BIOSIMILARS OF PROTEIN BASED DRUGS: CURRENT STATUS AND FUTURE DIRECTIONS

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What is a Biosimilar?

- Protein based drugs are made by living organisms.

- Recombinant technology has allowed the commercialization of protein-based or biological drug therapies.

- So a biosimilar is a protein based therapy that is biologically and clinically comparable to an innovator product.

- However, they are NOT generic copies of the original product.

- In Canada and the U.S., biosimilars are called “Subsequent Entry Biologics (SEB)” and “Follow on Biologics” respectively.
R&D Efforts are Shifting Towards Biologics

Products Receiving FDA Approval: 1993 to 2004

Source: IMS Data, Dec 2009
The Share of the Pharma Pipeline due to Biologics

Source: IMD Data, Dec 2009

- In Market: 11% Small Molecules, 89% Biologicals
- In Phase III: 38% Small Molecules, 62% Biologicals
Why have Biosimilars generated so much interest?

- In 2009, global sales of biologicals were approximately $130 billion (Kueppers, 2010).

- The patent expiration of the first generation biologicals has led to the development of alternative versions of these original products.

- By 2014, the global biosimilars market is expected to reach $19.4 billion.
The biosimilars market has huge growth potential

- By 2016, another $25 billion worth of biologicals will be going off patent.

- Therefore, several large generic and brand companies have gone into the biosimilars arena.

- These include Teva, Sandoz, Hospira, Mylan, Merck and Pfizer.
Making a Protein Based Drug is Complex

Adopted from Gottlieb, 2008
Which organisms produce biological products?

Approximately 90% of currently approved biologic products are produced from 3 living systems:

- E. coli
- Yeast
- Chinese Hamster Ovary (CHO) Cells

Microbial Fermentation

Mammalian Cell Culture
Why are Biosimilars NOT Generics of Existing Biologicals

- Traditional generic drugs are exact copies of existing drugs.

- However, biosimilars are much bigger than a typical generic copy of a small molecule.

- Biologicals are also made up of amino acids, which form unique folds and glycosylation patterns may also vary.

- Therefore, they are much more complex.

- Combined with the complicated manufacturing process, an exact copy of a biological cannot be made.
Complexity is a Key Attribute of Biological Products
Biosimilars: The Goal is Clinical Interchangeability

Chemistry, manufacturing and quality control

- Chemical, biological profile and purity must be compared to the reference product.

- Experience from brand companies is that glycosylation patterns are also affected by the manufacturing process.

- Since biosimilar companies do not have access to proprietary data from the brand company, how will they be able to measure the product quality attributes?

- Hence, biosimilar companies will need to establish a quality control strategy with data generated from their own product.
Red Cell Aplasia (RCA): The Epoetin Alfa Story

- In the 1990s, RCA was reported in patients who were receiving treatment with SQ epoetin alfa.

- After an intensive investigation, the most likely cause of the RCA was a formulation change leading to an interaction with the rubber stopper.

- This caused antibody formation against all circulating erythropoietin.
Biosimilars: Non-Clinical Studies

- Non-clinical pharmacology studies and in vitro potency relative to the reference product must be demonstrated.

- Pharmacokinetics: Equivalence in PK parameters in a relevant animal model must be demonstrated.

- Lack of meaningful differences in toxicology studies need to be demonstrated in animal models relative to the reference product.
Biosimilars: Clinical Considerations

- What types and how many studies should be conducted?

- What should the primary endpoint be in such trials; a surrogate endpoint, a drug activity signal or patient benefit?

- In the case of oncology, should it be RR, PFS or OS?

- Can the results from one disease site be extrapolated to another?

- As an illustration, Remicade and Enbrel are both anti-TNF biologicals approved for use in RA. However, Enbrel is not active in Crohn’s disease.
Equivalence Margins: How similar is similar enough?

- Clinical equivalence (not non-inferiority) trials must be undertaken for a biosimilar relative to the brand product.

- The European Medicines Agency (EMA) is the most advanced in providing guidance on clinical trials but they stop short at providing precise equivalence margins.

- Equivalence margins vary by product class and depend on what difference in outcome is considered clinically meaningful.
Equivalence Margins: How similar is similar enough?

- This is called the MCID or “Minimally Clinically Important Difference”.

- E.G. For the biosimilar interferon alfa, the MCID for response was 15%.

- For the biosimilar of filgrastim, the MCID was 1 day of severe neutropenia following chemotherapy.
Immunogenicity Concerns

- This is the ability of a substance to induce an immune response.

- Many factors can cause such reactions, but the tendency to form aggregates is one of the most common, since these may structurally simulate a viral particle.

