

Subsequent entry biologics – challenge and opportunity



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Definition

Biologic drugs are therapeutic agents produced using living cells which can come from animals, plants and microorganisms such as yeast and bacteria. Unlike the more common small molecule drugs, typically administered orally, biologic drugs are complex, large molecule drugs usually administered as an injectable.

“Subsequent Entry Biologics” (SEBs) in Canada are follow-on versions similar to an original biologic drug after the patent on the innovator’s drug has expired. SEBs are also referred to as similar biological medicinal product (biosimilar) in the European Union and follow-on protein product in the United States. The term “biosimilar” is also commonly used in Canada, Europe, the U.S. and around the world.^{1,2} Biosimilarity as defined by the U.S. Food and Drug Administration (FDA) means that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity and potency of the product.³

Are SEBs “Generic Biologics”?

SEBs are not “generic” biologics. From a regulatory standpoint, there are differences in the Health Canada approval pathway of generics and SEBs. Generic medicines—small molecules assessed and approved for use by Health Canada after the patent on the innovator drug molecule has expired—receive a Declaration of Equivalence (DOE) to the Canadian reference product, which includes a requirement for demonstration of pharmaceutical equivalence. From a policy perspective, depending on the province, once the DOE is provided by Health Canada, it is then up to the various provincial pharmacy regulatory bodies or provincial legislation to assess which drugs are deemed interchangeable and can be automatically substituted at the pharmacy. Unlike generic drugs, an SEB will always require clinical trials to support its approval as “biosimilar.” Health Canada’s guidance on SEBs indicated that approval through the SEB pathway does not necessarily mean the product can be substituted for the reference product used by the SEB to obtain approval. Many potential differences in protein structure in biologics can arise. Even minor structural differences can significantly alter the product’s safety, purity and/or potency. Health Canada is emphasizing that it is important to evaluate these differences and demonstrate biosimilarity. As noted above, it is up to the various provincial pharmacy regulatory bodies or provincial legislation to determine which drugs are deemed interchangeable and can be automatically substituted at the pharmacy. However, Health Canada does not currently support automatic substitution of an SEB for its reference biologic drug.^{1,4,5}

Provincial positions on substitution of SEBs

Currently, there is no standard approach to SEBs from the provinces. When asked whether a pharmacist can switch the original biologic prescription to an SEB, only two provincial pharmacist licensing bodies (Alberta and New Brunswick) that allow pharmacist prescribing (e.g. adapting a prescription via therapeutic substitution) have provided preliminary viewpoints to our question on substitution of SEBs for the branded biologic:

- SEBs and therapeutic interchange are complex issues. There should be clinical support and evidence that the SEB has similar therapeutic effects compared to what is prescribed by the physician.^a
- The drug switch must be for the benefit of the individual patient, after careful assessment of the patient, in collaboration with the patient and caregiver. It is not appropriate to do a therapeutic substitution just for formulary management.^b
- The pharmacist is required to communicate the switch to the physician (as per the Alberta Standard of Care for Pharmacists).

References

^a Personal communication. New Brunswick Pharmaceutical Society, Moncton, NB. Jan 18, 2012.
^b Personal communication. Alberta College of Pharmacists. Jan 23, 2012.



Approval of SEBs in Canada, the U.S., Europe and emerging markets

Canada: In March 2010, Health Canada provided guidance for sponsors with information and submission requirements for SEBs.⁴ A reference biologic drug is chosen by the manufacturer of the SEB to demonstrate similarity between the SEB and the drug authorized for sale, though not necessarily authorized for sale in Canada as a non-domestic reference product is permitted. The SEB manufacturer is responsible for showing biosimilarity between the SEB and the reference drug. As of December 2012, Omnitrope (somatotropin, a growth hormone) was the only SEB approved in Canada. Genotropin, a product that is not marketed in Canada, was its reference drug.

U.S.: Currently, Omnitrope (somatotropin) is the only product in the U.S. market that may fit the “biosimilar” approval pathway. The passage of the Patient Protection and Affordable Care Act (PPACA) in the U.S. in Q4-2011 allows for the introduction of biosimilar medications into the marketplace. The FDA subsequently provided draft guidance for the industry on biosimilar drug submissions³ with the Biosimilar User Fee Act in 2012. Since the U.S. accounts for the greatest portion of global spending on biologics, it is anticipated to be a key driver in long-term biosimilar market growth.^{2,6}

Europe: The European Medicines Agency (EMA) published a general guideline on biosimilars in 2005.⁷ It approved its first biosimilar product, the growth hormone Omnitrope (somatotropin) injection, in 2006. EMA guidelines are “class specific” with products grouped together such as human growth hormone, monoclonal antibodies, granulocyte colony stimulating factors (G-CSFs), among others.² The guidelines outline study designs, biomarkers and clinical end points that could produce potential differences with the reference products. Major biosimilars in Europe (approved 2006-2008) include somatotropin [Omnitrope (Reference: Genotropin), Valtropin (Reference: Humatrope)]; Epoetin alfa [Sandoz EPO, Abseamed, Epoetin alfa Hexal and Binocrit (Reference: Eprex)] and Filgrastim [Teva G-CSF, Tevagrastim, Ratiograstim, Filgrastim ratiopharm and Biograstim (Reference: Neupogen)]^{2,5,6}.

