MAJOR BIOSIMILARS IN THE MARKET CONTRIBUTING TO THE ECONOMY OF PHARMA INDUSTRY IN US AND THE IMPACT OF COVID-19 ON BIOSIMILARS MARKET GLOBALLY

Dissertation Submitted to

The IIHMR University, Jaipur

for the partial fulfillment for the award of the degree of

Master of Business Administration (MBA) in Hospital and Health Management/Pharmaceutical Management/Rural Management by

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Under the Supervision and Guidance of

Dr. Anoop Khanna

2021

DECLARATION BY STUDENT

I hereby declare that this dissertation titled 'Major biosimilars in the market contributing to the economy of pharma industry in USA and the impact of COVID on biosimilars market globally' is the bonafide record of my original research work. I declare that it has not been submitted to any other university or institution for the award of any degree or diploma. Information derived from the published or unpublished work of others has been duly acknowledged in the text.

(Signature)

Name of Student: Utkarsha Telang

Date: 23rd June 2021

CERTIFICATE

This is to certify that Utkarsha Telang in partial fulfillment of the requirements for the award of the degree of MBA (Hospital and Health Management)/MBA(Pharmaceutical Management)/MBA (Rural Management) from the IIHMR University, Jaipur has successfully completed her/his internship at ZS Associates during March 22, 2021 to June 19, 2021.

Place: New Delhi

Date: 23rd June 2021

Preceptor/Head of the Organization: Dr. Amudha Sharma

Name of the organization: ZS Associates

CERTIFICATE

This is to certify that dissertation titled 'Major biosimilars in the market contributing to the economy of pharma industry in USA and the impact of COVID on biosimilars market globally' is a record of the research work undertaken by (Name of Student) in partial fulfillment of the requirements for the award of the degree of MBA (Hospital and Health Management)/MBA (Pharmaceutical Management)/MBA (Rural Management) from the IIHMR University, Jaipur under my guidance and supervision and his/her approach to the research study has been sincere, scientific, and analytical.

Faculty Guide: Dr. Anoop Khanna

IIHMR University, Jaipur

Date

School Dean

IIHMR University, Jaipur

Date

ABSTRACT

Introduction- Biologic therapies have transformed the treatment of a wide range of diseases, including cancer and autoimmune disorders. Patents and other exclusivity periods for a number of biologics are about to expire or have already expired, paving the way for the development and approval of treatments that are comparable to licensed biologics known as "biosimilars". Also, due to the high cost of biologics, new legislation was passed to allow for the development of biosimilars, which will provide more treatment alternatives, enhance access, and reduce costs. US saw the approval of first biosimilar Zarxio in the year 2015 which was indicated for oncology supportive care. Since then, United States has seen a lot of biosimilars approvals and launches in the market. **Objectives-** The study aims to identify the major biosimilars in the market contributing to the economy of pharma industry in USA and the impact of COVID-19 on the uptake and adoption of biosimilars in the pharmaceutical market globally. COVID-19 is a very recent phenomenon and it has definitely affected biosimilar approval and availability and its supply in the major and emerging biosimilar markets globally.

Methodology- The study is exploratory in nature and is based on both qualitative and quantitative data. The data has been collected from various secondary sources. The study period includes the period from 2015 to 2021. Descriptive analysis has been carried out to identify the main biosimilars in the US and the effect of COVID-19 on the global biosimilars market and comparative analysis was done to identify the major differences between US and Europe biosimilars market.

Findings- Biosimilars will eventually account for a significant chunk of the US biologics market. However, the road to successful biosimilar adoption will remain difficult in these early phases, as considerable investments will be necessary to demonstrate similarity and interchangeability in order to maximize their potential. COVID-19, without a doubt, threw the entire healthcare business into a loop. As a result, it's no wonder that one of the top concerns among responders is how regulatory authorities, pharmaceutical companies, treatment locations, and patients will adjust as the pandemic continues.

Conclusion- Not only do many people believe biosimilars will (finally) get the attention they deserve, but there is also a focus on the policies that governments, regulators, and payers must

follow to guarantee we get the most out of these important medications. Some experts believe that 2021 will be the “year of the biosimilars”.

ACKNOWLEDGEMENT

I would like to express my deepest appreciation to all those who provided me the possibility to complete this report. I wish to express a special gratitude to my mentor Dr. Anoop Khanna (Mentor, IIHMR) who helped me in writing this report. His valuable guidance, suggestions and encouragement have helped me to improve my report.

I am extremely grateful to my organization mentor Dr. Amudha Sharma (Knowledge Management Manager, ZS Associates, New Delhi), for giving me some great insights and her point of views throughout my research. She has been very patient with me and has helped me with all my doubts related to the research.

I would like to thank the library staff of IIHMR University who have shown utmost cooperation and helped me with the resources needed to complete the report.

Lastly, I am indebted to my parents and family who motivated me to work on this report and also gave insights on the topic of my report. Their support throughout the making of this report was much needed.

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ABBREVIATIONS

FDA	Food and Drug Administration
EMA	European Medicines Agency
WHO	World Health Organization
BPCIA	Biologics Price Competition and Innovation Act
EU	European Union
PK	Pharmacokinetics
PD	Pharmacodynamics
PHS Act	Public Health Service Act
CAGR	Compound Annual Growth Rate
HCPCS	Healthcare Common Procedure Coding System
WAC	Wholesale Acquisition Cost
ASP	Average Sales Price
CVD	Cardiovascular Disease
GCC	Gulf Cooperation Council
KOL	Key Opinion Leaders

Chapter 1-Introduction

Biologics, such as certain vaccines, are known since the nineteenth century, and the first bacteria-generated biologic, human insulin, was approved by the Food and Drug Administration (FDA) of the United States in 1982. Vaccines such as the human papillomavirus for cervical cancer, gene therapies, tissues for transplant like tendons and ligaments, blood and blood products, e.g., platelets, recombinant proteins such as insulin, stem cell therapies that are used for cancers or genetic disorders and monoclonal antibodies which fight cancer and treat autoimmune diseases are all examples of biologics. Biologics are not a new concept and have been around for a long time. Since the 1980s, biologics made with modern recombinant DNA technology have been employed to treat a variety of ailments. However, as our understanding of biologics has progressed, they are now increasingly important in the management of autoimmune illnesses, cancer, and genetic problems. The number of biologics available has grown dramatically, and they now include therapies for the following conditions: Ankylosing spondylitis, rheumatoid arthritis, psoriasis, diabetes, multiple sclerosis, SLE, Crohn's disease, and ulcerative colitis which are all immune-mediated disorders. Leukemia, lymphoma, gastric, breast, and colon cancers are examples of specific cancers. Gaucher disease, Sickle cell disease, hemophilia, cystic fibrosis are all examples of rare genetic illnesses. Patents and exclusivity dates for several biologics are about to expire or have already expired, paving the way for the development and approval of treatments that are comparable to licenced biologics (known as "biosimilars"). Before receiving regulatory clearance, biosimilars are subjected to a thorough assessment utilising the criteria outlined in the biosimilar guidelines. Also, because of the increased cost of biologics, new laws were passed to allow for the development of biosimilars, which will provide more treatment alternatives, enhance access, and reduce costs. Following the resolution of exclusivity and intellectual property issues for a biologic, manufactures can seek authorization to commercialize a biosimilar, which is a highly similar version of the original biologic medication [1]. Biosimilar products must be highly similar to the original "reference product," according to the FDA. To be approved for use in the United States, biosimilars must demonstrate that they:

- Have the same mechanism of action, have the same strength and dosage, and can thus be taken in the same way as the original biologic medication.

- Do not have any clinically meaningful differences in safety or effectiveness when compared to the original biologic medication
- Maintain the same high manufacturing standards as the originals

By reducing unnecessary duplication of clinical trials, biosimilar development saves time and resources.

The FDA defines a biosimilar as a biological product that has been approved based on evidence that it is highly similar to an FDA-approved biological product known as a reference product and that the biosimilar and reference product have no clinically significant differences. It's been five years since the first biosimilar hit the market in the United States, allowing patients to obtain access to ground-breaking biologic-based treatments that help them control and treat life-threatening conditions including cancer and rheumatoid arthritis. Biosimilars are critical for doctors and patients to have a choice in their treatment options while also cutting overall healthcare expenditures. According to research, embracing biosimilars and patient choice will result in the necessary competition to expand access to biosimilars and biologics for 1.2 million patients. The EMA has allowed around 55 biosimilars. Under the Biologics Price Competition and Innovation Act of 2009, the US Food and Drug Administration (FDA) approved its first biosimilar (a biosimilar of filgrastim) in 2015. To date, the FDA has authorized 29 biosimilar medications, with more approvals and launches expected for 2021 in oncology, oncology supporting care, nephrology/oncology supportive care, and inflammation. Patients, clinicians, and payers may be able to access a choice of lower-cost treatment alternatives as well as therapeutic flexibility that they would not otherwise have. Biosimilars have achieved significant market share in different therapy areas. According to an IQVIA analysis, biosimilars are expected to save the US market more than $100 billion over the next five years. Some of the major participants in the biosimilars market are Pfizer, Innovent, Ganlee, Eli Lilly, Abbvie, Novo Nordisk, Roche, Novartis, Dong Bao, Johnson & Johnson, Amgen, Merck, and Sanofi-Aventis. COVID-19 seems to have the potential to have a big impact on the biosimilars industry, and it has posed a serious challenge to pharmaceutical companies working on biosimilar expansion. The FDA's approval of non-COVID treatments has been constrained during the current pandemic, which is predicted to slow the process of product approval and marketing, suffocating market development. Furthermore, most clinical studies had been postponed to deal with the COVID-19 outbreak

and limit the danger of infection among participants, so most pipeline goods were moving at a snail's pace in terms of research and development. As a result of the global lockdown and travel restrictions, there was a supply chain and raw material scarcity, which hampered biosimilar production. COVID-19 has had a significant market impact as a result of the aforementioned causes.

With development and regulations, biosimilars differ from both original biologic products and generic small molecule pharmaceuticals. A biosimilar is a biological product that has been approved based on a body of evidence establishing that it is structurally, functionally, qualitatively, and clinically efficacious and safe in comparison to an approved biological product (originator). Biosimilars are created with the goal of having "no clinically relevant variations of safety, between the biological product and the reference [originator] product." In contrast to small (chemical) drug molecules which can be completely structurally defined to produce generic versions, biologics are large and structurally complex products. As a result, biosimilars cannot be deemed generic counterparts to the original and must undergo further testing to ensure clinical efficacy and safety. Biosimilars and generic medicines are versions of brand-name medications that may provide patients with more economical treatment choices. Biosimilars and generics both go through distinct expedited approval processes to avoid duplicating costly clinical trials. Biosimilars, on the other hand, are not generics, and there are significant distinctions between them and generic medications.

Generic medications, for example, have the same active components as brand-name medications. In addition, a generic drug's maker must show that the generic is bioequivalent to the brand-name medicine. Biosimilar manufacturers, on the other hand, must show that their product is almost identical to the reference product, with the exception of tiny variations in therapeutically inactive components. Biosimilar makers must also show that there are no clinically relevant differences in terms of safety and effectiveness between the biosimilar and the reference product.[1] The way clinical trials are conducted during the development process is one of the fundamental differences between biosimilars and reference biologics. The aim of the trials is to determine the clinical effectiveness of the product with biological products. Whereas, in case of biosimilars, the aim is to show that the product is similar in

pharmacokinetics, pharmacodynamics, safety and immunogenicity to the biological reference product. In other words, the objective is to demonstrate that the scientific concept of comparability does not have any significant impact on the therapeutic final effect.[2]

Terms used to describe a biosimilar	
Biological Product	Food & Drug Administration regulates biological products and are used in disease and medical diagnosis, preventive treatment and management. Biological products are a diverse product category and are larger, more complex molecules than others. These products are often harder to differentiate than molecular drugs and can be manufactured through biotechnology in a life system, such as the microorganism, plant cell or animal cell. A variety of biological products approved in the USA, including therapeutic proteins (e.g. filgrastim), monoclonal antibodies (e.g. adalimumab), and vaccines are available (such as those for influenza and tetanus).
Reference Product	A single biological product already approved by FDA, for which a biosimilar product is comparable, is a reference product. A reference product based on a full complement of safety and efficiency data is approved, among other things. In order to ensure that the product is extremely similar and has no clinically meaningful differences, a biosimilar product is compared and evaluated with a reference product.
Biosimilar	A biosimilar is a biological product which is very similar to an existing approved reference product and has no clinically significant differences.
Interchangeable	An interchangeable product is a biosimilar product that meets additional requirements stipulated by the Biologics Price Competition and Innovation Act. In order to meet these additional requirements, information is required to demonstrate that an interchangeable product should yield the same clinical result as the

Product	reference product for any particular patient. FDA's high approval standards should assure health care providers that they are confident that an interchangeable product is safe and efficient, as they would for a reference product approved by the FDA.
Generic drugs	Generic drugs are made up of small molecules that are easy to duplicate and reproduce. A generic drug's active component is the same as a brand-name drug's active component.[3]

