Colloidal Intravenous Iron Preparations: Survey of Bioequivalence Recommendation and Quality of Submission in Abbreviated New Drug Applications (ANDAs)
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Purpose
Intravenous (IV) iron drug product is used as an important therapeutic treatment for iron-deficiency anaemia. However, developing generic products in this class of drugs can be very challenging due to the following reasons: 1) IV irons are colloidal suspensions instead of solutions; 2) the active pharmaceutical ingredient (API) is a macromolecular complex with an iron containing core enced in a hydrophilic carbohydrate shell; 3) assessment of pharmacokinetics (PK) of IV iron is difficult due to presence of endogenous iron and the complexity of iron metabolism; and 4) the characterization of physicochemical properties such as the colloidal structure and API complex stability are critical to drug safety and efficacy. In this study, we compared the properties of approved brand-name IV iron products and the product specific bioequivalence (BE) recommendations for different generic IV iron products. We surveyed the submission quality of BE study portions, and identified most commonly-occurring BE deficiencies in ANDA submissions in this class. The collected information is intended to assist the pharmaceutical industries to accelerate the approval of generic IV irons in the future.

Methods
The FDA’s “Orange Book” was searched for the approved brand-name IV iron products and the product characteristics were retrieved from the drug product labels available at Drugs@FDA. The FDA’s individual product BE recommendations for these specific generic IV irons were then collected. Finally, the quality evaluation of existing IV iron ANDAs submitted from 12/1/2005 to 5/9/2016 was performed based on the information in FDA internal database.

Results
Currently, there are five (5) brand-name IV iron products approved for clinical use in the United States (in chronological order): 1) INFED® (iron dextran), 2) FERRLECIT® (sodium ferric gluconate complex in sucrose), 3) VENOFER® (iron sucrose), 4) FERAHEME® (ferumoxytol), and 5) INJECTAFER® (ferric carboxymaltose). These IV irons are all colloidal suspensions with API as iron-carbohydrate macromolecular complex. However, they are different in the aspects such as 1) dose; 2) iron oxide core molecular formula and crystal structure; 3) carbohydrate ligand that is used to stabilize the complex and protect it against further polynuclearization; 4) iron-carbohydrate complex molecular weight and 5) complex thermodynamic and kinetic stability.

The Office of Generic Drugs (OGD) issued product-specific BE guidance recommendations for sodium ferric gluconate complex in sucrose and iron sucrose on June 2013, and March 2012 (revised on November 2013), respectively. To establish BE for these two products, the OGD currently recommends one in vivo single-dose parallel designed fasting study, one in vitro particle size distribution (PSD) study, in addition to qualitatively (Q1) and quantitatively (Q2) the sameness in formulation, and sameness in physicochemical properties such as iron core, carbohydrate shell, particle morphology and labile iron. Drug bound iron (DBI) are recommended as the basis of BE in the in vivo PK study, where DBI can be approximated by the difference between baseline uncorrected total iron (TI) and transferrin-bound iron (TBI) in serum in the aforementioned two IV irons.

From 12/1/2005 to 5/9/2016, only 11 ANDAs in this class have been evaluated from BE standpoint. The most common deficiencies were in the following categories:

1. Inadequate bioanalytical methodology in in vivo Fasting study:
   1) Conducting unjustified bioanalytical repeats;
   2) Failure to submit adequate long-term storage stability data;
   3) Inadequate study design such as not selecting correct matrix and reference standards for preparation of quality control samples and calibration standards, using surrogate matrix without justification, and inadequate validation when using same biological matrix as study analyte.

2. Insufficient understanding of drug product and BE guidance:
   1) 27.3% applications applying waiver as IV solution under 21 CFR § 320.22(b)(1) and missing all recommended studies;
   2) Using crossover in vivo fasting study design instead of the recommended parallel study design without justification;
   3) Missing formulation and comparative physicochemical properties data.

3. Incomplete ANDA submission:
   1) Failure to submit standard operating procedures (SOPs);
   2) Failure to submit required data and chromatogram;
   3) Missing validation report for analytical method.

Conclusion
Colloidal IV iron product is a unique and complex drug class that requires special considerations in generic drug development. The current ANDAs demonstrate a lack of understanding of drug characteristics, and recommendations in the product specific BE guidance and “Guidance for Industry: Bioanalytical Method Validation” when developing and validating the assay for endogenous compound that delay their approval. By understanding these issues, we hope to improve the submission quality and reduce the cycle of reviews, which will be of great benefit to the generic drug industry and the American public.