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Biosimilar medicines used for cancer therapy in Europe: a review

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This article provides an updated review of the biosimilar medicines approved for cancer therapy in the European Union (EU). First we discuss the most relevant aspects for the development and approval of biosimilar medicines. We then present the oncological biosimilar drugs currently used, which include epoetins (alpha and zeta), filgrastim, and monoclonal antibodies (rituximab, trastuzumab and bevacizumab). Among the clinical applications of biosimilar medicines, cancer therapy remains the main target area and more approved biosimilars are expected over the next few years, providing cost-effective drugs to more patients. Furthermore, comprehensive pharmacovigilance studies are going on, monitoring the marketed biosimilars, and providing more feasible information to clinicians regarding the safety and efficacy of these medications.

Introduction

The use of biotechnological techniques to produce drugs emerged after the development of genetic engineering methods for DNA manipulation, which allowed the exchange of genetic material between different organisms, creating new DNA molecules, named recombinant DNA (rDNA). These molecules are further introduced into different living systems to express proteins of therapeutic interest, called biopharmaceuticals. Thereby, a new era of therapeutics emerged, with recombinant human insulin the first biological medicine (also named biological or originator) to be developed, during the 1980s [1,2].

Over the years, some patents of the marketed biologicals have expired, resulting in the development of biosimilar medicines (also named biosimilars) [3–5]. These medicines were approved by the EU in 2005, and are defined as medicines that, when produced by a new manufacturer, show similar pharmacokinetic and pharmacodynamic properties to the respective biologic reference medicines. Accordingly, a biosimilar medicine must demonstrate the same quality, safety, and effectiveness as the original biological medicine. Thereby, an extensive physicochemical characterization should be performed, comparing the molecular structures of a biosimilar with its reference biological. Further biological similarity should be assessed by receptor-binding assays. Compared with synthetic generic medicines, the development and manufacture of biosimilars is complex and expensive, because their effectiveness and safety must be confirmed by clinical and/or preclinical data. Nonetheless, it is important to highlight that these procedures are cheaper than the those required for the development of biological medicines [4,5].

In the same way as other medicines, the introduction of a biosimilar medicine to the European market requires European Medicines Agency (EMA) approval, which guides the information to the European Commission (EC). The latter approves or rejects the introduction of the medicine to the market [5,6].

There are several clinical applications for biosimilar medicines, such as oncology, rheumatic and bowel diseases, psoriasis, and neutropenia [4,7,8]. In this context, cancer therapy has been showing significant advances [9].

Currently, there are 22 approved biosimilar medicines on the European market, which are divided into three groups [10]: epoetins (alpha and zeta), filgrastin, and monoclonal antibodies (rituximab, trastuzumab and bevacizumab). These medicines can be

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used directly, for treating the disease, or indirectly, to manage adverse effects related to other oncological therapies [3,9].

The end of several biological medicine patents led to the development of biosimilars, which have been continuously introduced into the market. In the near future, is expected that more biosimilar medicines will arise, reducing the costs of treatment and increasing the accessibility of patients to the biological therapy, with a positive impact on public health [3,11,12].

Here, we provide an update of the biosimilar medicines approved for cancer therapy in the EU.

Biosimilar medicines

Biosimilar medicines were introduced in Europe in 2005, following the expiration of the first biological medicine patent. In the same way as for synthetic medicines, during the biological medicine patent period, production of the respective biosimilar is not allowed other than by the biological manufacturer. When the patent expires, the biosimilar medicine can be produced by a new manufacturer. The active substance of this new medicine must be equivalent to the reference biological, showing similar pharmacokinetics and pharmacodynamics. In this context arises the concept of biosimilarity, which is the ability of the biosimilar medicine to show similarity to the original biological in terms of its quality, safety, and efficacy [3,8,13].

