EDITORIAL

Blooming of Biosimilars

Yogita S. Karandikar

Department of Pharmacology, SKNMC and GH, Pune, Maharashtra, India

INTRODUCTION

Many chronic and frequently disabling illnesses are now treatable using biological medications, which are frequently created by cutting-edge biotechnology. With 84 approvals in the EU and 35 in the US, biosimilars have been recognized for the past 17 years and account for about 90% of the global market. On its route to widespread adoption, biologic drugs' ascent and diversification have faced a number of obstacles and opportunities. In both the United States and Europe, the market for biosimilars has experienced significant growth. In nations where companies and businesses for the manufacture of biologics already exist, the market is likewise steadily growing.

WHAT IS A BIOLOGICAL PRODUCT?

- Biological products, also known as biologics, are used to treat a variety of disorders, such as cancer, inflammatory bowel diseases including Crohn's disease and ulcerative colitis, arthritis, kidney problems, diabetes, and chronic skin issues like psoriasis
- Large, complex compounds created from living sources including bacterial, yeast, and mammal cells are known as biologics
- Biologics naturally have many minute differences from batch to batch because they typically come from living creatures, and their structures are typically more intricate than those of conventional drugs. Biologics are hence frequently more difficult to make, purify, and process.

Access this article online	
Quick Response code	**Website:** www.mjbar.in
	Recevied on: 22/12/2022 **Accepted on:** 19/02/2023

There are numerous biologics that have been given the green light for use, including monoclonal antibodies, insulin, vaccinations, and allergenic goods.

WHAT IS BIOSIMILAR?

A biosimilar is a biological drug that is very similar to another biological drug that has already received approval (the "reference medicine"). The same pharmaceutical quality, safety, and efficacy standards that are used to other biological medicines are used to determine whether or not to approve a biosimilar.

Biosimilars are identical to a reference product in that they are created from the same kinds of live sources, administered to patients in the same way, and have identical strengths, dosages, potential therapeutic advantages, and potential adverse effects.

Patients who have already received the reference product (those with treatment experience) as well as those who have not (those with treatment naivety) may both use a biosimilar.

A proposed biosimilar or interchangeable biosimilar is compared to a reference product, which is a single biological product that has already received FDA approval. A complete set of safety and efficacy data is among the criteria used to approve a reference product.

A biological product that is very similar to and devoid of any clinically significant deviations from an FDA-approved reference product is referred to as a biosimilar. Modern methods that assess important qualities such as purity, molecular structure, and bioactivity are used to compare and assess a proposed biosimilar to a reference product. To demonstrate that there are no clinically significant variations between the proposed biosimilar and the reference product in terms of safety, purity, and potency (i.e., safety and efficacy), clinical studies comparing the two products are done.

Address for correspondence:
Yogita S. Karandikar, Department of Pharmacology, SKNMC and GH, Pune, Maharashtra, India.
E-mail: yogita.karandikar@gmail.com

ARE BIOSIMILARS THE SAME AS GENERIC DRUGS?

Because they are replicas of branded medications and may provide patients with more economical treatment options, biosimilars and generic medications are similar in certain aspects.

Generic medications are typically created by synthesizing chemicals, and as a result, each manufactured lot and each lot of the final product have the same active ingredient. However, biosimilars are often produced using live systems (such as animal cells and microorganisms like yeast and bacteria) just like their reference biological products. Because biological products, also known as biologics, are manufactured from live organisms, intrinsic variation – small changes to the protein molecule – is a normal aspect of the production process and is expected within each lot as well as between lots.

The manufacturer of a generic drug must, among other things, shows that the generic is bioequivalent to the brand-name medication for the FDA to approve it. Manufacturers of biosimilars, on the other hand, must prove that their product is substantially equivalent to the reference product, with the exception of minor variations in clinically inactive components. In addition, the safety, purity, and potency of the product (i.e., safety and effectiveness) must be shown to be same between the biosimilar and the reference product by the biosimilar makers.

