

Discussing Biosimilars with Patients: A Resource for Healthcare Providers

What are biologic drugs?

Biologic drugs (biologics) are complex protein molecules created inside a living cell.

Key messaging for patients:

- Biologic drugs are medications that are made from living cells, like animal cells, bacteria, or yeast. Many other drugs are made from chemicals.
- Biologic drugs are used to treat diseases including diabetes, Crohn's disease, and cancer.

What are biosimilars?

A reference biologic is the original branded drug approved by Health Canada. When the patent for a reference biologic expires, other manufacturers can sell highly similar copies of the reference biologic, known as biosimilars. A biosimilar is not necessarily identical to its reference biologic, but based on Health Canada's guidelines and approval standards for the pharmacokinetics, pharmacodynamics, safety and clinical efficacy of biologics, the two are highly similar. Health Canada dictates that there are no clinically meaningful differences between biosimilars and their reference biologic drugs in terms of quality, safety and efficacy.

Key messaging for patients:

- A biosimilar is a highly similar copy of an existing biologic drug.
- The existing biologic drug is called the "reference biologic" drug because it is the drug to which the biosimilar is compared.
- Because of how complex they are, reference biologics and biosimilars cannot be identical, but they are almost the same. A biosimilar and its reference biologic work in the same way and have the same safety and effectiveness.

How are biologics and biosimilars monitored?

Since biologics and biosimilars are made inside living cells, every batch of biologics and biosimilars that are produced is slightly different. The variability between batches is monitored by Health Canada. When a manufacturer makes changes to the process of how a biologic is made, they need to prove that the product is highly similar to the previous product and that there is no adverse impact upon safety or efficacy.

Key messaging for patients:

- Health Canada monitors both biosimilars and reference biologic drugs to ensure the products continue to be as safe and effective as when they were first approved.
- When a manufacturer changes the way it makes a biologic drug, they need to prove to Health Canada that the changes will not affect the safety of the drug or how it works.

How do biosimilars differ from generic drugs?

The active ingredients in generic drugs are exactly the same as the brand name drug. The natural variability and more complex manufacturing of biologics does not allow an exact replication of a biologic molecule.

Key messaging for patients:

- A generic drug is made from chemicals and has the exact same active ingredients (the chemicals that make the drug work) as a brand name drug. For example, you can buy ibuprofen as Advil (brand name) or a store brand (generic).
- A biosimilar is not identical to its reference biologic drug because they are very complex and are harder to reproduce than chemicals. This means that every batch of biologics and biosimilars made is a little bit different. Even though they are not identical, the biosimilar works the same as its reference biologic.

Will biosimilars work as well as the reference biologic? How have they been compared to their reference biologic?

For a drug to be deemed a biosimilar by Health Canada, the drug manufacturer must provide information to Health Canada to show that the biosimilar and the reference biologic drug are highly similar, and that there are no clinically meaningful differences between them. It is important to note that no biologic manufacturer (neither the reference nor the biosimilar manufacturer) can make exact copies of a biologic medication, so the manufacturers must ensure high similarity.

The biosimilar also needs to be studied in randomized, controlled trials to show that its efficacy is equivalent to the reference biologic. For example, biosimilar manufacturers for bevacizumab conducted Phase III trials that had 600-700+ patients with a single type of cancer (see the Health Canada Product Monograph for the details of the clinical trials used to approve biosimilars).

It is expected that if a patient is transitioned to, or started on, a biosimilar, they will have the same outcome as if they were treated with the reference biologic since there are no clinically meaningful differences between the two.

Key messaging for patients:

- You should expect to have the same results and the same side effects, whether you take a biosimilar or reference biologic drug.
- Drug manufacturers must prove to Health Canada that the biosimilar is as close to the reference biologic drug as possible. They must also prove that the biosimilar works just as well as the reference biologic. This is done through studies called clinical trials.

Are biosimilars safe?

Yes. Biosimilars that are approved by Health Canada have been evaluated in large clinical trials to determine not only their efficacy, but also their safety. These clinical trials have demonstrated that, when compared to the reference biologic, the approved biosimilars do not have any unexpected safety issues in treating patients (see the Health Canada Product Monograph for the details of the clinical trials used to approve biosimilars).

Key messaging for patients:

- Biosimilars are safe and work in the exact same way as the reference biologic drug to treat your cancer. There are no clinically meaningful differences between a biosimilar and its reference biologic drug.
- As with any drug, there is always a risk that you may have side effects. Your healthcare team will manage any side effects you may have.
- In the European Union, biosimilars have been used for many years to treat many diseases, including cancer. The European Union has never had to stop using any biosimilars because of safety issues or the drug not working.

If a biosimilar drug is studied in a single indication, how is it approved in other indications? Patients may ask “why was this drug studied in indication “X” but I have “Y”?”

Once a biosimilar has been shown to be highly similar to its reference biologic, a clinical trial is conducted. The clinical trial compares the reference biologic to the biosimilar in patients with a single disease (a homogenous patient population) where the reference biologic has shown to have a significant impact on that disease (a sensitive patient population). The purpose of conducting this clinical trial is to demonstrate that the biosimilar is equivalent to the reference biologic. Once equivalence is demonstrated, Health Canada can authorize other indications, as long as there is appropriate scientific rationale. This is sometimes called “extrapolating” indications.

In some instances, a reference biologic drug is publicly funded to treat patients for off-label indications (e.g., bevacizumab (Avastin) is publicly funded for cervical cancer, which is not an

approved indication). In this case, a jurisdiction may also choose to publicly fund the biosimilar for the same off-label indications as its reference biologic.