Table 1.1- Terms used to describe biosimilars

Difference between Biosimilars and Generic drugs

Characteristics	Biosimilars	Generic Chemical Drugs
Chemical structure	Complex, heterogenous, with differences in protein folding & glycosylation	Simple, well defined & chemically identical to a reference product
Analytical characterization	Almost impossible to fully characterize; similar but not identical to reference products	Ensures that active drug in a generic product is identical to that of a reference product
Manufacturing process	Very complex; produced in living cells, with several stages of purification and production	Relatively simple, uses organic medicinal chemistry reactions
Impact of a process change	Small changes in manufacturing process can alter final protein structure and function	Likely to be negligible because the end products are identical
Development cost	$100-200 million/molecule	$3-5 million/molecule
Immunogenicity	Immunogenic	Mostly immunogenic

Table 1.2- Difference between generics and biosimilars

Chapter 2- Review of Literature

Authors	Year	Study location	Salient Features
A. Sarpatwari, R. Barenie, G. Curfman, J. J. Darrow1 and Aaron S. Kesselheim1	2019	USA	They have assessed at the number, kind, and price of approved biosimilars under the BPCIA, as well as the journey to date, manufacturing, regulatory, and marketing hurdles, and compared the US experience to those of other countries. Based on their findings, they proposed some interventions and suggestions to improve the efficiency of ushering biosimilars to market. [5]
Stanton R. Mehr and Richard A. Brook	2019	USA	According to the study, In the United States, healthcare systems and payers are looking for significant cost savings from the use of biosimilars. Biologic drug prices continue to rise in the double digits, and biosimilars are seen as an important option for lowering costs and expanding access to biologics. However, according to one 2018 report, biosimilar products compete for US$3.2 billion (only 3% of biologic spending). Adoption of biosimilars has slowed in the United States due to a variety of market-specific factors. Short-term federal action is being taken to increase access to biosimilars. Despite the fact that biosimilars were

			introduced relatively late in the United States, some cost savings are now being realized. [6]
Sofia Konstantinidou Angeliki Papaspiliou Eleni Kokkotou	2019	USA, Europe	Biologics are commonly used therapeutic agents in cancer prevention and palliative care. Biosimilars, on the other hand, have entered the market as a result of high costs, global healthcare spending crises, and the expiration of biologics patents. When compared to their reference counterparts, biosimilars are less expensive drugs with comparable safety and toxicity profiles and no clinically significant differences. Therefore, biosimilars save people money on healthcare while also providing additional therapeutic choices. The current underutilization of biosimilars in clinical practice can be attributed, at least partly, to a unawareness of the benefits and limitations of biosimilars among patients and doctors. Strict regulatory frameworks and strong post-marketing surveillance of approved biosimilars are essential to ensure that these novel treatments are safe and successful in real-world settings. [7]
H Kim, Alten R, L Avedano, A Dignass, F Gomollon	2020		Price-competitive treatments can now reach patients more swiftly because of changes in regulatory methods and developer innovation. Pharmacoeconomic evaluations should be reassessed following biosimilar market introduction when clinically relevant to remove nonmedical barriers to biologic medication access, and successful physician engagement is critical to support patient confidence in biosimilars. To reap the fullest potential benefits of biosimilars in terms of cost reductions and enhanced patient

			access, multiple stakeholders' efforts and effective coordination are required.[8]
Kang HN, Thorpe R, Knezevic I, Casas Levano Chirachanakul P, Chua HM, Dalili D, Foo F	2020		The WHO gave guidelines for the regulatory assessment of biosimilars in 2009, and it has made significant efforts to help member states in implementing the guidelines' evaluation standards. Despite this attempt, a recent WHO study (conducted in 2019–2020) highlighted 4 significant challenges: a lack of resources; quality issues with certain biosimilars; and difficulty with biosimilar interchangeability and nomenclature. The study found various chances or solutions for regulatory agencies to address the aforementioned issues. [9]
Rathore AS, Bhargava A	2020		Because developed economies account for the majority of global biotherapeutics revenues, biosimilars have a profitable market in these countries. Biosimilar clearance factors in these jurisdictions are anticipated to have a significant impact on biosimilar uptake. To gauge the economic benefit of biosimilars, regulatory authorities must connect the requirements of clinical data to product complexity and product familiarity. [10]
R. Ronald Harvey	2017	USA	The resemblances and distinctions between biosimilars and their references, as well as generic pharmaceuticals, have been highlighted in this study. In oncology, biosimilar therapeutic proteins have the potential to reduce costs while maintaining the same safety and efficacy characteristics as their reference or originator drugs. Biosimilars differ from generic small-molecule pharmaceuticals in a variety of

			ways, including manufacturing procedures that are distinct from their reference products. Posttranslational alterations that can occur in various cellular manufacturing lines can alter biosimilars, and these modifications can influence protein structure, function, clinical pharmacology, and immunogenicity. These disparities are expected to be found, studied, and eliminated through iterative processes and substantial preclinical efforts, according to regulatory bodies.[11]
Nabhan, C., Parsad, S., Mato, A. R., & Feinberg, B. A	**2018**	**USA**	Physicians and other oncology stakeholders must understand how biosimilar cancer medications are regulated, licenced, and paid for, as well as their implications in a value-based care setting. Significant structural differences exist in biosimilar and generic drugs. Clinically inactive component biosimilars and their reference drugs may have minor changes without clinically relevant changes. As patents on a range of cancer biologics expire in the next few years, there will be more biosimilars. [12]
Christl, L. A., Woodcock, J., & Kozlowski, S.	**2017**		The US FDA devised a pathway for the development and licencing of biosimilar and interchangeable biological products with the enactment of the BPCIA of 2009. The US biosimilars program's regulatory framework and technical standards comprise a stepwise procedure that heavily relies on analytical methodologies to demonstrate that a proposed product is biosimilar to its reference product using "totality of the evidence". A high level of confidence in clinical performance

			can be achieved by combining analytical, pharmacological, and clinical data, all of which have limitations. A solid scientific effort has been put in place, despite the fact that doubts and concerns about the biosimilars approach still exist and may hinder uptake. With three biosimilars now on the market and other development projects in the pipeline, physicians can see a slew of new biosimilars hit in the coming decade.[13]
Joseph D. Tariman	**2018**		The objective of this article was to look into the history of biosimilars, as well as the regulatory paths and obstacles to biosimilar approval. The aim of this article was also to outline the patient and clinician hurdles to using biosimilars. A literature search was carried out to find papers that were particularly relevant to the development and regulatory paths of biosimilars in the Europe, United States, Canada and Asia. The opinions of patients and clinicians on safety issues, as well as concerns about immunogenicity and bioequivalence that restrict the use of biosimilars, have also been presented. Patients, prescribers, and doctors are concerned about biosimilars' clinical safety, efficacy, and tolerability.[14]
Vakil, N., & Fanikos, J.	**2019**		The focus of this research was to look into the causes for biosimilars' low penetration in the United States and Europe. To encourage the development of biosimilars, BPCIA established an approval pathway (351(k)) and interchangeability provisions. Ever since, 19 biosimilars have been approved and 7 have been commercialized through this route; however,

			biosimilars have a low penetration and utilization in the United States. Due to particular challenges in the US, such as rebates granted by the reference biologic's producer, biosimilar market penetration remains limited as compared to the EU.

Research Question

- What are the major biosimilars in the market contributing to the economy of pharma industry in USA?
- What is the effect of COVID-19 on biosimilars market globally?

Research Objectives

1) To analyze the current market scenario of biosimilars in USA.

2) To study the regulatory pathway for the approval of biosimilars in USA.

3) To identify the key differences in the USA and EU biosimilars market.

4) To identify the challenges and opportunities that lie in the acceptance of biosimilars in USA.

5) To study the effect of COVID-19 on the uptake and adoption of biosimilars globally.

Chapter 3- Methodology

The study is exploratory in nature and is based on both qualitative and quantitative data. The data has been collected from various secondary sources. The study period includes the period from 2015 to 2021. This period is so chosen because the first biosimilar was approved in United States in the year 2015. Secondary sources of data include journals, articles, websites, articles and reports released by various research groups. Descriptive analysis was carried out to identify major biosimilar playing in the US biosimilar market. In order to better understand the present biosimilar market value, a search for the countries of interest, particularly the USA, was also carried out. Comparative analysis to identify the major differences between US and Europe biosimilars market has been done. Europe has been chosen for comparison as Europe holds the maximum share of sales in the global biosimilars market. Descriptive analysis has been done to analyze the challenges and opportunities that will influence the adoption of biosimilars in the US the impact of COVID-19 on the uptake of biosimilars globally. Recommendations and suggestions have been provided for post COVID marketing of biosimilars and how to overall increase biosimilar adoption in the United States.

Chapter 4- Results ad Discussion

4.1 -Regulatory Approval Pathway for Biosimilars in US

To demonstrate similarity to the reference product, biosimilar manufacturers must submit relevant and necessary data to the FDA, including pharmacodynamic and pharmacokinetic. The FDA then determines if the level of resemblance between the biosimilar and the reference product is sufficient to allow for market approval. A permitted biosimilar should not cause any clinically meaningful differences in its safety and efficacy when compared to the reference product, according to the second critical component. Thus, biosimilars do not require new phase 3 clinical studies, which are required for the New Drug Application procedure. These are mostly optional. Biosimilars also don't have to show clinical efficacy and safety for every indication like the reference. As a result, the FDA may approve the biosimilar for some indications based on the idea of extrapolation, which states that data from one indication can be used to support use for another. The US pathway began in 2009, when the US Congress passed the Biologics Price Competition and Innovation Act (BPCI) permitting the FDA to approve the first US biosimilar, Zarxio, in 2015 [15]. The 2009 BPCIA established a streamlined approval process for biosimilars, which was the abbreviated approval pathway for biosimilars (351(k)). The European Medicines Agency (EMEA, now EMA) devised the regulatory approval procedure for biosimilar medicines in 2005, allowing the first biosimilar, Omnitrope, to be approved in 2006. A revised EU guideline went into effect in 2015, and the FDA produced the Biosimilars Action Plan in 2018 to encourage biosimilar development, approval, and commercialization in the United States. The BPCIA defined a process to help biosimilar and reference drug manufacturers resolve patent disputes. Analytical and clinical studies are all needed components of a 351(k)

application; however, the FDA may waive any of these requirements. Prior to the development of the 351(k) pathway, biosimilars or biosimilar-like medicines were approved via a few different methods. In other situations, a reference biologic was not available, so a 505(b) [2] approach, which is a hybrid of the abbreviated and new drug application processes, was used. Insulin (Baslagar®) and human growth hormone (Omnitrope®) are two examples of follow-on biologics that have been approved through this route. One of the BCPIA's main goals was to define interchangeability. If the biosimilar is deemed interchangeable, it will be mentioned in the Purple Book. When accessible, the Purple Book contains a list of all biologics, including biosimilars, as well as information on exclusivity and interchangeability. Several medical associations objected to a draft version of the interchangeability guidance released in 2017. In May of 2019, the final interchangeability guidelines for the industry was released. Other recent legislation has aided the development and approval of biosimilars on a nationwide scale. The biosimilar producer can sue the reference medication manufacturer under the recently approved CURES Act of 2018 if the latter refuses to give enough samples for the biosimilar developer to conduct necessary biosimilarity testing. While some federal effort in support of biosimilars has been ongoing, as detailed above, states have been working on biosimilar legislation at the same time. Currently, forty one states have implemented biosimilar legislation in various capacities. Four of the remaining nine states have laws in the works, while five have no plans to pass legislation in 2019. One concern is that the capacity for automatic substitution at the pharmacy level has been hampered due to a lack of interchangeability guidance at the federal level.[16]