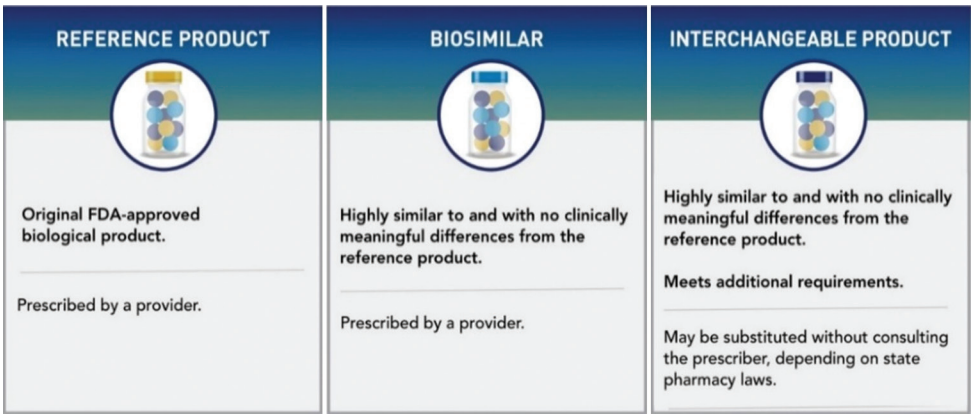
WHAT IS THE DIFFERENCE BETWEEN A BIOSIMILAR AND AN INTERCHANGEABLE BIOSIMILAR?

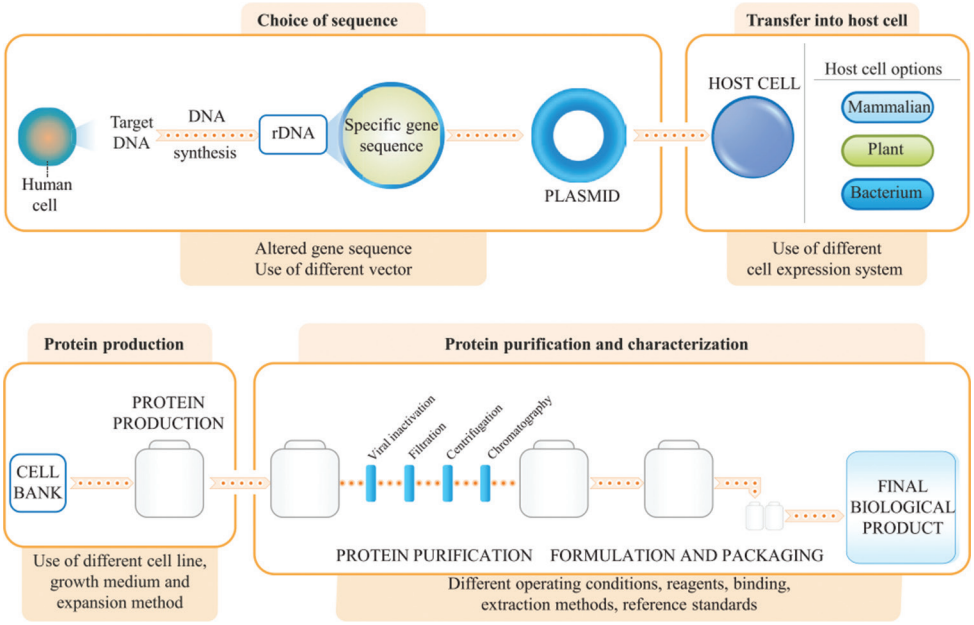
An interchangeable biosimilar product requires special authorization from the biosimilar producer. In accordance with state pharmacy legislation, a product that has been licensed as an interchangeable biosimilar may be used in place of the reference product at the pharmacy without the involvement of the prescribing health-care professional. Before prescribing a biosimilar, a doctor does not need to wait for it to be authorized as an interchangeable biosimilar. Health-care professionals and patients can be confident in the safety and efficacy of a biosimilar, whether or not it has also been approved as an interchangeable biosimilar, just as they would be for a reference product, because all biologics must pass the FDA's strict approval standards.

MANUFACTURING AND VARIATION

Complex and tightly controlled processes are used during the manufacturing process to create biologics and related biologics. The appropriate gene is copied onto a DNA vector as part of the procedure, and it is then introduced into a host cell. Following the expression of the protein, the appropriate cell line is chosen, and it is expanded in a growth medium using an appropriate expansion technique. The final biological product is processed using elaborate purification and validation processes. Depending on how the DNA sequence is chosen, how the product is cloned, transfected, amplified, purified, formed, and validated, the final product's features may vary.

