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Dawn and development of Biosimilars and its future market

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Abstract
Biologics, including biosimilars and their reference products, are complex compounds created in living systems by biotechnology. Multiple tiers of sophisticated, highly regulated manufacturing processes are combined with preclinical structural, functional, and biological assessments, as well as clinical efficacy and safety, including immunogenicity, investigations in the creation of biologics. Additionally, to ensure a high degree of similarity, a biosimilar must go through a comparability exercise at every stage of development, as outlined by regulatory agencies, to show that potential differences from the reference product are not clinically meaningful in terms of quality, safety, and efficacy (European Medicines Agency [EMA]) or safety, purity, and potency (US Food and Drug Administration [FDA]). The formation of a high degree of structural similarity with its reference product is at the heart of the biosimilar development process. To establish a high level of structural and functional resemblance, cutting-edge technology must be used.

Keywords: Biosimilar, Marketing Aspects, Development, Regulatory issues

Introduction
Biological medicines are essential treatment choices, and they include supportive-care agents as well as pharmaceuticals that are effective in a variety of therapeutic areas, including cancer and immune-mediated inflammatory diseases. Patent expirations for a number of biological products have prompted the development of 'biosimilars,' which have similar quality characteristics, biologic activity, safety, and efficacy to a licenced biological medicine (also known as the'reference' medicine) and are associated with lower development costs [1]. Only 29 biosimilars have been approved in the United States since Congress established a biosimilar approval process in 2010. Due to a mix of market forces and policies that have both delayed and discouraged the use of biosimilars in the United States, adoption has been gradual [2]. Market competitive economic theory does not help in the realm of health. To offer an example, one of the most crucial areas experiencing failure due to a lack of price competition is the pharmaceutical business [3]. One approach to achieve this is to provide a shortened registration procedure that allows an applicant to seek for marketing authorization of a patent-free drug by substituting non-inferiority bioequivalence studies for full clinical trials. The company must establish the generic product's quality, and because the active substance's safety and efficacy are already well recognised, the generic must demonstrate therapeutic equivalence with the original product through bioequivalence studies [4].

Development and approval of biosimilars
The creation of high-quality biosimilars is a multi-step, systematic, and reliable procedure, with approval based on the totality of evidence. The first stage entails a comprehensive molecular analysis of the reference medicine. This entails determining the critical features (or quality attributes) that determine the clinical properties of the reference medicine [efficacy and safety, pharmacokinetics (PK) and pharmacodynamics (PD), immunogenicity], as well as obtaining information on how these attributes vary and change over time. These data serve as the foundation for defining the parameters, or 'goal posts,' within which the biosimilar's qualities must fall [5, 6]. The following is a summary of the biosimilar development process fig. 1.

Mishra (2005) argued that the degree of motivation among owners varies according to the owners' perceptions of challenges and opportunities. Financing is one issue that might have a big impact on the owners' growth motivation. While previous research indicates that small businesses may have access to financing, there appears to be a reluctance among owners to employ external financing (Claessens 2006).

