BIOSIMILAR REGULATION IN CANADA

Attitude, Skills, and Knowledge in Oncology Biosimilars

This document summarises the national regulatory guidance on biosimilar medications in Canada. It is intended as a concise summary of the key guidance for biosimilar regulation and approval, available to download and share with your multidisciplinary team. It is part of a learning programme that provides material covering Canada, the EU, Japan, and the United Kingdom. More information and additional resources can be found at https://ask-biosimilars.com/.

1 Introduction

Regulated by: Health Canada

Definition of a biosimilar: A biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product (the reference product).

Approval process: Applies to all biologics where the sponsor seeks approval by demonstrating similarity to a suitable, previously approved biologic. A sponsor can apply for the indication(s) and condition(s) of use held by the reference product in Canada, also known as extrapolation of indications.

Requirements for approval: Both the biosimilar and reference product must be well characterised using modern analytical methods, which show that the biosimilar is similar to the reference biologic based on pre-determined criteria including comparative structural, functional, non-clinical and clinical studies.[1]

Reference product requirements: A reference product is a biologic drug authorised on the basis of a complete quality, non-clinical and clinical data package, and post-marketing surveillance, to which a biosimilar is compared to demonstrate similarity.[1] The reference product should have substantial, reliable data regarding safety and efficacy.

The same reference product must be used throughout the comparability programme. In certain circumstances, the biosimilar may be compared to more than one reference product (e.g., versions of the reference biologic sourced from the EU and USA). Bridging data that directly compare all the products are required.[1]

The dosage form(s), strength(s), and route(s) of administration of the biosimilar should be the same as the reference product.

A biosimilar authorised using a reduced data package should not be used as a reference product for another biosimilar submission.[1]

2 Manufacturing

Changes to manufacturing process: Require a comparison between the pre-change and post-change versions of the biosimilar. Comparisons with the original reference product are not required.

Biosimilar manufacturers generally will not have access to all information that allows precise replication of reference products

- Novel manufacturing processes may introduce changes not present in the reference product:
  - molecular modifications (e.g., glycosylation)
  - product-related substances (e.g., isoforms)
  - impurities

Differences from the reference product may have undesired consequences (e.g., atypical glycosylation) that influences the structure of the molecule

- Differences in expression
- Different excipients used for stability
- Changes in containers used for storage

3 Comparability

Guiding principle: Establish similarity between the biosimilar and the reference product based on a comprehensive comparability exercise, ensuring that the previously proven safety and efficacy of the reference product also applies to the biosimilar.

Data required: Typical chemistry and manufacturing data package and extensive data demonstrating similarity with the reference product using analytical techniques to detect potential product differences.

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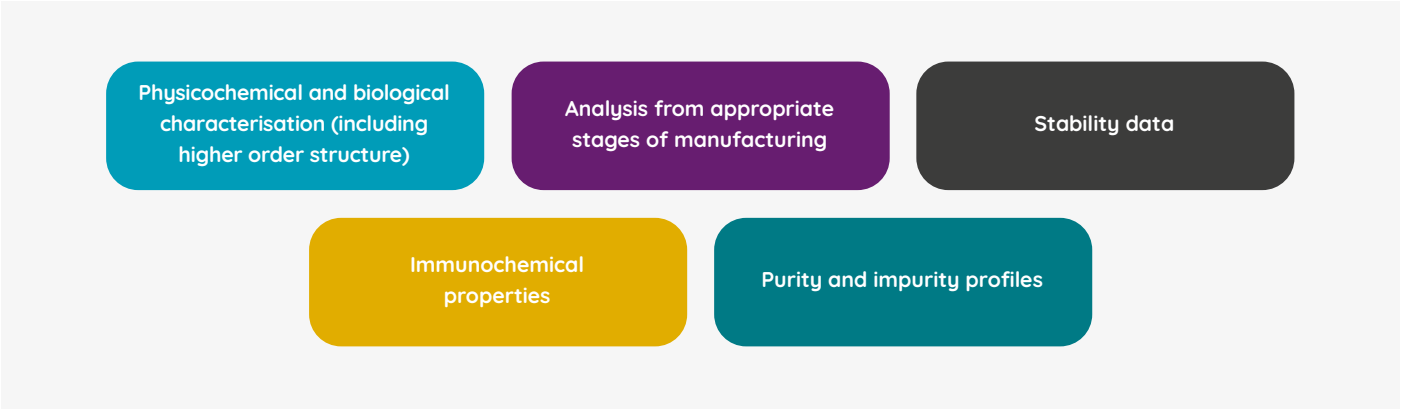

Non-clinical studies

Purpose: Structural and functional studies are generally considered to be more sensitive than clinical studies for detecting differences between a biosimilar and its reference product.[2]

In vivo non-clinical animal studies may not be necessary if structural, functional and extensive *in vitro* mechanistic studies indicate similarity.

3.1 Confirmatory pharmacokinetic trial

Purpose: Should exclude meaningful differences in pharmacokinetic characteristics (including absorption and elimination profiles) between the biosimilar and the reference product, showing that the differences in the manufacturing process produce no clinically meaningful differences.

