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What Private Drug Plan Managers should know about Biosimilars entering Canada's Healthcare Market

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Quick facts

- A biologic is a medicine made from living organisms or cells.
- A biosimilar is a copy of a biologic medicine that is similar, but not identical, to the original medicine.
- The Health Canada definition: “An SEB [biosimilar] is a biologic drug that enters the market subsequent to a version previously authorized in Canada, and with demonstrated similarity to a reference biologic drug.”[1]
- Although Health Canada uses the term “subsequent entry biologic” (SEB), the term “biosimilar” is also commonly used in Canada, Europe, the U.S. and around the world. Other terms such as “follow on biologics” have also been used.
- Health Canada states in its SEB guidance that biosimilars are not “generic biologics.” Unlike generic drugs, which are copies of synthetic (chemical) drugs, it is virtually impossible to manufacture a biosimilar, which is identical to the original biologic drug.

- Manufacturing a biologic is a complex process and even small changes in the process can affect the final product and how it could react in the human body. The difficult task of clinically proving the effects of interchangeability is also a concern in the U.S. The FDA has stated that "the agency will develop standards to ensure that products not deemed interchangeable are not inadvertently substituted for a reference product without the prescriber's consent."[2]

- Since a biosimilar will be similar to, but not the same as the innovator biologic, the decision to switch a patient to a biosimilar should be made by the physician and patient—not by the pharmacist or drug plan. Not all patients will react to a biosimilar in the same way as they would with the original biologic and risks exist for different immunogenic reactions, should a patient's biologic medicine be switched.

- Because biosimilar manufacturers have to invest in clinical development, manufacturing and post-approval safety monitoring programs, it is unlikely that biosimilars will generate the same savings associated with the introduction of traditional generic drugs.

- Cost should not be the primary driver for decision making—science and patient safety should lead decisions.

Foreword

This booklet contains the facts you need to know as a plan manager or advisor when considering private drug plan coverage of biosimilar drugs. Of prime importance is the understanding that the characteristics of biologic and biosimilar medicines mean that private insurance plans should require physician involvement in switching from the originator biologic to a biosimilar and that this process is different from that for small molecule drug generics. Patient safety is paramount.

Biotechnology-based medicines, or **biologics**, have greatly improved patient outcomes in many disease areas. This area of medical innovation will continue to gain importance as the field of personalized medicines grows. As patents covering biologic medicines expire, other manufacturers are able to enter the marketplace with their own versions of the originator biologics. These versions are known as **biosimilars**. While biosimilars are already marketed in Europe, there has been only one biosimilar approved in Canada to date. This will change in the coming years in therapeutic areas ranging from rheumatology to oncology.

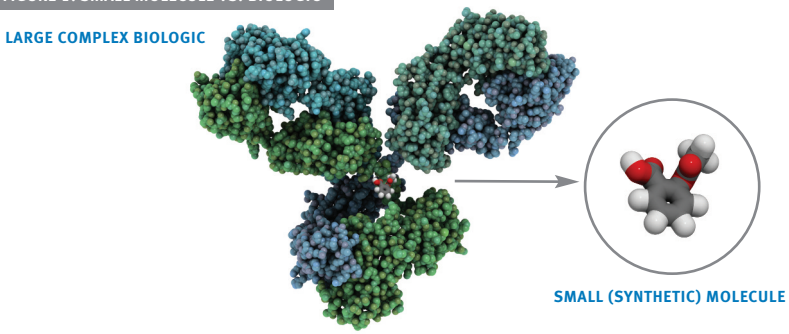
While plan managers have become used to considering plan coverage for generic drugs once brand-name synthetic (small molecule) drugs go off patent, this general practice should not extend to biosimilars. Health Canada guidelines state that biosimilars are not “generic” biologics. Biologics (made from living cells) will be affected by processing conditions. These, in turn, can result in products that behave differently when administered to patients. Since a biosimilar is not identical to the original biologic, biosimilars should not be deemed interchangeable with the original biologic medicines. The choice of which product works best is a decision best made between the physician and patient.