Recombinant DNA technology allows for the production of numerous therapeutic proteins in animal or microbial cells. These modified cells produce several copies of a therapeutic protein with the same amino acid sequence during the production process. Through a procedure known as post-translational modification, one or more amino acids in a specific protein can undergo very minor modifications. An example of a post-translational modification is the process of glycosylation, in which cells add sugar molecules to particular amino acids of the protein during protein synthesis. The protein molecules that are being created may have various sugars added to them. As a result, even though only one kind of protein is produced, the sugars that are added cause the protein molecules to differ significantly from one another. A mixture of these unique protein molecules with diverse sugars linked make up the final biologic. This holds true for interchangeable biosimilars, biosimilars, and reference items.





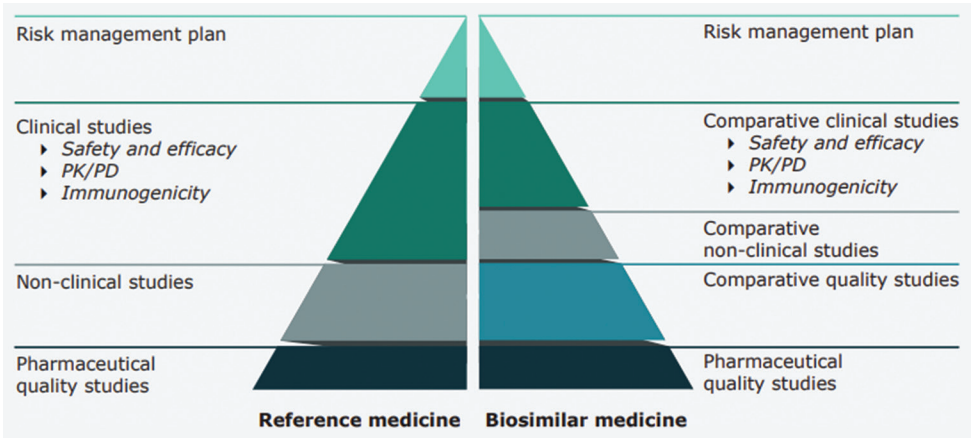
BIOSIMILAR REGULATORY APPROVAL PATHWAY

The streamlined approval process for biosimilars was developed to speed up development and cut costs without sacrificing efficacy and safety. In light of this, all biosimilar and interchangeable biosimilar products are authorized through the shortened 351(k) pathway based, in part, on a comparison of the biosimilar to the reference product.

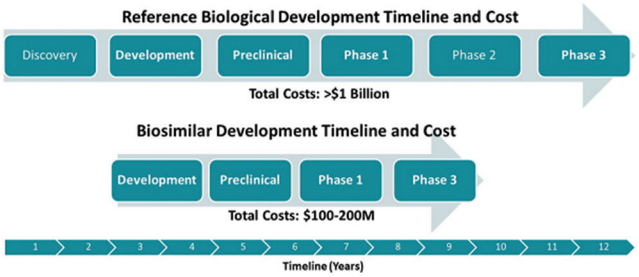
Biosimilar manufacturers are not required to produce the same set of nonclinical and clinical data as is necessary for the reference product. Instead, the maker of the proposed biosimilar offers comparable data, starting with a thorough analytical characterization and structural and functional comparison of the reference product and biosimilar. If necessary, animal investigations are carried out. The next step is that manufacturers carry out clinical comparisons between the proposed biosimilar and the reference product. These studies frequently include pharmacokinetics, pharmacodynamics, and immunogenicity, when appropriate. These comparative analytical, nonclinical, and clinical data taken together support the conclusion that a biosimilar is very comparable to and does not significantly differ from an FDA-approved reference product clinically.

As a result, biosimilar producers do not have to carry out as many pricey and time-consuming clinical trials (CT) as a producer of the reference product, which may result in quicker access to these drugs, more treatment alternatives for patients, and lower prices. To ensure that all approved biosimilars are as safe and effective as their reference products, the FDA's stringent standards are met by the streamlined approval process.

