



Overview Of Biosimilar and General Consideration for Biosimilar Drug Development

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Abstract

Biological medicines, often produced by cutting-edge biotechnology, have transformed the outlook for patients with many chronic and often disabling conditions. An increasing number of biological medicines are 'biosimilars' - medicines highly similar in all essential aspects to an already approved biological medicine. The current article focus on the overview of Biosimilar medicine and its regulation.

The Europe (EU) has pioneered the regulation of biosimilar medicines by establishing a solid framework for their approval and by shaping biosimilar development globally. USFDA requires biosimilar and interchangeable biological products meet the Agency's rigorous approval standards. That means patients and health care professionals will be able to rely upon the safety (and effectiveness of the biosimilar or interchangeable product, just as they would the reference product. Patents for many branded biologics will expire during the next few years, allowing biosimilars manufacturers to seek FDA approval for generic versions of these agents.¹

Since the EU approved the first biosimilar in 2006, healthcare professionals have gained increasing experience with their use. Today, biosimilars are an integral part of the effective biological therapies available in the EU, supported by adequate safeguards protecting patient safety.

These criteria have inspired debate and the emergence of several critical issues, such as to what extent the biosimilars pathway should be abbreviated, how much clinical data should be required for approval, or when an agent should be designated as comparable or interchangeable with an originator biologic.²

These parameters will determine the ease and cost for a manufacturer to develop and market a biosimilar and will also ultimately influence the price of these medications.²

As healthcare professionals are at the forefront of patients' care, it is vital that they have access to reliable information on these medicines: what they are and what scientific principles support their clinical development, approval and safety monitoring. Present article an efforts has been made with the important objective of development of the of biosimilars.

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Introduction

What Are Biologics and Biosimilars?

According to the U.S. Federal Code of Regulations (CFR), the definition of a biologic is "any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment, or cure of disease or injuries of man."³ According to USFDA "Biological products, or biologics, are

generally large, complex molecules that are made from living sources such as bacteria, yeast, and animal cells". Biologics were first developed in the 1980s using recombinant techniques to copy or improve on naturally occurring complex peptides, proteins, and glycoproteins.^{1,4,5} Since then, even more complex products, such as monoclonal

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antibodies, have been produced through the manipulation of the DNA in bacteria, yeast, or mammalian cells to produce therapeutic or diagnostic agents.^{1,6-8} Biologic therapies available today include enzymes, vaccines, human insulins, interferons, interleukins, erythropoietins, gonadotropins, granulocyte-colony-stimulating factors (G-CSFs), human growth hormones, monoclonal antibodies, blood coagulation modifiers, and tissue plasminogen activators.⁹ According to USFD below are the definition of Biological products and Biosimilar Products.

Biological Product

Biological products are regulated by the Food and Drug Administration (FDA) and are used to diagnose, prevent, treat, and cure diseases and medical conditions. Biological products are a diverse category of products and are generally large, complex molecules. These products may be produced through biotechnology in a living system, such as a microorganism, plant cell, or animal cell, and are often more difficult to characterize than small molecule drugs. There are many types of biological products approved for use in the United States, including therapeutic proteins (such as filgrastim), monoclonal antibodies (such as adalimumab), and vaccines (such as those for influenza and tetanus).

The nature of biological products, including the inherent variations that can result from the manufacturing process, can present challenges in characterizing and manufacturing these products that often do not exist in the development of small molecule drugs. Slight differences between manufactured lots of the same biological product (i.e., acceptable within-product variations) are normal and expected within the manufacturing process. As part of its review, FDA assesses the manufacturing process and the manufacturer's strategy to control within-product variations. These control strategies are put in place to help ensure that manufacturers produce biological products with consistent clinical performance.

Biosimilar Products

A reference product is the single biological product, already approved by FDA, against which a proposed biosimilar product is compared. A reference product is approved based on, among other things, a full complement of safety and

effectiveness data. A proposed biosimilar product is compared to and evaluated against a reference product to ensure that the product is highly similar and has no clinically meaningful differences.

