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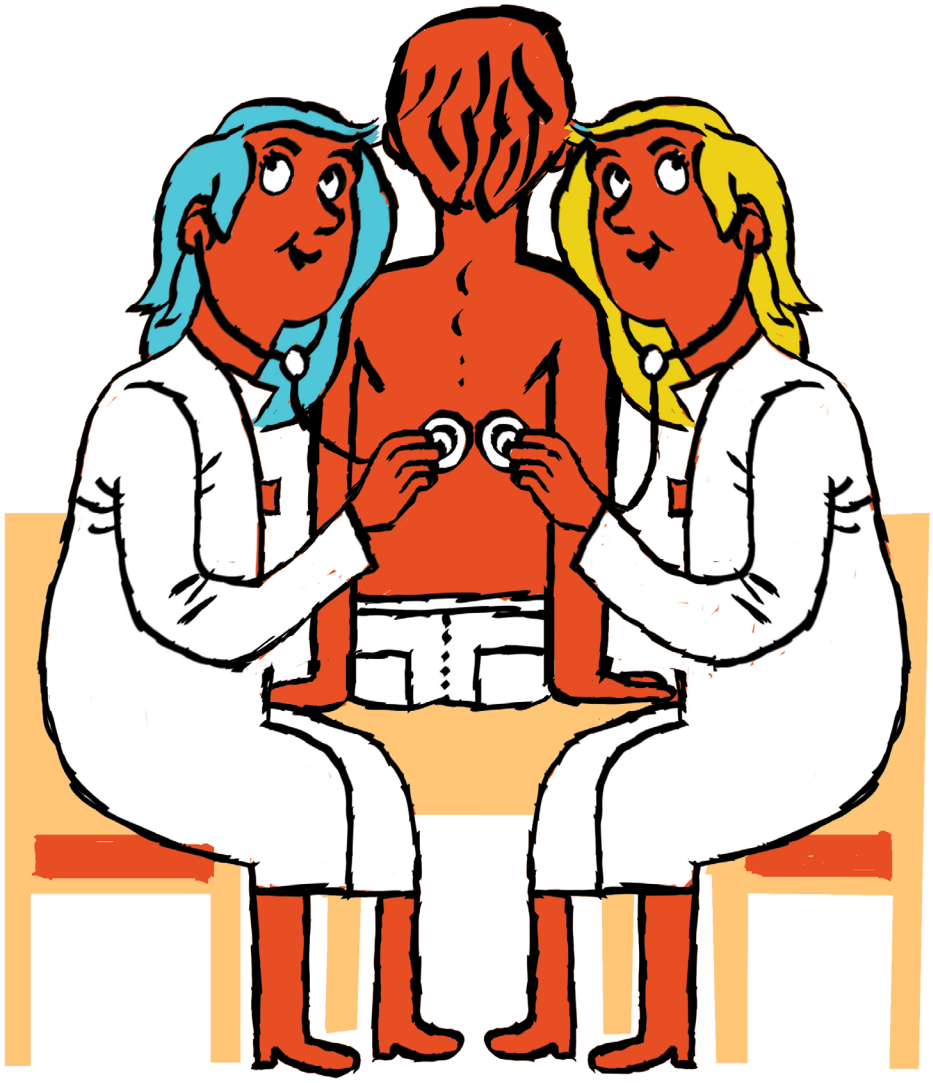

abstract

Objectives: to describe biosimilar drugs, their authorization process, quality requisites, and discuss controversial issues regarding their use. **Methods:** a review of the scientific literature published in Medline and regulatory documents was carried out (updated on 30 April 2015). **Results and conclusions:** biosimilar drugs are developed according to established and specific requirements from the EMA and have proven similar efficacy, quality and safety compared to reference drugs. They have cost-saving potential that can contribute to the sustainability of health care. Concerns raised on the use of a biosimilar drug are the same as those with the corresponding original drug. Head-to-head clinical trials and post-authorisation studies are carried out to clarify any concern.

Biosimilar drugs
Concept, regulation and controversies

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What is a biosimilar drug?

