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"Biosimilar" generic version of biologic products?

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ABSTRACT

Biosimilars are currently popular after the expiry date of patents for biological reference products have expired or soon will expire. Besides, this 'copycat' version of biologic products offers much lower costs as compared to the reference products, thus promoting better patient access to the treatment of certain diseases such as cancer, inflammatory diseases, skin disorders, and diabetes. This review aims to determine the differences between biosimilars and generic drugs and highlight some issues related to biosimilar products such as comparability, interchangeability, immunogenicity, extrapolation of indication, current legislation, pharmacovigilance, and naming system. Scientific sources from PubMed, Google Scholar, ScienceDirect, and Elsevier were accessed for preparation of this review article. Biosimilars are not generic drugs as they have a larger and complex structure as compared to generic drugs. Due to that, biosimilars are highly similar but not identical to the reference products. Many regulatory authorities have authorized biosimilars under a distinct regulatory process from that of the generic drugs and subjected them to comprehensive comparability studies with their reference products (analytical, nonclinical in vitro, in vivo studies, and clinical trials). Additional evidence from interchangeability studies, extrapolation of indication studies, immunogenicity profile assessments, and pharmacovigilance studies are also beneficial to assess the efficacy, safety, and quality of the biosimilar before and/or after receiving their regulatory approval. Biosimilars are different from generic drugs due to their complexity in structure and manufacturing process. More comprehensive studies are required to ensure their benefits outweigh the risks.

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1. Introduction

1.1. Definition of biosimilars

The rapid development of biosimilar products among pharmaceutical companies has become attention as patent protection for original biological therapies has expired or will soon expire (Carrascosa et al., 2018; Feagan et al., 2014; Geynisman et al., 2017; Kumar and Singh, 2014). Biologics or known as biopharmaceuticals are advanced drugs produced for a particular treatment of diseases related to cancer, skin disorders, and inflammatory diseases (rheumatoid arthritis, ankylosing spondylitis, ulcerative colitis, Crohn's disease, etc) (Combe et al., 2005; Reis et al., 2016). By definition, biosimilars are copies of drugs that are similar but not identical to the reference biological drugs (already received authorization) (Kumar and Singh, 2014; Reis et al., 2016). The biosimilar products have similar active substances to their reference products (RPs) but may have minor differences in their inactive constituents (Carrascosa et al., 2018; Feagan et al., 2014; Geynisman et al., 2017; Santos et al., 2019). Even so, biosimilar medicines are usually designed with the same dose for the treatment of the same diseases due to their comparable in terms of quality, safety, and efficacy to their reference products (Kumar and Singh, 2014; Reis et al., 2016). Examples of approved biosimilars in Europe are epoetin, filgrastim, growth hormone, and monoclonal antibodies (Feagan et al., 2014).

The European Commission (EU) was first introduced the 'similar biological medicinal product' in 2001 before the terms were changed to 'biosimilar' in 2005 following the European Medicines Agency (EMA) guidelines. The United States Food and Drug Administration (US FDA) also applied the same name years later (de Mora, 2015). The EMA described a biosimilar as 'a biological medicinal product encompassing a version of the active substance of an already approved original biological product' for which it is important to create a similarity with the RPs in terms of quality characteristics, biological activity, safety, and efficacy based on thorough comparability studies (Buske et al., 2017). Meanwhile, 'biosimilarity' according to the US FDA, is a biological product that is highly similar to the RP despite slight variations in clinically inactive elements and that there are no clinically significant differences in safety, purity, and potency between the biosimilar drugs and its RPs (Buske et al., 2017; Carrascosa et al., 2018; Geynisman et al., 2017).