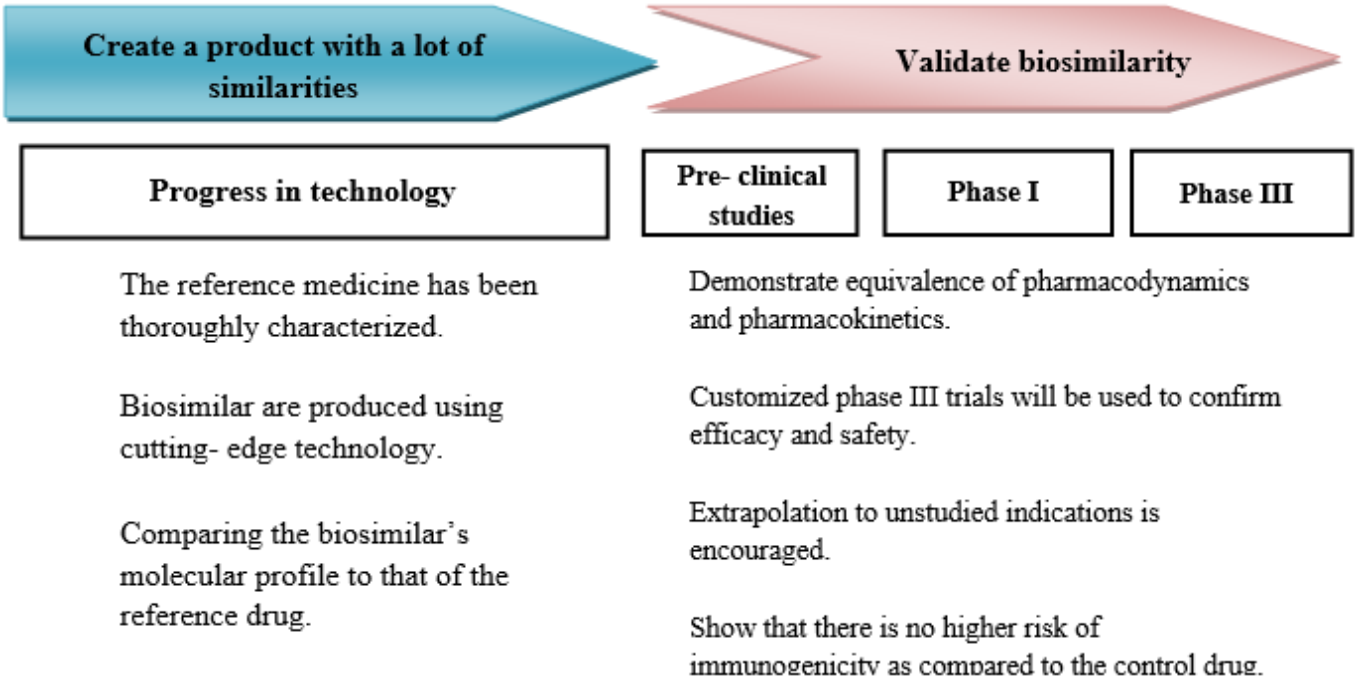

Fig 1: Overview of the biosimilar development process

The clinical program's purpose is not to demonstrate new safety and efficacy characteristics, as this has already been demonstrated for the reference. but to substantiate the absence of medicine. A comparison of clinically significant discrepancies in conjunction with the standard of care developing clinically Phase I pharmacokinetics/ pharmacodynamics testing is generally included in the development of biosimilars. Bioequivalence studies and a phase III confirmatory research in a vulnerable population. cation to show that there is no such thing as meaning. Compared to the, there are a number of clinical differences. A source of information [7, 8].

Biosimilars Development Challenges

First, because biosimilars are biologics, they are subject to the same rules that control

Bio-manufacturing processes, which, as previously stated, are extensively regulated globally. A biosimilar must meet all of the CMC (Chemistry Manufacturing and Control) requirements for biologic approval, but it must also meet the idea of similarity. A biosimilar is a biopharmaceutical product that is designed to be very similar to (comparable) to a previously approved innovative biopharmaceutical agent [9].

Regulatory issues in the creation of Biosimilars

Regulatory standards in the EU (European Union) and the United States have evolved in lockstep with the development of biosimilars in the past. In 2003, the European Union created a regulatory framework for biosimilars. The overall guideline on biosimilars issued by the Committee for Medicinal Products for Human Use (CHMP) went into effect in 2005, and a revised version was released in 2015. Both the overarching guideline and its sister guidelines (which address quality, nonclinical, and clinical concerns) have been amended in recent years to reflect the expanding experience with biosimilar's [10]. The United States FDA(Food And Drug Administration) has been significantly involved in defining biosimilar development standards and providing guidance to parties in recent years. The World Health Organization established a guideline on "similar biotherapeutic products" in 2010 [11]. However, because a biopharmaceutical's active component is a collection of big protein isoforms rather than a single molecular entity, as is the case with conventional smallmolecule medications, this approach cannot be applied to biosimilar's [12]. These are the steps involved in the production of biologic goods that are typical fig.2.

