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Biosimilars: An Emerging Therapeutic Approach

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ABSTRACT

A biosimilar is an extremely similar version of an existing medication. Biologics' cost, manufacture, administration, and clinical efficacy differ from those of chemically produced medications in certain aspects. Chemical and clinical equivalency to branded, original, low molecular weight chemical pharmaceuticals whose patents have expired defines generic medications. These are offered under a generic name and are practically the same thing as the original product. By 2020, many important biologics are expected to lose their patent protection, giving other biopharmaceutical companies the chance to create comparable biologics. After the first biosimilar was approved in early 2000, the use of biosimilars and similar biologics has expanded in recent years. One of the top producers of comparable biologics is India. In 2012, India created a new regulation for the pre- and post-marketing approval of comparable biologics. The biosimilar's mode of action mirrors that of its reference drugs and results in very comparable outcomes. Some disorders, including some forms of cancer, can be treated with biologics and their biosimilars. Additionally, numerous medical disorders are treated with biosimilars. Crohn's disease, arthritis, and ulcerative colitis.

KEYWORDS: Biosimilars, Similar Biologics, Generic Drug , Guidelines, India

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INTRODUCTION

A biosimilar is a biologic product that is extremely similar to a reference product, a biological product that has been approved by the Food and Drug Administration (FDA), and that differs from the reference product in neither terms of safety nor efficacy clinically meaningfully. However, due to the complicated structure of homologous biologics, which may be impacted by minute changes in sequences and posttranslational modifications, they are not perfectly identical to reference biologics[1].The use of biosimilars has the potential to significantly lower treatment costs overall. Biologics are made from natural resources like human, animal, or microbial tissue and are produced using a variety of biotechnology techniques like controlled gene expression, recombinant deoxyribonucleic acid technology, and antibody technology[2].By stopping the progression of the disease, reducing the symptoms, and enhancing quality of life, biologics have benefited patients with rheumatologic diseases, inflammatory bowel disease, malignant situations, dermatological ailments, and other connective tissue disorders[3].

Table no 1: Different Biosimilars in market for the disease.

Product name	Active drugs	Indications
Adfar	Adalimumab	Rheumatoid arthritis
Krabeva	Bevacizumab	Colorectal cancer
Herceptin	Trastuzumab	Colorectal cancer
Glaritus	Insulin glargine	Diabetes melitus
Grafeel	Filgrastim	Neutropenia

How Biosimilars differ from Generic drugs

Generic medications and biosimilar medications are two distinct concepts. The medicinal components in generic medications are the same as those in reference goods. They are made up of chemically produced, tiny molecules. The reference biologics and the biosimilar medications are very similar but not identical[4].Generic medications are distinguished from branded, original, low molecular weight

chemical medications by their chemical and therapeutic equivalent to those medications whose patents have expired. These are offered under a common name and are nearly identical to the original product. These are authorized via a streamlined registration process known as an abbreviated new drug application, together with a bioequivalence demonstration[5].Since chemical generics and biosimilars differ in a number of ways, it is not possible to evaluate or assess biosimilars using the same standards as chemical generics. Biopharmaceuticals are high-molecular-weight substances with intricate three-dimensional structures, as opposed to chemical medications with clearly defined structural boundaries and low molecular weight[6].

Table no 2: Difference between Biosimilars and Generic drugs

	Biosimilars	Generic drugs
Stability	Sensitive to changes in physical condition	More stable
Molecular weight	High	Low
Route	Injected/inhaled	Oral
Structure	Large and complicated	Smaller and complex

