

*Get to know
biosimilars*

A primer

Why biosimilars?

Biologics and biosimilars defined

Over 30 years ago, the advent of biologic medicines forever changed the way we treat serious illnesses, including inflammatory diseases and cancer. Biologics are produced in genetically-engineered living cells.¹ They include therapeutic proteins, which replace or augment beneficial human proteins, and monoclonal antibodies, which can strike disease targets with enhanced precision.² Biosimilars are biologic medicines that are **highly similar to existing licensed biologic products with no clinically meaningful differences** in terms of safety and efficacy.^{3,4}

Expanded access opportunity

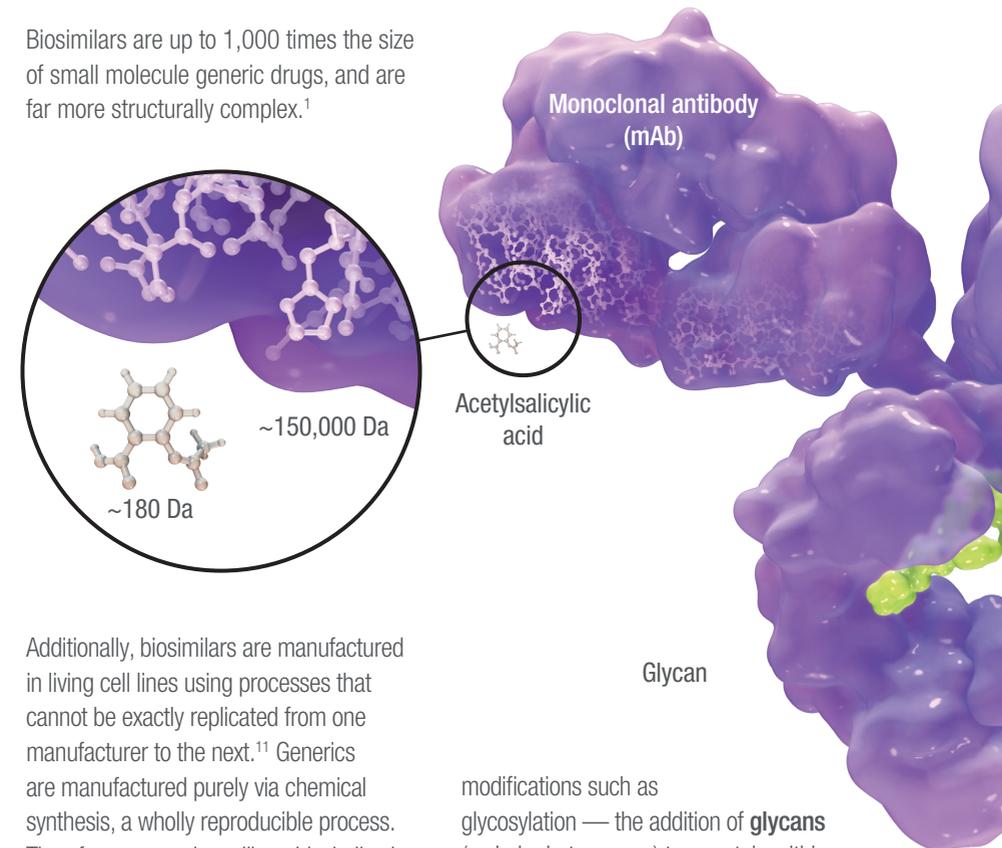
Biosimilars have the potential to improve patient access to biologic therapies.^{5,6,7} Efficiencies realized through abbreviated clinical trial programs and indication extrapolation may provide cost savings to the health care system.⁸ With \$67 billion in global sales of biologic medicines anticipated to go off patent by 2020,⁹ even modest reductions in the cost of biosimilar products could have a meaningful impact on health care systems around the world.⁸ For physicians and their patients, biosimilars provide additional therapeutic options.

	Biosimilars and biologics Monoclonal antibody	Generics Small molecule drug
Size	Large MW ~150,000 Da	Small MW ~180 Da
Structure	Complex with many possibilities for post-translational modification	Simple and well defined
Manufacturing	Manufactured in a unique cell line; only similar, but not identical, copies can be made	Predictable chemical process; identical copy can be made
Characterization	Difficult to characterize	Easy to fully characterize
Immunogenicity	Higher potential	Lower potential
Stability	Sensitive to storage and handling conditions	Relatively stable

Biosimilars have fundamental differences from generic small molecule drugs^{10,11,12,13, 14}

Biosimilars are not generic drugs

Biosimilars are up to 1,000 times the size of small molecule generic drugs, and are far more structurally complex.¹