The advent of biologic medicines

The biotechnology revolution brought about a new class of drug: the biologic. Biologics are therapies derived from living organisms or organic substances. In fact, many don't realize that insulin was an early biologic medicine. Before 1982, diabetic patients had to use insulin that had been extracted and purified from the pancreas of cows or pigs. Scientists subsequently discovered how to modify cells to cause them to express insulin in the laboratory, allowing the manufacture of insulin using that method.[3]

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. Today, there are over 200 biologics and vaccines on the market worldwide. Development of new biologic medicines may be our best hope for producing effective treatments for many diseases that currently have no cure.

FIGURE 1: SMALL MOLECULE VS. BIOLOGIC

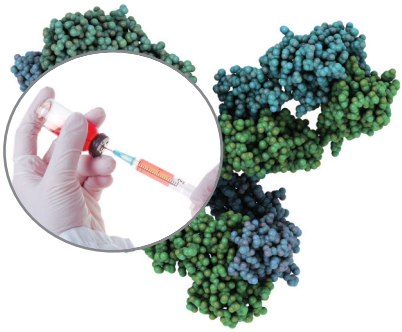


BIOLOGICS ARE DIFFERENT FROM SYNTHESIZED DRUGS

Drugs can be categorized as synthetically or biologically produced. Synthetic drugs like the familiar Aspirin® (acetylsalicylic acid) are created with simple chemical ingredients and are characterized as "small molecules." Biologic drugs are large, complex proteins (Figure 1). Unlike synthetic drugs that are often swallowed, biologics do not easily penetrate cell membranes and are not very stable in the stomach and intestines. As a result, biologics are most often injected or delivered intravenously.

FIGURE 2: SYNTHETIC DRUG

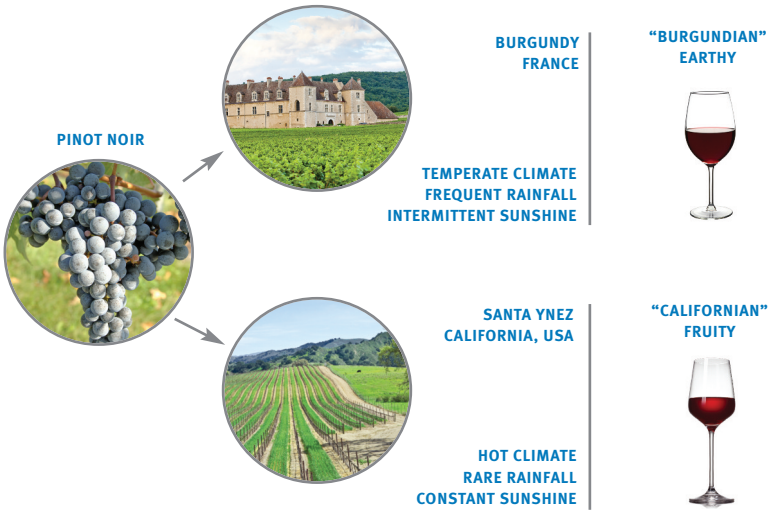
FIGURE 3: BIOLOGIC DRUG



MANUFACTURING OF BIOLOGICS IS MORE COMPLEX THAN MAKING SYNTHETIC DRUGS

Small molecule (or synthetic) drugs are produced by mixing ingredients together. Biologics are 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.

Just as wine grapes that are grown in different regions can result in different tastes, small manufacturing differences can significantly affect the nature of a finished biologic and the way it functions in the body.



BIOLOGICS HAVE BROUGHT TREMENDOUS PATIENT BENEFITS

The outcomes for patients treated with biologics have been remarkable. Treatment with a biologic has reduced deaths by half for those with non-Hodgkin's lymphoma.[5] The use of biologics has successfully addressed the progression of rheumatoid arthritis in patients by slowing or halting joint erosion.[6] Employers benefit because treatment of rheumatoid arthritis with biologics results in fewer lost work days and increased productivity.[7] Biologics have allowed patients to thrive after cancer diagnoses.[8]

Development of new biologic medicines may be the best hope for producing effective treatments for many diseases that currently have no cure. These include medicines for cancers, Alzheimer's disease, heart disease and autoimmune disorders.