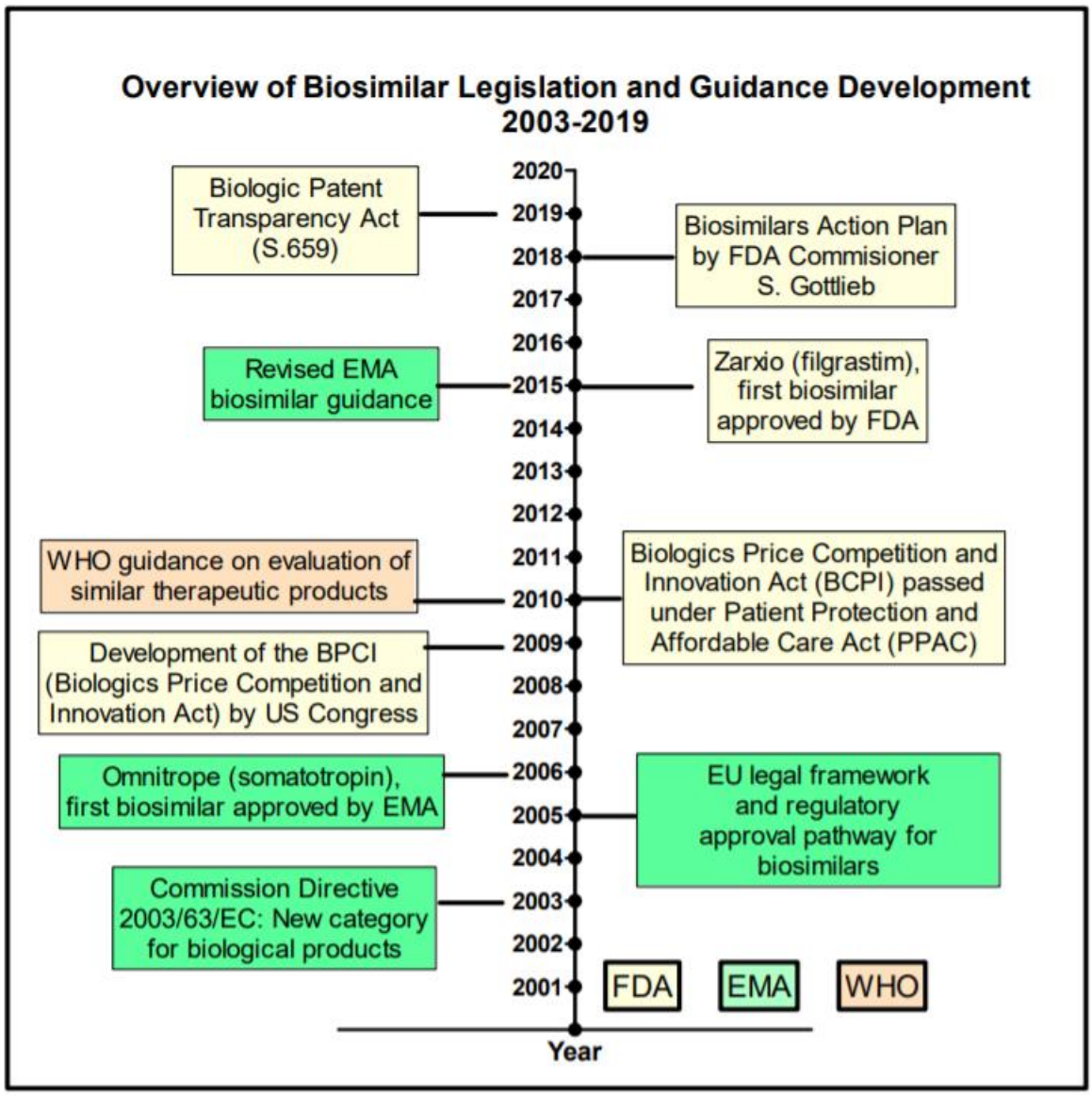
Overview of Biosimilar Legislation and Guidance Development 2003-2019
Biologic Patent Transparency Act (S.659)
Biosimilars Action Plan by FDA Commisioner S. Gottlieb
Revised EMA biosimilar guidance
Zarxio (filgrastim), first biosimilar approved by FDA
WHO guidance on evaluation of similar therapeutic products
Biologics Price Competition and Innovation Act (BCPI) passed under Patient Protection and Affordable Care Act (PPAC)
Development of the BPCI (Biologics Price Competition and Innovation Act) by US Congress
Omnitrope (somatotropin), first biosimilar approved by EMA
EU legal framework and regulatory approval pathway for biosimilars
Commission Directive 2003/63/EC: New category for biological products
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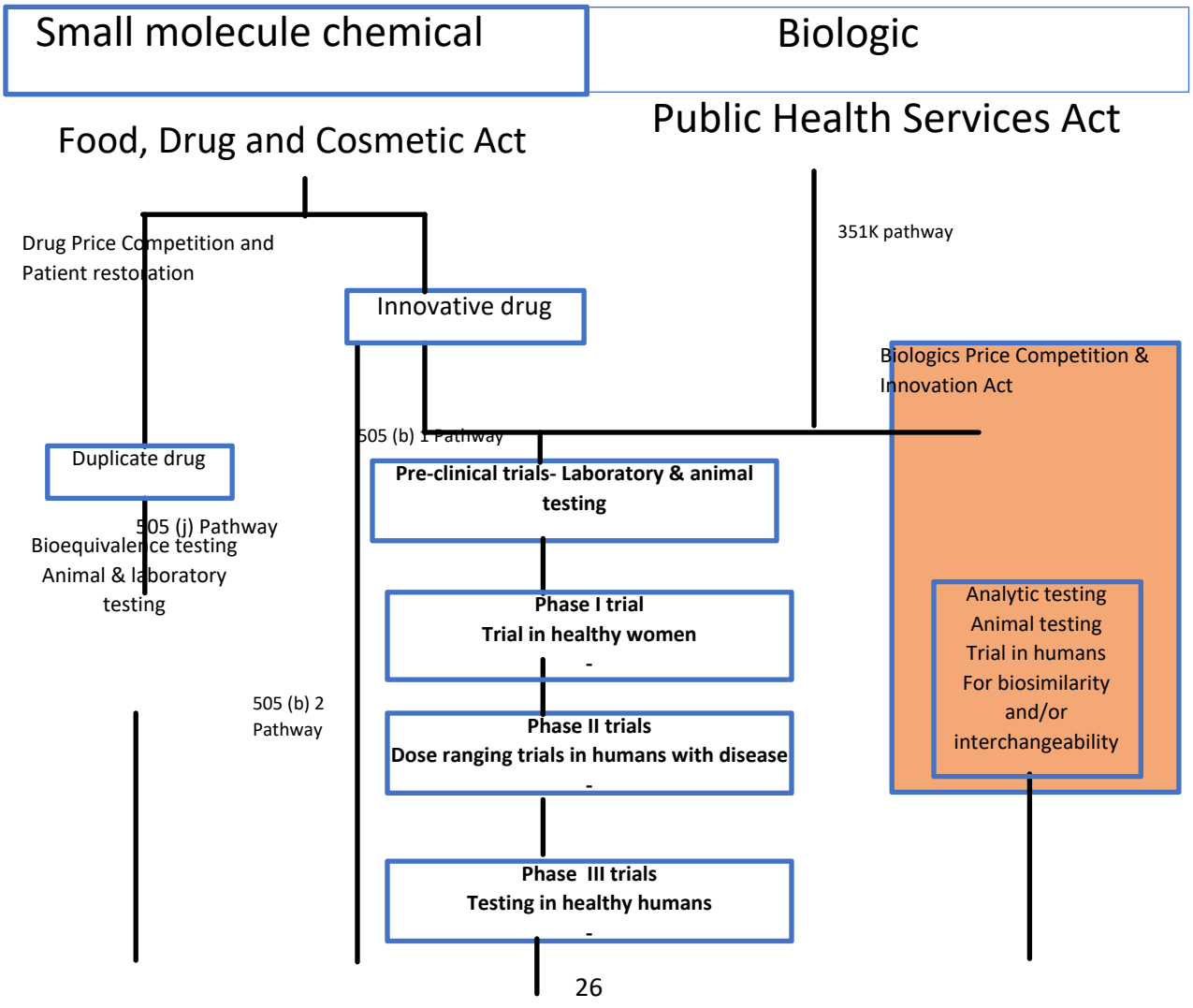
Figure 4.1- The chronology of biosimilars and guidelines by the WHO, FDA, and EMA

On March 23, 2010, **the Biologics Price Competition and Innovation Act of 2009 (BPCI Act)** was signed into law. The BPCI Law sets out the short licence pathway for biological products similar to or interchangeable with a reference product approved by the FDA.



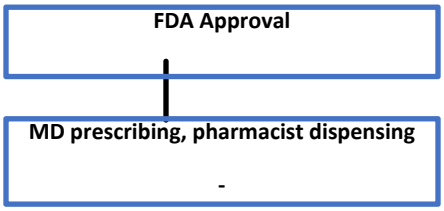


Figure 4.2- Food and Drug Administration (FDA) biosimilar approval pathway

Once an FDA-approved biosimilar or interchangeable product has been permitted, patients and health care providers will be able to rely on its safety and effectiveness in the same way that they would for the reference product to which the biosimilar was compared.[16]

The term **"biosimilar" or "biosimilarity**" refers to how closely a biological product resembles a reference product, notwithstanding minor changes in clinically inactive components; and In terms of product safety, purity, and potency, there are no clinically significant discrepancies between the biological product and the reference product.[17]

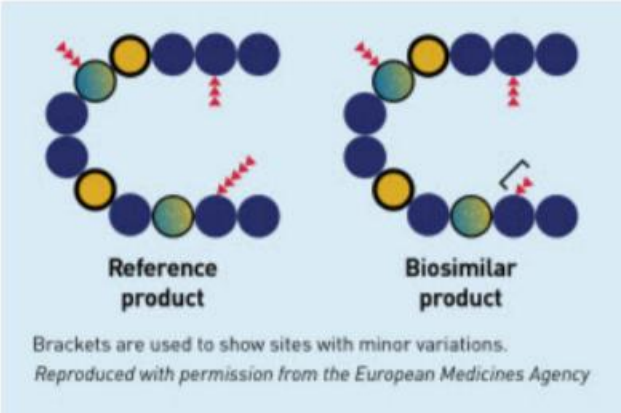


Figure 4.3- Reference product vs Biosimilar

A **reference product** is a single biological product licenced under section 351(a) of the PHS Act against which a biological product is evaluated in an application filed under section 351(k) of the PHS Act. A PHS Act section 351(a) application is a "stand-alone" application that must include all information and data necessary to demonstrate that the proposed product is safe, pure, and efficacious. A 351(k), on the other hand, must show that the proposed product is biosimilar to the reference product.[17]

Interchangeable or Interchangeability means that the biological product is biosimilar to the reference product, that it may yield the same clinical outcome as that of a reference patient in any patient; and that the risk of alternation or change of risk between the products and the reference product in safety and/or reduced efficacy for a product that is administered to an individual more than once is no greater than the risk of rising.

An interchangeable product may be substituted for it without the help of the health provider who prescribed the reference product.[17]

4.2- Market Scenario of Biosimilars in United States

The global biosimilars market was estimated at USD 28,235 million in 2020, and revenue of USD 103,638 million is predicted in 2026, representing a CAGR of 24.2 percent during the forecast period. The biosimilars market in the United States was worth US$ 436.1 million in 2018 and is expected to grow to US$ 17,696.0 million by 2026. During the projected period, the U.S. Biosimilars Market is expected to grow at a compound annual growth rate (CAGR) of 54.7 percent.

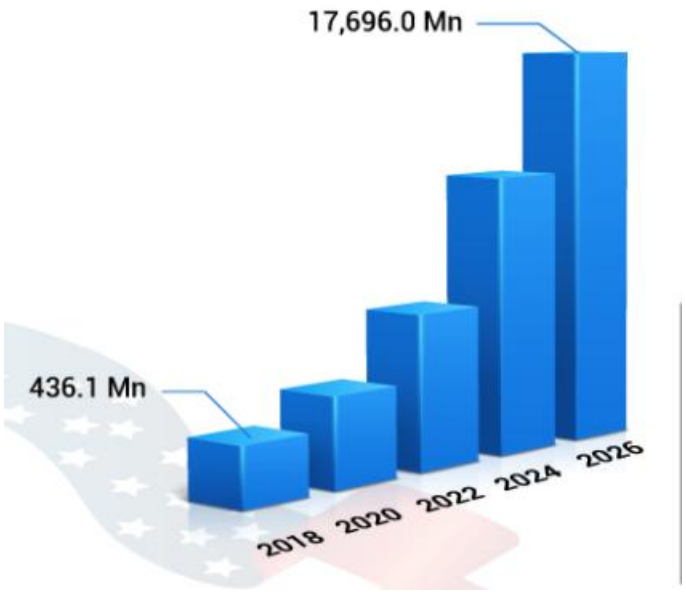


Fig 4.4- US Biosimilars Market (US$ Mn), 2018 to 2026
(Source: Medgadgets.com)

Five years after Sandoz' first biosimilar Zarxio was made available for prescription in the United States, the US biomarket can turn a turning point on the road to sustainability. Zarxio is the market leader in filgrastim. More than a quarter of Amgen's Neulasta business was biosimilar to pegfilgrastim. As per recent reports, the acceptance of trastuzumab and bevacizumab biosimilars is also increasing and satisfying. Even in a market where biosimilars haven't made enough progress (infliximab), the reference product's average sales price (ASP) has dropped by at least 20%. The key biosimilar companies operating in the US biosimilars market are Amgen, Mylan, Sandoz, Coherus Biosciences, Pfizer, Celltrion, Samsung Bioepsis, Boehringer Ingelheim Pharmaceuticals, and Hospira.[18]

Company	**Successful products based on >10% market share**
Amgen	Kanjinti
Coherus	Udenyca
Pfizer	Retacrit
Sandoz	Zarxio

Table 4.1- Biosimilar Manufacturers with Successful Brands in The U.S.

Kanjinti of Amgen Inc., Udenyca of Coheru Biosciences, Retacrit of Pfizer and Zarxio of Sandoz are the successful products which have more than 10% of market share in the US biosimilars market.

The first biosimilar approved by the US FDA was Zarxiso, by Sandoz Inc. on March 6, 2015, a biosimilar of filgrastim, having reference product Neupogen. The most recent biosimilar approval by US FDA was **Riabni** (rituximab-arrx) of Amgen Inc. on December 17, 2020. Riabni is the third biosimilar to Rituxan.[19]

The US Food and Drug Administration (FDA) has approved 29 biosimilars so far, as well as four follow-on biologics. The pipeline for biosimilars continues to grow, but only 20 of the 29 approved biosimilars have been launched so far. Biosimilars currently account for only 2.3 percent of the biologicals market in the United States. Despite the fact that the United States sells 60% of all biologicals, Europe accounts for 90% of worldwide biosimilars sales.[20]

The US FDA approved seven biosimilars in 2018, and another ten in 2019, bringing the total number of biosimilars approved to 26. Biosimilar approvals were predicted to decrease in 2020 due to the COVID-19 pandemic, but two biosimilars were approved before July 2020 and one biosimilar was approved in December 2020.

