International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

Biosimilars: An Overview

Dornala Chaitanya Dixit[1], Dr. M. Sri Ramachandra[2], P. Mrudhukamali[3], N. Sandhya[4]

[1] M. Pharm, (Ph. D), JNTUA, [2]M. Pharm, Ph. D, JNTUA
[3,4]B. Pharmacy, JNTUA

ABSTARCT

Therapeutic biosimilar products are similar to approved reference biologics. with no clinically significant differences in terms of safety. purity and potency. These products were developed after the patent on the original biologic drug expired. and must be evaluated according to strict regulations to ensure efficacy and safety. Biosimilar medicines Promote in the pharmaceutical market and various Increase patient access to treatment for chronic, life-threatening and autoimmune diseases. Biosimilars are the same type of source. (For example, organisms such as bacteria (e.coli, bacilius subtilis), mammalian cells (HEK293,NSO), plant systems (tobacco, corn)

Keywords: Reference products, immunogenticity, biologic product, demonstratingbiosimilarity.

1.0 INTRODUCTION:

The biologics arose in 1980 with an evolution in a group of medicines which were produced in living systems through biotechnological methods like recombinant DNA technology which distinguished them with chemical synthesis medicines. These differences arose the requisite of specific legislation suitable to these innovative medicines [1,2,3,4]. As illustrated in the preceding section, many diseases including cancer, diabetes, auto immune diseases, and multiple sclerosis are lethal. After they were started to be incorporated as the treatment option for patients, biological medicines proved that they are the significant health technology that is among the fastest growing segments of the pharmaceutical-industrial company, and millions of people's population of which may benefit from use of these products. As a result of the expiration of their patents, biosimilars surfaced as similar counterparts. However, to get there and establish themselves in this market they need to prove that they are as safe as their corresponding reference biologicals [4,5]. Biological or biopharmaceuticals refer to medicine derived from the biological process using living cells and can be categorized as those.

Drugs mimicking natural biological substances such as hormones. Biosimilars are follow on bio generics related to a biological that has already been approved (known as the reference product), therefore similar but not interchangeable. According to the Indian guidelines a "similar biologic" is a biological product/drug derived through rDNA techniques and where it is claimed that it is 'similar' in terms of safety, efficacy and quality to a reference biologic which has been approved by DCGI for safe use in India. The product that constitutes the biosimilar medicine is also like one of the biological reference medicines and is administered in the same dosage for the same disease.[6]

Biosimilars are entity based (including product-process), regulatory based (being under abbreviated testing) and market competition based (same manufacturers but different trade name). Biosimilars are also known as similar biological products, follow-up biologics, subsequent entry biological, second entry biological, bio generics multisource products and off patent biotech products as synonyms. The public and insurance companies opt for economic substitutes, but there is no research done on biosimilars' sustained

economic impact. There is the potential for the costs of therapy with biosimilars to increase. Biologics are a new generation of products to possess similar safety and efficacy profile to the reference off-patent biological. This is due to the fact that protein structure of biologicals is more readily 'alive', thereby more ready to trigger an acute and chronic immune response. The risk is relatively small with biosimilars, as stated previously, however some regulatory pathways are deemed necessary due to structural characteristics, bioprocess for manufacturing, and the risk of immunogenicity.

The challenges/risks involved in biosimilar include the fact that the two biosimilar may have distinct origin, the two biosimilars may have equivalent therapeutic effect, and may have different side effects, and thus must undergo test. [15] A biosimilar is a biological medicine that resembles another biological medicine already approved (the 'reference product' [RP]).9 The first biosimilar approved in the European Union was Omnitrope, a biosimilar of somatropin in 2006,10 while the first biosimilar approved in the United States was Filgrastim-SNDZ in 2015.11 As at January

2.0 Defining biosimilars

biosimilar is 'a biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product', where similarity means 'no relevant difference in the parameter of interest'. Said biosimilars should be developed solely in compliance with comparative procedures applied to reference biosimilars as provided by the regulatory authorities such as EMA or FDA.

The various rigorous processes implemented reduce the risk of any clinically relevant differences between the biosimilar and the reference product in terms of the totality of safety, purity and potency as stated by the FDA or quality, safety and efficacy as provided by the EMA. At present some products that are referred to as 'biosimilars' are approved for the treatment of RA in several countries that, when approving these products, lacked stringent regulations in terms of comparability as put forward by.

However, these products apparently conform to local requirements and should not be described as biosimilars but rather, intended copies. It is important for physicians to make the distinction between these and 'true' biosimilars that are EMA/FDA compliant, as well as the differences between biosimilars and other 'biological copies' Biosimilar is defined on the website of NHS England as "Biological medicine which has been shown not to have any clinically significant differences from the original medicine in terms of quality, safety or efficacy."

2.1 FDA Definition

According to FDA [2]: "The biologic product is highly similar to the reference product notwithstanding minor differences in clinical inactive components and that there are no clinically meaningful differences between the biologic product and the reference product in terms of safety, purity, and potency of the product". Thus, it makes clear that biosimilars are not exact copies of reference product, and that any differences in purity and potency between the biosimilar and reference product product must not be clinically meaningful.

3.0 History:

It can be noted that the bases of generics and biosimilars have been created during the enactment of several important laws. The Kefauver-Harris Amendments of 1962 stipulated that a drugs safety and efficacy had to be proved, and, they insisted that new safety reviews be done on drugs that were released between the years 1938 and 1962. In the late of 1960s the FDA formulated the new abbreviated drug application for

approval of generic drugs. The Drug Price Competition and Patent Term Restoration Act of 1984 also known as Hatch-Waxman meant that the FDA was empowered to accept applications for marketing generic copies of brand-name drugs introduced after 1962 without having to conduct efficacy and safety trials; at the same time, it granted owners of specific products ‘’505 days exclusivity for new products containing chemical substances that had not been approved by the FDA’.

Even more went further to advocate that within biosimilar product labeling should include a statement saying biosimilar is different from the reference product. Special attention was paid, too, to lobbying to ensure state legislatures would not pre-emptively ban interchangeable biosimilars. But when the originator companies discovered that it is not just another fad, they jumped on the bandwagon, just like they did with the generic drugs. Several major global players producing many of the first biologics then became the biggest biosimilar manufacturers. Thus, of 29 marketed in the United States biosimilars to date approved by the FDA, all but a few belong to the major pharma companies.

4.0 characteristics of biosimilars

While development and production of generic-equivalent small-molecule pharmaceuticals are not as complex as those for biopharmaceuticals and biosimilars, the production of generic-equivalent small-molecule pharmaceuticals is not a challenge. The only thing that is needed is proving that this generic product possesses the same active substance as the innovator product and a bioavailability study proving that the rate of absorption of the biosimilar and the reference product is the same.

Biosimilars however are not equivalent to the generics of innovator products. With this perspective the European Medicines Agency EMEA has formulated its biosimilar approval procedures. This is because a bio-similar has a different chemical composition from the innovating product. Since biopharmaceuticals are proteins of reasonable size and structure and can be manufactured only with the help of multiple steps…, biopharmaceuticals are much more complex than small-molecule pharmaceuticals. In contrast to more traditional chemical drugs, there is a direct correlation between the production of biopharmaceuticals and the characteristics of its product [4].