GAINING REGULATORY APPROVAL FOR BIOLOGICS

Before a biologic can be considered for approval for sale to the public by Health Canada, sufficient scientific evidence must be collected to show that it is safe, efficacious and of suitable quality. Biologics differ from other drugs for human use in that they must—in addition to the information required for other drugs—include more detailed chemistry and manufacturing information. This is necessary to help ensure the purity and quality of the product, including safeguarding against contamination from an undesired microorganism or another biologic.[9]

Entry of biosimilars onto the Canadian market

Some major biotechnology-derived medicines have lost or will soon lose patent protection and will become open to development and manufacture by other companies. These next entrants are referred to as biosimilars.

A biosimilar describes a copy of a biologic medicine that is similar, but not identical, to the original medicine. Health Canada defines a subsequent entry biologic 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."[10] While Health Canada uses the term "subsequent entry biologic" (SEB), the term "biosimilar" is commonly used worldwide, including Canada. Other terms such as "follow on biologics" have also been used.

Biosimilar medicines have been available in the European Union (EU) for several years. The necessary legal framework for biosimilar medicines was adopted in the EU in 2005[11] and the first biosimilar medicines (human growth factor) were approved by the European Commission in April 2006.[12]

Health Canada's guidance on biosimilars was developed in 2010.[13] To date, there is only one biosimilar approved for use in Canada. Health Canada issued a Notice of Compliance (a regulatory authorization issued to a manufacturer following satisfactory review of a product) to Sandoz Canada Inc. for the product Omnitrope™ (somatropin) in 2009.[14]

BIOSIMILARS ARE NOT "GENERIC BIOLOGICS"

Health Canada states that SEBs (biosimilars) are not considered "generic" biologics and that Health Canada approval of a biosimilar does not mean that the agency has declared it is equivalent to the original.[15] Since biologics are derived from living cells, small variations may have an impact on patient safety and efficacy. These may only be detected through the conduct of human clinical trials. Unlike generic drugs, biosimilars, by definition, are unlikely to be identical to the originator biologic. They are 'similar' but not identical. If a company submits data that supports that their product is effective, safe and of high quality, the product should be approved for sale—but marketing approval does not mean that a biosimilar is interchangeable with the originator product.

BIOSIMILARS ARE SIMILAR... BUT NOT IDENTICAL TO THE ORIGINAL MEDICINE

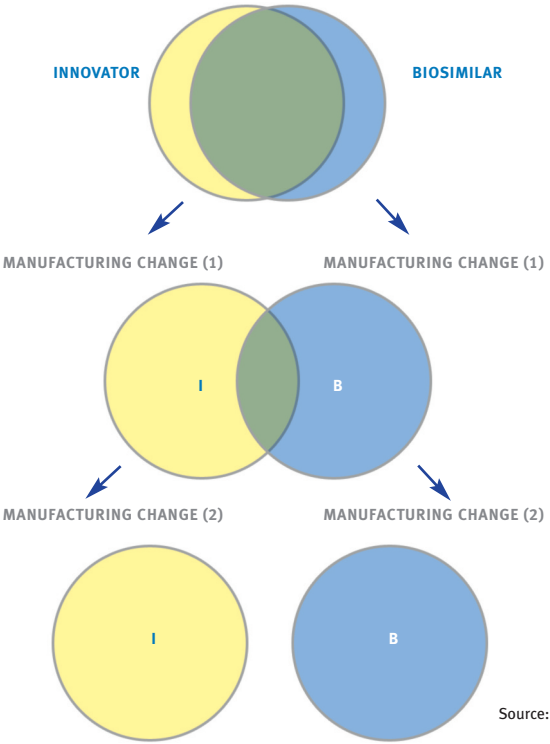
MANUFACTURING AND SUPPLY OF BIOSIMILARS

Every biologic is manufactured using a unique set of processes involving living cells and requiring several stages of production. Even small variations can alter efficacy, safety or availability of the resulting biotechnology medicine. Knowing which variations matter requires extensive manufacturing experience. Manufacturing processes, quality control and variances are proprietary to the originator company. Expiry of patents does not mean this information becomes public, so the product will need to be independently developed by the company manufacturing a biosimilar. As a result, the process to manufacture a biosimilar likely will not be exactly the same as the biologic drug and could result in a similar but still different final product.