COMPARISON OF DATA REQUIREMENTS FOR APPROVAL OF A BIOSIMILAR VERSUS THE REFERENCE MEDICINE



ORIGINATORS VERSUS BIOSIMILARS-DEVELOPMENT PATH



REGULATORY FRAMEWORK IN INDIA

In India, the Government of India's central drugs standard control organisation (CDSCO) is the top regulatory agency for biosimilars. Involved in the approval of biosimilars or comparable biologic products (SBPs) are two additional competent agencies, which are:

I. Review Committee on Genetic Manipulation (RCGM), a division of the Ministry of Science and Technology's Department of biotechnology (DBT). According to the DBT standards, the RCGM controls the import, export, research, preclinical approval, No Objection Certificate for CT, and other associated operations using genetically modified organisms (GMO)
II. The Department of Environment's Genetic Engineering Approval Committee (GEAC) oversees genetic engineering. GEAC serves as a statutory authority for the examination and approval of projects involving extensive use of GMO and their by-products in field applications, industrial production, research and development, and environmental releases. The requirements for the manufacturing process, quality considerations, pre-market regulatory requirements, including comparability exercises for quality, non-clinical and clinical studies, and post-market regulatory requirements for biosimilars, are included in the CDSCO recommended guideline.

INDIA-QUIET LEADER

From the year 2000, when it approved a biosimilar far earlier than the United States and Europe and released it on the market to treat hepatitis B, India became the go-to partner for biosimilars. By lowering the cost of treatment, biosimilars have improved patient accessibility for numerous malignant and non-malignant conditions. India was quick to respond to the need for and demand for biosimilars on a global scale by staying true to its research and scalable manufacturing capabilities. One hundred and twenty-seven biosimilars have been approved as of today.

Monoclonal antibodies for the treatment of different cancers and immune disorders, growth factors such as erythropoietin and granulocyte colony stimulating factor, human insulins for the treatment of diabetes mellitus, and other substances are examples of biosimilars that are readily available in India.

In 2006, patients in India received the first innovative biologic treatment, a monoclonal antibody called BIOMab EGFR for head-and-neck cancer. The first biosimilar Herceptin to be created by Biocon and Mylan was CANMab, which was introduced in India in 2014. Thereafter, more biosimilar versions were created. Insulin Glargine from Biocon was the first biosimilar from India to be commercialized in Japan in 2016. The commercial environment for biosimilars has been considerably altered by products such as Ogivri (trastuzumab), Fulphila (pegfilgrastim), produced by Biocon and Mylan in India and approved in the US, as well as government efforts like the National Biopharma Mission and the Atal Incubation Programmes. According to estimates, the biosimilars market in India would increase at a compound annual growth rate of 22% and reach US$ 12 billion by 2025.

Several businesses are expected to lose their respective biologics patents in the upcoming years, and India is well-positioned with its research and manufacturing capacities to assume its rightful position as the global leader in the provision of health-care solutions for the management of debatable diseases such as cancer, diabetes, and arthritis. To enhance their market share in these therapy areas globally as biologics such as Avastin, Humira, Aflibercept, Ranibizumab, and Levemir come off-patent, more Indian pharmaceutical manufacturing businesses will focus on biosimilar production.

COST SAVING BY BIOSIMILAR

India has a special opportunity to develop and introduce cost-effective biosimilar drugs that can treat both malignant and non-malignant conditions at the most competitive price point because it is a price-sensitive market.

For biosimilar approval in India, Phase I–II trials are normally not necessary unless they are deemed necessary under unusual circumstances. To establish bioequivalence, Phase III trials with 100 patients or more are required. Because of this, developing a biosimilar in India can cost anywhere between $10 and $20 million, allowing Indian businesses to sell their goods for 25–40% less than comparable biologics.

The cost of the adalimumab biosimilar in India is also considerably less than the cost of Humira in other countries; a prefilled carton containing two syringes is said to cost about $2,500 in the US. (Rs 203638.38) It is interesting to note that, with the exception of the Cipla brand, which costs roughly INR16,072, most Indian players appear to have set the prices of their adalimumab biosimilars to be in the range of INR 22,000–25,000 ($320–364). However, considering numerous patient assistance programs and other concessions, the price to patients is typically thought to be significantly lower. For patients who are enrolled in a patient assistance program by a doctor referral, the actual cost of Exemptia by Zydus Cadila ranges from INR11,000 to INR14,000 per month.