1.2. Biosimilar versus originators

Biologic drugs are synthesized biologically from living cells and resemble innate biological substances like hormones (Kumar and Singh, 2014). The recombinant DNA technology is used to develop protein-derived biologic drugs, which are 100 to 1000-times bigger than chemically synthesized drugs, making it difficult to characterize their molecular structures (Carrascosa et al., 2018). The same goes for biosimilar drugs, where they are manufactured

from living cells but with a different manufacturing process as biosimilar manufacturers do not have access to the history of the original biological product development (Reis et al., 2016). Due to that, the production of biosimilars becomes more complicated as the biosimilar creator needs to independently create a novel manufacturing procedure and adopt reverse-engineering manufacture to generate a drug that is extremely similar to the reference products (Carrascosa et al., 2018).

Naturally, biologic possesses a complex structure, and due to that, any post-translational adjustment especially glycosylation, and slight changes in the manufacturing process such as the degree of product aggregation, presence of external or internal impurities, and condition of the cell culture used could affect the physicochemical and functional characteristics of a biological drug (Buske et al., 2017; Carrascosa et al., 2018; Combe et al., 2005; Geynisman et al., 2017; Reis et al., 2016; Tesser et al., 2017). Because of these reasons, it is not possible to create an identical copy of a biological reference drug (Buske et al., 2017; Carrascosa et al., 2018; Combe et al., 2005; Feagan et al., 2014; Reis et al., 2016). Besides, it should be noted that all the variations that occur must not, as a concept of biosimilars, impact the clinical effectiveness or safety of biosimilars and must be comparable to their reference products (Geynisman et al., 2017; Reis et al., 2016). Therefore, it has been suggested that the deviation in the manufacturing process of a biosimilar should not be more than 15% compared to the original biological product (Reis et al., 2016).

The Biosimilar is replicating the well-known reference product, therefore the main benefit of biosimilars is that it can they offer cheaper and more affordable price for the treatment of diseases that requires expensive bio-originators (de Mora, 2015). A wide range of cheaper therapy options available in the market could increase patient access to the treatment and thus lead to a better patient outcome (Baji et al., 2015; Carrascosa et al., 2018; Geynisman et al., 2017). However, there is a concern that arises among healthcare practitioners and the consumers related to the fact that the quality, efficacy, and safety of the biosimilars should not be ignored even if the cost has been reduced (Reis et al., 2016). To ensure a close similarity in physicochemical and biological properties, safety, and efficacy, biosimilars require a detailed head-to-head comparison with the reference products (van de Vooren et al, 2015). Two biosimilars from different manufacturing backgrounds, for example, may produce the same therapeutic effect, but may also have different side-effects, thus individual and extensive studies need to be considered (Kumar and Singh, 2014). The pharmaceutical company may carry out a comparability evaluation on the quality properties of the related product to ensure that the pre-or post-modified biologic is comparable to its reference product in terms of quality, safety, and efficacy (Geynisman et al., 2017).

1.3. Biosimilars versus generic drugs

Since biosimilars are licensed and typically less costly than their reference products, they are often perceived to be the same as generic drugs (Buske et al., 2017). However, biosimilar drugs are neither generic drugs nor original drugs (de Mora, 2015). The reference products for biosimilars and generic drugs are biopharmaceuticals and chemically-synthesized products, respectively (Reis et al., 2016).

As mentioned earlier, a biosimilar drug contains an active substance that is purified extracted from natural sources living organisms such as living cell lines, microorganisms, tissue, or animals, and developed through biotechnology techniques (Geynisman et al., 2017; de Mora, 2015; Zangeneh and Dolinar, 2016). Because biologics are large and having a complex structure in nature, it is impossible to produce an exact copy of biologicy (Combe et al., 2005; Zangeneh and Dolinar, 2016). Examples of biologics are insulin, human growth hormone and monoclonal antibodies with the estimated number of atoms for the respective biologics is 700; 3,000; and 20,000 (Zangeneh and Dolinar, 2016). Thus, the biosimilar drug needs to undergo several testing from the physicochemical-biological studies to the evaluation of the production processes to ensure that its characterization and quality is comparable to the reference product even if it takes quite some time for the biosimilars to get regulatory approval (de Mora, 2015).

