

BIOLOGICS
VS.
SPECIALTY DRUGS

Not all specialty drugs are biologics, but biologics are usually classified as specialty drugs. Express Scripts Canada defines a specialty drug as "an injectable or non-injectable drug that is typically used to treat chronic, complex conditions."

Specialty drugs meet one or more of the following characteristics:

1. Requirement for frequent dosage adjustments and intensive clinical monitoring to decrease the potential for adverse effects, and increase the probability of improved outcomes;
2. Need for intensive patient training and compliance assistance;
3. Limited or exclusive product availability and distribution;
4. Specialized product handling and/or administration requirements;
5. Generally cost more than \$500 per month.

Biologics and biosimilars ... a new complexity in the world of medicines

The world of medicines grows increasingly complicated as innovation brings forward ever more complex products that improve the lives of Canadian patients.

The biologic category has been one of these advancements and biologics such as Enbrel® for rheumatoid arthritis and psoriasis and Herceptin® for breast cancer have radically changed patient outcomes.

Biologics are an increasing portion of drug reimbursement costs. According to the Express Scripts Canada 2011 *Drug Trend Report*, specialty drugs (of which biologics are an example) account for 19.5% of private drug plan spend, but less than 1% of the number of claims. The average amount for a specialty claim is \$1,242 vs. \$49 for other drugs. That amount grew 12% over 2010 vs. a decrease of 1.9% for other drugs.

And there's a new term to consider—subsequent entry biologics (SEB) or biosimilars—which have recently arrived on the Canadian market. An important evolution, biosimilars represent potential cost savings for private drug plans, but will be unlikely to have quite the same impact as generic substitution for brand-name synthetic drugs.

What is a biologic?

A biologic is a medicine made from living organisms or cells. Over the past 30 years, biologic medicines have provided treatment options for people who suffer from some of the most serious medical conditions. Diseases such as rheumatoid arthritis, cancer, rare blood disorders, multiple sclerosis, diabetes and HIV/AIDS can now be treated where no effective therapies were previously available.

The outcomes for patients have been remarkable. Treatment with Rituxan® has cut the number of deaths in half for those with non-Hodgkin's lymphoma.ⁱ The use of biologics has successfully addressed the progression of rheumatoid arthritis in patients by slowing or halting joint erosion.ⁱⁱ Employers benefit because treatment of rheumatoid arthritis with biologics results in fewer lost work days and increased productivity.ⁱⁱⁱ

SIZE & COMPLEXITY— SMALL MOLECULE DRUGS & PROTEIN

SIZE

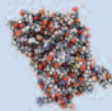
SMALL
MOLECULE
DRUG

Aspirin
21 atoms



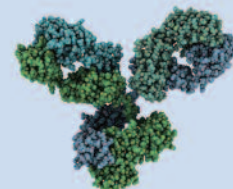
LARGE
MOLECULE
DRUG

hGH
3,000 atoms



LARGE
BIOLOGIC

IgG Antibody
25,000 atoms



COMPLEXITY

Bike
20 lbs



Car
3,000 lbs



Business Jet
30,000 lbs (without fuel)



What is the difference between synthetic and biologic drugs?

Drugs can be categorized as synthetically or biologically produced. Synthetic drugs are created with simple chemical ingredients and are characterized as “small molecules.” Biologic drugs are large, complex proteins (see diagram). Unlike synthetic drugs, biologics do not easily penetrate cell membranes and are not very stable in the stomach and intestines (the gastrointestinal system). As a result biologics are most often injected or delivered intravenously.

Biologics are also more complicated to make than synthetic drugs. They are produced by living cells (animal, bacteria and yeast) and are sensitive to minor changes in the manufacturing process. These changes can significantly affect the nature of a finished biologic and the way it functions in the body. Just as wine grapes that are grown in different regions can result in different tastes, small manufacturing differences can impact the efficacy or safety of biologics.

BIOSIMILARS ARE SIMILAR...

BUT NOT IDENTICAL
TO THE ORIGINAL MEDICINE



What is a biosimilar?

A biosimilar describes a copy of a biologic medicine that is similar, but not identical, to the original medicine. Health Canada defines a biosimilar as “a biologic drug that enters the market subsequent to a version previously authorized in Canada, and with demonstrated similarity to a reference biologic drug”.^{iv} (While Health Canada uses the term “subsequent entry biologic” (SEB), the term “biosimilar” is more commonly used in Europe, and “follow on biologics” is used in the U.S.)

Unlike generic drugs, which are copies of chemical drugs, biosimilar medicines are not identical to the original biologic drugs. Manufacturing a biologic is a complex process and even small changes in the process can affect the final product. Consequently, the biosimilar product will virtually never be identical to the original innovator brand. A Health Canada guidance document issued in 2010 states that SEBs (biosimilars) are not considered “generic” biologics. Approving a biosimilar does not mean that the agency has declared that it is equivalent to the original.^v

How are biosimilars approved?