COST DIFFERENCE BETWEEN REFERENCE AND BIOSIMILAR

INN	Reference	Biosimilar	Strength	Cost difference (%)
Filgrastim	Neupogen	Zarxio	300 mg	
Cost	$324.30	$275.66	300 mg	16.21
Filgrastim	Neupogen	Zarxio	480 mg	
Cost	$516.45	$438.98	480 mg	16.22
Infliximab	Remicade	Inflectra	100 mg	
Cost	$940/vial	$525/vial	100 mg	44
Bevacizumab	Avastin	Zirabev	100 mg	
Cost	$797/vial	$613	100 mg	23
Trastuzumab	Herceptin	Ogivri	150 mg	
Cost	$1,558	$1,325		15
Insulinglargine	Lantus	Semglee	10 mL vial	
Cost	$340.27	$118.38		65

COST COMPARISON OF BIOLOGIC VERSUS BIOSIMILAR IN RHEUMATOLOGY

Molecule	Innovator company price (INR) (6 months treatment)	Biosimilar price (INR) (6 months treatment)
Rituximab	4,80,000	2,40,000
Infliximab	4,80,000	2,40,000
Adalimumab	5,10,000	1,32,000
Etarnacept	108,000	84, 000

CHALLENGES

1. High Development Costs: Creating a biosimilar involves a large financial commitment as well as technical know-how and CT experience. Cost projections typically range from $100 to $250 million.
2. Emerging Regulatory Environment: Outside of Europe, most markets' regulatory environments for biosimilars are still very young in comparison to those for new chemical entities and small-molecule generics. In some cases, these environments are nonexistent, which makes international investments risky.
3. Manufacturing issues: The creation of biosimilars entails complex analytical sophisticated technology and procedures, increasing the risk of the investment, although barriers to building a biosimilars manufacturing capability are not prohibitive.
4. Branded mindset: Gaining stakeholders' trust may require altering business models and requiring many of the expertise, resources, and branded mentality of a typical revolutionary pharmaceutical company. It will be especially crucial to implement safety-related initiatives with the assistance of sales staff.
5. Balanced legislation: To safeguard and support innovative treatments, balanced legislation between biologics and new medications is necessary.
6. Market risk: The marketing of biosimilars is very risky because competition against innovative drugs and other competitors. Biosimilars have come of age over the past 17 years, with 84 approvals in the EU and 35 in the US, representing almost 90% of the world market.

CONCLUSION

Globally, the issues of an ageing population and the rise in the prevalence of chronic diseases are of major concern. It has been discovered that biologics are effective in the treatment of numerous chronic, life-threatening diseases. Since these powerful medications' patent protection has expired, biosimilars have become a promising new class of therapy choices. Similar to biologics, biosimilars are susceptible to modifications in manufacturing procedures as well as the intrinsic unpredictability of the system for producing or expressing proteins. No biosimilar hence cannot be technically or scientifically identical to the original product. As a result, developing reliable manufacturing and quality control systems is crucial to the creation of biosimilars. Biologics and the development of biosimilars so represent a solution to improve patient accessibility to biotherapeutic therapy in light of the ongoing rise in health-care spending.

EXAMPLE OF SOME OF THE BIOSIMILARS APPROVED IN INDIA

Product name	Active drug	Indications
Glaritus	Insulin glargine	Diabetes mellitus
Grafeel	Filgrastim	Neutropenia
Epofer	Epoetin alfa	Anemia
Adfar	Adalimumab	RA, Crohn's disease
Erbitux	Cetuximab	Colorectal carcinoma
Krabeva	Bevacizumab	Colorectal cancer
Herceptin	Trastuzumab	Breast cancer
Intacept	Etanercept	RA
Abcixirel	Abciximab	Autoimmune disease
Relibeta	Interferon beta-1a	Multiple sclerosis
Relipoietin	Epoetin alfa	Anemia, autologous blood transfusion, chronic kidney failure, HIV
Shankinase	Streptokinase	Arterial occlusions, deep vein thrombosis, pulmonary embolism
Razumab	Ranibizumab	Wet macular degeneration, macular edema, degenerative myopia
Terifrac	Teriparatide (parathyroid hormone)	Postmenopausal women with osteoporosis who are at high risk for fracture

How to cite this article: Karandikar YS. Blooming of Biosimilars. Med J Basic Appl Res 2023; 4(1):1-6.

Conflicts of Interest: None. **Source of support:** None.