Review Article

A Comprehensive review on Biosimilars; present & future

ABSTRACT:

For providing treatment about most complex disease like cancer,hormone inadequacy, kidney problems, life-threatening and many types of rare illnesses biologics are conducting a major role of the biopharmaceutical market. But there are many problems faces that's are a highly complex process, patent expires, cost effective etc. for those type of reason and more patient demand a similar drug is making which is as similar as biologics drug, simple making process, and less costly. A biologic is a medicine that is biosimilar medical product which is subsequently adaptation of the biologic product or almost an identical substitute of the original product which is manufactured by other brand of company. Although biosimilar drug has FDA approved for manufacturing but they also have to require a different approval for those drug marketing, since they are the reason why they are not a generic form of biologics. Biosimilar drug are not exact copy the originator drug, they are similarly designed the innovator drug. This paper mainly highlighted to the current scenario of biosimilar drug in biopharmaceutical field also the future result of this similar biologic drug in biopharmaceutical field. Biosimilars are hardly offer to promising that it was a beneficial and less cost-effective site for patient and doctors also.

Keywords: Biopharmaceutical market, Biologics, Biosimilars, Identical substitute, Innovator drug.

INTRODUCTION:

In the biopharmaceutical field one of the fastest developed sector is "biologics". Biologics drugs are originating from living cells through the biological process & imitation like natural biological essential as like hormones. Biologics are also benefitted with many types of complex diseases such as rheumatologic disease, inflammatory bowel disease, carcinogenic state etc. [1] Medication categorised as biologics are the most popular in worldwide, but there was a major drawback of this field that's are more costly that's why it's not affordable for major of patient. Especially within India that is a developing country in their people can't buy the product.[2] But currently, there is exists an opportunity after the patent or intellectual property claim is expire by the innovator company then a similar drug is making for all who can't afford the biologics. A biosimilar is a comparable biologic medication or product or drug that is generated by other brand of

company which has already been authorized by FDA but it was not a same copy of originator drug. It's a less of cost, it's having no medical significance but difference in safety & efficacy also effectiveness the innovator drug. [3,4]

Many medical professionals, including doctors, think that biosimilars are very effective and have a good influence on prescription prices. The expenses have gone down despite the fact there are greater quantities of biologics accesible, which has improved the patient experience in getting access to the life-saving medication. The Indian biosimilar industry is expected to develop at a 25.2% compound annual growth rate (CAGR) between 2022 and 2030, from its anticipated $349 million valuation in 2022 to $2018 million in 2030. [5,6]

BIOLOGICS:

Biologics, which are medications made from living things or that are parts of living things. In order to cure the medical problem, these proteins were produced using genetic engineering to target particular immune system components. Inflammatory bowel disease (IBD), rheumatoid arthritis (RA), and various types of cancer have all been considerably better managed because to biologics. Therapeutic formulations derived from human, animal, or microbiological sources are generated using a wide range of technologies and are referred to as biologics. A biologic drug called Human Insulin was the first to be sold in 1982. A few examples of biologics are recombinant proteins, tissues, cells, genes, vaccines, blood and blood components, and allergies.[7]

Many Complex molecules with large dimensions called biologics are created in living systems, such as microorganisms, animal, or plant cells. Most biologics are manufactured from via r-DNA technology. On the other side, a drug is typically produced by a chemical process, meaning that certain chemical components are mixed in a precise order to create the drug. Like pharmaceutical drugs, biologics drugs are mainly approved the application must be delivered to the relevant nations' regulatory bodies.[8] Biologics approval in the United States is governed by the US Food and Drug Administration (FDA), the Centre for Biologics Evaluation and Research (CBER), the Centre for Drug Evaluation and Research (CDER), and others. Biologics approval in Australia is governed by the Therapeutic Goods Administration (TGA), Therapeutic Goods Register of Australia (ARTG), and other organisations. The Food and Drug Administration (FDA) and the Central Drug Standard Organisation (CDSCO) oversee the clearance of biologics in India. [5,9]

BIOSIMILARS:

A drug is refers to as biosimilar that is very close in configuration and function to biologics or biological drug. Biosimilar drugs are 'similar' but not an 'identical' aspect to its referred products. After the expiration of patent(s) protection and regulatory data protection of the biological products or biologics then other biotech company or many pharma companies have achieved to marketed the duplicate or similar of the biologic products.[10] In order to develop and manufacture high-quality biosimilars, manufacturing proficiency and intrinsic scientific understanding are necessary. On other side drugs that are biosimilar have low complexity of both structural and molecular.