How a Biosimilar is developed 10

Before biologic drugs are ready to be used by patients, scientists and providers spend years developing, researching, and testing them in clinical trials to ensure these medicines are safe and effective. Manufacturing a biologic drug can take months and every part of the process must be carefully checked and controlled.

Manufacturing a biosimilar is much like manufacturing its reference biologic. The FDA requires biosimilars demonstrate no clinically meaningful differences and that they meet a rigorous scientific standard of similarity before they are made available to patients. Similarity is achieved and verified through a scientific process that confirms there is no clinically meaningful difference between the biosimilar and the original product, and that the biosimilar will perform in a patient the exact same way as the reference biologic. Similarity testing occurs multiple times throughout the development process.

The biosimilar development process occurs in three major stages: characterization and perfecting the process, confirmation of biosimilarity and approval.

Step 1: Product Development: Characterization and Perfecting the Process

In development, the first step is a thorough understanding of the reference biologic, accomplished through an examination of structure and function. This is known as characterization.

Once this information is obtained, the next phase is the development of the manufacturing process which delivers the highly similar therapy. State-of-the-art biological development technologies and highly-sensitive analytical tools are used to systematically engineer a biosimilar molecule to match the medicine's quality attributes that were identified in the characterization stage. This is an iterative process where each part of the manufacturing procedure is optimized in repeating steps. This continues until the manufacturing process consistently produces a highly similar molecular structure to the reference medicine.

Step 2: Biosimilar Confirmation via Studies and Regulatory Cooperation



Once similarity has been established between the biosimilar and the reference biologic medicine through analysis and testing, the next stage begins. The FDA reviews all the information and determine the additional non-clinical and clinical studies, if any, that will be required to confirm biosimilarity and interchangeability.

Clinical trials are generally required for biosimilar approval in highly regulated markets, such as the European Union (EU), United States (US), Japan, Canada and Australia. However, the scope and requirements for biosimilar clinical trials will depend on the data submitted. Where there is robust and convincing analytical data, for example, and additional data are required, a more tailored clinical trial program may provide a more effective way to demonstrate biosimilarity and interchangeability.

Step 3: Approval

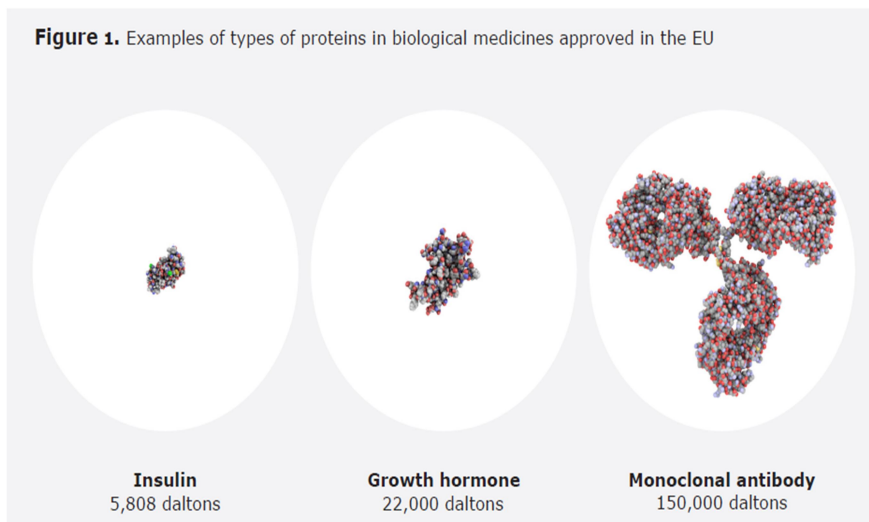
In the early stages of development, biosimilar manufacturers meet with the FDA to discuss a product development plan and approaches to

providing adequate scientific justifications throughout the review process. Before approving any product for patient use, the FDA looks at the totality of evidence and conducts a rigorous review of all the data to determine whether the applicable scientific standards have been successfully met. Once a biosimilar is approved, it can be produced and distributed in the United States.

Patients can expect to see the exact same safety and efficacy that they see in their brand biologic products in a biosimilar. Studies from all over world find that patients have the same kind of benefits whether they are on the original biologic or the biosimilar.

