Global Biosimilar Market: Growth, Trends and Forecast 2021

By

Neha Bala

Dissertation submitted for the partial fulfillment of the

MBA Pharmaceutical Management

Academic year, 2015-2017

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TO WHOMSOEVER MAY CONCERN

This is to certify that Neha Bala student of MBA Pharmaceutical Management from The IIHMR University, Jaipur has undergone internship training at The IIHMR University, Jaipur from 13th February, 2017 to 9th May, 2017.

The Candidate has successfully carried out the study designated to her during internship training and her approach to the study has been sincere, scientific and analytical.

The Internship is in fulfillment of the course requirements.

I wish her all success in all her future endeavors.

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CERTIFICATE BY SCHOLAR

This is to certify that the dissertation titled **"Global Biosimilar Market: Growth, Trends and Forecast 2021"** submitted by **Neha Bala** Enrollment No. **IIHMR-U/01/2015-17/0041** under the supervision of **Dr. Nirmal Kumar Gurbani** for award of **MBA Pharmaceutical Management** of the University carried out during the period from **13th February' 2017 to 9th May'2017** embodies my original work and has not formed the basis for the award of any degree, diploma associate ship, fellowship, titles in this or any other institute or other similar institution of higher learning.

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THE IIHMR UNIVERSITY, JAIPUR

CERTIFICATE BY SCHOLAR

This is to certify that all ethical issues have been considered while collecting data for my dissertation titled **"Global Biosimilar Market: Growth, Trends and Forecast 2021."**

Signature of student

Acknowledgement

The satisfaction and euphoria that accompany the successful completion of the project would be incomplete without the mention of the people who made it possible.

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To place on record, I owe a debt of gratitude to all my teachers for grooming me and my classmates for the inspiration needed to work with dedication and motivation throughout the project.

I hope that I can build upon the experience and knowledge that I have gained and make a valuable contribution towards the industry in coming future.

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Acronyms:

USD - US Dollars

NBE- New Biologic Entities

USFDA- United States Food Drug & Administration

ACA - Affordable Care Act

EU - European Union

WHO- World Health Organisation

CAGR- Compound Annual Growth Rate

BPCI - Biologics Price Competition and Innovation Act

TAs- Therapeutic areas

EMA- European Medicines Agency

INN - International Nonproprietary Naming

EPO- Erythropoietin

G-CSF- Granulocyte Colony-Stimulating

hGH - Human Growth Hormone

CHMP- Committee for Medicinal Products for Human Use

EEA - European Economic Area

PDP- Productive Development Partnership

CDSCO- Central Drug Standard Control Organization

DCGI- Drug Controller General of India

DBT- Department of biotechnology

COFEPRIS- Federal Committee for Protection from Sanitary Risks

RoW- Rest of the World

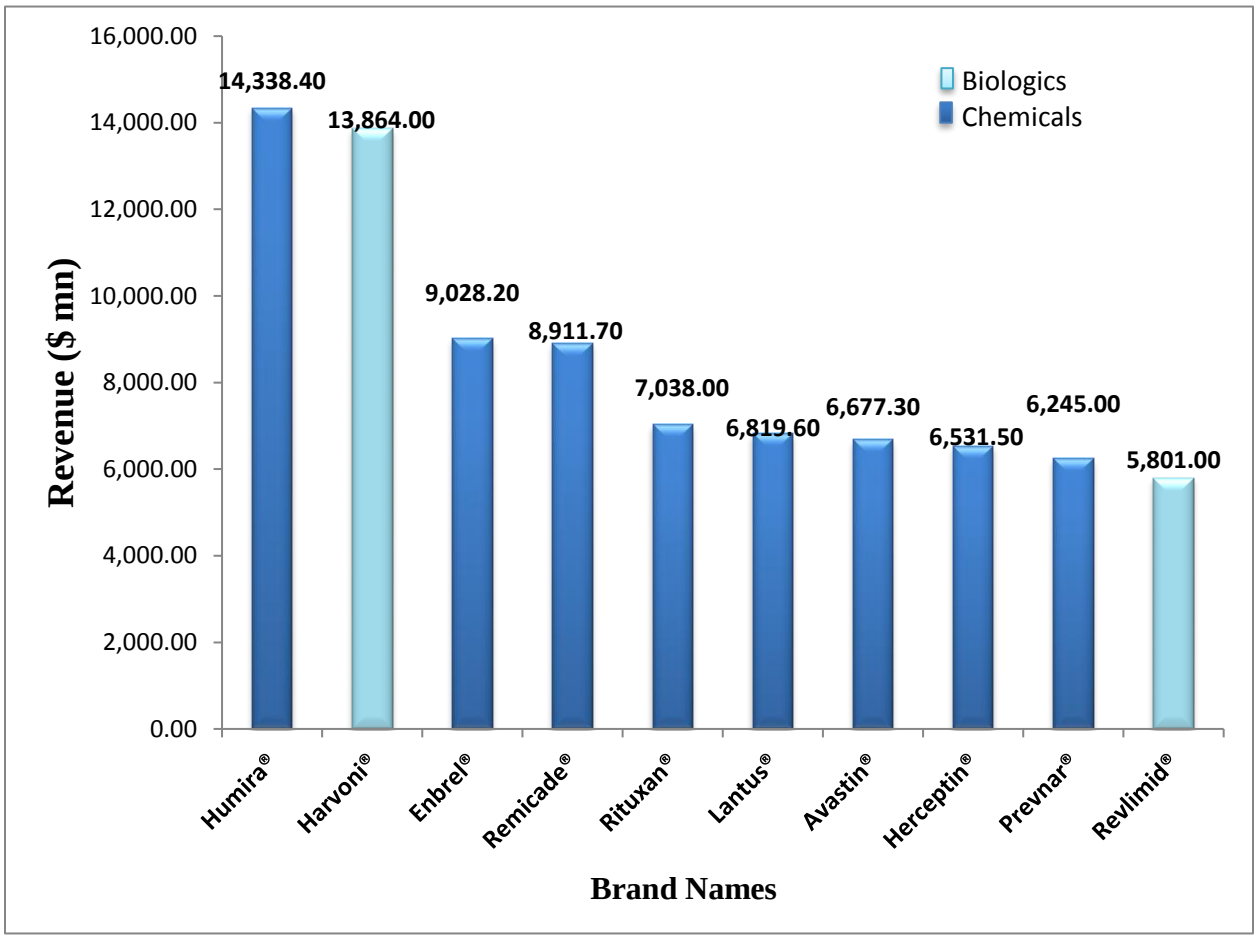
1. Introduction

Biologics are therapeutic proteins and include a huge range of products like monoclonal antibodies, recombinant therapeutic proteins, fusion protein, tissues, allergenic, somatic cells, gene therapy, blood and blood components, and vaccines. These are produced from natural resources, which include living systems of the host body, like cells of human and animal, bacteria and yeast. The interest in biologics has been escalating with the segment emerging as the primary growth driver in the overall pharmaceutical industry. Biological substances are derived from the biological resource and for which an amalgam of physical aas well as chemical and biological testing and the process of production also its control is essential for the characterization as well as verification of quality of the biosimilar.

Biologics are reforming the treatment of many major diseases in several therapeutic areas globally. Fundamentally it provides the benefit from spearheading breakthrough in the field of genetics, biochemistry and molecular biology from the past three decades. The evolution in the field of recombinant DNA technologies has ease the big scale production process of biological products, like monoclonal antibodies, human growth factors, fusion proteins and erythropoietin. Moreover, an improvement in the analytical technologies has empowered the betterment of characterization of the macromolecules, as well as nucleic acids and the proteins, which grants the screening as well as the identification of innovative biological product consisting of the complex structures as well as the varied therapeutic functional activity.

Biologics is becoming an elemental part of health care options available in the United States and abroad; over 900 vaccines and biologics are currently in clinical development for more than 100 diseases. There are many simple as well as complex biologics present in the market who is facing the loss of exclusivity now or in the coming years like Humira, Enbrel, Neupogen, Rebif, Herceptin, etc. Today, biologics represent more than 20% of the total pharmaceutical industry; valued at $987 Bn. In 2015, eight out of the top ten best-selling drugs globally were biologics. These eight biologics altogether generated US$65.6 billion in sales and resides of six Monoclonal Antibodies, one recombinant protein, and one vaccine.

Graph 1: Top 10 Best-Selling Drugs Globally by Revenue in 2015



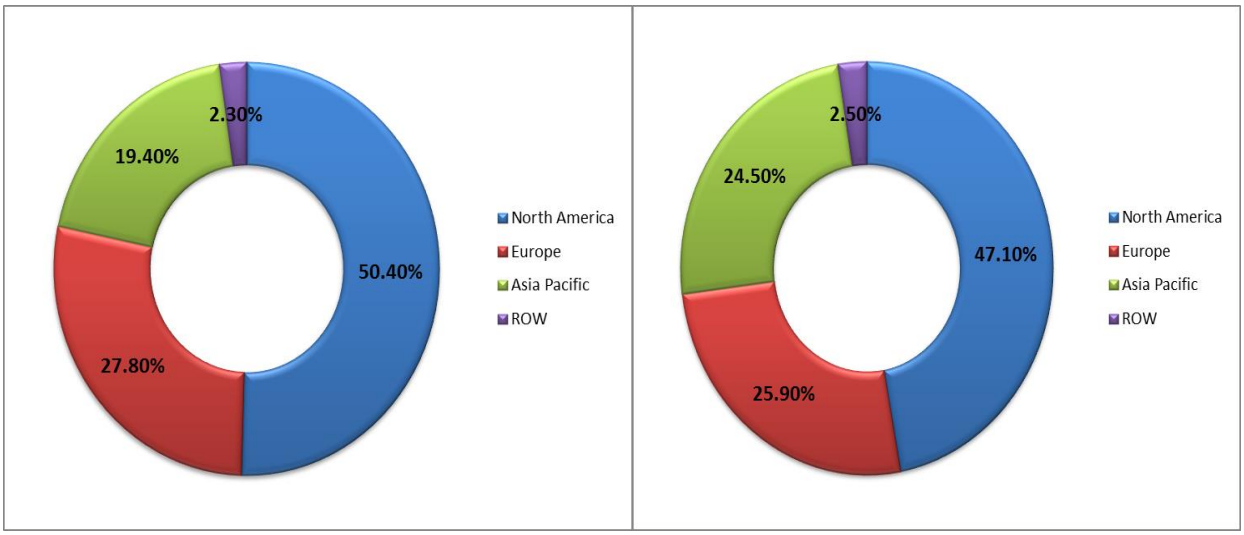
Source: *Frost&Sullivan, 2015.*

Global biologic products market is anticipated to surpass $390 billion by the end of 2020, and through that time biologics will acquire up to 28% of the global pharmaceuticals market share. On the other hand, the growth of biologics market is facing few challenges like price cutting order by the budgetary bodies.

There has also been a massive shift in investment from the historically dominant small molecules to large molecule biologics. Consequently, there has been a constant increase in the number of biologic drugs approved. As illustrated alongside, the average number of New Biologic Entities (NBEs) approved by USFDA surged from 3.2 in 2004-2008 to 5.8 in 2009-2013 and again almost doubled to 11.5 in 2014-2015. Maximum share of biologics is captured by North

America, whereas the second largest share is covered by Europe. Asia-Pacific is the fastest growing region in Biologics market sales, as the amount of expenditure on healthcare is increasing with increase in population.

Graph 2: Biologics Market: Regional Sales, Global from 2014-2015



Source: *Frost&Sullivan, 2015.*

Biosimilars represent a substantial part of the global biologic market. Biosimilars are considered as those biological products which are similar but not identical to the originator products. Generally, biosimilars are large-molecule weight molecules which are obtained from living cells with the use of genetic engineering. However, biosimilars are the therapeutic proteins which mean they are very complex and significantly larger molecule in comparison to the generic molecules which are small in nature. The synthesis of biosimilars is done by adopting genetic engineering as well as production of cell lines. Development of biosimilars also requires the clinical studies to prove the biosimilarity, efficacy and safety (which are not an essential requirement for the generics) and also the expenditure spend on the approval from regulatory bodies is also significantly higher than the generics. A typical generic can be synthesized in around $3 to 10 million, whereas a biosimilar cost of production is between $50 – 100 million.

2. Need of the study:

With the raising cost-effective health care demands, the governing bodies are taking many initiatives in order to decrease the over-priced treatments cost. In a country like the United States, the need for affordable healthcare has emerged on 2010, when Affordable Care Act (ACA) came into the law in 2010. Under this act hospitals, pharmacies, physicians, technologies come which together aims to ameliorate and access towards the unmet healthcare needs.

Biologics which are synthesized from living cells/biological sources aspires to treat many diseases like cancer, diabetes, multiple sclerosis, etc. Though biological medicinal products are helpful in the treatment of a number of chronic diseases, there is a stumbling block faced by the market which is the over-prices medicines. To overcome the accessibility problem governing bodies are now paying attention towards the substitution of such lifesaving medicines and these are known as “Biosimilars” or “Follow-on biologics” by making stringent guidelines for their approval to ensure the safety, quality and efficacy.

Follow-on biological products are the copycats of the innovator's product but are marketed over the discounted rates i.e. about 20-30% discount over the reference product which in turn builds an environment of healthcare for all, as those who were unable to access such medicines can now afford it. Hence, many manufacturers, as well as the regulatory bodies, are now paying attention towards this cost-effective segment.

The study helps to understand;

- Regulatory framework across the globe for both developed as well as developing market.
- The market potential of follow-on biologics
- Key challenges and opportunities faced by the biosimilars market
- Potential saving with the adoption of biosimilars
- Competitive landscape in biosimilars market

3. Literature Review:

According to Deloitte, report on "Winning with Biosimilars Opportunities in the Global Market" 2015; Over the past several years, biologics have gained significant traction in the pharmaceutical industry, representing more than $150 billion in global sales in 2013. By 2020 they are predicted to generate $290 billion in revenue and comprise 27 percent of the pharmaceutical market. Along with the increasing worldwide focus on improving health care access and the cost of care, presents an attractive opportunity for biosimilars manufacturers. Analysts expect the worldwide biosimilars market to reach $25-$35 billion by 2020. Since the first biosimilar approval in the European Union (EU) in 2006, there are now more than 700 biosimilars approved (~450) or in the pipeline (~250) globally. In major markets like the EU, regulators and payers have recognized the potential financial benefit of biosimilars and are driving their uptake. For example, France has initiated automatic substitution of select biosimilars over the reference products.

Aryls Consulting on March 2017, published a white paper "Market Access on Biosimilars" stated; With the expiry of patents of original biologics, a new market segment has emerged – the biosimilars. Biosimilars are poised to improve access to biological medicines and their scientific advancement. As of the beginning of 2017, 23 biosimilars in the EU and 4 biosimilars in the US have obtained marketing authorisation. Although the market uptake of biosimilars has been relatively slow to date, the future role of biosimilars in the biotech market is promising. With a growing number of patent expiries and clearer regulatory pathways, biosimilars have emerged as one of the fastest-growing categories in the biopharmaceutical sector. Biosimilars, which may contribute to considerable savings within health care systems over the next 10 years, might also widen access to treatments for life-threatening diseases such as cancer, multiple sclerosis and diabetes.

"In 2015, we witnessed some significant biosimilar milestones, including the finalization of some of the longstanding draft biosimilar guidances from the U.S. Food and Drug Administration, as well as the approval and launch of the first biosimilar in the U.S. With the evolution of this marketplace, education and informed choice are important components of biosimilar adoption and utilization. Payers, employers, patients, pharmacists, physicians, and

other key stakeholders all play a key role as the biosimilars market develops" by Duane H. Barnes**,** Vice President & General Manager**,** U.S. Value and Access, Amgen.

Review of the year 2016: Biosimilars by George Underwood published in Pharma Times, December 2016, stated that Biosimilars continued their upward trend in 2016 and cemented their position as one of the most important and exciting areas of drug development in the industry at the moment. Perhaps the biggest news was the FDA's greenlight for the first biosimilar of AbbVie's biologic Humira, the world's second best-selling drug. Amgen's Amjevita was been cleared for all eligible indications of its reference product, including moderate-to-severe rheumatoid arthritis, adult moderate-to-severe Crohn's disease and moderate-to-severe ulcerative colitis. Several questions surrounding biosimilars still remain. One lingering issue for healthcare systems is whether it is safe to switch a patient from an originator product to a biosimilar – although some of these concerns were eased when the NOR-SWITCH study, sponsored by the Norwegian government, found that switching from Remicade to Celltrion's biosimilar caused no safety or efficacy issues. As the market of biosimilar is increasing, Dr. Gaurav Narang, a healthcare industry specialist for Hewlett-Packard Enterprises, puts it this way: "The efficacy and safety of these products, in addition to an ability to treat previously untreatable diseases, is the single-largest influencing factor in the growth of this market."