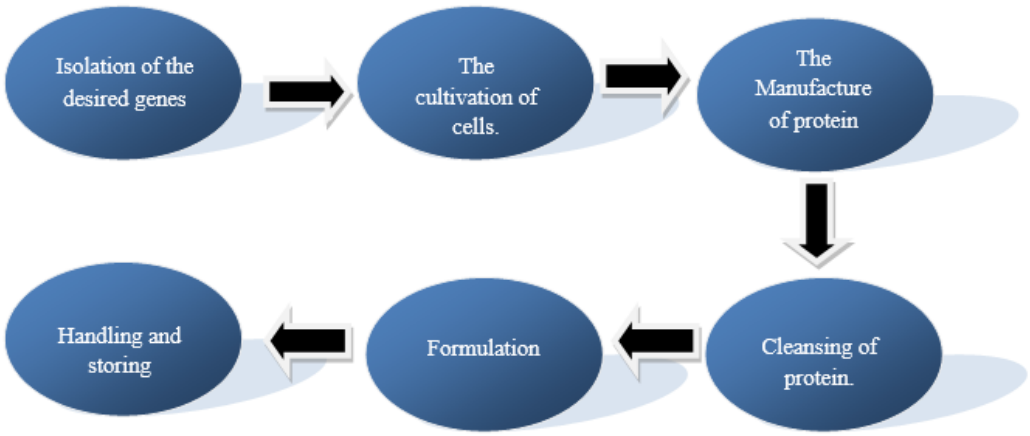

Fig 2: Steps in the production of biologic goods that are typical

As a result, the active ingredients in two medicines are very unlikely to be identical, and biosimilars, unlike generics, are just comparable to the innovator products, not identical. Because of these changes, biosimilars should not be licenced or regulated in the same way that traditional generic pharmaceuticals are [13].

Improvement of biosimilars

Biosimilars from the "first wave" were far more sophisticated than pharmaceuticals, yet biological molecules were comparatively simple. Multi-subunit, significantly post-translationally modified, and lipid-containing biosimilars are now being developed; nevertheless, these products may introduce new difficulties and risks [14]. Traditional major players/pharma giants that were formerly pioneers in the industry may strategically opt out of specific biosimilar development programmes, as their new competitors cut their way forward, with speed-to-market being an important criterion for profitable biosimilar development. The oncology landscape and its key stakeholders (prescribers, pharmacists, nurses, patients, reimbursing bodies, and manufacturers) will face many challenges with most monoclonal antibodies coming off patent by 2020, given the introduction of biosimilars, the existence of their originator biologics, and the creation of biobetters (improved versions of the originator biologics [15]. Many issues will face the cancer landscape and its main players (prescribers, pharmacists, nurses, patients, reimbursing bodies, and manufacturers). A better understanding of the impact of differences in quality attributes on clinical efficacy and safety [15]. a meaningful approach to collecting post-marketing safety data from biosimilars and their reference biologics; and efforts to globally converge regulatory requirements, including the potential use of a global reference product, are all ongoing challenges [16].

Recent advances in biosimilars

Biopharmaceuticals have changed the way people treat a variety of ailments, including anaemia caused by renal failure. The introduction of recombinant human (rh)-erythropoietin (EPO) has revolutionized the way we treat and manage patients with kidney disease, allowing us to reduce the hazards of blood transfusions. The term "biopharmaceutical" refers to recombinant protein medications created using biotechnology for the purposes of this review. The term "originator" refers to the first biopharmaceutical product that has been cleared for commercial release after passing all of the necessary safety and efficacy studies. Many patents for originator biopharmaceutical products are about to expire. A new generation of molecules known as "biosimilars" has emerged in their wake. Biosimilars are offshoots of original biopharmaceuticals that promise to be interchangeable with the tried-and-true originals, according to their manufacturers. These novel compounds are being eyed by health care professionals as potential cheaper replacements to original biopharmaceuticals. In practise, however, the situation is more complicated: when deciding between biosimilars and originator pharmaceuticals, a slightly lower market price is not the most important aspect to consider. Furthermore, biosimilars' therapeutic advantages must be thoroughly assessed [17].

Methodology of research

The purpose of this research was to find out how stakeholders felt about biosimilars. In order to better understand how stakeholders' activities may influence biosimilar acceptability in the future, NORC (National Opinion Research Center) at the University of Chicago performed quantitative and qualitative research on provider, patient, and payer perceptions of bio similars. National Opinion Research Center conducted two surveys, two focus groups, and 20 interviews, which included:

1. A patient survey of 618 people who had been prescribed a biologic drug in the previous 12 months to treat a specified condition.
2. Six hundred and two of hematology/oncology, rheumatology, gastrointestinal, dermatology, and ophthalmology specialists who often deliver biologic medications to their patients were studied.
3. In two 90-minute patient focus groups, a total of 16 patients taking biologic medications took part [18].