Emerging markets: China, Korea, India and Brazil are already manufacturing copied versions of patented biologics, yet approval pathways and definition of agents are less accurate. For example, Reditux, a copy of rituximab manufactured by Dr. Reddy's, has been available in India since 2007, but its approval has been based on a smaller body of evidence than is likely to be required in Europe or the U.S.² or Canada.

Estimation of drug cost of the first subsequent entry biologic approved in Canada as a percentage of brand

Currently, Omnitrope (somatotropin), a growth hormone, is the only SEB drug approved in Canada. There are three branded versions of somatotropin (Humatrope, Nutropin and Saizen) commercially available, each with varying prices depending on drug concentration and dosage format. A direct price comparison on a per mg basis between Omnitrope and the three branded versions is challenging since the dosing for somatotropin is weight-based and the mg concentration of different dosage formats differs between brands. If we assume the intended indication for use is the maximum indicated dose for pediatric growth failure due to inadequate endogenous growth hormone secretion for a 35 kg patient, and the cost/mg for the Omnitrope dosage format with the closest total mg contents to the weekly dose requirement from its comparators, the approximate weekly cost of the SEB Omnitrope is between 55-71% of the branded versions (which is equal to a discount of 29-45% off the brand name price). Other sources such as IMS Brogan are forecasting a price reduction of between 15-30% off the brand name price^{1,2,8} for future products.

Potential patent expiry of selected high impact biologics

A drug can have numerous patents and some common examples include: molecules, formulations, processes, polymorphs, pharmacokinetics, methods of treatment, salts, enantiomers, and impurity profile. Each patent may expire at different times over the course of a drug's life cycle. Table 1 lists dates of patents that have already expired on a number of top-selling biologics as accessed from the Health Canada patent registry (April 11, 2011) and the next earliest and latest patent expiry as accessed from the Health Canada patent registry (December 21, 2012). Despite the fact that patents have already expired, drug manufacturers may choose not to introduce an SEB in light of other existing patents or feasibility of marketing issues or other concerns as addressed below.



Table 1 Canadian patent expiry of selected top-selling biologics

Drug (generic name)	Enbrel (etanercept)	Humira (adalimumab)	Remicade (infliximab)	Aranesp (Darbepoetin Alfa)	Herceptin (trastuzu-mab)	Rituxan (rituximab)
Patent* already expired	2011-Jun 27.	—	2012-Mar-18	2010-Oct-15	2012-Jun-15	2012-Aug-29
Next Patent**	2013-Sep-14	2017-Feb-10	2017-Aug-01	2014-Aug-16	2016-Jul-23	2013-Nov-12
expiry and latest	2023-Feb-27				2021-May-18	2018-Jun-12

From Health Canada Patent Registry: <http://pr-rdb.hc-sc.gc.ca/pr-rdb/start-debuter.do?lang=eng>

* accessed April 11, 2011

** accessed Dec 21, 2012

Challenges of SEBs

- **Availability:** High costs are associated with the development of SEBs as this involves sophisticated technologies and processes, and good quality clinical trials are required for approval of SEBs. Therefore, fewer manufacturers are likely to enter into this space. There will likely be fewer SEB options available compared to the number of generics that come to market once a patent for a small molecule drug expires. For new entrants, there will be more demanding requirements in clinical development, market access, manufacturing, sales and marketing.
- **Cost:** Since SEBs are not considered to be “generics,” the Canadian provincial mandatory generic drug pricing rules would not apply to SEBs. As a result, we are unlikely to see heavy price discounting similar to the generic pricing model. Industrial analysts have predicted a price reduction of only 15-30% from the brand name biologics.^{1,2,8}
- **Acceptance by prescribers and patients:** SEBs targeting auto-immune disease require adequate clinical trial evidence to establish equivalent efficacy and safety to the reference biologic. Human safety data such as immunogenicity (the ability of an antigen to provoke an immune response) is always required for biosimilars before approval.^{4,9} Because the indications for use are likely in select patient populations, real-world experience with these drugs generally takes longer to accumulate. Physician and patient buy-in of these therapy options may take longer.²

Opportunities

Top pharmaceutical companies (such as Pfizer, Merck, Amgen and Biogen Idec) and generic companies (such as Teva) have already signed deals to develop biosimilars in emerging markets such as India.² Celltrion announced in July 2012 that it had secured approval for its biosimilar version of Remicade (infliximab) under the brand name Remsima in its domestic market of South Korea.¹⁰ Remsima has also been submitted to the European regulatory authorities. It is anticipated that biosimilars which achieved success in emerging markets domestically will likely compete in the U.S. in the longer term. In the U.S., upon establishment of legislation on follow-on protein products, the approval and launch of more follow-on protein products is anticipated.

SEBs are in their early development in Canada and still require acceptance from physicians and patients, and the degree of cost saving remains to be determined. However, they will likely result in cost savings for plan sponsors. For example, after similar clinical efficacy and safety have been proven between an SEB and the original reference biologic, a Maximum Allowable Cost program or Prior Authorization STEP therapy could be considered. We will continue to monitor the evolution of SEBs in the Canadian market and prospective programs that could incorporate SEBs to realize the potential cost savings.

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