IMS Institute for Healthcare Informatics, The Global Use of Medicines: Outlook through 2017; reports that "A growing share of all medicines are biologic, with biosimilars and non-original biologic (NOB) products now taking a small share of the total market The international biologics market may face turmoil if the drugs are deemed interchangeable while companies and payers adapt to saving tens of millions in annual drug budgets".

The growing global expenditure on biologics is predicted to reach US$221bn in 2017, and an estimated US$71bn in patented biologics will see their patents expire by 2020— these trends fuel the race to produce biosimilar products to sell at a discount and capture the market by The Business of Biosimilars Doug Long, Vice President, Industry Relations, IMS Health Inc. on March 2015.

Biosimilars are likely to gain increased acceptance over time. The increasing influence of evidence-based practice guidelines on payer coverage policy suggests that inclusion of biosimilars in such guidelines will help stakeholders appreciate their appropriate role in therapy. Physician and patient acceptance are important for market uptake in the U.S by Amgen 2016.

"Although biologic therapy is indicated for the treatment of numerous chronic inflammatory diseases, access to this therapeutic modality may be limited. The addition of biosimilars to the market may improve access to such treatments by increasing the number of biologic drugs available. Though the regulatory landscape concerning biosimilar development and approval is varied across different regions of the world, many countries are striving toward harmonization of accepted criteria, such as those set forth by the EMA, FDA, and WHO, which have established comparable principles and guidelines defining biosimilars and stringent processes required to develop and license a biosimilar. By undergoing the rigorous process of early stage analytical, structural, and functional comparative analyses between the biosimilar and originator product, the corresponding clinical data package may be tailored while maintaining the quality, efficacy, and safety of the biosimilar", concluded by Ewa Olech, MD, from Department of Internal Medicine, University of Nevada School of Medicine on "Biosimilars: Rationale and current regulatory landscape" published by Elsevier Inc. 2016.

4. Research Question:

What is the market potential of Biosimilars or Follow-on biologics?

5. Objectives:

The current study aims to determine the following objectives;

- To understand the regulatory framework in developed and emerging markets for the Biosimilars.
- To analyze the market growth of biosimilars in terms of its therapeutic area and geographical regions.
- To identify the key factors like strength, weakness, opportunities and threats which can influence the market growth.

6. Methodology:

Type of study:

- Descriptive, Secondary / Desk Research

Data Collection Tool:

- Information is collected from a number of publicly available as well as organizations financial reports.
- Public sources involve publications by different associations and governments, annual reports and statements of companies, white papers and research publications by recognized industry experts and renowned academia etc.

Statistical Analysis Software:

- MS Excel

Study Duration:

- Three months (13th Feburary'2017- 9th May'2017)

Biosimilars Definitions by different Regulatory Bodies

The EMA (2017) defines biosimilars as:

"A similar biological or 'biosimilar' medicine is a biological medicine that is similar to another biological medicine that has already been authorised for use. Biological medicines are medicines that are made by or derived from a biological source, such as a bacterium or yeast. They can consist of relatively small molecules such as human insulin or erythropoietin, or complex molecules such as monoclonal antibodies.

Biosimilars can only be authorised for use once the period of data exclusivity on the original 'reference' biological medicine has expired. In general, this means that the biological reference medicine must have been authorised for at least 10 years before a similar biological medicine can be made available by another company."

WHO

A biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product.

The FDA's (2017) definition is:

"Biosimilars are a type of biological product that is licensed (approved) by the FDA because they are highly similar to an already FDA-approved biological product, known as the biological reference product (reference product) and have been shown to have no clinically meaningful differences from the reference product. Minor differences in clinically inactive components are allowed. But there must be no clinically meaningful differences between the biosimilar and the reference product it was compared to in terms of the safety, purity, and potency of the product."

Source: 1 European Medicines Agency. Questions and Answers on biosimilar medicines (similar medicinal products). European Medicines Agency. September 27, 2017

2 World Health Organization. Expert Committee on Biological Standardization. Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs). World Health Organization. October 23, 2012.

3.United States Food and Drug Administration. Guidance for Industry: Quality considerations in demonstration biosimilarity to a reference protein product. Washington DC: United States Food and Drug Administration, 2017.

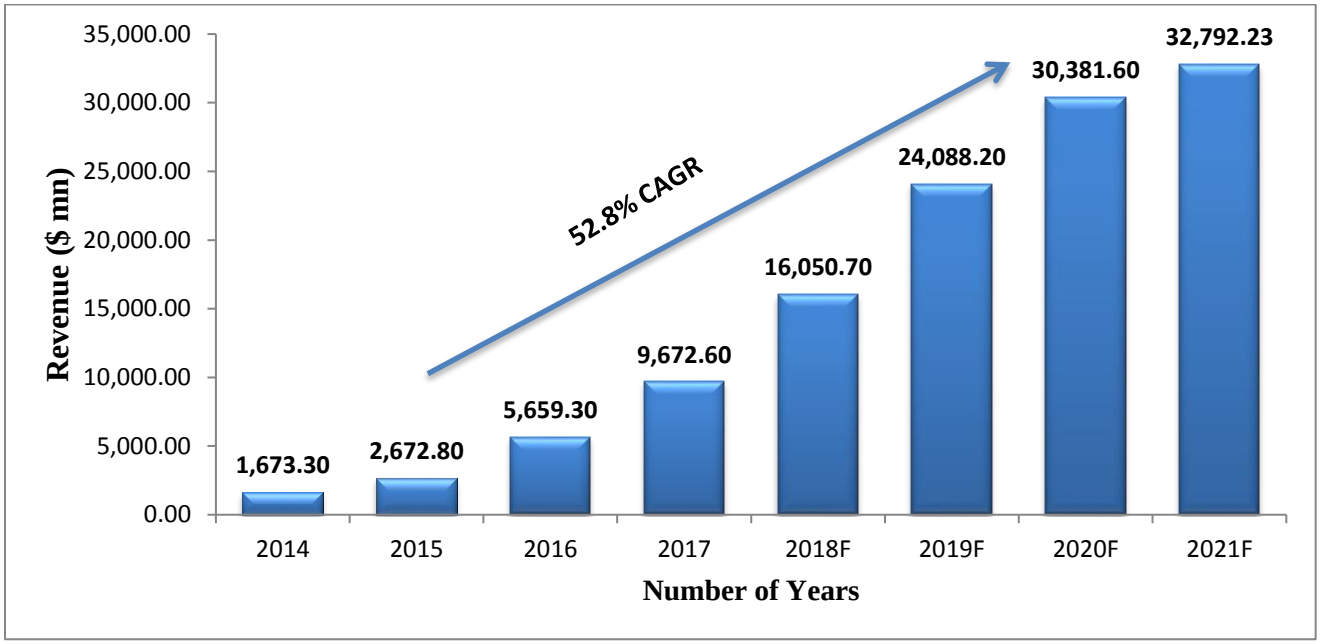
7. The Biosimilar/ Follow-on Biologics Opportunity

Around 40% of total biologic sales come from 12 biologics and those are facing the loss of exclusivity over the next 5 years, which valued at almost $55 billion in sales. Top 10 biologicals alone, will open up around $23 billion in sales to competition from biosimilars. Historically, pharmaceutical loss of exclusivity has opened up a significant market for generic drugs. With growing transformation in the overall pharmaceutical landscape towards biologics, biosimilars or follow-on biologics offer a hard to ignore the opportunity for innovative biotech and generic companies alike.

In 2013, thirty years after the Hatch-Waxman Act was registered into law in the US, generics covered for 86% of all dispensed retail prescriptions in the US. They are broadly characterized to have saved the economy close to $200 billion. The scrutiny over cost savings, affordability and access intensify multifold in the case of biologics. While biologics are addressing significant unmet medical needs, but the only obstacle in the path is that they are expensive, which in turn puts the burden on payers and patients and remain unaffordable to many. Cost of few of these therapies is more than $100,000 per treatment course on the basis of annual records. While biosimilars today are at a rather nascent pedestal, the potential to rationalize spending on drugs in developed economies and provide access in developing economies is expected to support the level of engagement that could dwarf the small molecule generics by 2030.

Historically, biologics have been more expensive than chemical drugs. In addition, because biologics are relatively new with unclear regulatory pathways, generics versions of biologics, or biosimilars or follow-on biologics, have not been a big part of the overall biologics market. With the emergence of well-defined regulatory pathways, escalating healthcare costs, technological advancements, innovations, and a large number of blockbuster biologics with near and medium term patent expiries, all these factors will become a key driver of future biologics market growth. The global biosimilars/ follow-on-biologics market is forecasted to rise at a CAGR of 52.89% from 2014 to 2021.

Graph 3: Sales Revenue of biosimilars 2014-2021



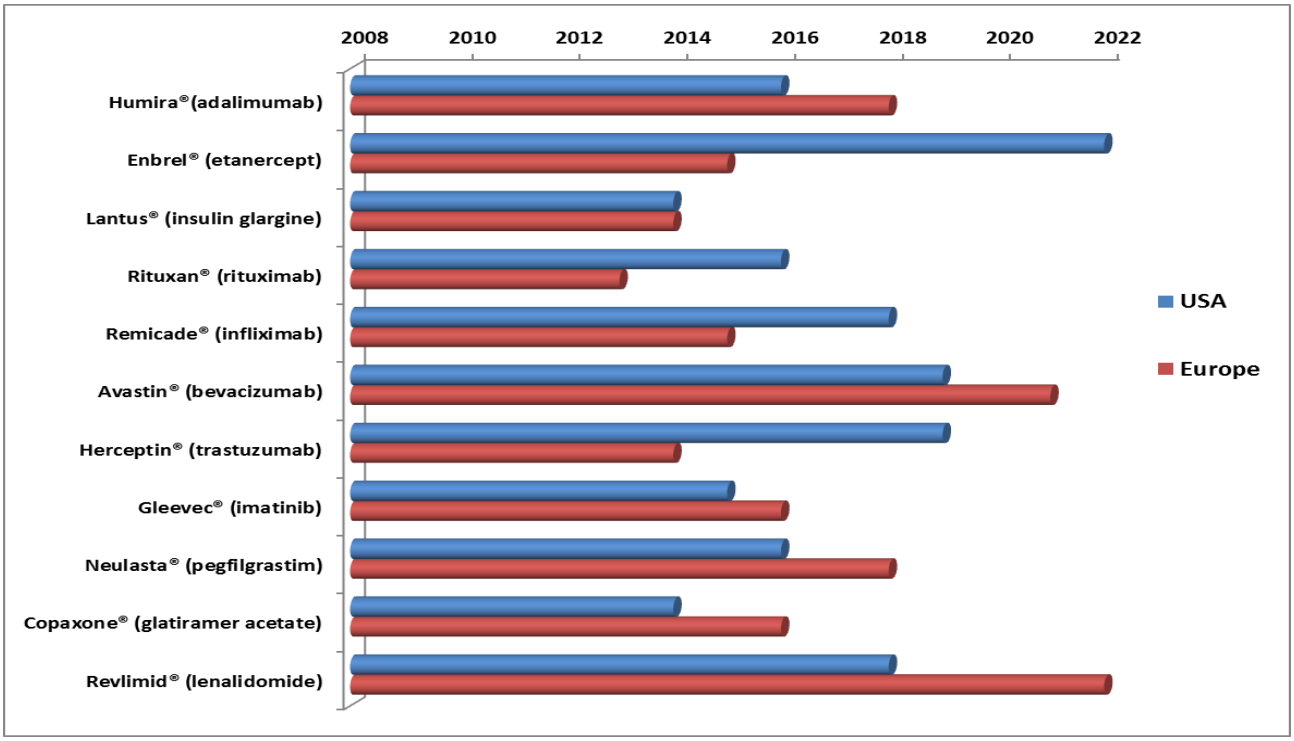
Source: *Frost & Sullivan, 2015*

Approval of very first biosimilar by EMA was in the year 2006. The product was Somatropin (human growth hormone) named Omnitrope® produced by Sandoz Inc. and today there is more than 700 biosimilars approved as well as present in the pipeline globally. In the United States, the Biologics Price Competition and Innovation (BPCI) Act, came into the law in 2010 as part of the Affordable Care Act (ACA), aims to create an new licensure pathway for the approval of biosimilar or follow-on biologic products. It wasn't until March 2015, though, that the U.S. Food and Drug Administration (FDA) announced the approval of the first biosimilar product launched in the United States, named Zarxio (filgrastim-by Sandoz Inc.), a biosimilar which is a substitute for Amgen's anti-infection drug Neupogen. Six months later, in September, manufacturer Sandoz Inc. announced Zarxio's U.S. market launch. On the contrary, Zarxio has been sold in Europe since 2006.

The loss of patent exclusivity between 2014 and 2022 for 11 established biologics products which capture the 48 percent of total biologic sales. In combined with increasing global attention on upgrading the access towards health care system and reducing healthcare price, presents growth opportunities for the biosimilars or follow-on biologics manufacturers in both developed and emerging markets. For example, France has initiated automatic alternative to select

biosimilars over the reference products and upcoming biosimilar launches in Germany are estimated to spur additional uptake and reimbursement opportunities. In most of the emerging markets, biologics currently have a little-to-no presence. However, limited patient access to affordable biologics and provider acceptance to low-cost therapies may open the door to increased biologics use among large pockets of non-consumption and pent-up demand, especially within the growing middle- to low- income population. Biosimilar players likely will need to adopt a long-term strategy in emerging markets that entails growing sales (at a smaller margin than in developed countries) among increasingly affluent and health-conscious consumers, and select therapeutic areas (TAs) that have the largest potential impact on the local population.

Graph 4: Patent expirations of major biologics 2014-2022

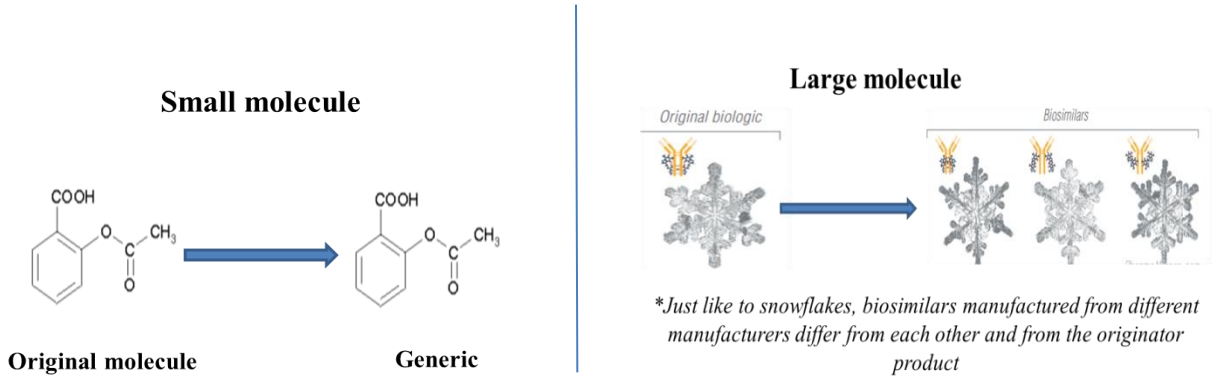


Source: *Winning with Biosimilars opportunities in global market, 2016*

7.1. Biosimilars are not generics:

In spite of the fact, generics which are small molecular compounds and biosimilars comes into the market only after the loss of exclusive rights of the innovator products, therefore biosimilars are not considered as the generics. Active ingredient which is present in the biosimilar has been identified as similar to innovator product, but because of the reason of the complex molecular nature of the biosimilars and their development inside the living systems, it is not feasible to exactly replicate the approved originator biologic. Hence, biosimilars are not identical to its originator biologic product and must undergo nip to tuck comparative studies with the originator product at every step during the development phase to ensure a high degree of similarity in terms of their physicochemical and functional characteristics, as well as safety, quality and efficacy.