Biosimilar medicines are planned to be administrated by the same route as the reference biological medicine, in an equivalent dosage, and to treat identical diseases, which means that the indications of the reference should be applied to the biosimilar. Thus, biosimilar medicines could be used to reduce healthcare costs [3,5].

During the approval of a biosimilar medicine, it should be demonstrated that it can treat the same conditions as its reference biological medicine, which is achieved by comparability studies, showing that the differences between both medicines are irrelevant for the therapeutic activity. As alternative, a biosimilar can be approved to treat only some of the clinical conditions used for the reference medicine [3,6,7,13,14].

Given their production process, which uses living systems, biosimilars always present with variability and, therefore, are not identical copies of the reference biological medicine. These differences comprise small variations and are called microheterogeneity, which can result in changes to the therapeutic activity and/or development of immunogenicity. In addition, current biologicals can be biosimilars of the initial same reference products. Every time a company produces a new batch, it has to send all the collected data to the EMA for evaluation, which allows differences of nonclinical significance to be recorded [4,9,15,16].

The development of a biosimilar starts with evaluation of its desired quality attributes and characterization [6,7,14]. Afterwards, a comparability study with the reference biological medicine is carried out in three steps [6]: (i) assessment of the physical, chemical, and biological properties; (ii) nonclinical tests; and (iii) clinical tests. In step (i), comparative evaluations of the molecular structure (e.g., between the primary structures of the proteins or their glycosylation profiles), biological activity (e.g. receptor binding and other cell-based bioassays), and analytical characterization are performed. Box 1 summarizes the most common physical, chemical, and biological assays that should be done to ensure that the originator biological and biosimilar molecules are as similar as possible. Steps (ii) and (iii) verify whether the small differences between the biosimilar and its reference biological affect the safety and efficacy of the developed medicine, by evaluating the benefits, risks, and immunogenicity. The full process of comparison between the two types of medicine are mandatory for introducing a new biosimilar to the market, with each case studied individually. Variations from the reference biological medicine should be justified before medicine approval [4,6].

BOX 1

The most common physicochemical and biological assays performed to assure similarity between originator biological and biosimilar molecules [3,9,17]

Physicochemical assays

Comparison of the amino acid sequences of the primary structure (peptide mapping)

Evaluation of the post-translational modifications (comparison of the glycosylation profiles by *N*-linked oligosaccharide profiling and/or glycan patterns)

Evaluation of heterogeneity (detection of isoforms)

Evaluation of purity and presence of residual process impurities (comparison of the levels of monomers and high-molecular-mass species)

Biological assays

Evaluation of the *in vitro* cell cytotoxicity

Demonstration of similar biological activity (*in vitro* receptor-binding tests)

In the same way as other medicines, biosimilars must meet some manufacturing requisites, with the producers inspected periodically by the regulatory entities [13]. Figure 1 summarizes the development process of biosimilar medicines.

Even though is accepted that a biosimilar will show small variations from the reference biological, the expressed primary amino acid sequence of both medicines must be the same. Thus, when a biosimilar medicine is developed, a detailed evaluation of the physicochemical and functional characteristics of the reference biological is performed. Furthermore, an analysis of the final product impurities, resulting from the manufacturing process, is carried out [4,9,15].

The clinical information that must be collected before the production of a biosimilar medicine depends on the active substance complexity and easiness of characterization. Regarding the clinical performance, the relevant point for a biosimilar development is the integration of all the analytical, pharmacological, and clinical data. Furthermore, the safety concerns indicated for the reference medicine and the possibility of extrapolating data from effectiveness and safety studies should be considered. In addition, for scientific and ethical reasons, is not recommended to repeat all the studies performed for the reference biological medicine. Nonetheless, the extrapolation of the therapeutic indications of biosimilars is controversial. Specialists state that the clinical evidence of the effectiveness of a biosimilar for one therapeutic indication does not necessarily mean that this medicine is effective for another indication for which the respective biological was approved [4,9,15,18,19].

