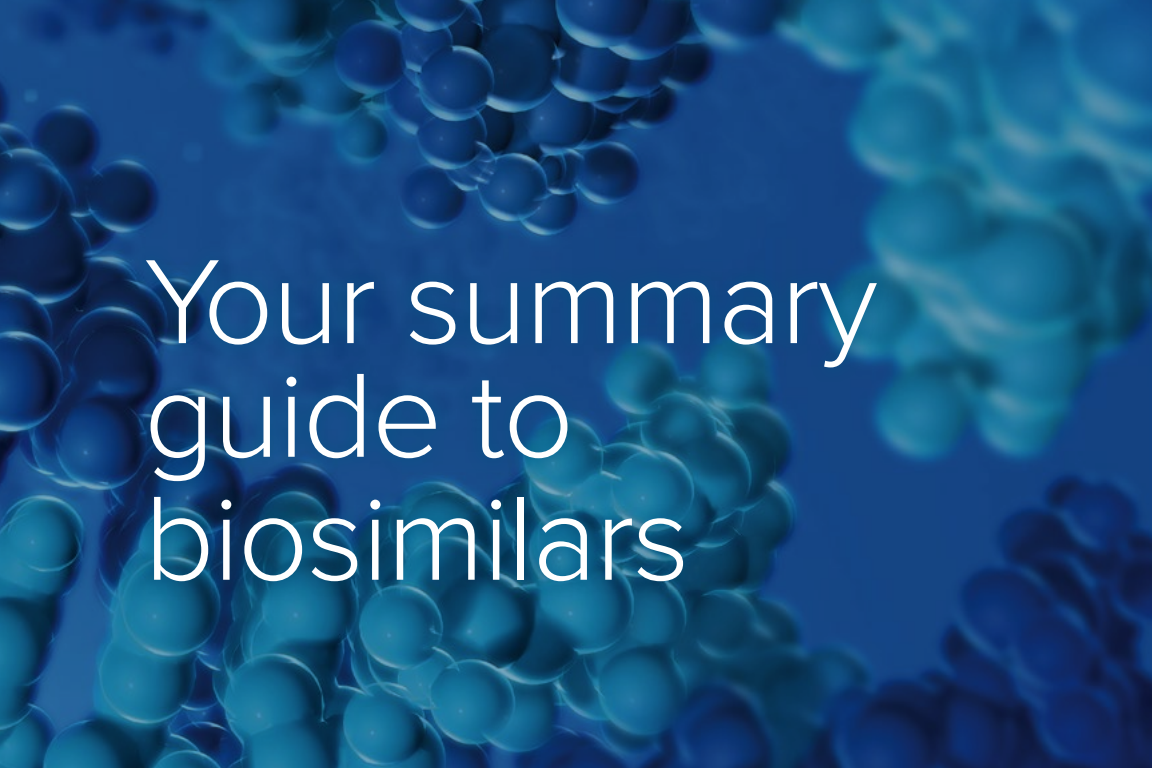

Your summary guide to biosimilars

From innovator biologics to biosimilar medicine

Amgen has over four decades of specialization in biologics.[1] Now, Amgen is leveraging this expertise toward developing biosimilar therapies. Our current biosimilars and any future biosimilar(s) will be produced in the same state-of-the-art facilities that manufacture our innovator biologics.

Amgen applies the same level of robustness and rigour to the development of both innovator and biosimilar medicines.

AMGEN® BIOSIMILARS

Amgen's experience and commitment

Amgen: Manufacturing biologics since 1981

While we manufacture some small-molecule drugs, our primary focus is on the production of biologics—an inherently complex process due to the sensitive and labile nature of these molecules. We therefore have a well-defined manufacturing process in place to produce an acceptable product on a consistent basis.[2,3]

*Founded **over 4 decades ago**, our focus and dedication to the healthcare industry are unwavering.*[1]

Amgen: Our commitment to patients

At Amgen, we are focused on the needs of patients, providing them with ***access to important medicines***. Today, ***tens of thousands of Canadians*** use Amgen medicines each and every year.[1]

*At Amgen, we continually strive to bring **more medicines to more Canadians** than ever before.*[4]