CURRENT STATUS OF BIOSIMILARS

The policy framework for the approval of biological products was first developed in Europe[7].The European Medicines Agency (EMA) authorized Omnitrope, a recombinant human growth hormone, as the first biosimilar in 2006[8].Filgrastim-sndz, a biosimilar to filgrastim (granulocyte CSF), was approved by the USFDA in 2015, much more recently than the USFDA had approved filgrastim in 1991.Nevertheless, the FDA has now approved a number of biosimilars for the treatment of cancer and other diseases. Pegfilgrastim-jmdb, which was most recently approved in June 2018, lowers the risk of infection after myelosuppressive chemotherapy. There are already a number of biosimilars created by biopharmaceutical companies that are utilized globally for a variety of conditions ranging from cancer and connective tissue illnesses to diabetes, ophthalmology, and respiratory ailments[9].In contrast to other nations, India has a vibrant biosimilar ecosystem, and as a result, Indian pharmaceutical companies have become market leaders for biosimilars worldwide. India granted approval for its first biosimilar significantly earlier than the US and EU. Although there were no clear guidelines available at the time for the development and marketing of biosimilar in India, the first biosimilar was approved and commercialized there in 2000 for hepatitis B. Since then, other biopharmaceutical companies have created and launched biosimilars in India. A recent USFDA approval for the marketing of a new biologic was received by an Indian biopharmaceutical company. The first biologic to receive FDA approval was Herceptin, a treatment for some types of stomach and breast cancer. Herceptin's active ingredient is trastuzumab, Additionally, this was the first comparable biologic produced by an Indian business to be given permission to be marketed in the US[1].There are already more than 100 Indian biopharmaceutical businesses involved in the production and promotion of biosimilars. By Indian regulatory agencies, biosimilars are referred to as "similar biologics". Although India was one of the first nations in the world to adopt the term "similar biologics," no formal guidelines were available for these products, and their approval processes are more onerous and call for more information than those for other generic medications. In order to address the problems and difficulties related to the development of similar biologics, the Department of Biotechnology (DBT) and the Central Drugs Standard Control Organization (CDSCO) developed "Guidelines on Similar Biologics: Regulatory Requirements for Marketing Authorization in India" in 2012, and it was updated in 2016.[10]These regulations cover the quality, safety, and efficacy of comparable biologics as well as the regulation of the production process. It addresses the regulatory requirements for comparable biologics both before and after launch. Biologics development and preclinical testing are supervised by DBT through the Review Committee on Genetic Manipulation. The Drug and Cosmetic Act (1940), Drug and Cosmetic Rules (1945), and Rules for Manufacture, Use, Import, Export, and Storage of Hazardous Microorganisms or Genetically Engineered Organisms or Cells (1989) (rules, 1989), all of which were notified under the Environmental (Protection) Act (1986), govern similar biologics in India[11].In contrast to the earlier requirement that the reference biologic for which the biosimilar is to be developed must be approved and marketed in India, this requirement has now been changed to include any of the member nations of the International Council for Harmonization (EU, Japan, US, Canada, and Switzerland). It also makes an effort to coordinate with other international organizations like the World Health Organization and the EMA. Indian guidelines state that biologics are created using a sequential process to demonstrate how closely a biosimilar's molecular and quality characteristics match those of reference goods[11,12].To capitalize on this enormous potential, Indian businesses are making a number of efforts to incorporate people in manufacturing and marketing. Vaccines, monoclonal antibodies, insulin, and recombinant proteins make up the majority of biosimilars that have been licensed and are being utilized in India. India now holds the distinction of being the world's second-largest vaccine

supplier. India has approved a number of biosimilars for use in treating various disorders[11-13].

Mechanism of Action

The biosimilar product's mode of action is identical to the biologic products. They imitate and provide results that are comparable to those of their reference products (such as biologic drugs), and they don't produce any clinically relevant differences in terms of safety and efficacy[12].The first is that the target/receptor for each activity/function of the biosimilar, binding, dose/concentration response, pattern of molecular signaling on target receptor engagement, relationship between biosimilar structure and target/receptor interactions, location and expression of the target/receptors, and mechanism of action in the condition of use should all be the same. The pharmacokinetics and biodistribution in different patient populations, variations in anticipated toxicities in each indication and patient population, and any other aspects affecting the safety and/or efficacy of the biosimilar in each indication and patient population should all be taken into consideration. Separate clinical trials should be done, according to the EMA and FDA, where the mechanism of action differs between different indications or is not fully understood[13].