Fig 4.5-Biosimilars approved in the US, per year

When a biosimilar is approved in the United States, it does not become instantly available to patients, and only one biosimilar became available each year between 2015 and 2017. However, six biosimilars were accessible to the patients starting in 2019 and continuing through July 2020. Patients have access to 20 biosimilars as of June 2021. [21]

Figure 4.6- Biosimilars marketed in the US, per year

There are 9 reference products Herceptin, Humira, Remicade, Rituxan, Neulasta, Avastin, Enbrel, Neupogen and Epogen in 4 therapeutic areas- Oncology, Oncology supportive care/ Immunology, Inflammatory and Haematology for which biosimilars have been approved. [22]

FDA approval of biosimilars distribution by Figure 4.7- Reference product, and Figure 4.8- Therapeutic Area (up to date)

Table 4.2- List of all the biosimilars, their reference product, their company, FDA approval date and Commercial launch dates have been given below-

S. No.	Biosimilar	Reference Product	Company	FDA Approval	Commercial Launch Date
29	Riabni (rituximab)	Rituxan	Amgen Inc.	December 17, 2020	January 2021
28	Hulio (adalimumab)	Humira	Mylan Pharmaceuticals Inc.	July 6, 2020	No earlier than July 31, 2023 per settlement
27	Nyvepria (pegfilgrastim)	Neulasta	Pfizer Inc.	June 10, 2020	
26	Avsola (infliximab)	Remicade	Amgen Inc.	December 6, 2019	July 2020
25	Abrilada (adalimumab)	Humira	Pfizer Inc.	November 15, 2019	No earlier than November 20, 2023 per settlement
24	Zeixtenso (pegfilgrastim)	Neulasta	Sandoz Inc.	November 4, 2019	November 15, 2019
23	Hadlima (adalimumab)	Humira	Samsung Bioepis Co., Ltd.	July 23, 2019	No earlier than June 30, 2023 per settlement
22	Ruxience (rituximab)	Rituxan	Pfizer Inc.	July 23, 2019	January 23, 2020

21	Zirabev (bevacizumab)	Avastin	Pfizer Inc.	June 27, 2019	December 31, 2019
20	Kanjinti (trastuzumab)	Herceptin	Amgen Inc.	June 13, 2019	July 18, 2019
19	Eticovo (etanercept)	Enbrel	Samsung Bioepis Co., Ltd.	April 25, 2019	-
18	Trazimera (trastuzumab)	Herceptin	Pfizer Inc.	March 11, 2019	February 15, 2020
17	Ontruzant (trastuzumab)	Herceptin	Samsung Bioepis Co., Ltd.	January 18, 2019	April 15, 2020
16	Herzuma (trastuzumab)	Herceptin	Celltrion, Inc.	December 14, 2018	March 16, 2020
15	Truxima (rituximab)	Rituxan	Celltrion, Inc.	November 28, 2018	November 11, 2019
14	Udenyca (pegfilgrastim)	Neulasta	Coherus BioSciences, Inc.	November 2, 2018	January 3, 2019
13	Hyrimoz (adalimumab)	Humira	Sandoz Inc.	October 30, 2018	No earlier than September 30, 2023 per settlement
12	Nivestym (filgrastim)	Neupogen	Pfizer Inc.	July 20, 2018	October 1, 2018
11	Fulphila (pegfilgrastim)	Neulasta	Mylan N.V.	June 4, 2018	July 26, 2018
10	Retacrit (epoetin alfa)	Epogen/ Procrit	Hospira Inc.	May 15, 2018	November 12, 2018
9	Ixifi (infliximab)	Remicade	Pfizer Inc.	December 13, 2017	No U.S. launch intended
8	Ogivri (trastuzumab)	Herceptin	Mylan GmbH	December 1, 2017	December 2, 2019
7	Mvasi (bevacizumab)	Avastin	Amgen Inc.	September 14, 2017	July 18, 2019
6	Cyltezo (adalimumab)	Humira	Boehringer Ingelheim Pharmaceuticals, Inc.	August 25, 2017	No earlier than July 1, 2023 per settlement
5	Renflexis (infliximab)	Remicade	Samsung Bioepis Co., Ltd.	April 21, 2017	July 2017
4	Amjevita (adalimumab)	Humira	Amgen Inc.	September 23, 2016	No earlier than January 31, 2023 per settlement

3	Erelzi (etanercept)	Enbrel	Sandoz Inc.	August 30, 2016	-
2	Inflectra (infliximab)	Remicade	Celltrion, Inc.	April 5, 2016	November 2016
1	Zarxiso (filgrastim)	Neupogen	Sandoz Inc.	March 6, 2015	September 2015

Analysis

Anti-competitive activity and other market and regulatory dynamics that now impede market uptake of biosimilars in the US could be reasons for the delays in launching biosimilars and the sluggish biosimilars market in the US. Other difficulties include payment practices that hinder the use of biosimilars and a lack of provider understanding of the efficacy, safety, and interchangeability of biosimilars. Despite these shortcomings, The biosimilars industry in the United States is well established and growing across a wide range of therapeutic areas. The FDA authorised seven biosimilars in 2018, making the number of biosimilars approved to 16. The FDA authorised ten biosimilars in 2019, changing the total number of biosimilars approved in the United States to 26. From 2015 to 2020, the number of biosimilars approved each year is shown in Figure 1. The continually rising number demonstrates the growing potency of biosimilars in the United States. The FDA has approved three biosimilars as of December 2020. The COVID-19 pandemic, which resulted in the shutdown of numerous businesses, is likely to have slowed biosimilar approvals. Furthermore, patients will have access to more biosimilars in the near future. Only three biosimilars were available at the end of 2018. However, six became available in 2019, followed by another seven in 2020. In comparison to previous years, Figure 2 depicts the huge growth in available biosimilars in 2019 and 2020. One more biosimilar, Riabni, which was launched in December 2020, is accessible on the market as of June 2021. The regulatory climate in the United States is changing to encourage the adoption of biosimilars.

Biosimilars price in United States

Biosimilars lower prices by offering considerable wholesale acquisition cost (WAC) and average sales price (ASP) savings at launch, as well as through cost competition, which leads to further savings over time. Manufacturers introduce biosimilars at a WAC price that is generally 15% to

37% cheaper than the WAC of the reference drug, as shown in Figure 5, and almost all biosimilar manufacturers launch at a WAC price that is 3% to 24% lower than the reference drug ASP. The ASP of reference products is beginning to decline due to competition from biosimilars. Biosimilar ASPs are also on the decline. The ASP for the infliximab reference product (Remicade), for example, has decreased by over 30%, while the ASPs for the biosimilars, Inflectra and Renflexis, have decreased by roughly 40%. The rate of adoption of biosimilars is growing over time. After 5 years, Neupogen (filgrastim) biosimilars account for over 75% of the market.

Figure 4.9-Comparison of WAC and ASP of Biosimilars and Reference products (Source: Amgen Biosimilars 2020 report)

Growth in Biosimilar uptake since launch

As seen in Figure 4.10, Over time, the acceptance rate of biosimilars generally increases. They have gained a large market share in most therapeutic fields in which biosimilars are introduced. Typically, biosimilar market shares ran from twenty percent to twenty five percent during the first year. After 5 years, NEUPOGEN biosimilars account for over 75% of the market. 29 Furthermore, when compared to later entrants, first-to-market biosimilars tend to grab a larger share of the market.

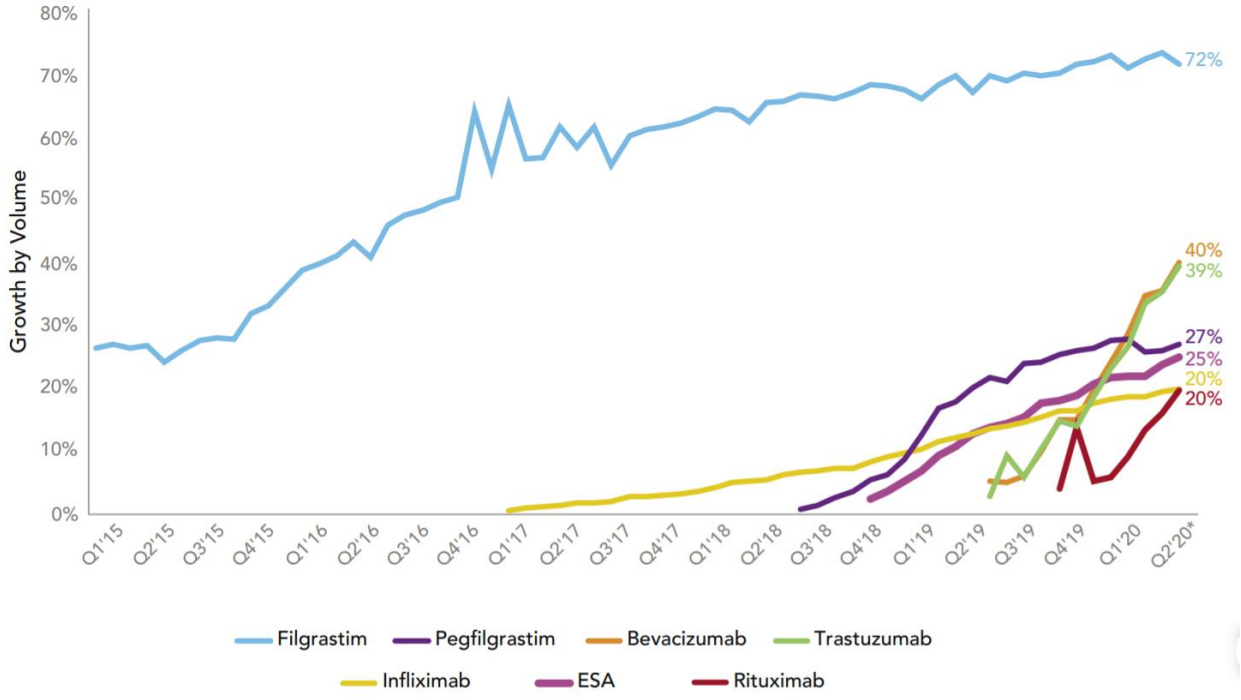


Figure 4.10- Biosimilars growth uptake curve in the US

Filgrastim, as shown in the above curve, has gained 72% growth by volume in the second quarter of 2020 when calculated since its launch in 2015.Similarly, bevacizumab and trastuzumab have grown in volume to 40% and 39% respectively since their launch in 2019.

Oncology biosimilars

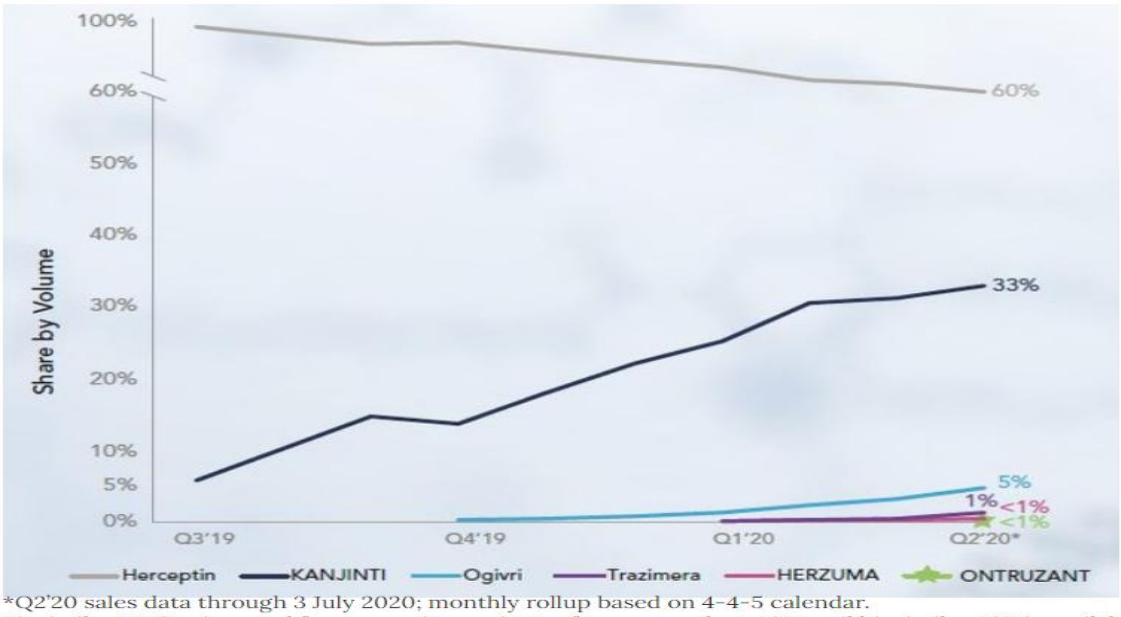
Trastuzumab, bevacizumab, and rituximab are the biosimilars available for oncology therapies in the United States. Biosimilars for oncology therapies have shown significant growth since their launch in the biosimilar market. Biosimilars of trastuzumab and bevacizumab, for example, contribute for a minimum of forty percent of total revenues. Although rituximab biosimilars are relatively young, they nevertheless account for 20% of sales by volume.[23]

Trastuzumab biosimilars

As of 2021, five trastuzumab biosimilars have been approved in the US for HER2-positive breast cancer: Ogivri, Herzuma, Ontruzant, Trazimera, and Kanjinti, and all five are on the market. As of 2018, only two biosimilars Ontruzant and Herzuma were launched in this class. The delay in the launch of approved trastuzumab biosimilars cost the industry an estimated $140 million in 2018.[24]

Trastuzumab's originator is Herceptin. Herceptin now has five competitors, all of which have WAC and ASP than it. [24]

Figure 4.11- Comparison Wholesale acquisition cost and average sales price of trastuzumab biosimilars to Herceptin
(Source: Analysource)