In contrast, generic drugs are small molecule drugs that are produced via chemical reactions and have a well-defined structure that is not affected by changes in the manufacturing process (Buske et al., 2017; Geynisman et al., 2017; Zangeneh and Dolinar, 2016). Aspirin, for example, is a low molecular weight drug comprised of about 21 atoms (Zangeneh and Dolinar, 2016). This is because the active ingredient in the generic drugs is not coming from innate sources such as living cells or complex biological systems (de Mora, 2015). The generic drugs can be developed in a short period as compared to the biosimilar drugs as only bioavailability studies are required for the generic drugs to determine their bioequivalence with their corresponding reference products (Geynisman et al., 2017; Reis et al., 2016). Therefore, it is possible to chemically synthesize a generic drug containing an identical copy of a clinically active substance that can exhibit equivalence properties to its original product in terms of quality, safety, and efficacy (de Mora, 2015).

Besides, the legislation process for biosimilars is different from the small-molecule generics due to the inherent complexity of the biologics (Geynisman et al., 2017). All of the generic drugs able to enter the marketplace easily and less costly under an established approval mechanism which is the Hatch-Waxman Act 1984 (Zangeneh and Dolinar, 2016). Meanwhile, more discrete regulations for biosimilars approval have been made by different regulatory authorities to emphasize several analyses and assessments that should be done in determining their biosimilarity to the reference products. Most of the guidelines from the EMA and US FDA for example, require the biosimilar manufacturers to conduct analytical studies (structural and functional), non-clinical, and clinical trials (if required) as systemic comparisons to the bio-originators (Geynisman et al., 2017; de Mora, 2015; Tesser et al., 2017). Even though clinical trials are an option; however, it helps in evaluating the comparative efficacy and safety of a potential biosimilar versus its originator by identifying variations through pharmacokinetics (PK) and pharmacodynamics (PD) studies, efficacy, and safety in the sensitive patient. Interestingly, the population used in the biosimilar to bio-originator comparative efficacy study might be different from the population used to test the originator's clinical efficacy alone (Tesser et al., 2017). Table 1 provides the characteristic of biosimilar and generic drugs.

1.4. Examples of biosimilars

Several biologics are currently growing in the marketplace such as erythropoietin (EPO), interferons, pegylated or non-pegylated granulocyte colony-stimulating factor (GCSF), insulin, growth hormone, blood and blood products, vaccines, and a variety of monoclonal antibodies (de Mora, 2015; Schellekens, 2009). A unique about biological drugs is that they can specifically target key mediators of specific diseases, therefore, exhibiting a particular physiological effect. The most common diseases that require biologics therapies are autoimmune inflammatory diseases (rheumatoid arthritis, psoriasis, ankylosing spondylitis, etc), diabetes, and cancer (Geynisman et al., 2017; Isaacs et al., 2015). Abasaglar and Basaglar respectively (Heinemann, 2016; Zangeneh and Dolinar, 2016). On March 6, 2015, the first biosimilar of leukocyte growth factors, Zarxio (filgrastim-sndz), developed by

Sandoz, has already been approved in the United States. It is a biosimilar to Neupogen (filgrastim) established by Amgen (Buske et al., 2017; Zangeneh and Dolinar, 2016). In contrast, the European Union had already approved the entry of simple and low molecular weight biosimilars into the clinical practice since 2006 and above onwards. These biosimilars are considered as 'first-generation' biosimilars and are primarily used as cancer supportive therapy to prevent the side effects of G-CSF filgrastim and erythropoiesis-stimulating agent epoetin alfa (Buske et al., 2017).