A biosimilar drug refers to any drug whose main active substance is biological, that is, synthesized or extracted from a biological source, and its characterization and determination requires physical, biological and chemical-related trials, as well as the control of the production process.[1] The definition is based on the origin of the drug and on the important role of the manufacturing process. Among these drugs we find recombinant proteins, monoclonal antibodies, haemoderivatives, immune-related products (such as serum, vaccines, and allergenic agents), advanced medicinal products derived from cellular, gene and tissue therapies, as well as non–recombinant active substances such as BCG for bladder instillation, or anti-T lymphocyte immunoglobulin.[2]

The Spanish Law 29/2006 on the rational use of drugs and health products included vaccines and other biological products under the "Special drugs" section, in reference to those requiring specific regulation. This group include, among others, medicinal gases, radiocontrast agents or herbal medicines.[3]

What is a biotechnology drug?

The increase in production, availability and safety of biological drugs is possible thanks to the development of biotechnology in recent years. Drugs derived from biotechnological methods represent the majority of the biological drugs available. Since the commercialization of recombinant human insulin in 1982, more products have emerged such as growth hormone, insulins, hematopoietic growth factors such as erythropoietin, filgrastim, pegfilgrastim, gonadotropine, alpha and beta interferons, etanercept, monoclonal antibodies such as infliximab, trastuzumab, bevacizumab, rituximab, adalimimab, coagulation factors such as VIII and IX and vaccines.

These drugs play a fundamental role in oncology, rheumatology, nephrology, gastroenterology and dermatology, in the management of anaemia related to renal failure or chemotherapy, febrile neutropenia, multiple sclerosis, rheumatoid arthritis, Crohn's disease, or different types of cancer.

Biotechnology drugs are obtained from living systems (animal or plant cells, bacteria, virus or yeast) in which genetic material is introduced through recombinant DNA technology and the required substance is produced.[4] The main differences with traditional small molecule drugs lie in the molecular structure and the manufacturing process.[5]

The manufacturing process involves living systems and consists of several stages such as cloning of a gene sequence, transfer of this sequence to a selected prokaryotic or eukaryotic medium of expression, and posterior purification. All these stages are sensitive processes and require precise control to obtain consistent results.

Small molecule drugs are normally produced by chemical synthesis through relatively simple reactions that depend on more feasibly controlled variables. This means that the overall characterization of biotechnology drugs is difficult and not as complete as drugs manufactured through chemical synthesis, and any modification during the production process (physical factors, extraction and purification techniques or biological substrate) could have an important impact on the characteristics of the final product.

In relation to structural differences, biotechnology drugs are molecules with a high molecular weight, from 10,000 daltons (filgrastim and pegfilgastrim) up to 150,000 daltons (rituximab). Small molecule drugs can vary between 180 daltons as in the case of acetyl salicylic acid and up to thousands of daltons in daptomycin. In relation to the nature of the components, biotechnology drugs are composed of glycoproteins, aminoacids, and carbohydrates, while small molecule drugs contain mainly carbon atoms, oxygen and hydrogen.

Biotechnology drugs possess primary, secondary, tertiary and quaternary structures, contain disulfide bridges, protein folding, combinations of various protein subunits and post-transduction modifications (glycosylation, oxidation, phosphorylation).

Both sequence and 3-D structure condition their activity and may influence the immunological capacity which could lead to important clinical consequences such as loss of efficacy, infusion-related reactions or anaphylaxis. However, the mechanism of action of small molecule drugs is determined by their chemical structure and given their small size, normally they are not immunogenic if not bound to proteins.

Infliximab is a monoclonal human and mouse anti-chimeric antibody produced in a mouse hybridoma through recombinant DNA technology and acts through high

affinity binding to the soluble and transmembrane forms of alpha TNF (Tumoral Necrosis Factor).[6] Beta epoetin is a glycoprotein produced in the ovaries of the Chinese hamster through recombinant DNA technology that acts as hormonal factor that stimulates the production of red blood cells by binding to the erythropoietin receptor.[7]

What is a biosimilar drug?

The biosimilar concept was introduced in the European legislation through the EC 2003/63/EC[8] and the EC Directive 2004/27/EC[9] and defines a biological drug as similar to another innovative drug of biological origin previously approved as the reference drug.

The legal basis of their regulation and authorization was previously established by the EC Directive 2001/83/EC (consolidated in 2009)1 differentiating biosimilars from generic drugs especially with regard to the provision of results from preclinical and clinical trials for approval.

