Team worthy

Brands.
Generics.
Biosimilars.

Teva Canada's Commitment[1,3,5]

In a complex world, Teva's mission is simple: to improve the lives of patients. As an innovator in Canadian medicine, this means we are committed to the future of manufacturing and delivering high-quality biosimilars to all Canadians.

As biosimilars continue to gain importance and acceptance in the Canadian market, we are dedicated to expanding our portfolio to continue delivering innovative biosimilars that patients and healthcare professionals can feel confident in.

We are looking forward to expanding our medicine cabinet to include a variety of state-of-the-art biosimilars and continuing to help improve the lives of Canadians.

When it comes to biosimilars, you can trust in Teva Canada as a key partner.

teva | Canada

Brands. Generics. **Biosimilars.**

teva

Trustworthy

Committed to a future in biosimilars[1-4]

At Teva, we understand that the Canadian healthcare market is changing with the increased availability of biosimilars. For this reason, we have commercialized safe and effective medications that you can trust. Our biosimilars are no exception.

The increased availability of our biosimilars on the Canadian market can contribute to the healthcare system by reducing costs, increasing competition, and improving drug accessibility for all. With over 1,200 products currently available, we are committed to expanding our portfolio and continuing to help Canadians.

Teva's vision is to be a leader in providing quality, affordable and accessible biosimilar medicines.

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Brands. Generics. **Biosimilars.**

Trustworthy. Team worthy.

Teva's Reputation[1,5]

Teva's mission is simple – to improve the lives of patients. We believe that everyone should have access to quality medicines whether it be for managing disease, fighting infections, or simply improving overall health.

As the world's leading provider of generic medicines, our unique perspective on the roles of each in our healthcare system helps us make sure everything we produce meets your needs. Whether you are a patient, a caregiver, a physician, a nurse or a pharmacist, you can be confident in Teva Canada's products and resources.

Teva Canada Innovation is proud to be part of Teva Pharmaceutical Industries Ltd. With one of the largest portfolios of any pharmaceutical company in the world, nearly 200 million people in 60 countries benefit from one of Teva's quality medicines every day.

teva | Canada

Brands. Generics. **Biosimilars.**

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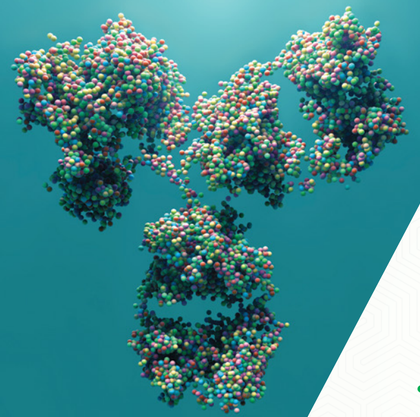


Key Differences between Biologics and Biosimilars[6-8]

Biologics, sometimes referred to as large-molecule drugs, are protein-based therapeutics. Biologics are produced using unique cell lines and are manufactured from natural sources such as human and/or animal cells, yeast, and bacteria.

Some key defining features of biologics include:[6]

- Being produced in living cell cultures
- Having high molecular weight
- Having complex, heterogeneous structure, and manufacturing process
- Being strongly process-dependent
- Being impossible to fully characterize molecular composition and heterogeneity
- Being unstable and sensitive to external conditions

Biosimilars are biologic medicines that are highly similar to their reference biologic drug, which has already been approved for sale. When producing biosimilars, the main difference from the reference biologic is in the clinically inactive ingredients being used in the manufacturing process. There are no clinically meaningful differences in the safety, purity, and potency of biosimilars when compared to the reference biologic.

Safety **Purity** **Potency**

It is important to remember that biosimilars are **NOT** generics.

Biosimilars are approved by Health Canada based on a thorough comparison to a reference drug and may only enter the market after the expiry of the reference biologic drug patents and data protection.[7,8]

Generic drugs are chemical based, small molecule drugs that are generally easy to copy.[9]

Biologics and biosimilars, on the other hand, are large, complex molecules developed inside living cells and are more difficult to replicate.

