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BIOSIMILARS: A COMPLETE REVIEW ON MANUFACTURING, FDA APPROVAL, CASE STUDIES

Ismail Khalid Hashmi [1] and Maaz Ahmed Shaik [*2]

KVK College of Pharmacy [1], Surmaiguda, Hayathnagar - 501512, Telangana, India.
Sultan-ul-Uloom College of Pharmacy [2], Hyderabad - 500034, Telangana, India.

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Correspondence to Author:
Maaz Ahmed Shaik

Student,
Sultan-ul-Uloom College of Pharmacy, Hyderabad - 500034, Telangana, India.

E-mail: Maazahmedshaik74@gmail.com

ABSTRACT: A developing class of medications called biosimilars is created to be used interchangeably with biologics. In living cells, biologics are often large, complicated proteins with a range of potential applications. Biologics are utilised to treat malignancies, endocrine problems, and inflammatory bowel diseases just within the discipline of gastroenterology. Despite the fact that many diseases can be effectively treated or managed with biologics, patient access is frequently constrained by their high cost. The creation of biosimilars is an effort to lower the cost of medical care. In terms of efficacy, side effect risk profile, and immunogenicity, biosimilars must be essentially equivalent to their reference biologics. Biosimilars go through fewer clinical trials than their reference biologics, despite the manufacturing process still requiring manufacture within living cells. As a result, the biosimilar medication is less expensive to produce and purchase than the reference biologic. Seven biosimilars have currently received FDA approval for use in the treatment of Crohn's disease, ulcerative colitis, and colorectal cancer. There are further biologics used to treat gastroenterological disorders for which no FDA-approved biosimilars exist. Although biosimilars have the potential to lower healthcare costs in the management of chronic diseases, they struggle to gain a sizable market share. Patients' hesitation to move from a biologic to a biosimilar and doctors' comfort in prescribing reference biologics rather than biosimilars are two major reasons for the delayed uptake of biosimilars. The establishment of a greater and more stable market share for biosimilars in comparison to their reference biologics will take longer time. To strengthen physician trust in biosimilars and patient comfort with biosimilars, more information proving the safety and efficacy of biosimilars, a greater selection of biosimilars, and further cost reduction of biosimilars will all be required. A "biosimilar" is a recently launched biologic product that, in terms of quality, safety, and efficacy, is comparable to an authorised "Reference Biologic" product. Biosimilars' main goal is to lower healthcare expenses related to the use of biologics and so broaden access to healthcare. The bioequivalence technique is not thought to be suited for the approval of biosimilars, in contrast to small molecule generics. They are already a key component of contemporary pharmacotherapy. Many original biotechnological drugs' patent protections have expired, which has sparked the creation of what are known as biosimilars or follow-on biologics. In order to create a product that is comparable to the original, biosimilars try to replicate the original technology that produced new biotechnology treatments. In the European Union, the first two biosimilars have just received approval, while one application was denied. In the foreseeable future, many additional biosimilars are likely to receive approval. Our knowledge of biosimilars is relatively limited at this point, and there are no long-term safety data, including information on immunogenicity. Although biosimilars are likely to reduce the cost of modern therapies, there are still some concerns that need to be discussed among doctors at this point, particularly with regard to the differences between biosimilars and generic versions of the traditional chemical drugs, the requirement for appropriate regulations, and the identification of potential biosimilar issues. The advantages of biosimilars, manufacturing process of biosimilars, approval of biosimilars, and also case study with relevant monographs will also be covered in this study.

INTRODUCTION: Drugs known as biologicals or biopharmaceuticals are created using living cells and a variety of biological processes to mimic hormones and other biological components.

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Since, biosimilar medications are merely authorised imitations of the original biological treatments, they are comparable but not identical.

A new class of medications known as "biosimilars" aims to offer the same level of safety and effectiveness as the biological substance they are meant to mimic. In 2005, there were 14 therapeutic medications that were easily accessible over 50 brands; nevertheless, by 2011, there were 20 therapeutic drugs throughout 250 brands. Insulin,

erythropoietin, chorionic gonadotropin, strepto-kinase, interferon, and heparin are examples of therapeutic products. The market for biosimilars is expanding quickly, providing great opportunity for businesses engaged in production, research, and development. The field of biologics is far more intricate than others. The production procedure of biologic products resolves the intricate 3D structure. However, even small alterations in these processes have the potential to significantly alter macromolecular structure and biologic medication effectiveness. Even small changes to these procedures can have a big impact. Examples of major safety applications include loss of effectiveness, abhorrent immunogenic responses (immunogenicity) and other unpleasant occurrences. Other factors include impurity levels, the extent of material collecting, and post-translational modifications [1].

