Biosimilar drugs as essential drugs: ethical and legal reflections

Los medicamentos biosimilares como medicamentos esenciales: reflexiones éticas y legales

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Abstract

This article reflects on the regulatory reforms that have taken place in recent decades with respect to the rational use of drugs, and the measures taken to reduce pharmaceutical expenditure. In this context, the high cost of biological therapies and the difficulties of access to them —especially in developing countries— should be highlighted.

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Biosimilar drugs have analogous health guarantees —similar or equivalent— to reference drugs but are not subject to patent protection and facilitate accessibility for patients, as well as the equitable distribution of therapeutic resources. In addition, some of them are included in the list of essential drugs of the World Health Organization (WHO).
The role of biosimilar drugs as essential drugs and the possibility of improving equitable access to these health resources through pharmaceutical provision are also examined.

Keywords: public health, accessibility, universal access, generic drugs, intellectual property.

1. Biological drugs

1.1. Concept of biosimilar drugs

According to the WHO, biosimilar bio therapeutic products are *bio therapeutic products*, i.e., biological drugs, similar in terms of quality, safety and efficacy to a previously authorized *reference bio therapeutic product* (1). In this regard, it should be recalled that these drugs are characterized by the fact that living organisms produce them.

Biosimilar medicines have health guarantees —quality, efficacy, safety, identification and information— analogous, similar, similar or equivalent to the original or reference biological medicines and, therefore, are sufficient to obtain a marketing authorization from the health authorities.

Given that most of the active principles of biosimilar medicines are obtained through biotechnological processes. It is in the territory of the European Union (EU) that such authorizations are granted by the European Medicines Agency, by virtue of the provisions of the Regulation of the EU 2019/5 of the European Parliament and of the Council, of 11/12/2018. This modifies the Regulation of the European Commission (EC) nº 726/2004, by which community procedures are established for the authorization and control of Medi-

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cines for human use and by which the European Medicines Agency is created, these are authorized by the EC.

In Spain, the authorization is granted by the Spanish Agency of Medicines and Health Products. This is the case of the following active ingredients: low molecular weight heparins, sodium chondroitin sulfate, and some commercial presentations of teriparatide.

Once the biosimilar medicinal products have been authorized by the centralized procedure, the laboratories holding the marketing authorization must initiate certain methods to market such medicinal products in the different EUA Member States, which are aimed, among others, at setting the conditions of financing by the public health services or setting the industrial sales price.

In this context, there are significant differences in access to biosimilar drugs in the EU, so that the purchase price varies from one Member State to another and not all of them may be available in all countries. Likewise, it can also happen that the authorized drug is not marketed, a situation that would lead to the revocation of the authorization if more than three years have elapsed, as occurred in the specific case of a certain drug authorized as a biosimilar.

Regardless of the regulatory body that decides on the authorization to place the drug on the market, a simplified or abbreviated regulatory procedure is followed, as it is unethical to demand the same requirements for the authorization of the latter as for the original or reference drugs, since such a scenario would entail a repetition of non-clinical and clinical trials. Not only would the scientific knowledge obtained during the development of reference drugs be ignored, but there would also be an unjustified abuse of experimental animals for drug development —with the corresponding bioethical repercussions—.

It should also be noted that the development of generic drugs is much more limited than that of reference drugs, which is why they can be marketed at lower prices and are of undeniable social interest. For example, clinical research is often reduced to bioequivalence studies (2).

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1.2. Relevance

Medicines of a biological nature play a very significant role in the pharmaceutical sector. They represent a benefit to the pharmaceutical provision of the National Health System since they present novel pharmacological action mechanisms that are different from drugs obtained through chemical synthesis processes. In this scenario, their introduction in therapeutics has led to far-reaching changes in the care protocols of numerous diseases, among others, in the field of oncology and hematology (3).

Their use also has a significant budgetary impact for public health systems (4). In 2018, the use of biologic drugs in the EU regulatory territory accounts for thirty percent of pharmaceutical expenditure (5). In 2020, such pharmaceutical expenditure has been estimated at around eight and a half billion euros (6).