According to FDA, An FDA-approved biologic that bears significant similarities to another biologic known as the original biologic is called a biosimilar. It is typical and expected that there will be slight variations in dosage amongst similar batches medication for both original biologics and biosimilars. It suggests that biologics are not very reproducible, which explains why biosimilars differ from their original biologic. [11]

DIFFERENCE BETWEEN BIOLOGICS, INCLUDING BIOSIMILAR AND GENERIC DRUG:

Anything that is originated from living things or contains parts of living things is called a biologic drug. They carried out of an extensive range of goods made from microorganisms, animals, and humans. Among them might be recombinant proteins, cells, genes, tissues, blood, or blood components. The size of the molecules in biologics, which can frequently be thousands of times larger compared to those in chemical drugs, is the main distinction between biosimilar and generic drugs. Whereas biologics are taken as injectables or in fusions, chemical and generic generally, drugs are taken orally as tablets, capsules, syrups, etc. Biologics, on the other side, can be extremely sensitive to this factor and must be stored and transported in a refrigerator condition. Generic drugs are likewise more stable and less sensitive to handling conditions.[12] Numerous complex diseases, including cancer and rheumatoid arthritis, which biologics are used to treat. Biologics are mostly utilized to treat illnesses for which there is no recognized treatment. The manufacturing regarding biologic drugs is far more complex and costly than that of conventional drugs. When a biologic drug's patent expires, other businesses can produce and market a biosimilar, which is an exact replica of the original biologic drug. Biosimilar are not perfect reproductions of the original drugs, unlike chemical drugs, which can be copied by generic companies. A perfect replica of the original biologic medication is nearly impossible to produce due to the complicated nature of manufacturing. However, since they function in the same manner and possess the same physiological effects, they are regarded as equal to the original medication. While biosimilars are heated similarly to generics, they are not biologic drug equivalents. Generics are exact replicas of the brand-name medications, but biosimilars resemble the reference biologics very closely but are not the equivalent. [13]

Properties	Generics	Biologic	Biosimilar
1. Molecular weight	< 500-900 Daltons	<1000	> 140,000 Daltons
2. Composition	Active ingredients that are identical to the innovative product	The novel product's active components are the same. Living organisms like cells and tissues may contain active proteins, nucleic acids, or complex combinations of these	Active proteins or peptides it's not identical but similar to innovator drug to a questionable extent.

		substances. Active proteins or peptides are somewhat similar to innovative drugs but not exactly the same.	
3. Manufacture	Synthesized in laboratory or derived from organic sources.	Biologically produced in host cell lines Changes in the production process might be costly. Reproducibility is challenging to prove.	Manufactured from genetic material of living cell cultures or DNA technologies
4. Adverse immune reaction	Lower potential and predictable	Higher potential and predictable	Higher potential and unpredictable
5. Origin	Living organism	Equivalent to the brand-name drug	Similar regarding the reference biologic
6. Cost	More expensive	Less expensive	Less expensive
7. Savings	Less savings	More saving than brand drug	More savings

Table no:1 Difference between Biologics, including Biosimilar and Generic Drug

DEVELOPMENT AND MANUFACTURING OF BIOSIMILARS:

Each and every biosimilar that is available on the marketplace starts its development process with a thorough analysis regarding the citation of the product. The process of creating a biosimilar involves several steps and a high level of expertise, requiring a thorough comprehension of the cited medication product. The process of assessing and creating a biosimilar involves several steps, as outlined below.[14]