Additionally, biosimilars are manufactured in living cell lines using processes that cannot be exactly replicated from one manufacturer to the next.¹¹ Generics are manufactured purely via chemical synthesis, a wholly reproducible process. Therefore, a generic, unlike a biosimilar, is an exact copy of its reference product. **The underlying differences in size, complexity, and manufacturing processes are why biosimilars are fundamentally different from generics.** One key reason a biosimilar cannot be identical to its reference biologic is due to post-translational

modifications such as glycosylation — the addition of **glycans** (carbohydrate groups) to a protein within the producing cell.¹ These are unique to each specific cell line and growth conditions and can have a profound impact on the molecule's biological effects, including drug clearance rates and immunogenicity.¹⁵ Therefore, **biosimilars are more complicated to develop and the regulatory pathway for approval is more complex** than for generic drugs.¹

The challenge of making biosimilars

Developing a biosimilar is a far more nuanced and complex process than developing a generic drug.¹⁵ Biosimilars, like all biologics, are produced through an intricate, multi-step process, using living cells. Moreover, the cell line and manufacturing process of the reference product are proprietary and belong only to the original manufacturer. Biosimilarity for antibodies can only be established through evaluation of the biosimilar in active comparator clinical trials and experiments with the reference product.⁴ Procurement and analysis of multiple batches of reference product establish a baseline to inform subsequent structural, and functional, biosimilarity tests.¹⁶

Critical Quality Attributes

Once a cell line is developed for the biosimilar, the candidate molecule is analyzed and carefully compared to the reference product using a number of characteristics, called Critical Quality Attributes (CQAs).¹⁶ CQAs are features associated with the drug product that can impact safety, potency,¹⁷ pharmacokinetics¹⁸ and overall quality.¹⁹ CQAs can include post-translational modifications to a protein. One example is the addition of oligomannose glycans, which impacts pharmacokinetic properties, reducing clearance time.¹⁸ Other post-translational modifications can alter the immunogenicity of a protein,^{10,15} impacting patient safety and efficacy.

Most reference product manufacturing information is proprietary, and not publicly available. Therefore, the biosimilar manufacturer must develop a new cell line and customize the manufacturing process.²⁰



Consistency is key

Once a cell line is selected for its ability to produce proteins highly similar in structure and biological function to the reference biologic, it is expanded to create a master and working cell bank containing several vials of cells.²¹ Most vials that are expanded in bioreactors for manufacturing come from the working cell bank. Mass production involves a number of proprietary steps and conditions, including the method of cell line expansion, bioreactor conditions, protein extraction and purification, formulation and packaging. A change to any of these can affect the complex structure of the biosimilar, potentially altering one or more CQAs.¹⁵

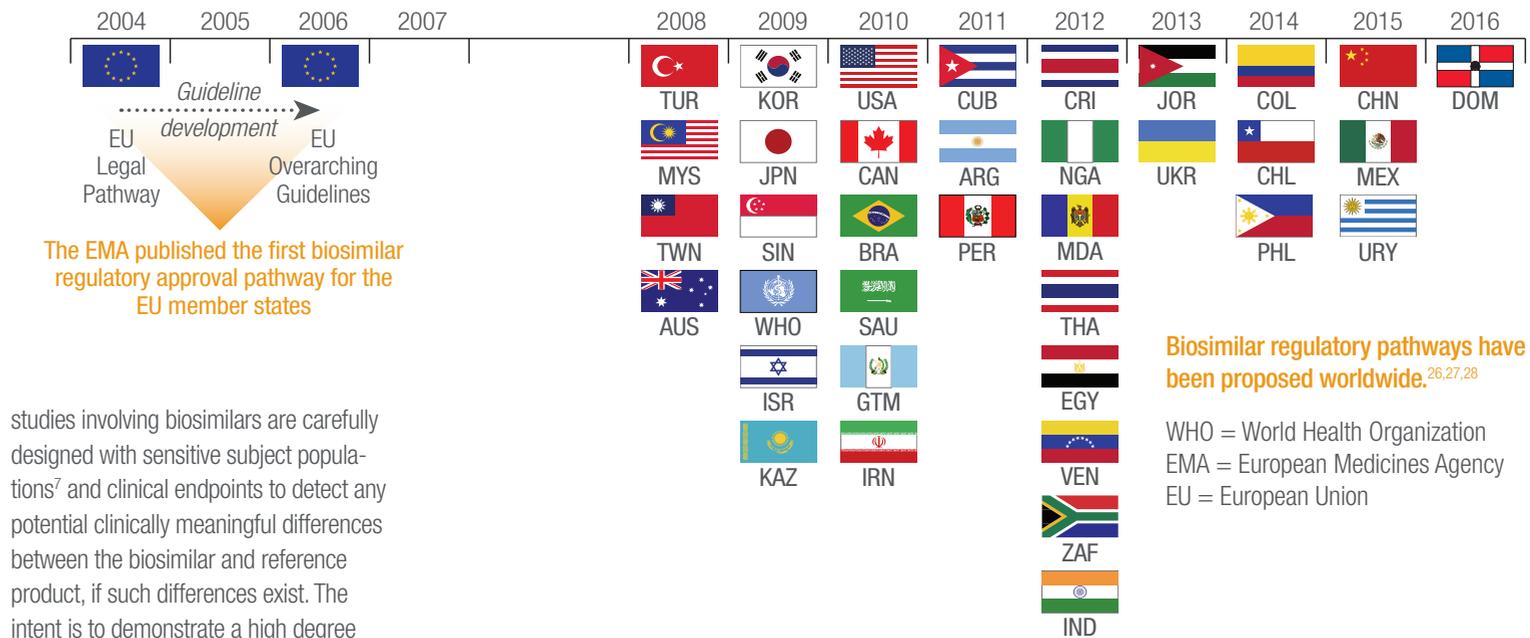
protein structure¹⁵, potentially changing its biological function.¹ It is, therefore, **extremely important to carefully monitor and control all aspects of production.** Moreover, when a process change is made for a biosimilar or an approved biologic, the manufacturer evaluates the relevant quality attributes, in consultation with authorities, to demonstrate that no modifications occurred that could impact the safety and efficacy of the product.^{4,22}

