



# Get to know biosimilars

A primer

# What are biosimilars?

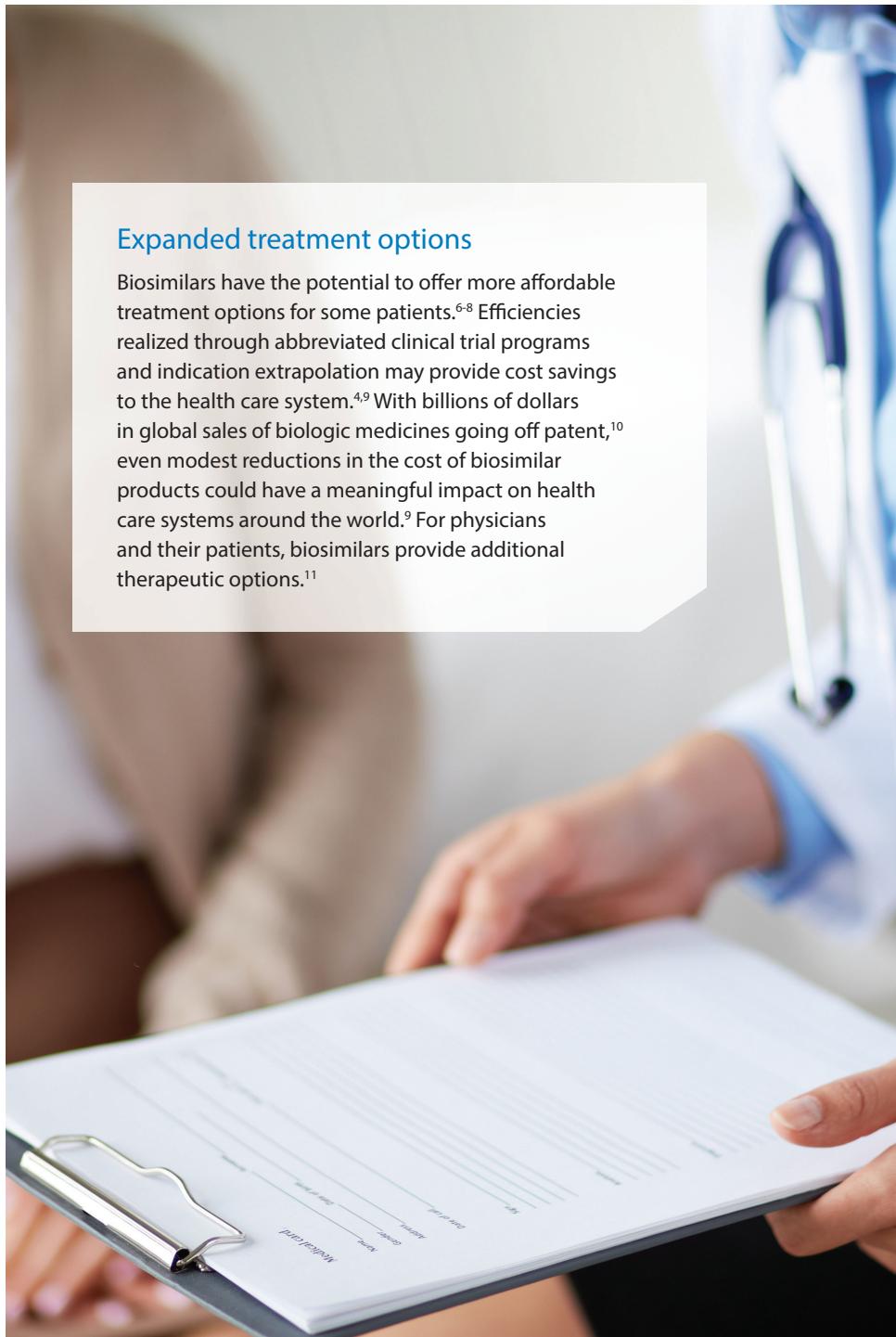
## Biosimilars defined

Over 40 years ago, the advent of biologic medicines forever changed the way we treat serious illnesses. Biologics are produced in genetically engineered living cells.<sup>1,2</sup> They include therapeutic proteins, which replace or augment beneficial human proteins, and monoclonal antibodies, which can strike disease targets with enhanced precision.<sup>3</sup> Biosimilars are biologic medicines that are highly similar to existing licensed biologic products with no clinically meaningful differences in terms of safety and efficacy.<sup>4,5</sup>



