

Developing BIOSIMILARS

The process and quality standards



Amgen is a leader in biologics, with over 35 years of experience in the discovery, research, development, and manufacturing of science-based medicines. Amgen biosimilars are manufactured according to the same high standards used for innovative biologic medicines.



INTRODUCTION



The goal of biosimilar development is to create a biologic drug product that is highly similar to the reference biologic product with no clinically meaningful differences in terms of safety and efficacy.^{1,2}

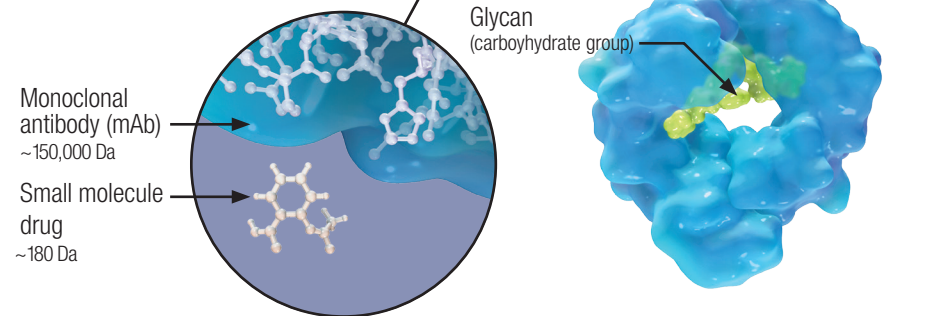


Manufacturing biosimilars is complex

Biosimilars are up to 1,000 times the size of small molecule generic drugs, and are far more structurally complex.³

Biologic proteins:
structurally and functionally complex^{2,4}

Small molecule generics:
completely defined and reproducible structures²



Why should physicians care about biosimilar manufacturing?

There is a strong relationship between the manufacturing process and characteristics of the final biosimilar.⁵ Even small changes in manufacturing can result in altered protein stability as well as impact post-translational modifications such as glycosylation — the addition of glycans (carbohydrate groups) to the structure of a mAb.^{5,6} Glycans can impact biologic activity and, by extension, affect overall efficacy, safety, and immunogenicity.⁵

Given the delicate nature of the manufacturing process, and that each manufacturer is required to develop a new process for each biosimilar, it is critical that appropriate safeguards be established to protect patients. To ensure the creation of high-quality products, biologic manufacturers should have significant:



- 1 Expertise with monoclonal antibodies
- 2 Understanding of the interplay between structure and function⁶
- 3 Quality control measures⁷
- 4 Reliability in product supply⁴
- 5 High-quality manufacturing to ensure batch-to-batch consistency⁸

PROCESS CUSTOMIZATION

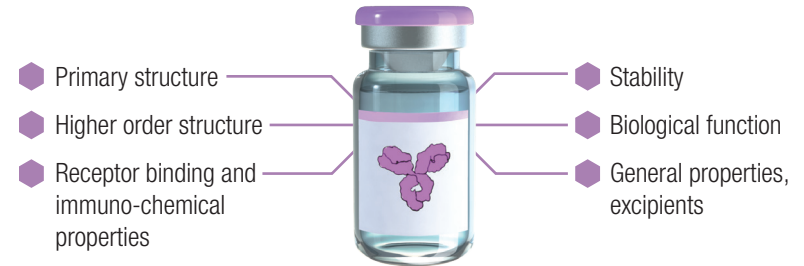


Reference product manufacturing information is proprietary, and not publicly available. Therefore, a biosimilar manufacturer must develop an entirely new customized process.⁹ This begins with characterizing the reference biologic to quantify its critical quality attributes (CQAs), characteristics that affect identity, purity, biological activity, and stability of a drug.^{6,10,11} A custom cell line is then created¹² and procedures developed for all manufacturing stages from cell cultivation and protein production through purification to formulation^{5,8,13} and packaging. Checkpoints are established at critical junctures during the manufacturing process to verify CQA similarity with respect to the reference product.⁶



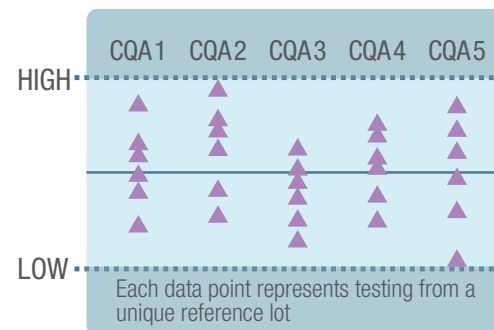
Characterization of reference product

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.^{6,10} A variety of robust physicochemical and functional assays are used for this purpose.^{6,14}



