Developing a European Pharmacopoeia monograph for non-biological complex drugs: What do we need to know?

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NanoDiaRA
Particles, Molecules & Cells · Diagnosis in-vitro & in-vivo · Rheumatoid Arthritis & Osteoarthritis

Berne, Switzerland
27./28.09.2013
Clinical data

Venofer® substitution by an ISS in stable HD patients (observational study)

<table>
<thead>
<tr>
<th>Period 1</th>
<th>Sept 2009 (3 mo)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum ferritin (µg/L)</td>
<td>533.8 (327.5)</td>
<td>457.7 (290.4)</td>
</tr>
<tr>
<td>TSAT %</td>
<td>49.3 (10.9)</td>
<td>23.3 (10.2)</td>
</tr>
</tbody>
</table>

↓ Serum ferritin* ↓ TSAT*
*checked every 3 mo

Rottembourg et al., Nephrol Dial Transplant 2011
Non-Biological Complex Drugs (NBCD)

- Synthetic, not a biologic
- Large molecular nanoparticle
- Polymeric (mix) product
- The entire complex is the active pharmaceutical ingredient
- The properties cannot be fully characterized by physicochemical analysis
- The manufacturing process is fundamental to create the product and difficult to control

Adapted from poster PHC030 17th EAHP conference 2011

A Iron sucrose (iron carbohydrates)
B Liposomal drugs
C Glatiramoids (polypeptides)
Complex Drugs

- Complex drugs cannot be fully characterized.
- The generic paradigm does not apply for intended copies of complex drugs.
- Demonstration of bioequivalence between originator product and intended copy requires alternative approach.
- Examples for complex drugs:
  - Therapeutic proteins – Biosimilars, Follow-up biologics
  - Low Molecular Weight Heparins (LMWH)
  - Nanomedicines: Liposomes, Nanoparticles et al.
  - Glatiromoids (Copaxone®)
  - Complex iron-carbohydrate drugs

Schellekens et al., Regul Toxicol Pharmacol, 2011
“Generic” medicinal product approval: There is something missing

**Generic paradigm**

- Small molecules (m.w. <500)
- Fully characterized

**Complex (non-biological) drugs**
- (m.w. range 43-150kDa)
- Not fully characterized

**Complex (biological) drugs**
- (m.w. range 5-150kDa)
- Not fully characterized

Schellekens et al., Regul Toxicol Pharmacol, 2011
Non Biological Complex Drugs (NBCD): Importance of terms

G. Borchard, B. Flühmann, S. Mühlebach, Regul Toxicol Pharmacol 2012;64:324-8
The EDQM and the European Pharmacopoeia

Gerrit Borchard, Université de Genève
Susanne Keitel, EDQM
European Directorate for the Quality of Medicines & HealthCare (EDQM)

- A Council of Europe Directorate, based on the Convention on the Elaboration of a European Pharmacopoeia (PA, 1964)
- Mission is to contribute to a basic human right: access to good quality medicines and healthcare
European Pharmacopoeia (Ph. Eur.)

- Protecting public health - one common compulsory standard.
- The Ph. Eur. is the official pharmacopoeia in Europe, complemented by national pharmacopoeias for texts of interest to only one Member State.
- **Mandatory** at the same date in 37 Member States (CoE) and the EU (decision of Ph. Eur. Commission).
The Pharmacopoeia in the EU Legislation

- **Legally binding** quality standards for **ALL** medicinal products in its member states, i.e. raw material, preparations, dosage forms, containers must comply with the Ph. Eur. requirements when they exist.

- Legislation foresees a mechanism to provide the pharmacopoeia authority with information on the quality of products on the market.

- An excellent tool to ensure that monographs are not cast in stone but routinely updated to reflect the state-of-the-art.
Non-Biological Complexes (NBC) Working Party

- Created in June 2011
- Based on an initiative by SwissMedic
- Decision by Ph. Eur. Commission to add on its work programme the elaboration of a monograph on *Iron sucrose concentrated solution*. 
Non-Biological Complexes (NBC) Working Party

Terms of reference
Elaboration of monographs on non-biological complexes (e.g., nanoparticle solutions, like for example iron sucrose concentrated solution) allocated to the group by the Commission
Working group

- Prof. Gerrit Borchard, University of Geneva (head)
- Prof. Heike Bunjes, University of Braunschweig
- Dr. Lino Liverani, Opocrin SpA, Modena
- Dr. Kim Nordfjeld, Pharmacosmos A.S., Holbaek
- Dr. Erik Philipp, Vifor Int. Ltd., St. Gallen
- Dr. Maria Rosa Virto Garcia, AEMPS, Madrid
Iron-carbohydrate drugs

- Colloidal formulations of polynuclear iron(III)-oxyhydroxide stabilized by a complex coating (?) of carbohydrates.