## Expanded treatment options

Biosimilars have the potential to offer more affordable treatment options for some patients.<sup>6-8</sup> Efficiencies realized through abbreviated clinical trial programs and indication extrapolation may provide cost savings to the health care system.<sup>4,9</sup> With billions of dollars in global sales of biologic medicines going off patent,<sup>10</sup> even modest reductions in the cost of biosimilar products could have a meaningful impact on health care systems around the world.<sup>9</sup> For physicians and their patients, biosimilars provide additional therapeutic options.<sup>11</sup>



# Biosimilars are not generic drugs

Biosimilars are more structurally complex than small molecule generic drugs and can be up to 1,000 times their size, as is the case with monoclonal antibodies.<sup>1,12</sup>

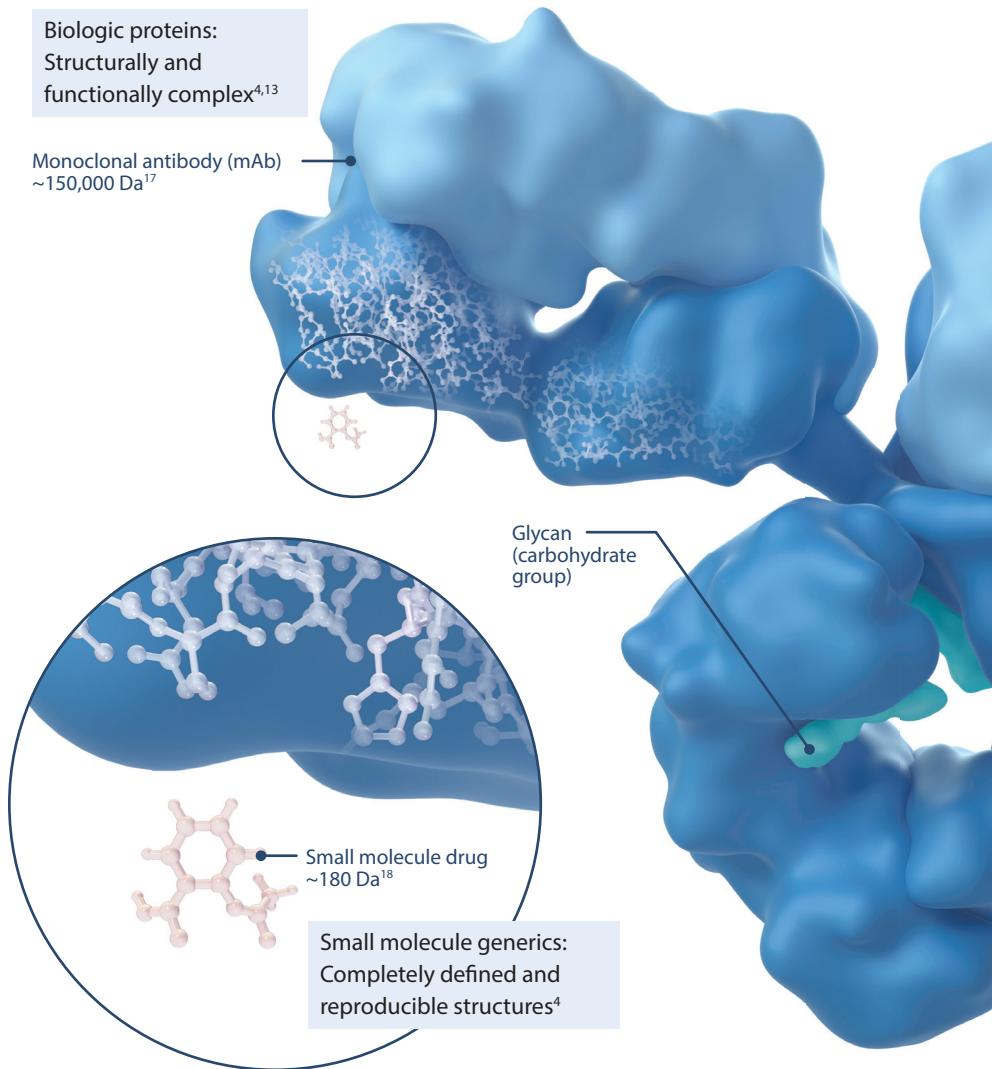
Additionally, biosimilars are manufactured in living cell lines using processes that cannot be exactly replicated from one manufacturer to the next.<sup>4,12-14</sup> Generics are small molecule drugs that have the same active ingredient as the reference product. Unlike a biosimilar, a generic is an exact copy of its reference product and is manufactured using a wholly reproducible process.<sup>15</sup>

Biosimilars have fundamental differences from generic small molecule drugs<sup>1,13,17,18</sup>