In fact, the quality of biopharmaceuticals is linked with the process of manufacturing. Intermediates, protein source and extraction / purification techniques lead to variability of the final product, which characterizes biopharmaceuticals. For example, the methodology of cellular-expression schemes and protein manufacturing are unique in a way that yields isoforms. However, small changes may result in differences in the three-dimensional structure of the protein, the number of acid–base variants and glycosylation. Some of the factors that will not be available to biosimilar manufacturers include the manufacturing process of the innovator products because it is the biosimilar manufactures’ knowledge. Consequently, it is impossible for biosimilar manufacturers to exactly mimic any protein product [2]. Furthermore, since analytical methods are unavailable for identifying or forecasting the biological and clinical profile or proteins, variability between biopharmaceutical goods can remain unseen [2]. Regulations and guidelines have to take into consideration such aspects of biosimilars while they differ from their reference products; Furthermore, there has to be proposals for Hardy and obligatory pharmacovigilance on biosimilar products.

The role of the manufacturing process was shown by the changes in the composition and bioactivity of products manufactured in other countries and regions of the world and pointed out that those products which were manufactured in countries other than the United States and Europe contain less of key components and have relatively lower activity. A study By analyzing 11 epoetin products from four

different countries (Korea, Argentina, China, and India) revealed the presence of different isoforms in the products under study and a large extent of deviation in relation to specifications concerning in vivo bioactivity. For illustration, in vivo bio activity values were found to be between 71 and 226 percent and five out of ten products did not conform with their own specifications [7]. Nevertheless, the AWP, Allegra and Cymbalta products are not controlled through the EMEA and FDA markets.

5.0 Biologics versus small molecule drugs

There are fundamental disparities between biologics and most other usual small molecule drugs primarily due to their differentiation in terms of source Small molecule drugs are usually chemically synthesized while a biological product is often produced mainly by cells or living beings [1]. This results in difference in structure, composition, method of manufacture, technology, intellectual property, formulation, in handling and dosing, in regulation, and in marketing. Consequently, the structure of biologics is more intricate compared to that of the low molecular weight drugs; biologics comprise primary (amino acid sequence) and secondary (α-helix, β-pleated sheet) that are folded from a complex three-dimensional conformation.[4]

In some biopharmaceuticals, a quaternary structure of the tertiary structures of individual proteins forms stable associations. These structures may then be elaborated by various forms of post-synthetic modifications and additions such as glycosylation or sialylation, these modifications may be necessary for biological activity. As a matter of fact, there are remarkable differences between biologics and other small-molecule drugs just because of origin difference Small-molecule drugs while biological products are produced is usually by cells organisms. This difference in origin results in difference in structure, composition, manufacturing methods and equipment, patents, formulation, handling, measuring, legislation, and selling. So, from the structural view, they are far more complicated than low molecular weight drugs – they possess primary (amino acid sequence) secondary (alpha helix, beta pleated sheet), and complex tertiary structures.[4]

In some biopharmaceuticals, tertiary structures of individual proteins form a quaternary structure which are stable in nature. Further to these formations, it was noted that these structures are usually subjected to post-synthesis modifications such as glycosylation or Sialylation, the latter of which may be vital for biological activity.[5] In addition, owing to its relatively big size and structure, the characterization of a biopharmaceutical poses a major daunting task. .Despite all the new, diverse methods for characterizing structure and physicochemical parameters, due to the high levels of complexity of the biopharmaceuticals, even if all those techniques are employed, the image will still be deficient. Usually, it is not rational to define these characteristics for any given product and they often depend upon the type of manufacturing process pharmaceutical companies.

the biosimilars safety and efficacy might be against by major pharmaceutical manufacturers would have dissipated, but it did not. Patients were reluctant to use these agents.And the same companies that once revolted against biosimilars adopted a new mantra:“Only we know how to same companies that once revolted against biosimilars adopted a new mantra:“Only we know how to make biosimilars because only we know how to make biological drugs.”In 2010 the Biologics Price Competition and Innovation Act (BPCIA) was singed into law and we saw a repeat of the same situation were originator companies objected to biologics as they had done to generics

But this time they got the audience because the stakes had risen higher than the mere way of living of individuals. The most frequent defense we received was that biological drugs have no well-defined

composition, and defining manufacturing process controls is critical to product quality. They argued that studying these controls was inconceivable because only innovator producers knew about them, and thus no firm could develop both efficiency and safety. It was seen that many big biologic companies having original biologics remained the largest sellers of biosimilars.

Out of the 29 biosimilars approved by the organisation to date, the majority of biosimilars are owned by large pharmaceutical firms. Observers may assume that the seeds of doubt about biosimilars safety and efficacy instilled by leading pharmaceutical companies would have been overcome but they weren't. These agents were not used much by the patients.

6.0 Biological medicines:

Bio-similar products have a far more complex and larger structure compared to small molecules [4]. Currently, they are divided into three main categories: Subsequently, depending on the therapeutic target, there can be categorized specifically: (1) products highly correlated with endogenous factors and which are used sometimes as a substition therapy; (2) mAbs, which directly bind to soluble or cell surface markers, inhibiting the corresponding cell signaling and its functional reactions; (3) produced proteins that mimick soluble receptors, antagonizing their receptors and fusion proteins.

In more detail, biological medicines are manufactured in the form of hormones, which include insulin, hormone deficiency, growth hormones, mAb such as management of autoimmune diseases and cancer, blood products such as people with hemophilia, immunomodulators such as interferon beta for multiple sclerosis, enzymes such as enzymes to dissolve blood clots, and vaccines used in disease prevention [8,10].logical medicines are produced as hormones (as is the case of insulin, hormone deficiencies, and growth hormones), mAb (e.g., the management of autoimmune diseases and cancer), blood products (e.g., individuals with hemophilia), immunomodulators (e.g., interferon beta, for multiple sclerosis), enzymes (e.g., for the removal of blood clots), and vaccines for the prevention of various diseases [8,10].Biological and medicines, including biosimilars, are known for their complex characteristics and high heterogeneity. It is also accepted that there may be some differences in properties between RPs and biosimilars. Nevertheless, minor differences between the reference biosimilar and the developed product have no substantial effect on the quality safety of the product because of the rigorous process of biosimilar development and approval. This therefore makes biosimilars to go through comparable biosimilarity studies in order to put forward strong evidences of their quality and safety in relation to the reference biopharmaceutical product. The chemistry of these products in terms of their physical, chemical and biological properties and investigations of the products' efficacy and safety in clinical human trials are contained in these studies.

.

7.0 Development and Regulatory Approval of Biosimilars

The process of biosimilars' approval and development is also very different from the process of innovative chemical or biological new active substances, The process of new biological drug approval generally falls within a time frame of approximately twelve years and includes research and development aimed at obtaining a suitable molecule. During the preclinical stage, which is a very important stage of drug development [19], the molecule is thoroughly examined. The process of bringing a drug to market typically involves several established phases: I, II, III, and IV. After a drug has been commercialized, they undertake phase IV. Whereas for generic medication the most straightforward process plays out since the issue of deficiencies of the drug molecule has been settled. Hence the only requirements are the release of the finished product and bioequivalence test results [18]. Because biosimilars are similar to the original molecules that already have identified product profile, they do not go through the discovery

and efficacy phase (phase II) and so the overall development time is less than eight years and it is cheaper by 10–20% [5,19,34]. However, as Figure 1 depicted, development of bioismilars passes through a phase III; however this phase III is not clinical trial as we understood, but a small clinical trial whose primary purpose is the efficacy and safety comparison. A significant aspect in the generation of biosimilars is to ensure that one aims to develop a biosimilar with a similar quantitative profile to that of the RP in terms of analytical and biological profile.