A biosimilar manufacturer may measure 100 attributes across 40 or more assays.¹⁵ Each manufacturer determines the extent of testing and discusses their plan with health authorities.²

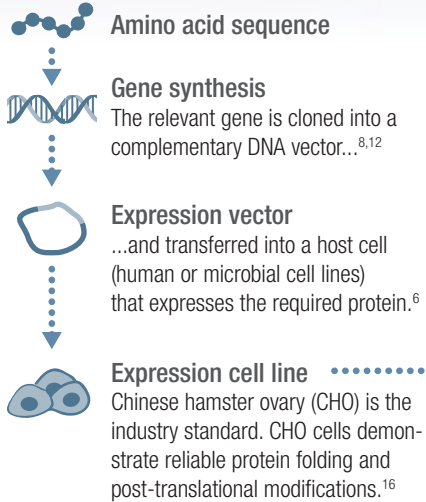
Range of acceptable variability of reference product CQAs



Multiple batches of reference product are tested in order to establish equivalence margins, or "goal posts" for each CQA, against which the candidate biosimilar will be evaluated.¹¹

Cell line creation^{8,12}

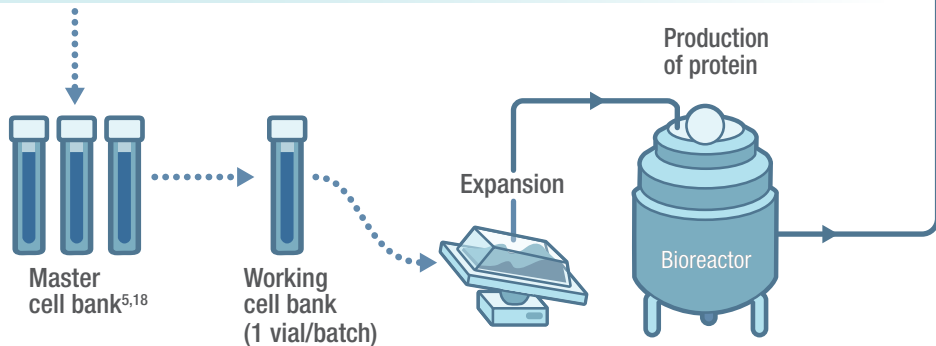
Recombinant DNA biotechnology allows large-scale production of the biosimilar mAb.¹²



Important considerations

Since each biologic is manufactured using a cell line unique to the manufacturer, no two biologics will be identical.¹⁷

Cultivation and production^{5,8}



The cell line that produces the required biosimilar protein with high similarity to the reference biologic is selected and then expanded in a fermentation medium to establish a master cell bank.^{5,12,18}

The cells from the master cell bank are cultured and produced in volumes of up to thousands of liters in large-scale fermentation bioreactors.^{8,12}

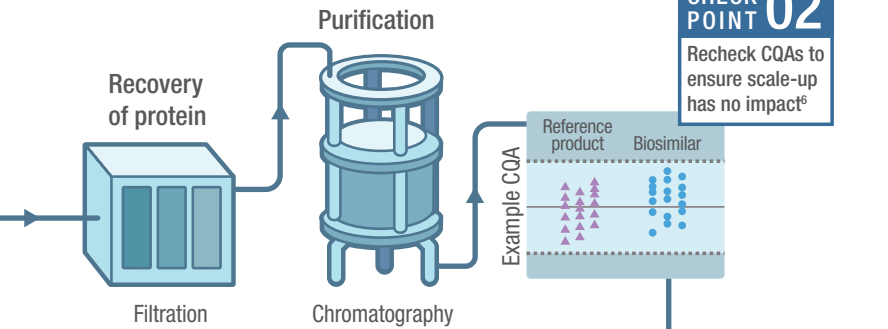
Isolation and purification^{5,8,19}

The biosimilar protein secreted into the culture medium is recovered through filtration or centrifugation⁸ and involves the separation of protein from cells and debris.¹⁹