Health Canada has stated that "clinical studies can support therapeutic interchangeability, but their relevance may not be long-lasting. Over time, as sponsors of biosimilars and reference biologics make independent manufacturing changes, differences could be introduced. For this reason, Health Canada does not support automatic substitution."[16] This biosimilar "drift" away from the originator biologic can be envisioned in the diagram below.

Manufacturers have a responsibility to ensure strategies are in place to minimize incidences and possible disruptions of product supply. This is true for all drugs, but is especially critical when those drugs are biologics and biosimilars. Biosimilars will inevitably differ from their originator products, and these differences may lead to differences with regard to dose, pharmacokinetics, immunogenicity, and adverse events. Maintaining a reliable product supply is critical.

DRIFT IN CRITICAL PRODUCT QUALITY ATTRIBUTES WITH MANUFACTURING CHANGES



Source: Dr. Amy Rosenberg (FDA)

PHARMACOVIGILANCE AND TRACEABILITY ARE IMPORTANT

Effective pharmacovigilance is particularly important in biologics. These products are complex and manufacturers' and regulators' knowledge of the products' safety profile continues to grow as experience with these products increases. For this reason, post-market surveillance or studies are critical to enhance the body of knowledge on the safety profile of the product. As a key example pertaining to biologic medicines, rare but significant immunologic effects may not be detected in conventionally-sized premarket clinical trials.

The European experience with Eprex® (epoetin alfa) illustrates these challenges and highlights the importance of an effective pharmacovigilance system. In that case, an unexpected number of cases of a severe immunogenic effect known as pure red cell aplasia (PRCA) were reported. Even with only three erythropoiesis-stimulating agents approved in Europe at the time, traceability to the responsible product took months of forensic research. The increased rate of PRCA was eventually attributed to a formulation change for that product (i.e., changing the stabilizer). With the arrival of biosimilars, there will be more products per class on the market and more challenge in assuring accurate attribution of events.

Switching of a patient from one biologic to another should be avoided, and prescription of a biosimilar should be made only after due consideration and a commitment to appropriately monitor for changes in clinical profile. This will help minimize the possibility of any unwanted immunogenic reactions. Post-approval tracking must be able to accurately and quickly match any adverse events to the correct drug.

As biosimilars are an evolving field, there is still much discussion concerning their naming conventions for biosimilars. In Europe, the originator and biosimilar sometimes share the same International Nonproprietary Name (INN). This could lead to confusion in attributing adverse events to the correct drug. Health Canada is in dialogue with the World Health Organization and other country regulators to develop potential solutions that ensure traceability and safety, particularly for patients with chronic diseases who receive medicines for prolonged periods.

PRODUCT SUBSTITUTION CARRIES RISK TO PATIENTS

Any substitution system that is not principled on caution and traceability may potentially create unnecessary risks to patient safety. Private drug plans should be aware of the risks that currently surround biosimilars and product substitution. Regulatory policies around the world consistently highlight the need to involve the physician in the decision-making process. The EMA has stated that "since biosimilars and biological reference products are not identical, the decision to treat a patient with a reference product or biosimilar medicine should be taken following the opinion of a qualified health professional."[18] The FDA has stated that "the agency will develop standards to ensure that products not deemed interchangeable are not inadvertently substituted for a reference product without the prescriber's consent."[19] Although Health Canada does not support substituting a biosimilar for the original biologic, each province has the authority to decide whether it will allow substitution in its provincial reimbursement plans or allow pharmacists to substitute for patients with private plan coverage. Private plans will have similar options.

As noted above, switching patients between biosimilars and originator products presents special, as yet not fully understood, challenges such as potential immunogenic reactions. In general, immunogenic responses to biologics are complex and may vary widely with regard to timing and mode of expression following initiation of treatment.[20]

Reimbursement considerations as biosimilars become available

INTERCHANGEABILITY IS NOT AN OPTION

Private insurers are becoming increasingly concerned about the cost of brand-name medications, especially with the recent cost-shifting that is taking place from the public to the private market. Automatic substitution of brand-name small molecule (synthetic) drugs with their generic versions is often included in private plans as the two products are considered interchangeable (see below).

