Biosimilar Development

What healthcare practitioners should know

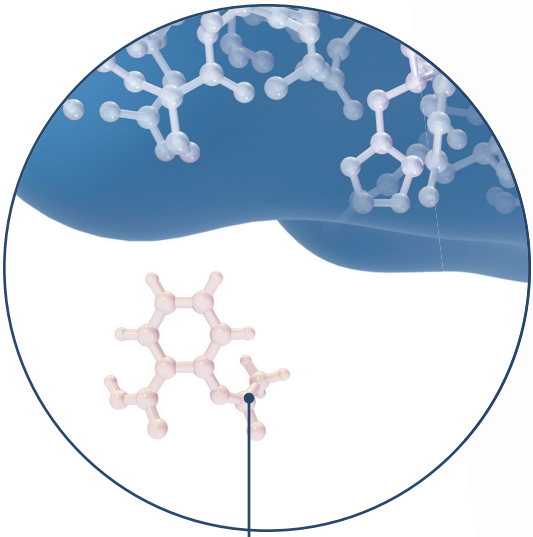
AMGEN® BIOSIMILARS

Biosimilarity

The goal of biosimilar development is to create a biologic drug product that is highly similar to a reference biologic product with no clinically meaningful differences in terms of safety and efficacy.[1-3]

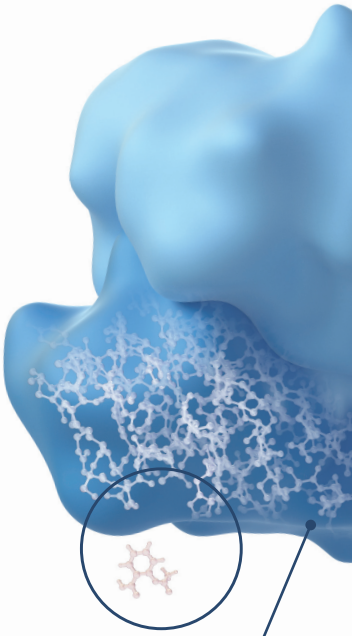
Complex molecules require specialized manufacturing

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.[4-6]



Small molecule drug
~180 Da[7]

Small molecule generics: Completely defined and reproducible structures[1,9]



Monoclonal antibody (mAb)
~150,000 Da[4,8]

