Are Biosimilar Cell Therapy Products Possible?

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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

Product Guideline	PK/PD	Efficacy
Recombinant Erthropoietins EMEA/CHMP/BMWP/94 526/2005	• Single dose cross-over studies, normal volunteers, s.c. & i.v. • Reticulocye count recommended pharmacodynamic marker	• At least 2 adequately powered, randomised, parallel group clinical trials • Patients with renal anaemia recommended (most sensitive model).
Low MW Heparins EMEA/CHMP/BMWP/11 8264/2007	• Convention PK not possible (heterogenous DS). • Suggest absorption/elimination characteristics incl. anti FXa,:FIIA as surrogates. Also TFPI activity	• Therapeutic equivalence in at least 1 adequately powered, randomised, double-blind, parallel group clinical trial. • Prevention of venous or arterial thromboembolism, or venous thromboembolism.
Somatropin (rhGF) EMEA/CHMP/BMWP/94 528/2005	• A single dose crossover study using s.c. administration • Healthy volunteers (suppression of endogenous GH production suggested). • IGF-1 is the preferred PD marker	• At least one adequately powered, randomised, parallel group clinical trial. • Treatment-naïve children with GH deficiency. • Comparative phase is at least 6 months (poss. 12 months).
Soluble human Insulin EMEA/CHMP/BMWP/32 775/2005	• A single dose crossover study using s.c. administration in type1 diabetes. • The double-blind, crossover hyperinsulinaemic euglycaemic clamp study.	• 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.
rh-IFN alpha EMEA/CHMP/BMWP/10 2046/2006	• Single dose crossover studies, s.c & i.v in healthy volunteers. • PD markers, such as β2 microglobulin, neopterin and serum 2´,5´-oligoadenylate synthetase activity	• Treatment-naïve patients with chronic hepatitis C. • Randomised, parallel group comparison against RMP, at least 48 weeks.

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.*