Recombinant genetic engineering techniques and manufacturing process improvements have advanced science at a very rapid rate, paving the way for the use of biological proteins in disease treatment. The treatment of damaging and fatal diseases like cancer, hepatitis, autoimmune disorders, neurodegenerative diseases, and orphan diseases depends heavily on the use of biological therapies. However, the cost of a biological therapy is more than that of a "traditional" chemical or synthetic drug. In markets where certain original biological drugs' patents or copyrights have expired, biosimilar medicines are now being introduced [2]. This is the best method for introducing affordable alternatives to the market and fostering competition. In this way, the patient can simply access and obtain these medications. These choices will be advantageous economically for the health sector.

Nomenclature of Biosimilars:

The nomenclature of biosimilars has two parts:

1. Core name
2. FDA designated suffix

Core names are often non-proprietary names that are shared by the approved product and the reference product. Four lower case letters make up the meaningless suffix, which is joined to the main name by a hyphen.

TABLE 1: EXAMPLES OF BIOSIMILARS

Biosimilar	Reference product	FDA approved date
Zarxio	Neupogen	March 6, 2015
Inflectra	Remicade	April 5, 2016
Amjevita	Humira	September 23, 2016
Ogivri	Herceptin	December 1, 2017
Fulphila	Neulasta	June 4, 2018
Truxima	Rituxan	November 28, 2018
Eticovo	Enbrel	April 25, 2019

In the future, biological drugs will play a significant role in healthcare. The availability of biosimilars is anticipated to grow globally as many patents expire. Registries with rigorous planning and implementation will produce high-quality data to aid in decision-making. The biologics known as "biosimilars" are quite similar to their reference products but not exactly the same. Biosimilars might expand patient access to potentially beneficial treatments at a lower price. The objective of a biosimilar development programme is to show that the biosimilars and the reference biologic product are "highly similar" in terms of analytical nonclinical and clinical data based on the locality of available evidence, rather than to replicate the efficacy and safety profile of a specific reference biologic. The safety and efficacy parameters are therefore of primary importance with regard to biosimilars.

Advantages of Biosimilars: Almost all healthcare system stakeholders may benefit from biosimilars. By providing a less expensive treatment option, they may cut expenses while giving patients additional options for care. In fact, patients can profit from the competition sparked by the entry of biosimilars into the market by receiving high-quality biologic treatments at lower costs when compared to the original biological medicine, the safety, effectiveness, and other data generated for biosimilars are significantly less. As a result, employing biosimilars for therapy results in lower costs.

It is expected that biotechnology medicines would make up 50% of the global pharmaceutical market in the future years.

1. These medications are being used in increasingly sophisticated therapeutic methods [3]. By 2016, it is anticipated that biologics will hold a $200–$210 billion market share globally.

2. The chance for the growth of biosimilars increases as the patent on biopharmaceuticals expires. Greater variety of treatment options, lower cost, and greater accessibility consistency of supply Populations, pharmacodynamic indicators, and end points that are sensitive to possible differences are studied specifically to address residual uncertainty.

3. Traditional generic medications have an operating profit margin of about 20%, but depending on the biosimilar product, profit margins might be as much as 30%. Biologic medications have evolved since they were initially used in the 1980s to become a vital component of contemporary medicine.

4. Biologic research and development advancements have pushed science's limits and provided people with cancer and other fatal diseases with access to life-saving medications.

5. Additionally, the treatment of chronic diseases like multiple sclerosis, diabetes, rheumatoid arthritis, and Crohn's disease has seen considerable breakthroughs because to biologic drugs. However, they are frequently linked to exorbitant costs and restricted patient access.

6. Biologics are cutting-edge therapy choices for patients with crippling and life-threatening diseases. Fortunately, biosimilars are starting to make their way into the market, giving many patients who depend on biologic therapy more affordable options.