- Iron core is taken up by RES, acting as short-term storage.

- Release from RES and utilization in erythropoiesis.

- Therapy of iron deficiency anemia in chronic kidney disease, pregnancy, malabsorption, etc.

Stein et al., Nature Rev Gastroenterol Hepatol, 2010
Kudasheva et al., J Inorg Biochem, 2004
FDA Draft guidance on Iron Sucrose (2012) recommends 2 studies to demonstrate bioequivalence

Clinical:
- single-dose, randomized, parallel
- Bioequivalence (90% CI) based on baseline-corrected total iron and transferrin-bound iron
- Analytes to be measured:
  - baseline adjusted total iron in serum
  - baseline adjusted transferrin-bound iron (TBI) in serum

In vitro:
- Particle morphology by atomic force microscopy (AFM) including a placebo product
- Particle diameter by dynamic light scattering $D_{10}$, $D_{50}$, $D_{90}$ and SPAN ($D_{90}$-$D_{10}$)/$D_{50}$
Comments to FDA Draft guidance on Iron Sucrose:
Subtle variations in the production process may lead to changes in:

- Structure of iron core
- Size, size distribution, complex molecular weight distribution
- Sucrose-to-iron ratio affecting stability and iron release
- ADME-T profile

Due to body deposition pattern of Iron Sucrose (RES uptake), sampling in serum is insufficient to determine bioequivalence.
Comments to FDA Draft guidance on Iron Sucrose:

- Committee for Medicinal Products for Human Use (CHMP) of EMA suggested non-clinical comparability studies including assessment of iron distribution in at least plasma, RES and target tissues in suitable animal models.

- The “Leiden proposal” of the Joint working Party on NBCD demanded at least comparison of safety in rodents, once pharmaceutical quality is assured (Schellekens et al., Regul Toxicol Pharmacol, 2011).

- *Therapeutic Equivalence*: If studies show lack of induction of oxidative stress

- *Interchangeability*: clinical studies necessary.
Therapeutic equivalence evaluation of Nulecit™ vs. Ferrlecit™ in a 3-years project

• NTBI formation and comparison in vivo: oxidative stress, inflammation?
• Physicochemical characterization incl. labile iron
• In vivo uptake of labile iron leakage compared to RLD
• Phagocytosis assay (RES uptake)
• Prospective, well-controlled studies on iron distribution in tissue (preclinical species)
• Compare NTBI levels in hemodialysis patients (cross-over)
Draft:

“Reflection paper on data requirements for intravenous iron-carbohydrate colloidal products developed in reference to an innovator medicinal product”

Start of consultation: 15/9/2013, end: 28/2/2014

EMA/CHMP/SWP/620008/2012
“...current scientific knowledge and regulatory experience for characterisation of nano-sized colloidal preparations indicate that quality characterisation on its own, would not provide sufficient assurance of the similarity between the two products, even if the quality tests performed show similarity. ...data from quality, non-clinical and human pharmacokinetic studies is required.”
“...Reflection paper should be read in connection with guidelines (among others):

- ICH Q5E section 1.4 Note for Guidance on Biotechnological/biological Products
- Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (Draft EMA/CHMP/BWP/247713/2012)”
Iron-carbohydrate drugs

• Quality characterisation of test product:
  Particle size/distribution, surface charge, specific surface area, structure/composition of carbohydrate, identification and control of intermediates in manufacturing process, labile iron, polymorphic forms, impurities (di/trivalent iron), microscopic morphology, in vitro release in clinically relevant media, degradation path, storage/in-use stability,…

• Bio-distribution studies:
  Relevant compartments: plasma (serum), red blood cells, RES (macrophages in spleen, liver), pharmacological (bone marrow) and toxicological (kidney, hepatocytes, lung, heart) target tissues
Iron-carbohydrate drugs

- Clinical:
  Pharmacokinetic studies
  Efficacy and Safety studies

- Post-marketing:
  Pharmacovigilance
  Risk Management Plan (RMP)
Overall Mission:
The NBCD joint working group has the mission to ensure that science-based appropriate and harmonized approval and post-approval standards are created and globally introduced for NBCD.

Strategic Imperatives:
1. **Awareness** – create full awareness among key stakeholders (e.g., RA) of issues of NBCD.
2. **Scientific Evidence** – establish strong scientific evidence to understand and support position.
3. **Approval Standards** – ensure appropriate regulatory approval standards are applied globally to all NBCD.
4. **Risk Management**
   - Interchangeability/Substitutability – establish non-substitutability of NBCD.
   - Pharmacovigilance – establish mechanisms to track specific brands post approval.
There are more things in heaven and earth, Horatio, than are dreamt of in your philosophy.

William Shakespeare, Hamlet