Biosimilars of monoclonal antibodies and other larger and more complex biologics are considered as 'second-generation' biosimilars because of their possible function in treating treat diseases rather than act as supportive agents as the 'first-generation' biosimilar do. CT-P13 (infliximab-dyyb) is the first 'second-generation' biosimilar that received approval from EMA in 2013 and the US FDA in 2016 (Buske et al., 2017; Ebbers, 2014). It is a biosimilar of infliximab, a monoclonal antibody targeting tumor necrosis factor which was used to treat rheumatoid arthritis (RA) and other autoimmune inflammatory diseases (Benucci et al., 2016; Braun and Kay, 2017; Buske et al., 2017). It was then marketed as Remsima by Celltrion and Inflectra by Pfizer (USA) and Hospira (Buske et al., 2017; Ebbers, 2014). Another biosimilar of monoclonal antibodies that has been approved by the EMA (2017) and FDA (2018) is CT-P10 (biosimilar to rituximab) which is indicated for the treatment of treat hematologic malignancies and rheumatoid arthritis cancer and It has been licensed for all same indications as rituximab (Buske et al., 2017). Table 2 shows the available biosimilars in the Europe and United States (US) market.

Table 1. Summary of the differences between biosimilars and generic drugs

Parameter	Biosimilars	Generic drugs	References
Definition	Biological medicines that are highly similar to an already-approved biologic, called reference product.	Drugs that contain identical active chemical substance as the chemically-synthesized reference drugs, whose patents have expired	Gherghescu and Delgado-Charro, (2021); van de Vooren et al. (2015)
Structure	Large and complex	Small and well-defined	van de Vooren et al. (2015)
Synthesis	Via biotechnology methods	Via chemical reactions	van de Vooren et al. (2015)
Types of study required	Systematic comparison studies that include analytical (structural and functional), nonclinical *in vitro* and *in vivo* studies, and clinical trials	Bioequivalence study	van de Vooren et al. (2015)
Period for approval	7- 8 years	4 years or less	Reis et al. (2016); Blackstone and Fuhr (2016)
Regulation	Differ based on the different countries regulatory	Hatch-Waxman Act 1984	van de Vooren et al. (2015)
Pricing	20-35% lower than the originators	50-80% lower than the originators	van de Vooren et al. (2015)
Prescribing and/or dispensing setting	Prescribed by doctors in hospital (most countries)	Prescribed by general physicians in day-to-day healthcare and primarily dispensed through community pharmacies in most countries.	van de Vooren et al. (2015)

2. Issues associated with biosimilars

2.1. Comparability/similarity

As mentioned previously, minor differences in the production process of biosimilars can change its' efficacy and safety. T, therefore, comparability testing has become a crucial part of the development of a biosimilar product (Baldrick, 2017). The EMA guidelines have made a requirement for a biosimilar product to undergo comprehensive comparability assessments to make sure that the product has a comparable profile in terms of quality, safety, and efficacy to the bio-originator (Locatelli and Roger, 2006). Numerous analytical testing is established to compare physicochemical and biological qualities between production batches of biosimilars (comparability) or between biosimilars with reference products (similarity). The physicochemical properties include weight, density, and stability while biological properties include activity and immunogenicity (Geynisman et al., 2017; Locatelli and Roger, 2006).

According to the EMA guidelines, biologic products with distinct primary structures their reference products are not considered as biosimilars (Ebbers, 2014). A biosimilar is comparable and similar to its bio-originator if they demonstrate the same characteristics such as the order of amino acid at the amino endpoint, the existence of disulfide bond, glycosylation, and other key factors involved in the folding of the protein (Reis et al., 2016). For example, the stability of a biologic molecule is depending on the glycosylation step because this step can prevent the molecule from deteriorating or degrading. In the absence of the glycosylation step, the biologics molecule becomes unstable and may generate immunogenicity reactions resulted from the excessive immune responses by the body (Locatelli and Roger, 2006; Reis et al., 2016).

Several studies suggest that additional data from nonclinical or clinical studies (PK and PD), clinical effectiveness and safety, immunogenicity, and pharmacovigilance studies may be required to prove that the biosimilar product is comparable and similar to the reference product (Geynisman et al., 2017). However, some researchers from Europe have different opinions whereby the in vivo PK or PD studies on the animal as well as toxicology studies rarely provide decisive important information to determine the biosimilarity and that the data may be necessary for the regulatory purposes only (Baldrick, 2017).