Figure 1: Difference between generics and biosimilars



7.2. Differences between generics drugs and biosimilars:

Biosimilars are different form generic products as they are the molecules with complex nature while generics are small molecules also development processes differs. In contrast to the small-molecule drugs, which typically have a molecular weight between 100 and 1000 Daltons whereas, biologics have a chemical structure that is orders of magnitude larger and more complex, commonly ranging from approximately 18–150 kilo Daltons. Additionally, as proteins,

biologics are highly complex molecules with a primary structure (e.g., amino acid sequence), a secondary structure (e.g., folding), a tertiary structure which is a result of interactions between these secondary structures, and potentially a quaternary structure that results from the combination of two or more individual protein subunits (e.g., hemoglobin). Small- molecule drugs, on the other hand, have much simpler molecular structures and those are easily produced by chemical synthesis. In contrast, biologics are commonly produced by living cells, including bacteria, plant, and mammalian cells, through the medium of specialized manufacturing and purification processes.

Table 1: Key difference between generics & biosimilars

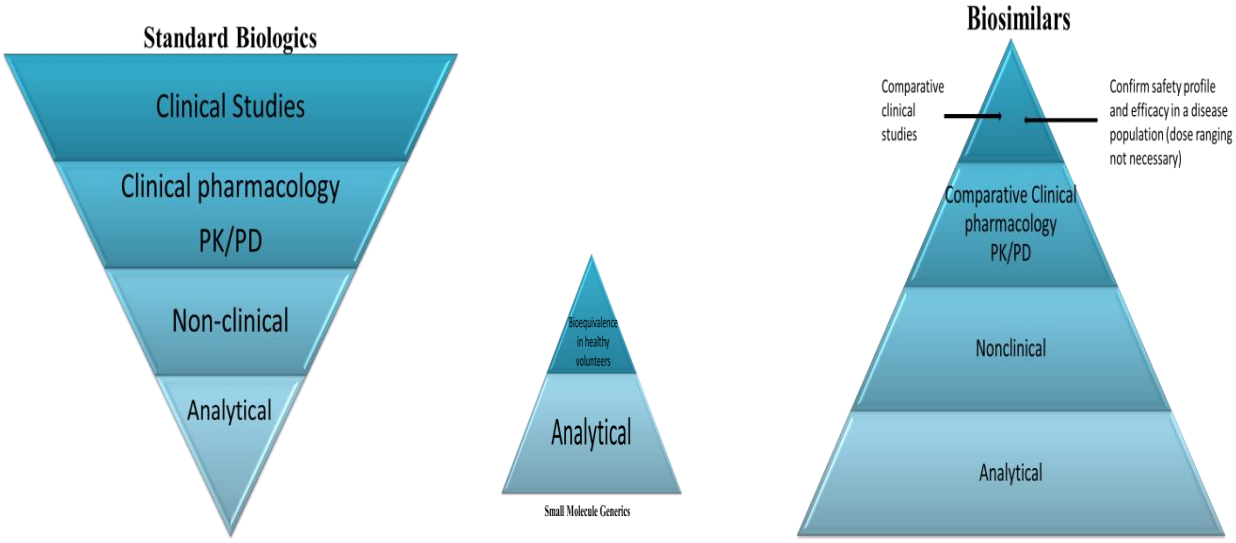
Generics	**Biosimilars**
Chemically synthesized	Living cells/Recombinant technology
Identical to the reference/originator product	Similar but not identical to originator product
Simple molecules i.e. 100-1000 Da	Complex molecules i.e. 6-15 k Da
80-90% discount over reference product	20-30% discount over reference product
Development time: 3-5 years	Development time: 8-10 years
Development cost: $1-5 Mn	Development cost: $100-200 Mn

Apart from differences in molecular structure and size, small molecule drugs and biologics also differs in their respective route of administrations. At the same time, chemically synthesized small-molecule drugs can generally be administered through the oral route, whereas biologics are more commonly delivered through the parenteral route of administration. On the contrary to chemical synthesis, which generally results in 95% of chemically identical molecules, the living systems in which biosimilars are produced are inherently variable and result in heterogeneity due to variations in post-translational modifications such as glycosylation. In addition, they may undergo physical and chemical degradation, including deamidation, cleavage, and aggregation. Therefore, biopharmaceuticals always consist of mixtures of variants of the same protein. It is

important to note, however, that lots are tightly controlled and monitored to remain within predefined acceptable limits by manufacturers and regulatory agencies.

Moreover, due to the large molecular size of biologics, they have the great potential to be recognized by the body as "foreign" agent and therefore, they possess the greater ability to trigger the immune system which produces an immune response (i.e., are more immunogenic) in comparison to that of small-molecule structure drugs. The small molecule drugs are commonly non-immunogenic in nature (i.e. too small to be recognized by the immune system). Biosimilars which are intended for chronic treatment, European regulatory guidelines recommend a 12-month head-to- head comparative clinical studies in which efficacy and safety, along with immunogenicity, are compared between the biosimilar and originator or reference product within the most sensitive population to detect potential differences.

Figure 2: Key differences in non-clinical and clinical studies between biologics vs generics vs biosimilars



8. Regulatory Considerations-the Global Landscape

The large and complex nature of biologic molecules, biosimilars do not provide guaranteed to be identical to similar to the innovator biologics. This is the reason, regulatory bodies have been concerned that unrecognized distinctive characteristics present in biosimilars may give the reduced efficacy or produce different adverse reactions. The process used for the production also poses challenges related to the quality assurance. Presently the regulations granted for biosimilar marketing approval require payers to demonstrate that the biosimilar is compatible to the reference biologic in analytic characterization and quality prospects. Biosimilars or follow-on biologics also must establish comparable clinical responses—that means developers must prove that there is no clinically meaningful difference between the biosimilar and the originator product in terms of safety, purity and potency or effectiveness.

8.1. EMA, FDA and WHO Frameworks

Guidelines developed by EMA, the U.S. FDA and the World Health Organization (WHO) set out general principles for a demonstration of comparability in terms of quality, safety, and efficacy. These guidelines generally suggest a risk-based, stepwise development approach that requires nonclinical *in vitro* and *in vivo* comparability studies as a first step. The progression begins with functional and physicochemical characterization and quality comparability assessments. Pharmacokinetic (PK) and pharmacodynamics (PD) studies are followed by clinical safety and efficacy trials. In certain cases, PK and PD studies may be sufficient to demonstrate comparability.

Despite the fact, EMA and U.S. FDA regulatory frameworks are similar in many ways, but there are several differences as well. The U.S. FDA draft guidances state more explicitly that robust comparability of physiochemical, immunochemical and functional properties may enable a smaller or more focused clinical program with the potential, in some cases, to conduct clinical studies with reduced trial populations. Another difference is the question of interchangeability—the automatic substitution of a biosimilar for an originator biologic without the prescriber's input. Currently, EMA guidelines do not address interchangeability whereas interchangeability is

clearly defined in U.S. law (BPCIA). However, the U.S. FDA has yet to issue specific guidelines on how it has designed to implement BPCIA provisions on interchangeability. The U.S. FDA states that it will continue to consider the type of information sufficient to enable regulators to the determination whether the biosimilar product is interchangeable with the reference or originator biologic.

Table 2: Approval year of regulatory pathways in various countries

Country	Year	Regulatory Pathway
Europe	2003/2004	Legal Framework
Australia	2008	Adopted EU Guidance
Japan	2009	Final Guideline
Korea	2009	Guidelines
USA	2010	Legal Framework
India	2012	Guidelines
China	2015	Guidelines

8.2. Diverse guidelines across the world

Over the course of time, the U.S. FDA, EMA and WHO regulatory frameworks will help to increase harmonization of biosimilars licensing pathways but regulation still varies widely across emerging nations or the developing market. Some, notably India, Singapore, Malaysia and South Korea, have issued biosimilars guidelines consistent with the EMA model. Others, like Russia, have neither specific regulations nor guidelines. A country like Russia regulates biosimilars in the same way as they do new biological products, requiring that they comply with similar requirements to earn market approval.

Table 3: Regulatory differences in developed and developing market

Factors	Developed Market		Developing Market		
	US	**Europe**	**India**	**China**	**Korea**
Regulatory Body	US FDA (US Food and Drug Administration)	EMA (European Medicines Agency)	CDSCO (Central Drug Standard Control Organization)	CFDA (China Food & Drug Administration)	Korean Food and Drug Administration (KFDA)
Framework Approval	2010	2005	2012	2015	2009
Choice of Reference Product	FDA licensed or non-U.S.-licensed: if able to create an acceptable relationship the referenced product	EMA licensed, or licensed in a country with same scientific & regulatory standards as EMA's if able to establish an acceptable bridge	Reference Biologic should be licensed or approved in India or ICH countries and should be the innovator product.	Approved in China or elsewhere during analytical and non-clinical studies; China approved if used in clinical studies	Reference drug already approved by the KFDA as a new drug
Requirements for Safety and Efficacy Studies	Necessary if residual uncertainties of biosimilarity are inferred from analytical, animal studies and clinical trials	Risk-based approach on a case-by-case basis; possible to approve biosimilars based on PK comparative study and supportive PD data	Structural and functional comparability between similar and reference product by studying the physicochemical properties	Potential simplification allowed if limited differences in previous studies and biosimilarity can be inferred from clinical PK/PD	Sensitive clinical test model to detect potential differences between the test and reference product, clinically relevant mechanisms of action is demonstrated

8.2.1. Developed Markets

Developed markets, such as the United States, EU5, and Japan, provide closer growth opportunities for biosimilars, supported by governments which provide a clear regulatory pathway and payers which are pushing uptake to contain costs. Earlier, the growth potential thus far has been a mix of reality and hype, as illuminated by the perceived underperformance of biosimilars in Europe in the past seven to eight years. Continued regulatory uncertainty, persisting fears from patients and physicians about biosimilars' "similarity," safety and efficacy, as well as the ongoing (frequently heated) arguments on automatic substitution and International Nonproprietary Naming (INN), is expected to build long-term barriers for widespread uptake of biosimilars. In these markets, innovation (i.e. in the form of bio-betters) is possible to beat imitation (i.e. in the form of biosimilars), especially in the United States.

Geographically, US capture most of the global spending on biologics and which in turn will become a key driver of long-term biosimilars market potential. Due to the advanced economies which bring the advantage of an established framework for biosimilars but to date uptake has been slow; Europe is the most progressive. European continues are tended to be the relatively mature region in case of biosimilars guidelines, and market access clarity is now emerging from several European countries with initial monoclonal antibody product adoptions setting the trend. While there has8 been higher than expected price erosion in certain European markets, this has also resulted in a significant share of the originator drug being gained by the biosimilar within two years from launch. The other developed countries have had a late response to regulatory framework for biosimilars, however in the present times with approval of 4 biosimilars in the USA (Adalimumab, biosimilar has been approved recently) and the current approval of Insulin Glargine biosimilar in Japan, the opportunity in these countries have become more substantial and tangible and it is proved with advent of time and the current pipeline of biosimilars the situation will only become better.

8.2.1.1. European Medicines Agency (EMA)

EMA was the first to set up guidelines for a biosimilar, which were pioneered in the year 2005. The regulatory approval typically takes up to 6-8 years to reach into the markets. There is a centralized procedure for all the EU member countries. It has been just over ten years since when the first market approval was granted to a biosimilar drug by the European Medical Agency (EMA) in the Europe. Since then, almost 23 biosimilar drugs has received marketing authorisation in the EU by EMA, 2017. Europe represents the most advanced market for biosimilars, which accounts for almost 80% of global spending on these large-molecules. On the other hand, despite the fact of acquiring a strong legislative foundation, till date, only a few manufacturers have been able to launch biosimilars in the region. These consists of a mixture of existing generics houses, the generics arms of major companies as well as new ventures, most notably Sandoz/Novartis, Stada, Hospira, Medice and Ratiopharma (Teva Pharmaceuticals). Biosimilars are established majorly in three therapeutic areas in Europe which are Erythropoietins (EPOs) used for the treatment of anemia caused by renal dialysis, Granulocyte Colony-Stimulating (G-CSF) factor for lowering the white blood cell counts after chemotherapy, and Human Growth Hormone (hGH) used for treating growth hormone deficiencies.

After a decade, the market uptake of biosimilars has been disappointing and is recognized as an underperformance in Europe. Furthermore, the competitive performance of the biosimilars in Europe is found to be heterogeneous in nature, both across the countries as well as drug classes, with erythropoietin having a much lower market share of biosimilars across the European countries in comparison to filgrastim. Reasons for such slower than expected uptake in Europe include the lack of automatic substitution of biosimilars and the physicians as well as patients inadequate awareness about the biosimilars. Extensively different reimbursement systems across the European countries also appeared to be market uptake hurdle.

Out of the five major EU countries, the market share (in terms of Treatment Days = TDs) of erythropoietin biosimilars ranged from 11% in the UK to 78% in Germany in 2015. On the contrary to erythropoietin's heterogenic situation, the market share (TDs) of filgrastim

biosimilars varied from 78% in Germany and Spain to 98% in the UK in 2015. After two years of the first marketing authorizations, the market share (TDs) of infliximab biosimilars in the 5 major EU countries spanned from 4% in France to 13% in Spain. With reference to price erosion, there are wide variations across the 5 major European countries as well as the different drug classes. The price reduction of erythropoietin biosimilars versus the originators or reference product price, prior to the loss of exclusivity (LoE), ranged from 1% in the UK to 57% in Germany in 2015. Prices of originators are eroding remarkably and aligning with the biosimilars price, especially in countries like Germany and Spain. Filgrastim biosimilars also showed considerable price drop, up to 48% in comparison to the originator's price before the loss of exclusivity.

Exclusivity period:

- 8 years of data exclusivity.
- 8+2 years of marketing authorization exclusivity.
- +1 year marketing exclusivity for every second significant new indication during the time of data exclusivity period.
- No exclusivity for the 1st interchangeable product.
- European Regulatory Authority: EMEA & CHMP

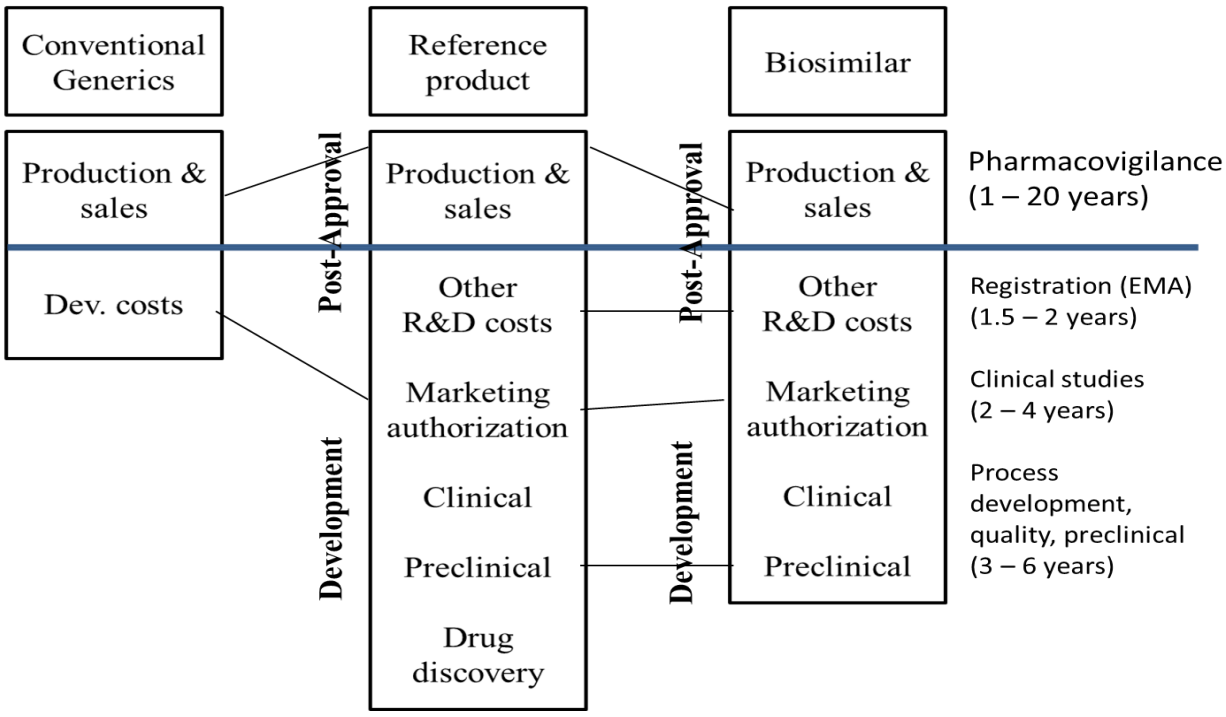
Table 4: List of EU-approved Biosimilar medicines (March 2016)

Active Substance	Name of biosimilar medicine	Date of European Commission authorization	Marketing authorization holder	Reference Product
SOMATROPIN	Omnitrope®	12-04-06	Sandoz	Genotropin®
EPOTIN	Abseamed®	28-08-07	Medice	Erypo®/Eprex®
	Binocrit®	28-08-07	Sandoz	
	Epoetin alfa HEXAL®	28-08-07	Hexal	
	Retacrit®	18-12-07	Hospira	
	Silapo®	18-12-07	Stada	
FILGRASTIM	Biograstim®	15-09-08	AbZ-Pharma	Neupogen®
	Ratiograstim®	15-09-08	Ratiopharm	
	TevaGrastim®	15-09-08	Teva	
	Filgrastim HEXAL®	06-02-09	Hexal	
	Zarzio®	06-02-09	Sandoz	
	Nivestim®	08-06-10	Hospira	
	Grastofil®	18-10-13	Apotex	
	Accofil®	18-09-14	Accord Healthcare	
INFLIXIMAB	Inflectra®	10-09-13	Hospira	Remicade®
	Remsima®	10-09-13	Celltrion	
FOLLITROPIN ALPHA	Ovaleap®	27-09-13	Teva	Gonal f®
	Bemfola®	27-03-14	Finox Biotech	
INSULIN GLARGINE	Abasaglar®	09-09-14	Eli Lilly	Lantus®
ETANERCEPT	Benepali®	18-01-16	Samsung Bioepis	Enbrel®

Source: *EMA, 2017*

Table 3 displays the list of biosimilar drugs approved in Europe till March'2016. The maximum biosimilars are developed in the therapeutic area of Erythropoietin for the treatment of anemia or blood disorders, Human growth hormone for the treatment of growth hormone deficiency, Insulin for lowering the increased blood glucose level.