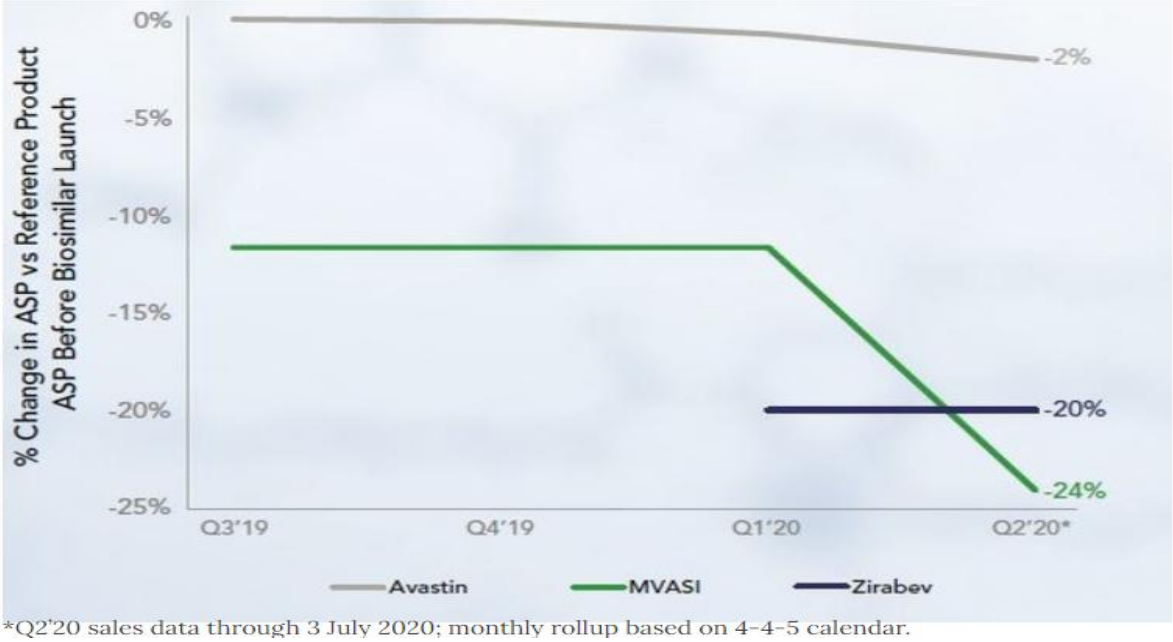


*Q2'20 sales data through 3 July 2020; monthly rollup based on 4-4-5 calendar.
Biosimilar WAC price used for comparing against reference product ASP until biosimilar ASP is available.
ASP: average sales price; WAC: wholesale acquisition cost.
Source: Analysource.

Figure 4.12- ASP of trastuzumab products at biosimilars launches

Bevacizumab biosimilars

Avastin is the reference product for all the bevacizumab biosimilars. This product now has two competitors with lower WAC and ASP than Avastin. Zirabev, the second biosimilar to hit the market, has a lower ASP than Mvasi, the first. Mvasi's ASP is currently lower than Zirabev's, and both remain lower than Avastin's, despite the fact that Avastin's ASP has fallen by 2% since biosimilar market introduction. Mvasi and Zirabev were approved in September 2017 and June 2019, respectively, in the United States. Bevacizumab biosimilars have seen rapid uptake, with Mvasi taking 38 percent of the market in just nine months.



*Q2'20 sales data through 3 July 2020; monthly rollup based on 4-4-5 calendar.

Figure 4.13-Change in ASP vs Reference product ASP before bevacizumab biosimilar launch

At the time of Mvasi's launch in July 2019, its WAC price was 15% less ($677) than the WAC price of Avastin ($797) while its ASP was less than 12% ($677) than the ASP of Avastin ($767).

The WAC price of Zirabev which was launched in January 2020 was even lower than the WAC price at which Mvasi was launched. It was 23% less than the WAC price of Avastin and its ASP was 19% less than the ASP of Avastin in Jaunary 2020. (Figure 4.13)

Fig 4.14- Bevacizumab Biosimilars WAQ and ASP in comparison to Reference Product at Launch

(Source: Analysource)

Rituximab biosimilar

Rituxan is the company that created Rituximab. There are now two competitors to Rituxan that were launched with lower WAC and ASP. Ruxience, the second biosimilar to hit the market, had a lower ASP than Truxima. As shown in Figure, the use of rituxumab biosimilars has been limited thus far. Within the first couple of quarters, Truxima had a 17 percent market share, whereas Ruxience had a 3 percent market share. With Rituxan competition still in its early stages, it's unclear whether the future will go on a different path. In the United States, Ruxience and Truxima were approved in July 2019 and November 2018, respectively. Riabni is the third biosimilar of Rituxan launched in January 2021.

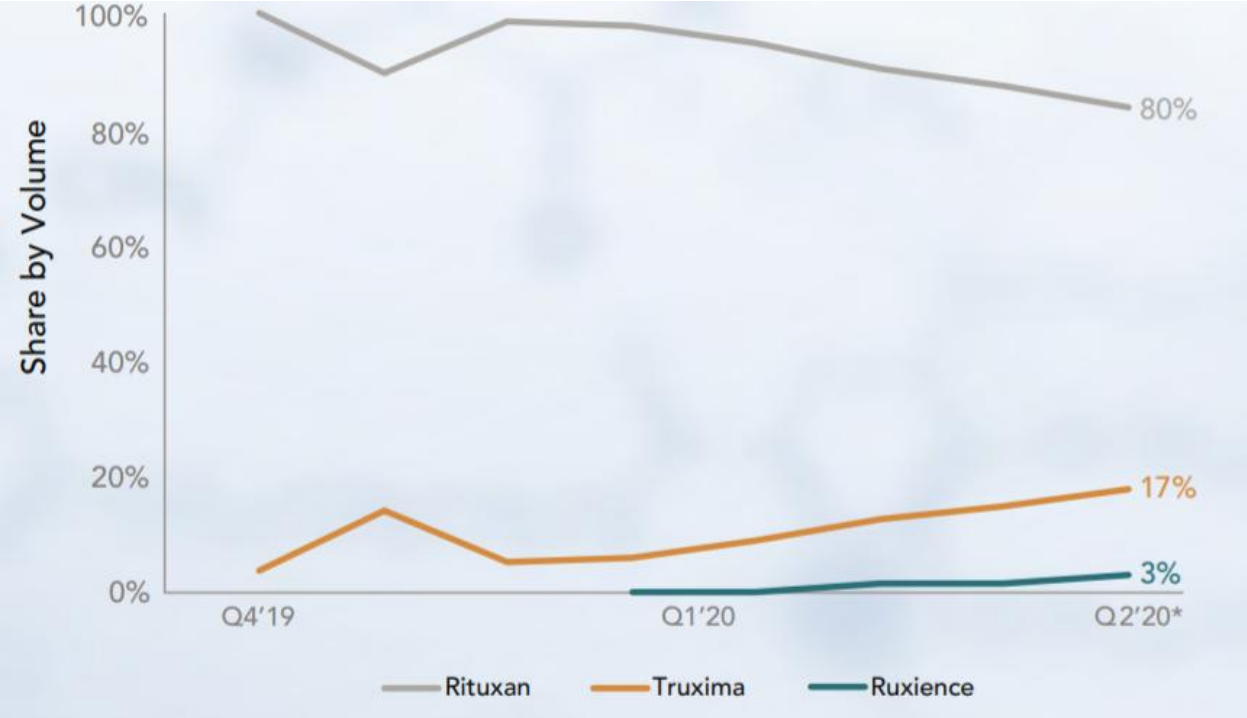


Fig 4.15- Biosimilar Uptake Curve for Rituximab Products
(Source: IQVIA)

Supportive Care biosimilars in Oncology

Pegfilgrastim, filgrastim, and **epoetin alfa** are the biosimilars available for oncology supportive treatment. The most developed biosimilar category in the United States is oncology supportive care. Granix was authorised by the FDA in 2012, but not through the BPCIA-created procedure.

Pegfilgrastim biosimilars

Since 2018, three pegfilgrastim biosimilars have entered the market to compete with Neulasta (pegfilgrastim). All three biosimilars were released at WAC with ASP discounts compared to the reference product. Udenyca, the second biosimilar, was released around the same time as Fulphila,. Ziextenzo was released with a WAC that was 37% lower than the reference product's

and at a lower price than the first two biosimilars. Udenyca and Ziextenzo, on the other hand, both launched at a premium to Fulphila's ASP. Pegfilgrastim biosimilars, on the other hand, have a distinct uptake pattern than other biosimilars, with the first biosimilar to debut capturing the majority of the market share. Udenyca (21 percent share) is the leading pegfilgrastim biosimilar by market share. It was the second pegfilgrastim biosimilar to emerge. Fulphila, the first pegfilgrastim biosimilar to hit the market, has a 6% share. Ziextenzo, the newest pegfilgrastim biosimilar, has achieved 1% market share since its debut in late 2019.Neulasta, Fulphila, and Udenyca ASPs have all decreased with time. By volume, biosimilars now account for roughly 30% of all sales.

Filgrastim biosimilars

Since 2015, two filgrastim biosimilars have been approved and introduced to compete with the reference drug Neupogen, including Granix in 2013. (filgrastim). Granix was authorised under the terms of a Biologics License Application. Nivestym was launched at a discounted WAC to Zarxio. Both filgrastim biosimilars' ASPs had dropped significantly by the first quarter of 2020, whereas Neupogen's ASP had stayed reasonably stable.[25]

Growth Uptake Curves for Pegfilgrastim and Filgrastim biosimilars have been shown below-