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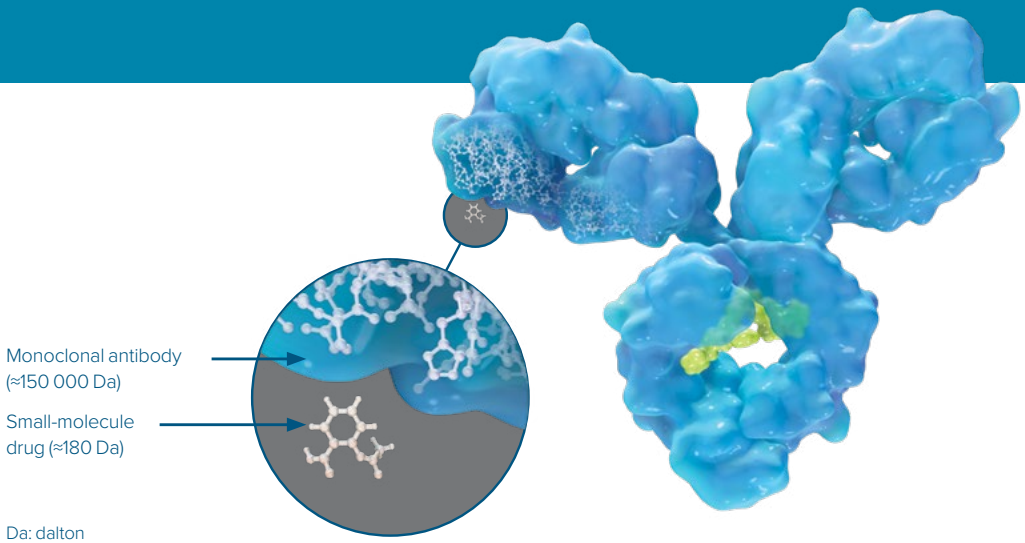
Introduction

What are biologic medicines?

Biologics are **produced through the metabolic activity of living cells** and can include anything from blood components and cytokines to **therapeutic proteins** and **monoclonal antibodies**. The use of living cells as part of the manufacturing process coupled with proprietary operations makes it **challenging to replicate the molecule exactly**.[2,3]



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*Biologics are up to **1 000 times the size** of small-molecule drugs and can be **far more complex**, structurally.*[3,5,6]

What are biosimilar medicines?

A biosimilar is a biologic that is **highly similar** to a biologic that has already been authorized for sale (also known as a reference biologic). Due to the size, complexity and natural variability of biologic drugs, and because biologic drugs are made in living cells rather than with chemically synthesized drugs, a biosimilar and its reference biologic can be shown to be similar, but not identical.[2]

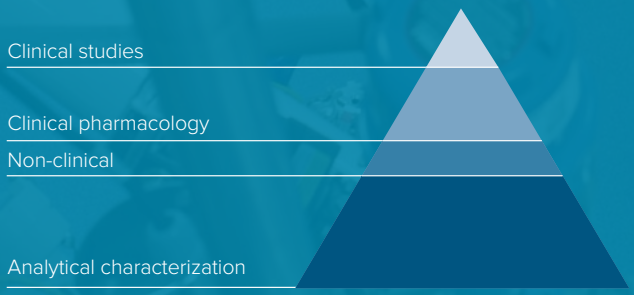
A biosimilar and its reference biologic are considered similar on the basis that there are no clinically meaningful differences in safety and efficacy between them.[2]

Establishing biosimilarity

In addition to the typical chemistry and manufacturing data that is expected for a new biologic drug, biosimilars **must provide extensive data demonstrating similarity with the reference biologic**.[3]

Health Canada requires a clinical study program designed to show that there are no clinically meaningful differences between the biosimilar and the reference biologic.[3]

Biosimilar development



Analytical characterization studies

A side-by-side characterization should be performed to directly compare the biosimilar and the reference biologic. The significance of any differences should be evaluated. When demonstrating biosimilarity, appropriate techniques are used to compare the following properties:[3,7]

