
Are Biosimilar Cell Therapy Products Possible?

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Consulting on Advanced Biologicals

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

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Consulting on Advanced Biologicals

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 Erythropoietins EMEA/CHMP/BMWP/94 526/2005	<ul style="list-style-type: none"> Single dose cross-over studies, normal volunteers, s.c. & i.v. Reticulocyte count recommended pharmacodynamic marker 	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Convention PK not possible (heterogenous DS). Suggest absorption/elimination characteristics incl. anti FXa, FIIa as surrogates. Also TFPI activity 	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> A single dose crossover study using s.c. administration Healthy volunteers (suppression of endogenous GH production suggested). IGF-1 is the preferred PD marker 	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> A single dose crossover study using s.c. administration in type1 diabetes. The double-blind, crossover hyperinsulinaemic euglycaemic clamp study. 	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Single dose crossover studies, s.c & i.v in healthy volunteers. PD markers, such as $\beta 2$ microglobulin, neopterin and serum 2',5'-oligoadenylate synthetase activity 	<ul style="list-style-type: none"> 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

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 5x10⁶/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.*