Figure 3: Regulatory Pathway for Biosimilars in Europe



The above flow chart shows the regulatory pathway for the biosimilar approval in Europe. It is clear that the timeline and pathway for the approval of biosimilars are way much similar to that of the reference or originator product.

On October 23, 2015, the EMA website listed 19 license biosimilars, though it should be noted here that this number comprises of multiple biosimilar versions of some of the same originator products [i.e. erythropoietin, somatropin (human growth hormone), and filgrastim]. The comprehensive experience obtained with licensed biosimilars has led to a powerful regulatory

pathway in the European Union, along with several guidelines issued and revised through time by the EMA, which covers quality, non-clinical, and clinical aspects of the development of biosimilar mAbs, as well as explicit guidelines for immunogenicity assessment. Current revisions directed to the release of an updated overextended biosimilar guidelines in 2013, which was adopted by the CHMP on October 2014. At the outset, the EMA required the biosimilarity examination to be conducted with an originator product licensed in the European Economic Area (EEA). The amended guidance states, that in order to boost global development of biosimilars and bypass unessential clinical trials, certain clinical studies, and in vivo nonclinical studies may be alternatively conducted with non- EEA authorized reference products (from a region with similar regulatory requirements), which in turn provided justification to both and cross-over studies are performed. Cross-over data between the biosimilar candidate, the EEA, and the non–EEA-authorized products should comprise analytical as well as Pharmacokinetic and Pharmacodynamics studies.

Interchangeability and substitution remain fundamental concerns with reference to the biosimilars. In consonance with the European Generic and Biosimilar Medicines Association (EGA), interchangeability pertains to the prescription of a biosimilar in place of the reference or originator product by the physician, while substitution means that pharmacists are allowed to dispense a biosimilar without the prescriber's knowledge. Automatic substitution is used when the pharmacist is authorized by the law to dispense the biosimilar in place of the originator product. EMA regulatory guidelines do not consist guidance on interchangeability and substitution because conclusion on these issues is regulated at the national level. Many European countries showed their disagreement on the automatic substitution of biosimilars.

In contrast to the previous stance, by the MEB now accepts interchangeability of biosimilars under certain conditions. As per the new guidance, switching between biological (whether originators or biosimilars product) is permitted, but only if there is adequate clinical monitoring is performed and the patient is completely informed by the same. In addition, MEB suggested that detailed product and batch information is to be recorded in the patient's file in order to assure the identification of the product. France passed similar legislation in 2013 which allowed the substitution, only under certain criteria such as whether a biosimilar can only be substituted for new patients and if the prescriber has not written "non-substitutable". Safety is another key

consideration for any medicine. Thus, for all the biologics, most of the regulatory agencies, including the EMA, require post-marketing surveillance for biosimilars as well.

8.2.1.2 US Food and Drug Administration

Following the Patient Protection and Affordable Care Act (Affordable Care Act) which was signed by President Obama on 23rd of March 2010, a compressed approval pathway was created for biological products that are determined as "biosimilar" to or "interchangeable" with a biological product. Such sanctioned provisions are also known as the Biologics Price Competition and Innovation Act of 2009 (FDA, 2017). The Biologics Price Competition and Innovation Act (BPCIA) were registered into law in 2010, and it established the approval pathway for biosimilars in the United States. On the basis of provisions in the BPCIA, the FDA has further created a framework outlining a step-by-step approach in which all data for a biosimilar i.e. Analytical, nonclinical and clinical studies and it is evaluated in a head-to-head comparison with the reference or the originator product. At the same time, a biosimilar may require hardly any clinical trials in comparison to its reference product to obtain FDA approval; it may also require a greater number of analytical characterization, as well as nonclinical and clinical pharmacology data. Presently, the FDA does not require any comparative analytical as well as clinical studies between biosimilars, which means biosimilar will be evaluated only in comparison with the designated reference or originator product.

A biosimilar product may be approved for one or more than one disease indications for which the originator product is approved, without undergoing clinical testing in such conditions. This is known as extrapolation. On the basis of analytical and clinical data submitted to determine the biosimilarity between the reference as well as biosimilar product in one studied indication, in such condition the FDA may provide approval to the additional indications if scientific justification is provided by the biosimilar sponsor. Scientific justification for extrapolation must contain the following issues for the tested and extrapolated indications of use like the mechanism of action, pharmacokinetics, immunogenicity and differences in expected toxicities in different patient populations.

Much long-awaited FDA draft guidance on interchangeability, was issued on January 2017, which highlights the FDA's expectation on the totality-of-the-evidence and step-wise approach toward the demonstration of interchangeability.

As the cost of biologics in the United States is touching the ceiling, it will become necessary for biosimilars to deliver on their promise of creating competition, which disproportionately accounts for about 20 percent of the U.S. drug spend; the biosimilars or the follow-ons must first hit the market. Till date, the US FDA has approved two biosimilars: Sandoz Inc.'s Zarxio, referencing Neupogen (filgrastim, Amgen Inc.), and Celltrion Inc.'s follow-on to Remicade (infliximab, Janssen Biotech Inc.), which will be marketed in the U.S. by New York-based Pfizer Inc. as Inflectra.

Table 5: List of US FDA-approved biosimilar medicines (March 2016)

S. No.	Active substance	Name of Biosimilar medicine	Date of US FDA authorization	Marketing authorization holder	Reference product
1.	FILGRASTIM	Zarxio®	3/6/2015	Sandoz	Neupogen®
2.	INFLIXIMAB-dyyb	Inflectra®	4/5/2016	Pfizer	Remicade®
3.	ETANERCEPT-szzs	Erelzi®	8/30/2016	Sandoz	Enbrel®

Source: *US FDA, 2016*

The above table shows the biosimilars which were approved by US FDA. The first biosimilar which was approved by FDA was Zarixo® in 2015. Zarixo® is a monoclonal antibody which is used to increase the number of white blood cells. Inflectra® and Erelzi® were approved in the year

of 2016, FDA. It is anti-inflammatory medicine, which is used for the treatment of rheumatoid arthritis, Crohn's disease and ulcerative colitis.

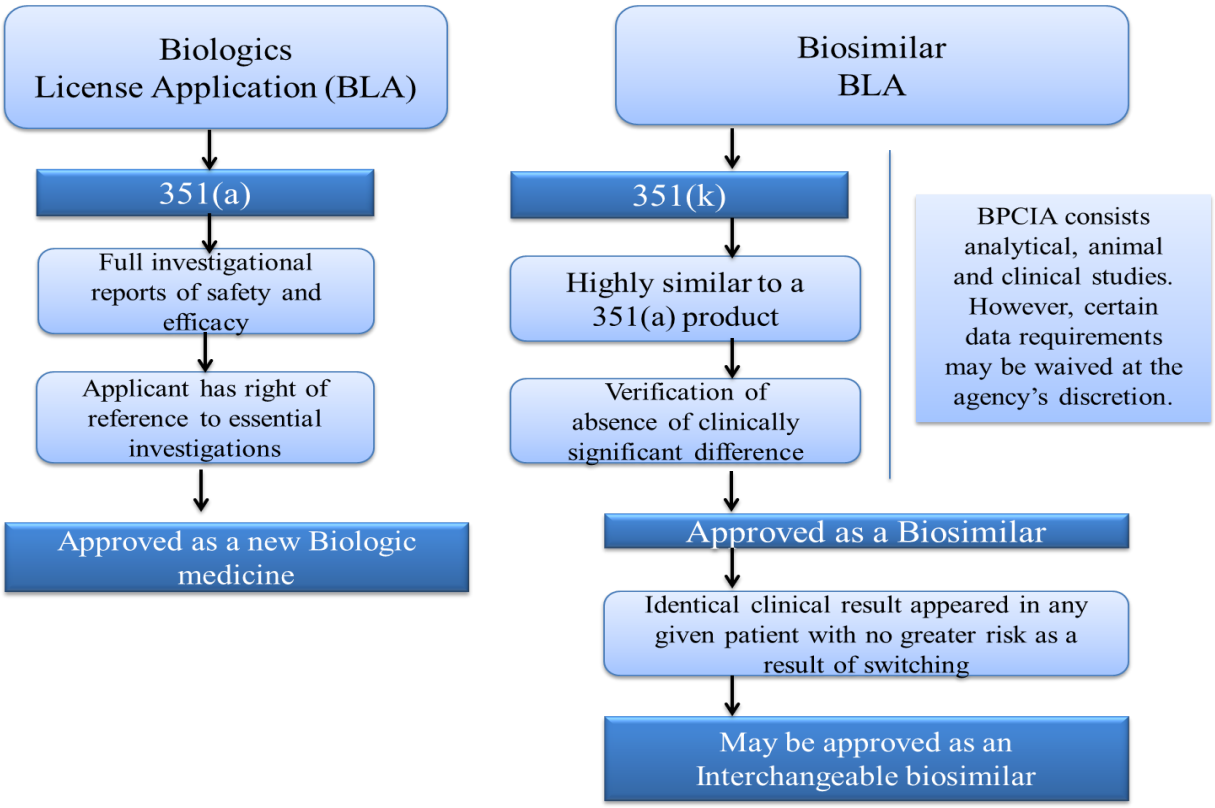
Exclusivity period:

- 4 years of data exclusivity
- 12 years of marketing authorization exclusivity
- 1 year of exclusivity period for the 1st interchangeable product
- Regulatory Authority name is Public Health Service Act by BPCI

In U.S, biosimilars bill became law in the year 2010 and the FDA's first guidance was released on biosimilars was in 2012. Biosimilars can get approval by using the abbreviated pathway under section 351(k) of Public Service Act under BPCIA (Biologics Price Competition and Innovation Act of 2009). Data bundle is comprehensive in the case of the biologic 351(a) compare to Biosimilar 351(k), but the standard for approval remains the same. Until now, there are only 3 Biosimilars are approved in the US. Regulatory ambiguity still remains to be broken down in the case of interchangeability. Label present over the biosimilar has to indicate its relation to the reference product. In the case of pediatrics, study or assessment is required if the product is biosimilar but not required if the product is interchangeable. Transition study is mandatory for biosimilars. Biosimilars launched in the US can have the same International same nonproprietary name (INN name). However, the US FDA has not approved any such biosimilar with the same INN name till date. In U.S, biosimilars bill became law in the year 2010 and the FDA's first guidance was released on biosimilars was in 2012. Biosimilars can get approval by using the abbreviated pathway under section 351(k) of Public Service Act under BPCIA (Biologics Price Competition and Innovation Act of 2009). Data bundle is comprehensive in the case of the biologic 351(a) compare to Biosimilar 351(k), but the standard for approval remains the same. Until now, there are only 3 Biosimilars are approved in the US. Regulatory ambiguity still remains to be broken down in the case of interchangeability. Label present over the biosimilar has to indicate its relation to the reference product. In the case of pediatrics, study or assessment is required if the product is biosimilar but not required if the product is interchangeable. Transition study is mandatory for biosimilars. Biosimilars launched in the US can have the same

International same nonproprietary name (INN name). However, the US FDA has not approved any such biosimilar with the same INN name till date.

Figure 4: U.S. Biosimilar Approval Pathway



Source: *Trends in Biosimilar Report, Amgen 2017*

Evolution of the U.S. Biosimilar Market:

On July 2014 FDA accepts an application for the first biosimilar in the United States. Thereafter three active filings for biosimilars pending review on December 31, 2014. FDA issued two final guidance documents for the Scientific and Quality Considerations while Demonstrating Biosimilarity to a Reference Product on April 2015. On September, the first biosimilar was launched in the US and also Centers for Medicare and Medicaid Services finalized

reimbursement provisions for follow-ons. And a milestone is set by the US government in the direction of the accessibility of healthcare by all.

8.2.2 Developing Market

Developing market remains an important element of any biosimilar assets strategy given the potential for early revenue streams by the virtue of lower regulatory barriers. However, there is no particular standard prescription and it is composed of countries with a mixture of out-of-pocket, payor, capitation as well as other Government payment models. In the introductory five years, exclusive or semi-exclusive partnerships with local players might be an important factor for market access in several RoW markets i.e. providing country a specific consideration such as Productive Development Partnership (PDP) framework in Brazil.

Presently, emerging or developing markets represent a smidgen of total world biologic sales in terms of value. Treatment costs for flagship biologics are still lower as compared to the developed markets, despite the existing demand. For example, the treatment cost of MabThera® in Brazil is three times lower than its cost in UK and six times lower than in the US. Furthermore, a recent Kantor Health Survey found that 20 percent of the developing market autoimmune patients use a biologic, with the distribution of biologics fluctuating from 29 percent in China to 12 percent in Russia and 6 percent in Brazil. This may demonstrate the presence of large pocket of non-consumption, especially within the growing middle- income class.

Sales of biologics could be significant, but they are frequently facing a hurdle in the path by high out-of-pocket expenditure and consumer's low ability to pay such high prices. Because of such reason sales growth often ends up being a pricing game i.e. originators are moving into a biosimilars play by providing heavy discounts to their branded product(s), as well as competitors are moving into exclusivity deals with customers. In India, a Deloitte survey showed a result that prescribers are willing to prescribe a first-line critical therapy only if it was offered at a 60 to 70 percent discount.

From the regulatory viewpoint, biosimilars approval pathways have been defined for most developing markets, although they are still in a state of constant change in China and Russia.

Most of the pharma emerging markets, including China, India, Brazil, and Mexico, have developed their own regulatory pathway for the approval of biosimilars. In comparison with the European framework, these countries generally set a lower barrier in terms of clinical trial requirements and regulatory control. This empowers the local manufacturers to enter into the pharma emerging markets; however it also potentially provides a lower cost entry point to the international players. Going ahead, government initiatives are foreseen to boost up the biosimilars market in southeast Asian countries, predominantly as a means for sustaining their domestic industry. Particularly in South Korea, came up with a plans to become a leading biosimilars player in the market, by actively expanding its world-class clinical trials as well as production infrastructure, reinforcing global export capability, building research and development, cultivating bio-specialized manpower, legal along with system supporting strategies. Even if, the biologics market itself is at an early stage in the pharm emerging economies it is broadening fast and biosimilars will, in turn, play an essential role in its future growth. However, the exclusive nature of these developing countries might see a market which will evolve over a time in completely distinct fashion.

8.2.2.1. India

In India, biosimilars guidance was established in 2012. About 80% of the pharmaceutical spending in India is an out-of-pocket expenditure. An Indian market player has an extensive experience with generics and has made their pathways to other countries as well through exporting. But the biggest hurdle faced by the Indian market players is an image of manufacturing unsafe as well as poor quality drugs. Association of the global pharmaceutical companies and the domestic companies is providing benefit to enhance the quality of biosimilars marketed in India. Approximately 19 biosimilars are present in the development pipeline with a large proliferation of non-original biologics. With the large middle-class population growing with disposable income that prefers to go for the branded products, hence it opens up an excellent opportunity for the branded biosimilars. Almost 70% of the country's population is considered as a rural i.e. low-income class and which turns the head of budgetary bodies to focus on the cost of therapy. 20-30% discount over the originator biologics may not be sufficient for such area of population.

