

# Breast Cancer & Biosimilars

Recommendations on  
Use, Implementation and  
Patient Communications



Canadian Breast Cancer Network  
Réseau canadien du cancer du sein

## Introduction:

Biologic treatments have been approved and used in Canada for several decades, marking the beginning of an exciting time for the treatments of many diseases, as these therapies truly changed the outcomes for many patients living with chronic, and often fatal diseases. These diseases include Crohn's disease, psoriasis, and breast cancer, among others. Biologics include a wide range of products such as vaccines, blood and blood products, allergenics, gene therapies, tissues, and organs. Biologics come from living organisms and may be produced using biotechnology. In contrast to most drugs that are chemically synthesized, and their structure is known, most biologics are complex mixtures that are not easily identified or characterized. Biological products, including those manufactured by biotechnology, tend to be heat sensitive and vulnerable to microbial contamination. Therefore, it is necessary to ensure biologic manufacturing processes comply with strict rules, to prevent contamination, which differs from most conventional drugs.<sup>i</sup> The results are complex molecules that cannot be chemically produced exactly (as most traditional drugs are), such that identical copies (like generics) cannot be made.<sup>iii</sup>

Biosimilars are defined as drugs that are highly similar to a reference biologic drug that has already been approved for sale (also known as a reference product). Unlike generic drugs, which are chemically identical to an existing drug, biosimilars are similar to their reference products, but due to their large size and complexity, are not actually identical.<sup>iv, v</sup>

Biosimilars have been available in Canada since 2009, with the approval of Omnitrope<sup>®</sup> for growth hormone deficiency.<sup>vi</sup> As of December 2018, 10 biosimilars have been approved in Canada and are being used to treat diseases ranging from Crohn's disease to arthritis to psoriasis.<sup>vii</sup>

**Table 1: Health Canada approved biosimilars<sup>\*</sup>**

Product name	Active substance	Therapeutic area	Authorization date	Manufacturer / company name
Brenzys <sup>®</sup>	etanercept	Ankylosing spondylitis Rheumatoid arthritis	31 Aug 2016	Merck Canada
Erelzi <sup>™</sup>	etanercept	Ankylosing spondylitis Juvenile idiopathic arthritis Rheumatoid arthritis	3 Aug 2017	Sandoz
Grastofil <sup>®</sup>	filgrastim	Neutropenia	7 Dec 2015	Apotex
Hadlima <sup>™</sup>	adalimumab	Rheumatoid arthritis	8 May 2018	Samsung Bioepis
Inflectra <sup>®</sup>	infliximab	Ankylosing spondylitis Crohn's disease <sup>†</sup> Psoriatic arthritis Psoriasis Rheumatoid arthritis Ulcerative colitis <sup>‡</sup>	15 Jan 2014	Hospira
Lapelga <sup>™</sup>	pegfilgrastim	Neutropenia	5 Apr 2018	Apotex
Mvasi <sup>™</sup>	bevacizumab	Colorectal cancer NSCLC	17 Oct 2018	Amgen
Omnitrope <sup>®</sup>	somatropin	Growth hormone deficiency in adults and children	20 Apr 2009	Sandoz
Remsima <sup>®</sup>	infliximab	Crohn's disease <sup>†</sup> Ankylosing spondylitis Psoriatic arthritis Psoriasis Rheumatoid arthritis Ulcerative colitis <sup>‡</sup>	15 Jan 2014	Celltrion
Renflexis <sup>®</sup>	infliximab	Crohn's disease Ankylosing spondylitis Psoriatic arthritis Psoriasis Rheumatoid arthritis Ulcerative colitis	22 Mar 2018	Samsung Bioepis

