Biosimilars: What Can We Learn From the Past?

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Biopharmaceuticals

- Introduced in the beginning of the 1980s
- More than 150 products marketed
- Over 370 products in development for a wide range of serious conditions

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Patent Expiration of Biopharmaceuticals

<table>
<thead>
<tr>
<th>Patent company</th>
<th>Product</th>
<th>Indication(s)</th>
<th>EU patent/market exclusivity expires</th>
<th>USA patent/market exclusivity expires</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genentech</td>
<td>Neupogen® (erythropoietin)</td>
<td>Growth disorders</td>
<td>Expired</td>
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</tr>
<tr>
<td>Abbott</td>
<td>Humalog® (insulin lispro)</td>
<td>Diabetes</td>
<td>Expired</td>
<td>Expired</td>
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<tr>
<td>Genzyme</td>
<td>Ceredase® (alglucerase); Cerezyme® (imiglucerase)</td>
<td>Gaucher disease</td>
<td>Expired</td>
<td>Expired</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>Streptase® (streptokinase)</td>
<td>Ischaemic events</td>
<td>Expired</td>
<td>Expired</td>
</tr>
<tr>
<td>Genzyme</td>
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<td>Expired</td>
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</tr>
<tr>
<td>Biogen / Roche</td>
<td>Biogen / Roche</td>
<td>Fabrazyme® (agalsidase beta)</td>
<td>Expired</td>
<td>Expired</td>
</tr>
<tr>
<td>Amgen</td>
<td>Neupogen® (erythropoietin)</td>
<td>Anaemia, leukaemia, neutropenia</td>
<td>Expired</td>
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**Definitions**

<table>
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<tr>
<th>Low molecular weight drug</th>
<th>Classical medicinal pharmaceutical product</th>
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</thead>
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<tr>
<td>Generic drug</td>
<td>Chemical and therapeutic equivalent of low molecular weight drug whose patent has expired</td>
</tr>
<tr>
<td>Biopharmaceuticals</td>
<td>“A medicinal product developed by means of one or more of the following biotechnology practices: rDNA, controlled gene expression, antibody methods”</td>
</tr>
<tr>
<td>Biosimilar, or similar biological medicinal product</td>
<td>A biological medicinal product referring to an existing one and submitted to regulatory authorities for marketing authorization by an independent applicant after the time of protection of the data has expired for the original product.</td>
</tr>
</tbody>
</table>

*EMEA definition
FDA definition: "Follow-on biologics"

**Manufacture of Chemically-based Drugs vs Protein Product**

**Chemically-based drugs**
- Made by adding and mixing known chemicals and reagents
- Using a series of controlled and predictable chemical reactions

**Therapeutic proteins**
- Made by harvesting the substances produced and secreted by constructed cells

**FDA Guidance**
- "Unlike small molecule drugs, whose structure can usually be completely defined and entirely reproduced, proteins are typically more complex and are unlikely to be shown to be structurally identical to a reference product."

**Why Biopharmaceuticals are Different**

- High molecular weight
- Complex three-dimensional structure
- Produced by living organisms, therefore often heterogeneous
- Difficult to characterize completely by physico-chemical analytical methods or bioassays
- Prone to eliciting an immune response

*Biosimilars are not generic biopharmaceuticals*
Complexity of Protein Structure

Proprietary Cell Lines

Manufacturing Drift
Current Market Approval of Generic Low Molecular Weight Drugs

Demonstration of 'essential similarity':

- Same qualitative and quantitative composition in terms of the active substance
- Same physico-chemical form
- Bioequivalence in healthy volunteers

Can this established concept also be applied to biosimilars?

Clinical Evidence of Safety and Efficacy: Innovator Biologics vs SEBs

- Subsequent Entry Biologic
- Innovator biologic

Pharmacokinetics and Immunogenicity

All of these factors directly or indirectly contribute to or are influenced by protein heterogeneities and can impact PK and/or immunogenicity
**Immunogenicity: The Issues**

- It is impossible to predict all biological or clinical properties of biopharmaceuticals by physical chemical characterization

- The human immune system is highly efficient in detecting differences between biopharmaceuticals and endogenous proteins

- In vitro detection is assay dependent

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**Factors Influencing Immunogenicity**

- Product-related factors
  - Sequence variation
  - Glycosylation
  - Host cells
  - Contaminants and process-related impurities
  - Formulation
  - Handling and storage

Although important factors have been identified, there are still several unknowns

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**Factors Influencing Immunogenicity (cont.)**

- Patient factors
  - Route of administration: SC > IM > IV
  - Dose and treatment duration
  - Concomitant diseases and/or medication
  - Genetic factors

- Unknown factors

Changes in the manufacturing process, and inadequate handling and storage of a drug, may alter its immunogenicity
**Immunogenicity: Effects**

- Immune responses to biopharmaceuticals can vary from no perceptible effect to significant clinical effects:
  - Generalized immune effects (allergy, anaphylaxis)
  - Neutralization of exogenous protein (loss or enhancement of drug efficacy)
  - Neutralization of the endogenous protein (serious adverse event)

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**Significant Clinical Effects of Antibody Formation**