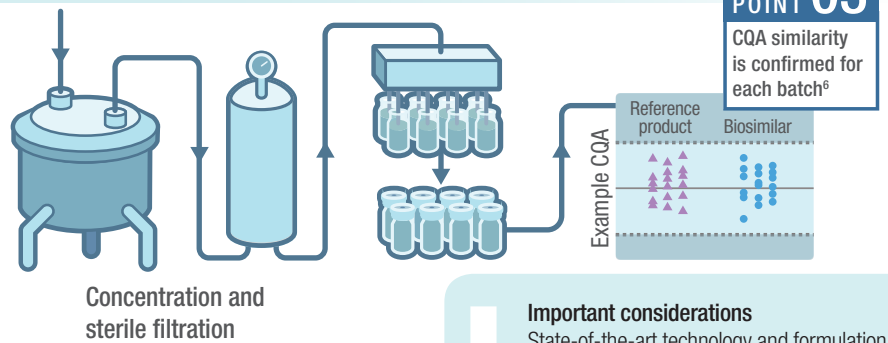
The volume of the product-containing fraction is reduced utilizing techniques such as high-affinity adsorption.¹⁹ Product purification is done utilizing techniques like chromatography,¹² in which various elements such as buffers and impurities are removed before the final product is obtained.⁸

Important considerations

Biosimilar CQAs are sensitive to variations in the manufacturing process. Vigorous quality systems ensure that modifications in a biosimilar due to the manufacturing process fall within established margins for variability, and therefore aren't anticipated to adversely impact safety and efficacy of the product.²⁰



Formulation, fill, and finish^{13,20}



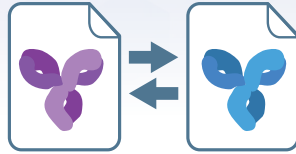
The concentrated protein is formulated using ultrafiltration techniques such as diafiltration.¹³

The formulated bulk then undergoes final sterile filtration, after which it is filled into vials, syringes, or cartridges and stored under appropriate conditions to maintain shelf life.¹³

Important considerations

State-of-the-art technology and formulation strategies are required to achieve high product purity and stability.¹³ Differences between the biosimilar and reference biologic in formulation, excipients or primary packaging are identified and their potential impact on stability and clinical performance assessed.⁶ Stability studies under multiple stress conditions are used to establish a lack of meaningful differences in degradation profiles.⁶

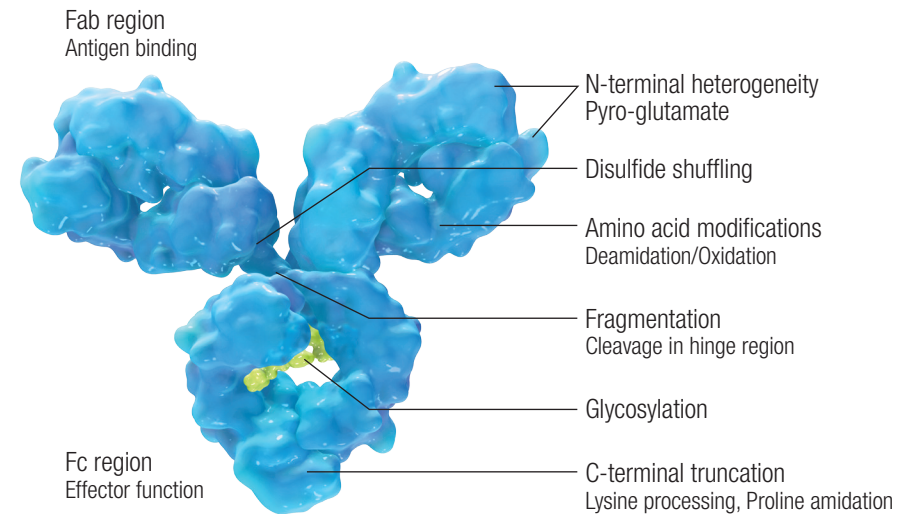
ESTABLISHING BIOSIMILARITY



Similarity is established by the totality of the evidence, including analytical characterization, nonclinical evaluation, pharmacokinetic/pharmacodynamic (PK/PD) data, immunogenicity data, and comparative clinical studies.² Highly similar analytical and PK/PD data infer a lower likelihood of clinical differences between a biosimilar and its reference product.¹⁴

Analytical characterization

The biosimilar protein's primary (ie, amino acid sequence) and higher-order structures (ie, secondary, tertiary, and quaternary) are analyzed. The enzymatic post-translational modifications (eg, glycosylation, phosphorylation), potential variations (eg, oxidation), and intentional chemical modifications (eg, PEGylation sites) of the protein are additionally assessed.²



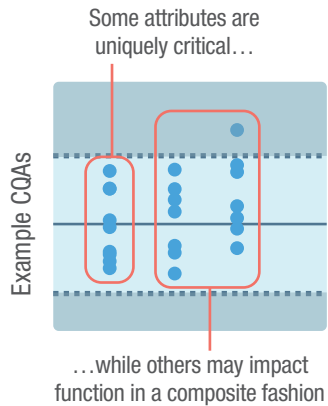
Sites where heterogeneity is commonly observed on a monoclonal antibody.^{21,22}