Table 6: List of Biosimilars in India

Company name	Product name	Active substance	India launch year
Biocon	Basalog	Insulin glargine	2009
Wockhardt	Biovac	Hepatitis b	2000
Wockhardt	Wepox	Epoetin alfa	March 2001
Wockhardt	Wosulin	Human insulin	13 August 2003
Sb/merieux alliance	Shanferon	Interferon alpha	2 April 2002
Sb/merieux alliance	Shanpoietin	Erythropoietin	January 2005
Sb/merieux alliance	Shankinase	Streptokinase	June 2004
Dr. reddy laboratories	Reditux	Rituximab	30 April 2007
Reliance life sciences	Relipoietin	Epotein alfa	2008

Source: *Biosimilar Current Status in India 2017, Asian J Pharm Clinical Research, Vol. 10, Issue 1.*

In India the biosimilars primarily consists of vaccine, streptokinase (indikinase, shankinase, STPase), recombinant proteins and diagnostics, granulocyte colony stimulating factor (GCSF–Grastim, Neukine), erythropoietin (hemax, epofer, wepox, ceriton, epofit), hepatitis B vaccine (Shanvac B, Revac B, Enivac B, Biovac B, Genevac B, Bevac), insulin (wosulin, insugen, recosulin), interferon alpha 2B (shanferon), Rituxinab (MAb), epidermal growth factor receptor (anti-EGFR) MAb–(reditux, bioMABEGFR). Present status of biosimilars in India is elaborated in Table 5. There are currently more than 10 biopharmaceutical companies involved in the development of biosimilar products.

Key Point:

- Regulatory Authority name is CDSCO, DCGI & DBT
- Recently established guidelines for the regulation of biosimilars
- The reference or originator biologic must be licensed in India, if not then it should be licensed or marketed for at least 4 years in a country within a defined regulatory pathway.

8.2.2.2. China

China issued a draft for biosimilars guidelines in 2015, once a well-defined regulatory pathway for biosimilar approval is established in the country. The market will be very attractive not only because of the potential volume but also because of the growing ability to pay by the people. As comparable to the tight controls consisting of the international companies to establish partnerships or use the domestic pharmaceutical distributors. For the successful manufacturing as well as marketing of the biosimilars will require the partnerships between the domestic companies with the international market players. Lack of prescriber's faith and enthusiasm for the non-branded drugs will aggravate for the biosimilars. Therefore, there must be a medium by which the prescribers were educated about biosimilars.

Key Point:

- Regulatory Authority name is: State Food and Drug Administration (SFDA)
- Present regulations pathway lacks in the clarity.

8.2.2.3. South Korea

South Korea is one of the most mature biosimilar "development" markets. Empowered by the exceptional support from the South Korean government with 35% of the national medical research and development budget was invested into the development of the biosimilars in 2012. South Korean government has set a goal for the domestic biopharmaceutical market players, in order to capture the 22% of the global biosimilars market by 2020. Twelve biosimilars have been approved and another 36 biosimilars are presently in the pipeline. To win the race in the domain of high-risk and complex development of monoclonal antibody (mAb) biosimilars with 17 mAbs present in the pipeline.

Table 7: The list of approved biosimilars of Korean origin

S No.	Biosimilar	Approval Date	Name of Company
1.	Etanercept	8-Sep-15	Samsung Bioepis
2.	Etanercept	11-Nov-14	Hanwha Chemical
3.	Trastuzumab	15-Jan-14	Celltrion
4.	Somatropin	Jan-14	Sandoz
5.	Infliximab	23-Jun-12	Celltrion
6.	Infliximab	4-Dec-15	Samsung Bioepis

Source: *IMS MAT Mar'15 Data*

The South Korean biopharmaceutical industry is a rapidly emerging consisting a huge potential; in the household as well as in the export market. The sale of biopharmaceutical domestic market was around $3 billion in 2013 and is rising at the CAGR of approximately 6%. Korea was one amongst the country who has adopted the biosimilar regulation in its early stage (its regulations is similar to EMA).

The Korean biopharmaceutical companies have actively established partnerships with global pharmaceutical companies such as:

- Hanwha Chemical enrolled in a mutual agreement with Merck to market Enbrel® biosimilar, globally.
- Samsung Biologics settled a joint venture with Biogen Idec to manufacture biosimilars.
- Celltrion and Pfizer to manufacture as well as market Remicade®.

8.2.2.4. Russia

Russia aims to boom its domestic pharmaceutical market and increase the market share of domestic players from 20% in 2012 to 50% by the end of 2020. The strong and foremost preference of local manufacturers will be collaborating with the international companies. Indicative of the boom in domestic industry, with a rituximab biosimilar, developed by the Russian company Biocad, was the first monoclonal antibody biosimilar approved in Russia in April 2014. Around eight biosimilar molecules are in the development pipeline.

8.2.2.5. Mexico

Mexico is established and government supportive market for biosimilars. Demand for biosimilars prompted by high out-of-pocket health care expenditure (estimated at +90%). Due to the significant existence of non-original biologicals known as “bio limbos” which has not undergone any marketing authorization consistent with globally accepted standards. Biosimilars development was led locally by the Probiomed which obtained six biosimilars approvals, including a version of Rituxan®.

Key Point:

•Regulatory Authority name is COFEPRIS or Federal Committee for Protection from Sanitary Risks in Mexico

•Semi-regulated market for biosimilars

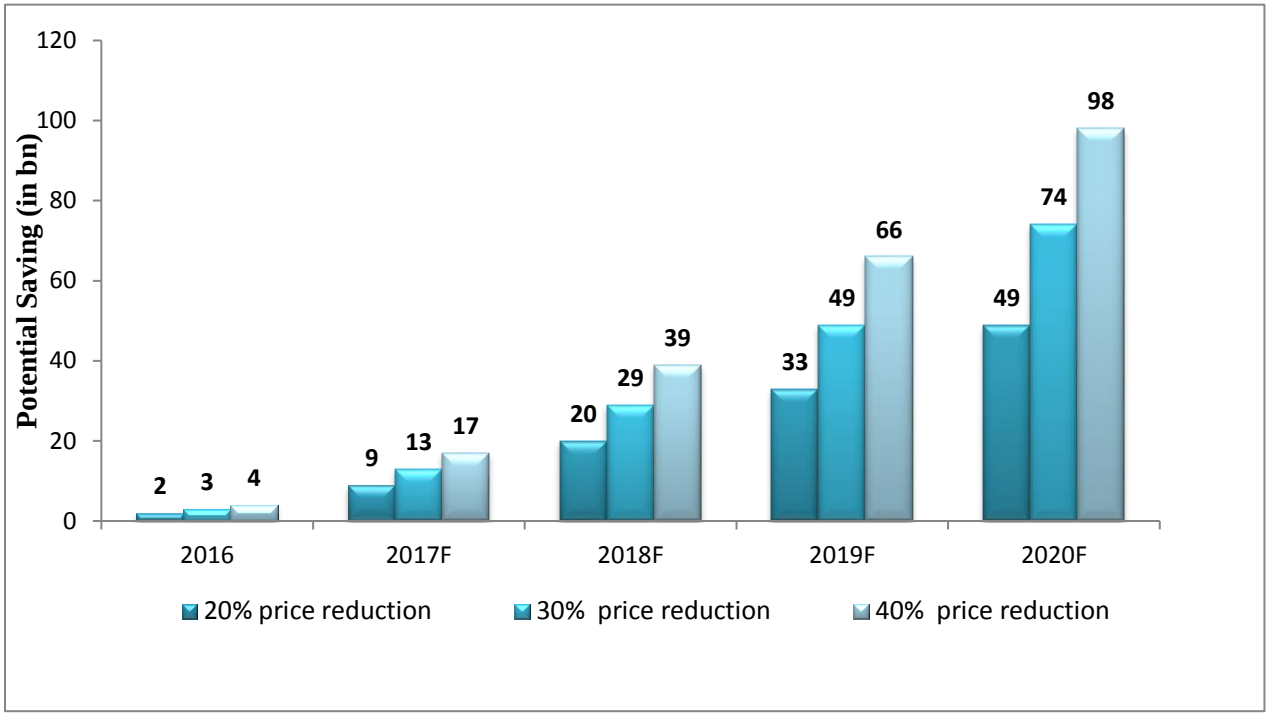
9. Potential savings with the use of follow-ons

With the ability to treat many unmet requirements, there has been no denying the importance of biologics in improving the prospects of health care across the world. Many times it is viewed as a miracle drug, as they endeavor hope where once there was only despair. Biologics transforms patients' life and provide them cures and treatments for diseases that used to be the cause of death or a diagnosis of chronic despair. All that hope and promise of healthcare comes at a price – a huge price which brings for much of the revenue biologics produce and which can turn the orphan drugs into blockbusters drugs. With some per-patient prices striking hundreds of thousands of dollars per year, which is well above the average cost of small-molecule drugs and generics, however many biologics are prohibited in emerging markets which are facing increasing number of geriatric populations as well as an increase in chronic diseases such as diabetes, hypertension.

In Peru, for instance, where breast cancer is one of the leading causes of death amongst women, the most effective treatments are out of the reach for most of the patients. Genentech Inc.'s Herceptin (trastuzumab) worth about $47,500, which is approximately eight times Peru's gross national income per capita of $5,880, by Public Citizen. In China, hemophilia A is a serious health care question, given the size of the population. Therefore, China accounts for a quarter of the world's hemophiliac A patients population who are deprived of the existing treatments which are available in the market, such treatments are either insufficient or too costly. The two approved recombinant adoptions are available in the market – Kogenate from Bayer Healthcare and Pfizer Inc.'s Xyntha which costs around $1,000 up to $10,000 per month depending on a patient's bleeding episodes.

On an average, a biologic is 22 times more expensive in comparison to the small-molecule drugs, which creates the potential for cost savings by the introduction of biosimilars. The Congressional Budget Office predicts that the first U.S. approved biosimilar could save payers and patients approximately $6 billion over the next decade by creating competition.

Graph 5: Potential savings in Europe from 2016-2020



Source: *IMS Health, MIDAS, IMS Health Market Prognosis; IMS Institute for Healthcare Informatics, Dec 2015*

With the market open for biosimilar competition, the overall healthcare domain has comprehended the potential savings of more than €10 billion in the EU5 region from 2016 to 2020. This competition is based on the direct competition between originator molecule and biosimilar molecule. From graph 5 it is clear that there is a potential saving from biosimilars usage. If there is 30% reduction in the cost per treatment per day for a disease over eight major originator biologics, who are scheduled to lose their exclusivity in 2016 to 2020 driven by the biosimilar competition existing in the marketplace. This could lead to the possible savings of about €15 billion in the next five years.

In the coming five years, the cumulative savings earned by the use of biosimilars in the reigns like Europe and US together could save from €49 billion to €98 billion (as shown in the graph5). The expansion of actual savings is comprehended on the factors like the uptake of this market by the payers as well as regulatory policies development and implementation continuously changing in the healthcare system.

10. Market Drivers

1. Cost-effective health care: With the changing scenario for biosimilars has arrived at a time when the global pharmaceutical market is facing the joint impact from the two major events i.e. a phase of number of loss of exclusivity of major biologics capturing the major share in the overall sale of key pharmaceutical products, as well as the economic catastrophe standing in front of the healthcare system with a pressure to reduce the cost of the current treatment options.

Whereas, payers present in the developed markets, confined economic expansion and continuous pressures on healthcare system makes the loss of exclusivity a true comprehensive dividend, which in turn enables much-needed savings. On the other hand, as potential savings from the generics start to decline in many countries over the upcoming 5 to 10 years at the same time it is necessary to find new ways to reduce the expenditure and payers are facing an urgent need to cross this obstacle. Biologics is amongst the premium pharmacotherapies which are currently available, and now even this area is facing the patent expiration. This consecutively brings the opportunity towards biosimilars.

2. Raising demand for alternatives: Despite the fact of constant demand from the payer's side to reduce the cost of the available treatments, there is a continuous demand in the cost effective substitute to biologics which, therefore, boosts the follow-ons market potential. Since the 1980s, there has been a number of biologics developed and launched in the market. Some of the major recombinants are insulin's, human growth hormones, erythropoietin's, monoclonal antibodies along with others.

3. Loss of exclusivity drives new potential: The loss of patent expiration between the years 2014 to 2022 for eleven well-established biologics which has covered almost 48 percent of total biologic sales, number of top-selling major biologic brands which includes products like Herceptin, MabThera, Enbrel, Humalog, and Remicade is going to face patent expiration in the coming five to eight years. This ultimately opens up a path for the follow-ons to deepen its roots in the biopharmaceutical market.

4. Therapeutic Area: Presently, there is a major transfer of the market towards diseases like cardiac disorders, cancer, and diabetes. There is a possible treatment option available for such diseases with the large molecules. But due to the high cost of the treatment and lower affordability by the middle-income class of population towards such treatment options, the demand for the biosimilars rises.

5. Prescribers support: Prescribers are the important influencers and they are the one who has the right to decide between originators product or the biosimilar product. There must be a consideration to provide adequate or upgrade their knowledge about the follow-on biologics. As the physicians are the one who will prescribe the cost-effective treatment options to the patients.

11. Restraints

1. Regulatory ambiguity: The regulatory policies set by the governing bodies for biosimilars are still in a flux. There are many major markets which are still facing the challenge to develop and full proof pathway for biosimilars approval. In the emerging markets, the pathway for the approval of biosimilars should be more structured.

2. Manufacturing complexity: Unlike small molecules, the time, risk and cost of biologics manufacturing are much higher, also these products are further passed to the consumers at a relatively higher cost. Though, a generics cost somewhere between $1 million to $5 million for its development, a biosimilars costs between $100 million to $200 million in its development. Follow-on biologics are way much complex to develop as well as manufacture because of the variability between one living cell to another. This is the reason that a biosimilar is not an exact copy of its originator product.

3. Competition: Follow-on biologics are facing competition from mainly two sources and those are biobetter manufactured by branded companies and brand consciousness from consumers. Biosimilars are expected to engross firstly in “brand-on-brand” feuding with their originator or reference therapies. Also, as generics are providing heavy discounts to the public, the amount of discounts provided by the biosimilars is much lesser than generics. The cost of development for a biosimilar is much more than the generic, which makes the biosimilars market less attractive to payers.

4. Reimbursement: Repayment of the money spent on the drug by the third-party. Profit framework and relative policies will be going to produce an impact on the uptake of follow- on biologics. Policy varies, from whether the drug falls in the pharmacy or medical benefit. So far, not even a single biosimilar approved in the US as of January 2017 comes under the pharmacy benefit.

12. SWOT Analysis

Biosimilars or Follow-on biologics is the fastest growing business with a hypothesis to have a strong economic value in the forthcoming years. However, there are a number of threats present in the market which will, in turn, restrict the growth of this industry.

1. Strengths

- Decrease in the price and identical originators product
- Notably lesser time as well cost is required to develop than the originator product
- High rates of return on investment than the development of a new compound
- Biosimilars are easy to get approval from the regulatory authorities in comparison to biologics.
- Small-molecule has been open-handedly accepted by the consumers, government as well as the industry. So, it is anticipated that its successor will also be widely accepted by the industry.
- With rapidly increasing health care costs, and with growing lower to the middle-income population the demand for cost-effective medicines has been increased. Thus, the scope of biosimilars expands.

2. Weaknesses

- Biosimilars regulatory approval pathway is still in the ambiguous state in many countries.
- Physicians play a major role in prescribing the biosimilars to patients. But, still there are many physicians who have not adopted the large molecules and they prefer to prescribe the originator medicines.
- In developing the market, the discount on biosimilars is lower than the heavy discount provided by the generics. While generics give 80-90% discounts on the reference product to the consumers, follow-on biologics provide only 20-30% discount over the originator product. This makes it even more difficult to afford by the middle to lower income people.

- Inadequate knowledge is present about the products to the patients as well as prescribers. There must be such awareness programs run by the budgetary bodies to spread the knowledge to the consumers, dispensers, as well as the prescribers.
- Lack of funds provided by the government in the developing markets. As the cost of the development is much higher than the small molecules development.

3. Opportunities

- Biosimilars is a swiftly rising market in Bio-pharmaceutics sector.

- As the biologics available for the treatment many chronic diseases, their cost for the treatment is also touching the ceilings. Biosimilars or the follow–on biologics provides a substitute option to the buyers, dispensers and the physicians. Because the price of the biosimilar is comparatively lower than the originator's product.