Table 2. Biosimilars that are available in the Europe and US market

Bio-originator (active substance) and year of expiration	Biosimilar; Year of approval (EMA or FDA)/progress status	References
Etanercept (EMA; 2015, FDA; 2028)	Benepali (EMA; 2016) Erelzi (EMA; 2017, FDA; 2016)	Braun and Kay (2017); Buske et al. (2017); Carrascosa et al. (2018); Geynisman et al. (2017)
Epoetin alfa (EMA; 2004, FDA; 2015)	Abseamed (EMA; 2007) Binocrit (EMA; 2007) Epoetin alfa hexal (EMA; 2007)	Bennett et al. (2014); Buske et al. (2017); Geynisman et al. (2017)
Epoetin zeta	Retacrit (EMA; 2007) Silapo (EMA; 2007)	Buske et al. (2017)
Teriparatide	Terrosa (EMA; 2017)	Buske et al. (2017)
Somatotropin (EMA; 2003, FDA; 2008)	Omnitrope (EMA; 2006)	Buske et al. (2017); Geynisman et al. (2017); Isaacs et al. (2015)
Adalimumab (EMA; 2018, FDA; 2016)	Amgevita/Solymbic (EMA; 2017) Amjevita (FDA; 2016) Cyltezo (EMA; 2017, FDA; 2017) Imraldi (EMA; 2017)	Braun and Kay (2017); Buske et al. (2017); Carrascosa et al. (2018); Geynisman et al. (2017)
Insulin glargine (EMA; 2014, FDA; 2014)	Abasaglar (EMA; 2014) Lusduna (EMA; 2017)	Buske et al. (2017); Geynisman et al. (2017)
Rituximab (EMA; 2014, FDA; 2018)	Truxima (EMA; 2017)	Bennett et al. (2014); Braun and Kay (2017); Buske et al. (2017); Geynisman et al. (2017)
Filgrastim (EMA; 2006, FDA; 2013)	Biograstim (EMA; 2008) Filgrastim hexal (EMA; 2009) Zarzio (EMA; 2009, FDA; 2015)	Bennett et al. (2014); Buske et al. (2017); Geynisman et al. (2017)
Infliximab (EMA; 2015, FDA; 2018)	Flixabi (EMA; 2016), Renflexis (FDA; 2017) Inflectra/Remsima (EMA; 2013, FDA; 2016) Ixifi (FDA; 2017)	Baji et al. (2015); Braun and Kay (2017); Buske et al. (2017); Carrascosa et al. (2018); Geynisman et al. (2017)

2.2. Interchangeability/ automatic substitution

Another interesting issue related to biosimilar products is whether they can be used effectively and safely to treat a patient who is newly diagnosed with a particular disease and whether those currently on reference product therapy can be switched to their biosimilar with the same effectiveness and safety outcomes (Benucci et al., 2016). Automatic substitution or interchangeability can be defined as the substitution of an original drug to other drugs with similar characteristics or vice versa (Reis et al., 2016). If the loss of efficacy and safety of a biosimilar is less harmful than administrating the bio-originator alone, then, the interchangeability between the reference drug and the biosimilar drug might be feasible (Carrascosa et al., 2018; Geynisman et al., 2017; Reis et al., 2016). However, it is important to note that, interchangeability is a higher standard than biosimilarity (Heinemann, 2016). Therefore, not all biologic products with biosimilarity evidence can be interchanged or automatically switched with their reference products (Zangeneh and Dolinar, 2016) as their natural complexity in structure could lead to distinct clinical results, thus affecting the safety of the patient (Geynisman et al., 2017).

The interchangeability issue is usually governed at the state level rather than at the federal level (Geynisman et al., 2017). In the United States, a biosimilar may substitute a bio-originator product or vice versa without the intervention of the healthcare provider if it has been approved as an 'interchangeable biologic product' from the FDA (Geynisman et al., 2017; Heinemann, 2016). For example, healthcare professionals may start either bio-originator or biosimilar products on their newly diagnosed patients. However, they are not advisable to substitute the bio-originator with biosimilar if they have started the bio-originator in the first place, and vice versa, except the drug, is 'an interchangeable biologic drug' (Zangeneh and Dolinar, 2016). Interchangeability, on the other hand, is not explicitly specified in the European regulations, and the EMA does not issue this classification. The EMA guidelines mentioned, instead, that interchangeability for biosimilars should be decided by the members of the EU of states (Geynisman et al., 2017; Heinemann, 2016). Consequently, some countries ban the replacement of a biosimilar for a bio-originator and other countries specifically allow it (Geynisman et al., 2017; Santos et al., 2019).