Biosimilars for perception

Doctors believe biosimilars are as safe and effective as brand biologics, and they are confident in prescribing them. Biosimilars are equally safe and effective as brand biologics, according to more than three out of four physicians polled, with only a small percentage claiming they are less so. In talks, prescribing physicians consistently stated that the safety and efficacy of biosimilars compared to the brand are not deterrents to prescribing them. Group purchasing organizations (GPO) leaders also expressed great trust in biosimilars' safety and efficacy, with one claiming that they

are almost comparable to brands [19].

Efficacy, quality and safety

Before a biosimilar product can be approved for marketing, the quality, safety, and efficacy of the product must be approved by the relevant regulatory body, which necessitates a suitable comparability exercise. The EMEA (European Medicines Evaluation Agency) requires that the biosimilar product and the originator product be compared to see if there are any noticeable differences. Because the quality of a protein product influences its safety and efficacy, a quality comparison between the biosimilar and the innovator product is critical. Biopharmaceutical manufacture is recognized to be a multistep process that includes cloning the right genetic sequence into a carefully selected expression vector, selecting a suitable cell expression system, scale-up and purification, and finally formulation of the end product [20]. Fig.2

Biosimilary production

Biosimilars go through a rigorous manufacturing process. Scale-up production methods and technology approaches Since the introduction of biosimilars, A distinct gene must have similar features to the generic product. At the start of the manufacturing process, a gene relating to the product is isolated. The separated gene is then introduced into a vector. Cloning into circular DNA vectors is the recommended approach. A appropriate host cell is then used for cell expression after this stage. Yeasts and E. coli are two of the most commonly employed host cell types in biosimilar manufacturing. To propagate host cells, cell culture techniques are used. Following cell culture characterization, a thorough protein purification process is carried out, followed by a chromatography-based protein synthesis step. Biosimilar medications should be preserved and utilized until they are needed [21]. It shows the steps of manufacturing biosimilars fig.3.