- Many developed, as well as developing countries, pay attention towards this market, because of the rising demand of affordable treatment cost. The regulatory bodies are working to prepare a more structured framework for the approval of biosimilars.

- Biologic medicines are useful for the treatment of many chronic diseases like cancer, diabetes, blood disorders along with others, and the treatment is very effective for the cure. Hence, a cost-effective alternative provides scope to lead in the marketplace.

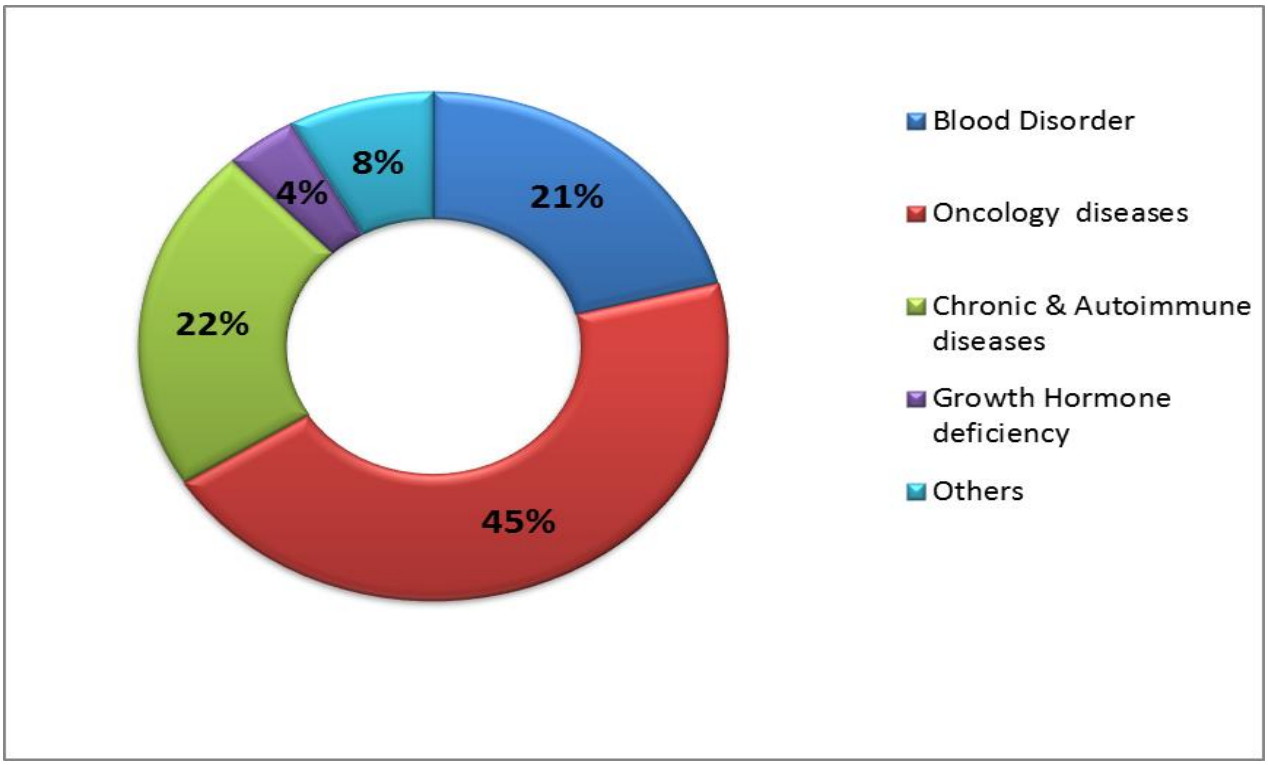
3. Threats

- A Large amount of investment is required for the growth of this industry.
- Week regulatory framework creates the risk towards the growth of biosimilar industry.
- Guideline varies for the approval of biosimilars from one region to another. Which creates an ambiguous environment for the market players developed the product.

13. Global Biosimilars / Follow-On-Biologics Market by Therapeutic Area

Biosimilar market on the basis of its therapeutic area is segmented into the following categories i.e. oncology diseases, blood disorders, growth hormone deficiency, chronic and autoimmune diseases, and others. Oncology diseases therapeutic area generates the maximum revenue as these are expensive products and are often used. With the increasing number of patients suffering from cancer, the commercial usage of oncology drugs has been increased. On the other hand, number of patent expiration has increased the potential of biosimilars applications in the therapeutic area of chronic and autoimmune diseases, Global biosimilars or follow-on biologics market on the basis of therapeutic area is presently dominated by the oncology disease therapeutics, which accounted for a revenue of $1202.7 million in 2015 and is anticipated to gather approximately $16 billion by 2021, registering a CAGR of 56.7% during the forecasted period.

Graph 6: Market share of biosimilars therapeutics



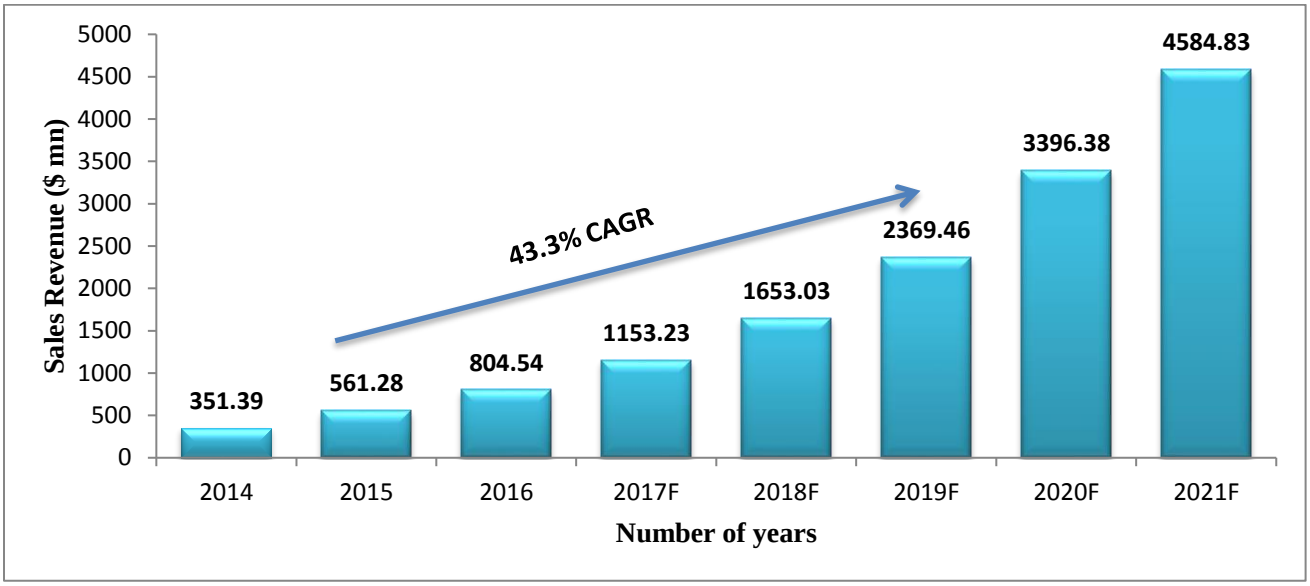
Source: *IMS, 2015*

- The above graph shows the market share of biosimilars or follow-on biologics in 2014 from various therapeutic areas.
- Oncology has captured the biggest market share of 45% out of all the therapeutic areas, as the number of patients with cancer is increasing with increase in demand for the medicines.
- Chronic and autoimmune diseases have garnered the second largest market share of 22% because of the increase in the number of biosimilars approval application due to loss of exclusivity of many major products in the approaching years.
- A Blood disorder has covered the market share of 21% in the therapeutic area.
- Growth hormone deficiency has captured the share of 4%, and the digits will increase in the future due to the major biologics in this area is facing off-patent.

13.1. Blood Disorders:

When any non-desirable thing occurs in the blood stream or with the blood components than it leads to a condition of a blood disorder. Blood disorders mainly affect three main components of the blood i.e. red blood cells (RBC), white blood cells (WBC) or the platelets. It can lead to condition, where thinning of blood takes place. This disorder is treated by using the products which are derived from human plasma or animal sources i.e. biologics, nowadays recombinant biologics are also in trend. Blood disorders are well treated by using erythropoietin and many biosimilars are there present in the market like Cresp®, Biograstim®, Filgrastim Hexal®, along with others.

Graph 7: Sales revenue of Blood disorders biosimilars forecast 2021



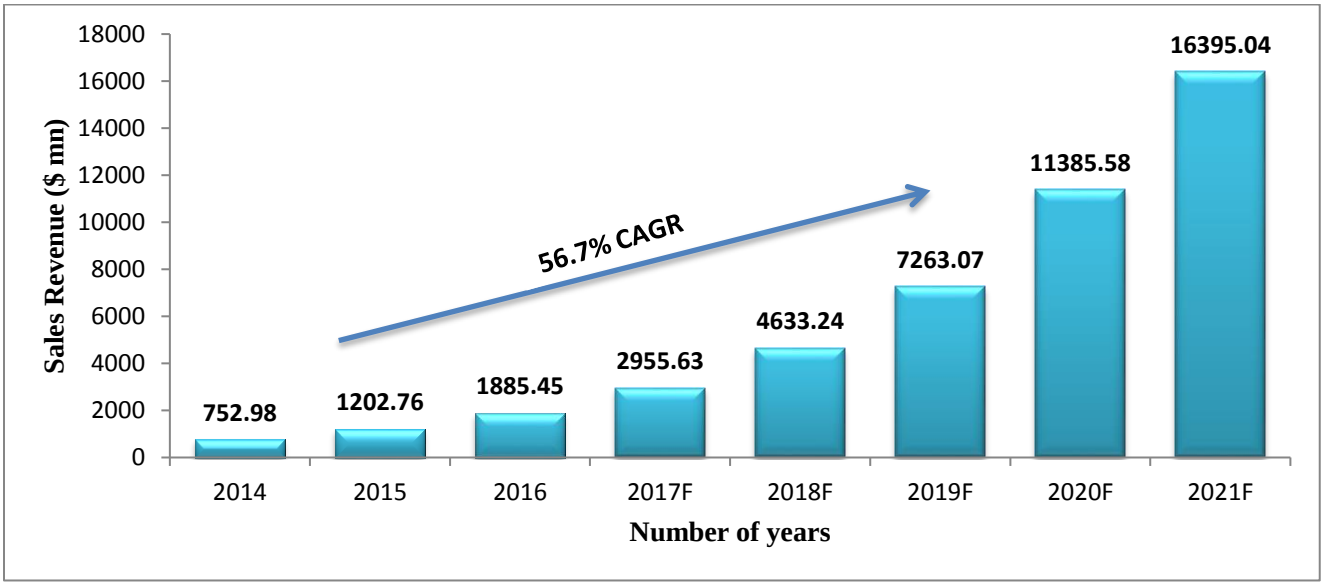
Interpretation

- The blood disorders therapeutic area is expected to reach around $4 billion by 2021. The market of blood disorders biosimilars will increase as there are a number of blockbuster biologics which are going to expire by 2020.
- Many blood disorders drugs are in the development pipeline, which will, in turn, increase the sales of this therapeutic area.

13.2. Oncology Diseases:

The promising cost-effective biosimilar medicines is gradually becoming an integral part of the society, as buyers, as well as regulatory bodies, is paying attention towards this market. It is significant that affordable medicines have increased the patient access towards many treatments available in the market. Oncology garners the biggest segment in the pharmaceutical industry, as their number of patients suffering from cancer is very high. F. Hoffmann-La Roche AG mature products like Avastin, Herceptin, Rituxan is facing sales cannibalization from biosimilars. There is a potential saving of $188 million in the US was found from patients switching to epoetin biosimilars. Thus, moving towards biosimilar will, in turn, increase the savings spend on medicines. There are more than 500 oncology products in the development phase, which then increases the possibility to increase the uptake of biosimilars future and will attract the sponsors to invest in this sector.

Graph 8: Sales revenue of Oncology diseases biosimilars forecast 2021



Interpretation:

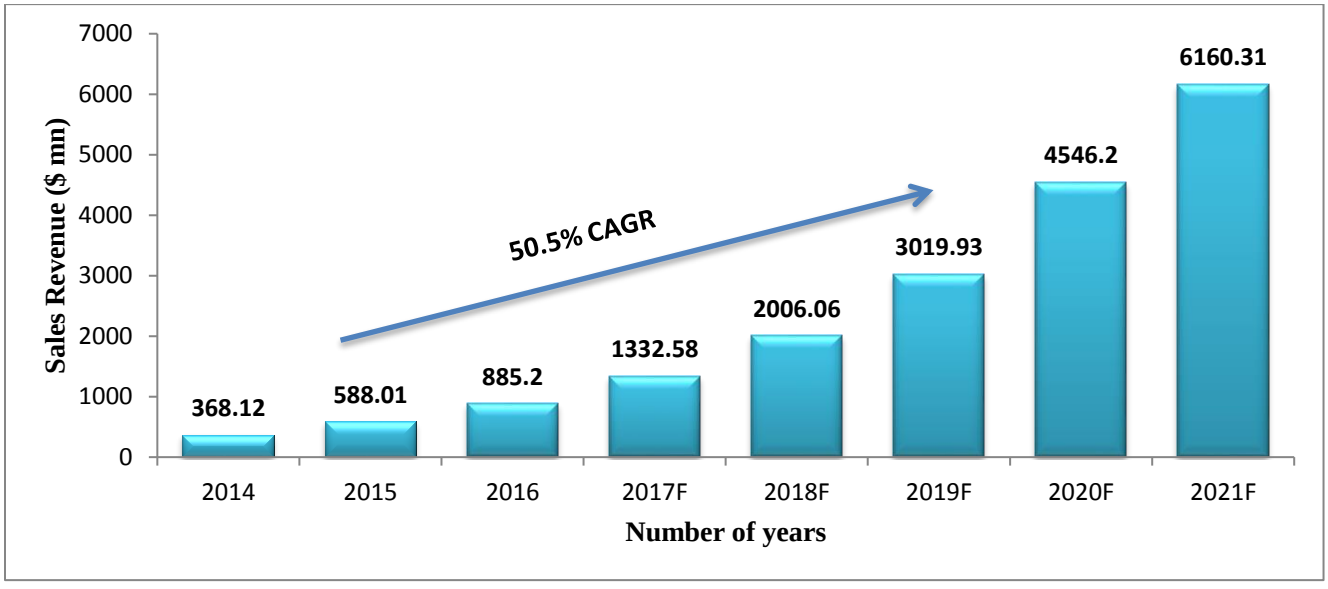
- As the graph depicts the sale of oncology biosimilars will increase from $752 million and reach to approximately $16 billion by 2021
- The major biosimilar players in oncology segment are Binocrit®, TevaGrastim®, Biograstim®, Grastofil® along with other biosimilars.

- With the expiration of patent of many blockbuster biologics in oncology like Herceptin, Gleevec, etc. has to boost up the market and will likely to do the same as there are many other patent drugs going to expire by 2020.
- More extensive commercial usege of oncology products has increased the cost structure of the oncology market.

13.3. Chronic and Autoimmune Diseases:

Autoimmune disorders are the consequence of the loss of ability of the immune system to differentiate between self- and non-self-antigens. Their incidence in the worldwide population is around 5%; these disorders are chronic and degenerative, being a major cause of disability resulting in an impact on the quality of life of the patients. Three scenarios have converged to provide a specific opportunity for biosimilars in autoimmune diseases: growing demand for biologics due to successful clinical use; the nearing of patent expiry for the four top-selling biological brands; and the search to reduce health costs due to the financial crisis.