Key messaging for patients:

- Biosimilar drugs do not need to be studied in all of the indications (specific diseases or conditions that a drug is used to treat) for which the reference biologic drug is approved.
- Once a manufacturer has shown that the biosimilar works the same way as its reference biologic on a specific disease, they can ask Health Canada for all of the indications that the reference biologic is approved for.
- Sometimes drugs (biologics or drugs made with chemicals) may be covered by the public health care system in diseases that have not been approved by Health Canada – this is called off-label use. If a reference biologic has been publicly funded for off-label use, the biosimilar may also be publicly funded for off-label use.

A patient was switched to a biosimilar and their disease progressed. Why did this happen?

When treating cancer, there can be many reasons why a patient's disease may progress. Many biologic drugs (reference biologics and biosimilars) are prescribed in combination with chemotherapy because the combination is better than either agent alone. When a patient's disease progresses, it is likely that the combination of the biologic drug and chemotherapy is no longer effective at treating the patient's cancer, not that the biologic drug (either the biosimilar or reference biologic) is the cause for the disease progression. This can happen regardless of whether a patient was started on a reference biologic drug, started on a reference biologic drug and then switched to a biosimilar, or started on a biosimilar and then either remained on the biosimilar or was switched to another biosimilar.

It is important to note that a clinical trial cannot predict the outcomes of an individual patient. Clinical trials can only tell us what results to expect when treating patients who are similar to those in the clinical trial and are receiving the same therapy.

Key messaging for patients:

- There can be many reasons why your cancer may have progressed. It is likely that if it has, it is because your treatment – which may include chemotherapy and biologic drugs – has stopped working.
- If your treatment stops working it would have happened regardless of whether you were taking a reference biologic or a biosimilar, even if you were switched from one to another.

Will patients be monitored while on biosimilars?

Regardless of whether patients are on a reference biologic drug or biosimilar to treat their cancer, they will be monitored in the same way.

Key messaging for patients:

- When receiving cancer treatment, your healthcare team will always monitor you for any big or small changes that may be caused by your disease or treatment.
- You will be monitored in the exact same way, regardless of whether you are being treated with the biosimilar or reference biologic drug.

What oncology biosimilars are expected in the near horizon?

Bevacizumab, trastuzumab, and rituximab currently have biosimilars with NOCs (Notice of Compliance) and are expected to come to market in the near future. As the patents for oncology biologics expire, more biosimilars will be entering the market.

Key messaging for patients:

- The cancer drugs that will have biosimilars in the near future are bevacizumab, trastuzumab and rituximab.

Have biosimilars been used elsewhere? Are they new in Canada?

European Experience

Since 2006, the European Union (EU) has been treating patients with biosimilars for many diseases, and in 2017 they began to use therapeutic biosimilars in oncology.

Over the years, there has not been a single biosimilar withdrawn from the EU due to safety or efficacy issues.

Canadian Experience

Since 2016, Canada has used biosimilars to treat diseases including diabetes, Crohn's disease and arthritis, and in 2017 biosimilars for supportive care were introduced for oncology.

Many of the same biosimilars used in Europe are now going to be used in Canada.

Key messaging for patients:

- The European Union (EU) has been treating patients with biosimilars for many diseases since 2006. In 2017, they began to use biosimilars to treat cancer. The EU has never had to stop using any biosimilar because of safety issues or the drug not working.

- Canada has been treating diabetes, Crohn’s disease and arthritis patients with biosimilars since 2016. In 2017, Canada began using biosimilars to treat the side effects of cancer treatment.
- Many of the same biosimilars used in Europe are now going to be used in Canada.

What is the benefit of implementing (or funding) biosimilars? Why is Canada implementing biosimilars now when other countries have been using them already?

When a reference biologic is approved by Health Canada, the drug is protected by a patent. This means that only the innovator company can produce and sell the drug. Once the patent expires, other companies are allowed to sell highly similar copies of the drug (biosimilars). In Canada, patents on some reference biologics are starting to expire. Since it is less expensive to develop a biosimilar, biosimilar manufacturers can offer the drug at a lower price. This will help reduce costs for the healthcare system, private insurance companies, and even patients who may be paying out-of-pocket. The savings from using biosimilars can be reinvested into the healthcare system and can help increase access to new innovative cancer treatments, which can help improve patient outcomes.

Key messaging for patients:

- Biosimilars cost less than their reference biologic drug because they are less expensive to produce. The health system can benefit from the lower cost of biosimilars because the money saved can be spent on giving patients access to the newest and best treatments.

Where can I find more information about biosimilars?

You can find more information online at cancercareontario.ca/biosimilars.

Healthcare professionals may also be asked the questions below. Responses to these questions will depend on jurisdictional policies. You are advised to refer to your jurisdictional or institutional policies to help form responses to these questions.

- Why am I being switched to a biosimilar from a reference biologic?
- I was switched to a biosimilar, and then switched again to a new biosimilar. Why? (e.g., geographic, shortage, market share value-based)
- Must I switch to the biosimilar? Do I have any other choices?
- Under what circumstances can I change back to the reference biologic?
- What if I move? Will I be able to take the same biologic/biosimilar?
- Are biosimilars covered under provincial drug plans?

References

1. Health Canada. 2019. *Fact Sheet: Biosimilars*. <https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/fact-sheet-biosimilars.html>
2. Health Canada. 2016. *Guidance Document: Information and Submission Requirements for Biosimilar Biologic Drugs*. <https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/information-submission-requirements-biosimilar-biologic-drugs-1.html>
3. ICH Expert Working Group. 2004. *ICH Harmonised Tripartite Guideline: Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process Q5E*.
4. Health Canada. 2019. *Biosimilar biologic drugs*. <https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/biosimilar-biologic-drugs.html>