Structural heterogeneity can potentially impact:

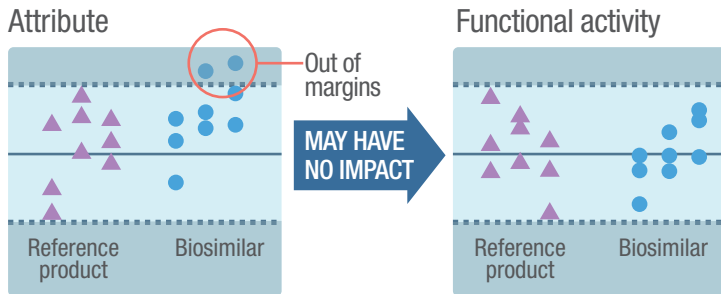
- Mechanism of action
- Immunogenicity
- Pharmacokinetics
- Ligand binding
- Effector functions

Structural and functional comparison

The structure of the biosimilar candidate is closely compared with that of the reference biologic. The biosimilar then undergoes additional functional comparative testing to ensure that its biological activity, potency, and mechanism of action are highly similar to those of the reference biologic.⁶



Structural and functional attributes of the biosimilar are evaluated against the reference product's CQA predefined margins.^{11,23}



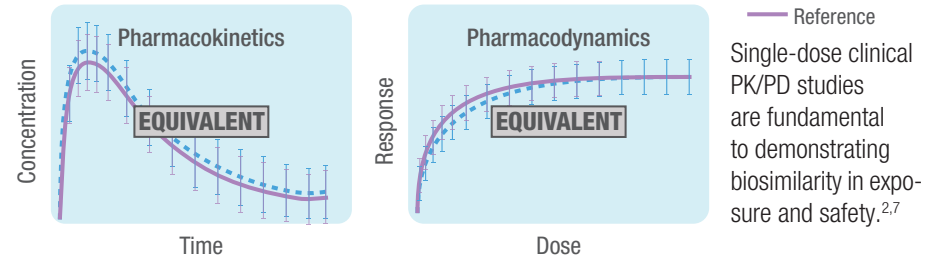
Certain small structural differences may be permissible, provided they are shown to not impact function, and by extension, clinical safety or efficacy.²

Important considerations
Identified differences can be further addressed in clinical studies.⁶

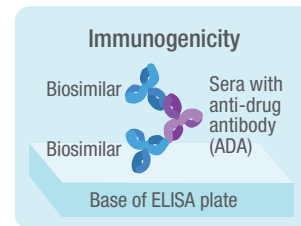
Clinical pharmacology and immunogenicity

PK/PD and immunogenicity analyses of a biosimilar are needed, as these profiles cannot be adequately predicted from functional assays and physiochemical characterization alone.²

Phase 1 subject/healthy volunteer study



Single-dose clinical PK/PD studies are fundamental to demonstrating biosimilarity in exposure and safety.^{2,7}



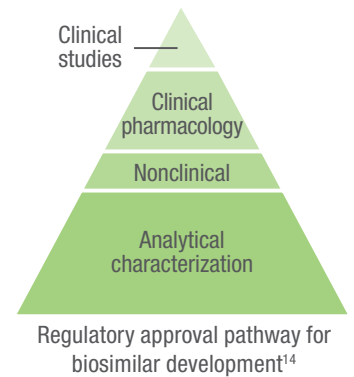
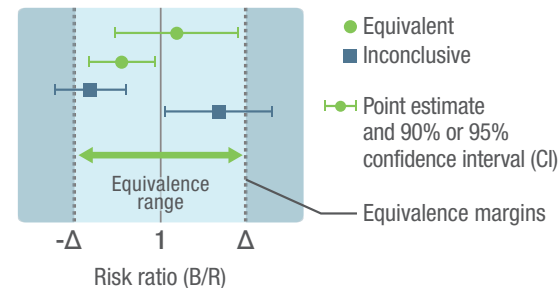
Sera from healthy subjects tested on an ELISA assay to detect ADAs.