Graph 9: Sales revenue of Chronic and Autoimmune disorders biosimilars forecast 2021



Interpretation:

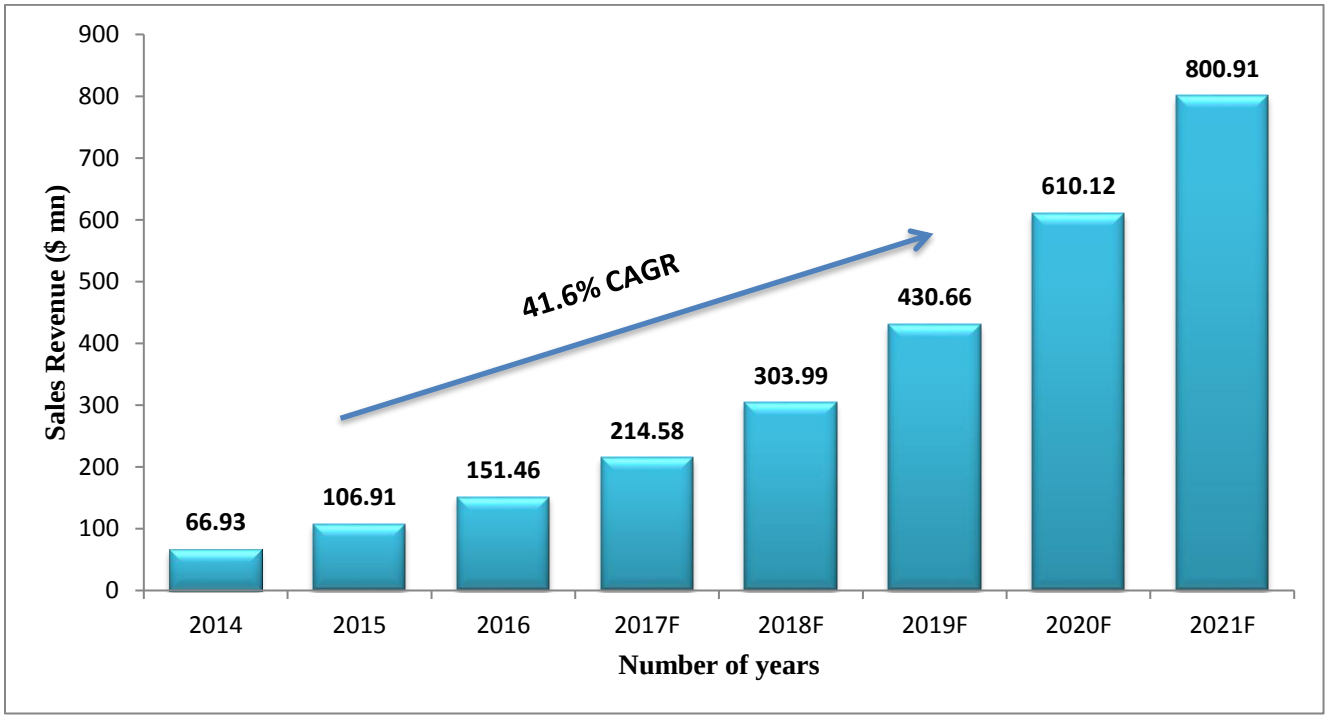
- The market covered by autoimmune disease therapies is the second largest market in biosimilars segment.

- The sales revenue will increase with the number of products which will soon going to face loss exclusivity.

13.4. Growth Hormone Deficiency:

A number of recombinant human growth hormone (rhGH) products are available for the treatment of pediatric growth disturbances, including somatropin (Omnitrope®, Sandoz, Kundl, Austria). Omnitrope® is a rhGH approved by the EMA in 2006; approval was granted via the biosimilar regulatory pathway, on the basis of comparable quality, safety, and efficacy to the reference product (Genotropin®, Pfizer, Sollentuna, Sweden). Omnitrope was the first biosimilar to be approved in the global pharmaceutical space and despite having a 30% lower price than Pfizer's Genotropin (somatropin [rDNA origin]), the drug initially failed to penetrate the GHD treatment market. After Sandoz re-strategized the Omnitrope brand and introduced improved delivery options and newer formulations, the biosimilar giant was able to make inroads into the market, albeit very gradually. Nevertheless, the originator drugs continue to dominate the arena in terms of patient share

Graph 10: Sales revenue of Growth hormone deficiency biosimilars forecast 2021



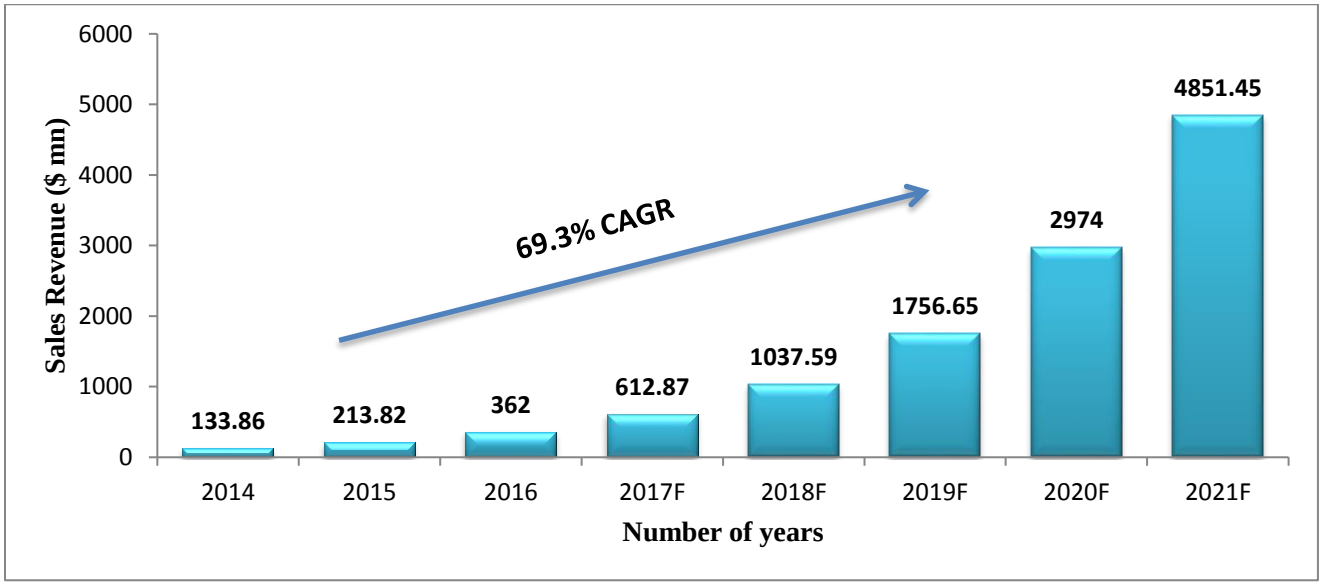
Interpretation:

- Though the market share of the growth hormone is less, but with time the sale will grow and growth hormones will show its presence and deepen its root in the biosimilars market.
- High costs of biologics available in the market will provide the opportunity to this segment to attract the costumers as well as with patent cliff, it will attract the sponsors to develop mores biosimilars in this segment

13.5. Others:

Many biologics medicines other than their traditional use for oncology, autoimmune diseases, etc. are also going to lose their exclusivity by 2020. These includes dimeric fusion proteins, anti-tuberculosis drugs etc. which will make their presence in the world of biosimilars market and will contribute to enhancing the profit of this sector.

Graph 11: Sales revenue of others biosimilars category forecast 2021



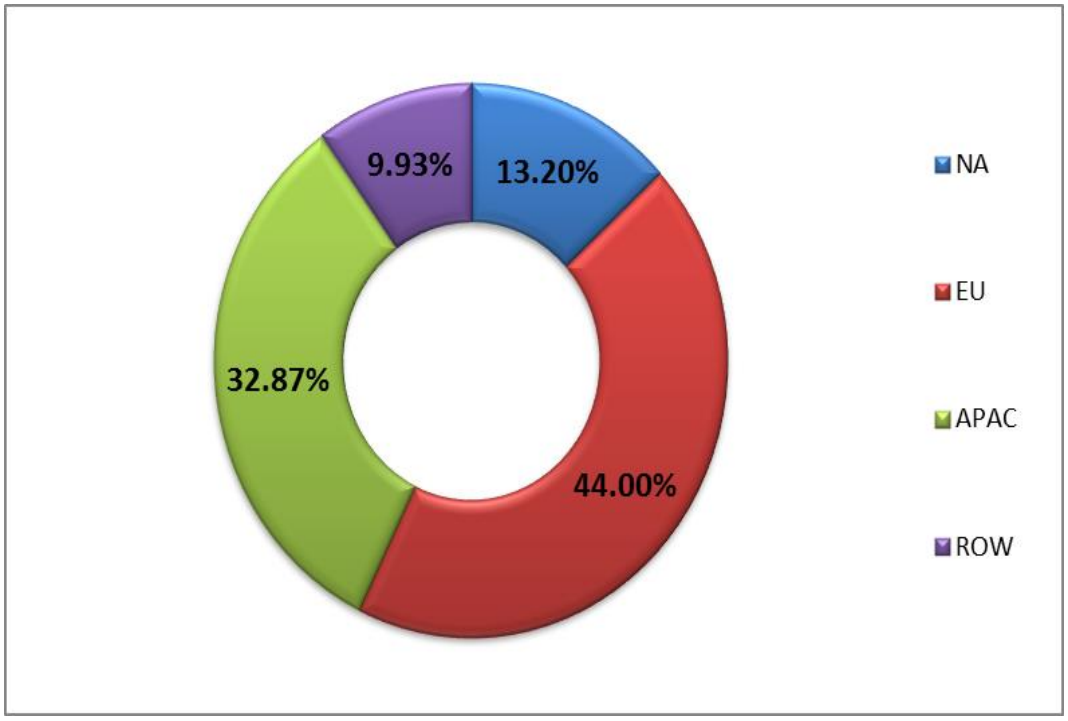
Interpretation:

- Many vaccines, proteins as well as anti-tuberculosis biologics are going to expire which will be going to add value to the biosimilars market.

14. Global Biosimilars or Follow-On-Biologics Market by Geography

Globally, biosimilars market is driven because of the following factors like increase in geriatric population, growing occurrence of diabetic patients and chronic and acute disorders, regulatory bodies' supportive initiatives and raising the cost of the biologics medicines. All these factors contribute to the growth of the biologics market. However, the developing/emerging pharmaceutical market with semi or unregulated environment brings opportunities in front of the biosimilars market.

Graph 12: Market share of biosimilars by geography



On the basis of geographical, global biosimilars market is dominated by European region; the major reason behind this market is the more advanced and structured regulatory framework for the approval of biosimilars. The Asia-Pacific region is anticipated to be the fastest growing market supplemented by a huge number of patient pools along with the significant demand for cost-effective therapeutics.

Based on geography, the disposable gloves market is segmented into the following regions i.e.:

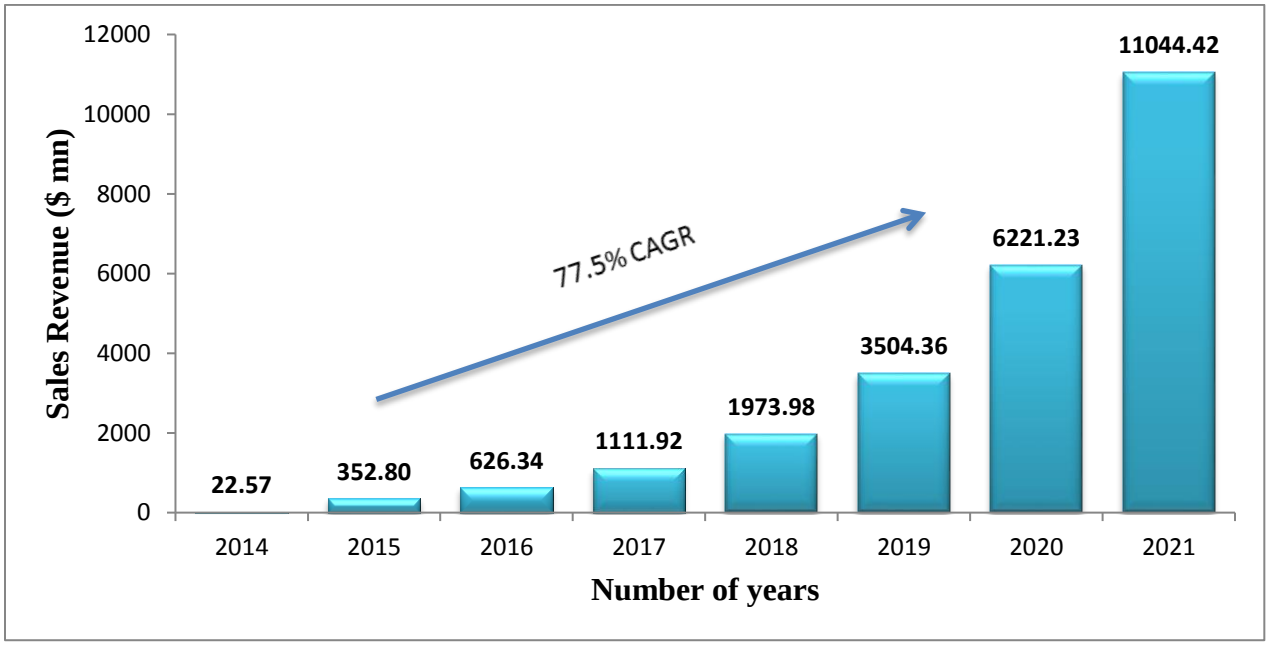
- **North America**: It includes U.S., Canada

- **Europe**: It includes U.K., France, Germany and others
- **Asia Pacific**: It includes India, China, Japan, South Korea, Australia and others APAC regions
- **Rest of the world:** It includes Latin America, Middle East, and Africa

14.1. North America:

By the end of 2015, U.S FDA approved its first biosimilar named Zarxio®. Then after the successful adoption by the consumers and physicians, regulatory bodies gave approval to two more biosimilars in 2016 named Inflectra® and Erelzi®North. Where Zarxio® is used to treat the lower numbers of leukocytes. Inflectra® and Erelzi®North are used for the treatment of Crohn's disease, rheumatoid arthritis. North America biosimilars market is estimated register sales revenue of approximately $11 billion over the forecasted period.

Graph 13: Sales Revenue of biosimilars in North America, forecast 2021



Interpretation:

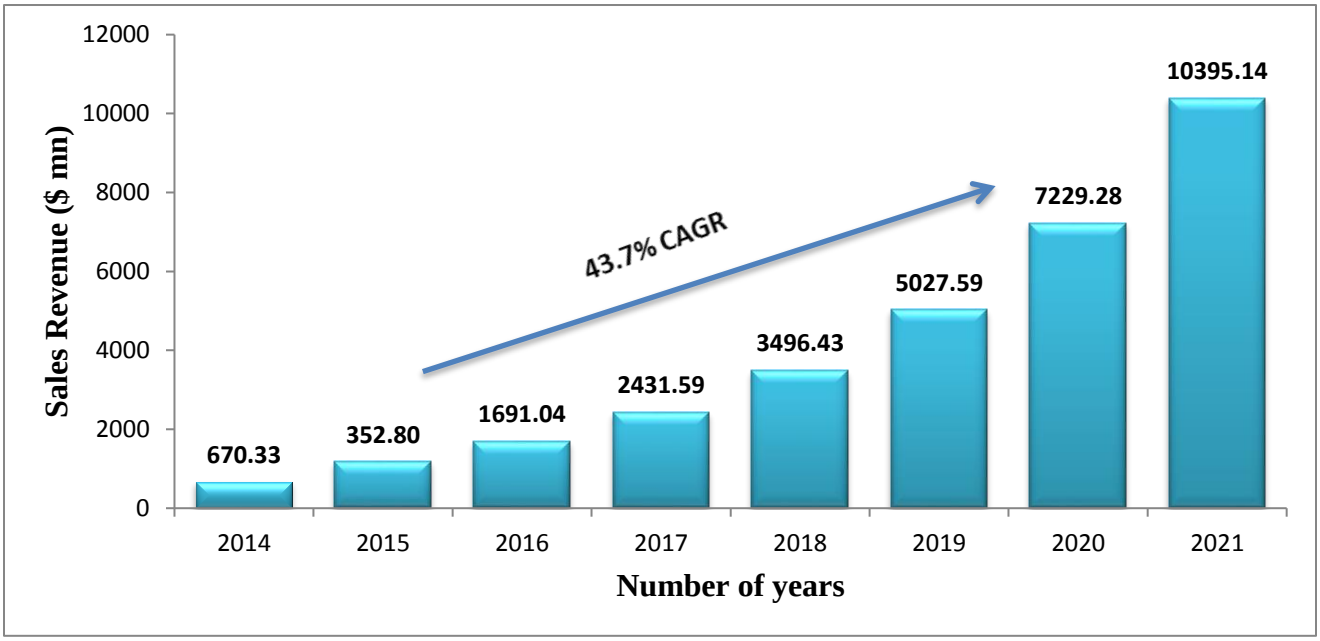
- The reason behind such tremendous growth of biosimilars market in North America is a loss of exclusivity of a number of top selling biologics, increasing number of biosimilar approval, which has encouraged the development of biosimilars.
- Especially after Zarixo® hit the US market, there is the wave of changes in the dynamics of the market. As there are a number of other biosimilars standing in the pipeline to get the approval. This exceptional change brings a CAGR of 77.5% for the forecasted period.