Besides, the US FDA recommends any researchers to conduct switching trials (minimum two switch periods) by alternating exposures to the possible interchangeable and bio-originator products to identify any raises in the risk of patient safety or drug efficacy compared to the regular administration of the bio-originator alone (Carrascosa et al., 2018; Geynisman et al., 2017). Most studies scientifically found that switching a reference product to its biosimilar does not produce any undesirable safety issues, particularly in the treatment of inflammatory diseases (Benucci et al., 2016; Braun and Kay, 2017; Carrascosa et al., 2018). In general, interchangeability is possible, secure, efficient, and cost-effective especially for the continuality of national healthcare systems, despite a thorough evaluation of the adverse events and immunogenicity of the substitution is remain essential (Benucci et al., 2016).

2.3. Immunogenicity

The manufacturing of biosimilars is also becoming an issue that is related to a possible increase in immunogenicity. Immunogenicity is defined as the ability of a drug to generate an immune response by producing antibodies. The formed antibodies not only can cause smaller allergic reactions or anaphylactic but also can neutralize the biological products as wells the endogenous proteins and constituents (Reis et al., 2016). As a result, patients treated with biological products may receive a lack of treatment efficacy (Combe et al., 2005). Several determinants can influence the

immunogenicity of biosimilars, among them is the high molecular weight and complex structure of biologics in nature (sequence variation, glycosylation), manufacturing complexity, impurities from the manufacturing process (cell lines or media constituents), formulation, storage, handling and patient factors (comorbid conditions or previous exposures) (Bennett et al., 2014; Combe et al., 2005; Feagan et al., 2014). These factors may trigger an unwanted immune response, whose incidence is not clinically predictable and impossible to be excluded without clinical trials (Feagan et al., 2014; Reis et al., 2016). Clinically, the immunogenicity of a future biosimilar should be contrasted with the originator. The novel comparative glycoprotein analyses that focus on pre-approval immunogenicity assessment should be developed to determine whether the incidence of anti-drug antibodies varies from that of the originator (Bennett et al., 2014; Tesser et al., 2017). Furthermore, the EMA and the Summary of Product Characteristics (SmPC) are still responsible to continuously and closely monitor biosimilar products in the market to ease the traceability of any unwanted adverse events (Reis et al., 2016).

2.4. Extrapolation of indications

Extrapolation of indications refers to the approval of a biosimilar to have more than one indication of the licensed reference product with scientifically justified data from clinical trials in at least one of the most susceptible populations (Braun and Kay, 2017; Buske et al., 2017; Carrascosa et al., 2018). A susceptible population is a population where possible variations are most likely to be observed between the reference product and the biosimilar (Buske et al., 2017; Carrascosa et al., 2018). Most researches have determined that the indication extrapolation should never be permitted and that clinical evidence is needed for all indications (Ebbers, 2014). The extrapolation of indication is only allowed if the efficacy and safety of a biosimilar in comparability assessments, clinical trials, and immunogenicity profile in various populations (patient with the greatest risk of immune response and immune-related adverse reactions) are proved to be safe and effective without any significant variations occur between the data obtained from the reference product and the biosimilar (Buske et al., 2017; Feagan et al., 2014; Reis et al., 2016). Many researchers agree that the indication extrapolation help to reduce the development costs by decreasing several clinical trials needed for multiple indications before approval of a biosimilar product (Braun and Kay, 2017; Carrascosa et al., 2018; Geynisman et al., 2017). For example, Flixabi, an EMA-approved biosimilar, has only been tested in rheumatoid arthritis (RA) patients, but is also authorized for all of the indications of the reference product including psoriasis, arthritis-related psoriasis, and inflammatory bowel diseases (IBD) such as ulcerative colitis and Crohn's disease (Geynisman et al., 2017).