Thus biosimilar drugs have been defined as products of biotechnological origin (generally recombinant proteins) manufactured according to the specific requisites established by the EMA (European Medicines Agency) in relation to quality, efficacy and safety, comparable to the innovator reference drug, and once the patent of the latter has expired.[10] In the European Union and the EMA these agents are known as biosimilars, similar biological medicinal products, while within the USA, the FDA denominates them as follow-on biologics or follow-on protein products. The WHO has named them similar biotherapeutic products, and in Canada, subsequent entry biologics.[11]

What is and what is NOT a biosimilar drug?[5,12]

The following are not included in the category of biosimilar drugs:

- Generic and innovator drugs
- Non-innovator biological drugs (me-too biological) developed with no direct comparison with the reference drug.
- Biological products that have not proven similar to the reference product and therefore should undergo the complete process of authorization.
- Second generation drugs that incorporate structural and/or functional modifications and should undergo an authorization process comparable to the first generation drugs. Some drugs have been developed this way such as, pegfilgrastim and alfa-2b peginterferon. The chemical conjugation of filgrastim and interferon alfa-2b with a polymeric chain of polyethylene glycol produces pegylated forms with higher molecular weights. This modifies their physical and chemical characteristics and their pharmacokinetics and allows for a reduction in the number of required administrations (one per cycle for pegfilgrastim and a weekly dose in the case of peginterferon).

The WHO, EMA, FDA and other regulatory agencies have developed specific regulations for biosimilar drugs

Biosimilar drugs authorisation is granted when equivalence with the reference drug is proven

Biosimilar drugs per se:

These are copies of previously authorized biosimilar drugs once their patents have expired and both having shown to be similar. Biological drugs are rather complex entities, whether innovative or biosimilar, that can only be produced by living systems. The way they are produced can provoke a certain degree of natural variability in the molecules of the same active substance and among the different batches of the medications. Therefore although small differences may be acknowledged, when a biosimilar drug is authorized, the differences are not clinically relevant, and do not affect either the safety profile or efficacy.[13] The different key characteristics of both biosimilar and generic drugs are summarized on table 1.

How are biosimilar drugs regulated?

Biotechnology drugs are authorized in Europe through the EMA following a centralized procedure.[14] They should undergo evaluation from the Committee for Medicinal Products for Human Use (CHMP), constituted by representatives from each one of the National Drug Regulatory Agencies in the European Union, as well as experts in areas of special interest. This committee issues a scientific opinion that is transmitted to the EMA which then releases a final resolution. The authorization for commercialization through this procedure is valid in all EU countries and the European Economic area as well.

The European Public Assessment reports (EPAR) are published at the EMA website and include a summary of the scientific evidence that supports the authorization for commercialization.[15] Given the complexity and heterogeneity of this class of drugs, the EU has developed

a specific regulatory framework based on different and more complex principles than those employed for generic drugs. The directives and guidelines applicable to biosimilar drugs are available on the EMA website and are summarized in table 2.

On a global scale, the EMA is a pioneer in developing regulation frameworks to establish the requisites for approval of these products[4] and some countries such as Australia, Canada, Switzerland or Japan have followed its principles. In 2010, the WHO published a guideline on the evaluation of biosimilars (Similar Biotherapeutic Product Guideline) based on the EMA's model and with the aim of harmonizing regulations worldwide.[16]

The EMA General guideline is the Guideline on similar biological medicinal products.[15,17] Both biosimilars approval and changes in the manufacturing process of a biologic drug share the same standards for authorization. The main principle for authorization is the demonstration of similarity between the biosimilar and the reference drugs through a complete and thorough comparison of quality, efficacy, biological activity and safety. The requisites in the case of biosimilars are more complex and include clinical studies. In the last review of this guideline (April 2015) extrapolation of indications with appropriate scientific justification is accepted, as well as the possibility of using an authorized comparator outside the European Economic Area.[18]

Table 1. Key characteristics of both biosimilar and generic drugs.

