release Profiling is a Pragmatic Approach to Augment Physicochemical Characterization

- Physicochemical Characterization (PCC) Challenges
  - Inter-lab variability, dilution of formulations (buffers other reagents), instrumentation
- Labile iron (LI) profiles are informative to confirm no significant differences exist in the rate and extent of LI release and support other *in vitro* dissolution techniques
- *In vitro* profiling in serum matrices is technically easy and potentially more sensitive, eliminates confounders of ambient physiological conditions
- More generic formulations and lots need to be studied to evaluate a preliminary IVIVC model

Zheng et al. AAPS J, 2017, Pai AB et al. Clin Transl Sci, 2017

Summary

- BE for IV iron is uniquely challenging
- Evaluating labile iron release profiles represents pragmatic approach to potentially augment PCC for BE of generic IV iron formulations
- Clinician awareness regarding the complexity of IV iron formulations and BE challenges remains limited
- Postmarketing surveillance and medication use evaluations will be important to understand clinical safety and outcomes of generic IV iron formulations