7. Biosimilars have the potential to increase market competition and increase patient access to essential treatments [4].

8. Biologic use is expanding as a result of an ageing population and a rising need to treat chronic illnesses. And biosimilars will be crucial in enhancing patient access to necessary medications in a setting where health decisions are increasingly based on value and cost.

9. By 2025, the introduction of new biosimilars might increase access to biologic treatments for an additional 1.2 million patients and result in consumer savings of up to $250 billion. This gives those who previously had either forgone therapy or settled for less effective medication more affordable access, expanding the range of treatment options for people with chronic illnesses and enabling a larger usage of biologic medications generally.

Manufacturing of Biosimilars: The manufacturer of Similar Biologics should create a manufacturing procedure that produces a product of equivalent quality to the Reference Biologic in terms of identity, purity, and potency. Biosimilar production processes should be validated and proved to be very consistent and resilient. If the host cell line used to make the Reference Biologic is revealed, it is preferable to use the same host cell line to make the Similar Biologics. To avoid the introduction of specific types of process-related impurities that might have an adverse effect on clinical outcomes and immunogenicity, as well as to minimise the potential for significant changes in product quality attributes (QAs), any adequately characterised and suitable for intended use cell line may be used in the alternative to develop a Similar Biologic. Amgen, a US-based biotech behemoth, outlines the procedures required in producing a biosimilar. Biosimilars are manufactured in living organisms using recombinant DNA technology, as compared to the chemical synthesis essential for generics.

Biosimilars are more difficult to manufacture than standard small-molecule generics, owing to their larger and more complicated molecules. This means that they are not manufactured via traditional chemical processes, but rather in living cells, with purification being a vital stage in the process. As a result, even modest modifications in the production process can result in major variations in efficacy or immunogenicity [5].

When it comes to biologicals, it has even been remarked frequently that "the method is the product." It should not come as a surprise that Amgen claims that when creating monoclonal antibodies, they first perfect this *in-vitro* before choosing and expanding the best cell lines. In large-scale bioreactors, these cell lines are then repeatedly replicated, and the business then double- and triple-checks for batch-to-batch uniformity. All this while utilising specialised operational procedures.

Amgen creates its biologicals utilising living cells that are designed to produce a huge quantity of therapeutic proteins. To develop a consistent, high-quality active ingredient, a number of culturing and purification procedures are necessary since those cells are extremely sensitive to the environment created during their synthesis and handling. Biosimilars are equally complicated to produce as original biologicals are. Amgen, however, notes that producing biosimilars "has its own set of complexity" [6].

The first issue is that only the reference product's amino acid sequence is known for manufacturing a biosimilar. The biosimilar candidate must then undergo extensive preclinical optimization. Amgen highlighted four phases for creating a biosimilar:

1. Cell Line Creation
2. Cultivation and Production
3. Isolation and Purification
4. Formulation, Fill and Finish

Cell Line Creation: Expression vectors are created during gene synthesis using the known amino acid sequence and can then be utilised to create expression cell lines. The critical quality attributes (CQAs) of the chosen clones are subsequently examined.

Cultivation and Production: The clones that fall inside the allowed parameter range for the critical quality attributes (CQAs) are then used to build a master cell bank. A functioning cell bank of one vial each batch is created from this master cell bank. The protein is subsequently synthesised in a bioreactor after expansion.

Isolation and Purification: Filtration is used to recover the protein. This is followed by chromatography purification and comparison with the reference product. The critical quality attributes (CQAs) are then re-checked to confirm that the parameters have not been affected by the scale up.

Formulation, Fill and Finish: After that, the product is concentrated and sterile filtered before being filled. A new comparison with the reference product is performed, and critical quality attributes (CQAs) similarity for each batch is confirmed.

Amgen now has four authorised biosimilars Adalimumab biosimilars Solymbic and Amgevita, bevacizumab biosimilar Mvasi, and trastuzumab biosimilar Kanjinti are all accessible in Europe. The American Food and Drug Administration has given the go-ahead to Amjevita (adalimumab-atto), Avsola (infliximab-axxq), Kanjinti (trastuzumab-anns) and Mvasi (bevacizumab-awwb).