	Biosimilar drugs	Generic drugs
Molecular structure		
	Complex	Simple
	Difficult to reproduce High molecular weight Immunogenic capacity	Easily reproducible Low molecular weight No immunogenicity
Development		
Time	6-7 years	2-3 years
Investment	30-100 million	0,6-4 million
Regulation		
Authorization	Centralized (EMA)	National
Approval	Biosimilarity	Bioequivalence
Need for clinical trials	Yes	No/bioavailability
Pharmacovigilance	Special	Common
Substitution	No	Automatic
Commercialization		
	Patent expires	Patent expires

Tabla 2. Guías de la EMA de los medicamentos biosimilares.

General statements	*Guideline on Similar Biological Medicinal Products*	CHMP/437/04 Rev 1 23 October 2014
Quality	*Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1)*	EMA/CHMP/BWP/247713/2012 24 May 2012
Non-clinical and clinical studies	*Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issue*	EMEA/CHMP/BMWP/42832/2005 Rev1 18 December 2014
Drug-specific guidelines	Recombinant human insulin and analogues Growth hormone Interferon alfa Interferon beta Follicle-stimulating hormone	Recombinant erythropoietin G-CSF Monoclonal antibodies Low-molecular-weight heparins

The Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (EMA/CHMP/BWP/24771/3/2012) came into effect in December 20[14,15,19] and establishes the criteria for similarity in quality. It guarantees the equivalence between the biosimilar and reference drugs in terms of molecular characteristics and consistency of the manufacturing process. In all cases comparisons should be carried out with the same reference drug. Studies should have sufficient power to detect all existing similarities and possible differences.

Quality criteria include compliance with the Good Manufacturing Practices and processes, formulation studies that show stability, comparability and integrity of the main substance and head-to-head studies versus the reference drug in terms of molecular structure and biological activity.

Any difference detected in the profile of impurities or substances related to the product or process should be justified and can require additional safety and clinical efficacy studies.

The requisites in relation to non-clinical and clinical development are described in the Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues.[20] This document came into effect on July 1st, 2015. Firstly, in vitro studies are carried out and later the studies that are judged necessary to be performed are determined. Clinical studies include pharmacokinetic and pharmacodynamic studies followed by studies on clinical efficacy and safety. In some cases, comparative studies on the pharmacokinetics/pharmacodynamics relationship (PK/PD) are informative enough to show clinical comparability.

Clinical trials necessary for authorization are carried out in patients diagnosed with the disease under study and the biosimilar is directly compared to the reference drug. In the case of infliximab biosimilar, a double-blind, randomized clinical trial including 606 adults with rheumatoid arthtritis was carried out. Patients received either the biosimilar or the reference drug for 30 weeks in association with methotrexate. The primary endpoint of efficacy was change from baseline in symptoms of the disease measured through the ACR20 scale.[21]

In addition, another clinical trial on 250 patients with ankylosing spondylitis was carried out to prove that plasma levels of biosimilar and reference drugs were equivalent. The clinical trials to evaluate the efficacy and safety of biosimilars of filgrastim were carried out in patients with cancer and the primary endpoint was "neutropenia duration".

Finally, there are Specific Therapeutic Group Guidelines[22] that include the requisites in regard to the type of clinical and non-clinical studies, characteristics of trials and the possibility of extrapolating data on immunogenicity. These

Safety concerns raised on the use of a biosimilar drug are the same as those with the corresponding original drug

are based on the level of complexity and mechanism of action of each drug class. Currently there are guidelines on insulin, human somatotropin, erythropoietin, granulocyte-colony stimulating factor, alpha interferon, low molecular weight heparin, monoclonal antibodies, follicle stimulanting hormone (FSH) and beta-interferon.

In conclusion, the authorization process of a biosimilar drug regulated by the EMA is based on a thorough comparison versus the reference drug that includes physical, chemical and biological characterization, PK/PD studies, comparative clinical trials, and immunogencity studies among others. All this guarantees that biosimilar drugs comply with quality, efficacy and safety criteria.[13] All reports are publicly available at the EMA website along with the guidelines, directives and regulations.

Controversies surrounding biosimilar drugs

Are biosimilar drugs less safe than the innovator drug?