Key features of biological medicines¹¹

Most biological medicines in current clinical use contain active substances made of proteins. These can differ in size and structural complexity, from simple proteins like insulin or growth hormone to more complex ones such as coagulation factors or monoclonal antibodies (figure 1).



Bio manufacturing strictly regulated

The manufacture of biological medicines tends to be more complex than for chemically-derived molecules. Most biological medicines are made by biotechnology, often using sophisticated cell systems and recombinant DNA technology. The EU legislation imposes strict requirements for the manufacture of all medicines:

EU manufacturers must hold a manufacturer's license and are legally obliged to comply with Good Manufacturing Practice (GMP), the agreed standards to obtain a medicine with proven quality.

National regulatory authorities in the EU regularly inspect manufacturing sites for compliance with GMP requirements.

If some manufacturing steps take place outside the EU, then non-EU manufacturers, importers and wholesale distributors are obliged to follow the same strict requirements and are also regularly inspected.

For biological medicines, some of the GMP requirements have been adapted to take into account their specific nature (e.g. use of appropriate aseptic techniques, refrigeration and other storage conditions, stability, transport etc.).



Biosimilars -International Cooperation¹²

In an era when increasing demands are being made on the world's healthcare services, generic and biosimilar medicines provide a major benefit to society by ensuring patient access to quality, safe and effective medicines while reducing the cost of pharmaceutical care. The European Medicines Agency is liaising with international partners

- Health Canada (finalized Guidance on Subsequent Entry Biologics published in March 2010)
- Japan (Guideline on quality, safety and efficacy of follow-on biologics was published in March 2009)
- WHO (Guidelines on Evaluation of Similar Biotherapeutic Products adopted in October 2009)
- FDA (Abbreviated approval pathway for Biosimilars created via the Patient Protection and Affordable Care Act, signed on March 23, 2010) -ongoing liaison and exchange
- CHMP guidance also adopted by, e.g.: Australia, Malaysia

Global development of biosimilars¹²

- Directive 2001/83/EC states that the chosen reference medicinal product must be a medicinal product authorised in the Community.
- The set-up of the biosimilar development is not specified in the Directive. However, the implementing guidelines state that the

reference medicinal product authorised in the Community should be used throughout the development.

- Can requirements for the sourcing of reference product evolve to allow for parts of the comparability exercise to be performed with reference medicinal product sourced outside the Community?

Inherent degree of variability¹¹

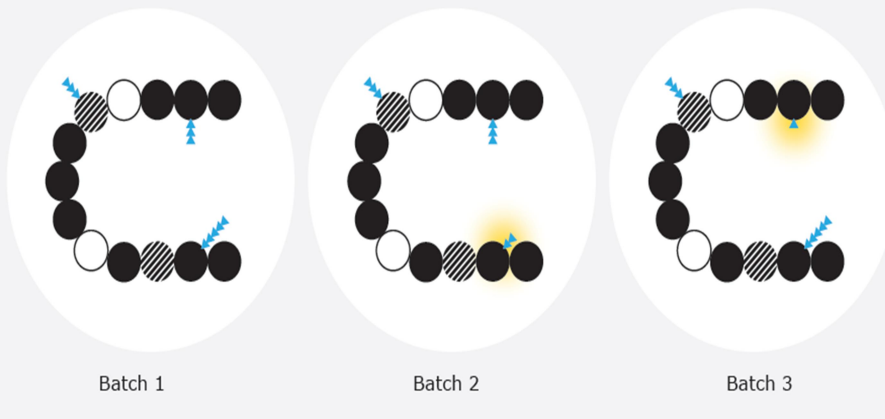
Biological medicines are made by living organisms, which are naturally variable. Thus, the active substance in the final biological medicine can have an inherent degree of minor variability ('microheterogeneity'). This minor variability must fall within the acceptable range to ensure consistent safety and efficacy. This is done by adjusting the manufacturing process to guarantee that the active substance fits into the desired specifications range.

This degree of minor variability can be present within or between batches of the same biological medicine (figure 2), particularly when manufacturing processes are modified during the commercial life of the medicine (e.g. increasing production scale). Strict controls are always applied to ensure that, despite this variability, there is batch-to-batch consistency and that the differences do not affect safety or efficacy. In practice, variability (within a batch or batch-to-batch) is very low when using the same manufacturing process.