<sup>\*</sup>Data collected on 23 January 2014, updated on 14 December 2018

<sup>†</sup>Added to approved indications on 14 June 2016

NSCLC: Non-small cell lung cancer

Source: Health Canada

The Canadian Breast Cancer Network (CBCN) has been observing the evolution of this new treatment space carefully, knowing that an increasing number of biosimilars are likely to be approved for use in cancer treatment; breast cancer, in particular, is primed to be impacted by the biosimilar market, as patents for breast cancer treatments are among the first to expire.<sup>vii</sup>

While there are many opportunities that come along with the entry of biosimilars, such as significant cost-savings to the health care system, they also bring with them a host of unanswered questions. For example, considerations regarding the regulation of biosimilars and how patient safety, treatment choice, and pharmacovigilance will be maintained. Further, there may be questions about whether the same rules apply to the oncology space, where treatments are approved based on survival improvement, in comparison to other disease states when a biosimilar may be approved based on symptom / disease management to treat a chronic disease.

To help understand the different perspectives to these and other questions, CBCN conducted two national virtual roundtables – one with breast cancer patients and one with medical oncologists. Insights were collected from seven patients and six medical oncologists. The following paper outlines some observations, key take-aways and recommendations that resulted from those roundtables.

## Background on Biosimilars:

The first biosimilar was approved for use in Europe in 2006, and in Canada in 2009. It then took almost another decade for biosimilars to reach approvals in the US (2015).<sup>xi</sup> In March 2010,<sup>ii</sup> Health Canada finalized the [guidelines](#)<sup>iii</sup> that outline the necessary documentation to submit for an approval review of a biosimilar. This submission requires extensive data to demonstrate that the biosimilar treatment has comparable characteristics and efficacy as the original biologic drug, such as submitting characterization studies conducted in a side-by-side format.<sup>iii</sup> Health Canada looks at ensuring the similarity between the biosimilar and its reference treatment, so the type of data required for a biosimilar to be authorized is different from the information needed for a new biologic treatment because the requirements are on determination of similarity.

In some circumstances, Health Canada may authorize a biosimilar for the treatment of multiple other conditions or diseases, even if no clinical studies have been done in each specific disease state (for example, use of TNF inhibitors in inflammatory bowel disease when the data was focused on rheumatoid arthritis). Health Canada can also elect not to authorize a biosimilar for a specific condition or disease type, if they believe there are scientific and benefit / risk-based considerations.

In oncology, biosimilar products are currently being developed for potential use in routine cancer treatment. In 2018, Health Canada approved Mvasi™, a biosimilar for bevacizumab (Avastin™). This treatment has been authorized for use in treating metastatic colorectal cancer and locally advanced, metastatic or recurrent non-small cell lung cancer, and is the first biosimilar authorized for the treatment of cancer in Canada.<sup>xv</sup> Other biosimilars in development include those for the treatment of chronic lymphocytic leukaemia and some forms of non-Hodgkin's lymphoma.

In breast cancer specifically, biosimilars are currently being developed for the treatment indications for trastuzumab (Herceptin™) and have recently been approved by the FDA.<sup>xvi</sup>

‡The Health Canada guidance document "Guidance Document: Information and Submission Requirements for Biosimilar Biologic Drugs" was updated in November 2016.

## Understanding and Awareness of Biosimilars:

Prior to the CBCN roundtable with seven women living with breast cancer, we conducted an hour-long session during which we provided unbiased, fact-based education about reference biologics and biosimilars to ensure everyone had the same level of understanding. It was evident that this was required as several members of this group had little to no awareness of the existence of biosimilars, or their difference from reference biologics. We do, however, recognize that having held the larger discussion with the same group following the education session, we gleaned insights and perspectives from a group of women who were likely more educated than the average patient might be about biosimilars and their potential use in the treatment of breast cancer.

CBCN did not hold an education session with the clinicians prior to our virtual roundtable. The physician group consisted of six medical oncologists from across the country. We observed that amongst the physician group, there was a range of understanding of biosimilars with respect to several key considerations such as: monitoring, safety and efficacy, European experience with biosimilars and patient communications. Given that, one of the opportunities identified was ongoing education for the medical community to ensure consistent understanding of current research / practices and to build confidence in evidence-based prescription practices with biosimilars.