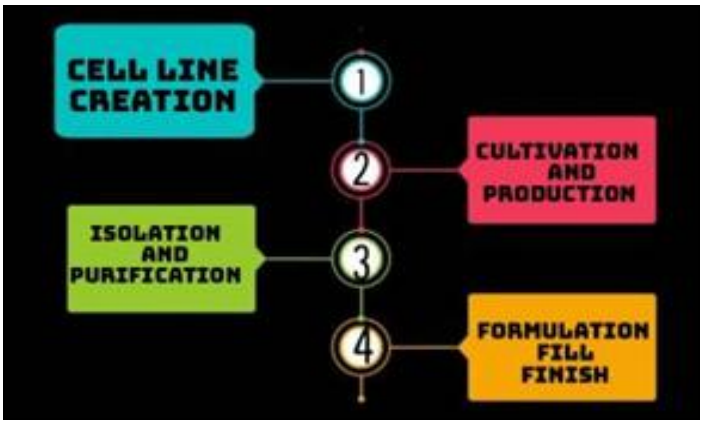

FIG. 1: THIS FIGURE DEPICTS THE STEPS INVOLVED IN THE MANUFACTURING OF BIOSIMILARS

Approval Process of Biosimilars by FDA: To assure the efficacy, safety and quality of these goods, all biological products that have received FDA approval, including reference products and biosimilar products, are put through extensive testing. A single biological product that has already received FDA approval is referred to as a reference product and is used to contrast a potential biosimilar product. It is acceptable to submit a "standalone" application that must include all the information and specific requirements to prove the reference product's efficacy and safety.

Clinical trials for the illness indications requested by the producer are frequently included in the data and information required to prove the safety and effectiveness of a reference product. No clinically significant differences exist between a biosimilar and an existing FDA-approved reference product in terms of safety, purity, or potency. A biosimilar development program aims to demonstrate how the proposed biosimilar product and the reference product are biosimilars rather than separately proving the drug's safety and efficacy [7].

To prove that a suspected biosimilar product is identical to an FDA-approved reference product, its creator generates a tonne of data comparing the two. A methodical approach is used to create and analyse the comparative data, starting with a thorough analytical (structural and functional) characterization and comparison of the products, then moving on to animal studies, if appropriate, and lastly to comparative clinical investigations. As a result, this pathway is used to approve all interchangeable biosimilar goods as well as biosimilar products by comparing the biosimilar to the reference product. Biologics are often created in cells; therefore, the production process always involves some inherent variation.

Millions of slightly different copies of the same protein (for example, an antibody) can be found in a single lot of biologics, such as therapeutic proteins like monoclonal antibodies. During the production of the reference product and the biosimilar, this inherent variance can be anticipated. To prove bio similarity, the biosimilar's maker provides copious data contrasting the suggested biosimilar with the FDA-approved reference product.

The nonclinical and clinical data needed for the reference product are not required for biosimilar manufacturers to produce. Instead, the proposed biosimilar's creator provides comparable data, beginning with a detailed analytical characterization and functional and structural comparison of the reference product and proposed biosimilar. If necessary, animal investigations are carried out. The next step is that manufacturers conduct clinical comparisons between the proposed biosimilar and the reference product. These studies frequently compare pharmacokinetics, pharmacodynamics, and immunogenicity, if necessary. The combination of these comparative analytical, nonclinical, and clinical data supports the conclusion that a biosimilar resembles an FDA-approved reference medicine very closely and that there are no clinically significant differences between the two.

The FDA's assessment of the reference product's safety and efficacy can subsequently be used by the biosimilar manufacturer. As a result, biosimilar producers do not have to carry out as many pricey and time-consuming clinical trials as a producer of the reference product, which may result in quicker access to these drugs, more treatment alternatives for patients, and lower prices. To ensure that all approved biosimilars are as safe and effective as their reference products, the FDA's stringent standards are met by the streamlined approval process. Some of the examples of biosimilars that has been approved by FDA along with the date of approval are listed below [8].