Safety issues are a main concern regarding biosimilar agents. These problems are shared with reference drugs and originate from possible infections and alterations in the immune response.[23]

Immunogenicity is the specific capacity of a substance to induce an immune response. These reactions can be potentially severe and range from anaphylaxis to the development of neutralizing antibodies, which could lead to a reduction in efficacy or the development of severe adverse reactions. However, the development of such reactions is not easily predictable, and in the case of very rare reactions, the incidence could reach 1-3 cases/100,000 patients and so it is not possible to detect them in pre-authorization clinical trials.

The Spanish Decree RD 577/2013 that regulates pharmacovigilance in humans[24] establishes that biological drugs should be subject to additional and particularly rigorous and intense surveillance by the health authorities. The pharmaceutical manufacturer should present a risk management plan that describes in detail the potential

risks of the product and/or special clinical situations that should be approved by the EMA. It should also include a pharmacovigilance plan to report adverse drug reactions and further safety studies apart from those presented for authorization.

In the case of biosimilar drugs, the additional information required also depends on the previous experience with the innovator drug, which can vary among different therapeutic subgroups.

Safety concerns of biological drugs are shared among innovator and biosimilar drugs. For instance, an increment in the incidence of pure red blood cell aplasia was observed in patients that received treatment with innovator recombinant erythropoietin, which was related to a change in its formulation.[25]

Can the indications of a drug be extrapolated to biosimilar drugs?

This issue is still controversial. The extrapolation of efficacy and safety data from one therapeutic indication to another is possible though not automatic, and should be carried out based on scientific evidence both from non-clinical and clinical studies. If the biosimilar agent has proven comparable to the reference drug for a specific indication through physical, chemical, structural, in vitro tests and also clinical efficacy and safety data, then this information can be extrapolated to other indications of the reference drug.

The extrapolation of indications has been carried out more simply in the case of erythropoietin and colony stimulating factors, while it has been stricter in cases of monoclonal antibodies given their mechanism of action and the implicated receptors. In the case where a reference monoclonal antibody is indicated for cancer treatment then the scientific justification, clinical and non-clinical data on quality should be thorough and relevant.[13,17,22]

The authorization a filgrastim biosimilar was based on studies carried out on healthy volunteers for the prevention of chemotherapy induced neutropenia. The extrapolation of the indications allows for its use in cell mobilization of peripheral blood stem cells. This extrapolation is based on phase I studies that show that the mechanism of action of both is the same, namely the direct stimulation of the surface receptor of the neutrophil precursors.[26] The recent authorization of infliximab biosimilars is based on clinical trials on rheumatoid arthritis and more extrapolations have been extended to psoriasis and Crohn's disease.[21]

Immunogenicity is the main safety concern and depends on factors related to the patient, disease and the drug

Is therapeutical interchange and substitution of biosimilar drugs admissible?

The EMA evaluation before authorization of biosimilar drugs does not include recommendations on interchange or substitution for the reference drug, as this aspect is the competency of each member state of the European Union at national level.[17,19,20]

Therapeutic interchange is considered if the drugs are clinically equivalent and interchangeable. One agent can be substituted for another of different composition to reach the same of higher desired effect, based on a previously known, accepted and established protocol. However, this concept is different from a substitution per se, in which the drug dispensed is different from the original drug prescribed, and without the knowledge of the prescriber.[23,27]

The Spanish Order SCO/874/2007 establishes that biological drugs are an exception for the possible substitution by a pharmacist. The area of application of this norm has caused controversy regarding whether hospital pharmacists should be allowed to make these substitutions. Currently in Spain, the majority of biological drugs are prescribed by hospital doctors and are dispensed by the hospital pharmacies. The selection of drugs is carried out by a committee formed by both physicians and pharmacists from different clinical departments and they should really decide on the convenience of including biosimilars and their role with respect to reference drugs.[23,27]

How to ensure biosimilar drugs tracking?

Medicines tracking provides relevant information on their effects throughout its life cycle. According to the Spanish Decree RD 577/2013 that regulates pharmacovigilance in humans,[24] appropriate measures should be implemented to identify the name and batch of any biological or biotechnological drug when any alert is issued regarding an adverse drug reaction. The name of the medicine is fundamental for clear identification, safe prescription and dispensation.[23]

Biosimilar agents for the same reference drug are assigned the same identification (ICD, international common denominator). As there might be various biosimilar drugs for one reference drug, it is essential to know at any time what drug has been administered to each patient.