Figure 2. Example of variability between different batches of a biological medicine

Consecutive batches of the same biological medicine may show a small degree of variability (yellow shadow) within the accepted ranges, for example in glycosylation (sugar molecules attached to the protein, which are represented by small blue triangles). The amino acid sequence (represented by circles) and biological activity of the protein remain the same in all batches, even when these minor differences in sugar chains are present.



Strict control of the quality of biological medicines

The quality of all medicines (biological and non-biological) approved in the EU is rigorously proven. For biological medicines, this includes studying their specific physicochemical properties, biological activity, purity, sterility and stability to ensure that all the required standards are met before batches are released for marketing

Biosimilar medicines: definition and features¹¹

A biosimilar medicine ('biosimilar') is a medicine highly similar to another biological medicine already marketed in the EU (the so-called

'reference medicine')^{13,14}. Companies can market approved biosimilars once the period of market protection of the reference medicine expires (after 10 years).

Since biosimilars are a type of biological medicine, all features pertinent to biological medicines apply. Due to the natural variability of the biological source and to the manufacturing process unique to each manufacturer, minor differences can occur between the biosimilar and its reference medicine (table 1 and figure 3). Strict controls are always in place during manufacturing to ensure that minor differences do not affect the way the medicine works or its safety. Thus, these differences are not clinically meaningful in terms of safety or efficacy.

Table 1: Specific features of biosimilar medicines

Highly similar to the reference medicine	The biosimilar has physical, chemical and biological properties highly similar to the reference medicine's. There may be minor differences from the reference medicine which are not clinically meaningful in terms of safety or efficacy.
No clinically meaningful differences compared with the reference medicine	No differences are expected in clinical performance. Clinical studies that support the approval of a biosimilar confirm that any differences will not have an effect on safety and efficacy.
Variability of biosimilar kept within strict limits	No differences are expected in clinical performance. Clinical studies that support the approval of a biosimilar confirm that any differences will not have an effect on safety and efficacy.



Same strict standards of quality, safety and efficacy	Biosimilars are approved according to the same strict standards of quality, safety and efficacy that apply to any other medicine.
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When the active substance is a protein, both the biosimilar and the reference medicine must contain the same protein (i.e. amino acid sequence) and the same '3D' structure (folding of the protein). Amino acid sequence and folding are the main factors that determine biological activity, which must be the same for the biosimilar and the reference medicine. For the finished medicine, both biosimilar and reference medicine must have the same posology and route of administration. Some differences may be allowed if they have no effect on safety and

efficacy - for example differences in the formulation of the medicine (e.g. excipients), presentation (e.g. powder to be reconstituted versus solution ready for injection) and administration device (e.g. type of delivery pen).

To date, the great majority of biosimilars approved in the EU contain proteins as active substances. Table 2 lists the classes of biological medicines for which biosimilars have been approved in the EU.