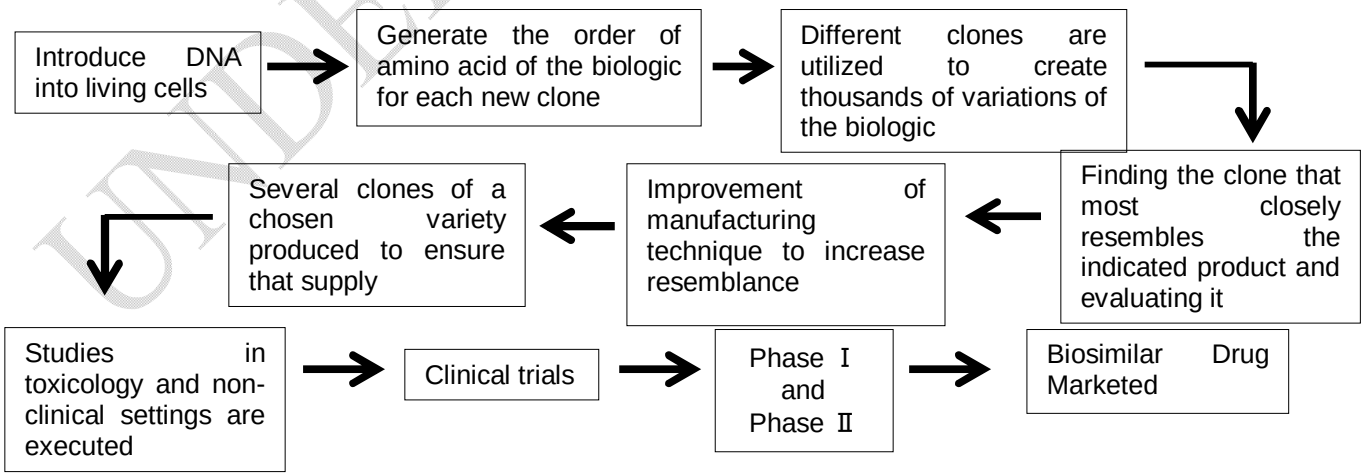

Table no:2 Development and Manufacturing of Biosimilars

CLINICAL TRIALS:

In first stage regarding clinical trials, some healthy volunteers or patients are select to test for body function when in contrast to the reference product in terms of biology. Secondly, the patient which are selected for clinical trials are noticed is the biosimilar drug work on their way. Thirdly, check and evaluate the both product safety and efficacy as the mentioned.

The clinical trial must follow best practices within the field and evaluate appropriate clinical parameters using statistical analysis. [15]

CHALLENGES:

Due to the complicated and variable nature of biologics and biosimilars, the approval process is difficult for both manufacturers and regulatory agencies, such as the European Medicines Agency (EMA), the Food and Drug Administration (FDA) of the United States, and the New India Guidelines. Non-inferiority trials and equivalency trials are the two types of trials that are similar enough to be approved.[6,16]

ROLE OF FDA: In general, the FDA recommends non-inferiority trials that the manufacturer conduct a product test. The reference medication is utilized to evaluate the biosimilar product using a predetermined equivalency margin. To ensure that identify clinically significant variations in both safety and efficacy, the margins must be substantiated by available data from a scientific perspective. Following the completion of all testing procedures, the FDA has approved similar biologic drugs, and they are now on their way to the EMA. [17]

ROLE OF EMA: It is not possible to test superiority or inferiority in an equivalency trial; only equivalency can be assessed. Randomised equivalency trials with parallel groups and sufficient power are preferred by the EMA. There is one significant difference between the methods used to determine sample size in a superiority design and an equivalency trial.[18]

QUALITY SAFETY, EFFICACY AND IMMUNOGENICITY REGARDING THE ITEM:

The production method used by the manufacturer to produce biosimilars raise questions about quality and safety, and before they able to accepted for marketing, their efficacy must be accepted by the appropriate regulatory body. This requires a suitable comparability study. The effect of the production procedure and their starting materials regarding product excellence has been better understood thanks to the recent International Conference on Harmonization Q8 guidelines on the FDA's Design Quality and Process Analytical Technology programs as well as pharmaceutical development. To ensure that there are no appreciable changes, the EMEA must compare the originator product and the biosimilar product. The effectiveness and safety of a protein product are influenced by its quality, hence comparing the originator

and biosimilar products is crucial. Thus, the production procedure used to produce a biosimilar should demonstrate that it can yield a superior quality product and meet the same quality standards as any newly established biologic manufacturers. The methodology needs to take into consideration the scientific understanding that allows biosimilar manufacturers to employ more sophisticated processes than those utilized on developing an original product. [19]