Regarding clinical practice, the substitution of originator biologics by biosimilars is controversial and more clinical studies have been recommended to evidence the similar efficacy and safety. In theory, patients with a positive response to a biological medicine

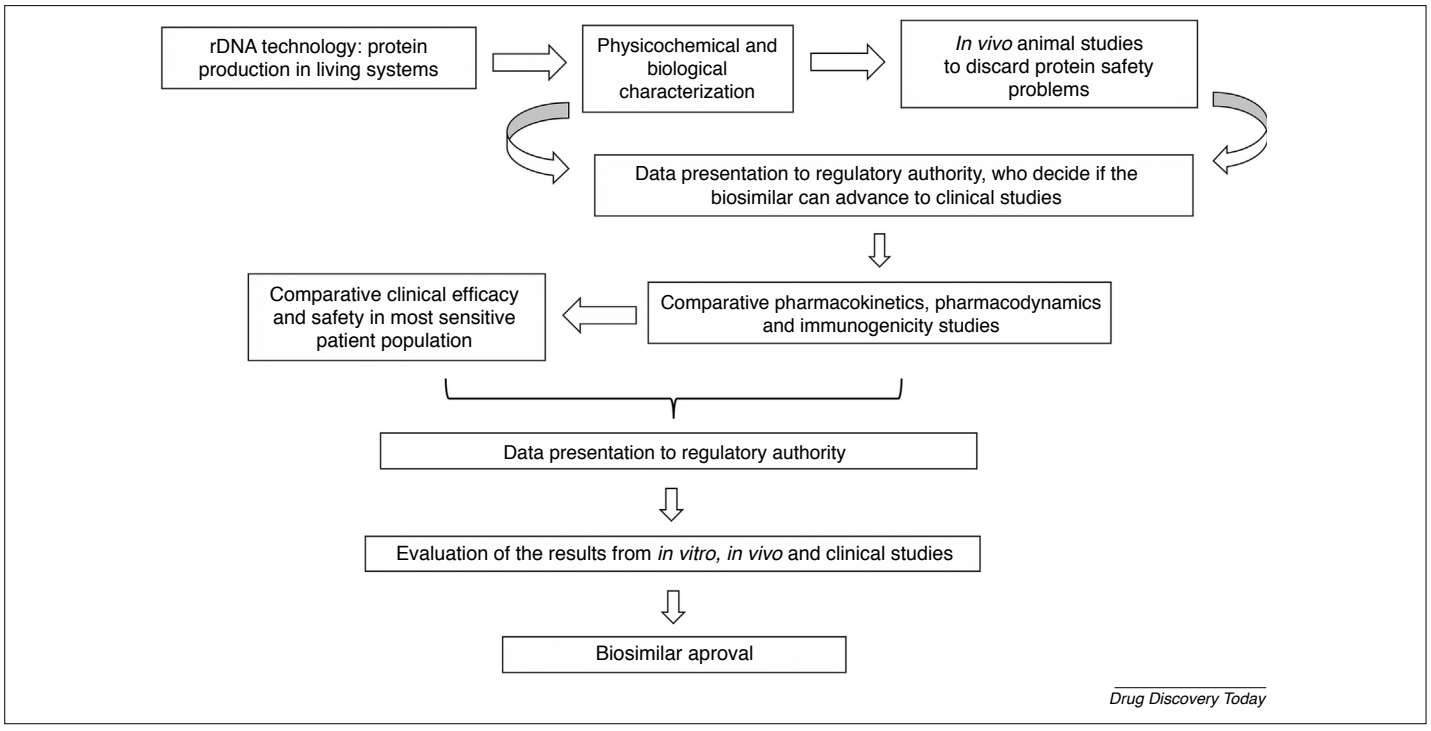

FIGURE 1

Summary of the development process of biosimilar medicines.