7.1 Demonstration of analytical similarity -comparative Quality studies

The process of biosimilars' approval and development is also very different from the process of innovative chemical or biological new active substances,The process of new biological drug approval generally falls within a time frame of approximately twelve years and includes research and development aimed at obtaining a suitable molecule. During the preclinical stage, which is a very important stage of drug development [19], the molecule is thoroughly examined. The process of bringing a drug to market typically involves several established phases: I, II, III, and IV. After a drug has been commercialized, they undertake phase IV.

Whereas for generic medication the most straightforward process plays out since the issue of deficiencies of the drug molecule has been settled. Hence the only requirements are the release of the finished product and bioequivalence test results [18]. Because biosimilars are similar to the original molecules that already have identified product profile, they do not go through the discovery and efficacy phase (phase II) and so the overall development time is less than eight years and it is cheaper by 10–20% [5,19,34]. However, the development of biosimilars passes through a phase III; however, this phase III is not clinical trial as we understood, but a small clinical trial whose primary purpose is the efficacy and safety comparison.

A significant aspect in the generation of biosimilars is to ensure that one aims to develop a biosimilar with a similar quantitative profile to that of the RP in terms of analytical and biological profile.The qualitative and quantitative evaluation of the characterization of the purity and impurities of the product and the manufacturing process contributes to product safety, and it must be analyzed qualitatively and quantitatively separately, using various methodologies [21]. Since working with biological sources can produce high risk to product quality and safety, it is essential to estimate the shelf life and characteristics of those materials.

Anticipation of such factors aids in decision making of use and deposition In essence, insight into these variables support appropriation of use and storage. All associated process related species have to be identified (Host cell DNA & proteins, reagents used in the process, downstream impurities, etc.) along with the risk that they may pose (immunogenicity, etc) [16]. The thermal stability assessment compares the forced degradation profiles and degradation products

8.0 Pharmacokinetic and Pharmacodynamic Studies of biosimilars:

The development of a biosimilar generally begins with a study designed to demonstrate that the proposed biosimilar exhibits comparable pharmacokinetic (PK) and pharmacodynamic (PD) properties when measured against the reference product (RP) [21]. The design of this study is influenced by various factors, including the clinical context, safety considerations, and the pharmacokinetics of the RP. Consequently, this study is conducted only after the biosimilar has been thoroughly characterized [12, 16].

PK assessments are essential for evaluating the drug's bioavailability, which encompasses aspects such as absorption, distribution, time dependence, and interaction with blood components. On the other hand, PD studies are crucial for confirming that the biosimilar's effectiveness in the target tissue matches that of the RP and that the underlying mechanism of action remains consistent. In certain instances, comparative

PK/PD studies alone may suffice to establish that the clinical outcomes are similar [12].

Effifcacy studies:

Studies on efficacy allow for the analysis of significant differences in treatment outcomes. The primary aim of these studies is not just to demonstrate effectiveness but to confirm that clinical performance is comparable to existing treatments [12]. To achieve this, randomized parallel-group comparative clinical trials are essential, with double-blind designs being preferable. Additionally, appropriate efficacy endpoints must be established. It's crucial that the methods used to detect potential differences related to a product are sensitive enough to minimize the impact of individual or disease-related factors. To ensure a high-sensitivity study, the selected population should closely mirror the one specified in the approved indication for the reference product (RP). This approach facilitates the identification of differences in efficacy between the proposed biosimilar and the RP.

9.0 Safety Evaluation

The safety issues related to the biosimilar play a major role in comparability studies. Accordingto the usual procedures in the development of biological medicines, the biosimilar's safety profile is built across the entire clinical program—during phase I PK/PD studies and phase IIIdirect comparison studies [**12**]. To establish the similarity between a biosimilar and its RP, it is necessary to assess and comparethe type, severity, and frequency of any adverse events (AEs) that may occur. Additionally, any potential safety risks arising from variations in the manufacturing process must be taken into consideration [**12**]. Moreover, immunogenicity must also be intensively studied, due to thepossible immunogenic character of biologicals. The length of the immunogenicity study shouldbe rationalized based on individual cases, since it relies on factors such as the duration of the treatment, drug release, and the time that it takes for the immune response to manifest. If thereis an increase in the immunogenic profile of the biosimilar in relation to the RP, this can becomea problem for the risk–benefit analysis (this does not occur if the immunogenic profile is lowerin the biosimilar) [**4**,**12**].

10.0 Post-Marketing Monitoring of Safety of Biosimilars.

Pharmacovigilance (PV), grounded in Good Pharmaceutical Practices, aims to evaluate the risks linked to medicinal products. This evaluation is crucial because the effectiveness of these products relies on their ability to elicit an immune response. Additionally, there is a risk of hypersensitivity reactions, an increased likelihood of other side effects, and potential variations in the production process. Consequently, manufacturers must implement a robust PV system that can identify, assess, and mitigate any drug-related adverse events (AEs) during the manufacturing process. PV systems should not only categorize the type and severity of AEs to identify new class-based risks but also include a template to track the frequency of each AE over time. When submitting a candidate for approval, it is essential to provide a concise overview of the intended plan along with a risk management strategy that aligns with current European Union regulations and pharmacovigilance guidelines.

10.1 Patient Needs

Patients often express concerns regarding the safety and efficacy of biosimilars incomparison to reference biologic products. One significant worry is that the lower cost of biosimilars may compromise their quality and effectiveness.

11.0 Biosimilar Naming, Labeling, and Pharmacovigilance

The labelling and names of a biological product can provide a optimal intelligibility of an particular agent and all other essential information which is relevant to the patients and allprimary hospitals (who can

tasked to provide minimal health care). The therapy of a biosimilars products before, during and after use is very essential to the patients for minimisingthe prescribing errors and safety of a patient. and, mainly to allow the immunogenicity andadverse drug events in post marketing reports of a specific agent.

The labeling of biosimilars should contain all the information that would be relevant to the prescriber, pharmacist, and others in the decision-making process, including preclinical and clinical study data which would support a finding of biosimilarity or interchangeability. Labeling also should be sufficient to indicate whether the described studies were done using the biosimilar or reference product. Resulting in March 2016, the FDA published the draft guidance of the proposed requirements for the labeling of biosimilar products 19. The bio similarity statement label should include a statement to describe the relationship of the biosimilar to the reference product In addition, all content in the label should be identified for source if they were obtained from either the reference product or the biosimilar.