Design: When appropriate, studies should be in healthy subjects, as they are usually a homogeneous and sensitive population. Patient enrollment is appropriate where the disease state can substantially alter pharmacokinetics, pharmacodynamics or both and this disease state is included in the desired product authorisation.

If scientifically justified pharmacodynamic markers relevant to the mechanism of action are known, pharmacodynamic studies should also be conducted.

3.2 Efficacy trials

Requirements: Exclude clinically meaningful differences in efficacy and safety between the biosimilar and the reference biologic. Efficacy trials may not be needed, e.g., if there is a clinically relevant pharmacodynamic endpoint.

3.3 Safety trials

Requirements: Safety and comparative immunogenicity data in humans are required for authorisation.[2]

Comparative immunogenicity studies: Exclude clinically meaningful differences in immunogenicity such as those that:

- alter pharmacokinetics
- induce anaphylaxis
- neutralise the product, the endogenous protein or both.

This may include competitive ligand-binding assays or cell based assays.

3.4 Extrapolation from one therapeutic indication to another

Once a biosimilar is shown to be highly similar to the reference product with no clinically meaningful differences, the biosimilar **may** be authorised for the same indications as the reference product.[2] This process is called extrapolation and is intended to avoid conducting unnecessary clinical studies.

A biosimilar **may not be authorised for all indications** if:

- not requested by the manufacturer
- mechanism of action is expected to be different for a different approved disease state not studied in the biosimilar authorisation dataset (e.g., bevacizumab for wet age-related macular degeneration)[3]
- intellectual property protection exists for a particular indication with the innovator biologic.[2]

3.5 Pharmacovigilance

Risk management plan: Details procedure for monitoring for immunogenicity following authorisation of the biosimilar. The risk management plan is an important part of the regulatory submission.

Manufacturer responsibilities

- Establish a monitoring system for side effects.
- Periodic re-assessment of risk–benefit analysis and reporting of such.
- Report any new information about serious side effects to Canada Vigilance Program through Health Canada.
- Notify Health Canada about any studies with new safety information.
- Request authorisation for any major changes to the biosimilar (e.g., manufacturing process or recommended use).[2]

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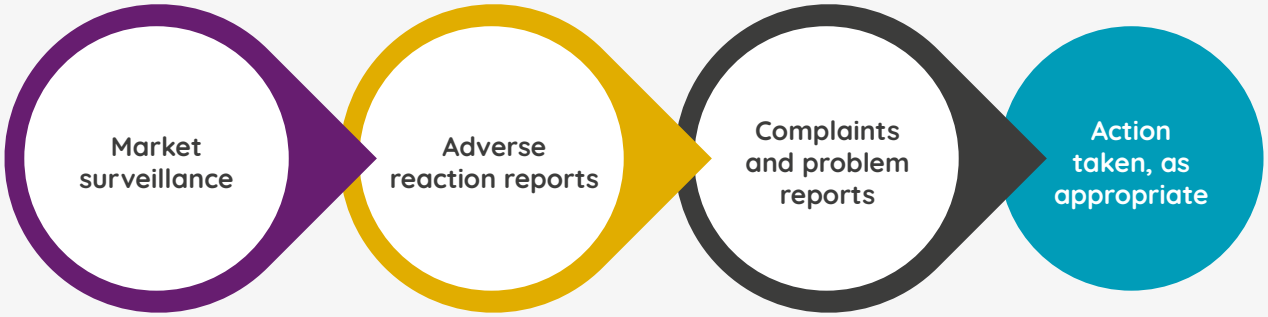
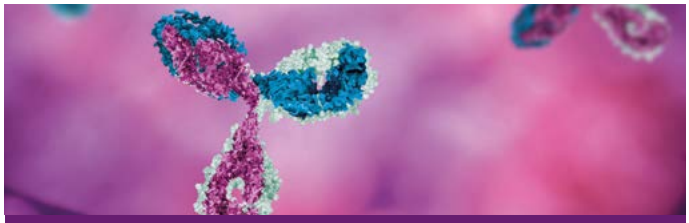
Monitoring by Health Canada: Conducted for all drugs, including biosimilars.[2]



4 Interchangeability

Definition: The ability for a patient to be changed from one drug to another equivalent drug, usually at the pharmacy level, without the intervention of the prescriber. Where products have been deemed interchangeable, a pharmacist may dispense any of the interchangeable products.[2]

Authorisation of a biosimilar by Health Canada does not mean it is considered to be interchangeable with the reference product. Products are declared as being interchangeable at the provincial or territorial level.[2] It is important to refer to local policies.



In an authorised indication, no differences in efficacy or safety are expected following a change in routine use between a biosimilar and its reference product.

References

1. *Health Canada. Guidance Document Information and Submission Requirements for Biosimilar Biologic Drugs*. Available at: https://bit.ly/3K4dYw3 [Accessed February 2022].
2. Health Canada. *Biosimilar biologic drugs in Canada: Fact Sheet*. Available at: https://bit.ly/3njf9OC [Accessed February 2022].
3. Bro, T., et al., Off-label use of bevacizumab for wet age-related macular degeneration in Europe. *Graefes Arch Clin Exp Ophthalmol*. 2020;258(3):503–511.

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