- Better reimbursement policy, high pricing of biologics medicines and focus of Trump government towards reducing the healthcare burden on the consumers, by approving more biosimilars in the country.

14.2. Europe:

Europe is the mature market for biosimilars. In Europe, filgrastim (Neupogen®) biosimilars have captured more than 50 percent of market share of short-acting G-CSF. With time and raising faith in Biosimilars, it is anticipated that the number will grow in the near future. As Europe was one of the regions with early adoption of biosimilars and is considered to be the developed market for the same. There are currently more than 20 biosimilars approved and marketed in the European market as per the EMA, March 2016 report.

Graph 14: Sales Revenue of biosimilars in Europe, forecast 2021



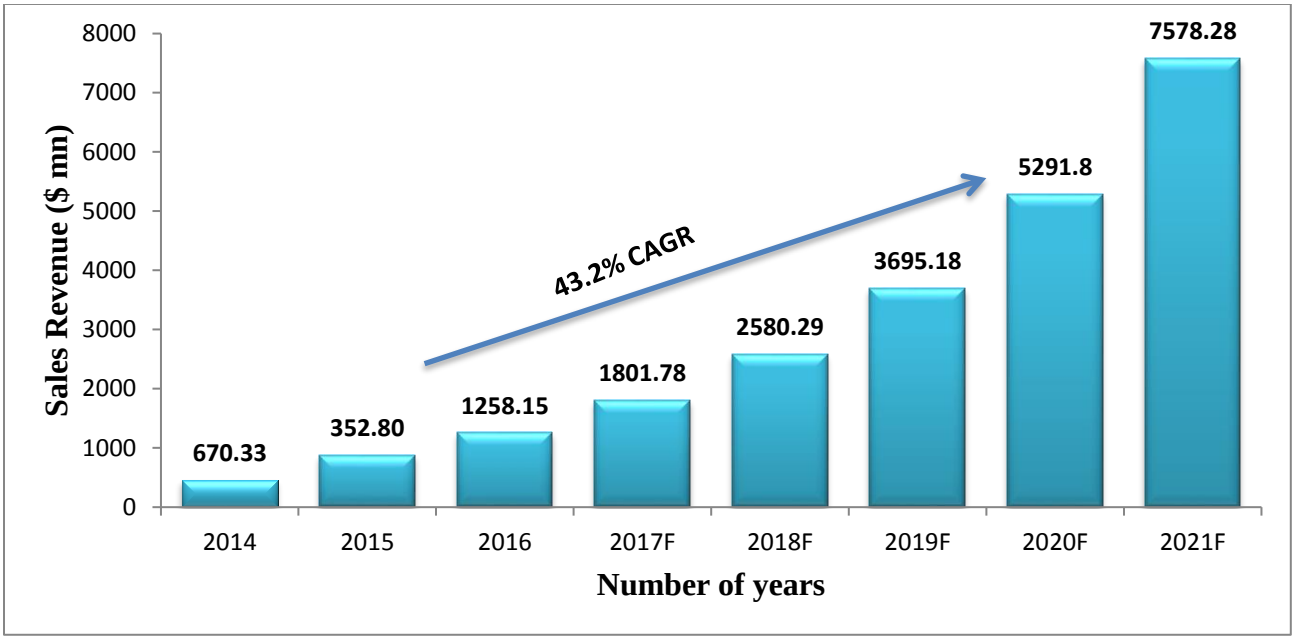
Interpretation:

- Europe is the mature market for the biosimilars. It has covered the biggest market share in this sector.
- By providing a wide ambit of treatment options available to the prescribers, buyers and payers have open the gate for those patients who were unable to reach to the treatment options from which they were deprived before the launch of biosimilars.

14.3. Asia Pacific:

India is very well placed to tap into the biosimilars opportunity that will come up in the next 15 years. Several Indian firms such as Dr. Reddy, Biocon, Zydus, Intas, Aurbindo and others have already made concerted investments and are at an advantageous position to participate in this lucrative market.

Graph 15: Sales Revenue of biosimilars in Asia Pacific, forecast 2021



Interpretation:

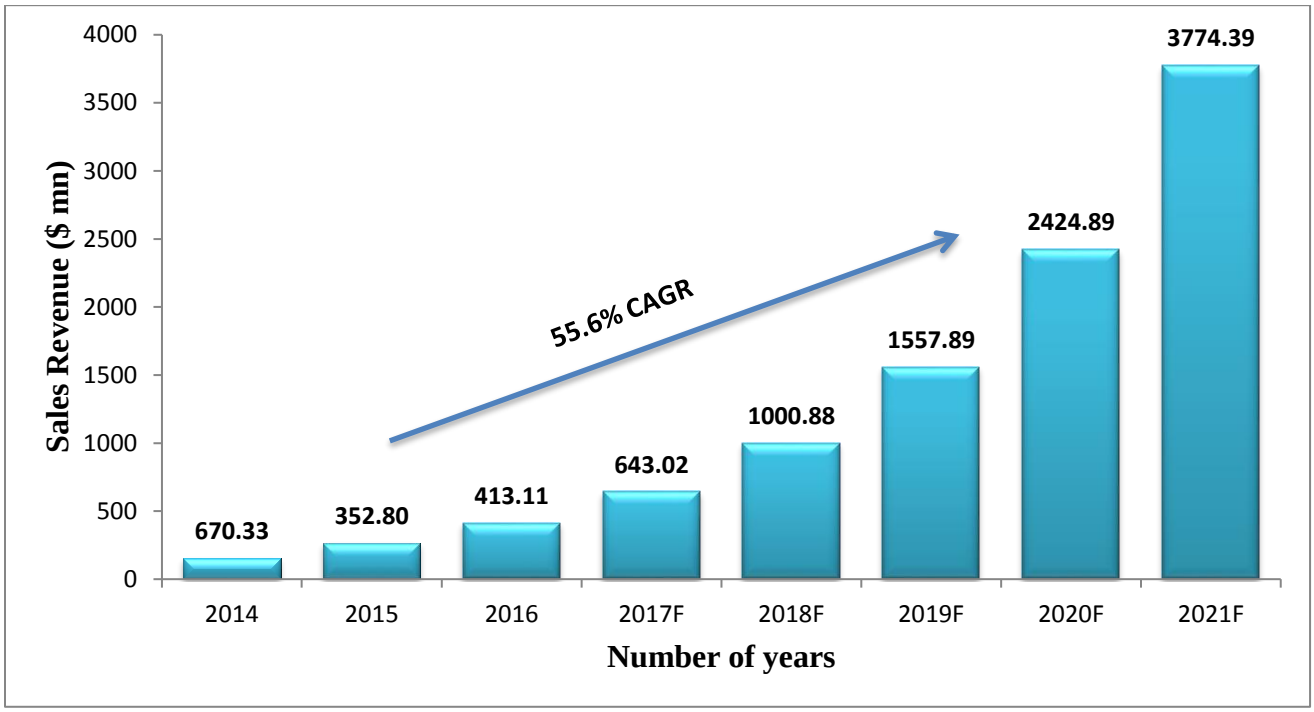
- Asia pacific is one the mature market for biosimilars, as many countries like South Korea, India among others were the early adopters of biosimilars and has a number of medicines present in the market.
- It is anticipated that follow-ons market will grow with the rate of 43.2% over the forecasted period.
- The growth rate is comparatively slower than the North-America's market as many countries included in this region like Russia, China is still struggling with the stringent guidelines for the approval.

- The biosimilars have a bright scope in Asia pacific region, as presently a number of international as well as domestic market players are joining hands together to work in this sector.

14.4. Rest of World:

RoW consist countries like Africa, Middle-east region, Brazil are having the demand of cost-effective healthcare but due to the unstructured regulatory pathway and high price tags on the biosimilars will, in turn, make the growth rate downwards.

Graph 16: Sales Revenue of biosimilars in Rest of the world, forecast 2021



Interpretation:

- Biosimilars is gaining appreciation in the emerging markets, due to constant pressure over governing bodies for the price reduction of overpriced biologics. And the regulatory bodies is paying attention towards this need of the society by providing funds, framing the pathway for approval in a structured form, also encouraging the foreign market leaders to come and work in collaboration with the domestic players.

15. PEST

The dynamic nature of global socioeconomic, technological advancements and patent expiration and political influences altogether affect the market of biosimilars.

15.1. Political Environment:

It is significant that whenever there is a change in the political environment it indirectly affects the industry and regulatory pathways. There has been a constant demand from the payers to fasten the approval rate of a product by the FDA, as there are a number of products present in the pipeline for development. Hence, the governing bodies are also creating pressure on the FDA to increase the approval rates which open the opportunity for biosimilar products as well. Also, with the Brexit movement, if British will move out then it will stand few challenges in front of the Europe as EMA is situated in London and many expertise's is likely to lose. This can affect the biosimilar market as well.

15.2. Global Socioeconomics

Globally recession has created an impact on the governing bodies in the recent years. This had a major mark over the economies of the developed as well as developing countries, as there was a loss of jobs, government funds, inflation, etc. Some of the developing countries are still trying to overcome these effects. Presently there is a drive in developed as well as developing countries to control the costs by implementing the appropriate measures, which also proposes to subsidize the copies of biologics. This measure could be an easy quick fix to reduce the healthcare cost. However, these cost reductive measure should be adopted by controlling the quality, safety, and effectiveness of biosimilars.

15.3. Technological Innovations

Technological advancements have always played an important factor in the development of any sector. With the advancements in DNA recombinant technologies have improved the selection methods for large producing cell lines. Also, the introduction of cost-effective disposable bioreactors has added to reduce the idle time production time, which in turn decreased the overall cost of production. In addition, with the development of high binding efficiency matrices and its application in Chromatography has removed the blockage in downstream processes which thereby increased the manufacturing process output. All these advancements in the bio-manufacturing has increased the production yields, growth in the level of protein expressions, decreased the cost, and also increased the profitability and leads towards the cost-effective manufacturing of biosimilars.

16. Competitive Landscape:

16.1. Sandoz

- Mission: We will be the main provider of high-quality, affordable medicines, helping secure long-term access to healthcare for people around the world.
- Sandoz FY 2014, sale for biosimilars was $514 million with a growth rate of 19%.
- Sandoz is the only company which is having 3 biosimilars approved and marketed in Europe.
- Name of the biosimilars marketed in Europe is Omnitrope®, Binocrit® , and Zarzio®.
- Also, Sandoz was the first who got approval for biosimilar by US FDA.
- Presently, there are 2 biosimilars approved and marketed in the US, namely Zarxio® and Erelzi®.
- Currently, there are 5-6 biosimilar molecules in the development phases.

16.2. Teva

- Tevagrastim® (short-acting G-CSF) was the first biosimilar Granulocyte colony-stimulating factor which was approved by the EMA in September 2008. On the basis of clinical trials, Tevagrastim® has been approved in EU for a number of indications. Hence, it is marketed in many European countries. Tevagrastim® is also marketed as Ratiograstim® and Biograstim® in the European regions.
- Additionally, other competing short-acting G-CSF biosimilars are anticipated to launch in 2016-2017 in the United States,
- Granix® was the first new G-CSF which was approved in the United States for more than ten years and was approved by the Biologics License Application by US FDA in 2012 and launched in November 2013. However, Granix® was not counted as a biosimilar in the United States.

16.3. Stada

- Collaboration agreement with Gedeon Richter for two monoclonal antibodies
- Product pipeline includes monoclonal antibodies

16.4. Pfizer

- Pfizer's biosimilars portfolio consist Inflectra® (biosimilar infliximab), Nivestim® (biosimilar filgrastim) and Retacrit® (biosimilar epoetin zeta) in the international markets.
- Sales revenue in FY 2014 was $63 million, in the biosimilar sector.
- In 2009, Hospira which was acquired by Pfizer signed an agreement to produce and market few biosimilar molecules with Celltrion Inc. and Celltrion Healthcare, Co., Ltd. This includes Inflectra™ (infliximab) used for the treatment autoimmune diseases. In Europe, Inflectra™ has launched in 36 markets.
- Celltrion acquires the right to market its infliximab product in the same European markets where Hospira is marketing.
- In September 2015, to wipe out few redundancies in Pfizer's biosimilar products pipeline. As a result of this, Pfizer decided to return Celltrion rights which were acquired by Hospira by returning two potential biosimilars to Rituxan® (rituximab) and Herceptin® (trastuzumab).
- 8-9 biosimilar products are currently in the developing phase of different clinical trials.

16.5. LG Life Sciences

- Leading biosimilar maker with antibody biosimilars in the pipeline
- LG Life science and Machida to co-develop and commercialize biosimilars in Japan

16.6. Amgen

- Amgen is having one product approved and market known as Amjevita® (adalimumab-atto)
- Presently there are 6 molecules in the pipeline of Amgen named ABP 501(biosimilar adalimumab), ABP 980(biosimilar trastuzumab), ABP 215 (biosimilar bevacizumab), ABP 798 (biosimilar rituximab), ABP 710 (biosimilar infliximab), ABP 494 (biosimilar cetuximab).

16.7. Eli Lilly

- Presently, many products including Cyramza, Erbitux, Trulicity, and Portrazza, and many of the new molecular entities (NMEs) are in the developing phase i.e. present in the pipeline.

168. Biocon

- Currently, Biocon consists one of the biggest portfolios of generic insulins as well as biosimilar protein therapeutics. These products are in the last stage of the development phase including six biosimilar molecules present in Phase III clinical trials, named rh-Insulin, Glargine, Trastuzumab, Adalimumab, Pegfilgrastim, and Bevacizumab.
- Biocon is holding a strong position in the Indian market, strongly in the insulin biosimilar segment.

16.9. Merck

- Merck and Hanwha Chemical of South Korea enter into partnership for development of the biosimilar version of Enbrel
- Merck –Paraxel strategic alliance for global clinical development of biosimilars

16.10. Dr. Reddy's Lab

- Global biosimilar sale revenue in 2012 was $26 million, with the growth rate of 45% over 2011
- One of the companies with early movement to take over the advantage by proving its commercial presence in more than 13 countries
- The partnership agreement with Merck is going to lead at a steady pace. The company is presently performing the early development of the product, technology transfers as well as Phase-I trials.
- DRL accounts approximately 15-20% of the total R&D spending which is around $ 45-65 million.
- It has 4 biosimilars which are marketed in EM with 2 Investigational New Drug Application filings in the USFDA.
- 2 biosimilar molecules are in the clinical trials named Rituximab and Pegfilgrastim.
- Collaboration with Merck Sereno (FY2012) for the developed markets is considered to be the risk sharing strategy.
- DRL also has 10 biosimilar molecules in the pre-development or in the evolution phase with a cumulative market size of $37billion.

17. Conclusion:

Rising demand for affordable healthcare is prevailing everywhere; to fill such need gaps many initiatives are taken by the government bodies like encouraging the use of cost-effective alternatives by promoting biosimilars and generics, improving the reimbursement policies, and providing subsidiaries on the over-prized medicines.

Biologics is the class of biopharma products which is majorly used for the treatment of chronic autoimmune diseases like diabetes, and cancer. Out of the global sale of top ten pharmaceuticals, eight were biologics in 2015 which reflects the potential of the biologic market. Apart from the fact that biologics are used as life-saving drugs, the major drawback it faces is the high cost of the therapy and due to this reason, many patients are deprived of these life-saving remedies. To surpass such reason, "copy biologics" or "biosimilars" or "follow- on biologics" are approved by the government. Biosimilars are the exact copy of biologics but it provides a discount on the original product.

Regulatory bodies are majorly concerned with the quality, safety and effectiveness of the biosimilars this is the reason why the approval pathway for them is stringent. Developed market like Europe is having a structured pathway for the approval of biosimilars. US FDA has recently approved 4 biosimilar products, as the country realize the out-of-pocket expenditure spent on healthcare is very high and to save such expenditure one should adopt alternatives. Developing markets like India, South Korea, Russia, China has also emerged as a potential market for the growth of biosimilars because of the large patient pool, government initiatives in the prospect of optimizing the current healthcare treatment options, and high incidence of the chronic diseases. The large market potential in emerging market is evident by a number of collaborations between domestic and international market players of biosimilars. The biggest segment of biosimilars market is oncology disorders, followed by chronic and autoimmune diseases and blood disorders. Major reason for the growth of these segments is the patent cliff of the biologics in the forthcoming years.

Biosimilars is the future of biopharmaceuticals, as it fulfills the unmet needs of the society and also provides access to healthcare. Regulatory bodies should develop a clear and structured pathway for their approval in both developed and developing the market, also awareness amongst the physicians, patients, and payer for the biosimilars should be spread.

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