The Health Canada approval pathway for biosimilars is significantly different than the pathway used for generic entries for synthetic drugs. Because they are new entities, biosimilars will be required to follow the new drug submission pathway to Health Canada and submit clinical trial, full chemistry and manufacturing data. It is, however, a reduced data package, as not all information required for the originator biologic will be required by Health Canada for a biosimilar—some areas of reduced requirements are in toxicology and early phase testing.

Upon approval they will not be declared bioequivalent to reference drugs and will be regulated like any other new biologic drug. One of the biggest challenges biosimilar manufacturers face is that, although they may intend to “copy” a biologic drug, it is almost impossible to replicate the manufacturing process. Just as you may try to replicate one of your mother’s favourite recipes, it may never turn out exactly the same in your kitchen, not because you aren’t using the same ingredients, but because you use a different oven, or the dough takes longer to rise because you live in a different city, with a different altitude and climate.

SMALL MOLECULE GENERIC

Bioequivalence:

Manufacturers must conduct studies to determine whether their version is bioequivalent to the original drug—that is, that the generic version releases its active ingredient (the drug) into the bloodstream at virtually the same speed and in virtually the same amounts as the original drug.

Interchangeability and Substitution:

Theoretically, any generic drug that is bioequivalent to its trade-name counterpart may be interchanged with it.

The Merck Manual Home Health
Handbook
www.merckmanuals.com/home

Provincial government regulations determine when pharmacists are permitted to substitute (or interchange) a generic drug when a brand name drug is prescribed (see below). In most provinces, when a product is considered bioequivalent, a pharmacist is permitted to substitute a generic drug for a brand name drug without consulting the physician.

Because Health Canada has advised that it will not declare bioequivalency between the biosimilar and the reference brand name drug,^{vi} provincial government regulations will not likely permit pharmacists to substitute the biosimilar for brand name drug without consulting a physician. To date, no country has allowed for automatic substitution. Therefore, in order for the pharmacist to dispense the biosimilar, the physician has to specifically prescribe the biosimilar.

What does this mean to private drug plan costs?

Once proven safe and effective, biosimilars will be an option for some patients and may reduce the overall costs of delivering lifesaving biotechnology medicines. Biosimilars are new to Canada—currently there is only one (Omnitrope®) approved for use. Consequently, the difference in price between the original biologic and the biosimilar is uncertain at this time.

Although several big budget biologic drugs' patents will expire over the next few years, biosimilar drugs likely won't generate the same savings associated with the introduction of traditional generic drugs due to the above-mentioned differences.

BIOLOGICS AND BIOSIMILARS— CHALLENGES REMAIN FOR GOOD PATIENT OUTCOMES

THEY ARE NOT INTERCHANGEABLE. Not all patients will react to a biosimilar in the same way as they do to the original biologic. The decision to prescribe one biologic over another should be based on a healthcare provider's personal clinical evaluation of the patient's healthcare needs and enable follow-up to assess performance.

NAMING PROTOCOLS MATTER. As biosimilars are not identical to the original products, they should be clearly labelled and have distinct names—both brand and “generic” names—to ensure that the patient receives the drug that the physician intends, and that the source of any adverse events can be accurately traced.

POST-MARKETING SAFETY MONITORING IS STILL IMPORTANT. To ensure adequate safety for patients, the monitoring of biosimilars should adhere to the same strict standards as those used to monitor original medications.

MANUFACTURING STANDARDS AND ADEQUATE SUPPLY ARE CRITICAL. Given the potential risks of switching a patient's biologic treatment, it is critical that product supply be robust. A supply shortage of a medicine can mean patient treatment and outcomes may be significantly impacted.

- i G. A. Salles, J. F. Seymour, P. Feugier, F. Offner, A. Lopez-Guillermo, R. Bouabdallah, L. M. Pedersen, P. Brice, D. Belada, L. Xerri, Rituximab maintenance for 2 years in patients with untreated high tumor burden follicular lymphoma after response to immunochemotherapy. *J Clin Oncol* 28:155, 2010 (suppl; abstr 8004).
- ii Aslam Anis, Wei Zhang, Paul Emery, Huiying Sun, Amitabh Singh, Bruce Freundlich, Reiko Sato, The effect of etanercept on work productivity in patients with early active rheumatoid arthritis: results from the COMET study. *Rheumatology* 2009; 48: 1283-1289.
- iii Diane Lacaille, Work Loss in Rheumatoid Arthritis: Can We Prevent It? *Int J Adv Rheumatol* 2010;7(4):107-13.
- iv Health Canada. Guidance For Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs) http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/guides/seb-pbu/seb-pbu_2010-eng.php.
- v Ibid.
- vi Letter from Health Canada to Provincial & Territorial Drug Plan Directors, July 29, 2010.