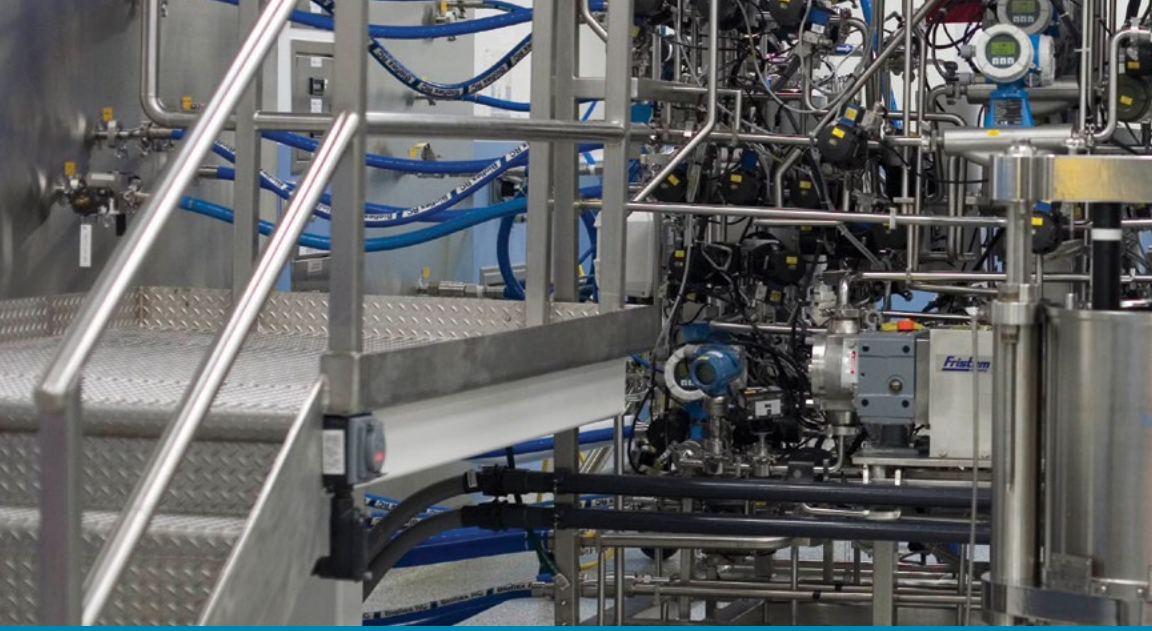
- Physicochemical properties
  - Primary (amino acid sequence) and higher-order structures (i.e. secondary, tertiary, and quaternary)
  - Enzymatic post-translational modifications (glycosylation, phosphorylation)
  - Intentional chemical modifications (PEGylation sites)
- Biological activity
- Immunochemical properties
- Purity, impurities, and contaminants

Protein heterogeneity

Because biologics are produced by living organisms, an inherent degree of structural heterogeneity occurs. Consequently, the desired biologic product can be a mixture of anticipated post-translationally modified forms that do not negatively impact the desired product's safety and efficacy. The manufacturer should define the pattern of heterogeneity of the desired product and demonstrate consistency with that of the lots used in preclinical and clinical studies. If a consistent pattern of product heterogeneity is demonstrated, an evaluation of the activity, efficacy, and safety (including immunogenicity) of individual forms may not be necessary.[3,7]

Examples of protein heterogeneity include:[7]

- Terminal amino acid sequence variants
- Aggregation
- Glycosylation
- Truncation/fragmentation



Comparative structural and functional studies

To be considered a biosimilar, the weight of evidence should be provided by structural and functional studies.[3]

The demonstration of similarity does not signify that the quality attributes of the two products being compared are identical, but that they are highly similar. This means that:

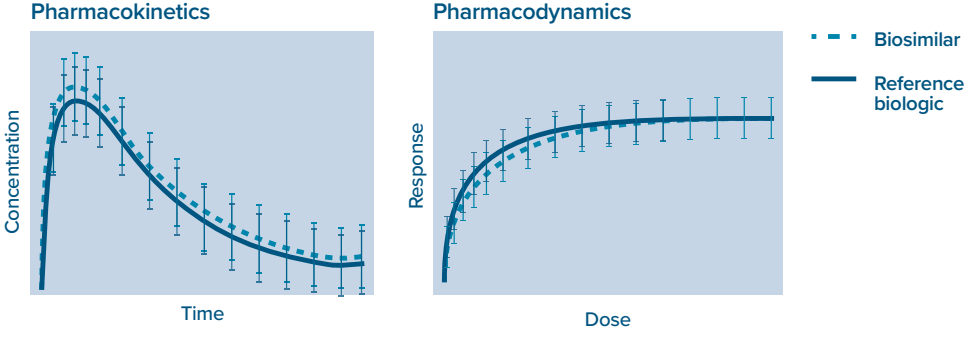
- the existing knowledge of both products is enough to predict that any difference in quality attributes should have no impact upon safety or efficacy; and
- the reference biologic's clinical and non-clinical data are also relevant to the biosimilar.

Clinical studies

The purpose of the clinical studies is to show that there are no clinically meaningful differences between the biosimilar and the reference biologic.[3]

Pharmacokinetic and pharmacodynamic (PK/PD) studies

Comparative PK studies should be conducted to rule out differences in pharmacologic characteristics between the biosimilar and the reference biologic. They should be carried out in healthy subjects when appropriate as they are usually considered to be a homogeneous and sensitive population. Comparative PD studies should be combined with PK studies, in which case the PK/PD relationship should be characterized.[3]