Clinical pharmacology studies need to be performed to show that the bioavailability of the proposed product is same as that of the reference product, and they should be incorporated in labeling – in probably greater details than in generic drugs or in the label of the reference product. Thus, for correct pharmacovigilance, it is important that physicians, pharmacists and patients can differentiate between biopharmaceutical products. It is sometimes difficult to associate certain events with a particular product if different products have the same INN, while reports do not contain other information that would help sort products by pharmacovigilance.

Supporting this concept is the EMEA; this has given it such importance. The position statement of the EMEA also supports the disclosure of the specific medicinal product given to the patient 'to enable pharmacovigilance monitoring of the dispatched medication' [3]. The EMEA does not involve in decisions about INNs; this task is performed by a committee of the World Health Organization with advice from an international expert panel. It would seem reasonable for this committee to allocate distinct INNs to biopharmaceuticals. This would assist in enhancing the right prescription and distribution of biopharmaceuticals. The EMEA should consider requiring comprehensive labeling of biosimilars so that physicians and pharmacists can make informed decisions. Because biosimilars are not equivalent to reference products and because unique efficacy and safety data will be available, labeling should include these data. Furthermore, labeling should note those indications that are based on extrapolation of data.

12.0 Current and Future Biosimilars products in oncology

The first biosimilar to be approved by the FDA was filgrastim-sndz for the treatment of cancer in March 2015, approval of which has led to several approvals likely in the future in the United States within the oncology segment. Currently, 23 biosimilar have been approved in EU since 2006 and 16 of these are indicated for cancer; two of recent biosimilar are CT-P10 and L01XC02, they are manufactured rituximab. More than 300 biosimilar are in pipeline in Asia-Pacific region than in United States and Europe with 50. However, tbo-filgrastim is another G-CSF that is available on the market; it was not approved as a biosimilar as there was no such pathway at the time of submission; instead, a full Biologic Licensing Application was made.

Further agents in supportive care and for active treatment are still under development in the developmental stage. Notably, most firms that manufacture referred branded reference products, beside regular new entrant firms which were specifically developed with the objective of developing, licensing and marketing biosimilars are also in the process of enhancing biosimilars. A look at the biosimilar products discussed at the Generics and Biosimilars Initiative website also confirms that developing these proteins is not without

a risk for firms. For instance, the application of biosimilars of rituximab (n = 2) and pegfilgrastim (n = 1) have been withdrawn from regulatory submissions, which imply that there are concerns in some fashion with some aspects of production or use when compared with the reference agent.

12.1 Biosimilars used in cancer treatment:

One or more biosimilars are now approved for use by the US Food and Drug Administration for some of the brand name biologics used in the treatment of cancer .

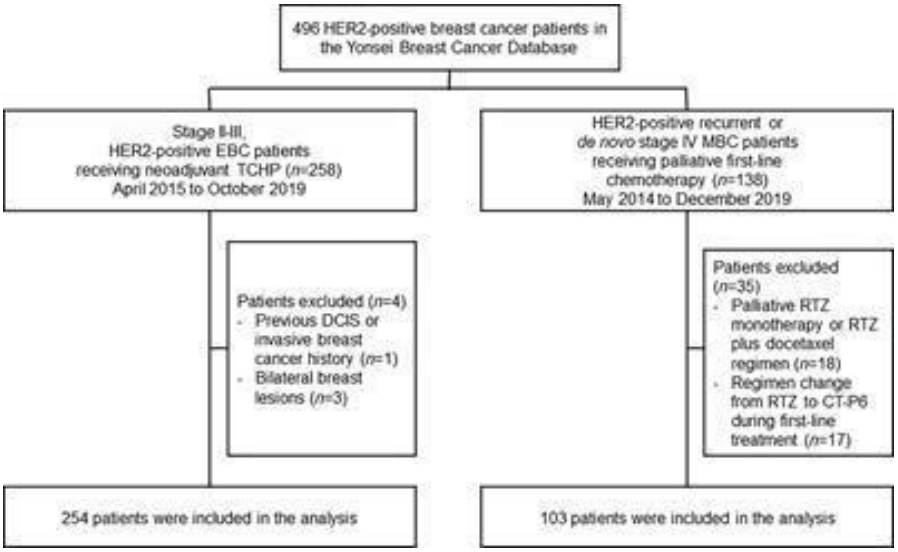

FIG.1: Biosimilars used in the cancer treatment

Biosimilars are an important aspect of modern medicine, particularly for biologic therapies. For the biologic medicine bevacizumab, commonly known as Avastin, several biosimilars are available, including Mvasi, Zirabev, Alymsys, Vegzelma, and Avizivi. These alternatives provide similar therapeutic effects and can help improve patient access to treatment. In the case of rituximab, marketed as Rituxan, there are also biosimilars available. Truxima and Ruxience are two notable options that offer similar efficacy and safety profiles, making them viable alternatives for patients requiring this treatment.

Trastuzumab, known as Herceptin, has several biosimilars on the market as well. These include Ogivri, Herzuma, Ontruzant, Trazimera, Kanjiniti, and Hercessi. Each of these biosimilars aims to provide effective treatment for conditions like breast cancer, ensuring that patients have access to necessary therapies.

For filgrastim, which is marketed under the name Neupogen, there are several biosimilars such as Zarxio, Nivestym, Releuko, and Nypozi. These options help manage neutropenia in patients undergoing chemotherapy, enhancing their overall treatment experience. Epoetin alfa, known by brand names like Epogen or Procrit, has a biosimilar called Retacrit. This biosimilar is used to treat anemia, particularly in patients with chronic kidney disease or those undergoing chemotherapy. Lastly, for denosumab, marketed as Xgeva, the biosimilar Wyost is available. This treatment is crucial for patients with bone-related conditions, providing an alternative that can help manage their health effectively.

13.0 FDA- Approved Biosimilars products:

Biosimilars Name	Approval date	Reference product
Otulfi (Ustekinumab)	September 2024	Stelara
Pavblu (aflibercept)	August 2024	Eylea
Enzeevu (aflibercept)	August 2024	Eylea

Biosimilars Name	Approval date	Reference product
Epysqli (eculizumab)	July 2024	Soliris
Ahzantive (aflibercept)	June 2024	Eylea
Nypozi (filgrastim-txid)	June 2024	Neupogen
Pyzchiva (Ustekinumab)	June 2024	Stelara
Bkemv (eculizumab)	May 2024	Soliris
Yesafili (aflibercept)	May 2024	Eylea

TABLE-1: FDA approved biosimilars

13.1 Basic Development of biosimilars:

Biosimilar development requires several steps: choice of right reference biologic, understanding the critical molecular characteristics of the chosen reference biologic and creating a process of manufacturing that will closely mirror the physical and biological characteristics of the reference biologic product. The EMA and the FDA guidelines mentioned that since biosimilars do not need to go through usual preclinical and clinical studies that normally accompany the development of new biologics, the biosimilars will have to go through a similar approval process.

The purpose of this article is to improve an understanding of the preclinical development and evaluation processes of biosimilars needed to fulfill the requirements of regulatory authorities before the clinical trials of biosimilars in humans. The biosimilar development process: Reference Biologic Product that helps in elucidating the importance of the reference biologic product Choice of right reference biologic products in the development of biosimilars is a crucial factor to be taken care of. The way to obtain an adequate dataset through which a biosimilar could be determined is through the actual procurement of the reference biologic product by purchasing one from a major market for instance USA, EU, Japan, etc. [18]. By regulation, the amount to be administered and the route also are determined by the reference biologic product against which the biosimilar is compared in the assessment of similarity.