could receive the respective biosimilar, reducing the costs of therapy. Nonetheless, regulatory agencies have expressed concerns about this automatic substitution, because of the lack of studies demonstrating the efficacy and safety of biosimilars. The main issues are related to the assurance of no immunogenicity and toxicity, and a lack of therapeutic activity. Notwithstanding, there is no reported evidence of differences in the safety profile of biosimilars compared with biologicals, and most regulatory agencies approve the use of biosimilars in patients who have already been successful treated with biologicals. Concerning automatic substitution, the position of regulatory agencies diverge. For example, the EMA accepts the exchange of one drug by other with the same therapeutic activity, which could be done by the prescriber or at the pharmacy. However, national authorities of each EU member state are responsible for the approval of the interchangeability status (i.e., whether the substitution or automatic substitution is allowed). In most states, automatic substitution is prohibited, even though payers might order a substitution as a cost-saving measure [20,21].

According to the systematic increase in marketed biosimilars, more studies evaluating the risk–benefit of substitution and automatic substitution between biologicals and biosimilars are required. In this sense, controlled clinical trials regarding the transfer of biologicals to biosimilars are necessary. Furthermore, the efficacy and safety of multiple switching between biologicals and biosimilars or between different biosimilars remain uncertain, and direct access to the results of clinical practice is needed [20,21].

Current biosimilar medicines are divided into eight classes [22]: epoetins, filgrastim, insulins, growth hormones, interferons, monoclonal antibodies, follitropin, and low-molecular-weight heparins. Here, we are focus on biosimilars used for cancer therapy.

Biosimilar medicines for cancer therapy in the EU

Given their high therapeutic potential, biological medicines are used for the treatment of several types of cancer. These medicines can be used directly to treat the disease, or indirectly to manage adverse effects resulting from other oncological treatments. However, the high cost of biological medicines limits access to these treatments in many countries, which constitutes a public health problem [3,9].

The expiration of several biological medicine patents is expected over the next few years, resulting in the development of more biosimilars. In terms of cancer therapy, the biologicals that are going to expire soon are mainly monoclonal antibodies. Thus, several studies with biosimilar monoclonal antibodies have been carried out and some approvals were requested for commercialization of the respective medicines in the EU [3,10,12,23].

During clinical practice, oncologists should keep in mind that some of the marketed biosimilars are not identical copies of their biological reference medicines. Therefore, safety risks for patients and/or poor therapeutic effectiveness might occur [3,23]. These problems have been raising much concern among clinicians and several studies have been carried out to evaluate the efficacy and security of biosimilars.

Table 1 presents the biosimilar medicines used for cancer therapy that have been approved for commercialization in the EU, and below we summarize the results of the most relevant studies related to the use of these biosimilars.

Epoetins

There are five epoetin-based biosimilar medicines that can be used as alternatives to Eprex® and Erypo® (reference biological medicines), and are divided according to the type of epoetin:

TABLE 1

Biosimilar medicines approved as cancer therapies in the EU

Active substance					
Epoetin		**Filgrastim**	**Monoclonal antibody**		
Alpha	**Zeta**		**Rituximab**	**Trastuzumab**	**Bevacizumab**
Abseamed®	Silapo®	Hexal®	Ritemvia®	Kanjinti®	Mvasi®
Binocrit®	Retacrit®	Nivestim®	Rituzema®	Ontruzant®	
Hexal®		Ratiograstim®	Rixathon®	Trazimera®	
		Tevagrastim®	Riximyo®	Herzuma®	
		Zarzio®	Truxima®		
		Udenyca®	Blitzima®		

Abseamed®, Hexal® and Binocrit® for alpha epoetin, and Retacrit® and Silapo® for zeta epoetin [10,24–27]. These epoetins are reproductions of the human erythropoietin (EPO), which have identical efficiency for stimulating bone marrow to produce red blood cells [28–31]. In normal physiological conditions, EPO is produced by the kidneys and its quantity is changed or suppressed in patients with kidney disorders or undergoing chemotherapy, who have high risk of developing anemia. To circumvent these conditions, alpha or zeta epoetin is used, avoiding the need for patients to undergo blood transfusions [24–31].