<table>
<thead>
<tr>
<th>Consequence of antibody</th>
<th>Biopharmaceutical</th>
</tr>
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<tbody>
<tr>
<td>Loss of efficacy</td>
<td>Insulin</td>
</tr>
<tr>
<td></td>
<td>Streptokinase</td>
</tr>
<tr>
<td></td>
<td>Staphylokinase</td>
</tr>
<tr>
<td></td>
<td>Adenosine deaminase</td>
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<tr>
<td></td>
<td>Salmon calcitonin</td>
</tr>
<tr>
<td></td>
<td>Factor XIII</td>
</tr>
<tr>
<td></td>
<td>Interferon-α2</td>
</tr>
<tr>
<td></td>
<td>Interferon-β</td>
</tr>
<tr>
<td></td>
<td>Interleukin-2</td>
</tr>
<tr>
<td></td>
<td>Gonadotropin-releasing hormone</td>
</tr>
<tr>
<td></td>
<td>Denileukin diltios</td>
</tr>
<tr>
<td></td>
<td>Human chorionic gonadotropin</td>
</tr>
<tr>
<td></td>
<td>Granulocyte-macrophage colony-stimulating factor</td>
</tr>
<tr>
<td>Neutralization of native protein</td>
<td>Megakaryocyte-derived growth factor</td>
</tr>
<tr>
<td></td>
<td>Erythropoietin</td>
</tr>
</tbody>
</table>

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**Percentage of ADAs to Adalimumab Over Time**

- Number of patients with available serum samples are shown.

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Median Adalimumab Concentration Over Time

Sustained Disease Activity and Remission in Patients with and without Anti-adalimumab Antibodies

An Example from Nephrology: Complexity of the Biopharmaceutical Epoetin-Alfa

- Natural human erythropoietin is a glycoprotein hormone with large carbohydrate side-chains
- Recombinant human erythropoietin (e.g. epoetin alfa) is heterogeneous, consisting of several different isoforms
- Different epoetin alfa isoforms have different biological properties
Pure Red Cell Aplasia (Diamond-Blackfan Syndrome)

- Uncommon immune disorder
- Antibody response to erythroblasts in the bone marrow
- Absence of precursors leads to anemia
- Associated with immune disorders, drug therapy, malignancy, parvovirus infection
- Recombinant EPO

ESAs and Pure Red Cell Aplasia

- First reported 1998
- “Epidemic” by 2002 ~ 200 cases
- Associated with s.c. administration
- Severe concern in nephrology community
- What is the cause?
- Withdrawal?

ESAs and Pure Red Cell Aplasia

- Cause identified 2004
- Change in plasticizer in stoppers – resulted in adjuvant activity – formation of anti EPO antibodies
- Illustrates need for supply chain controls and pharmacovigilance systems post-market
**Biosimilars ESAs and PRCA**

- Multiple cases of PRCA reported from Thailand
- Related to biosimilar ESAs
- Cause? – Manufacturing vs. others

*Wish J. et al. Kidney Int. 2011;80:11-13*

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**Data Extrapolation**

The use of efficacy/safety data as a surrogate for efficacy/safety in a population/regimen that has not been studied

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**Expert Opinion on Extrapolation**

Summit on Regulatory and Clinical Topics Related to SEBs

- The mechanisms of action of the TNFa antagonists are not completely understood, and that subtle molecular differences in a biologic drug may alter binding to targets in the body and lead to different clinical effects

- It may not be possible to extrapolate clinical data for a monoclonal antibody in one indication to other rheumatologic indications because of differences in:
  - dose
  - duration of therapy
  - efficacy of monotherapy vs. combination therapy
  - stated claims of efficacy for those indications

### Interchangeability

<table>
<thead>
<tr>
<th>Health Authority</th>
<th>Canada (Health Canada)</th>
<th>Europe (European Medicines Agency)</th>
<th>USA (FDA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Position</td>
<td>Outside of mandate (provincial authority)</td>
<td>Outside of mandate</td>
<td>Biosimilar authorization framework allows for possibility of interchangeable designation</td>
</tr>
<tr>
<td>Position</td>
<td>HC does not support automatic substitution</td>
<td>2007 - decision on using biosimilar should be made by qualified HCP</td>
<td>Biosimilar</td>
</tr>
<tr>
<td>Position</td>
<td></td>
<td>+2022 - Biosimilars are not the same as generics, which have simpler chemical structures and are considered to be identical to their reference medicines</td>
<td></td>
</tr>
<tr>
<td>Naming</td>
<td>Health Canada prefers unique brand name</td>
<td>European Commission Directive Dec 2012</td>
<td>No official position</td>
</tr>
<tr>
<td></td>
<td>Position on INN remains to be determined</td>
<td>Brand name should be used for Rx logic</td>
<td>No biosimilars approved to date</td>
</tr>
</tbody>
</table>

### Health Canada Guidance on SEBs

- Authorization of an SEB is not a declaration of pharmaceutical or therapeutic equivalence to an innovator. SEBs are not “generic” biologics
- Health Canada does not support “automatic substitution”, but does not have jurisdiction on interchangeability of SEBs and innovators.

### Expert Opinion on SEBs

**A Viewpoint from Canadian Researchers**

- SEBs must have an acceptable safety and efficacy profile
- SEBs are not interchangeable with each other nor with brand name biologics
- Each biologic product must have a unique product name...Given the fact that SEB products are not identical to innovator products and could have significantly different clinical outcomes...
- Cost must not override safety and efficacy
- Strict post-marketing surveillance must be followed
Conclusions

• Biosimilars cannot be considered generic biologics
• Because immunogenicity is largely unpredictable, the assessment of a biosimilar must be based on:
  – a thorough risk-benefit analysis
  – robust post-marketing risk-management programs
• Physicians and pharmacists should remain alert to unexplained changes in efficacy or side-effects
• Extrapolation and Interchangeability are important issues for patients and physicians that will bear careful monitoring