To ensure there is clear understanding of some terms used within this white paper, please consider the following:

- *"Health Canada recommends that a decision to switch a patient being treated with a reference biologic drug (innovator product) to a biosimilar should be made by the treating physician in consultation with the patient and taking into account available clinical evidence and any policies of the relevant jurisdiction." – Health Canada*
- *"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 doctor who wrote the prescription. In Canada, the authority to declare two products interchangeable rests with each province and territory according to its own rules and regulations." – Health Canada*

## The Patient Perspective:

During the patient roundtable we touched upon three key topics including: 1) how to best communicate information about biologics / biosimilars to those diagnosed with breast cancer; 2) recommendations on the implementation and roll-out of biosimilars in Canada including thoughts around the process of biosimilar approvals and approval for indications that the reference biologic may not have received (including different stages of a disease), and interchangeability; and 3) considerations around cost-savings.

**"We have to figure out a way to provide us (patients) with the information so it's not so overwhelming. There's got to be a better way."**

– Patient participant

From this, there were five key take-aways that summarize the discussion:

### 1. Lack of confidence / trust in biosimilars:

There was a general feeling of distrust in biosimilars due in part to their name. Once the patient group understood that biosimilars were named to connote the fact that they were not identical to biologics, but instead "similar" to them, the patients became concerned that they would be receiving "second class" treatment and were left feeling unsure that the biosimilars worked as well as reference biologics. As such, it is important for the medical community to be aware of the reassurances the patient may require.

### 2. Treatment efficacy and side effects:

Questions were raised as to whether a potentially fatal disease, such as breast cancer, was factored into the analysis and subsequent approval of biosimilars. There was a sentiment that biosimilars used in the treatment of cancer should undergo a more stringent review process than those used in treating chronic conditions. Confidence was further lost given the lack of original clinical research for biosimilars, which the patient group felt implied the potential for lack of efficacy of biosimilars and the potential for unknown side effects. The lack of long-term data left them feeling uncomfortable as to how these drugs would affect them in the long-term or interact with the myriad of other medications they might be taking. Finally, there were questions raised around additional side effects that may arise from switching from a biologic to a biosimilar. It was noted that cancer patients often will not report every side effect they experience as there could be many. Sometimes they only report the more significant ones. Finally, there were concerns raised around extrapolation of data that would allow for approval of a biosimilar in a disease state where clinical studies were not done.

### 3. Communications with patients:

The patient group felt very strongly that there is a need for clear communication to be made available to them to help inform them about biosimilars. Further, they may require assurances that their treatment is the best possible choice to treat their cancer, which should be communicated to them via their treating physician. Communication can start with a dialogue with their physician, however, it will be imperative to have print / online reference materials for review following an appointment.

Specifically, it was stressed by these women that the potential of being switched to, or placed on, a biosimilar raised their anxiety level considerably; especially if their current treatment appeared or was documented to provide clinical benefit. It was imperative to them that their physicians were made aware of the impact this could have on a patient's mental health, and to both acknowledge and manage it properly. However, the group also strongly implored that they trust their oncologists and would follow their advice – they just want to be informed. This point was also identified in the recent [Lived Experience](#) report that CBCN published, which found that breast cancer patients want to be better informed – through increased access to information so they can better understand their diagnosis and make informed decisions.

These patients often feel as if they have lost all control. Not understanding or not being part of the treatment decision-making process would exacerbate this feeling.

**“You’re wanting as much control as you can get, but you already have no control, so you’re searching for it.”**

– Patient participant

It may also be helpful to communicate to the patient that biosimilars have been used in other countries – primarily those in Europe – for many years before they were approved for use in Canada, and that no new safety concerns have been identified.

