Relevant Challenges in Determination of Bioequivalence of Generic IV Iron Formulations

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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

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

In vitro Labile iron release profile
Incubate six iron complex formulations in PBS and serum.

In vivo NTBI formation profile
Inject six iron complex formulations in rats at 40 mg/kg

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

In vitro to in vivo correlation
Relationship of labile iron to NTBI formation
Use a systems analysis approach to establish a relationship between in vitro labile iron data with in vivo NTBI data

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

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Physicochemical Characterization

- Ideal: PCC is able to reliably identify differences among RLD and generic candidates that would predict labile iron release.
- Dilemma: Formulation complexity and variable stability profiles of IV iron formulations creates challenges in reliability and reproducibility of PCC.

![Graph showing MW/Mn and Mz/Mn values for various iron formulations.](image-url)
Polydispersity Assessment: Field Flow Fraction-Quasi-elastic Light Scattering
## Assessment of Labile Iron Release

*In Vitro*

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

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*

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

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

Questions?