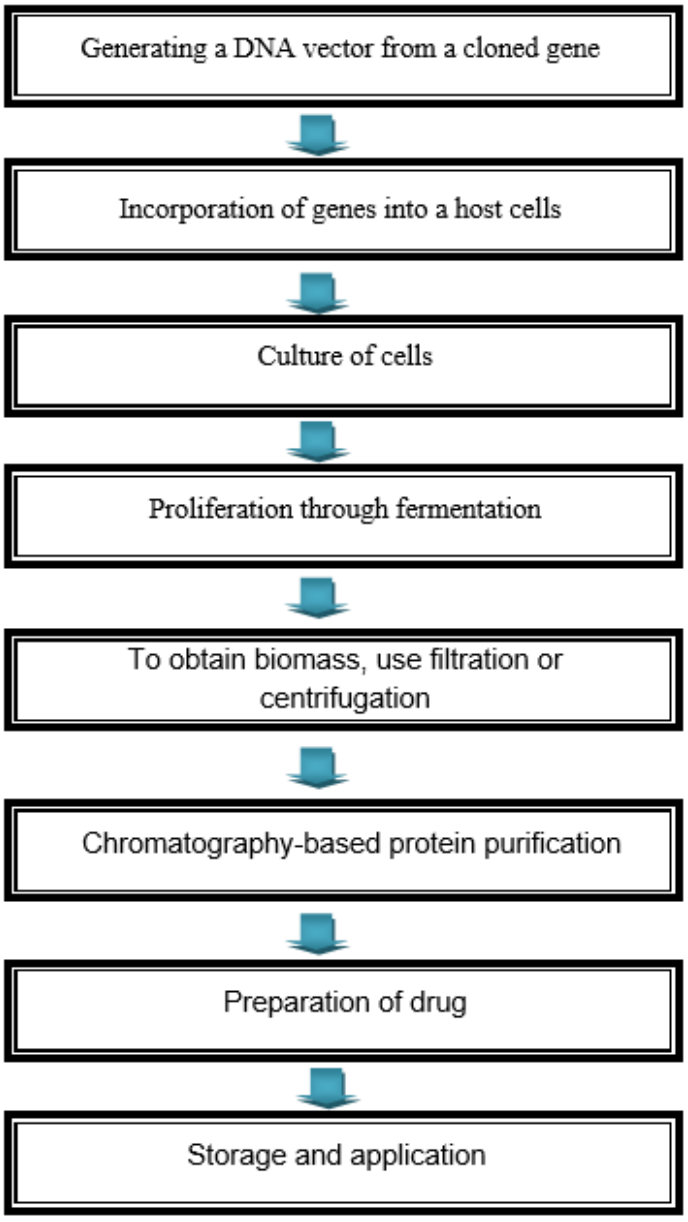

Fig 3: Steps in the manufacturing of Biosimilar

Biosimilar manufacturing and marketing aspects

Biosimilar fabrication is fraught with legal, manufacturing, and marketing issues, making it one of the most expensive pharmaceutical development concepts. The main motivation

for utilizing biosimilar products instead of the original product is to save money. Biosimilars provide patients with more cost-effective options while also fostering a conducive environment for the future development and marketing of biological therapies. Promoting biosimilar production appears to be a key opportunity. However, at this point, understanding the dynamics that drive biosimilars is a huge issue. Because biosimilars are not exact copies of the reference product, preclinical and clinical investigations of biosimilars should be conducted with an approved reference product as a control. Biotechnological pharmaceuticals, on the other hand, will become a significant element of the health sector, with a surge in the number of biological products and biosimilar drugs providing alternative therapies and increasing patient access by lowering treatment cost [22]. The WHO Biosimilar Regulatory System has adopted internationally accepted guidelines for the market launch of bio therapeutic medicines that are safe, dependable, and of comparable quality. The WHO regulatory system's principal goal is to assist and ensure that local regulatory authorities comply with international bio therapeutic development standards. Other countries later adopted these principles on their own, however few countries were allowed to create their own rules based on existing models [23].

Market for Biosimilars

Global Scenario: Between 2017 and 2025, the global biosimilars market is expected to reach $46.0 billion, growing at a CAGR of 33%. Geographically and by product class, the worldwide biosimilar market has been split. It is divided into four sections: Europe, Asia Pacific, North America, and the Rest of the World. Europe, which is the largest, accounts for around 35 percent of worldwide market share, followed by Asia Pacific and North America, which account for 30 percent and 27 percent of global market share, respectively. The rest of the globe accounts for 8% of the total [24]. The approval and indications of new biologics are decided by centrally regulated authorities. The different countries can then formulate their own rules regarding price, purchase, use of biosimilars, and interchangeability decisions. As a result, Europe's developed markets are more established, with varying levels of biosimilar penetration. The demand for biosimilars is increasing due to a variety of causes including increased awareness of biosimilars among doctors and pharmacists, various incentives, purchasing policies, and distribution channels for these medications. Europe currently leads the worldwide biosimilars market, followed by Asia Pacific, which holds a significant market share in this area. The cheap production cost of biosimilars, skilled labour force, increased desire for less expensive therapeutics, and high frequency of chronic diseases are all factors driving the provincial biosimilars market expansion in Asia Pacific countries. The FDA authorised the first biosimilar product, Zarxio, in March 2015 [25]. Global scenario in market analysis as shown in figure 4.