#### 4. Need for guiding principles for the use of biosimilars in oncology treatment:

The women in this group felt that specific parameters needed to be established around the use of biosimilars for breast cancer treatment (which can be extrapolated for other cancers). These considerations were likely not taken into account for the use of biosimilars in other areas. Things to consider within these guidelines could include: the type of breast cancer the patient has, what stage the cancer is in, whether the cancer is recurrent, and the age of the patient. There should also be emphasis on the need to always do what is best for the patient, not what provides the best cost-savings, while ensuring that safety, efficacy, side effects, and mental health are all included in the decision-making process. It is also noteworthy that all of the participants agreed that interchangeability should not be allowed for biosimilars. Doctors should always be in control of the treatment choice (along with the patient).

**“I’m interested in saving money, but more interested in saving my life.”**

– Patient participant

#### 5. Application of cost-saving:

The patient group understood and were pleased with the potential cost-savings associated with the use of biosimilars, especially if treatment outcomes were equally successful as reference biologics. However, their hope was that the savings from the breast cancer biosimilars would be reinvested back into breast cancer research or providing access to existing treatments. If the patients were the source of the savings, then the patients should be the benefactor of the savings.

#### Summary:

Overall, these women are focused on beating and surviving their cancer, and failing that, living as healthily as possible for as long as they can. They are eager to have as much control over their fate, and their fight with cancer, as they are able, including their treatment decisions. Ultimately, the patients trust their health care providers to do what is best for them and to use the best evidence-based treatment protocol to manage their disease and have a successful outcome.

## The Physician Perspective:

In many ways, the physician roundtable mirrored the patient session, with adaptations to allow the physicians to comment on some of the points made by the patient group. It also touched upon opinions pertaining to the use of biosimilars to treat breast cancer, considerations around the implementation of biosimilars into the health care system, as well as thoughts on how to communicate with and educate patients and other health care professionals.

From this group, we extrapolated four key take-aways, which included:

#### 1. Experience and comfort in use:

It appeared from the conversation that there was a range of familiarity with biosimilars and the use of them to date, and for some, a lack of awareness of the likely impending arrival of biosimilars into the breast cancer treatment landscape. In particular, some physicians were more aware than others of the details of the use of biosimilars in European countries, including the length of time used there and treatment outcomes. Some stated their discomfort in extrapolating data from the metastatic setting to the curative one, meaning specific outcome data should exist before that type of approval should be granted. Finally, there is a need to ensure awareness across the medical community that Health Canada does not currently recommend interchangeability for biosimilars.

## 2. Implementation:

There were many elements of implementation that this group of physicians felt strongly should be taken into consideration. For example, the following were raised during the roundtable:

- Switching should not be required for any patient who is on an existing reference biologic. Further, if interchangeability is ever introduced, the stage of the tumour should be taken into the consideration, in that a change likely should not be made for a treatment that has an indication in one stage, but not another
- Agreement that strict adherence to monitoring / post-marketing surveillance of biosimilars will be essential to building industry confidence. Monitoring outcomes, toxicity, and side effects must be mandatory
- Consideration around assurances for drug supply from manufacturers with biosimilars and the impact that this could have on patients, especially those in the oncology space
- As more biosimilars enter the market to treat a given disease state, the importance of naming conventions and computer coding will become more important for drug tracking purposes and pharmacovigilance. This is an area the whole group was aligned needs to be factored into the approval of biosimilars in Canada and successful post-marketing surveillance
- Currently, manufacturers of reference biologics offer support programs to patients that aim to make the process easier and smoother should private acquisition be required. The physician group felt that the onus would be incumbent upon the manufacturers of the biosimilar to consider doing the same

## 3. Communication with patients:

There was considerable debate around how much and what to tell patients about prescribing a biosimilar. Some of the participants felt that it was imperative to tell the patient, in a reasonable manner, about the decision to use a biosimilar. The group all agreed that the name “*biosimilar*” could be confusing and might cause undue stress amongst the patient population. It was mentioned that physicians should communicate that our regulator, Health Canada, is extremely rigorous and its review and approval processes are of high quality. Given that, physicians trust Health Canada’s decisions, and so should patients. Ultimately, it was agreed upon that until biosimilars are a “standard of care”, it is incumbent upon the healthcare system and the physician to communicate the decision to use a biosimilar with the patient.