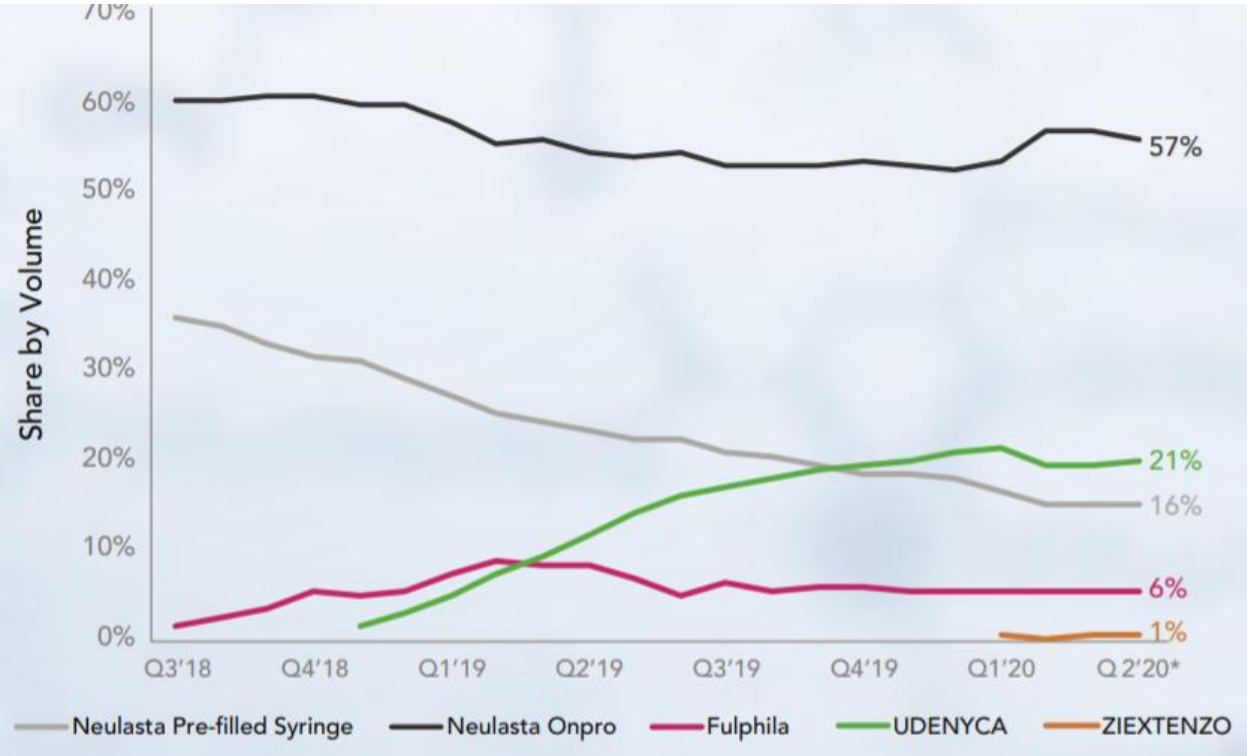


Figure 4.16- Biosimilar Uptake Curve for Pegfilgrastim Products

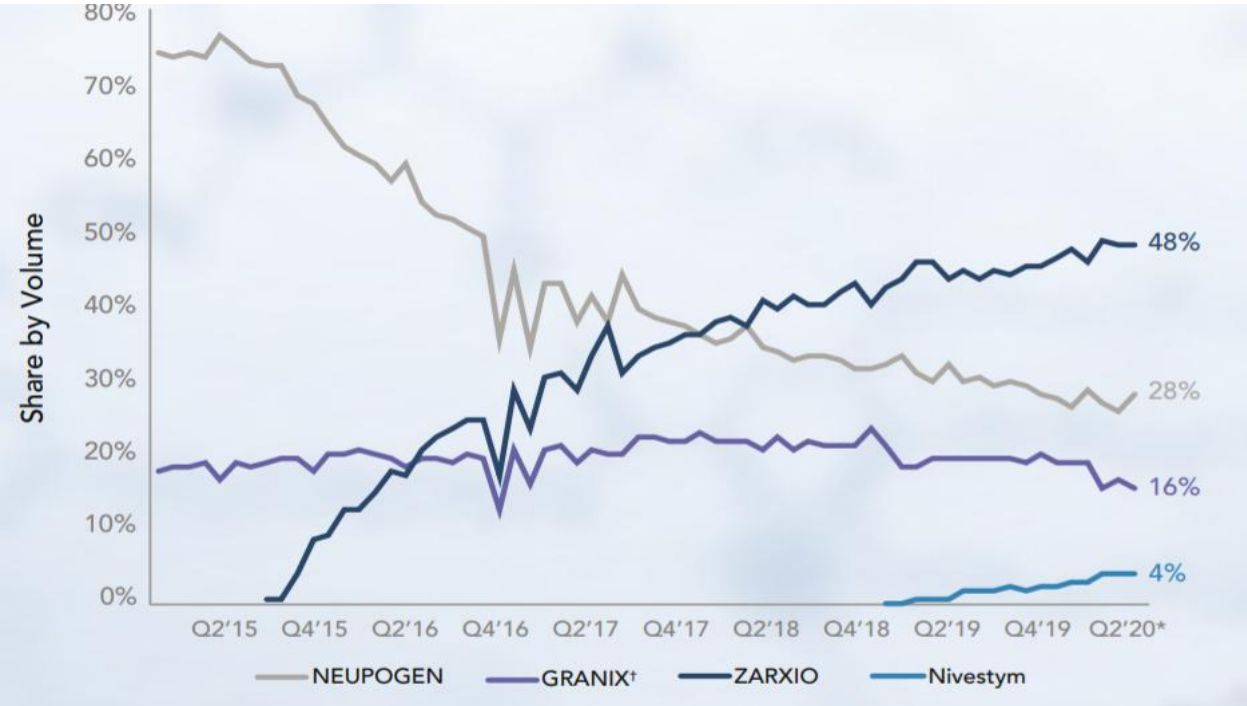


Figure 4.17 Biosimilar Uptake Curve for Filgrastim Products

Nephrology/ Oncology supportive care

Epoetin alfa is a drug used for supportive care. It is not a cancer treatment. Epoetin alfa is a drug that is used to treat anaemia caused by chemotherapy.[26]

Since 2018, Retacrit, a biosimilar of epoetin alfa, has been available to compete with the reference drugs Epogen and Procrit (epoetin alfa). Despite the fact that Epogen and Procrit are the same molecule, they are sold by two separate businesses in 2 distinct therapeutic applications. Furthermore, they have separate WACs but the same ASP. In comparison to the reference products Epogen and Procrit, Retacrit was released with WAC and ASP discounts. By second quarter of 2020, Retacrit's average selling price had dropped substantially since its ASP was established in April 2019. Following the advent of Retacrit, Epogen and Procrit have been steadily declining. Within 18 months of debut, Retacrit has a 25% market share, whereas Epogen's share has stayed reasonably consistent at roughly 60%.[25]

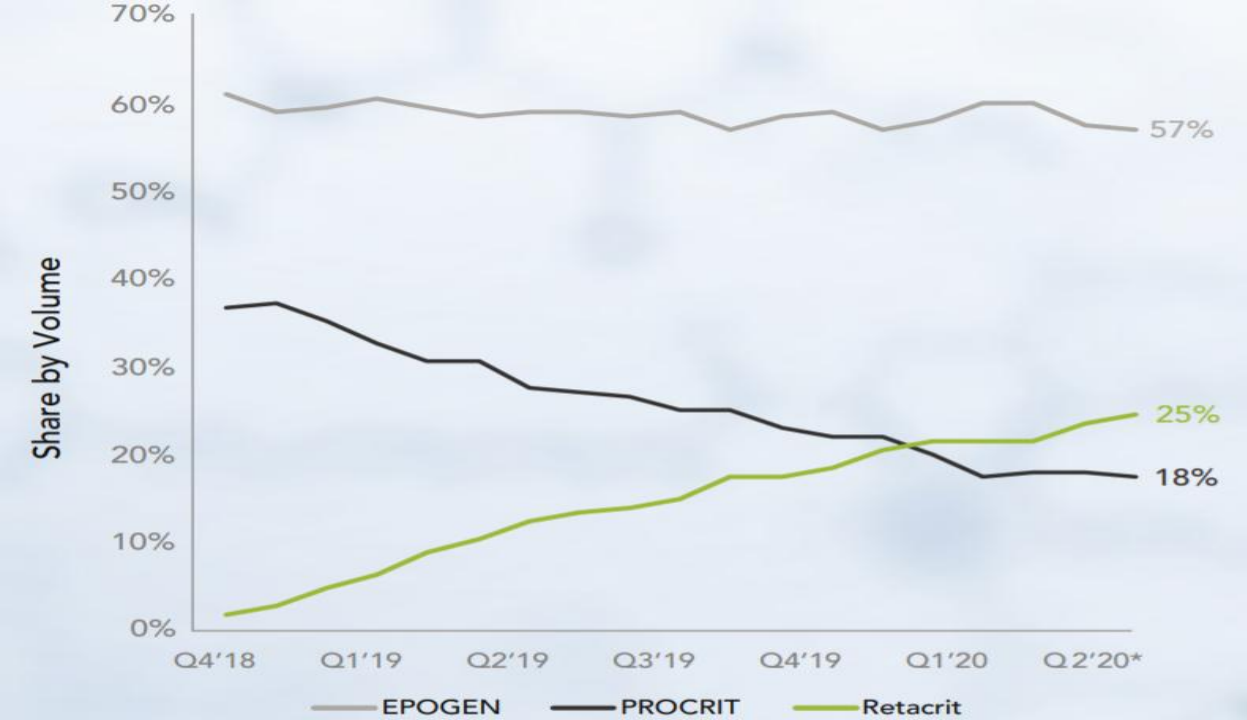


Figure 4.18-Biosimilar Uptake Curve for Epoetin Alfa Products
(Source: IQVIA)

Inflammatory biosimilars

Inflammatory biosimilars include **Infliximab, adalimumab and etanercept.** These are used for managing conditions such as Crohn's disease, ankylosing spondylitis, etc.

Infliximab biosimilars

Anti-inflammatories account for 3 of the main six top-selling biologics, which could contribute to huge cost savings for biosimilars in this class. Avsola, a biosimilar of infliximab, was approved by the FDA in December 2019 and was available commercially in July 2020. Inflectra, Renflexis, and Avsola are three infliximab biosimilars that released in 2016, 2017, and 2020 to compete with the reference medicine Remicade (infliximab). Ixifi is another infliximab biosimilar that has been approved by the US FDA, however there are no plans to launch it in the US market at this time. All infliximab biosimilars were released with a WAC discount compared to the reference product. Almost all biosimilars in the United States have launched at a discount to the reference product's ASP; however, Inflectra and Avsola have launched at a premium to Remicade's ASP. Renflexis, the second biosimilar, debuted at a WAC discount to the first

biosimilar, Inflectra, and offered WAC and ASP savings over the reference drug. After the advent of Renflexis, the second infliximab biosimilar, the ASPs for Remicade, Inflectra, and Renflexis plummeted practically every quarter. Inflectra and RENFLEXIS both had a 10% market share by early 2020, after a difficult start, while REMICADE, the reference product, had an eighty percent market share..[25]

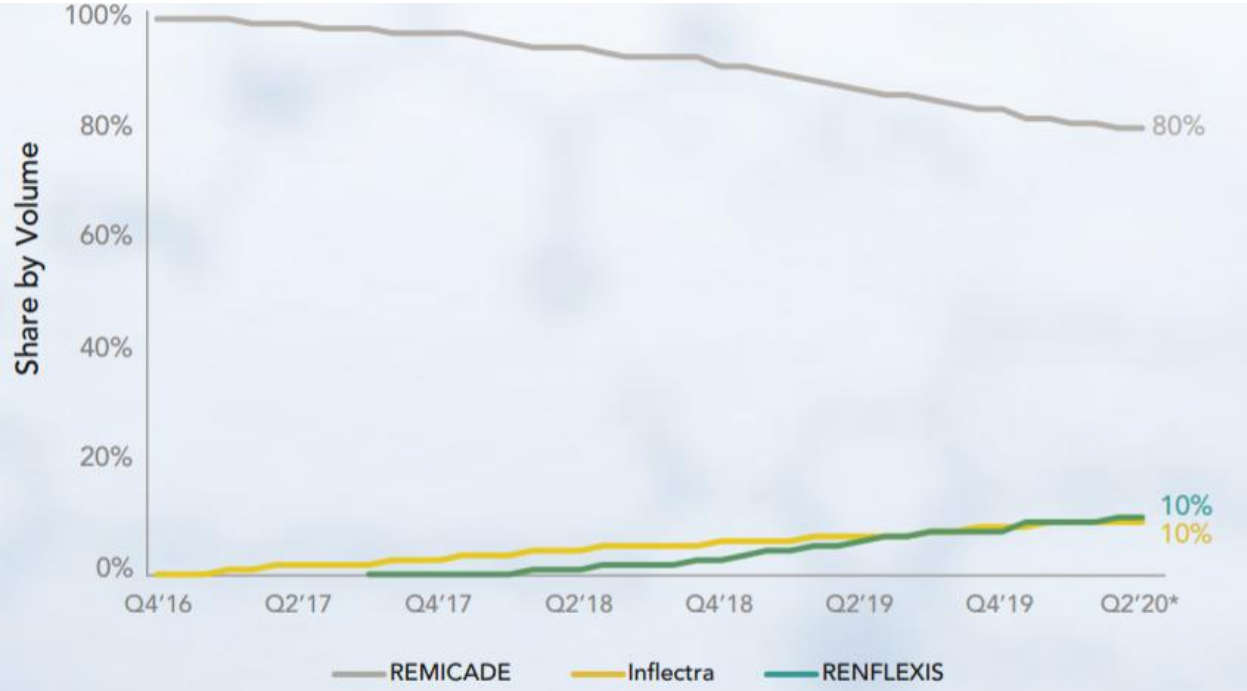


Figure 4.19-Biosimilar Uptake Curve for Infliximab Products

The other two inflammatory biosimilars adalimumab and etanercept are approved by the US FDA but haven't been available or launched in the US market for patients. However, none of the adalimumab biosimilars are yet on the market in the United States, as each biosimilar applicant has signed a license agreement with AbbVie that allows them to begin marketing in the United States only until after a specific date in 2023.[27]

4.3- Challenges in the adoption of biosimilars in US

By providing a less expensive version of biologics and have been shown to be effective therapy alternatives for patients with chronic illnesses, biosimilar adoption opens doors for manufactures and expands options for payers, clinicians, and patients. Biosimilars, according to experts, are a possible solution to rising prescription costs as long as the industry encourages competition. According to recent research, biologics could save $54 billion in direct biologic medication costs between 2017 and 2026. This amounts to around 3% of total expected biologic spending for the same time period, with a range of between $24 and $150 billion. However, biosimilars are hampered by issues like as manufacturing methods, interchangeability, and nomenclature, which hinder them from doing what they were supposed to do: cut costs while benefiting patients. Although biosimilar medications can be a less expensive alternative to brand-name medications or biologics, they come with a number of challenges-

1. Approximately 50% or more of the data contained in biosimilar agents approval applications concern manufacturing processes. But biosimilar medicines do not mandate clinical trials to be conducted, which can create uncertainty regarding the integration of biosimilar drugs in evidence-based clinical practice guidelines.
2. There are mainly 2 sources of competition for biosimilars: branded companies' bio betters and consumer brand awareness. Biosimilars are expected to compete largely with their

reference medicines on a "brand-on-brand" basis. In addition, unlike generics, which have substantial reductions, biosimilar savings might be negated by rebates and service agreements for branded biologics, making biosimilars less appealing. [28]

3. Interchangeability is another important challenge for biosimilars in the future. An "interchangeable" drug produces the same clinical results and does not have a greater concern for safety than the reference drug. Without having to consult the prescriber, pharmacist can replace an interchangeable biosimilar with a reference product. Interchangeability is risky as it poses a threat to patients' safety and because different countries have different biosimilar rules. However, no biosimilar in the USA has currently been approved as interchangeable, but in the future, it will be a challenge for biosimilars to the reference products' markets.
4. Nomenclature for biosimilars has also been problematic. The FDA has issued recommendations on how it would handle biologics and biosimilars with nonproprietary names. All biologics, both reference products and biosimilars, will have the same core drug substance name, according to the guidelines. [29]