Biosimilars and biologics Example: monoclonal antibody		Generics Small molecule drug
Size	Large MW ~150,000 Da	Small MW ~180 Da
Structure	Complex and variable	Simple and well defined
Manufacturing	Manufactured in a unique cell line; only similar, but not identical	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

MW = Molecular weight; Da = Dalton

One key reason a biosimilar cannot be identical to its reference biologic is due to post-translational modifications such as glycosylation, which are unique to each producing cell line and growth conditions. Post-translational modifications can have a profound impact on the molecule's effects such as biologic activity, efficacy, safety and immunogenicity.<sup>6,16</sup> Because of the distinct properties of biologics, they are more complicated to develop and the regulatory pathway for approval is more complex than for generic drugs.<sup>1</sup>



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.<sup>4,8,12</sup>



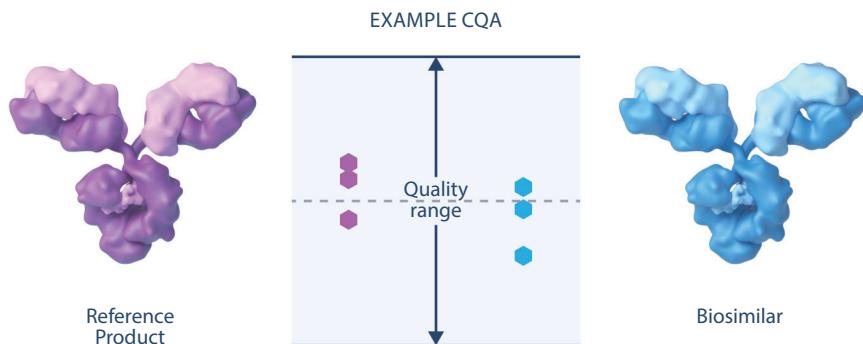
# The challenge of making biosimilars

Developing a biosimilar is far more nuanced and complex than developing a generic drug.<sup>8</sup> Biosimilars are produced through an intricate, multi-step process, using living cells.<sup>7,17</sup> This manufacturing information for the reference product is proprietary.<sup>8,12</sup> The biosimilar manufacturer must therefore develop a new cell line and manufacturing parameters that result in a highly similar product.<sup>4,12</sup>

## 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).<sup>19,20</sup> CQAs are defined as attributes important to the identity, purity, biological activity or stability of the biologic.<sup>20</sup> Therefore, biosimilars require robust regulatory pathways in order to deliver high-quality, reliably supplied therapeutic options to patients.<sup>21</sup>

Structural and functional attributes of the biosimilar are evaluated against the predefined reference product CQA quality ranges.<sup>20,21</sup> Key functions are matched with adequate consideration to assay and process variability and reference lot history.<sup>2,21</sup>



## Consistency is key

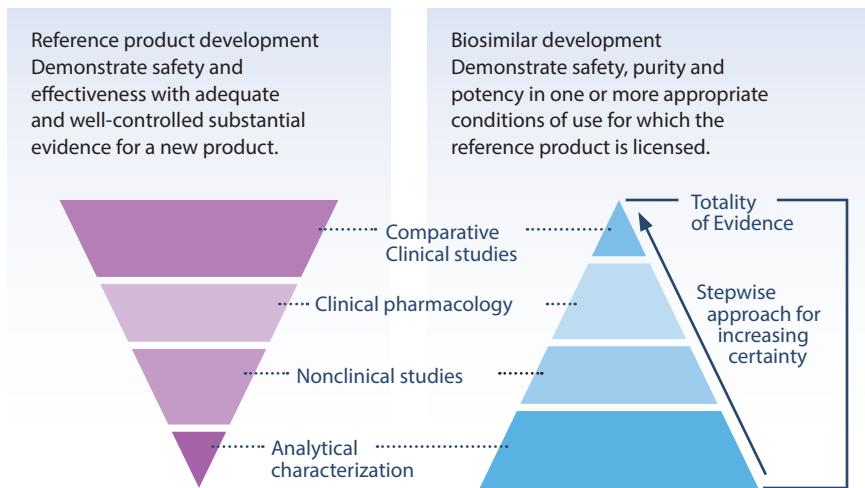
The cell line selected to make the biosimilar is expanded to create a master cell bank.<sup>7,14</sup> Mass production involves a number of proprietary steps and conditions, including cell line expansion, bioreactor conditions, protein extraction and purification, formulation and packaging.<sup>7,12,17,22</sup> A change to any of these can affect the complex structure of the biosimilar, potentially altering one or more CQAs and impacting its biological function.<sup>1,8,23</sup> It is, therefore, extremely important to carefully monitor and control all aspects of production.<sup>3,21</sup>