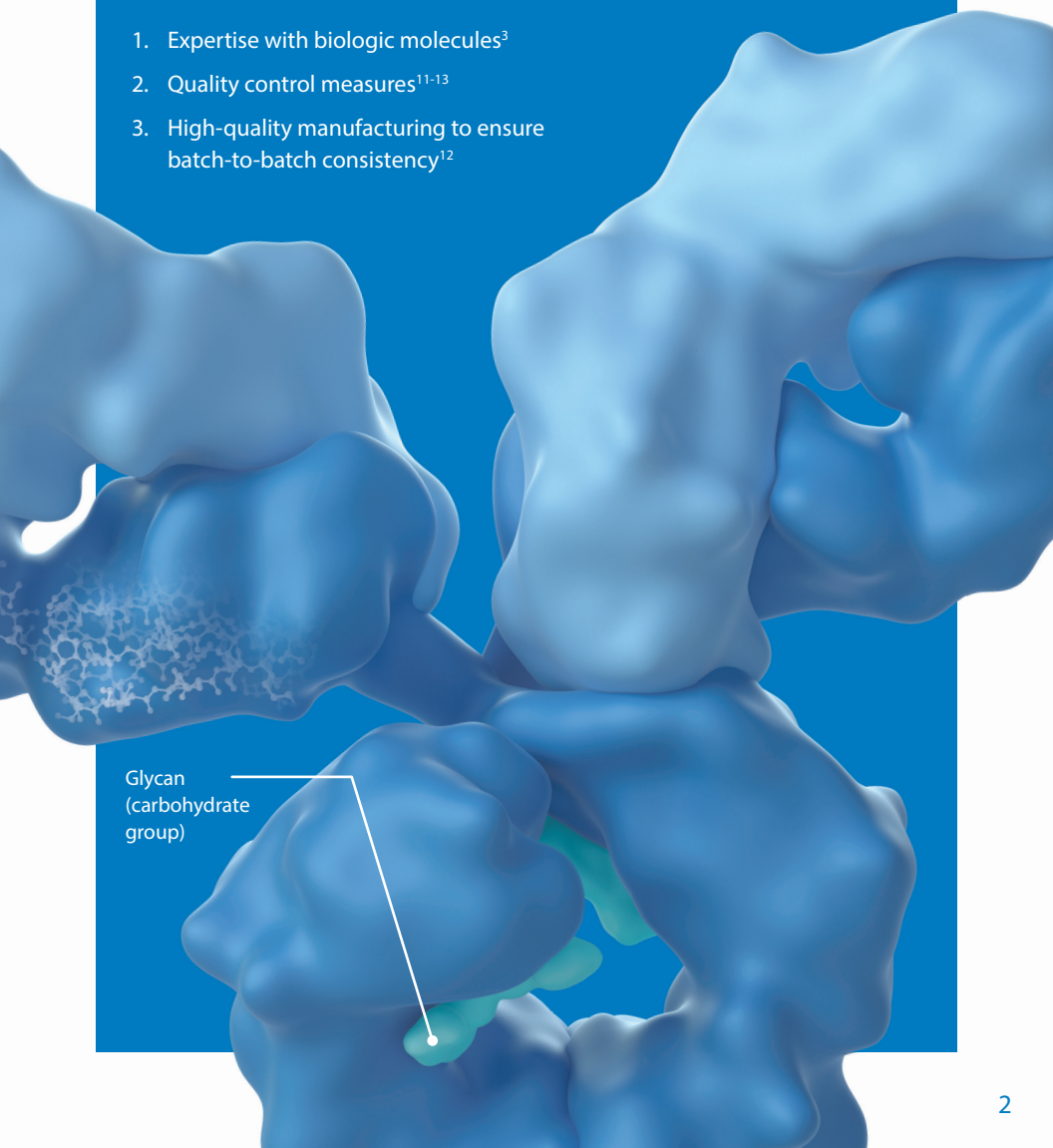
Biologic proteins: Structurally and functionally complex[1,5]

Manufacturing considerations

A strong relationship exists between the manufacturing process and characteristics of the biosimilar.[10] Even small changes in manufacturing can result in altered protein stability and impact post-translational modifications such as glycosylation.[10] Glycans can impact biologic activity and affect efficacy, safety and immunogenicity.[10]

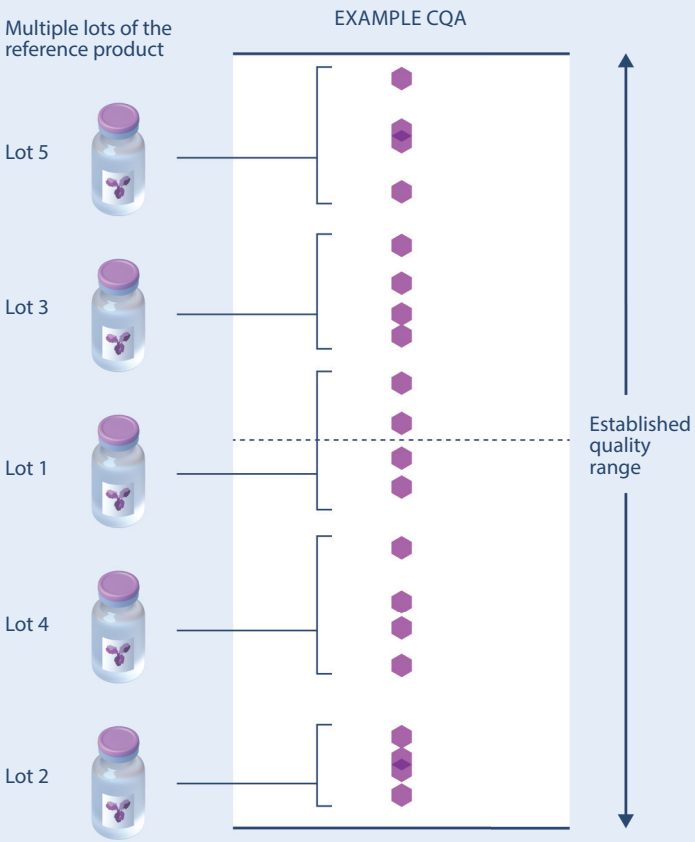
It is, therefore, essential that a biosimilar maker meet sufficient standards in the development and manufacture of biologic drugs, including:

1. Expertise with biologic molecules[3]
2. Quality control measures[11-13]
3. High-quality manufacturing to ensure batch-to-batch consistency[12]



Process customization

Reference product manufacturing information is proprietary, and not publicly available. Therefore, a biosimilar manufacturer must develop a new customized process.[1,5,10] This begins with characterizing the reference biologic to quantify its critical quality attributes (CQAs), characteristics that affect identity, purity, biological activity and stability of a drug.[1,13,15,16] A custom cell line is then created and procedures developed for all manufacturing stages from cell cultivation and protein production through purification to formulation and packaging.[5,8,10,17] Checkpoints are established at critical junctures during the manufacturing process to verify CQA similarity with respect to the reference product.[6,13]



Range of acceptable variability of reference product CQAs
Multiple batches of reference product are tested in order to determine the quality ranges and/or raw data/graphical comparisons, against which the candidate biosimilar will be evaluated.[13,15]

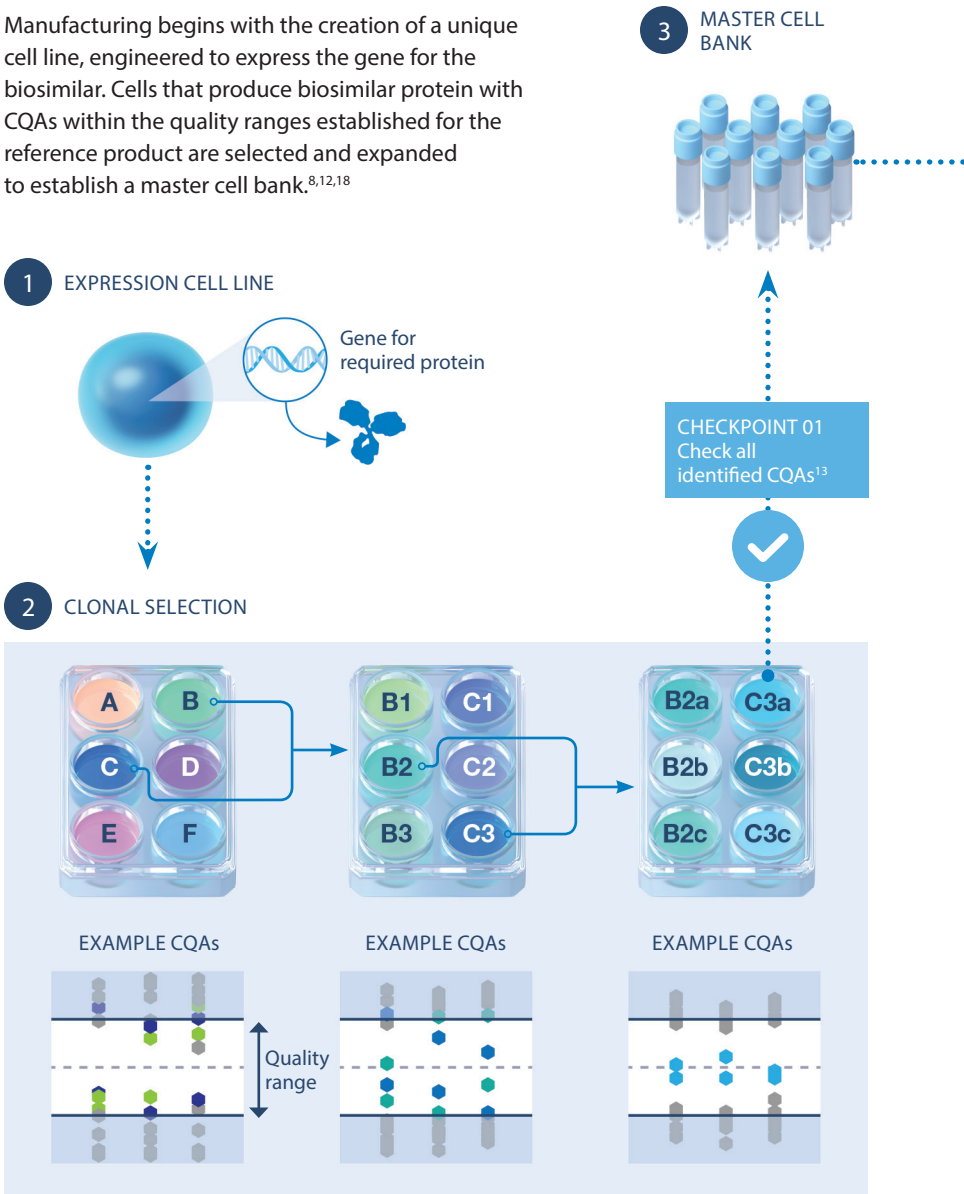
Characterization of reference product

The commercially acquired reference product is characterized to identify the product's CQAs, characteristics that affect identity, purity, biological activity and stability of a drug.[13,16] A variety of analytical and functional assays are used for this purpose.[6,13] Each manufacturer determines the extent of testing and discusses their plan with health authorities.[1]

The manufacturing process

Cell line creation

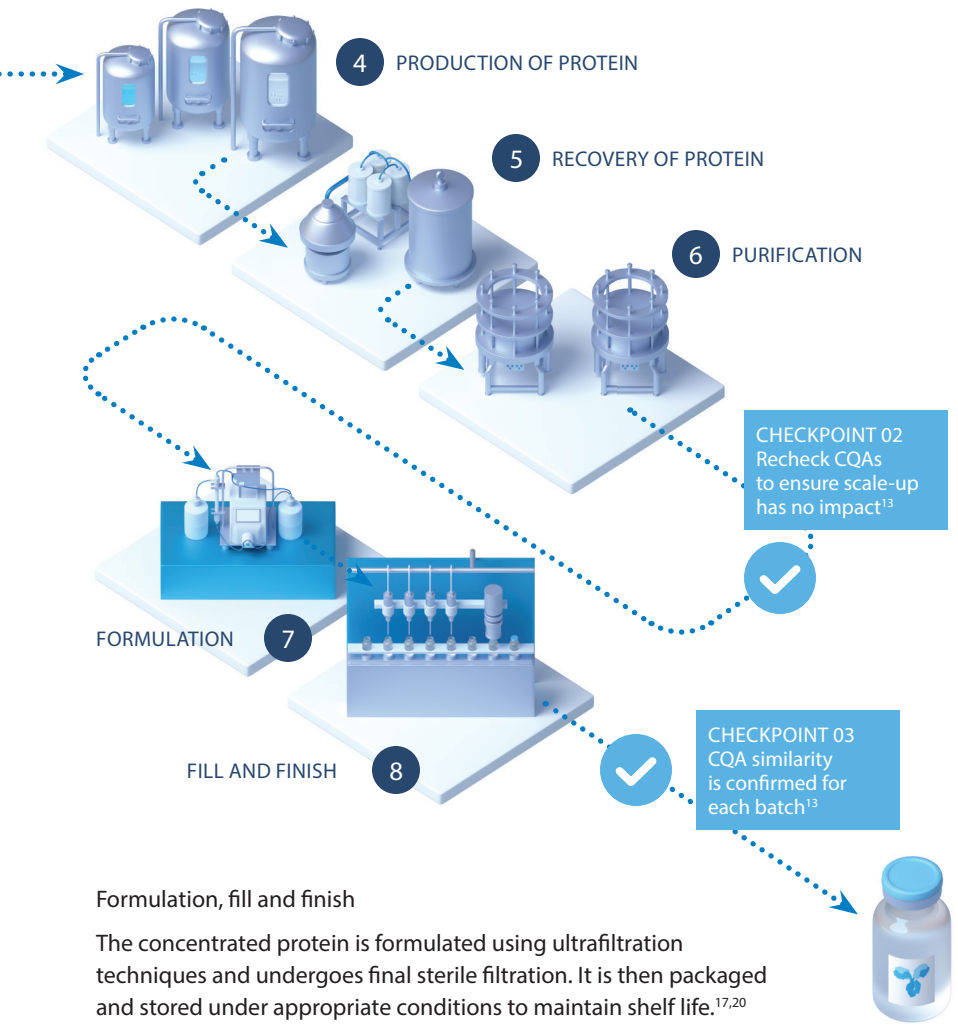
Manufacturing begins with the creation of a unique cell line, engineered to express the gene for the biosimilar. Cells that produce biosimilar protein with CQAs within the quality ranges established for the reference product are selected and expanded to establish a master cell bank.[8,12,18]