Insights for immunogenicity are initially determined with an immunocompetent patient population using a single-dose clinical study.^{2,7}

Clinical studies

Active comparator clinical studies confirm no clinically meaningful differences in safety and efficacy between the biosimilar and reference product.²

Equivalence studies are powered to demonstrate any significant differences between the biosimilar (B) and reference (R) product.⁷



QUALITY IN MANUFACTURING



The manufacturing process can impact a protein's structure and can alter its biological properties.^{2,6,21} 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



Quality control in manufacturing

Amgen has adopted "Quality By Design" (QbD) guidance, which integrates quality control into the manufacturing process.²⁴

QbD guidance specifies continuous monitoring of:²⁰



Laboratory



Materials



Production



Packaging,
labeling



Facilities,
equipment

QbD manufacturing involves:²⁵

- 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 ensure product continuously meets quality standards

Important considerations

While QbD is not mandated by health authorities, it is advisable for numerous reasons. Notably, by requiring a comprehensive understanding of a product and its development process, QbD reduces mistakes in manufacturing in order to assure consistent quality.²⁶

Risk assessment following a process change to an approved biologic

Manufacturers frequently make changes to the manufacturing process to improve quality, efficiency and reliability.²⁸ When a change is made, rigorous risk assessments are performed in alignment with international guidelines* to confirm that there is no impact on quality, safety, and efficacy of the biologic.^{2,10,20}

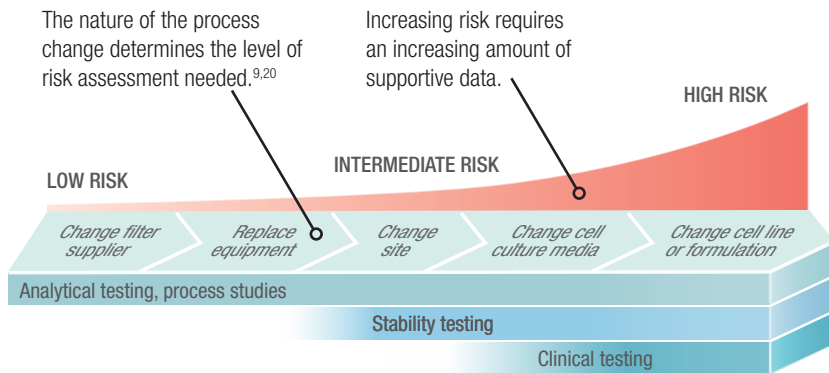


Figure adapted from Lee JF, et al. *Curr Med Res Opin.* 2012;28(6):1053-1058. With permission from Informa UK Ltd.

Approved biologics have established quality specifications with acceptable ranges of variability. Attributes are continuously monitored to ensure they meet these quality specifications and consistency is maintained from lot to lot.²⁷ This intrinsic variability does not mean a reference product becomes a biosimilar of itself over time.

Important considerations

Evaluating manufacturing process changes is distinctly different from demonstrating biosimilarity, which is a more complex process.² With a manufacturing change, prior knowledge of the process can be leveraged to assess the impact of a change. For a biosimilar, a new molecule must be created without knowledge of the originator product's manufacturing process.⁴

*ICH Q5E, International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use guidelines on the comparability of biotechnological/biological products subject to changes in their manufacturing process.²⁸

Comparability is not the same as biosimilarity

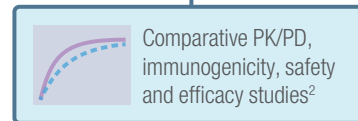
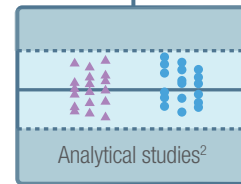
Demonstrating that a proposed product is biosimilar to a reference product typically will be more complex than assessing the comparability of a product before and after manufacturing changes made by the same manufacturer.

- USFDA. *Guidance for industry: Scientific Considerations.* 2015.²

Demonstrate Biosimilarity

Different manufacturer, new product compared with reference biologic

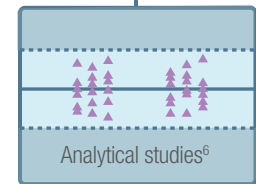
? No access to the originator's product history or manufacturing process and must establish own process⁹



Demonstrate Comparability

Same manufacturer, same product tested before and after change

Extensive knowledge about product, manufacturing process, established controls, and acceptance parameters²



Depending on risk of process change, nonclinical and clinical studies may/may not be necessary²⁰

Summary

Developing a biosimilar begins with reference biologic characterization.¹⁷ 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.² The characteristics of a biosimilar are impacted by the manufacturing process.² Robust quality systems and risk assessments ensure that there is strict control over the biosimilar's quality attributes, and by extension, its safety and efficacy profile.^{6,20}

At Amgen, our mission is to serve patients, and quality is a cornerstone of all of our activities. Our biosimilars are manufactured according to the same high standards as our innovative biologic medicines. Amgen's biosimilar clinical development program is designed to stringently assess high similarity of biosimilars relative to their reference biologics.

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