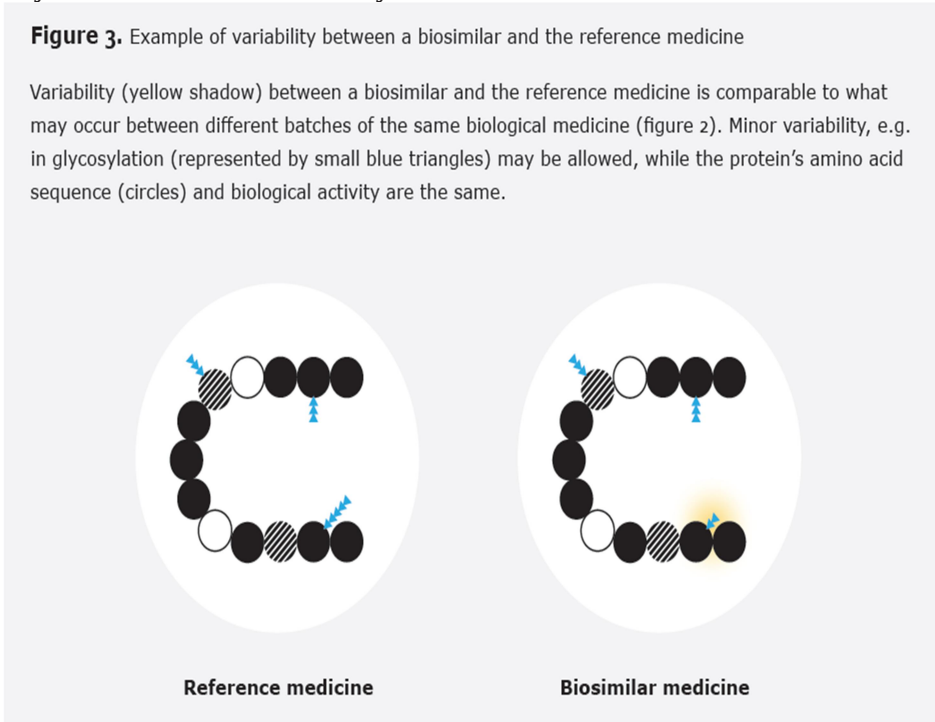


Table 2: Classes of biological medicines for which a biosimilar is currently approved in the EU

Polysaccharides	
Low-molecular weight heparins	Enoxaparin sodium
Proteins	
Growth factors	Epoetin Filgrastim Pegfilgrastim
Hormones	Follitropin alfa Insulin glargine Somatropin (growth hormone) Teriparatide Insulin lispro



Fusion proteins	Etanercept
Proteins	
Monoclonal antibodies	Adalimumab Infliximab Rituximab Bevacizumab Trastuzumab

Why biosimilars are not considered generic medicines¹¹

A biosimilar is not regarded as a generic of a biological medicine. This is mostly because the natural variability and more complex manufacturing of biological medicines do not allow an exact replication of the molecular microheterogeneity.

Consequently, more studies are needed for regulatory approval of biosimilars than for generics to ensure that minor differences do not affect safety or efficacy. Table 3 compares development and characteristics of generics and biosimilars.

Table 3: Comparison of development and characteristics between generics and biosimilars

Generic medicine	Biosimilar medicine
Usually produced by chemical synthesis	Obtained from a biological source
Generally possible to obtain exactly the same molecule	Possible to reproduce the molecule to a high degree of similarity due to unique biomanufacturing methods and natural biological variability
Mostly smaller molecules, easier to characterise	In general, larger, structurally more complex molecules, which require multiple technologies for their characterisation
Full data requirements on pharmaceutical quality	Full data requirements on pharmaceutical quality, plus additional quality studies comparing the structure and biological activity of the biosimilar with the reference medicine
Development based on demonstration of bioequivalence (i.e. that the generic and the reference medicine release the active substance into the body at the same rate and to the same extent under similar conditions)	Development based on demonstration of biosimilarity using comparability studies (comprehensive head-to-head comparison of the biosimilar with the reference medicine to show high similarity in chemical structure, biological function, efficacy, safety and immunogenicity)
Generic medicine	Biosimilar medicine
Clinical data requirements are mainly pharmacokinetic bioequivalence studies	In addition to comparative pharmacokinetic and pharmacodynamic studies, safety and efficacy data may be required, particularly for more complex biological medicines
All indications approved for the reference medicine can be granted based on	Efficacy and safety have to be justified in each indication. However, confirmatory clinical trials with the biosimilar are usually not needed in every indication that has been



demonstrated bioequivalence, without the need for further clinical data

approved for the reference medicine. After demonstration of biosimilarity, extrapolation of data to other indications is possible if the scientific evidence available addresses all specific aspects of these indications

Conclusion

Biosimilars are expected to be an essential component in reducing health care costs and enhancing patient access to important, often lifesaving medications.¹⁵

By demonstrating biosimilarity, a biosimilar can rely on the safety and efficacy experience gained with the reference medicine. This avoids unnecessary repetition of clinical trials already carried out with the reference medicine.¹¹

It is hoped that the FDA will soon finalize these regulatory guidelines, clarify unanswered questions, and establish a biosimilars pathway that is based upon sound scientific principles.^{15,16}

Demonstration of biosimilarity relies on comprehensive comparability studies with the reference medicine. If a biosimilar is highly similar to a reference medicine, and has comparable safety and efficacy in one therapeutic indication, safety and efficacy data may be extrapolated to other indications already approved for the reference medicine. Extrapolation needs to be supported by all the scientific evidence generated in comparability studies (quality, non-clinical and clinical)¹¹.