Because of their large molecular weight and size, the body's immune system recognizes biologic medicine despite its complexity, allowing for a variety of immunologic responses. Since the first biologic, Humulin, was the initial one to be authorized administered by the Food and Drug Administration (FDA), the international biologics industry has advanced significantly. Due to the development of antibodies against the medication, there was a decrease in effectiveness in the original infliximа treatment for rheumatoid arthritis. This may have negative effects on the effectiveness (neutralizing antibodies) and raise it's possible that infusion reactions or anaphylaxis. Small adjustments made to any biosimilar production step may be the reason behind variations in cell behaviour, which may ultimately have an effect on the product's quality or structural details. Age, gender, and the subsequent medications taken can all have an impact on a patient's response and need to be taken into account. Currently available data there is little information available on the immunogenicity profiles of biosimilar products. This should be taken into consideration by regulators and biologics producers as they attempt to strike the ideal balance between preapproval Data specifications as well as post-marketing efficacy and safety, even though opinions on this matter may differ. This will be crucial when deciding which drug product is accountable for any safety incidents. [14]

SUBSTITUTIONISSUES:

Generally Substitution with biosimilars has different controls and motivations than with generics. Chemically synthesized generic medications can be interchanged with their original counterparts because of the fact they are interchangeable, offer the identical medicine effect, and are more affordable. Such irrational replacement in the event that a biosimilar may result in unfavourable side effects or even the therapy's failure. It matters to prescribers and pharmacists because a pharmacist can use a biosimilar to replace a reference medication that is prescribed. [20]

PHARMACOVIGILANCE:

All medicines, including both biosimilar and biologics, should under-go pharmacovigilance testing. The small number of patients evaluated throughout the registration process for biosimilars is taken into consideration in pharmacovigilance studies for biosimilars. It is defender for these studies that these and adverse events for other's are reported in a timely manner. Only a certain how many patients use the product during the pre-marketing phase, so identifying immunogenic reaction episodes necessitates a very thorough instead of thorough pharmacovigilance program. The amount of power of adverse reactions and how they are managed might not be known if there are no validated methods available. Complete information about the medication received, including itsreference or biosimilar, proprietary name, International Non-proprietary Name (INN), and the precise dosage given, must to be incorporated into the ADR oversight. [21]

NAMING AND LABELLING OF BIOSIMILARS:

For easily recognizable to physicians, pharmacists and patients and also easily recognizable International Non-proprietary Name (INN) it is important to each biosimilar drug has given appropriate naming and labelling also. According to the recommendations of a global expert advisory panel, a World Health Organization committee is carrying out this activity. This name can help prescribers, pharmacists, and dispensers avoid confusion given that it's a public property. When a medication's specific name is used in the event of an adverse event, pharmacovigilance is made simpler. Labelling should include unique safety and efficacy information for biosimilars, since they cannot be substituted for reference products. Additionally, indications that are founded on data the appropriate extrapolation method is noted in the labelling. [22]

BIOSIMILAR MARKET IN INDIA:

In India, biosimilars mainly include vaccines, recombinant proteins, monoclonal antibodies, diagnostics, insulin (wosulin, insugen, and cosulin), erythropoietin (hemax, epofer, wepox, cereiton, and epofit), and hepatitis B vaccine (ShanvacB,RevacB,EnivacB,GenevacB,BiovacB,Bevac),that have been approved for sale in India by a competent body based on a comprehensive dossier and a track record of safe usage in the country. In India, many of the companies that deal with biopharmaceuticals are actively engaged in the creation, manufacturing, and distribution of biosimilar medicinal goods.

It is anticipated that the biosimilars market in India would expand at a compound annual growth rate (CAGR) of 25.2% between 2022 and 2030. [14]

INDIAN REGULATIONS AND GUIDELINES FOR BIOSIMILAR PRODUCTS:

As mentioned in The Indian regulatory Guidelines, or "Draft Guidelines on Similar Biologics: Regulatory Requirements for Marketing," the Indian regulatory system for biosimilar drugs authorization in India," were made public by the Department of Biotechnology (DBT) in June 2012. The regulatory process by which a comparable biologic can claim to be identical to an established reference biologic is described in these guidelines. These Indian guidelines about comparable biologics are therefore similar to the USA and EU's biosimilar guidelines in many ways. India is marketing biosimilar products using a "sequential approach," which is comparable to the "stepwise method" used by the US and EU.