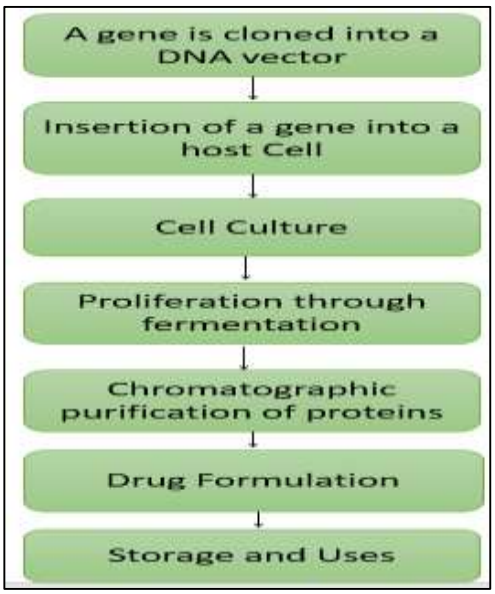

Figure no 1: General Mechanism of Action

GUIDELINES

The United States Department of Health and Human Services is the parent organization of the Food and Drug Administration (FDA and USFDA). Through the regulation and oversight of food safety, pharmaceutical medication safety, vaccine safety, and other areas such as biopharmaceuticals, the FDA is in charge of safeguarding and promoting public health. In 2014, the World Health Assembly passed a resolution requiring the WHO Secretariat and Member States to enable access to biotherapeutic products in a way that ensures their effectiveness, safety, and quality. WHO has made great efforts to harmonize the language and the regulatory framework for biosimilars globally since the organization released its guidelines for regulatory examination of biosimilars in 2009[14].Regulations and guidelines that apply the Drugs and Cosmetics Act of 1940, the Drugs and Cosmetics Rules of 1945 (as amended from time to time), and the Rules for the manufacture, use, import, export, and storage of hazardous microorganisms or genetically engineered organisms or cells of 1989 (Rules, 1989) are the laws that apply to similar biologics. These laws were notified under the Environment (Protection) Act of 1986. The following list of applicable rules is provided:Guidelines for the Safety of Recombinant DNA, 1990

• Preclinical and clinical data generation guidelines for rDNA vaccines, diagnostics, and other biologicals, 1999

• CDSCO industry advice, 2008:Submission of the Clinical Trial Application for Safety and Efficacy Assessment Post-approval changes in biological.

Biotechnological and Biological Products Documents: Preparation of Quality Information for Drug Submission for New Drug Approval: Guidelines and Handbook for Institutional Biosafety Committees (IBSCs), 2011.

Guidelines on Comparable Biologics: Regulatory Requirements for Marketing Authorization in India, 2012[15].