Important considerations
Since each biologic is manufactured using a cell line unique to the manufacturer, no two biologics will be identical.[19]

Cultivation and production

Cells from the master cell bank are cultured and expanded in large-scale bioreactors.[8,12] The biosimilar protein is recovered and purified using techniques such as chromatography.[8,20]



Formulation, fill and finish

The concentrated protein is formulated using ultrafiltration techniques and undergoes final sterile filtration. It is then packaged and stored under appropriate conditions to maintain shelf life.[17,20]

Important considerations
Biosimilar CQAs are sensitive to variations in the manufacturing process. Rigorous quality systems check that process-related variations in a biosimilar fall within established margins and therefore aren't anticipated to adversely impact safety and efficacy of the product.[6,10,12,21]

Establishing biosimilarity

Biosimilarity is established by the totality of the evidence, including comparative analytical (structural and functional) characterization, nonclinical evaluation, comparative clinical PK/PD data and additional comparative clinical studies.[1,2] Highly similar analytical and PK/PD data infer a lower likelihood of clinical differences between a biosimilar and its reference product.[22]

PK = Pharmacokinetic; PD = Pharmacodynamic

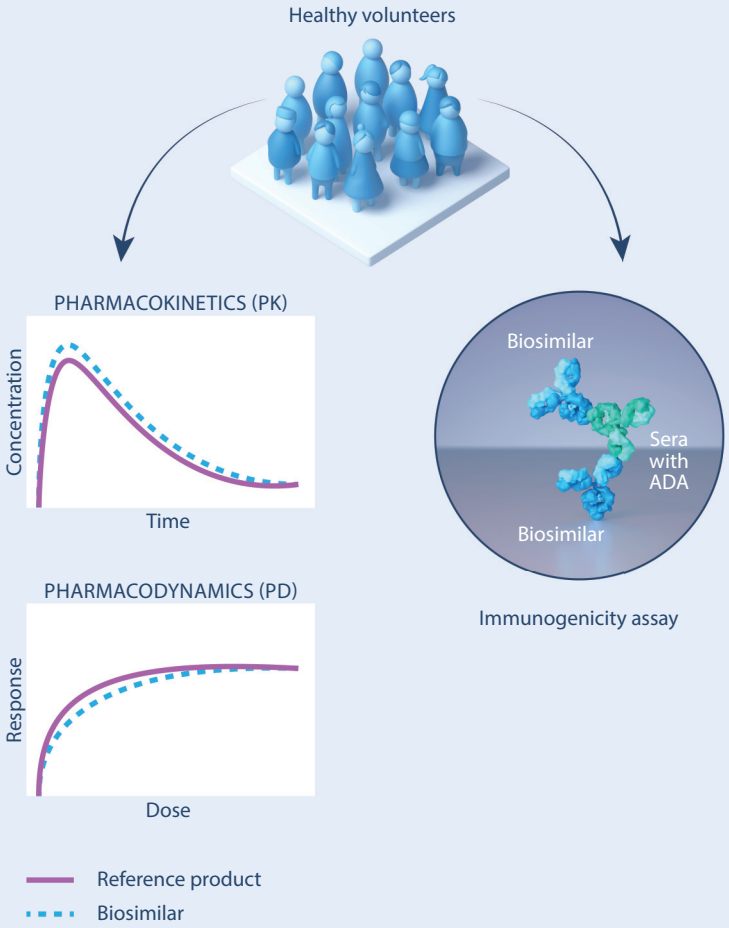
Structural and functional comparison