Although the nomenclature of biosimilars has raised some controversy,[27,28] according to the EU legislation they should all have either a brand name or the name of the active substance along with the name of the manufacturer. In addition alerts on any adverse drug reaction require the registration of the active substance, brand and batch. Biosimilars' tracking should be ensured, a requirement shared with innovator drugs.

Do biosimilar drugs comply with criteria of cost-effectiveness when commercialized?

Biosimilar drugs marketing creates competition with innovator drugs and opens the opportunity to reducing costs and increasing access to a greater number of patients. This is important, especially in scenarios like the current financial crisis, and so they can contribute to the sustainability of health systems. The development cost of a biosimilar drug is estimated to be 25% cheaper than the original molecule. This discount rate is less than in the case of the generic drugs (up to 80%). This is justified given the higher production costs and time required for development. The investment required to develop a biosimilar drug is estimated to be 30-100 million euros during 6-7 years, compared to the development of a generic drug estimated between 0.6-4 million euros and taking 2-3 years of research work.[19]

In a study carried out to evaluate the efficacy of a filgrastim biosimilar, 1302 cancer patients undertook at least one cycle of chemotherapy with G-CSF to prevent neutropenia. The proportion of patients presenting neutropenia and fever (2.2%) or severe neutropenia (8.5%) was similar to that observed in studies carried out with the reference drug. Data published by the Intercontinental Marketing Services (IMS) point out that during 2011 the savings derived from the use of the filgrastim biosimilar in substitution of the original drug was 85 million euros in 17 member countries of the UE, an estimate based on the price of the original drug and the volume of sales of the biosimilar drug.[30]

Biosimilar drugs marketing

Pharmaceutical costs represent a considerably high share of the overall health care budget. In Spain, these costs are estimated at 17.4% in the primary care setting and nearly 25% when including hospital based medicines.[29]

The introduction of biotechnology drugs has improved the efficiency of treatments in many diseases such as cancer, multiple sclerosis, rheumatoid arthritis, anemia, hepatitis C and other autoimmune diseases, but its elevated costs has an important impact on the health care budget. The cost of treating certain diseases could be over 100,000 euros per patient-year, which explains the increment in pharmaceutical costs at hospital level.[31]

The extrapolation of indications is accepted provided both drugs are comparable and share the same mechanism of action

According to the Institute for Healthcare Informatics this tendency is common in all developed countries and the trend will persist in the future. Biological drugs are a fast growing segment in the market. In 2000, only one out of the 10 top drugs in sales was biologic, while in 2008 these drugs represented some 50%. Biologic drug sales in 2010 increased to 134,000 dollars in Australia, Canada, and the European Union.[32]

Although the USA bears the greatest part of worldwide costs of biological drugs up to now there were no biosimilar drugs on the market.[20] In March 2015 the FDA authorized Zarxio (filgrastim), manufactured by Sandoz, the first biosimilar drug approved in the USA. Europe has the most advanced market for biosimilar drugs representing 80% of world consumption.[31]

In the European Union the first patents of biological products expired in 2001 and the first biosimilar drug was approved by the EMA in 2006 (Omnitrope, a growth hormone biosimilar drug). Up to now the EMA has evaluated 22 biosimilars. Of these, Alpheon, alpha-2a interferon was rejected for not adequately proving comparable to Roferin-A (differences with regard to impurities, stability, and the proportion of patient's relapses).

There are two other biosimilars that have been withdrawn from the market for commercial reasons at the manufacturer´s request: Valtropin (somatropin biosimilar and Filgrastim ratiopharm (filgrastim biosimilar) (table 3).

In February 2015 the EMA the first two monoclonal antibodies were marketed (Inflectra and Remsina, infliximab biosimilars), after the biological reference drug's patent had expired (Remicade).