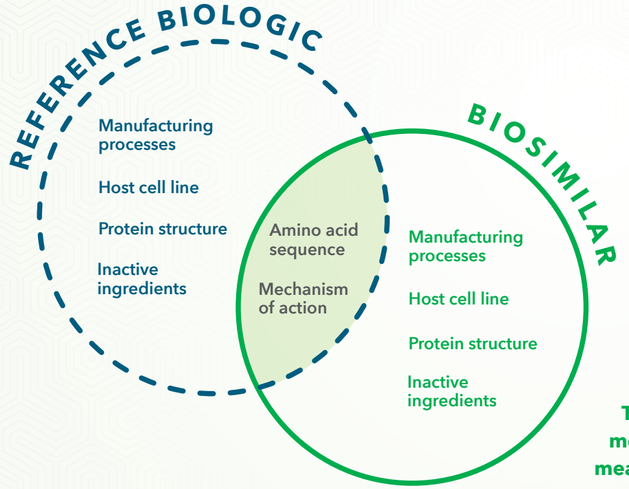
Establishing the Differences between Small Molecule Drugs and Biologics[6,7]

Key differences between small molecule drugs and biologics

Characteristic	Small molecule drug	Biologic
Production type	Chemical synthesis	Produced using living media
Molecular weight/size	Low/small	High/large
Structure/ characterization	Well defined	Complex, not well defined
Manufacturing reproducibility	Easily reproducible	Content, quality and purity are strongly associated with manufacturing process and environmental factors; not easily reproduced
Reverse engineering of the manufacturing process	Yes	No, proprietary nature of production and undefined nature of characterization of the product make an exact reproducibility impossible
Stability	Very stable	Sensitive to environmental factors
Immunogenicity	No (for the most part)	Yes

The Manufacturing Process of Biosimilars[6,7]

Biosimilars are manufactured using living cells or organisms. The manufacturing processes of biologics and biosimilars are typically more complex. Through the manufacturing process, many potential differences in protein structures can arise and therefore, biosimilars are unlikely to be structurally identical to their reference products.



Biosimilars are manufactured in living cells, which cannot be exactly replicated from one manufacturer to another. Teva Canada is committed to ensuring that any biosimilar we manufacture is produced in state-of-the-art facilities and made with the highest quality agents.[6,7]

The amino acid sequence and the mechanism of action have no clinically meaningful differences.[6]

Critical Steps of the Biosimilar Manufacturing Process[6]

Due to the complex nature of manufacturing biosimilars, there are a number of critical steps to help ensure the integrity of the drug between batches. These steps include:

Cell expansion

Different cell line, growth media, method of expansion

Cell production in bioreactor

Different cell line, growth media, bioreactor conditions

Recovery through filtration or centrifugation

Different operating conditions

Purification through chromatography

Different binding and elution conditions

Characterization and stability

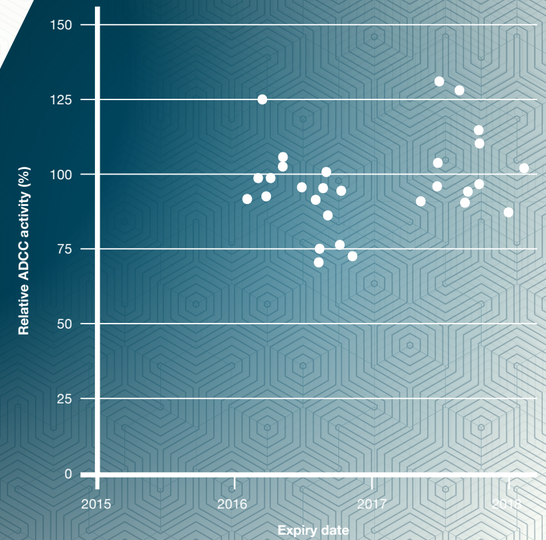
Different methods, reagents, reference standards

Batch-to-batch variability among biologics and biosimilars[7]

While critical steps and quality control methods are taken to ensure the integrity between each batch of manufactured biologic and biosimilar, some degree of variation between batches is a normal part of the manufacturing process.