UNDERSTANDING SMALL MOLECULES AND THEIR GENERICS

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

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.*

This same practice cannot be followed when considering biosimilars—biosimilars are not generic biologics. They are not considered interchangeable. As noted earlier, substituting biologics (or substituting a biologic with a biosimilar) risks altering a patient's response to a medication. The impact of substitution on patient outcomes must be considered and biosimilars must be prescribed only by physicians who deem such actions appropriate.

	SYNTHETIC (CHEMICAL) DRUGS	BIOLOGIC DRUGS
Health Canada declares bioequivalency	✔	✘
Provincial regulations determine whether a pharmacist can substitute a generic version without consulting a physician	✔	NOT ANTICIPATED
Private drug plans promote generic substitution	✔	NOT RECOMMENDED

PLAN COSTS SAVINGS MAY NOT BE SIGNIFICANT

Biosimilar manufacturers have to appropriately invest in clinical development, complex manufacturing and post-approval safety monitoring programs similar to that of originator drugs, which can be expensive. While there is little experience in Canada, studies based on other countries' experiences suggest that the price differential between originator biologics and biosimilars is likely to be smaller than that between brand name synthetic drugs and their generic versions. While differences in acquisition prices between originator and conventional generic drugs of up to 80% have been observed, differences between originator biologics and biosimilars are more likely to be in the region of 15–30%.[21]

Patient-physician choice must be respected

Cost should not be the primary driver for decision making on product substitution from biologic to biosimilar—science and patient safety should lead decisions. Until data demonstrates no additional risk from switching, patients should not be switched from one biologic product to another (whether brand name biologics or biologic to biosimilar) as this may potentially increase the risk of an adverse reaction. That decision should be based on a healthcare provider's personal clinical evaluation of the patient's healthcare needs and enable follow-up to assess performance. Pharmacists should not make substitution decisions without the consent of the prescribing physician.

Conclusion

Society needs innovator companies to continue research...without innovation, there can be no new cures or treatments. Biosimilars extend the therapeutic options, but do not create new therapies. Although they don't target new illnesses, biosimilars may expand access to biologic therapy, provided they are sufficiently safe, effective and used in an appropriate and well-monitored setting.

Q. What are biosimilars?

A. When the period of patent protection expires on a biologic drug, other manufacturers may market copies of the compound. To be approved for sale, a biosimilar must demonstrate that it is a "similar biological medicinal product" to an already approved biologic drug, known as the originator drug. The determination of "similarity" is made by the regulatory agency on a product-by-product basis. While Health Canada uses the term "subsequent entry biologic" (SEB), the term "biosimilar" is commonly used worldwide, including Canada. Other terms such as "follow on biologics" have also been used.

Q. Why are biosimilars not considered generic copies of the original biologic drug?

A. When the patent has expired on a pharmaceutical (chemical) drug, other companies may make generic copies using the same drug formula. A generic drug is made from the same ingredients and has the same chemical structure as the original drug.

To be approved, generics do not need to have undergone clinical trials (testing in patients to demonstrate efficacy and safety). The generic only needs to show that the active ingredient is available to the body at the same rate and to the same extent as it is with the original drug. A generic is generally considered to be bioequivalent (works in the body in the same way) as the original drug.

A biosimilar is *not* a generic copy of the original biologic. It is not considered to be bioequivalent. There are several reasons for this. A biologic drug is much bigger and more complex than a chemical drug. For biologics, it is not only the chemical structure of the protein but also the way this structure is folded that determines how it works. The manufacturing process for biologics is so complex that it is virtually impossible for a biosimilar manufacturer to generate an identical medicine to the originator biologic.

Q. Is a biosimilar interchangeable with the original biologic drug? Can a biosimilar be substituted for an original biologic?

A. Interchangeability means that one drug can be exchanged for another with the expectation that it will have the same effect (health benefit) and no difference in safety (adverse effects or long-term negative outcomes). Many generic versions of chemical drugs are deemed to be interchangeable with the original patented drug, though this is not always true for all generics and all patients. Unlike generic chemical drugs, biosimilars are not considered to be bioequivalent to the original drug. The regulatory agencies in Europe (European Medicines Agency) and Canada (Health Canada) do not assess and do not designate interchangeability or substitutability of the biosimilar with the original biologic.