- Given these risks and the small patient safety and efficacy database, the EMA requires a rigorous pharmacovigilance program post approval.
Extrapolation across indications

- Can efficacy and safety demonstrated in one indication be extrapolated to all approved indications?

- Can become a highly contentious issue for biosimilars in Canada.

- Extrapolation has been done by brand companies after a change in the manufacturing process (e.g. Aranesp).

- Extrapolation in a possibility in Canada, but will need to be address on a case by case basis.
The Biosimilar Approval Process in Europe

Figure 1  Overview of biosimilar guidelines developed by EMEA.
### Biosimilars Approved in Europe

<table>
<thead>
<tr>
<th>Biosimilar (manufacturer)</th>
<th>Reference product (manufacturer)</th>
<th>Date of approval</th>
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<tr>
<td><strong>Human growth hormone</strong></td>
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<tr>
<td>Omnitrope® (Sandoz)</td>
<td>Genotropin (Pfizer)</td>
<td>April 2006</td>
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<tr>
<td>Valtropin® (Biopartners)</td>
<td>Humatrope (Ely Lilly)</td>
<td>April 2006</td>
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<td><strong>Epoetin</strong></td>
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<td>Abseamed® (Medice Arzneimittel Pütter)</td>
<td>Eprex (Janssen-Cilag)</td>
<td>August 2007</td>
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<tr>
<td>Retacrit® (Hospira)</td>
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<td>December 2007</td>
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<tr>
<td>Binocrit® (Sandoz)</td>
<td></td>
<td>August 2007</td>
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<tr>
<td>Epoetin alfa Hexal® (Hexal Biotech)</td>
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<td>August 2007</td>
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<tr>
<td>Silapo® (STADA Arzneimittel)</td>
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<tr>
<td><strong>Granulocyte colony-stimulating factor</strong></td>
<td>Neupogen (Amgen)</td>
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<tr>
<td>Filgrastim Hexal® (Hexal Biotech)</td>
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<tr>
<td>Biograstim® (CT Arzneimittel)</td>
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<td>Nivestim® (Hospira)</td>
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<td>Zarzio® (Sandoz)</td>
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<td>February 2009</td>
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<tr>
<td>Ratiograstim® and Filgrastim Ratiopharm® (Ratiopharm)</td>
<td></td>
<td>September 2008</td>
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<tr>
<td>Tevagrastim® (Teva Pharma)</td>
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What kind of data do physicians want to see?

Physicians were asked to indicate the level of clinical trial data they require to begin prescribing biosimilars.

Percentage of Physicians Requiring Trial Data in Each Category

- Efficacy versus reference biologic (i.e., head to head or non-inferiority):
  - U.S. physicians: 73%
  - French physicians: 74%
  - German physicians: 72%

- Immunogenicity:
  - U.S. physicians: 35%
  - French physicians: 51%
  - German physicians: 57%

- Pre-marketing safety:
  - U.S. physicians: 50%
  - French physicians: 56%
  - German physicians: 41%

Source: Decision Resources, 2010
Market penetration in Europe has been slow.....
But it seems to be picking up:
Biosimilar penetration of EPO alfa by country

Source: IMS MIDAS June 2011.
In 2008, Health Canada (HC) issued draft guidelines for stakeholder comment.

The main stakeholder concerns were related to IP protection, the reference product used and interchangeability.

This was followed by the 2010 release of a final guidance document.
GUIDANCE FOR SPONSORS: Information and Submission Requirements for Subsequent Entry Biologics (SEBs)
Where are the provincial payers with respect to Biosimilars?

- There is no standardized approach to assess biosimilars in the provinces.
  - In the short term, it is unlikely that interchangeability will be permitted.
  - The provinces are also seeking guidance from HC and CADTH.
  - Educational programs around biosimilars will be critical to shape future thinking and policy.
The needs of nurses, pharmacists and physicians: my prediction….

- Clinical practice is highly evidence based.
- If only one or two head to head trials with surrogate endpoints are available, adoption of biosimilars will be modest.
- Patient safety, especially across indications will also be a concern.
- Given the limited data, biosimilars will likely be seen as a new medical therapy by clinicians.
- If payers mandate the use of a lower cost biosimilar, they will likely get “push back” from health care practitioners.
Conclusions

- Biosimilars represent a high risk undertaking, but given the market size, companies will continue to develop these products.

- Eventually, the regulatory pathways will be streamlined and development costs will be reduced, which will lower the risk of biosimilar drug development.

- Cost constraints will also make biosimilars more attractive to payers.

- Wisely, Health Canada is taking the European approach and engaging with all of the key stakeholders to develop clear approval pathways.

- Until comprehensive safety and efficacy data is available, biosimilars should be seen as a change in therapy.
Biosimilars of Biological Drug Therapies
Regulatory, Clinical and Commercial Considerations

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