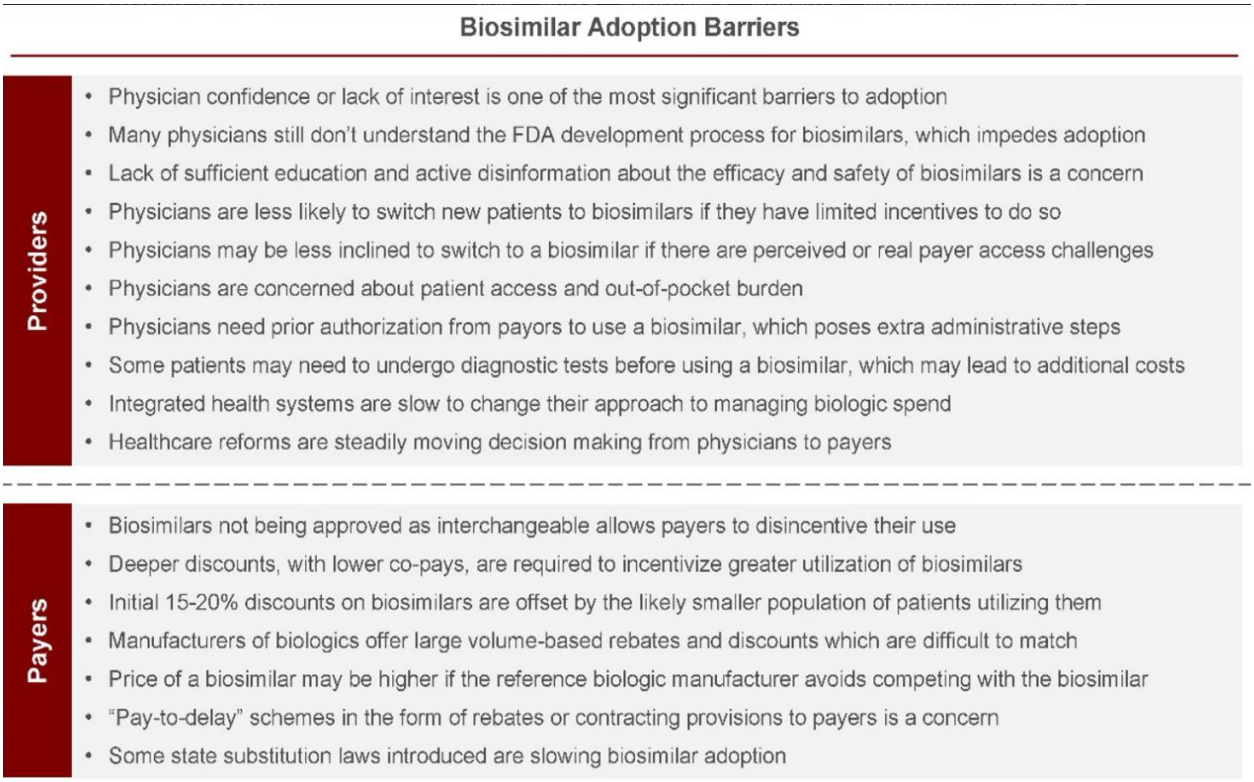


Figure 4.20- Biosimilars adoption barriers

Also, patent disputes and restricted deals that favour innovator products are impeding the emergence of biosimilars.[30] The latter, according to Okon, is the because of pharmacy benefit managers and payers. There are various misconceptions about biosimilars. These are some of them:

- Patients refuse to take them
- Physicians are unaware of them
- Doctors won't prescribe them because they're not as effective as the originals
- Biosimilar naming suffixes and CMS coding are suffocating growth
- Biologics are "natural monopolies" that prevent biosimilars from entering the market

Example- Challenges for the adoption of trastuzumab biosimilars in oncology- Patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer now have more alternatives because of oncology biologics, which are one of the fastest-growing categories of pharmaceutical development. This patient population is being impacted by the introduction of many oncology biosimilars, with five trastuzumab biosimilars approved by the FDA as of the end of 2019; however, only two have been commercially marketed. But in the United States, barriers to adoption of therapeutic oncology biosimilars include a lack of targeted education for physicians and patients, lingering worries about efficacy and safety, and practices such as "pay-for-delay." Multiple challenges, primarily related to cost of care, limit the acceptance of oncology biosimilars, including drug pricing, patient access, formulary inclusion, and treatment management algorithms.[31]

4.4- Opportunities for biosimilars in US

Biosimilars are widely used in the prevent and treat a variety of chronic diseases, including diabetes, cancers, cardiovascular disease (CVD), autoimmune diseases, kidney failure, haematological diseases, and infectious diseases. Another key reason that is expected to fuel the market for biosimilars is the growing geriatric population. Furthermore, they are increasingly being preferred over traditional biologics, owing to their lower prices as compared to their parent biological medications. Biosimilars are increasingly being promoted by government and private organizations as an alternative to traditional biologics and synthetic medicinal products. This will continue to be a primary driver of the biosimilars business. The market for biosimilars will be aided by the high price of existing biological medications and the constantly expanding pharmaceutical industry. Patients will continue to be the main beneficiaries of discounted biosimilar prices, which will have a significant impact on overall biosimilar sales. Innovator price reductions with significant discounts are a recent and ongoing trend among manufacturers in growing biosimilar markets. This will continue to be a common trend throughout the forecast period, propelling the worldwide biosimilars market forward. Moreover, biosimilar manufacturers are likely to experiment with different production volumes or scales. The potential profitability of producing numerous biosimilar drugs in the same facility could be a positive growth opportunity for biosimilar manufacturing companies. A lot of major manufacturers are concentrating on strategic partnerships. Furthermore, a growing number of companies are outsourcing the production of biosimilar products. Both of these factors will benefit the market in the next years. [32]

Biosimilars are increasingly being chosen by private and public insurers as preferred items for their plans above their reference counterparts. In 2019, United Healthcare, for example, identified two biosimilars as preferred products for commercial and community health plans. Between 2019 and 2020, Congress will consider measures to improve physician reimbursement for biosimilars in and to create a "shared savings" model to encourage physicians to transition patients to biosimilars. Biosimilars have bipartisan support, and the new Biden administration is expected to continue this trend. The promotion of generic and biosimilar competition, which has been a primary FDA objective in recent years, will surely remain a top concern for the

new administration, according to Pharma Letter. Sandoz, a Novartis division and a global leader in generic pharmaceuticals and biosimilars, will continue to fulfil its commitment of being a pioneer for new medicines in this rapidly growing industry, ensuring that more patients and health-care systems have access to low-cost therapies. With more than 15 molecules in various stages of development, the business already has a strong biosimilars pipeline.

Biosimilars have the ability to save United States' health system $100 billion. Biosimilar drugs' cost savings can be used to treat more patients, and they have the potential to save the US healthcare system up to $100 billion over the next five years (2020-2024). These savings can then be re-invested in healthcare systems, with direct benefits to patients in the form of enhanced access and treatment. [33]

4.5- Differences in the US and Europe biosimilars market

Biosimilar adoption in the United States has lagged behind when compared to Europe, which has led the way in biosimilar approvals and use since 2006. Much of the disparity in biosimilar adoption can be attributed to basic differences in regulatory processes and market dynamics between the US and the EU.[34]

Biosimilars are typically marketed in Europe soon after approval and shortly after the originator biologicals' patents expire. However, in the United States, this is not always the case, with launch dates sometimes occurring years after FDA clearance. Biosimilars of the adalimumab biological Humira are one clear example of an original company delaying the launch of biosimilars in the United States. AbbVie filed patent lawsuits against a slew of biosimilars manufacturers, finally reaching deals with them to postpone the sale of adalimumab biosimilars until at least June 2023.[35]

President Barack Obama signed the Biologics Price Competition and Innovation Act of 2009 (BPCI Act) into law on March 23, 2010. However, the United States has been slow to adopt biosimilars since then. A regulatory framework for biosimilar approval was developed in the European Union (EU) in 2003, and biosimilars have been licensed by the European Medicines Agency (EMA) since 2006. In Europe, 69 biosimilars have been approved, with practically all of them going on the market right once.

In comparison, the US Food and Drug Administration (FDA) had only approved 29 biosimilars as of January 2021, with only 18 having been released in the country thus far.

But why is there such a disparity between the United States and Europe, and why are so many biosimilars still unavailable in the country? Market disparities could be one of the reasons. In three respects, Europe differs from the United States:

Difference in approval/ Market maturity

Europe was the first in the world to establish a regulatory mechanism for biosimilars to access the market and compete with reference biologics fifteen years ago. Omnitrope (somatropin), the first EU biosimilar, was approved by the European Medicines Agency (EMA) in 2006. The Biologics Price Competition and Innovation Act (BPCIA), which was included in the Affordable Care Act of 2010, established a biosimilars pathway in the United States. Zarxio, whose reference biologic is Neupogen, was approved by the US Food and Drug Administration (FDA) in 2015. (filgrastim).

Number of competitors

Almost universally, the EU has approved more biosimilars than the US for each reference biologic. Neupogen (filgrastim) and Neulasta (pegfilgrastim), for example, each have seven biosimilars approved in the EU, compared to two and three biosimilars approved (and marketed) in the US, respectively. Only Herceptin (trastuzumab) has as many approved biosimilars in the US (five) as it has in the EU. However, biosimilars certified by the European Medicines Agency (EMA) are not always available in every EU nation, and the FDA currently has more than 30 biosimilar applications under consideration (FDA, 2019b), compared to 14 at the EMA (GaBI, 2020b).

Biosimilar market share

The most successful US biosimilar to date (Zarxio) has captured over 55% of the filgrastim market in the United States (Hagen, 2020). Biosimilars, on the other hand, have had a slow acceptance in the United States. According to a new review of the largest US commercial health plans' biosimilar coverage decisions, only 14% of those decisions granted biosimilars preferential coverage (Chambers et al., 2020). While Europe is typically credited with considerably higher biosimilar uptake – up to 100% in some situations - the continent's dominance in this sector is frequently exaggerated. While some European nations have a large biosimilar market share in particular therapeutic areas, biosimilar adoption varies widely across

Europe and by product class. In 2018, 16 European nations used more than 90% of filgrastim and pegfilgrastim biosimilars, but just 27% of filgrastim and pegfilgrastim biosimilars were used in Ireland (IQVIA, 2019b). Norway and Denmark had the highest adoption of anti-tumor necrosis factor biosimilars (adalimumab, etanercept, and infliximab), with 81 percent and 96 percent, respectively, whereas every other country had less than 50 percent (IQVIA, 2019b)

In short, despite its longer presence, the European biosimilars industry is not much different from the US market. However, there are many lessons that the United States can learn from Europe's experience, both cautionary and beneficial.[36]

4.6- Impact of COVID-19 on the uptake of biosimilars

The COVID-19 pandemic has posed significant hurdles for the pharmaceutical industry, particularly biosimilar makers. The FDA has responded by requiring pharmaceutical companies to rigorously check their supply chains. Despite worries about COVID-19, including regulatory delays, the biosimilar industry may experience good market growth. For example, Samsung Bioepis received FDA clearance in 2020 for Ontruzant, a 420 mg multi-dose vial Herceptin biosimilar that not only matches the originator's dosage options but is also more cost-effective. This drug was approved by the FDA in 2019 as a 150mg single dose vial. Merck will market both, and Ontruzant will eventually join the other trastuzumab biosimilars on the market in the United States. The COVID-19 pandemic, however, has had an impact on supply and demand, making it difficult for manufacturers to predict. On the supply side, worldwide lockdowns have disrupted supply chain procedures in hubs such as China, India, and the United States. For example, the FDA reported the first case of a drug shortage caused by COVID-19 in February 2020. Despite the fact that all manufacturers have been attempting to reduce the chance of supply shortages, businesses who rely on facilities in Europe and Asia may be the most vulnerable in terms of supply. . For instance, Pfizer/Celltrion biosimilar product Inflectra, whose manufacturing facility is in South Korea, is exposed to supply risk.[37]

The pharmaceutical industry has been actively debating the problems facing current discovery and clinical development activities, as well as bracing for greater market access restrictions and possible supply chain interruptions, since the COVID-19 virus surfaced earlier in 2020. Because of COVID-19, most pharmaceutical and biotechnological industries are focusing their R&D departments on finding new molecules or leads to treat the COVID-19. The coronavirus disease 2019 (COVID-19) pandemic will continue to have an impact on the biopharmaceutical industry as it expands. Biosimilars are no exception, and their impact on adoption and uptake is complex. COVID-19 has had and continues to have an impact on biosimilars in numerous ways:

- **Healthcare providers (HCP) and other medical decision-makers' inaccessibility :** For most HCPs and hospital decision-makers, COVID-19 is currently dictating their priorities: Patient care, the evolving coverage and payment landscape of the COVID-19 and the adequate supply of beds and personal protective equipment must be maintained. Institutions may not have the resources to continue evaluating complex biosimilar-related decisions during this time, so they may opt for the status quo, the reference product, or the existing favored biosimilar product until the dust settles. The uptake of biosimilars will be slowed as a result of this. Uptake of the therapeutic cancer biosimilars launched in the United States so far may be particularly adversely hit as doctors defer to their current therapy alternatives to avoid additional disruption
- **Repurposed contracting and marketing activities:** Although social distancing techniques have interrupted many routine account manager operations, contracting can be done effectively using digital media. This is especially true for biosimilar manufacturers with established contacts or clients looking for rapid cost savings who aren't yet engaged with COVID-19 management. Contracting negotiations and discussions are being postponed by several financial decision-makers (pharmacy directors, medical directors). Account managers can now concentrate on bringing accounts on board for biosimilars while deferring "pull-through" sales activity. Also, companies planning to launch biosimilars this quarter or next may decide to postpone marketing or perform a soft launch, which would mean supplying product, utilising digital or nonpersonal channels, and contracting via tele-detailing

