

Biosimilar biologic drugs in Canada: Fact Sheet

A biosimilar is a biologic drug that is highly similar to a biologic drug that was already authorized for sale.

Health Canada authorizes biosimilars for sale using the same rigorous regulatory standards for quality, efficacy and safety as for all other biologic drugs.

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Biologic drugs and their uses

Biologic drugs come from living organisms or from their cells. They are often made using biotechnology. Examples of biologic drugs include insulin, growth hormones and antibodies. Biologic drugs are used to treat diseases and medical conditions including:

- anemia
- diabetes
- psoriasis
- hormone deficiency
- rheumatoid arthritis
- some forms of cancer
- inflammatory bowel disease

Biologic drugs are generally larger and more complex in composition than chemically produced pharmaceutical drugs.

In Canada, biologic drugs are listed in Schedule D of the *Food and Drugs Act*.

Biosimilars explained

A biosimilar biologic drug, or biosimilar, is a biologic drug that is highly similar to a biologic drug that was already authorized for sale. There are no expected clinically meaningful differences in efficacy and safety between a biosimilar and the biologic drug that was already authorized for sale.

We call the drug that was already authorized a reference biologic drug because it is the drug to which the biosimilar is compared.

We authorize biosimilars for sale based on a thorough comparison to a reference biologic drug. A biosimilar may enter the market after the expiry of the reference biologic drug's patents and data protection.

Biosimilars versus generic drugs

Biosimilars are not the same as generic drugs.

Generic drugs are small molecules that are chemically synthesized. They contain identical medicinal ingredients to their reference products.

A biosimilar and its reference biologic drug can be shown to be highly similar, but not identical. This is because biologic drugs:

- are often large and complex
- are made from living cells rather than with chemicals and so are naturally variable

Compared to generics, more studies are needed for the regulatory authorization of a biosimilar in order to demonstrate that it is highly similar to its reference biologic drug.

How we regulate biosimilars in Canada

In Canada, we regulate biosimilars as new drugs under the *Food and Drugs Act* and the *Food and Drug Regulations*.

We have developed a robust, science-based regulatory framework for authorizing biosimilars for sale.

Biosimilars are manufactured to the same regulatory standards as other biologic drugs and are authorized after a scientific evaluation by Health Canada.

The [Guidance Document: Information and Submission Requirements for Biosimilar Biologic Drugs](#) helps manufacturers comply with the laws and regulations governing the authorization of biosimilars for sale in Canada.

Our rigorous standards for authorization mean that you can have the same confidence in the quality, efficacy and safety of a biosimilar as in any other biologic drug.

Information requirements for initial authorization of a biosimilar

Biosimilar manufacturers must provide information to Health Canada that demonstrates the similarity of their biosimilar to the reference biologic drug. They demonstrate similarity using comparative studies via a step-wise approach:

- beginning with structural and functional studies
- continuing with human clinical studies

Because the purpose of these studies is to demonstrate similarity, the type of data required to support biosimilar authorization differs from that required for a stand-alone biologic drug.

To obtain authorization to sell an innovator drug containing a new active substance (such as a reference biologic drug), manufacturers must independently demonstrate the quality, efficacy and safety of the drug. Generally, authorization of an innovator drug requires stand-alone "pivotal" phase III clinical trials to establish efficacy and safety in each disease or medical condition that the drug is intended to treat.

To obtain authorization to sell a biosimilar, manufacturers must independently demonstrate the quality of the drug and perform comparative studies to demonstrate highly similar structure, function, efficacy and safety to a previously authorized reference biologic drug.

We require manufacturers of all biologics (innovator or biosimilar) to demonstrate that they can consistently manufacture and release the drug using a suitable control strategy. We may also conduct an evaluation of the drug-manufacturing site and targeted in-house laboratory testing.