In Europe sales of biosimilars increased from 3.3 million in 2007 to 162.1 million euros in 2010.[32] Biosimilar penetration rate in the European market is up to now reduced and varies across different States and drug classes. In 2013

biosimilar drugs represented 4.9% of all biotechnology drugs in Europe. The causes of the differences depends on the different local health policies on prices and reimbursements, different influence exercised by interest groups and attitudes to their use, as well as drug related factors per se. In Germany, biosimilar drugs' consumption has increased at a faster pace than in France, England or Austria. All these countries have a higher consumption than others like Spain, Belgium or Italy where the increase in use is rather slow.[30,32]

In 2012 Germany and France accounted for half of the market share of biosimilar drugs (73.1 and 58.1 million euros respectively), while consumption in Spain was 30.7 million euros.The behaviour of the biosimilar market is quite different. For instance, filgrastim use is steadily increasing in all countries whereas somatropin is not.[30,32]

Biosimilar drugs have been launched into the market much faster than their respective reference drugs. Reference drugs and biosimilars are marketed some 4.2 years and 11.8 months, respectively, after EMA's approval.[32]

A possible effect of the introduction of biosimilar drugs in the market is a better access of the patients to biological drugs in general, with an increase in the consumption of both biosimilar and the reference drug. For example, in the United Kingdom, filgrastim biosimilars marketing lead to doctors prescribing filgrastim as the first-line therapy instead of pegfilgrastim. However the commercialization of second generation biological drugs, new therapies or the indication for new administration routes can make doctors switch from biosimilar drugs to newer biotechnology drugs.

Table 3. Biosimilar drugs assessed by the EMA.

Commercial Name	INN	Status	Date of authorization	Indication
Abseamed	epoetin alfa	Authorized	28/08/2007	Symptomatic Anemia
Binocrit	epoetin alfa	Authorized	28/08/2007	Symptomatic Anemia
Epoetin Alfa Hexal	epoetin alfa	Authorized	28/08/2007	Symptomatic Anemia
Retacrit	epoetin zeta	Authorized	18/12/2007	Symptomatic Anemia
Silapo	epoetin zeta	Authorized	18/12/2007	Symptomatic Anemia
Filgrastim Hexal	filgrastim	Authorized	06/02/2009	Febrile Neutropenia
Zarzio	filgrastim	Authorized	06/02/2009	Febrile Neutropenia
Nivestim	filgrastim	Authorized	08/06/2010	Febrile Neutropenia
Biograstim	filgrastim	Authorized	15/09/2008	Febrile Neutropenia
Filgrastim ratiopharm	filgrastim	Withdrawn	15/09/2008	Febrile Neutropenia
Ratiograstim	filgrastim	Authorized	15/09/2008	Febrile Neutropenia
Tevagrastim	filgrastim	Authorized	15/09/2008	Febrile Neutropenia
Accofil	filgrastim	Authorized	18/09/2014	Febrile Neutropenia
Grastofil	filgrastim	Authorized	18/10/2013	Febrile Neutropenia
Bemfola	follitropin alfa	Authorized	27/03/2014	Anovulation
Ovaleap	follitropin alfa	Authorized	27/09/2013	Anovulation
Inflectra	infliximab	Authorized	10/09/2013	Rheumatoid arthritis
Reļima	infliximab	Authorized	10/09/2013	Rheumatoid arthritis
Abasaglar (prev. Abasria)	insulin glargine	Authorized	09/09/2014	Diabetes mellitus
Alpheon	interferon alfa-2a	Withdrawn	-	Hepatitis C
Omnitrope	somatropin	Authorized	12/04/2006	Growth disorders
Valtropin	somatropin	Revoked	24/04/2006	Growth disorders

The Market in Spain

In 2000 the market for biotechnology drugs in Spain accounted for 28 billion euros, 30% of the overall expenditure of the National Health Service and 46% of the hospital costs. Between 2006 and 2012 they presented a yearly increment of 9% and market share increased from 17 to 24%.[31]

However, biosimilar drugs represent a small part of the overall market. In 2009, out of 3.3 billion euros spent on biological drugs, biosimilars accounted for 155.6 million euros (4.1% of all the biological drugs). A similar share was observed in France, United Kingdom, far below that of Germany, Austria or Sweden.

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Conclusions

Biosimilar drugs have been developed according to the specific requirements established by the EMA.

They have proven comparable to reference drug in terms of efficacy, quality and safety.

They reduce drug expenses and contribute to the sustainability of the health systems.

Concerns raised on the use of a biosimilar drug are the same as those with the corresponding original drug. Head-to-head clinical trials and post-authorisation studies are carried out to clarify any concern.

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