14.0 Biosimilars approval process:

For similar biological medicinal products, they are called biosimilar, clinical trials are essential but not merely the bioequivalence studies that are required for the registration of a generic small molecule drug product. According to the EU Directive 2001/83/EC as amended, where a biological medicinal product which is like a reference biological product does not satisfy the conditions in the definition of generic medicinal products the results of appropriate pre-clinical tests or clinical trials regarding those conditions must be supplied. However, the problem is to understand which non-clinical and clinical programme is mandatory for gaining authorization. The applicant is encouraged to describe in detail how the strategy used in showing that the biosimilar and the reference product are alike in terms of quality, safety and efficacy.

The degree to which comparability can indeed be demonstrated will go very far in determining how many nonclinical and clinical trials the biosimilar applicant is likely to have to carry out. Sufficient documentation has to be provided on the comparability assessment by the applicant to the EMEA and data on any adverse immune biological activity to the therapeutic protein must be included in the dossier. Other post-marketing pharmacovigilance plans are also believed to be be part of the biosimilar dossier. Safety and efficacy are well proven in the active substances of generics medicines. Bioavailability It should be easy to show that the same dosage and dose of the generic and reference product are established, for the

bioavailability of the generic medicines must be proved with the reference product. All the controls and standards regarding all manufacturing, preparation, and processing of the product, if that is quality.

14.1 Regulatory recommendations:

The EMEA has developed a regulatory guideline for approval of biosimilars and it can alsodevelop a general legal pathway by the European union. The approval process will varyaccording to the product due to its substantial differences between biopharmaceutical products In particular, the amount of clinical product data available for the product may depend on the inherent variability of efficacy endpoints and the availability of validated surrogate markers .In ecumenical the approval of biosimilars will be based on the demonstration of comparable safety and efficacy of a reference product to an inventor according to the to a relevant patient population (comparability).

EMEA guidelines will allow with proper justification the extrapolation of data for different therapeutic indications or from one therapeutic indication to another will permit the use of biosimilars in indications for which it has not been formally studied. Due to sometimes biopharmaceuticals although infrequently associated with serious adverse events to monitor the efficacy and safety of a biosimilar products post approval. The pharmacovigilance programs and immunogenicity testing can also require EMEA guidelines. The importance of immunogenicity testing and pharmacovigilance is illustrated bythe recent approval of biosimilars growth hormone Omni trope.

During development and production of these products were transferred from one facility to another. While equivalent testing demonstrated no identify differences between the end products and these facilities. The difference was only observed with respect to the immunogenicity which was subsequently resolved by the manufacture prior to approval. Now currently there no legal pathway in the united for the approval of biosimilars and according to the US food and drug administration was not yet developed guidelines recording these types of products.

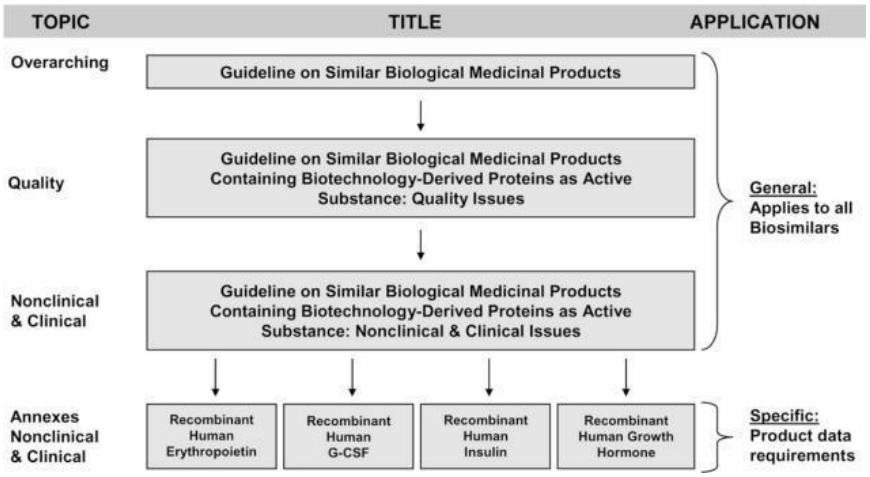

Fig 2: Steps for approval of biosimilars

14.2 Specific- product regulatory guidelines:

According to the present guidelines EMEA no biosimilar G-CSFs have been approved yet; but the clinical model for biosimilar demonstrating clinical similarity to the reference product in case of this application is prophylaxis of severe cytotoxic chemotherapy induced neutropenia. induced neutropenia. In the case of chemotherapy regimens where frequency and duration of severe neutropenia have been established, a two-

arm comparability study is advised Whereas in the case of other chemotherapy regimens, a three-arm comparability study involving a placebo arm is necessary. The guidelines also enable generalization of the results for the other indications of the reference product, provided that the mechanisms of action are similar, though no requirements are provided. Other approaches, for instance pharmacodynamics in healthy subjects, may also be permitted in the establishment of comparability if rationalized.

The EMEA also acknowledges that erythropoietin is one of the most contentious products in the development of biosimilar agents., Thus, according to the practical guidelines of the EMEA, the comparability studies should be conducted in patients with anemia of chronic renal failure; Two randomised clinical studies are required.; Comparability of the clinical efficacy of erythropoietin, for both i.v. and s.c., must be shown.

Current EMEA guidelines also permit extrapolation of safety and efficacy data from patients for one indication to other indications, where extrapolation can be well reasoned extrapolation approval of a drug which has not been evaluated in indications for a particular clinical trial. Thus, extrapolation has been used in drugs and it has rationality, but it is only suitable if only refashioning, modifying or using it in other related diseases with similar symptoms.

In general, the EMEA has approved the prospect of using data extrapolation for biosimilar to which certain substantiation. The logic is that if biosimilar is highly like the innovator product for one indication, there is basis to extend the approvals of biosimilar for all indications of the innovator product. The challenger biosimilar manufacturer must provide an adequate scientific distinction – although what 'adequate' means is not always clear. For different indications, the mechanism of action might be dissimilar, and, in this case, the biosimilar manufacturer may be required to present more data. The recent approval of two biosimilar growth hormones included extrapolation of clinical data of some indications.

In the case of Omnitrope, several comparability studies to the reference product Genotropin were conducted, these include quality studies, pharmacokinetic and pharmacodynamics, clinical efficacy and safety and immunogenicity studies [32]. Although the effectiveness and safety postmarketing trials comparing Omnitrope with the reference product were undertaken only in children with growth disorders, the product information of Omnitrope seems to be much the same as Genotropin including the indication for use in adult patients.

Reasons for the extrapolation of data between the innovator and biosimilar growth hormone products appear to include: One may list the following characteristics in favor of growth hormone: (1) extensive past clinical experience that has not revealed any significant safety problems; (2) large margin of safety for the drug; (3) relatively infrequent reports of neutralizing antibodies; (4) possibility to describe the structure and biological activity of growth hormones by physicochemical and biological properties; and (5) availability of numerous assays to characterize the active substance, as well as These criteria although useful in ordinary biopharmaceutical products such as growth hormones, can be deemed irrelevant in medicated line of casually complex biopharmaceutical products and in the critically ill.