2.5. Legislation/approval for marketing

Biosimilars only can be authorized after the patent expiration of bio-originators has reached. For example, patent of protection for biologic references is set to be expired after 10 years by the European Union (EU) and after 12 years by the 2009 Biologics Price Competition and Innovation Act (BPCIA), United States (Bennett et al., 2014). As mentioned earlier, new legislation and approval guidelines are established for the approval of biosimilar products as they do not subject to Hatch-Waxman legislation, which is legislation for the approval of generic drugs. In March 2010, President Obama had signed legislation for the biosimilars known as The Affordable Care Act, into the national law (Zangeneh and Dolinar, 2016). The regulatory process for biosimilar development needs more data than for small-molecule generics, due to the complexity of the biologics (Geynisman et al., 2017). According to the guidelines developed by the EMA and FDA, the requirements for approval of a biosimilar are more stringent as they must demonstrate comparable quality, similarity, efficacy, and safety to a bio-originator (Reis et al., 2016). Roughly, biosimilar development including its approval period only takes about 7-8 years to complete (Reis et al., 2016) as compared to the development of novel biologic drugs which takes about 8 to 12 years (Geynisman et al., 2017). Recently approved biosimilars are summarized in Table 3.

Table 3. Newly approved biosimilars (USFDA, 2021)

Biosimilar name	Approval date	Reference product
Riabni (rituximab-arrx)	December 2020	Rituxan (rituximab)
Hulio (adalimumab-fkjp)	July 2020	Humira (adalimumab)
Nyvepria (pegfilgrastim-apgf)	June 2020	Neulasta (pegfilgrastim)
Avsola (infliximab-axxq)	December 2019	Remicade (infliximab)
Abrilada (adalimumab-afzb)	November 2019	Humira (adalimumab)
Ziextenzo (pegfilgrastim-bmez)	November 2019	Neulasta (pegfilgrastim)
Hadlima (adalimumab-bwwd)	July 2019	Humira (adalimumab)
Ruxience (rituximab-pvvr)	July 2019	Rituxan (rituximab)
Zirabev (bevacizumab-bvzr)	June 2019	Avastin (bevacizumab)
Kanjinti (trastuzumab-anns)	June 2019	Herceptin (trastuzumab)
Eticovo (etanercept-ykro)	April 2019	Enbrel (etanercept)
Trazimera (trastuzumab-qyyp)	March 2019	Herceptin (trastuzumab)
Ontruzant (trastuzumab-dttb)	January 2019	Herceptin (trastuzumab)

The EMA and FDA have established a stepwise procedure for biosimilars comparability study with the reference products prior to their development. This involves a biosimilarity presentation that based on the analytical assessments (physical, chemical, biological activity), nonclinical *in vitro* and *in vivo* comparison analysis, and lastly, clinical trials programs (includes comparative clinical PK and PD studies) to confirm that the a biosimilar product has comparable effectiveness, safety, and immunogenicity to its reference product (Buske et al., 2017; Carrascosa et al., 2018; Santos et al., 2019). The analytical assessments are conducted to compare the 1) molecular structure of both biologics' products such as their primary structures of the proteins or their glycosylation profiles, and 2) biological activity such as receptor binding and other bioassays related to living cells (Santos et al., 2019). Meanwhile, the aim of the nonclinical *in vitro* and *in vivo* analysis is to determine and evaluate whether the differences in the physicochemical and structural properties clinically significant. The clinical trials will be conducted if additional information related to toxicity analysis is needed (Carrascosa et al., 2018; Ebbers, 2014; Geynisman et al., 2017; Reis et al., 2016).