Structural and functional attributes of a biosimilar are evaluated against the predefined CQA quality ranges of the reference product.[13,16] Key functions are matched with adequate consideration to assay variability, process variability and reference lot history.[3,13]

Important considerations
Identified differences in attributes can be evaluated in clinical studies to confirm no clinically meaningful differences exist between the products.[13]

Clinical pharmacology and immunogenicity

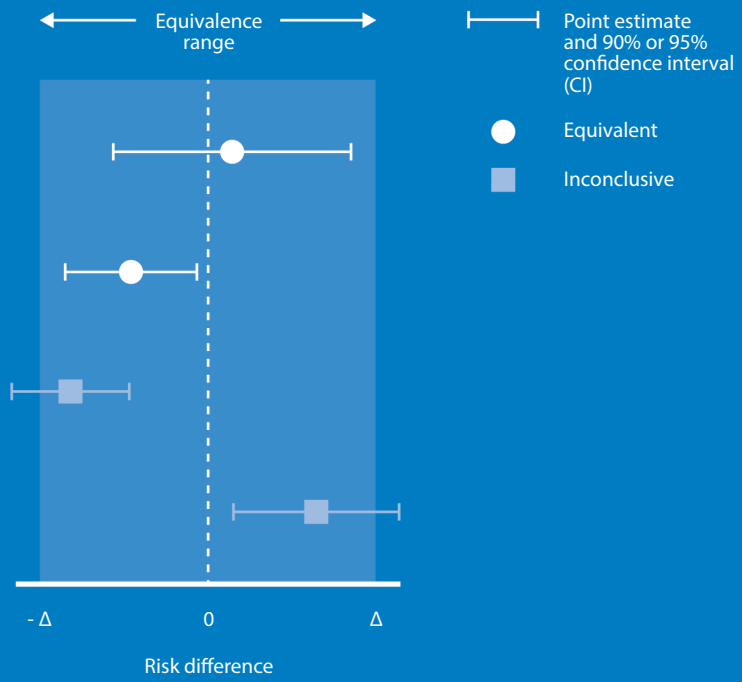
Comparative human PK/PD studies are fundamental to demonstrating similarity in safety and drug exposure over time. These profiles cannot be adequately predicted from in vitro characterization and functional assays alone.[1] Initial insights for immunogenicity are determined using a single-dose clinical study with an immunocompetent patient population.[1,3]



Comparative clinical studies

A comparative clinical efficacy and safety assessment is the final stage to support a demonstration of biosimilarity.[3,6] Biosimilar clinical studies are designed to detect clinically meaningful differences between a biosimilar and its reference product, should they exist, in a sensitive patient population, using a sensitive endpoint.[2,3,23] These studies use an equivalence design that is based on meta-analysis of historical data for the reference product and a balance of statistical and clinical considerations, and feasibility.[23]

Risk difference	=	% of patients reaching endpoint with biosimilar	-	% reaching endpoint with reference product