One disadvantage of data extrapolation is that the risks for using a biopharmaceutical could be different depending on the disease indication (e.g. cancer vs other diseases). This concern has a parallel with cytotoxic chemotherapy, where the differences in biology of the neoplasms between adults and children, or in physiology between adults and children will often prevent direct translation of clinical activity data from the adult to children [43]. It is also important to remember that there may be differences caused by the fact that the treated patients had chronic neutropenia, noted during the therapy with recombinant G-CSF, or neutropenia developed as a result of chemotherapy.

Because patients with chronic neutropenia are not immunocompromised, they may be at an increased likelihood of producing antibodies to biopharmaceutical agents; however, no antibody-related treatment problem has arisen to the present with current G-CSF products. There is an element of logic in data extrapolation if relevant standards are attained, but such a connection of indications for this product should be clear to doctors and customers through the procedure for its approval.

It is important that the physicians' pharmacists, and patients know what specific data is available for a given indication and what indications are derived by extrapolation. For such a reason, interested physicians and pharmacists, who will be reading the SmPC of Omnitrope, will not realize that the drug was approved based on data that are quite different, that different from the data in the label, and that the claim of Omnitrope in the management of adult patients with GHD was originally based on extrapolated data [32, 44]. A better and more realistic concept, which would not result in misleading information, would be an extension of the SmPC.

Role of biosimilars in the treatment of rheumatic diseases:

Biological therapeutics for management of rheumatic diseases has increased patient's prognosis greatly. With some of these 'reference (originator) products' facing their patent cliff, copy versions are being developed. Specifically, owing to inherent challenges predominantly in manufacturing 'copies' of biological therapeutics, physicians have argued whether biosimilars hold offsetting biological activity, effectiveness and toxic potential to the reference biologicals both in the emergent and steady state.

These precocious apprehensions are not without rationale since even slight changes in manufacturing procedures that occur intermittently with reference biologicals may transform biological functions and/or immunogenicity and consequently may modify the safety and Biological agents vary from small replacement hormones to very large complex molecules including monoclonal antibodies (mAbs) and soluble receptor constructs (Cepts)—large, complex three dimensional protein molecules that have a higher order structure and are therefore challenging to emulate.

There are some differences in the post-translational modifications, like glycosylation that may be changed with the cell lines and/or manufacturing processes making the correspondent products similar but not equivalent to the initially approved 'reference' agents, therefore the term 'biosimilar' instead of 'bioidentical' is used. The notion of protein modification as a means of changing biological activity is particularly relevant for complex biopharmaceuticals, including mAbs and Cepts.

14.3 Properties of biosimilars: how similar is similar enough?

That is, the microheterogeneity is inherent in the variability within the batch to batch for any biological agent and sometimes these major shifts occur accompanied by changes in manufacturing processes; the level of variability is then quantified in the quality control of each batch. With manufacturing processes for biologicals being improved continually, the batch sizes are large and a single batch normally used in the EU or USA may represent the entire year's usage of a particular reference product. In the case of biosimilar products, regulatory and scientific development of such products require determination of 'tolerable standards' of variation from the reference product.

If these comparisons are to a single batch, then these parameters will be less broad that the batch-to-batch variation of the referent product.50 The fact is that biosimilar mAbs and Cepts are, by their nature, different from the reference medication and, for this reason, cannot in any way be rendered entirely like the latter. However, the following basic features must be retained (Table 5). All kinds of comparability testing, in vitro and animal studies remain insufficient for the assessment of biosimilarity and biological and clinical

activity of therapeutic mAb10; the only way to evaluate the efficacy and safety of biosimilar is in RCTs in patients with the disease. Prior concerns in immunogenicity of biological products due to low utility of standardized assays for antibiological antibodies have been overcome by the availability of biosimilars leading to enhanced development of clinical assays with sensitivity to higher circulating levels of mAbs and Cepts51.

Will biosimilars be successful?

Whether rheumatic diseases will be treated by biosimilars/pつと depends on rheumatologists' trust in them; highly demanding regulatory approval procedures aim to create such trust. So far, biosimilar utilization is low across European and U.S markets,2,58 which might be due to a smaller absolute price differential of 15–30% compared with generic drugs while offering ~80–90% savings.58,59 It is unclear at present whether there would be similar savings on biosimilar mAbs and Cepts in highly regulated markets. In other areas of the world, the economic constraints and substantial cost benefits available have mandated the use of 'intended copies' despite an awareness that their safety and efficacy are not well-defined.17 Electrochemical 'true' mAbs and Cepts, several 'reference product' manufacturers are currently involved in biosimilar development and production,21, 22, 60–63 thus suggesting that this area is of considerable interest.

Study plan for biosimilars: is the study designed: Design details Primary purpose: Treatment Allocation: randomised Interventional Model: parallel assignment: Masking: Quadruple (Subject, treater

The summary of Primary and Secondary outcome measurements using biosimilars is as follows:

Rituximab Pharmacokinetics and CD19+ B-cell Dynamics:

1. **AUC 0-T (Rituximab):** Reflects total drug exposure from administration (time 0) to the last quantifiable concentration. Measurements: Predose (Day 1) to 2016 hours post-infusion.
2. **AUC 0-T (CD19+ B-cells):** Measures total B-cell count from administration to the last measurement. Time points: Baseline, Weeks 2, 3, 5, 9, 13, 17, 21, 25.
3. **Minimum Post-baseline CD19+ B-cell Count:** Lowest B-cell count after baseline. Time points: Same as AUC 0-T (CD19+ B-cells).
4. **Time to Minimum B-cell Count:** Duration (weeks) to reach the lowest B-cell count after baseline.
5. **Duration of B-cell Depletion (τB-cell):** Time (days) B-cell count remains <0.3 cells/µL. Measurements align with AUC 0-T.
6. **B-cell Recovery:** Proportion of participants whose B-cell counts recover to ≥50% of baseline by Week 25.

Disease Activity and Functional Assessments:

1. DAS28-CRP (Disease Activity Score):
   - Low Activity (DAS ≤3.2): Assessed by visit.
   - Remission (DAS <2.6): Assessed similarly.
   - P-value of 9999 indicates non-applicable statistical analysis.

2. HAQ-DI (Health Assessment Questionnaire - Disability Index):

- Tracks change in functional ability from Baseline to Week 25.
- Categories: Dressing, arising, eating, walking, reaching, gripping, hygiene, and common activities.
- Scored 0 (no difficulty) to 3 (extreme difficulty), averaged across categories.

