Are Biosimilar Cell Therapy Products Possible?

Christopher A Bravery
cbravery@advbiols.com

Introduction

- Overview of principles of biosimilar products
  - Key product characteristics necessary for biosimilars
- Scientific and Regulatory barriers
- Practical considerations
- Covering
  - Patient-Specific (Autologous)
  - Off-the-Shelf (Allogeneic/xenogeneic)
- Conclusions
**Scope**

- This presentation focusses on cell-based medicinal products, e.g. those for which an EU MAA is necessary.
  - Arguments are likely to broadly apply to US BLA's but the specifics have not been explored.

**Why am I asking the question?**

- Investors, CEO’s etc often mention data protection periods in relation to cellular products.
- Data protection means your clinical data (public domain) can be borrowed for generics and biosimilars IF you can demonstrate the active substance is equivalent (or biosimilar).
- Means an abridged MA is possible;
  - Generics, article 10.1
  - Biosimilar, article 10.4*
  - *Assuming no patents are infringed.*

*Directive 2001/83/EC
Why Biosimilar and not Generic?

Physicochemical characterisation alone is not adequate to demonstrate the quality of biological medicinal products.

- From 2001/83/EC; Annex I (as amended by Directive 2003/63/EC), part I:
  - A biological medicinal product is a product, the active substance of which is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physico-chemical-biological testing, together with the production process and its control.

Biosimilar Paradigm

- To confirm the results of physicochemical measurements and bioassays (e.g. potency), some non-clinical and clinical data are necessary.
  - confirm safety
  - confirm toxicity (differing process-related impurities, differing excipients etc)
Guideline Recommendations

<table>
<thead>
<tr>
<th>Product</th>
<th>PK/PD</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recombinant Erythropoietin (rHuEPO)</td>
<td>Single dose crossover studies, normal volunteers, s.c. &amp; i.v.</td>
<td>At least 2 adequately powered, randomised, parallel group clinical trials. Patients with renal anaemia recommended (most sensitive model).</td>
</tr>
<tr>
<td>Low MW Heparin</td>
<td>Convention PK not possible (heterogeneous DS).</td>
<td>Therapeutic equivalence in at least 1 adequately powered, randomised, double-blind, parallel group clinical trial. Prevention of venous or arterial thromboembolism.</td>
</tr>
<tr>
<td>Somatropin (rhGH)</td>
<td>A single dose crossover study using s.c. administration. Healthy volunteers (suppression of endogenous GH production suggested).</td>
<td>At least one adequately powered, randomised, parallel group clinical trial. Provided that clinical comparability can be concluded from PK and PD data, there is no anticipated need for efficacy studies on intermediary or clinical variables.</td>
</tr>
<tr>
<td>Soluble human insulin</td>
<td>A single dose crossover study using s.c. administration in type 1 diabetes.</td>
<td>Provided that clinical comparability can be concluded from PK and PD data, there is no anticipated need for efficacy studies on intermediary or clinical variables.</td>
</tr>
<tr>
<td>rh-IFN alpha</td>
<td>Single dose crossover studies, s.c. &amp; i.v in healthy volunteers.</td>
<td>Treatment-naïve patients with chronic hepatitis C. Randomised, parallel group companion against RMP. at least 48 weeks.</td>
</tr>
</tbody>
</table>

Practical Considerations

**Buying the Innovator Product**

- **Patient-specific products (autologous)**
  - How would you get the innovator product?
  - Unlikely to be ethical to obtain donor material, split and send half to innovator and use half to make biosimilar and then…….. randomise which they get?

- **Cost of commercial products:**
  - LAVIV will likely cost $3,100 - $5,000*
  - Carticel: $25,000
  - ChondroCelect: €20,000
  - Provenge: $93,000
  - co.don chondrosphere: €6,000
  - C-Cure for cardiac indications: €35,000
  - Heartcelligram: $19,000

*http://www.facialplasticsurgery.net/laviv.htm
Practical Considerations
Buying the Innovator Product

• Off-the-shelf (allogeneic) current prices:
  • Apligraf: $1,250 (2007)
    • Apligraf® ($34.47/cm²)
  • Dermagraft: $1,425 per application
    • Dermagraft® ($38.93/cm²)
  • Cartistem for cartilage repair: $40,000 (500µl/cm² at 5x10^6/ml)
    • ~ $8,000 for 1 million cells or 0.8 cent/cell.

Practical Considerations
Using the Innovator Product

• Regulator’s magic 3 will not capture variability in batches
• Off-the-shelf definitely >3 different batches
  • May need to consider different donors (how would you know?)
• Patient-specific, maybe >30
• Unit size small so hard to do many tests,
  • especially the vital bioassays unless units can be pooled (same batch).
• Stability
  • Frozen, not such a problem since shelf-life likely to be long
  • Fresh, may not be time to do all tests; freezing would alter the product and invalidate analytics.
Practical Considerations
Process Development

• Starting material (donation) need to know what material is donated
  • In many cases straightforward
  • In case of e.g. hESC, likely need to be the exact same hESC line since these differ considerably.
• Unclear MoA means difficult to design process without knowing the rationale used by innovator (may have changed)
  • Simple expansion retaining characteristics
  • Complex maturation/activation/(de-)differentiation

Practical Considerations
Process Development

• Where the release tests are different to the innovator, the regulators would not be sure they provided the same control
  • e.g. different marker for identity/purity (is DS the same?)
  • potency assay using different principle
  • Potency assays generally not quantitative and often ‘surrogate’ assays. In many cases this would make comparability of potency difficult/impossible.
Practical Considerations

Biosimilarity Evaluation

• Complexity of active substance
  • How many characteristics would you need to compare?
  • How many bioassays
  • Non-clinical models more difficult than for proteins
    • Rapid rejection
    • Species differences

• Clinical
  • No PK/PD
  • Few validated biomarkers available generally
  • Most cell therapies take a long time to have effect
    • E.g. chondrocyte products – how do you show equivalence?

Conclusions

• Biosimilar Cell-Based Medicinal Products are not likely to be possible in the foreseeable future
• Data protection period are therefore irrelevant
BUT
• Predictions are difficult, especially about the future.