For example, alterations to the cell line or its growth conditions could affect post-translational modifications.¹⁵ Likewise, altering protein extraction or purification techniques could impact

A biosimilar typically has around 250 in-process quality tests during manufacturing, compared with around 50 tests for a small molecule generic.²³

Biosimilars require robust regulatory pathways

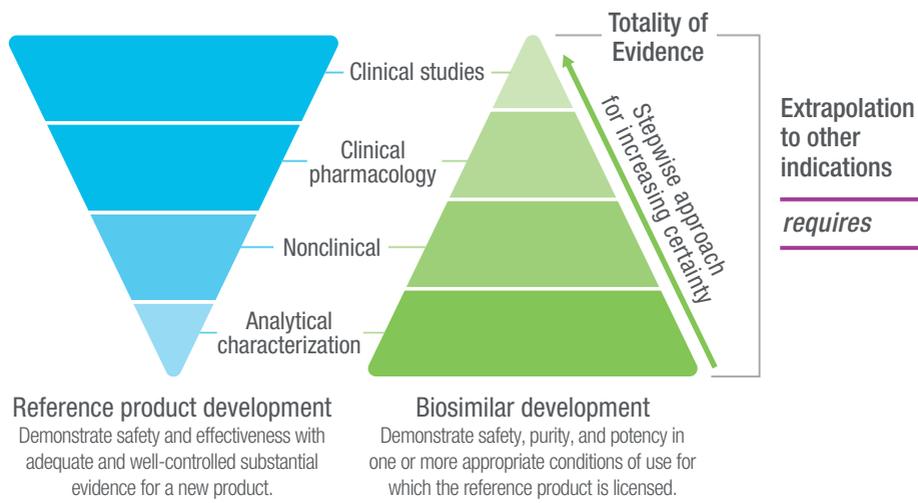
The biosimilar approval pathway requires the manufacturer to demonstrate similarity with the reference product for quality, safety and efficacy.⁴ Specifically, the biosimilar must demonstrate that it has no significant clinical differences to the reference product.^{3,4,24} Before marketing authorization is granted, biosimilar manufacturers must submit robust data consisting of extensive analytical chemistry, manufacturing and control (CMC) studies, and both non-clinical and clinical evidence.^{4,17} The **totality of evidence** must be used to evaluate a biosimilar for market approval.⁴ Clinical



studies involving biosimilars are carefully designed with sensitive subject populations⁷ and clinical endpoints to detect any potential clinically meaningful differences between the biosimilar and reference product, if such differences exist. The intent is to demonstrate a high degree of similarity rather than independently re-establish safety and effectiveness.⁴

Biosimilar regulatory pathways have been proposed worldwide.^{26,27,28}

WHO = World Health Organization
EMA = European Medicines Agency
EU = European Union



Extrapolation of indications

Extrapolation of safety and efficacy data from the studied biosimilar indication(s) into non-studied indications that are approved for the reference product can reduce the development

program length^{29,30} and cost.^{29,31} While extrapolation is not automatic, it may be accepted provided the totality of evidence coupled with scientific justification can address any identified differences.^{4,23}

Totality of evidence + Knowledge of the reference product + Scientific justification evaluating the following:⁴

- Is the mechanism of action expected to differ across indications?
- Is the immunogenicity expected to vary in different patient populations?
- Does the PK, PD, and biodistribution vary across patient populations?
- Are there differences in expected toxicities in different indications and patient populations?