In fact, many of the processes involved in the manufacturing contribute to batch variation such as: the choice of DNA vector or host organism, the type of bioreactor and media used to grow the cell in, the purification process, and the post-production handling of the drug.

Variations of Herceptin® (biologic) batches



Adapted from Kim *et al.* 2017.[8]

ADCC: antibody-dependent cell-mediated cytotoxicity.

Critical Steps of the Biosimilar Manufacturing Process[7]

There can be anywhere between 5–35 changes in the manufacturing processes after a biologic has been approved and is on the market. These changes contribute to the variation of biologics over time. Similar manufacturing changes would be anticipated with new biologic products and with biosimilars.

Post-approval manufacturing changes of biological products have always been governed by the global regulatory agencies, and manufacturers are required to conduct a comprehensive assessment of these changes and the impacts on the final quality of drug products. All changes are reviewed and pre-approved by Canadian regulatory agencies.

Teva has a well-established and trusted history in manufacturing and supplying medications, with a robust product line featuring **over 1,200 brand-name and generic medicines.** We are committed to building on this history through the investment and development of biosimilars in Canada.[1-3]

Manufacturing quality control[6]

Manufacturers use various methods to ensure consistency of the product across the life cycle. The quality assurance process monitors the following:

Quality system*

Materials systems

Facilities and equipment system

Production system

Laboratory control system

Packaging and labelling

* Ensures overall compliance with current good manufacturing practice and internal requirements.

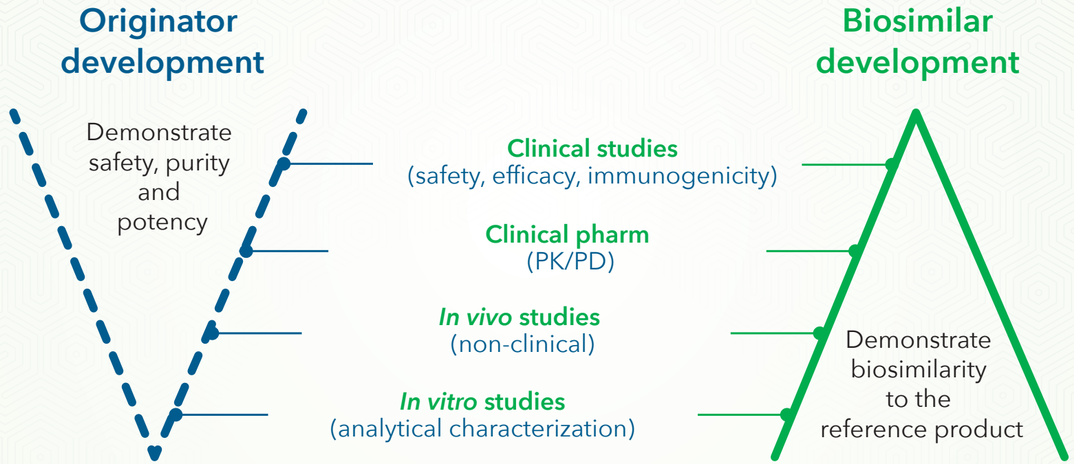
The Regulatory Approval Pathway for Biosimilars in Canada[8]

Health Canada has developed a robust, science-based regulatory framework for biosimilars that reflects many approaches adopted by other major drug regulatory agencies. Health Canada's rigorous standards for authorization mean that patients and health care providers can have the same confidence in the quality, safety and efficacy of a biosimilar as any other biologic drug.

How is similarity between a biosimilar and reference biologic drug demonstrated?