1. **Cimerli** (ranibizumab-eqrn) - August 2, 2022
2. **Fylnetra** (pegfilgrastim-pbbk) - May 26, 2022
3. **Alymsys** (bevacizumab-maly) - April 13, 2022
4. **Releuko** (filgrastim-ayow) - February 25, 2022
5. **Yusimry** (adalimumab-aqvh) - December 17, 2021
6. **Rezvoglar** (insulin glargine-aglr) - December 17, 2021
7. **Byooviz** (ranibizumab-nuna) - September 17, 2021
8. **Semglee** (insulin glargine-yfgn) - July 28, 2021
9. **Riabni** (rituximab-arrx) - December 17, 2020
10. **Hulio** (adalimumab-fkjp) - July 6, 2020

Case Studies on Biosimilars:

Case Study 1: "Rheumatoid Arthritis [RA] is a persistent, auto immune disorder which mainly influence the synovial joints. This disease is characterized by inflammation, production of auto-antibodies, swelling, stiffness, pain in synovial joints.

RA eventually progress to lungs, skin, eyes, heart, kidneys and patients are more prone to cardio vascular diseases, mental health issues in future. TNF-α, interleukins [IL-6,8,9] secreted by macrophages, t-cells are the main inflammatory mediators which activates the cascades of the reactions involving in the RA. One of the approaches in the treatment of RA is by utilizing the FOOD AND DRUG ADMINISTRATION [FDA] approved biologics used in reducing the inflammation" [9]. The drawbacks of these biologics include high cost which limits the patients to access them. The overture of biosimilars is cost effective and have emerged as a new promising option for RA treatment and are expected to provide new treatment options against the disease in the near future [10].

TABLE 2: FDA APPROVED BIOLOGICS AND BIOSIMILARS FOR THE MANAGEMENT OF RHEUMATOID ARTHRITIS AND INFLAMMATORY CONDITIONS

Biologics [Reference Drug]	Brand Name	Biosimilar	Manufacturer
Infliximab	Remicade®	Inflectra* Infimab	Hospira(pfizer) Epirus Biopharmaceuticals
Etanercept	Enbrel®, Erelzi®	Eticovo* Nanercept Etacept	Samsung Bioepis Nanogen cipla
Rutiximab	Rutixan®	Truxima* Ruxience ABP 798	Hospira(pfizer) Amgen

***Inflectra-(infliximab-dyyb) [11]:**

Molecular weight: 149,100 Daltons.

Physical form: white lyophilized powder stored in vial (Type 1 glass) with-out preservative.

pH: 7.2

T1/2: 8-10 days

VD: 3-4 litres.

Administration: reconstituted with 10ml sterile water for injection, Intra venous infusion. It should not be infused with other medications.

Dosage form & Strength: Injection- 100 mg of lyophilized infliximab-dyyb in a 20 mL vial.

MOA: a chimeric monoclonal antibody, supress binding of TNFα with its receptors.

Clinical uses: Approved by FDA in 2016 and indicated for rheumatoid Arthritis, Ulcerative colitis, Crohn's disease, Psoriatic arthritis.

***Truxima–(rituximab-abbs) [12]:**

Molecular weight: 145 kD

Physical form: colour less to yellow solution stored in vial (Type 1) with-out preservative.

pH: 6.2,

$T^{1/2}$: 22 days.

Administration: Intravenous infusion. Do not administer as an Infusion bolus or push.

Dosage form & Strength: Injection-100 mg/10 mL (10 mg/mL) in single-dose vial, 500 mg/50 mL (10 mg/mL) solution in single-dose vials.

MOA: Binds to CD 20 on the surface of B-cell and leads to the lysis of B-cells.

Clinical uses: Approved by FDA in 2018 and indicated for Rheumatoid arthritis, Non-Hodgkin's Lymphoma.

***Eticovo - (etanercept-ykro) [13]:** Molecular weight: 150 kilodaltons.

Physical form: clear to opalescent, colourless to pale yellow solution in a single-dose prefilled syringe (Type 1 glass) with-out preservative.

pH: 6.2 ± 0.3

Administration: Sub- cutaneous administration.

Dosage form & Strength: 25 mg/0.5 mL and 50 mg/mL solutions in a single-dose prefilled syringe for injection.

MOA: Binds to TNFα and suppress its interaction with TNFα receptors and decreases inflammation.