The Environment (Protection) Act, 1986 is notified by the FDA's 1940 Drugs and Cosmetics Act, 1945 Drugs and Cosmetics Rules (as amended from time to time), and 1989 Regulations governing the production, application, import, export, and storage of hazardous microorganisms and genetically modified organisms (Rules, 1989). [23]

AUTHORITIES FOR APPROVAL OF BIOSIMILAR PRODUCTS:

The Central Drugs Standard Control Organization (CDSCO) and the Review Committee on Genetic Manipulation (RCGM) are the committees that can approve biosimilar products; c) the Genetic Engineering Appraisal Committee (GEAC); and d) the Institutional Biosafety Committee (IBSC). The product is first tested

by the aforementioned authorities. Once the testing period has ended and the product has passed their tests and studies, Authorities have certified the product and given it the green light to be marketed. [24]

PRESENT AND FUTURE STATUS OF BIOSIMILAR:

The “Drug and Cosmetic Act” of India states that biological products are regarded as new drugs. Goods destined for Indian markets are overseen by the Drug Controller General of India, The DCGI, also known as the Department of Biotechnology (DBT) and DCGI, is the Drug Controller General of India. The 1940 Drugs and Cosmetics Act and the 1945 Drugs and Cosmetics Rules cover the regulatory history pertaining to the import, manufacture, and sale of drugs. Ensuring that human drugs are safe, effective, and meet prescribed quality standards, as well as that marketed cosmetics are safe to use, is the primary goal. within India, the manufacturing process and promotion of biosimilars is carried out by over 100 biopharmaceutical enterprises. A biopharmaceutical company from India recently received approval from the USFDA to market their innovative biologic. The FDA approved Herceptin, a biologic utilized to addressed certain types of stomach and breast cancer, as the initial biologic. Herceptin's active ingredient is trastuzumab. Moreover, this was the first product of its kind made through an Indian company and authorized for sale in the United States.

India is an essential player in the production and application of biosimilars, despite on-going growth and evolution in the US market. A large percentage of medical professionals, including physicians, think that biosimilars are highly effective and positively impact prescription costs. The experience of patients receiving the life-saving drug has been enhanced by the reduced cost, even though the item is an exact replica of biologics. India’s biosimilar marketplace is anticipated to expand at a compound annual growth rate (CAGR) of 25.2% between 2022 and 2030, from a projected valuation of $349 million in 2022 to $2018 million in 2030. [25,26]

CONCLUSION:

Biosimilar medications are essentially not identical replicas of biological drugs that have already received approval. As a result of this, even though it isn't a generic, it is a comparable product. Biosimilar and originator products never get the few substitution rules, so they must be treated differently than generic products when it comes to substitutions. According to Indian guidelines, a "similar biologics" is defined as a biological item or drug created through genetic engineering that is said to resemble a reference in kind biologics that has been approved for safe use in India through the FDA, EMA, CDSCO, GEAC, and IBSC about security, effectiveness, and caliber. For efficient prescription practices and patient safety, it is crucial to recognise knowing the differences between innovator and biosimilar products with regard to safety, effectiveness, and immunogenicity. India, the world's largest producer of biosimilars, needs to establish appropriate pharmacovigilance programs, nomenclature regulations, and effective guidelines.

REFERENCES:

1. Mehmood Y. Comprehensive Review on Manufacturing Process and Characterization of Biosimilar Drugs. International Journal of Applied Sciences and Biotechnology. 2018 Jun 29;6(2):53-62.
2. Khraishi M, Stead D, Lukas M, Scotte F, Schmid H. Biosimilars: a multidisciplinary perspective. Clinical therapeutics. 2016 May 1;38(5):1238-49.
3. Sekhon BS, Saluja V. Biosimilars: an overview. Biosimilars. 2011 Mar 15:1-1.
4. Nandagopal A, Shakeel Y, Tirunagari M. Biosimilars: current scenario and challenges in India. ACTA Pharmaceutica Sciencia. 2018;56(1).
5. Radovan D. Biosimilar development–an overview. Medical Writing. 2019 Jun 1;28:20-7.
6. Roger SD, Mikhail A. Biosimilars: opportunity or cause for concern. J Pharm Pharm Sci. 2007 May 18;10(3):405-10.
7. Harvey RD. Science of biosimilars. Journal of oncology practice. 2017 Sep;13(9_suppl):17s-23s.
8. Rathore A, Krull I. Biosimilars: Introduction, concerns, and opportunities. LCGC North America. 2010 Aug 1;28(8):598-608.
9. Uhlig T, Goll GL. Reviewing the evidence for biosimilars: key insights, lessons learned and future horizons. Rheumatology. 2017 Aug 1;56(suppl_4):iv49-62.
10. Hariprasad SM, Gale RP, Weng CY, Ebbers HC, Rezk MF, Tadayoni R. An introduction to biosimilars for the treatment of retinal diseases: a narrative review. Ophthalmology and Therapy. 2022 Jun;11(3):959-82.
11. Bhojaraj S, Kumar TD, Ghosh AR, Sushmitha BS, Ramamurthy S, Velusamy T, Ramesh T, Jayanthi MK, Essa MM, Chidambaram SB, Qoronfleh MW. Biosimilars: an update. International Journal of Nutrition, Pharmacology, Neurological Diseases. 2021 Jan 1;11(1):7-16.
12. Chadwick L, Zhao S, Mysler E, Moots RJ. Review of biosimilar trials and data on etanercept in rheumatoid arthritis. Current rheumatology reports. 2018 Dec;20:1-9.
13. Krishnan A, Mody R, Malhotra H. Global regulatory landscape of biosimilars: emerging and established market perspectives. Biosimilars. 2015 Feb 17:19-32.
14. Islam MS, Alam MU, Amin M. A Global Perspective of the Prospects and Challenges of an Awaiting Revolution of Biosimilars. Bioj. Sci. Technol..2015;2:7-16.
15. Desai PN. The emergence of the biosimilars: a threat or an opportunity for biopharmaceutical innovation system?. Asian Biotechnology and Development Review. 2016 Jul 1;18(2):3-26.
16. Kumar R, Sigala S, Malgarini RB, Pimpinella G, Pani L, Pecorelli S, Memo M. Biosimilars: regulatory status and implications across the world. J Pharmacovigil. 2016;4.
17. Misra M. Biosimilar: current perpectives and future implications. Indian JPharmacol, 2012; 44: 12-4
18. Malipatil NB, Haridas K, Prithvi SD. An overview of biosimilars. Asian Journal of Pharmaceutical and Clinical Research. 2015 Jan 1;8(5):23-7.

19. Mehra A, Kaur H, Fatima A, Noor A, Gupta K, Shukla A, Tripathi K, Joshi A. Biosimilars: Novel Emerging Field of Biomedicine. International Journal of Pharmaceutical Sciences and Nanotechnology (IJPSN). 2021 Sep 1;14(5):5588-93.
20. Declerck PJ, Simoens S. A European perspective on the market accessibility of biosimilars. Biosimilars. 2012 Nov 16:33-40.
21. Ravindran RS. Role of Patents in Biosimilar Drug Development and Public Interest. Journal of scientometric research. 2020 Jul 23.
22. Ghosh A, Das A. Biologics or biosimilars: What is the difference?. Indian Journal of Dermatology, Venereology and Leprology. 2016 Nov 1;82:683.
23. Rushvi P, Charmy K, Nirav C, Narendra C. Biosimilar: an emerging market opportunities in india. Pharmaceut Reg Affairs, 2016; 5: 165.
24. Sattigeri B, Alamchandani RR, Karelia PS. Biologics and biosimilars: Role in modern pharmacotherapy and importance of pharmacovigilance. International Journal of Research in Medical Sciences, Alamchandani RR et al. Int J Res Med Sci. 2014 May;2(2):382-6.
25. Cohen HP, Turner M, McCabe D, Woollett GR. Future evolution of biosimilar development by application of current science and available evidence: the developer's perspective. Bio Drugs. 2023 Sep;37(5):583-93.
26. Zhang Q, Sun C, Wu J, Wu J, Zhang X, Liu Y, Dou C, Qin H, Zhang Q, Zhou R, Hu W. Pharmacokinetic similarity study comparing the biosimilar candidate, LY05008, with its reference product dulaglutide in healthy Chinese male subjects. Expert Opinion on Biological Therapy. 2023 Aug 3;23(8):727-35.