# Biosimilars require robust regulatory pathways

The biosimilar approval pathway requires the manufacturer to demonstrate similarity with the reference product for quality, safety and efficacy. Specifically, the biosimilar must demonstrate that it has no significant clinically meaningful differences to the reference product.<sup>2,4,5</sup> 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.<sup>4,5,21</sup> This totality of evidence is used to evaluate a biosimilar for market approval.<sup>4</sup> Clinical studies involving biosimilars are carefully designed with sensitive subject populations and clinical endpoints that can facilitate the detection of clinically meaningful differences between the proposed biosimilar and the reference biologic, if such differences exist.<sup>2,4,5,16</sup> The intent is to demonstrate a high degree of similarity rather than independently re-establish safety and effectiveness.<sup>2,4,24</sup>

Totality of Evidence proposed by regulatory authorities to demonstrate biosimilarity<sup>4,25</sup>



	Originator	Biosimilar	Generic
Clinical studies (safety, efficacy, immunogenicity)	Establish clinical benefit and risks	Demonstrate no clinically meaningful differences	Not required
Clinical pharmacology (PK/PD)	PK profile and dose finding	Demonstrate bioequivalence and PK similarity	Demonstrate bioequivalence
Nonclinical studies	In vivo toxicology profile and proof of concept	Toxicology and exposure similarity, when relevant	Not required
Analytical characterization (structure and function assessment)	Quality profile	Quality profile and analytical similarity	Quality profile and structural identity

## Biosimilar definitions vary by jurisdiction

US Food and Drug Administration (FDA)<sup>4</sup>

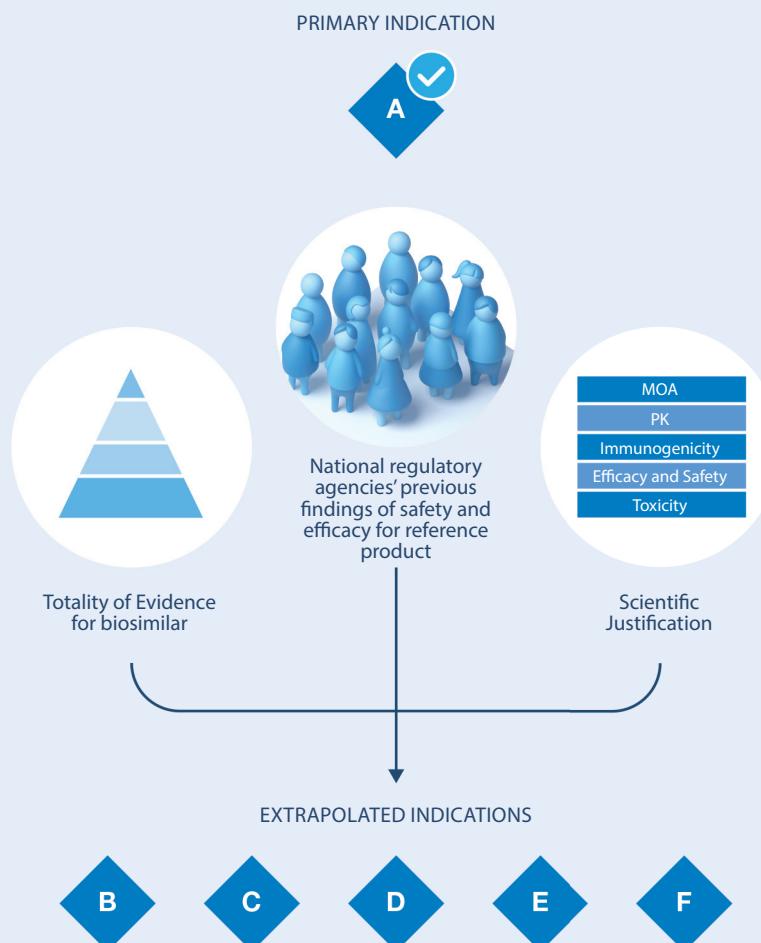
A biologic therapeutic that is highly similar to a reference biologic and shows no clinically meaningful differences from it in terms of safety, purity and potency (eg, safety, efficacy, immunogenicity, quality characteristics or biological activity).

European Medicines Agency (EMA)<sup>5</sup>

A biological medicinal product that contains a version of the active substance of an already authorized biological medicinal product and demonstrates similarity to the reference medicinal product in terms of quality, characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise.