PK = Pharmacokinetics; PD = Pharmacodynamics

Totality of Evidence proposed by regulatory authorities to demonstrate biosimilarity²⁵

Pharmacovigilance, traceability and naming

Rigorous pharmacovigilance is essential for all biologics to protect patients and ensure any adverse events are quickly detected, reported and attributed to the correct product and manufacturer.^{32,33} The ability to track and trace all biologic medicines and biosimilars throughout the product life cycle is critical to enhancing patient safety.

Physicians and pharmacists need accurate data on adverse events linked to specific treatments to facilitate optimal prescribing for each of their specific patients. Under the current International Non-proprietary Name (INN) system, a single name may be used for a reference biologic or biosimilar, making traceability difficult or even impossible.^{6,34,35}

This can result in an adverse event reporter being unable to identify which medicine was implicated in an adverse event.³² Likewise, a treating physician may not know precisely which medicine a pharmacist gave to a patient.^{34,36} In response to these concerns, health authorities have proposed a more rigorous naming system in which a unique four letter code called a biologic qualifier is added to the non-proprietary name in order to distinguish biosimilars from reference products and from each other.^{33,35} Memorable qualifiers, rather than random naming, may help assist with traceability measures and overall clarity.³⁷



Not all biologics are created equal

It is important to distinguish between biosimilars, biobetters, and non-comparable biologics. **Non-comparables** (also known as 'biocopies', 'biomimics', 'intended copies', and 'nonregulated biologics')³⁸ are copies of licensed biologic medicines that are marketed in some countries, but have not followed the rigorous regulatory pathway required for biosimilars.³⁸ Although non-comparables may contain the same amino acid sequence as the reference product, they have not been subjected to the same strict analytical, non-clinical and clinical comparative evaluations prior to market approval as biosimilar regulatory pathways mandate.⁶

The WHO has issued a road-map for member states to review non-comparables with the same stringent regulatory assessments as that of current biosimilar review standards.⁷

As a result, these products may have clinically significant differences in quality, efficacy and safety from their reference products. Certain non-comparables have been shown to have reduced biological potency or higher rates of adverse events,^{39,40,41} underscoring the importance of following a stringent regulatory pathway for the approval of all biologic medicines.

Biosimilars are biologics, but are not ...

Biobetters⁴² Improved versions of reference biologics. If a biosimilar candidate demonstrates superiority, it is subject to the originator pathway for regulatory approval.

Biomimics or biocopies³⁸ Marketed in some countries without having been subjected to rigorous clinical testing or evaluated according to the biosimilar regulatory pathway.

Generic drugs^{43,44} Small-molecule, chemically synthesized drugs that use the same active ingredient, strength, dosage form, route of administration, and conditions of use as the reference product.

Glossary

Biologic A substance derived from a living organism or its products that is used in the diagnosis, prevention, or treatment of disease. Examples of biologic medicines include recombinant proteins, allergy shots, vaccines, and hematopoietic growth factors.⁴⁵

Biosimilar A biological product that is highly similar to a licensed reference biological product notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.^{3,4}

Critical Quality Attribute A physical, chemical or biological property that must be within an appropriate limit, range, or distribution¹⁹ to ensure the desired safety, efficacy and pharmacokinetics of a drug.¹⁷

Extrapolation The process by which a proposed biosimilar product may be licensed in one or more additional conditions of use for which the reference product is licensed, if appropriate scientific justification is provided, the patent landscape allows for it, and the totality of evidence addresses any identified differences between the biosimilar and reference product.⁴

INN (International non-proprietary name) Allocated by the World Health Organization, an INN identifies pharmaceutical substances or active pharmaceutical ingredients. Each INN is unique, globally recognized and is public property. An INN is also known as a generic name.⁴⁶

Master Cell Bank Vials of unique, genetically modified cells replicated for manufacturing a biologic medicine.²³ The working cell bank is derived from the master cell bank.²¹

Non-comparables Copies of licensed biologic medicines that are marketed in some countries, but have not followed the rigorous regulatory pathway required for biosimilars. Also known as 'biocopies', 'biomimics', 'intended copies', and 'nonregulated biologics'.³⁸

Reference Product A previously licensed product used as the comparator for head-to-head comparability studies with the biosimilar in order to show similarity in terms of quality, safety, and efficacy.^{3,24} A reference product is sometimes referred to as the innovator or originator product that the biosimilar is intended to copy.

Small-molecule Generic A small-molecule, chemically synthesized drug that uses the same active ingredient, strength, dosage form, route of administration, and conditions of use as the reference product on which it is based.^{43,44}

Totality of Evidence The totality of data and information used by regulatory authorities to evaluate a biosimilar for market approval. Included are structural and functional characterization, nonclinical evaluation, PK and PD data, immunogenicity data and the results of comparative clinical studies.^{4,17}

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