Quality in manufacturing

The manufacturing process can impact a protein's structure and can alter its biological properties.[1,10,13] Rigorous quality standards and ongoing internal manufacturing oversight ensure that the safety, purity and potency of a biosimilar remain highly similar to those of the reference product over time.[6,12,21]

Amgen has adopted "Quality by Design" (QbD) guidance, which integrates quality control into the manufacturing process.[24] QbD guidance specifies continuous monitoring of:[25]

Laboratory

Packaging, labeling

Materials

Facilities, equipment

Production

QbD manufacturing involves:[26]

- Enhanced product understanding (identifying CQAs of product)
- Enhanced process understanding (determining how the attributes of raw materials and process parameters impact CQAs)
- Risk management and control strategy to help ensure product continuously meets quality standards

A specialized process for quality medicines

Developing a biosimilar begins with reference biologic characterization.[1] A custom manufacturing process must then be developed, involving many steps from cell line creation through formulation, fill and finish of the final product. Throughout these steps, an iterative process of characterization and testing is used to evaluate the degree of similarity between the biosimilar and reference biologic.[3,5,8] The characteristics of a biosimilar are impacted by the manufacturing process.[1,10,13] Robust quality systems and risk assessments help ensure that there is strict control over the biosimilar's quality attributes, and by extension, its safety and efficacy profile.[12,21,25]

Glossary

Biologic drug 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.[4,12]

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.[1,2,12]

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.[3,16]

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.[18,20]

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.[2,12]

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.[27]

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.[1]

References

1 United States Food and Drug Administration. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. 2015.
2 European Medicines Agency. Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues. 2014.
3 Markus, et al. BioDrugs. 2017;31:175-187.
4 Sekhon, et al. Biosimilars. 2011:1;1-11.
5 Lee, et al. Curr Med Res Opin. 2012;28:1053-1058.
6 European Medicines Agency. Biosimilars in the EU Information guide for healthcare professionals. 2017.
7 Bayer. Aspirin Comprehensive Prescribing Information.
8 Dranitsaris, et al. Drugs. 2011;71:1527-1536.
9 Declerck. GaBI J. 2012;1:13-16.
10 Mellstedt, et al. Ann Oncol. 2008;19:411-419.
11 World Health Organization. Guidelines on evaluation of similar biotherapeutic products (SBPs). 2009.
12 Desanvicente-Celis, et al. Immunotherapy. 2012;4:1841-1857.
13 United States Food and Drug Administration. Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations. 2019.
14 Camacho, et al. Cancer Med. 2014;3:889-899.
15 McCamish, et al. Clin Pharmacol Ther. 2012;91:405-417.
16 International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH harmonised tripartite guideline Q11. 2012.
17 Bee, et al. J Pharm Sci. 2011;100:4158-4170.
18 Kresse. Eur J Pharm Biopharm. 2009;72:479-486.
19 Genazzani, et al. BioDrugs. 2007;21:351-356.
20 Hesse, et al. Trends Biotechnol. 2000;18:173-179.
21 International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH harmonised tripartite guideline Q5E. 2004.
22 Kozlowski. US FDA Perspectives on Biosimilar Biological Products. Presented at: 2014 Biotechnology Summit; June 13, 2014; Rockville, MD.
23 Isakov, et al. Am J Ther. 2016;23:e1903-e1910.
24 United States Food and Drug Administration. Guidance for Industry Quality Systems Approach to Pharmaceutical CGMP Regulations. 2006.
25 Ramanan, et al. BioDrugs. 2014;28:363-372.
26 United States Food and Drug Administration. Guidance for Industry Q8(R2) Pharmaceutical Development. 2009.
27 United States Food and Drug Administration. Generic Drug Facts. 2018. www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/ucm167991.htm

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. Amgen Biosimilars are backed by our four decades of experience in the research, development, manufacturing, and supply of innovator biologics.

For more information on
Amgen and biosimilars, visit:
http://www.amgenbiosimilars.com

Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
www.amgen.com

AMGEN®