The first two EPO biosimilars were approved in 2007 by EMA, after Phase 1 and Phase 2 clinical trials demonstrated their comparability to Eprex®/Erypo®. Afterwards, postauthorization studies reported the existence of molecular structural differences (in the glycosylation profiles) between these biosimilars and the reference medicines, recommending a more comprehensive analysis of the data obtained from clinical practice [32]. These observations raised apprehension among oncologists, who were skeptical about the similar therapeutic efficacy of EPO biosimilars compared with the reference biological. Moreover, safety concerns related to the risk of patients developing pure red cell aplasia (PRCA) after using EPO biosimilars were highlighted. Therefore, some clinicians did not prescribe these biosimilars, despite their use reducing the cost of treatments and facilitating the access of patients to biological therapy. However, the increasing number of pharmacovigilance studies has since shown that these biosimilars are effective and well tolerated as renal anemia and postchemotherapy treatments [33,34].

Filgrastim

Filgrastim is the recombinant form of the cytokine granulocyte colony-stimulating factor (G-CSF). This glycoprotein increases bone marrow production of neutrophils, and is frequently used in patients with post-chemotherapy neutropenia. Furthermore, filgrastim is used in patients with leukemia or chronic neutropenia who were submitted to destructive bone marrow treatments before transplant [35]. There are five filgrastim biosimilar medicines available on the European market as alternatives to Neupogen® (reference biological medicine), namely Hexal®, Nivestim®, Ratiograstim®, Tevagrastim®, and Zarzio®, although other biosimilars have been withdrawn [10,36]. The first filgrastim biosimilar in the EU was Zarzio®, which was approved in 2009 for the same indications as its reference medicine. Thus, Sörgel *et al.* [37] performed comparability studies with this biosimilar and the reference Neupogen®. The results of physicochemical tests showed that both molecules had identical primary, secondary and tertiary structures, and purity profiles. The biologic comparability was demonstrated *in vitro*, evaluating G-CSF-induced proliferation in murine myelogenous leukemia cells, and the affinity for receptor binding. Furthermore, the same researchers carried out Phase 1 and 3 *in vivo* studies in healthy and neutropenic volunteers, respectively. The results of Phase 1 studies confirmed the existence of comparable pharmacodynamics and pharmacokinetics between the tested biosimilar and the reference, whereas Phase 3 trials evidenced their efficacious and safety for breast cancer treatment with no immunological response [38]. Later, these researchers performed analogous experiments, demonstrating a high similarity between another biosimilar filgrastim (EP2006), the US-approved originator filgrastim and EU-approved originator filgrastim [39]. In other study, Skrlin *et al.* [40] evaluated the similarity of the biosimilar Nivestim® with the reference Neupogen®. The results of the experiments suggested that both medicines had similar molecular characteristics, purity, and biological activity.

Recently, the EMA approved Udenyca® (pegfilgrastim) as a biosimilar of the originator Neulasta®, which constitutes a long-acting version of filgrastim [41]. Nakov *et al.* [42] carried out a randomized, double-blind, two-way crossover study in healthy male and female volunteers to determine whether there were any significant differences between originator and biosimilar pegfilgrastim. The results showed that both medicines had similar pharmacokinetics, pharmacodynamics, immunogenicities, and safety profiles.

Monoclonal antibodies

Currently, there are three biosimilar monoclonal antibodies approved by the EMA for cancer therapy (rituximab, trastuzumab, and bevacizumab) as alternatives to MabThera® (reference biological medicine). In terms of rituximab, there are six biosimilars on the European market: Ritemvia®, Rituzema®, Rixathon®, Riximyo®, Truxima®, and Blitzima® [10].