In order to authorize a biosimilar, we evaluate whether the information provided by the manufacturer is complete and whether it shows that:

- the biosimilar and the reference biologic drug are highly similar
- there are no clinically meaningful differences in efficacy and safety between the biosimilar and the reference biologic drug

As for all biologics, when Health Canada authorizes a biosimilar for sale, we issue:

- a Notice of Compliance (NOC)
- a unique Drug Identification Number (DIN)

Roles of structural and functional, non-clinical and clinical studies

Extensive side-by-side structural and functional studies give the foundation of evidence for authorizing a biosimilar. These studies compare the characteristics of the proposed biosimilar and the reference biologic drug, including:

- product stability
- biological activities
- physicochemical properties
- immunochemical properties
- purity and impurity profiles

Structural and functional studies are generally considered to be more sensitive than clinical studies for detecting differences between a biosimilar and its reference biologic drug.

Non-clinical and clinical studies address potential areas of remaining uncertainty after comparative structural and functional studies have established high similarity. Non-clinical studies in cells compare the effects of the proposed biosimilar and the reference biologic drug. The purpose of clinical studies in humans is to show that there are no clinically meaningful differences in efficacy and safety expected between the proposed biosimilar and the reference biologic drug.

Clinical study programs for biosimilars are tailored to the individual product. They include comparative pharmacokinetic studies and an assessment of immunogenicity. If appropriate markers are available, comparative pharmacodynamic studies should be carried out. A comparative efficacy study is usually required.

The study populations, statistical margins and clinical endpoints used in comparative studies of a biosimilar can differ from those used in the studies supporting authorization of the reference biologic drug. However, they must be sensitive to potential differences between the biosimilar and the reference biologic drug.

Because biologic drugs and biosimilars are a diverse group of products and each is manufactured by independently established processes, the specific data requirements for biosimilar authorization can differ between products. For all biosimilars, authorization is based on all of the evidence given to Health Canada, including a complete quality data package and data from comparative structural, functional, non-clinical and clinical studies.

Authorizing indications

An indication is a term that means the use of a drug to treat a specific disease or medical condition. Many biologic drugs are authorized for more than one indication.

Once studies show that the biosimilar is highly similar to the reference biologic drug with no clinically meaningful differences, Health Canada can authorize the biosimilar for the same

indications as the reference biologic drug, based on the previously-established efficacy and safety of the reference biologic drug in each indication. This concept is often called extrapolation or extension of indications, and it avoids the unnecessary repetition of clinical studies.

Authorization of each indication is also supported by scientific knowledge and the medical literature about the:

- biosimilar
- reference biologic drug
- mechanism of action of the drug in the specific diseases or medical conditions involved

Patients and prescribers can have confidence in the use of a biosimilar in each indication authorized by Health Canada.

Why some biosimilars are authorized for fewer indications than the reference biologic drug

A biosimilar can be authorized for all or some of the indications as its reference biologic drug.

The indications authorized for a particular biosimilar depend on factors such as, that:

- Indications can be patented at different times. Indications under intellectual property protection cannot be authorized until the protection expires.
- The biosimilar manufacturer chooses which indications they wish to seek for the product. Health Canada does not force a manufacturer to apply for indications that the manufacturer does not wish to have in Canada.

Health Canada's [Summary Basis of Decision](#) (SBD) documents explain the basis for our decisions on biosimilar authorization. The SBD also gives details on which indications the biosimilar sponsor did and did not seek authorization.

Product monographs for all biosimilars are available in the [Drug Product Database](#). Product monographs give necessary information for how to use a new drug effectively and safely. The first section of Part I of the product monograph lists the authorized indications for the drug.

Immunogenicity and how we address it for biosimilars

The immune system has evolved to recognize foreign substances in the body. Biologic drugs are usually given by injection, which can cause the body's immune system to react to them. This reaction is referred to as the immunogenicity of the product.

Often, immunogenicity can only be detected using sophisticated laboratory tests and has no impact on the patient. In other cases, immunogenicity can impact patient safety, for example by causing an adverse reaction, or affect how well the drug works.