## 4. Cost implications:

The physician group was more pragmatic on the likelihood of being able to earmark the cost savings from the use of biosimilars and channel the funds back into research or drug access, feeling that this would be challenging due to the structure and funding model of the health care system. They were aligned that the cost savings are important if not imperative, but that they should not be the determinant of which treatment to select for a patient. In some cases, the short-term use of a reference biologic vs. a biosimilar in oncology treatment will not amount to significant cost savings due to its short use. What is more impactful is the potential cost saving achieved with the use of a biosimilar for chronic disease management over the course of 20 years.

“‘Biosame’ would be better than biosimilar. But this is the reality.”

– Physician participant

“From a quality perspective, the Health Canada process is among the most rigorous in the world... We really can be proud of the systems we have in Canada.”

– Physician participant



### Summary:

The most surprising observation from the physician group was the range of excitement, complacency or reluctance to use biosimilars for the treatment of breast cancer. Some within the group were eager and ready to start using them, while others felt that it would be mandated for them to use them for new patient starts and were resigned to this inevitability. That said, the group trusted the decision of Health Canada and Provincial Cancer Agencies/Tumour Groups and felt that, in all likelihood, the biosimilars would behave and work in the same way biologics do. There was also acknowledgement of the large potential cost-saving benefits that biosimilars will bring to the Canadian health care system.

### Conclusion:

**CBCN recognizes the opportunity that the entry of biosimilars brings to both patients and the Canadian health care system. However, to ensure both the safety and comfort of Canadian breast cancer patients, we have the following recommendations:**

1. It will be incumbent upon patient groups, cancer care agencies and health care professionals to ensure patients receive educational materials about biosimilars. These resources need to find the right balance between providing context and information without elevating the anxiety of patients. There should also be additional information available to patients through online content – ideally in both written and video formats.
2. Physician associations and medical institutions need to inform and educate health care professionals (ranging from nurses to pharmacists to physicians) about the role of biosimilars in breast cancer treatment, including providing research and data of their use in other countries. This information should be accompanied by some short, simple and clear points that health care providers can use when communicating with patients (in addition to directing them to the CBCN website for more detailed information).
3. The Canadian government will need to take special care and provide clear direction of how to manage the treatment landscape once more than one biosimilar is available to treat breast cancer. This would include naming conventions, computer coding and identification of the ideal stage and type of breast cancer.
4. For the foreseeable future, CBCN recommends that the provinces should not mandate interchangeability between biologics and biosimilars. CBCN does not recommend that any patients who are being successfully treated with a reference biologic be switched off their treatment. Further, if the treating physician is comfortable, they can consider placing a patient not currently on treatment onto a biosimilar, but they should not be mandated to do so. Or, if a patient is requesting the use of a biosimilar, together with their physician, they can choose to do so.
5. Health Canada should regulate the provinces, institutions and biosimilar manufacturers to fund and conduct post-marketing surveillance and share data on treatment outcomes.

## Acknowledgements:

The following individuals generously contributed their time and expertise to the development of this whitepaper:

### Breast Cancer Patients:

Jenn Abbott, Ontario  
Cathy Ammendolea, Quebec  
Carmela Bocale, Saskatchewan  
Katie Davidson, Ontario  
Diana Ermel, Saskatchewan  
Tamara Kelly, Ontario  
Bev Martin, Manitoba  
Wendy Panagopoulos, Nova Scotia  
Jackie Van Ryswick, Ontario

