Biosimilar Battlegrounds - *What is new in biosimilars and where?*

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Biosimilars are second entry biologic drugs. They rely in part on data from an already-approved reference product to reduce the time and cost burden of generating clinical trial data to support their regulatory approval. Biosimilar approvals are analogous to generic pharmaceutical approvals except that biologics are larger and more complex than conventional pharmaceuticals. There is significant controversy about biosimilars and the appropriate data threshold requirements for their approval.

The stakes are high for regulators reviewing biosimilar data trying to ensure high similarity of the biosimilar to the innovator product. This is particularly the case for complex products such as monoclonal antibodies used in oncology where the intent is curative and it is an all-or-nothing phenomenon. Switching a cancer patient between different antibody drugs because the biosimilar is not working the same, or as well, as the branded product is a situation to be avoided. Patient safety is a paramount consideration for regulators.

The present article provides a brief snapshot of some biosimilar development initiatives in Canada and abroad.

European Union

Europe, via its European Medicines Agency (EMEA), is leading the way in approving biosimilars and providing guidance to industry. It has published guidelines for six classes of biologics: insulins, granulocyte-colony stimulating factors, erythropoietins, somatropins (human growth hormone; HGH), low-molecular weight heparins and interferon alphas. Europe also published draft guidelines in 2010 on a monoclonal antibody class. This is a very significant challenge because antibody drugs are much larger and more complex than single chain recombinant proteins such as somatropin and insulin.

At least 14 biosimilars were approved by the EMEA as of Spring 2011, including two somatropins, five erythopoietins and seven granulocyte colony-stimulating factors (filgrastims).

Sandoz (a division of Novartis) has three biosimilar products on the market in the EU. Sandoz manufactures biosimilar versions of HGH, filgrastim and human erythropoietin. Teva Pharmaceutical Industries Ltd. is also currently marketing three biosimilars: erythropoietin, filgrastim and HGH.

Sandoz has a phase II clinical study on rituximab. Rituximab is a monoclonal antibody directed against a B-cell surface protein. It treats non-Hodgkin's lymphoma, chronic lymphocytic leukemia and rheumatoid arthritis. Rituximab is a large and complex protein for treatment of a potentially life-threatening disease, so it can be expected to be closely scrutinized by regulators deciding whether to grant biosimilar approval.

Merck established Merck BioVentures in December 2008 for biosimilar development. In 2010, Merck stated that it had two biosimilar candidates in development and anticipated having five biosimilars in development by 2012. Merck has also partnered with the Korean company Hanwha Chemical Corporation to develop a biosimilar version of etanercept.

Teva has four biosimilars in end phase II clinical trials: follitropin alfa, glyco - PEG-G-CSF, and rituximab. Teva also has two other biosimilars in end phase III clinical trials. Teva Pharmaceutical Industries Ltd. purchased the Ratiopharm Group in 2010 in an effort to expand its generic operations in Europe, which at that time had received approval for one biosimilar (filgrastim) in the EU.

Pfizer partnered with Indian biotechnology company Biocon in 2010 to market a biosimilar version of human insulin worldwide. Pfizer expects to gain approval for its biosimilar insulin in Europe by 2012 and in the U.S. by 2015. The involvement of Pfizer in the biosimilar space is of interest to industry-watchers, since Pfizer has a very strong focus on developing its own innovator products in conventional pharmaceuticals, not second entry products.

Another interesting trend is companies well known in other industries moving into the biosimilar business, such as Samsung. Samsung has invested between $250 million and $390 million (depending on the report) in a partnership with Quintiles Transnational Corp. to develop biosimilars.

United States

Some biosimilars such as somatropin (human growth hormone) have been approved in the US under 'old' laws regulating biologics. The same pathway has been used by other biosimilars of older biologics. Other examples of subsequent entry biological products approved by the FDA are glucagon, hyaluronidase, and calcitonin salmon recombinant.

The US government approved a new, abbreviated pathway for biosimilar approvals in 2010. The FDA is already willing to accept applications for approval the pathway. Acceptance is on a confidential basis so we do not know the extent to which there is activity on the new pathway. Initial regulatory guidance from the FDA on applying for biosimilar approval is imminent. Biosimilar companies are watching developments in the US with great interest. One interesting pair of bedfellows announced in December 2011 is innovator Amgen and generic Watson Pharmaceuticals. They will make oncology antibody biosimilars (no biosimilars of Amgen's products).

Canada

Canada published a SEB guidance document in 2010. About the same time, Sandoz received approval for its human growth hormone (Omnitrope). Canada has approved of the general approach taken by the EMEA guidelines. It is fair to say that Canada is open for business to biosimilars. The small Canadian market is of secondary interest to many multinational pharmaceutical companies, which may explain why there has not been more action in Canada.

There is not a lot of biosimilar development activity by Canadian-based companies. It would be in Canada's benefit to provide incentives encourage local companies to continue to invest in both innovative biologic and biosimilar biologic drug development, particularly where Canada has developed unique expertise and has a competitive edge.

In 2008, Apotex announced a biosimilar development collaboration with Intas Biopharmaceuticals Limited and Kwizda Pharma to produce a biosimilar GM-CSF (Granulocyte-Macrophage Colony-Stimulating Factor).

SemBioSys and Plantform Corporation are developing plant-based expression systems for biosimilar production. They each have proprietary protein-expression systems that are different from the expression systems used by many innovator biologic companies (eg. single cell systems, such as yeast, are most commonly used for biologic drugs). Health Canada's guidance document states that differences in the manufacturing process will be considered in the comparability assessment. It is unclear the extent to which a plant-based product will be able to rely on innovator product data. Companies will be preparing to address these regulatory issues.

Cangene Corporation (majority owned by Apotex) manufactures recombinant therapeutic proteins. Cangene has FDA and Health Canada-approved biologics. Cangene has previously developed its own versions of established products using proprietary host systems. It has gone through the formal new drug application process but could potentially move more towards the biosimilar pathway, for example with its GM-CSF in development. There are a number of other contract development and manufacturing companies with expertise in therapeutic protein manufacturing and development that have the potential to partner with other companies. Therapure Biopharma Inc. is an example of a biopharmaceutical company with expertise in producing therapeutic proteins and biosimilars.

It is clear from the above high level view that there is a lot of ongoing international biosimilar development. Most of the market leaders are based outside Canada. However, there are Canadian companies that are working hard to develop a foothold in biosimilar drug development. As with conventional pharmaceuticals, there is enough space in the international biologic marketplace for both brand name companies and biosimilar companies. Canada would only stand to benefit from nurturing its expertise in biologic drug development, preferably leading to a cluster of companies with different, diverse R&D strength in either innovator biologics or biosimilars.