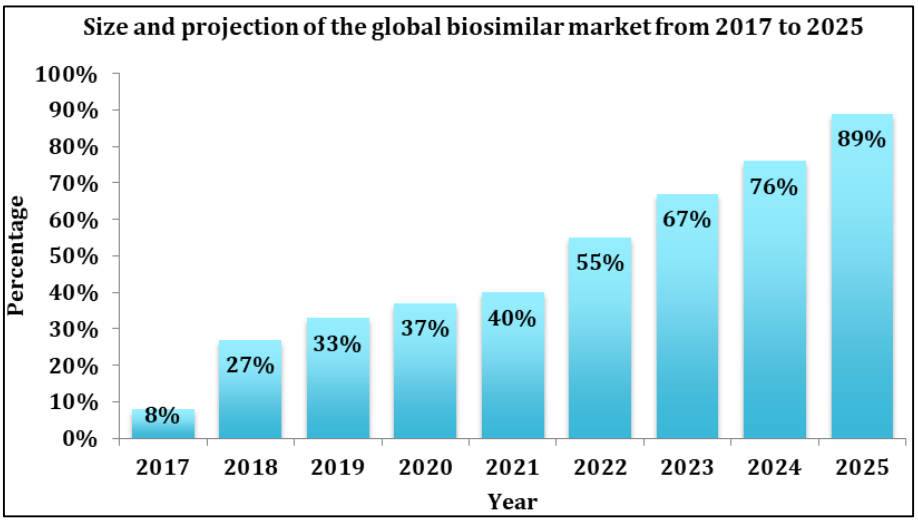

Fig 4: Global Scenario in Market Analysis

Many markets, various opportunities

While developed markets will continue to be a major priority for biologics companies, our research suggests that developing countries will be the primary source of long-term growth. These markets, which haven't gotten nearly as much attention as biosimilars, are primed to flourish, but will necessitate unique strategies and techniques.

Developed markets: Such as the United States, the EU, and Japan offer biosimilars near-term growth opportunities, aided by governments that are issuing clear regulatory pathways and payers that are pushing uptake to keep costs down. However, as evidenced by biosimilars' perceived underperformance in Europe over the last seven to eight years, the growth potential has been a mixture of reality and hype. Continued regulatory uncertainty, lingering patient and physician concerns about biosimilars' "similarity," safety, and efficacy, as well as the ongoing (often contentious) debates over automatic substitution and International Nonproprietary Naming (INN), will almost certainly create long-term barriers to widespread adoption. Innovation (in the form of bio-betters) is likely to triumph over imitation (in the form of biosimilars) in these markets, particularly in the United States.

Emerging markets: Large pockets of non-consumption and untapped demand in emerging markets – characterised by limited physical and financial access to currently high-priced biologics – offer promising long-term growth prospects. Aside from macroeconomic factors like high GDP growth

rates, rising purchasing power parity, and rising health-care spending, there is a strong regulatory focus on cost containment and treatment access (especially where there is a growing middle class). Despite the fact that the health care and payer systems in emerging market countries differ, studies have shown that cost is a significant barrier to biologics use in all of them, and that physicians would increase prescription rates if less expensive biosimilar alternatives were available [26, 27].

Biosimilars market in India

In terms of quality, stability, characterization, specification, efficacy, safety, preclinical attributes, clinical attributes, pharmacokinetics and pharmacodynamics, toxicity, and immunogenic tests, biosimilar products should be comparable to the reference product. In the year 2000, India approved its first' similar biologic' for a hepatitis B vaccination, demonstrating its support of the concept. Because of the regulatory procedures for biosimilar approval in India, the development of biosimilars costs roughly 10-20 million dollars. In comparison to generic pharmaceuticals, biosimilar manufacturers confront numerous challenges in the areas of discovery, clinical improvement, manufacturing, registration, and product marketing [33].

Current market situation

Six-year trend in comparison to last year

In the United States, the biosimilars business is well-established and expanding across a wide range of therapeutic areas. Seven biosimilars were approved by the Food and Drug Administration (FDA) in 2018, bringing the total number of approvals to 16 (fig.5). In 2019, the FDA authorized ten more biosimilars, increasing the total number of biosimilars approved in the United States to 26 [28]. The number of biosimilars approved each year from 2015 to 2020 is displayed. The ever-increasing number illustrates the growing strength of US biosimilars. Three biosimilars will be approved by the FDA in 2020 [28]. The COVID-19 outbreak and subsequent shutdown hampered biosimilar approvals, but another wave is expected in the future.