Clinical uses: Approved by FDA in 2019 and is indicated for Rheumatoid arthritis, Psoriatic Arthritis, Ankylosing Spondylitis.

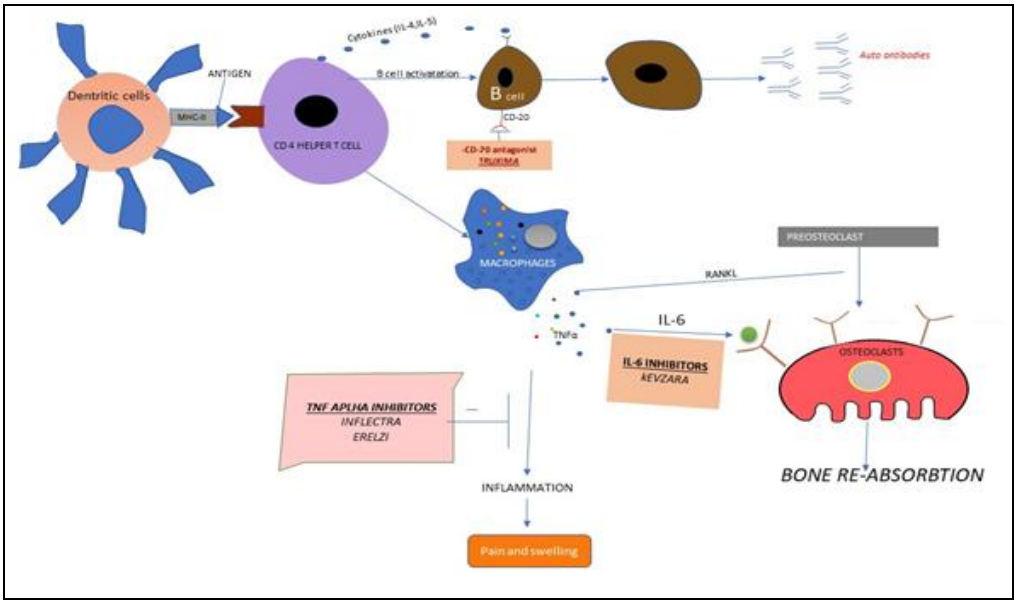

FIG. 2: THIS FIGURE DEPICTS THE MECHANISM OF ACTION OF BIOSIMILARS ON THE MEDIATORS OF INFLAMMATION

Case Study - 2: "Cancer is fundamentally a metabolic disease which involves uncontrolled proliferation of normal cells and tumour cells. A localized tumour growth, condition known as benign tumour; eventually spreads to system, a condition known as malignant tumour. The malignant tumour is life threatening because the tumour invades the body *via*. Lymphatic and blood circulations. Cancer effects from tissue to organs such as skin, lung, colon, uterus, breast, bladder, blood *etc*. The risk factors which lead to cancer are termed as Carcinogens, includes UV radiation, smoking, hormones, obesity, alcohol, virus [human papillomavirus], age and so on. The pre-eminent treatment involves immunotherapy that utilizes biologics to boost the immune system" [14].

Biologics limit the access to patient because of their exorbitant cost. However leading oncology biologics patents have expired and various biosimilars for the treatment have been authorised potentially with lowered price without limiting the access to the patients [15]. However, only few biosimilars are approved by US FDA for oncology therapy. Biologics approved by FDA for treatment are listed in the table:

TABLE 3: FDA APPROVED BIOLOGICS AND BIOSIMILARS IN ONCOLOGY

Biologics [Reference drug]	Brand Name	Biosimilars	Manufacturer
Bevacizumab	Avastin®	Mvasi*	Amgen
		Zirabev	Pfizer
		Alymsys	Mabxience
Rituximab	Rituxan®	Truxima*	Celltrion
		Rixathon,	Sandoz GmbH
		Riximyo.	Sandoz GmbH
Filgrastim	Neupogen®	Zarxio*	Sandoz
		Nivestym	Hospira
		Biograstim	ABZ Pharma GmbH
Pegfilgrastim	Neulasta®	Fulphila*	Mylan/Biocon
		Udenyca	Coherus
		Ziextenzo	Sandoz GmbH
		Pelmeg	Cinfa Biotech S.L.
Epoetin alfa	Epogen®	Retacrit*	Hospira
Trastuzumab	Herceptin®	Ogivri*	Mylan
		Herzuma	Celltrion
		Ontruzant	Samsung Bioepis
		Trazimera	Pfizer
		Kanjinti	Amgen

Mvasi [bevacizumab-awwb] [16]:

Molecular weight: 149 kD

Physical form: colourless to pale yellow solution stored in vial (type 1) without preservative

pH: 6.2

$T^{1/2}$: 18-19 days

Administration: Intravenous infusion. Co-administration with dextrose solution and glucose solution is prohibited. Do not administer as an IV push or bolus.