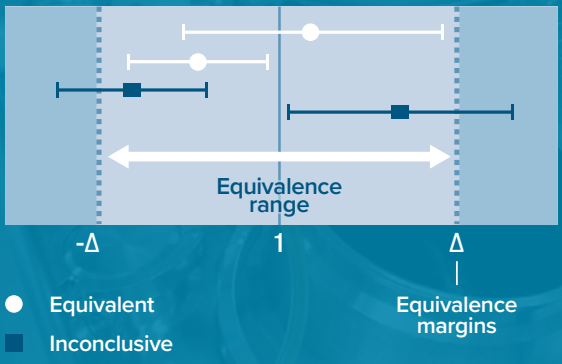


Immunogenicity studies

The purpose of comparative immunogenicity studies is to rule out clinically meaningful differences in immunogenicity between the biosimilar and the reference biologic.[3]

Clinical trials

A comparative clinical trial is important to rule out clinically meaningful differences in efficacy and safety between the biosimilar and the reference biologic. The trial should be adequately sensitive to rule out clinically meaningful differences within predefined comparability margins.[3]



In line with the principle of similarity, equivalence trials are generally preferred.[3]

Manufacturing a biologic or biosimilar

Quality in manufacturing

A well-defined manufacturing process with its associated process controls helps ensure that an acceptable product is produced on a consistent basis. Following manufacturing process changes, the manufacturer generally evaluates the relevant quality attributes of the product to demonstrate that modifications did not occur that would adversely impact the safety and efficacy of the drug product.[3,8]

> *Manufacturing process critical control points are identified to detect process changes that may affect product characteristics.[3]*

Elements of a total control strategy designed to help ensure product quality and consistency include the following:[3,7]

- Product characterization
- Adherence to good manufacturing practices
- Validated manufacturing process
- Raw materials testing
- In-process testing
- Stability testing

Quality control in manufacturing

What is *Quality by Design*?

Quality by Design is a systematic approach to development that begins with predefined objectives and emphasizes **product and process understanding** and **process control**, based on sound science and quality risk management.[9]

> *Amgen has adopted a Quality by Design approach to biosimilar development.*

A *Quality by Design* approach to biosimilar development could facilitate continual improvement and innovation throughout the product lifecycle. It includes:[9]

- Systematic evaluation, understanding, and refining of the formulation and manufacturing process, including:
  - identifying the **material attributes and process parameters** that can have an effect on product CQAs; and
  - determining **functional relationships** that link material attributes and process parameters to product CQAs.
- Using the enhanced product and process understanding in combination with quality risk management to establish an appropriate **control strategy**.

> ***CQAs: Critical quality attributes***
> *A CQA is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. CQAs are generally associated with the drug substance, excipients, intermediates (in-process materials), and drug product.*[9]

Process changes are occasionally necessary to improve the manufacturing process or comply with changes in regulatory requirements. Following any process change to a commercialized biologic or biosimilar, companies generally evaluate the relevant quality attributes of the product to ascertain that the pre- and post-change product is comparable in terms of quality, safety, and efficacy.[3,8]

Authorization of indications

A biosimilar manufacturer can request authorization for all indications held by the reference biologic. The decision to authorize the requested indications is dependent on the demonstration of similarity between the biosimilar and reference biologic drug based on data derived from comparative structural, functional, non-clinical, and clinical studies.[3]

Where similarity has been established, indications may be granted even if clinical studies are not conducted in each indication, sometimes referred to as “extrapolation.” A detailed scientific rationale for each indication request is necessary.[2,3]

Scientific rationale for extrapolation should consider:

- the mechanism(s) of action;
- pathophysiological mechanism(s) of the disease(s) or conditions involved;
- safety profile;
- dosage regimen;
- clinical experience with the reference biologic drug; and
- any case-by-case considerations.

Extrapolation refers to the process through which a biosimilar can be marketed for indications where clinical studies were not done. Once studies have ***shown that a biosimilar is highly similar to the reference biologic****—with no clinically meaningful differences—Health Canada can authorize a biosimilar for the same indications as the reference biologic drug.*[2]

Frequently asked questions

Are biosimilars generic biologics?

According to Health Canada:[2]

"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; and*
- *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."[4]

Are biosimilars and reference biologics interchangeable?

Interchangeability refers to the ability for a patient to be changed from one drug to another equivalent drug by a pharmacist.[4]

Authorization of a biosimilar is not a declaration of equivalence to the reference biologic, so the products are **not automatically interchangeable**. The authorization to do so rests with each province and territory.[2]

What about switching?

In the context of biosimilar use, Health Canada defines "switching" between authorized products as "a change from routine use of one specific product to routine use of another specific product."[4]

Be prepared to discuss biosimilars with your patients.
Health Canada encourages patients to talk to their healthcare practitioners if they have questions about switching between biologics.[2]

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