Biosimilar manufacturers must provide information to Health Canada comparing the biosimilar with the reference biologic drug. Similarity is then demonstrated using a step-wise approach beginning with structural and functional studies and continuing to human clinical studies.

Regulatory pathways of originator biologics vs. biosimilars[7]



Varying approval processes for biologics, biosimilars and generics[11]

- Unlike generic drugs, biosimilars are not equivalent to the reference product because their chemical characteristics cannot be precisely duplicated during the manufacturing process.

Health Canada reviews each biosimilar as a new drug. It does not consider a biosimilar to be bioequivalent or interchangeable with the reference product.

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On the contrary, generic drugs must meet Health Canada's standards for bioequivalence.

Biosimilar extrapolation[8]

The term extrapolation is often used to refer to the authorization of a biosimilar for indications where clinical studies were not done. Because a biosimilar is very similar in structure and function to a reference biologic drug with well-established safety and efficacy, clinical studies do not need to be repeated for each indication. Instead, Health Canada may authorize a biosimilar for use in more than one indication because of the rigorous demonstration of similarity between the biosimilar and the reference biologic drug.

Biosimilar interchangeability[8]

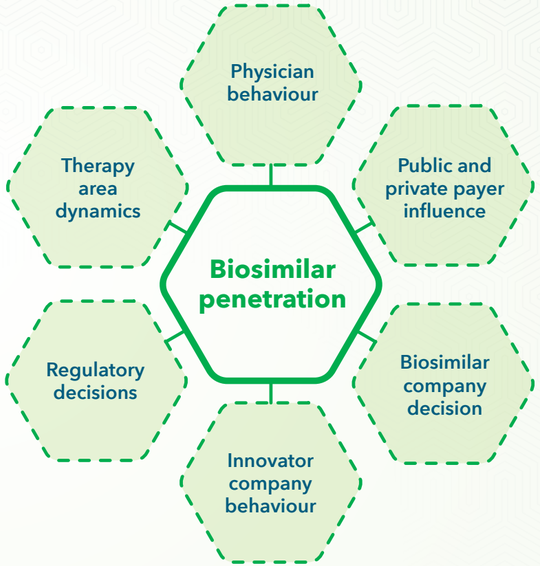
In Canada, the term "interchangeability" often refers to the ability for a patient to be changed from one drug to another equivalent drug by a pharmacist, without the intervention of the doctor who wrote the prescription. The authority to declare two products interchangeable rests with each province and territory according to its own rules and regulations.

At Teva Canada, We Believe in a Sustainable Healthcare System[12,13]

The future of biosimilars in Canada

The increased availability of biosimilars along with recent policy changes to promote biosimilar switching are expected to result in significant cost reductions for relevant classes of biologics in Canada. These endeavours should help to offset the pressure from new higher-cost medicines in coming years. However, there are a number of varying organizational level factors that will have an influence on the future of biosimilars in the Canadian market.

At Teva, we recognize that the increased use of biosimilars offers significant opportunities and benefits for Canadians. That's why we are focusing our research and development efforts on innovative biologics and biosimilars while remaining dedicated to providing products that both consumers and providers can **trust**.[13,14]



The Benefits of Biosimilars in the Canadian Market[6,12,15-17]

The sustainability of the Canadian healthcare system

While biosimilars are still new in the Canadian landscape, they are quickly gaining notoriety. As of April 2022, a total of 31 biosimilars had been approved for use in Canada. Although their adoption in Europe has been faster than in Canada, there has been a steady trend towards the acceptance of biosimilars in our healthcare system. While uptake has had some challenges, the inclusion and availability of biosimilars are expected to further increase. Biosimilars contribute to the sustainability of the healthcare system via:

Reduced cost

Biosimilars typically cost less than their reference biologics

Increased competition

Biosimilars introduce competition, which in turn may also help reduce costs

Improved drug accessibility

Savings from biosimilars could be put towards funding for other much-needed therapeutic areas

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