Dosage form & Strength: Injection: 100 mg/4 mL (25 mg/mL), 400 mg/16 mL (25 mg/mL), no preservative

MOA: Mvasi binds to VEGFA and inhibits the binding of VEGF with its surface receptors.

Clinical uses: approved by FDA in 2017 for the treatment in metastatic colon cancer, lung cancer, metastatic renal carcinoma.

Zarxio (filgrastim-sndz) [17]:

Molecular weight: 18,800 Daltons.

Physical form: Colour less to yellow solution stored in pre-filled syringe (type 1 glass) without preservative.

V_d: 150 ml/kg

$T^{1/2}$: 3 – 7 hours.

Administration: sub-cutaneous or intravenous infusion. For IV dilution with 5% dextrose solution is required. Dilution with saline is strictly prohibited.

Dosage form & strength: injection with 2 dosage strength- 300 mcg/0.5 mL and 480 mcg/0.8 mL in a single use pre-filled syringe with an ultra safe needle.

MOA: It is a Hematopoietic Growth Factor, which binds to granulocyte colony- stimulating factor and increases the growth of neutrophils.

Clinical uses: Approved by FDA IN 2015 for Chronic Neutropenia, Acute Myeloid Leukaemia, Patients undergoing with Bone Marrow treatment.

Retacrit (epoetin alfa-epbx) [18]:

Molecular weight: 30,400 Daltons.

Physical form: Clear, Colourless solution stored in single dose vials (type 1 glass) without preservative.

pH: NaOH / Hcl added to adjust pH 7.0 – 7.5 $V_{d:}$ 49.3 mL/kg

$T^{1/2}$: 4 – 13 hours.

Administration: sub-cutaneous or intra venous, do not dilute and combine with other solution.

Dosage form & strength: Injection- 2,000 Units/mL, 3,000 Units/mL, 4,000 Units/mL, 10,000 Units/mL, and 40,000 Units/mL.

MOA: It induces erythropoiesis.

Clinical uses: Approved by FDA in 2018 and is indicated for the patients with Chemotherapy induced Anaemia, Chronic Kidney Diseases, Patients undergoing vascular surgery.

Ogivri (trastuzumab-dkst) [19]:-

Molecular weight: 148 kDa.

Physical form: clear – pale yellow lyophilized powder stored in vials (Type 1) without preservatives.

P^H: 6 after dilution.

$T^{1/2}$: 12 – 19 days

Administration: reconstituted with bacteriostatic water for injection containing 1.1% benzyl alcohol as Intra venous infusion. Do not use Dextrose (5%) as diluent. Do not use as an IV push or Infusion bolus.

Dosage form & strength: For Injection: 150 mg lyophilized powder in a single-dose vial.

For Injection: 420 mg lyophilized powder in a multiple-dose vial.

MOA: It suppress the growth of HER2-positive human tumour cells.

Clinical uses: Approved by FDA in 2017 and is indicated for metastatic breast cancer, metastatic gastric cancer, adjuvant breast cancer.

Fulphila (pegfilgrastim-jmdb) [20]:

Molecular weight: 39 kD

Physical form: Clear colourless solution stored in pre-filled syringe (type 1 glass) with-out Preservative.

pH: 4.0

T $^{1/2}$: 15 – 18 hours.

Administration: Sub-cutaneous Administration after 24 hours and in between 14 days of chemotherapy is prohibited.

Dosage form & Strength: Injection- 6 mg/0.6 mL in a single use pre-filled syringe with an ultra safe needle.

MOA: It binds to the receptors present on hemopoietic cells and initiates the division and differentiation of the neutrophils.