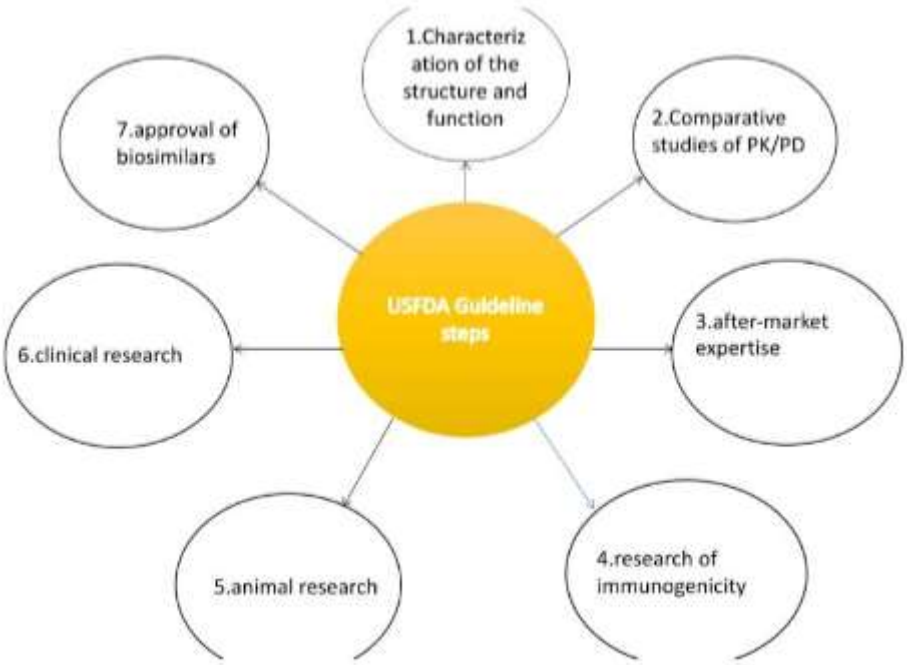

Figure no 2: USFDA Guideline Steps

Biosimilars safety and efficacy

FDA carefully examines the information supplied by pharmaceutical firms and takes a number of actions to verify that all biosimilars satisfy requirements for patient use, as it does with all medicine approvals. A biosimilar can be trusted to be just as secure and efficient as the original biologic by patients and medical professionals. FDA takes the same measures it does for all drugs to help assure the safety and efficacy of biosimilars.

You should consult your medical professionals and other reliable sources of information about your unique condition before making any treatment decisions and find out more about the available biosimilar therapies.

A significant area of Important therapy possibilities for a variety of illnesses is biosimilars[16,17].

Biologics and their biosimilars can be used to treat some diseases, including certain types of cancer

Trastuzumab (Herceptin) is an illustration of a biological drug. This medication targets cancer. Breast cancer and advanced stomach cancer are both treated with it. Herzuma and Ontruzant are two examples of biosimilars for this medication. Another biological drug is rituximab (Mabthera). A targeted medicine, that is. It's employed to treat: Leukemia chronic lymphocytic Non-cancer related illnesses several non-Hodgkin lymphoma kinds Truxima, Ruxience, and Rixathon are among the biosimilars of this medication. Additionally, numerous medical disorders are treated with biosimilars. Adalimumab, or Humira, is used to treat, for instance:

1. rheumatoid
2. Ulcerative colitis caused by Crohn's illness Imraldi, Amgevita, Hyrimoz, Idacio, and Yuflyma are some of the biosimilars for this medication.[18].

RISK AND MANAGEMENT

A typical individual medicinal product will have multiple risks attached to it, and each risk will vary in terms of severity, individual patient impact, and public health impact. Each risk can be managed in four steps: risk detection, risk assessment, risk minimization, and risk communication. In order to ensure that the benefits outweigh the dangers by as wide a margin as feasible, both for the individual patient and for the population as a whole, the notion of risk management should take this into account. The "Risk Management Plan" (EURMP) is divided into two sections: risk minimization and pharmacovigilance. It describes how a product's safety will be tracked and evaluated to lower risk.

The creation of a risk management plan is broken down into four sections:

1. Safety requirements
2. Plan for pharmacovigilance
3. Assessing the need for risk-reduction measures.
4.A risk-reduction strategy[19].

Figure No 3 : Risk Management Steps

PHARMACOVIGILANCE

The same criteria that govern generic medications do not apply to biosimilars. Although the reference medicine and the biosimilar may have identical efficacy, the biosimilar may have a distinct safety profile in terms of the kind, severity, or frequency of adverse effects. To detect all potential variances, pre-authorization clinical study data typically fall short. Therefore, during the post-approval phase, including ongoing risk-benefit analysis, close ongoing monitoring of the clinical safety of comparable biological medical products is required. The risk management plan"(EU RMP) and pharmacovigilance program of the biosimilar applicant must be submitted with the application to the European Medicines Agency (EMEA), along with a description of any potential safety concerns with the similar biological medicinal product that may arise from variations in the manufacturing process from the reference biologic[19].

CONCLUSION

Biosimilars have the potential to improve patient accessibility for a variety of malignant and nonmalignant illnesses by reducing the cost of care. Since the first biosimilar was used, the development and use of "biosimilars or similar biologics" have increased substantially. Multiple biologics that are identical to one another are frequently approved by regulatory bodies for the treatment of numerous carcinogenic and non-cancerous disorders. India is a significant producer of similar biologics on a global scale. A thorough analysis is needed for biosimilars to be more broadly accessible and cost-effective. Factors such as the incredibly complex ingredients that make biosimilar products Before biosimilars' marketing authorization is given, a lot of criteria need to be carefully considered.

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