For these reasons, an assessment of immunogenicity is required for the authorization of a biosimilar. Studies showing that there are no expected clinically meaningful differences in immunogenicity between the reference biologic drug and the biosimilar are usually required.

In addition, we request a Risk Management Plan for all biologic drugs, including biosimilars. This plan explains how the manufacturer will monitor immunogenicity after the biosimilar has been authorized.

How we monitor the safety of biosimilars after they have been authorized

Health Canada monitors the safety of all drugs on the market, including biosimilars by:

- conducting market surveillance
- monitoring adverse reaction reports
- investigating complaints and problem reports
- taking action as appropriate

Each manufacturer must do its part for drug safety, including:

- setting up a system to monitor reported side effects
- periodically re-assessing whether the drug's benefits outweigh its risks
- reporting any new information received about serious side effects to Health Canada
- notifying Health Canada about any studies with new safety information
- requesting authorization for any major changes to:
 - the manufacturing process,
 - the dosage regimen, or
 - the recommended uses of the drug

Health Canada requests that manufacturers submit and maintain a Risk Management Plan (RMP) for all biologics, including biosimilars. RMPs set out activities to be carried out by drug manufacturers to monitor and detect potential safety signals following market authorization. The RMP of a biosimilar generally includes monitoring and risk minimization activities that are similar to those in place for the reference biologic drug.

Health Canada has not observed unexpected post-authorization safety signals for biosimilars marketed in Canada. The efficacy and safety profiles of biosimilars authorized in Canada remain in line with those of their reference biologic drugs. Health Canada receives drug safety information from other jurisdictions including the United States and the European Union. Biosimilars have been used for over 10 years in the European Union and unexpected safety signals have not been identified.

Safety-related updates to biosimilar product monographs

We require all drug manufacturers to ensure that the product monograph (label) for each of their products is up to date and supports effective and safe conditions of use.

At the time of authorization, the safety information in the product monograph for a biosimilar is based on information in the reference biologic drug product monograph. Once authorized, a biosimilar is considered a "stand-alone" product.

Because a biosimilar and its reference biologic drug are not identical and are manufactured by independent processes, newly identified safety issues that affect the reference biologic drug may or may not affect the biosimilar and vice-versa.

We require biosimilar manufacturers to monitor the post-market safety profile of their own product and make safety updates to the biosimilar product monograph as appropriate. Biosimilar manufacturers should also monitor the reference biologic drug product monograph, assess any updates and reflect them in the product monograph for the biosimilar.

Health Canada requests that all potentially affected manufacturers assess the need to update their product monographs when:

- a safety update is made to the product monograph of:
 - a reference biologic drug
 - a biosimilar
 - any other drug with shared active ingredients
- the plausibility of a drug class effect is established

Manufacturers should respond to the letter of advisement within 30 days, and, if warranted, submit changes to their product monograph for review by Health Canada.

In addition, under the *Protecting Canadians from Unsafe Drugs Act (Vanessa's Law)*, we can issue notices and orders for label changes in a much shorter timeframe, if needed to prevent injury to health.

Comparing Canada's biosimilar regulatory framework with those of other countries

The key principles we use to evaluate biosimilars align with those of other regulators and international organizations such as the:

- European Medicines Agency (EMA)
- United States Food and Drug Administration (FDA)
- World Health Organization (WHO)

Moreover, Health Canada's position on the use of biosimilars is consistent with the [International Coalition of Medicines Regulatory Authorities](#), which includes key international regulatory partners from:

- Australia
- The United States
- the United Kingdom and
- the European Union

We engaged a wide variety of stakeholders when developing the regulatory framework for biosimilars. We review our approach to regulating biosimilars on an ongoing basis in response to:

- best practices
- experience gained
- scientific evidence and advances

Naming convention for biologic drugs including biosimilars

The naming convention for biologic drugs, including biosimilars, consists of a unique brand name, as well as the non-proprietary (common/proper) name, without the addition of a product-specific suffix. The non-proprietary name is generally the International Nonproprietary Name (INN) assigned to the active ingredient by the World Health Organization (WHO). Biosimilars share the same non-proprietary name as their reference biologic drug and are distinguished by their unique brand names and other product-specific identifiers such as the Drug Identification Number (DIN).