### Medical Oncologists:

Dr. Stephen Chia, MD, FRCPC, Medical Oncologist at BC Cancer Agency and Assistant Professor of Medicine, University of British Columbia, Vancouver  
Dr. Karen Gelmon, MD, FRCPC, Medical Oncologist at BC Cancer Agency and Professor of Medicine, University of British Columbia, Vancouver  
Dr. Anil Abraham Joy, MD, FRCPC, Medical Oncologist at Cross Cancer Institute and Professor of Oncology, University of Alberta, Edmonton  
Dr. Nancy Nixon, MD, FRCPC, Medical Oncologist at Tom Baker Cancer Centre, Calgary  
Dr. Sandeep Sehdev, MD, FRCPC, Medical Oncologist at The Ottawa Hospital, Ottawa  
Dr. Jawaid Younus, MD, FRCPC, Medical Oncologist at London Health Sciences Centre, Assistant Professor of Medicine, University of Western Ontario, London

Financial support for the development of this white paper was provided by a variety of Canada's leading research based pharmaceutical companies. The content of the document exclusively reflects the consensus from the members of the patient and physician steering committees and CBCN who had full editorial control.

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- i Current Oncology. "Perspectives in Oncology: The evolution of biosimilars in oncology, with a focus on trastuzumab." Available at: <http://www.current-oncology.com/index.php/oncology/article/view/3942/2762>. Accessed December 2018.
  - ii U.S. Food and Drug Administration. "What Are "Biologics" Questions and Answers." Available at: <https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cber/ucm133077.htm>. Accessed December 2018.
  - iii Biotechnology Innovation Organization. "How do Drugs and Biologics Differ?" Available at: <https://www.bio.org/articles/how-do-drugs-and-biologics-differ>. Accessed December 2018.
  - iv National Center for Biotechnology Information (NCBI). "Biosimilars Part 1: Proposed Regulatory Criteria for FDA Approval." Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3737980/>. Accessed December 2018.
  - v U.S. Food and Drug Administration. "Biosimilar and Interchangeable Products." Available at: <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm580419.htm#biological>. Accessed December 2018.
  - vi Financial Post. "Biosimilars on the cusp of making waves in Canada's pharmaceutical sector." Available at: <https://business.financialpost.com/investing/outlook/biosimilars-on-the-cusp-of-making-waves-in-canadas-pharmaceutical-sector>. Accessed December 2018.
  - vii <http://www.gabionline.net/Biosimilars/General/Biosimilars-approved-in-Canada> (Last accessed: Dec 18, 2018)
  - viii Molecular Diversity Preservation International. "Concepts and Challenges of Biosimilars in Breast Cancer: The Emergence of Trastuzumab Biosimilars." Available at: <https://www.mdpi.com/1999-4923/10/4/168/pdf>. Accessed December 2018.
  - ix Government of Canada. "Fact Sheet: Biosimilars." Available at: <https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/fact-sheet-biosimilars.html>. Accessed December 2018.
  - x National Center for Biotechnology Information (NCBI). "Ten years of biosimilars in Europe: development and evolution of the regulatory pathways." Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5440034/>. Accessed December 2018.
  - xi Pharmacy and Therapies. "Zarxio: The First Biosimilar Approved By the FDA." Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5215272/>. Accessed January 2019.
  - xii 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.html>. Accessed: December 28, 2018.
  - xiii Ibid.
  - xiv Generics and Biosimilars Initiative. "Health Canada approves Inflectra biosimilar for extra indications." Available at: <http://www.gabionline.net/Biosimilars/News/Health-Canada-approves-Inflectra-biosimilar-for-extra-indications>. Accessed February 2019.
  - xv Canadian Agency for Drugs and Technologies in Health (CADTH). "Mvasi For Metastatic Colorectal Cancer/Non-Small Cell Lung Cancer Biosimilar – Details." Available at: <https://www.cadth.ca/mvasi-metastatic-colorectal-cancer-non-small-cell-lung-cancer-biosimilar-details>.