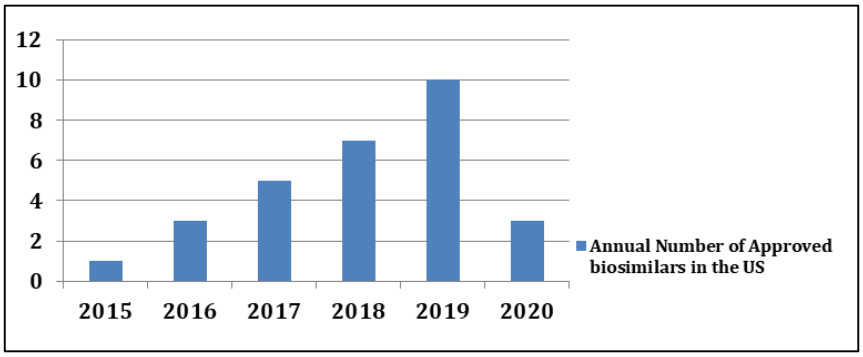

Fig 5: Annual Number of Approved Biosimilars in the United States

Furthermore, patients will have access to more biosimilars in the near future. There were only six biosimilars available by the end of 2018. Six more biosimilars will be ready in 2019, followed by another seven in 2020 (fig.6). Compares the number of biosimilars available in 2019 and 2020 to previous years [29].

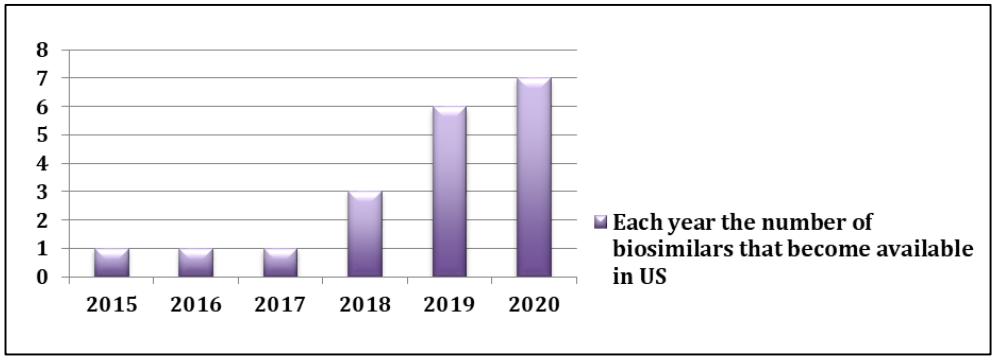

Fig 6: Each year, the number of biosimilars that become available in the United States increases.

Uptake of biosimilars is growth

Biosimilars have achieved considerable share in the majority of therapeutic areas where they have been introduced, as shown in Biosimilars have gained significant share in the majority of therapeutic areas where they have been introduced. Furthermore, when compared to later entrants, first-to-market biosimilars tend to grab a larger share of the market [30].

The future perspectives

Many firms' patents will expire in the coming year, providing a chance for other biopharmaceutical companies to investigate the prospect of developing biosimilar treatments. The worldwide biosimilar market is estimated to expand by $10 billion by 2020, and many companies are likely to enter this attractive sector. Biosimilars are a major actor in the world of biosimilars production and use [31]. In 2015, the Indian biosimilar market was worth around $300 million. Domestic revenues are close to $250 million, and they're rising at a 14 percent compound annual growth rate. India exports a whopping US$51 million worth of biosimilar or comparable biologics. In comparable biologics or biosimilars,

India has the potential to become a worldwide player. According to a 2016 ASSOCHAM-Sathguru analysis, biosimilars offer the Indian biopharmaceutical industry a US$240 billion worldwide opportunity, with the domestic market estimated to expand to US$40 billion by 2030. According to the Institute of Medical Sciences' health-care assessment, Indian biopharmaceutical companies involved in the development and marketing of biosimilars will have a similar opportunity [32].

Conclusion

To be designated biosimilars, biotherapeutics must go through a rigorous development process and a step-by-step comparability exercise to show that any potential variations have no impact on the product's clinical performance when compared to the reference product, using the "totality of evidence**.** Biosimilars have the potential to make many malignant and nonmalignant diseases more accessible to patients by lowering treatment costs. Since the first biosimilar was used, the development and use of "biosimilars or similar biologics" has grown significantly. Regulatory bodies approve a variety of comparable biologics for the treatment of a variety of malignant and noncancerous disorders every year. India has solidified its position as a worldwide player in the production of comparable biologics. Because of its growing population, it is also a big market for similar biologics. Although India's potential is great and expectations are high, the hurdles of maintaining leadership are vast and intimidating.

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