- **Shortages in the supply:** COVID-19 causing the supply and demand that manufacturers struggle to anticipate is dramatically different. On the supply side, processes in hubs like China, India and the United States in the manufacturing and supply chain are being disrupted by global lockdowns. Conflated factors on the demand side make it difficult to predict demand. On the one hand, patients delay in seeking treatment, notably for methods of less convenient administration such as infusions, which may result in reduced number of patients and general demand. On the other hand, storage and demand for subcutaneous or oral formulations can lead to a rise in demand for some products, although the volume of patients is decreasing. The FDA reported the first case of

drug shortage because of the pandemic in February 2020. Although all manufacturers work to mitigate the risk of supply shortages, biosimilar manufacturers relying on European and Asian facilities can be particularly vulnerable in terms of supply.[38]

Company	Biosimilar Products	Manufacturing Locations
Pfizer/Celltrion	Inflectra	South Korea
Mylan/Biocon	Fulphila and Ogivri	India
	Semglee	Malaysia
Sandoz/Novartis	Prefilled syringes and devices for Sandoz biosimilars and Novartis reference biologics	Austria
	Binocrit	Slovenia

Table 4.3- Biosimilars and companies affected (supply) due to COVID

- **Delays in clinical trials and approvals of biosimilars:** Due to issues monitoring protocols, deprioritization in favor of more immediate acute care needs, and patients' incapacity to travel to appointments, most clinical studies are likely to be postponed. Aside from the logistical and prioritizing issues, manufacturers fear the risk of study participants catching the disease, resulting in inferior outcomes. The FDA has already issued instructions on how to handle clinical trials in the event of a pandemic. All of the aforementioned complication concerns are expected to jeopardize biosimilar approval dates set for the end of 2020 and 2021 under the Prescription Drug User Fee Act/Biosimilar User Fee Amendments
- **Increased budgetary pressure can hasten the post-crisis adoption of biosimilars:** Without a doubt, the current situation is putting a strain on the health-care system, with many providers waiving copays, coinsurance, and out-of-pocket charges as a result of

COVID-19. Although the long-term impact on the economy and healthcare system is unknown, one thing is certain: after the crisis, providers will actively seek ways to compensate for the additional costs they are currently incurring, and biosimilars will be more important than ever to deliver on their promise of cost savings to the healthcare system. In the interim, as the situation develops, it will be critical to keep an eye on what manufacturers of reference medicines and biosimilars are doing to assist providers

- On the demand side, patients postpone seeking therapy, especially for less convenient delivery such as infusions, resulting in decreased patient volume and, eventually, reduced total demand. Because therapeutic oncology biosimilars are concerned about the frequency and length of patient visits to hospitals, biosimilar utilization could be harmed. Biosimilar makers will be unable to use face-to-face rep interactions, a branded method that appears to be valued today, because to a lack of medical reps in the pharma business due to COVID. As a result, biosimilar use may be significantly impacted.

Despite the challenges faced by the global biosimilars market due to the unprecedented times of COVID-19, there is a hope for biosimilar market to rise and have a significant share in the biologics market. It is expected that:

With government support, local biosimilar production is likely to rise by 8-10% in the next 3-4 years, resulting in more MNC-domestic collaboration-

Countries such as Saudi Arabia and the UAE are the leading GCC countries and continue to invest in local production projects for greenfields, in particular biosimilars. GCCs In the next three to four years, the localization agenda will be accelerated by favorable public policies (e.g., screening high-priced, exportable flags) and by encouraging local R&D-intensive production of biosimilar monoclonal antibody drugs to control rheumatoid arthritis, psoriatic arthritis and cancer.

Biosimilars with strong patient support programmes will have the most success in the region-

With COVID-19 cases continuing to rise, attempts to return to normalcy are in jeopardy, and patients' reliance on drugs to manage their chronic diseases, whether biologics or biosimilars, is unlikely to slow or halt. Several pharmaceutical companies are providing comprehensive and holistic patient support programmes, including financial assistance (access) etc. According to Frost & Sullivan research, brands with patient support programmes for access will experience a 6% increase in prescription rate in the next 12 months, while brands with patient support programmes for assistance will see a 10% increase in prescription rate. If biosimilars are combined with patient assistance programmes such as telemedicine, e-pharmacy, and home nursing support, we will be able to grab around 50% of the entire market share in the Middle East and North Africa region by 2025.

Following COVID-19, virtual communication between drug companies and physicians will be the new norm-

Medical representatives of biopharmaceutical companies work on prototypes that enable them to connect in productive virtual surroundings and engage with doctors. Through various digital platforms such as , webinars, and virtual events, biosimilar companies in the region have a significant chance to share the latest developments in the biosimilars market. [39]

Recommendations

To date, several biosimilars have been approved by the FDA and the European Medicines Agency (EMA). Because numerous prominent biologics will lose exclusivity in the future decade, the biologic industry will be a $100 billion plus opportunity in the United States alone. Even if biosimilars only gain a small share of the market, the healthcare system will save tens of billions of dollars over the next ten years. Immunology has more than fifty biosimilars approved in various markets around the world, including Adalimumab, Infliximab, Etanercept, and Rituximab. Due to a variety of circumstances such as regulatory processes and market access, the market penetration of these biosimilars differs by location. If there is healthy competition, the economics of these biosimilars should be appealing. Some of these biosimilars could face considerable economic hurdles in public health systems where tender offers are common. Economic savings from biosimilars may not be as large as those found with generics until a large number of biosimilars reach each class (eighty to ninety percent).

Biosimilar value proposition

In order to optimize economic potential, the value case for adopting biosimilars must resonate with payers, providers, and patients. The lower cost of a biosimilar as compared to the reference

drug is only one part of its value proposition. Patients and doctors, for example, want to know how the biosimilar compares to the reference product in terms of efficacy and safety. Patients might be interested in learning more about the biosimilar's available support services, while doctors might be interested in learning pharmacovigilance monitoring data. That is why, it is critical to articulate the value proposition in order to meet the needs of various stakeholders.

The long-term worth of biosimilars must be understood by payers

Payers have a tendency to make coverage and reimbursement decisions with a short term approach. Biosimilars' market access is determined by criteria such as the innovative biologic's reference pricing, degree of competition, contracting dynamics, and product support. The first biosimilar frequently charges a higher price, which gradually declines as more biosimilars join the market. The market share of the first biosimilar with exclusivity tends to be disproportionately large. However, when more biosimilars enter a therapeutic class, payers may begin to see them as commodity products, similar to how generics are already viewed. Biosimilars' market access issues have become more complicated in recent years. Biosimilars, for example, are less appealing in some circumstances due to aggressive contracting and volume-based rebates/discounts offered by biologic producers. Given their high utilisation levels, the volume/rebate relationship frequently benefits branded biologics. A widely used biologic, for example, could be able to provide a significantly greater rebate to entice payers. In certain circumstances, their non-preferred status is due to a lack of interchangeability/indication extrapolation status, however this may change in the future. In several parts of Europe, it is mandatory to use biosimilars for all new patients.[40]

Physicians must develop greater experience and confidence in biosimilars

Multiple clinical trials and real-world evidence have been used to provide extensive efficacy and safety data for innovator biologics. This richness of information instils trust in physicians and their perspectives of biologic usage. About the biosimilars, doctors should decide whether or not

to discuss the option with a patient and how best to do so at first. The therapy area, disease condition, patient's state, current therapies, insurance, and the physician-patient interaction all play a role in this decision. Physicians must grasp the value of a biosimilar drug, including economic benefits, despite the fact that payer coverage is often entangled with physician decisions. When it comes to developing patient treatment methods, physicians have strong preferences. As a result, biosimilar manufacturers aim to ensure that physicians don't limit biosimilar use due to a lack of understanding of value. The following are a few strategies that could be taken:

- Raise physician awareness of the benefits of biosimilars so that they can (a) feel more confident about starting new patients on biosimilars
- Help doctors comprehend the financial implications of biosimilars, which might (a) lower total healthcare costs for the system and (b) lower extra expenses for patients

Physicians in Europe are much more comfortable prescribing biosimilars now that they are more aware of their benefits. Local governments also offer physician offices performance incentives to encourage them to adopt biosimilars more quickly. In the United States, a similar situation might evolve. [41]

Biosimilars must become much more well-known among patients

Biosimilar companies must provide patients with a similar level of experience and support as innovator biologics do through their experiential support programmes. Questions about the variations in the biosimilar that could carry a threat to the patient frequently arise in the minds of patients.

Biosimilar manufacturers can take the following steps for this-

- Increase the patient's knowledge of biosimilars and their clinical and economic advantages so that they understand how to cut their spending.
- To promote better access and compliance of patients with programmes

Recommendations to increase post COVID uptake of biosimilars-

With COVID-19 putting enormous financial strains on payers, hospitals, and patients, the government is searching for long-term strategies to reduce healthcare expenditures and patient out-of-pocket payments. As a result, faster regulatory reforms to support the biosimilar category are expected. Drug manufacturers should prioritize selecting free economic zones and hotspot regions with the most incentives to produce locally and collaborating with local pharmaceutical enterprises that meet high quality and technological criteria. [42]

With COVID-19 cases continuing to rise, attempts to return to normalcy are in jeopardy, and patients' reliance on drugs to manage their chronic diseases, whether biologics or biosimilars, is unlikely to slow or halt. Many pharma companies are providing comprehensive and holistic patient support programmes, including financial assistance (access) as well as other value-added services (assistance) such as online doctor consultations, in-home diagnostic support, home delivery of medicines, etc. According to Frost & Sullivan research, brands with patient support programmes for access will experience a 6% increase in prescription rate in the next 12 months, while brands with patient support programmes will see a 10% increase in prescription rate. If biosimilars are combined with patient assistance programmes such as telemedicine, we will be able to grab around 50% of the entire market share in the Middle East and North Africa region by 2025.[42]

Companies planning to introduce new biosimilars in 2021 should plan for a soft launch and use digital tools and technologies to engage Key Opinion Leaders in their marketing efforts (KOLs). As a long-term plan, companies having biosimilars in their portfolio should start conversations and training sessions with major physicians of different therapy areas and other experts in the country, and then encourage them to move to digital platforms. To succeed in the post-COVID-19 world, biopharmaceutical businesses must rethink their strategic business models and embrace digital technology.

The main limitations of the study were-

As COVID-19 is a very recent phenomenon, its impact on uptake of biosimilars globally or across different geographies is not adequate. Moreover, the availability of quantitative data for it is also insufficient. Also,

the reports with data about US market scenario of biosimilars are highly priced and cannot be downloaded or viewed for free.

Conclusion

It's been five years since the 1st biosimilar hit the market in the United States, paving the way for patients to gain access to novel biologic-based medications that help them manage and treat severe illnesses including cancer, rheumatoid arthritis, and other life-altering illnesses. Biosimilars are crucial in continuing to provide clinicians and patients with choice in their care plans while also lowering overall healthcare expenditures, as we've seen over the last five years. Indeed, studies show that because biosimilar adoption has advanced in recent years, the United States is on course to save $100 billion in drug expenses over the next five years. According to research, embracing biosimilars and patient choice will result in the necessary competition to

expand access to biosimilars and biologics for 1.2 million patients. It's critical that the biosimilar market maintains its momentum from last year's performance in 2021.[43]

The trend toward biologics is attractive because it has the potential to provide targeted medicines with fewer adverse effects. Biologics have changed the way cancer, autoimmune illnesses, and other diseases are prevented, diagnosed, and treated. Biosimilars can enhance therapeutic accessibility, and expiring biological patents are an exciting time for both. The FDA drug approval standards ensure the safety, quality and efficacy of the product will not be jeopardised regardless of whether the treatment is biological. Both pioneering ideas point to exciting future development in cancer and other complex diseases, irrespective of whether a treatment is chosen. [44]

We live at a time when biologic medications are widely available, but many patients cannot afford them. Biosimilars are quite similar to commercially available reference biologics that have been previously approved. They increase market competitiveness and patient access to crucial medicines. If the pharmaceutical industry supports biosimilars in the same way that biologics are supported in terms of insurance coverage, it might lead to quicker general adoption and give doctors additional choices so they can make the greatest clinical decisions for the patients. Biological medications have a more complex and time-consuming production procedure than small molecule drugs. Furthermore, biosimilar development necessitates comprehensive characterization to demonstrate high similarity to the original molecule, which is a current regulatory requirement. Biosimilar medication manufacture, on the other hand, remains at a fast-increasing demand providing not only a benefit to patients but also a significant profit opportunity for pharmaceutical companies.

When the Affordable Care Act included biosimilar legislation, it was a game changer, there was a lot of enthusiasm since it was hoped that biosimilars would lower expenditure and total healthcare expenses. A few biosimilars have been approved, their adoption in the United States has been slow due to intellectual property issues, price and contractual issues, payer constraints, and incentives that aren't entirely aligned to allow doctors and patients to use biosimilars. Despite of less transparency and a better grasp of health economics, physician and patient awareness of biosimilars continues to grow.[45]

COVID-19, without a doubt, threw the entire healthcare business into a loop. As a result, it's no wonder that one of the top concerns among responders is how regulatory authorities, pharmaceutical companies, treatment locations, and patients will adjust as the pandemic continues. Not only do many people believe biosimilars will (finally) get the attention they deserve, but there is also a focus on the policies that governments, regulators, and payers must follow to guarantee we get the most out of these important medications. Some experts predict that 2021 will be the "year of the biosimilar," when many stakeholders finally resolve the access constraints that are hindering biosimilar adoption and implement legislative measures that will not only eliminate these barriers but also save us money in the long run.[46] Biosimilars will eventually account for an important chunk of the US pharma market. However, the road to prosperous biosimilar uptake will remain difficult in these early phases, as considerable investments will be necessary to demonstrate similarity and interchangeability in order to maximize their potential.

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