Future of biosimilars regulations:

Medical reaesarchbiosimilarsVaccinesimmunotherapeutic It can also offers the benefits and some of the challenges in achieving global regulatory equivalence. the variations in regulations between countries, which highlights the many hurdles biosimilar vaccines and immunotherapy agents either now face or are likely to encounter during their development and approval. Such discrepancies often result in delayed market entry, higher development costs and stifled innovation. Current regulatory landscape

The development of biosimilars is a stringent process which covers analytical, functional and nonclinical testing followed by clinical trials. Citation12 The main challenges regarding this development are: the selection of the right reference medicine that needs to prove similarity in quality, safety and efficacy based on a cascade of studies

14.4 Benefits of global regulatory alignment on biosimilars

By aligning the common technical requirements in different countries, this, in turn speeds up global and national drug approval. As this borderline form of regulation by accommodation aligns, it is in line with the uniform regulatory review framework and potentially eliminates end-runs to each regulatory body and redundant several testings which constitute a drain on resources. As a result, the system not only shortens the time required to introduce drug products in the global market but also helps their faster introduction at country level. Instead of wasting time and resources meeting diverse national standards for approval, manufacturers can pursue a single submission strategy which accelerates global patient access on the one hand and saves substantial financial and business resources on the other. (3) Trade harmonization to permit greater access of food and pharmaceuticals along with faster approval for novel drug agents, which can lead to patients like you receiving treatments earlier than they could otherwise (thus causing the have note benefitadoxes)

14.5 Immunogenicity of Biosimilars

Overall, immunogenicity is a challenging event to predict with antibodies. Biologic industry of global has a way come the long from first drug (Humulin i.e. insulin) US of food and administration Immunogenicity was attenuated in a clinical trial of the original infliximab in RA through the induction of anti-drug antibodies, 2) testing of biosimilar somatropin during clinical development identified an increased

CONCLUSION:

Biosimilars offers a promising solution to the high cost of biologic treatments, making them more accessible to a broader range of patients. While they are not identical to the reference biologics, they are proven to be highly similar in terms of quality, safety ,efficacy through rigorous regulatory assessments. The increasing use of biosimilars can help address the growingdemand for biologic therapies, drive down healthcare costs, and improve patient access to essential treatments. However, challenges such as regulatory complexities, market uptake, and physician familiarity remain and must be addressed to fully realize the benefits of Biosimilars. As the market evolves, biosimilars are expected to play a key role in transforming the landscape of healthcare, offering greater affordability and expanding therapeutic options for patients worldwide.

REFERENCE:

1. Regulations.gov. Citizen petition from AbbVie, Inc. FDA. Published June 3, 2015.Accessed February

16, Van den Bemt BJ, den Broeder AA, Wolbink GJ, et al. cycle: an open-labelpharmacokinetics cohort study: BMC Musculoskelet Disord, 2011; International Regulatory Harmonization | FDA. 2020. https://www.fda.gov/drugs/cder- international-program/international-regulatory-harmonization#:~:text=ICH's%20mission%20is%20to%20achieve,the%20most%20resource%2Defficient%20manner(open in a new window).

2. Mascarenhas-Melo F, Diaz M, Gonçalves MBS, Vieira P, Bell V, Viana S, Nunes S, Paiva-Santos AC, Veiga F. An overview of biosimilars—development, quality, regulatory issues, and management in healthcare. Pharmaceutic [Internet]. 2024;17(open in a new window)(2(open in a new window)):235. doi:10.3390/ph17020235. (Open in a new window) View
3. Ingrasciotta, Y.; Cutroneo, P.M.; Marciano, I.; Giezen, T.; Atzeni, F.; Trifiro, G. Safety ofBiologics, Including Biosimilars: Perspectives on Current Status and Future Direction. *DrugSaf.* 2018, *41*, 1013–1022. [Google Scholar] [CrossRef]
4. Ingrasciotta, Y.; Cutroneo, P.M.; Marciano, I.; Giezen, T.; Atzeni, F.; Trifiro, G. Safety ofBiologics, Including Biosimilars: Perspectives on Current Status and Future Direction. *DrugSaf.* 2018, *41*, 1013–1022. [Google Scholar] [CrossRef]
5. European Commission. What You Need to Know about Biosimilar MedicinalProducts. *Consensus Information Paper [Internet]*. 2013. Available online: https://ec.europa.eu/docsroom/documents/8242 (accessed on 7 February 2024).
6. Ramanan, S.; Grampp, G. Drift, evolution, and divergence in biologics and biosimilarsmanufacturing. *BioDrugs* 2014, *28*, 363–372. [Google Scholar] [CrossRef]
7. Beninger, P. Pharmacovigilance: An Overview. *Clin. Ther.* 2018, *40*, 1991–2004. [GoogleScholar] [CrossRef] [PubMed]
8. Markus, R.; Liu, J.; Ramchandani, M.; Landa, D.; Born, T.; Kaur, P. Developing the totality of evidence for biosimilars: Regulatory considerations and building confidence for the healthcare community. *BioDrugs* 2017, *31*, 175–187. [Google Scholar] [CrossRef] [PubMed]
9. Blackstone, E.A.; Joseph, P.F. The economics of biosimilars. *Am. Health DrugBenefits* 2013, *6*, 469–478. [Google Scholar] [PubMed]
10. Mellstedt, H.; Niederwieser, D.; Ludwig, H. The challenge of biosimilars. *Ann.Oncol.* 2008, *19*, 411–419. [Google Scholar] [CrossRef]
11. Singh, A.; Kalaivani, M.; Srivastava, S.; Goyal, R.K.; Gupta, S.K. PostmarketingSafety ofBiosimilars: Current Status, Challenges, and Opportunities in the Spontaneous Reporting System. *Ther. Innov. Regul. Sci.* 2020, *54*, 667–680. [Google Scholar] [CrossRef]
12. Burton C, Oskouei S, Pietryga M, Salsi J. Biosimilars market leaders discussion. Presented at: GRx+Biosims; October 21-23, 2024; Rockville, MD. Jeremias S. FDA approves first denosumab biosimilars. The Center for Biosimilars®. March 5, 2024. Accessed October 31, 2024. https://www.centerforbiosimilars.com/view/fda- approves-first-denosumab-biosimilar Jeremias S. FDA approves first Eylea biosimilars. The Center for Biosimilars. May 20, 2024. Accessed October 31, 2024. https://www.centerforbiosimilars.com/view/fda-approves-first-eylea-biosimilars
13. Policy proposals to achieve long-term sustainability of infused biosimilars in the U.S.IQVIA Institute for Human Data Science. October 17, 2024. Accessed October 29,2024. https://www.iqvia.com/library/insight-brief/policy-proposals-to-achieve-long-term- sustainability-of-infused-biosimilars-in-the- us?utm_campaign=2024_2024_PolicyPropBiosims_INSTITUTE_TC&utm_medium=email&utm_source=Eloqua