More information on biologic drug naming is available in Health Canada's [Notice to Stakeholders - Policy Statement on the Naming of Biologic Drugs](#). A [What We Heard Report](#) summarizing the results of the 2018 Consultation on the Naming of Biologic Drugs is also available.

Identification of biologic drugs, including biosimilars, in prescribing, dispensing and adverse drug reaction reporting

Biologic drugs, including biosimilars, should be clearly identifiable to the product-level in prescribing, dispensing and adverse drug reaction reporting. This is particularly important as biosimilars enter the market and there are more biologics with the same non-proprietary name.

All biologics authorized by Health Canada will have a unique brand name, a non-proprietary (common/proper) name of the active ingredient, and a unique Drug Identification Number (DIN). Each product dispensed to a patient will also have a specific lot number. To facilitate product-level identification of biologic drugs, including biosimilars, Health Canada recommends that the unique brand name and the non-proprietary name as well as other product-specific identifiers, such as the DIN and the lot number, be used throughout the medication use process. Product-specific identifiers should be included in adverse drug reaction reports to facilitate the traceability of an adverse reaction to a specific suspect drug product.

Biosimilar availability in Canada

The following factors affect the availability of biosimilars in Canada:

- Canada has a small population compared to other world markets. Manufacturers may decide to submit first to larger markets, such as the United States and the European Union.
- Reference biologic drug intellectual property (patent, data protection and/or Certificate of Supplementary Protection) expiry dates can differ between Canada and other countries.
- Provincial/territorial and private payers make decisions as to whether or not to list drugs authorized by Health Canada on their formularies.

Interchangeability

In Canada, the term "interchangeability" often refers to the ability for a patient to be changed from one drug to another equivalent drug, by a pharmacist, without the intervention of the prescriber who wrote the prescription.

Health Canada's authorization of a biosimilar is not a declaration of equivalence to the reference biologic drug. The authority to declare two products interchangeable rests with each province and territory according to its own rules and regulations.

Switching

In the context of biosimilar use, Health Canada considers switching between authorized products to refer to a change from routine use of one specific product to routine use of another specific product.

Biosimilars are authorized by Health Canada for the indications listed in the Product Monograph. Patients and health care providers can have confidence that biosimilars are effective and safe for each of their authorized indications. No differences are expected in efficacy and safety following a change in routine use between a biosimilar and its reference biologic drug in an authorized indication.

If you have any questions about changing from one biologic drug to another, you should speak to your health care practitioner.

Biosimilars and your drug benefit program

Funding through drug benefit programs is not guaranteed when Health Canada authorizes a biosimilar or other biologic drug for sale.

In Canada, drugs are reimbursed by federal, provincial and territorial public plans and by private plans. Each jurisdiction decides which drugs they will or will not cover, whether there are specific coverage criteria, and at what amount or percentage of cost is covered.

Advertising and other messaging about biosimilars

As biosimilars emerge onto the market, advertising and other messaging from industry must respect applicable laws and refrain from misrepresenting the quality, efficacy and safety of biosimilars that have undergone rigorous review by Health Canada.

More information about biosimilars authorized in Canada

1. Health Canada's [Drug Product Database](#) contains product specific information, including product monographs for drugs authorized for sale in Canada.
2. [Regulatory Decision Summaries](#) briefly explain Health Canada's decisions for drugs seeking market authorization including biosimilars.
3. [Summary Basis of Decision](#) documents explain Health Canada's decisions for drugs seeking market authorization including biosimilars in detail.
4. The [Canada Vigilance Adverse Reaction Online Database](#) contains information about suspected adverse reactions (also known as side effects) to health products.
5. [Submissions Under Review](#) lists certain drug submissions currently under review by Health Canada.

For further information on biosimilars, please contact:

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