In doing so, the agency will need to find the proper balance between rigorous data and testing requirements and providing a cost-efficient, expedited pathway for biosimilar approval.¹⁷

Extrapolation is not a new concept but a well-established scientific principle used routinely when biological medicines with several approved indications undergo major changes to their manufacturing process (e.g. to introduce a new formulation). In most of these cases, clinical trials are not repeated for all indications and changes are approved based on quality and in vitro comparability studies. All indications of biological medicines (including biosimilars) have been granted based on sound scientific evidence¹¹.

Robust evidence is critical to ensure drug efficacy and safety, but in order to encourage the availability of biosimilars, it cannot be too burdensome to dissuade company sponsors from developing and introducing biosimilars to the market^{2, 5}

Reference

Calo-Fernández B, Martínez-Hurtado J. Biosimilars: Company strategies to capture value from the biologics market. *Pharmaceuticals*. 2012;5(12):1393-1408.

Hirsch BR, Lyman GH. Biosimilars: Are they ready for primetime in the United States? *J Natl Compr Cancer Network*. 2011;9:934-943.

Hoffman JM, Li E, Stevenson JG. Preparing for biosimilars: Scientific, regulatory, and practice management issues for pharmacists. Live webcast, 47th ASHP Midyear Clinical Meeting and Exhibition; Las Vegas. December 3, 2012; Available at: www.ashpadvantagemedia.com/downloads/handout_biosimilars.pdf. Accessed February 26, 2013.

McCamish M, Woollett G. The state of the art in the development of biosimilars. *Clin Pharmacol Ther*. 2012;91(3):405-417.

Blackstone E, Fuhr J. Innovation and competition: Will biosimilars succeed? *Biotechnol Healthcare*. 2012;9(1):24-27.

Lee JF, Litten JB, Grampp G. Comparability and biosimilarity: Considerations for the healthcare provider. *Curr Med Res Opin*. 2012;28(6):1053-1058.

Simoens S, Verbeken G, Huys I. Biosimilars and market access: A question of comparability and costs? *Target Oncol*. 2012;7(4):227-231.

Simoens S. Biosimilar medicines and cost-effectiveness. *Clinicoeconomic Outcomes Res*. 2011;3:29-36

Ogbru O. *Why drugs cost so much*. Available at: www.medicinenet.com/script/main/art.asp?articlekey=18892. Accessed February 26, 2013.

<https://biosimilarscouncil.org/resource/how-a-biosimilar-is-developed/>

https://www.ema.europa.eu/en/documents/leaflet/biosimilar-s-eu-information-guide-healthcare-professionals_en.pdf

EMA- Presentation Biosimilars in the European Union - regulatory perspectives

ICH GCG ASEAN Training Workshop on ICH Q5C, 30-31 May 2011, Kuala Lumpur

European Medicines Agency: Similar biological medicinal products (overarching guideline). CHMP/437/04 Rev. 1. http://www.ema.europa.eu/docs/en_GB/document_library



ary/Scientific_guideline/2014/10/WC500176768.pdf.
Accessed on 6 March 2017.

European Medicines Agency: Similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. EMEA/CHMP/BMWP/42832/2005 Rev. 1. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/01/WC500180219.pdf. Accessed on 6 March 2017.

Nick C. The U.S. Biosimilars Act: Challenges facing regulatory approval. *Pharm Med.* 2012;26(3):145-152

Rana JB, Chang DY. Pharmacist perception of biosimilar agents in the U.S. *Pharmacy Purchasing Products.* 2012;9(7):8

Barlas S. FDA readies new guidance and user fee program for biosimilars: Drug interchangeability and user fees are contentious issues the FDA must resolve: Is the FDA up to the task? *Biotechnol Healthcare.* 2012;9(2):28-29