14. Jeremias S. Sandoz report: a unified approach to overcoming drug shortages. The Center for Biosimilars®. October 10, 2024. Accessed October 30,
15. 2024. https://www.centerforbiosimilars.com/view/sandoz-report-a-unified-approach-to- overcoming-drug-shortages
16. Inserro A. Biosimilar Medicare Part B payment boost begins. The Center for Biosimilars.October 3, 2022. Accessed October 30,
17. 2024. https://www.centerforbiosimilars.com/view/biosimilar-medicare-part-b-payment-boost-begins
18. N, Carden MJ, Sargent M. Humira biosimilar adoption: hints of progress or signs ofdoom? Presented at: GRx+Biosims; October 21-23, 2024; Rockville, MD.
19. Burisch J, Claytor J, Hernandez I, Hou JK, Kaplan GG. The cost of inflammatory boweldisease care - how to make it sustainable. *Clin Gastroenterol Hepatol*. 2024:S1542- 3565(24)00729-8. doi:10.1016/j.cgh.2024.06.049
20. Dranitsaris G, Amir E, Dorward K. Biosimilars of biological drug therapies: Regulatory,clinical and commercial considerations. Drugs. 2011;71:1527–36. doi: 10.2165/11593730- 000000000-00000. [DOI] [PubMed] [Google Scholar]
21. Crommelin DJ, Storm G, Verrijk R, de Leede L, Jiskoot W, Hennink WE. Shifting paradigms: Biopharmaceuticals versus low molecular weight drugs. Int J Pharm. 2003;266:3– 16. doi: 10.1016/s0378-5173(03)00376-4. [DOI] [PubMed] [Google Scholar]
22. Brockmeyer C, Seidl A. Binocrit: assessment of quality, safety and efficacy ofbiopharmaceuticals. Eur J Hosp Pharm Pract. 2009;15:34–40. [Google Scholar]
23. Schellekens H, Casadevall N. Immunogenicity of recombinant human proteins: Causes and consequences. J Neurol. 2004;251(Suppl 2):II4–9. doi: 10.1007/s00415-004-1202-9. [DOI] [PubMed] [Google Scholar]
24. The New India Guidelines on Similar Biologics. 2012. Oct, [Last accessed on 2013 Jul16]. Available
25. from: http://www.biospectrumasia.com/biospectrum/analysis/3021/biosimilars-guidelines-a- step-direction-india#.UehBf6DRiSo .
26. Roger SD. Biosimilars: How similar or dissimilar are they? Nephrology (Carlton) 2006;11:341–6. doi: 10.1111/j.1440-1797.2006.00594.x. [DOI] [PubMed] [Google Scholar]
27. Duerden M. Prescribing advice needed for new biosimilar biological drugs. Prescriber.2007;18:1–2. [Google Scholar]
28. Schellekens H, Ryff JC. 'Biogenerics': The off-patent biotech products. Trends Pharmacol Sci. 2002;23:119–21. doi: 10.1016/S0165-6147(00)01967-2. [DOI] [PubMed] [GoogleScholar]
29. Joshi SR. Biosimilar insulins: Are they really 'similar'? J Assoc Physicians India.2009; 57:38–41. [Google Scholar]
30. Weise M, Bielsky MC, De Smet K, Ehmann F, Ekman N, Narayanan G, et al. Biosimilars-why terminology matters. Nat Biotechnol. 2011; 29:690–3. doi: 10.1038/nbt.1936. [DOI] [PubMed] [Google Scholar]
31. Malhotra H. Biosimilars and non-innovator biotherapeutics in India: An overview of the current situation. Biologicals. 2011; 39:321–4. doi: 10.1016/j.biologicals.2011.06.018. [DOI] [PubMed] [Google Scholar]
32. .Rathore A. Development and commercialization of biosimilars in India. BioPharm Int.2011;24:36–40. [Google Scholar]
33. Haselbeck A. Epoetins: Differences and their relevance to immunogenicity. Curr Med Res Opin.

2003;19:430–2. doi: 10.1185/030079903125002063. [DOI] [PubMed] [Google Scholar
34. Wadhwa M, Thorpe R. The challenges of immunogenicity in developing biosimilarproducts. IDrugs. 2009;12:440–4. [PubMed] [Google Scholar]
35. Li J, Yang C, Xia Y, Bertino A, Glaspy J, Roberts M, et al. Thrombocytopenia caused by the development of antibodies to thrombopoietin. Blood. 2001;98:3241–8. doi: 10.1182/blood.v98.12.3241. [DOI] [PubMed] [Google Scholar]
36. Thomas TK. Patent for biosimilar drugs may be made mandatory. The Hindu BusinessLine. [Last accessed on 2013 Jul 15; Published on 2008 May 06]. Available from: http://www.thehindubusinessline.in/2008/05/06/stories/2008050651531000.htm
37. Locatelli F, Del Vecchio L, Pozzoni P. Pure red-cell aplasia "epidemic" – Mystery completely revealed? Perit Dial Int. 2007;27(Suppl 2):S303–7. [PubMed] [Google Scholar]
38. Schellekens H. Biosimilar epoetins: How similar are they? Eur J Hosp Pharm.2004;3:243–7. [Google Scholar]
39. Keithi-Reddy SR, Kandasamy S, Singh AK. Pure red cell aplasia due to follow-on epoetin. Kidney Int. 2008;74:1617–22. doi: 10.1038/ki.2008.230. [DOI] [PubMed] [GoogleScholar]
40. Yang J, Joo KW, Kim YS, Ahn C, Han JS, Kim S, et al. Two cases of pure red-cell aplasiadue to anti-erythropoietin antibodies. J Nephrol. 2005;18:102–5. [PubMed] [Google Scholar]21.European Medicines Agency. Marvel Lifesciences Ltd. withdraws its marketing authorization applications for insulin human rapid marvel, insulin human long marvel and insulin human 30/70 mix marvel. [Last accessed on 2013 Jul 15]. Available
41. from: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2009/11/WC500015335.pdf .
42. Guideline on Similar Biological Medicinal Products. London: CHMP/437/04; 2005. [Lastaccessed on 2013 Jul 15]. Available from: http://www.ema.Europa.eu/human/biosimilar/0437004en.pdf . [Google Scholar]
43. Derived Proteins as Active Substance; Quality Issues. London: EMEA/CHMP/BWP/49348/2005; 2006. [Last accessed on 2013 Jul 15]. Guideline onSimilar Biological Medicinal Products Containing Biotechnology. Available from: http://www.ema.europa.eu/odfs/human/biosimilar/4934805en.pdf . [Google Scholar]
44. Derived Proteins as Active Substance: non Clinical Issues. London: EMEA/CHMP/BMWP/42832/2005; 2006. [Last accessed on 2013 Jul 15]. Guideline on Similar Biological Medicinal Products Containing Biotechnology. Available from: http://www.ema.europa.eu/odfs/human/biosimilar/4283205en.pdf . [Google Scholar]
45. European Medicines Agency. Committee for medicinal products for human use. Guidelineon similar biological medicinal products. [Last accessed on 2013 Jul 15]. Available from: http://www.ema.europa.eu/pdfs/human/biosimilar/043704en.pdf .
46. European Medicines Agency. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1)2012. May 24, [Last accessed on 2013 Jul 15]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/05 /WC500127960.pdf .
47. European Medicines Agency. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. 2006. [Last accessed on 2013 Jul 15]. Available from:

http://www.emea.europa.eu/pdfs/human/biosimilar/4283205en.pdf .

48. European Medicines Agency. Guidance on similar medicinal products containing recombinant erythropoietins. 2006. [Last accessed on 2013 Jul 15]. Available from: http://www.emea.europa.eu/pdfs/human/biosimilar/9452605en.pdf .
49. Pavlovic M, Girardin E, Kapetanovic L, Ho K, Trouvin JH. Similar biological medicinalproducts containing recombinant human growth hormone: European regulation. Horm Res.2008;69:14–21. doi: 10.1159/000111790. [DOI] [PubMed] [Google]