## 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 and cost.<sup>2,30</sup> While extrapolation is not automatic, it may be accepted provided the totality of evidence coupled with scientific justification can address any identified differences.<sup>4,5</sup>



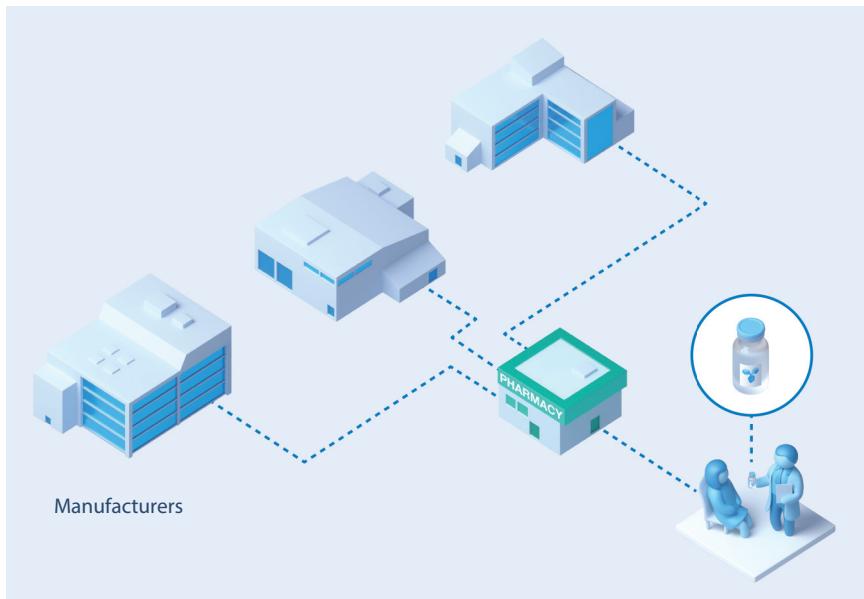
# Pharmacovigilance, traceability and naming

Rigorous pharmacovigilance is essential for all biologics to protect patients through adverse event detection, reporting and attribution to the correct product and manufacturer.<sup>31,32</sup>

In the United States, if a biosimilar has been designated interchangeable, it may be substituted for its reference product in accordance with state law.<sup>33,34</sup> In the EU, the decision to allow interchangeable use and substitution is made at the national level.<sup>24</sup> In order to facilitate accurate prescribing, dispensing and pharmacovigilance, every biosimilar should have a distinguishable nonproprietary name to distinguish it from its reference product and from other biosimilars.<sup>32</sup>

This ability to identify a biologic medicine through all of the systems linked to pharmacovigilance is critical to enhancing patient safety.<sup>8,32</sup>

The ability to trace a product to its manufacturer is important for pharmacovigilance.



# 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 ‘non-regulated biologics’)<sup>35</sup> are copies of licensed biologic medicines that may contain the same amino acid sequence as the reference product, but have not been subjected to the same strict analytical, non-clinical and clinical comparative evaluations prior to market approval that biosimilar regulatory pathways mandate.<sup>36</sup>

As a result, non-comparables may have clinically significant differences in quality, efficacy and safety from their reference products.<sup>36</sup> Certain non-comparables have been shown to have reduced biological potency or higher rates of adverse events, underscoring the importance of following a stringent regulatory pathway for the approval of all biologic medicines.<sup>36-39</sup>

Biosimilars are biologics, but are not...

## Biobetters<sup>40</sup>

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

## Biomimics, biocopies or non-comparables<sup>35,36</sup>

Copies of licensed biologic medicines that have not been subjected to rigorous clinical testing or evaluated according to the biosimilar regulatory pathway.

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.<sup>41</sup>

## 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.<sup>1,7</sup>

**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.<sup>4,5,7</sup>

**Critical quality attribute** A physical, chemical or biological property that must be within an appropriate limit, range, or distribution to ensure the desired safety, efficacy and pharmacokinetics of a drug.<sup>2,20</sup>

**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.<sup>4,5</sup>

**Master cell bank** Vials of unique, genetically modified cells replicated for manufacturing a biologic medicine. The working cell bank is derived from the master cell bank.<sup>14,22</sup>

**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’<sup>35</sup>

**NRA** National regulatory agencies

**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. A reference product is sometimes referred to as the innovator or originator product that the biosimilar is intended to copy.<sup>5,7</sup>

**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.<sup>15</sup>

**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.<sup>4</sup>

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As a world leader and innovator in biologics for patients with life-threatening and chronic diseases, Amgen is proud to produce biosimilar medicines in pursuit of its mission: to serve patients. We're committed to the development of biosimilars because of the additional treatment options they provide to patients and the positive impact they can have on the entire health care system.

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Amgen and biosimilars, visit:  
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