Q. What factors should be considered in deciding between a biosimilar and the original biologic?

A. A biosimilar receives regulatory approval based on clinical and nonclinical similarity to the original (reference) drug. However, a biosimilar is not an exact copy of the original biologic drug, so the decision to take a biosimilar or the original biologic should be made by the prescriber and the patient based on individualized factors. These factors may include cause, status and responsiveness of the disease as well as the person's perception of tolerability, manageability of the therapy, and impact on functioning and quality of life.

A biologic may cause an immune reaction to the active ingredient, to a stabilizer or another ingredient, or to an impurity from the manufacturing process. The safety profile of the original drug, including immunogenicity, may not extend to the biosimilar. Even minor changes in the process can lead to significant changes in the final product, and this may alter the risk of immunogenicity of the biosimilar relative to the original biologic.

Q. Are biosimilars cheaper than biologic originators?

A. With only one biosimilar launched in Canada, it is difficult to speculate how biosimilar companies will price their products. Having said that, the production of a biosimilar is much more complicated than a small molecule generic and therefore the development costs are higher, which means there are unlikely to be similar cost savings.

Glossary of terms

Adverse event: The occurrence of an undesirable, unpleasant or life-threatening reaction to a medicinal product.

Antibody (pl: antibodies): Antibodies (also known as immunoglobulins, abbreviated to Ig) are proteins that are found in blood or other bodily fluids. Antibodies are used by the immune system to identify and neutralize foreign objects, such as bacteria and viruses.

Bioequivalence: Manufacturers of synthetic (small molecule) drugs 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.[22]

Biologic: A product derived from a living organism (from animal products or other biological sources) that is used in the diagnosis, prevention or treatment of disease. Examples of biologics include recombinant proteins, allergy shots, vaccines, and hematopoietic growth factors.

Biologics and Genetic Therapies Directorate (BGTD): The Canadian federal authority within Health Canada that regulates biological drugs (products derived from living sources) and radiopharmaceuticals for human use in Canada, whether manufactured in Canada or elsewhere.

Biosimilar: A term for attempted copies of innovator biologics approved through a regulatory pathway that allows an abbreviated data package. The full name established by the European Union is “similar biological medicinal products.”

Biotechnology: Technology based on biology, especially when used in agriculture, food science, and medicine. The United Nations Convention on Biological Diversity defines biotechnology as "any technological application that uses biological systems, living organisms or derivatives thereof, to make or modify products or processes for specific use."

Chemical drug or chemical medicine: Refers to medicines that are manufactured without the involvement of living organisms.

Clinical trial: A test in which a drug is given to humans to establish how it works in the body and measure the nature and extent of any intended or unintended consequences.

Efficacy: The desired impact that a medicine or treatment has when administered to a human.

FDA: The U.S. Food and Drug Administration, the federal agency responsible for evaluating marketing applications for medicinal products, food and cosmetics to be approved in the United States.

Health Canada: The Federal department responsible for helping Canadians maintain and improve their health, while respecting individual choices and circumstances.

Immune system: The collection of mechanisms within the body that protects against disease by identifying and attacking foreign substances in the body. An immune response is how the body recognizes and defends itself against bacteria, viruses and substances that appear foreign and harmful.

Interchangeability: Theoretically, any generic synthetic (small molecule) drug that is bioequivalent to its trade name counterpart may be interchanged with it.

International Nonproprietary Name (INN): The official nonproprietary or generic name given to a pharmaceutical substance, as designated by the World Health Organization (WHO).

New Drug Submission (NDS): An application submitted to Health Canada seeking approval to market a novel biologic in Canada. The application contains a description of the trials and results, formulation, dosage, drug shelf life, manufacturing protocols, packaging information, etc.

Notice of Compliance (NOC): A notification indicating that a manufacturer has complied with relevant sections of the *Food and Drug Regulations*. Notices of Compliance are issued to a manufacturer following the satisfactory review of a submission. A medicine cannot be sold in Canada without an NOC.

Pharmacovigilence: The pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects, particularly long- and short-term side effects of medicines.

Small molecule drugs: Chemical compounds that have a defined structure and characteristics.

Substitution: When a pharmacist decides to switch from a branded or innovator medicine to a generic or biosimilar medicine without the prescribing physician's approval.

Vaccine: A biological preparation used to establish or improve immunity to a particular disease.

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