Rituximab

Rituximab is a genetically engineered chimeric anti-CD20 monoclonal antibody formed of mouse and human portions. This antibody induces B lymphocyte depletion, and is used to treat B cell malignancies, such as several types of haematological cancer (follicular lymphoma, diffuse large B cell lymphoma, non-Hodgkin lymphoma, chronic lymphocytic leukemia, and Burkitt lymphoma) and autoimmune diseases (rheumatoid arthritis and granulomatosis with polyangiitis, and microscopic polyangiitis)

[23,43–45]. Several studies have been carried out to evaluate the efficacy of rituximab biosimilars for cancer therapy compared with the reference biological. For example, Lamanna *et al.* [46] studied the specific in-use stability of Rixathon®/Riximyo® to ensure that formulation and handling practices did not compromise product safety and efficacy. The results demonstrated a non-influence on the physicochemical stability of the biosimilars after formulation dilution for intravenous infusion, in terms of its shelf-life, temperature, light exposure, dilution factor, and storage. Jurczak *et al.* [47] evaluated the outcome of untreated advanced follicular lymphoma using a rituximab biosimilar in combination with other chemotherapeutic agents (cyclophosphamide, vincristine and prednisone). The authors carried out a 24-week Phase 3 clinical study and demonstrated efficacy, safety, pharmacokinetics, pharmacodynamics, and immunogenicity comparable to the reference biological. From the results of this study, it was concluded that the use of rituximab biosimilar provides an advantageous therapeutic cost-saving option over rituximab. In other study, Candelaria *et al.* [48] assessed the potential differences between pharmacokinetics and pharmacodynamics of a rituximab biosimilar and the reference MabThera® in patients with diffuse large B cell lymphoma. The results showed that the systemic exposure and variability of the biosimilar were similar to the reference. Furthermore, depletion of B cell CD20+ was comparable between the tested medicines. Recently, Franceschetti and Caldeira [49] reported the results of a study related to the prescription of rituximab biosimilars for the treatment of non-Hodgkin lymphoma. The evaluations were carried out in five EU countries, between July and September 2017. The authors observed an increase in the preparation of the biosimilars over the reference medicines, despite the latter remaining the most prescribed.

Trastuzumab

Trastuzumab is a recombinant humanized monoclonal antibody that interferes with the human epidermal growth factor receptor 2 (HER-2). In certain types of breast cancer, HER-2 is overexpressed and causes uncontrolled cellular proliferation. Thus, trastuzumab is used to treat HER-2-positive breast cancers in combination with other chemotherapeutic agents, with improved outcomes demonstrated in both metastatic and early disease phases [50]. However, because of economic reasons, access to this medicine is limited to a small number of patients. The market introduction of trastuzumab biosimilars might increase access to this therapy for more patients, because these medicines are cheaper [51,52]. Currently, four trastuzumab biosimilars of the reference Herceptin® have been approved by the EMA: Ontruzant® [53], Kanjinti® [54], Trazimera® [55], and Herzuma® [56].

Pivot *et al.* [57] carried out the first human clinical Phase 1 study to evaluate the pharmacokinetic equivalence between a trastuzumab biosimilar candidate and the reference Herceptin®. The study was performed in healthy male volunteers, who randomly received an intravenous single dose of 6 mg/kg of both medicines. The results showed that the biosimilar candidate was well tolerated and with no safety concerns after single-dose administration. In another paper [58], the same authors reported the results of a Phase 3 clinical trial regarding the safety, immunogenicity, and survival outcomes after neoadjuvant-adjuvant therapy in patients with early or locally advanced HER-2-positive breast cancer. The results of this study supported the similarity between the trastuzumab biosimilar candidate and the reference biological, previously reported by the authors [58]. Recently, Waller *et al.* [59] reported the results from a Phase 1 study, conducted in healthy male volunteers, which demonstrated similarity between a trastuzumab biosimilar and the reference biological, with regard to pharmacokinetic bioequivalence and safety, when administered as a single-dose 8 mg/kg intravenous infusion over 90 min.