Clinical uses: Approved by FDA in 2018 and is indicated as a prophylactic drug for the patients undergoing cancer therapy to prevent drug induced Fibrile Neutropenia.

CONCLUSION: Over the past ten years, the regulation of the biosimilars business has expanded significantly. The biosimilars business is primed for further expansion since the patents on some of the most often prescribed biologics are about to expire. The biosimilars-driven market competition could endanger the pharmaceutical industry's monopoly. In the complex web of intellectual property rights, it frequently appears that the pharmaceutical behemoths are stymieing the biosimilars industry. In order to address some murky issues in the marketing and prescription of biosimilars, regulatory authorities will need to offer a more concrete framework in the upcoming years. This, along with practitioner and consumer education, innovative development, and business models, can pave the way for the development of brand-new, immensely successful biosimilars. Pharmacovigilance will be necessary to identify any safety and effectiveness issues that may develop as a result of the usage of biosimilars. Further, a single approved organisation should be in charge of and ensure global acceptance for the rules governing the name and labelling of biosimilar products. The ability of the biosimilar producers to provide a consistent product over the long term has yet to be established, despite the fact that biosimilars have started to enter the worldwide market. The European Medicines Evaluation Agency (EMEA) guidelines currently only serve as a road map, leaving difficult areas to be further researched and monitored, despite the fact that European legislation is in place to evaluate and provide marketing clearance for biosimilars. Case-by-case consideration should still be given to approving biosimilar products.

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REFERENCES:

1. Bhupinder Sekhon, Vikrant Saluja Biosimilars: An overview March Biosimilars 2011; 1(1): 1-11 DOI:10.2147/BS.S16120License CC BY-NC 3.0
2. Davio K: Oncologists address the role of biosimilars in cancer care at NCCN annual conference. The Center for Biosimilars. 2018.Generics and Biosimilars Initiative. Biosimilars versus generics [www.gabionline.net]. Mol, Belgium: Pro Pharma Communications International; [cited 2020 May 29].
3. Socinski MA, Curigliano G, Jacobs I, Gumbiner B, MacDonald J and Thomas D: Clinical considerations for the development of biosimilars in oncology. MAbs 2015; 7: 286–293. [PMC free article] [PubMed] [Google Scholar]5ccccc
4. Niazi SK: Biosimilars: Harmonizing the Approval Guidelines. Biologics 2022; 2: 171–195. https://doi.org/10.3390/ biologics2030014
5. Mehmood Y: 2018 Int. J. Appl. Sci. Biotechnol. Vol 6(2): 53-62 DOI: 10.3126/ijasbt.v6i2.20418
6. Generics and biosimilars initiative: amgen manufacturing of biologics (Effecve 15th August 2016)
7. www.Fda.gov Biosimilar Product Regulatory Review and Approval
8. Judith Stewart, How many biosimilars have been approved in the United States? Medically reviewed by Judith Stewart, B.Pharm. Last updated on Aug 17, 2022.
9. Kritika Chaudhari, Salman Rizvi and Basharut A Syed: Rheumatoid arthritis: current and future trends. 2016; 10.1038/nrd.2016.21.
10. Vasco C. Romão, Edward M. Vital, João Eurico Fonseca & Maya H: Buch Right drug, right patient, right time: aspiration or future promise for biologics in rheumatoid arthritis? Arthritis Research & Therapy 2017; https://doi.org/10.1186/s13075-017-1445-3.
11. Inflectra – product monograph; FDA 2016.
12. Truxima – product monograph; FDA 2018.
13. Eticovo – Product monograph; FDA 2019.

14. Blackadar CB: Historical review of the causes of cancer. World J Clin Oncol 2016; 7(1): 54-86 10.5306/wjco.v7.i1.54.
15. Konstantinidou, Papaspiliou A & Kokkotou E: Current and future roles of biosimilars in oncology practice (Review); Oncology Letters. 2019; 19 (1): 45-51 https://doi.org/10.3892/ol.2019.11105.
16. Mvasi- Product monograph; FDA 2017.
17. Zarxio- Product monograph; FDA 2015.
18. Retacrit- Product monograph; FDA 2018.
19. Ogivri- Product monograph; FDA 2017.
20. Fulphila- Product monograph: FDA 2018.

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