2.6. Pharmacovigilance (post-marketing monitoring or surveillance)

It is no doubt that pharmacovigilance study is essential for biosimilar products because they are manufactured differently from that of reference products (Kumar and Singh, 2014) and some of

them also can be interchanged with the reference products or with other biosimilars (Braun and Kay, 2017). The EMA regulatory agency has made post-marketing surveillance as one of the components for the regulatory approval application in Europe (Carrascosa et al., 2018), as most clinical trials unable to detect rare or uncommon possible safety cases (Geynisman et al., 2017). On the contrary, no specific pharmacovigilance is issued by the FDA yet, instead, the authority recommends the biosimilar manufacturers to discuss with relevant regulatory agencies on product-specific, post-marketing monitoring plan (Carrascosa et al., 2018). Besides, biosimilar manufacturers are required to provide information on how they will track immunogenicity, novel safety signs, and safety in extrapolated indications (Braun and Kay, 2017). The adverse reactions associated with biosimilars may occur after a wide use in a larger number of patients over a longer period (Kumar and Singh, 2014). By conducting the post-marketing monitoring, a safety profile of biosimilars, and a risk management strategy for any reported adverse events could be established and submitted to the regulatory authorities (Reis et al., 2016).

2.7. Naming

There is no international standardization regarding biosimilar naming (Bennett et al., 2014). However, the global standard for naming medicinal products is the World Health Organization (WHO) International Nonproprietary Names (INN) system (Geynisman et al., 2017) which remains voluntary (Bennett et al., 2014). Initially, the WHO guidelines suggest naming biosimilars using the INN together with a trade name and developer's name for identification of particular products until recently, the WHO has released a proposal to apply to all biologics a special, additional, and independent identification code (known as biological qualifier). The biological qualifier is used to classify each biologic and to assist in the prescribing and dispensing of biologics, their pharmacovigilance, and global usage (Geynisman et al., 2017).

The US FDA has no definite guideline for the biosimilar naming; however, the members of the agency had published a draft on this issue, called 'Nonproprietary Naming of Biological Products', and invited any interested parties to join together. Based on the proposal, they recommend to name the biosimilar products with the same INN as the reference products and use 4 nonsensical, four-letter case suffixes to differentiate one another. For example, filgrastim-sndz (Geynisman et al., 2017; Zangeneh and Dolinar, 2016), adalimumab-atto, etanercept-szzs, and infliximab-dyyb (Geynisman et al., 2017). On the other hand, the EMA encourages to name biosimilars with the same INN as their bio-originators without additional suffix (Bennett et al., 2014; Geynisman et al., 2017), but, a special name may be assigned to active substances (Bennett et al., 2014). Most European Union members of states agreed that the use of the same non-proprietary name for biosimilars and bio-originators would create trust in biosimilar products among healthcare practitioners and the community. They also agree with the EMA Biosimilar Summary of Product Characteristic (SmPC) guidelines which suggest that the trade name and the batch number are adequate to identify the biologic products (Geynisman et al., 2017). Besides, as requested by the US Generic Pharmaceutical Association, the same INN as the bio-originator may be applied to the biosimilars after comparability and interchangeability studies have been determined. The original biologic manufacturers also ask the biosimilar manufacturers to sell their marketed products with special names to assist with adverse event monitoring and reporting (Bennett et al., 2014).

3. Conclusion

In conclusion, biosimilar products are the 'generic' version of original biologic products but both of them are not identically the same. This is due to their complexity in molecular structures as well as differences in their manufacturing process. They are approved by the regulatory agencies once the reference product's patent has expired and are sold in the market at a lower price than the reference products. The variations between the biosimilars and the reference products must not produce clinically meaningful manifestations in terms of quality, efficacy, and safety to the various population of patients. Thus, to ensure their comparative effectiveness and safety, some regulatory authorities have developed a new guideline to assist manufacturers in developing their biosimilar products. Most of the guidelines require the biosimilars to undergo extensive comparability studies as well as extra studies including switching trials, immunogenicity studies, indication extrapolation studies as well as post-marketing surveillance as there is limited information on the efficiency and safety of biosimilars to a particular type of population as compared to their reference products.

Conflict of interest

No potential conflict of interest was reported by the author.

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