Bevacizumab

Bevacizumab is a recombinant humanized monoclonal antibody that targets vascular endothelial growth factor (VEGF), a protein responsible for endothelial cell proliferation and new blood vessel formation. VEGF suppression reduces tumor growth, because the cancer cells are not supplied with oxygen and nutrients. Thereby, bevacizumab is used in patients with metastatic colorectal cancer, nonsquamous non-small-cell lung cancer, metastatic kidney cancer, glioblastoma, cervical cancer, metastatic breast cancer, and advanced epithelial ovarian, fallopian tube, or primary peritoneal cancers. Recently, a bevacizumab biosimilar (Mvasi®) was approved by the EMA as an alternative to the reference Avastin® [60,61]. Thus, Peraza *et al.* [62] studied the potential of a bevacizumab biosimilar for clinical approval. They evaluated the molecular structural similarity of the two compounds by peptide mapping, demonstrating that the amino acid sequence of the bevacizumab biosimilar was identical to that of its reference biological. The existence of similar biologic activity was tested *in vitro,* via inhibition of VEGF-induced cell proliferation in human umbilical vein endothelial cells and binding to VEGF isoforms. Finally, nonclinical *in vivo* toxicity studies were carried out in cynomolgus monkeys, and nontarget-mediated toxicity was assessed in rats, to compare the toxicity between the bevacizumab biosimilar and the reference. The authors concluded that the bevacizumab biosimilar and the reference biological medicine showed similarity and that the former could be approved for clinical use. In another investigation, Seo *et al.* [63] performed comprehensive comparability analytical studies regarding the physicochemical, structural, and biological similarity of a bevacizumab biosimilar and the reference biological. The results showed that both molecules had an equivalent amino acid sequence, post-translational modification profiles, and similar VGF-binding activity and potency. These extensive characterization studies allowed the authors to conclude that the bevacizumab biosimilar and the reference biological molecules have similar structural, purity, and biological attributes.

Concluding remarks

Biosimilar medicines constitute one of the most innovative realities of therapeutics. In contrast to synthetic medicine manufacture, the production of biosimilars presents many variables that are related to the diversity of the living host organisms used. Therefore, EMA approval processes for biosimilar medicines differ from those for generic medicines. Accordingly, during biosimilar development, comparative studies are required that demonstrate similar efficacy to the reference biological, without immunogenicity and safety concerns. The clinical applications of the reference biological medicine are extrapolated to the biosimilar when both demonstrate identical mechanisms of action, effectiveness, and safety profiles. However, depending on the therapeutic objectives, a biosimilar medicine is unlikely to include all the applications of the originator biological.

Concerning cancer treatment, biological therapy has been extensively used, individually or as adjuvant therapy, and the results are promising. The expired patents allowed the development of several biosimilar medicines, creating effective alternatives to existing biologicals. These new medicines are advantageous for patients, because some of the adverse effects of the reference biologicals are avoided. Moreover, biosimilars have lower production costs, because of the ability to extrapolate from studies of the reference biological medicine. This is a major advantage of using biosimilars over biologicals, leading to economical therapies, with a significant positive impact on public health. Nonetheless, the substitution, automatic substitution, and extrapolation between biologics and biosimilars remain controversial and more clinical studies are required to confirm their similarity.

Currently, there are 22 biosimilar medicines approved for cancer treatment in the EU, which can be divided in three groups, according to the active substance: epoetins (alpha and zeta), filgrastim, and monoclonal antibodies (rituximab, trastuzumab and bevacizumab).

The number of biosimilars has been increasing, with more marketed medicines expected over the next few years, providing cost-effective treatments to more patients. Among the different clinical applications of biosimilar medicines, cancer treatment remains the main target area. Thus, comprehensive pharmacovigilance studies are going on, monitoring the marketed biosimilars, and providing more useful information to clinicians regarding the safety and efficacy of these medicines.

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