The difficulty of access to medicines especially in developing countries, is well known and constitutes a public health problem (7). In many developing countries, there is a lack of appropriate drug distribution systems, which further exacerbates the differences in patients' access to these goods of social interest (8). This problem is aggravated for biological drugs, since many of them require special temperature conditions for their distribution, storage and custody (9,10).

In order to avoid restrictions on patients' access to biological therapies for economic and/or geographical reasons —that is, independently of therapeutic issues— it is absolutely necessary to devise strategies to guarantee the sustainability of health insurance and, at the same time, to provide —or facilitate— patients with the pharmacological treatments they need in an equitable manner - regardless of their purchasing power.

Although patents "contribute to the public interest by encouraging research and innovation leading to new and better drugs" (11). There is no doubt about the need for patents to expire after a finite period of time in order not to slow down innovation by the pharma-

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ceutical industry, since the malicious -or abusive- use of patents leads to the establishment of monopolies that determine the high prices of drugs (12,13). In the 21st century, there have been numerous conflicts between intellectual property rights —patents— and human rights —the right to life, to health protection, to access to medicines— with the latter being weighted in favor of private rights (13-15).

It is in this context, in which economic resources are limited, there are terrible inequalities in access to drugs, and due to the need for governments to supply drugs to meet the health demands of the population, that biosimilar drugs take on great importance. These products, which are of unquestionable social interest (13,16), can be introduced on the markets once the exclusive exploitation rights of the patent of the reference or original biological drug have expired (17), and will then be marketed at lower prices compared to the latter.

2. Rational use of drugs

The third generation of legal standards for drugs normally demands requirements relating to their quality, safety and efficacy, but also incorporates those related to pharmacovigilance and the assessment of results, information surveillance, control of advertising and promotional activities, and, in short, mechanisms to ensure their rational use (18,19).

According to what was established by the WHO in 1985, rational use of drugs exists when patients receive the medication appropriate to their clinical needs, in doses corresponding to their individual requirements, for an adequate period of time and at the lowest possible cost.

The rational use of drugs is related to the following factors (20): a) appropriate selection of these resources; b) correct information on drugs; c) treatment with the right dosage and for the right length

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of time; d) implementation of health education activities among citizens; e) control of adverse effects; f) adequate regulation in the pharmaceutical sector, especially with regard to advertising and self-medication; g) adequate public financing of drugs.

Similarly, third-generation legal texts also aim to provide greater protection of citizens' rights —e.g., public health— and, at the same time, to control the public budget allocated to pharmaceutical provision, given the limited economic resources and the need to meet the population's health demands.

3. Public financing of drugs: a brief critique

While it is true that, in the Spanish legal system, medicines are part of the pharmaceutical provision, in accordance with the provisions of Law 16/2003, of 28 May, on Cohesion and Quality of the National Health System, where it should be noted that the third paragraph, of the first section of Article 92 of the Royal Legislative Decree 1/2015, of July 24, which approves the revised text of the Law on Guarantees and Rational Use of Medicines and Health Products, establishes that the financing of medicines in the National Health System is selective, not indiscriminate and that it attends to general, objective and published criteria. We would like to refer exclusively to letter d) [...] "Rationalization of public spending on pharmaceuticals and budgetary impact on the National Health System".

Thus, as of 04/11/2021, the Spanish National Health System has issued more than five thousand resolutions of non-funding of drugs for human use. First of all, let us look at an example of a biological drug and at the same time an orphan drug; elosulfase alfa, an enzyme used in substitution therapies —in patients who have a deficit of this biocatalyst— with a treatment for a specific type of mucopolysaccharidosis, etcetera.

In this regard, it should be recalled that for a drug to be designated as an orphan drug in the EU, it must meet one of the following

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conditions: (a) it is intended for the diagnosis, prevention or treatment of a life-threatening condition, or involves a chronic capacity, and does not affect more than five persons per ten thousand in the EU, at the time the application for designation is submitted; b) it is intended for the diagnosis, prevention or treatment, in the EU, of a life-threatening, seriously debilitating or serious and chronic condition, where, without incentives, the marketing of such a drug would generate, in the EU, sufficient profits to justify the necessary investment. Likewise, it is required that there is no satisfactory method authorized in the EUA for the diagnosis, prevention or treatment of such a condition or that, if such a method exists, the drug would be of considerable benefit to those suffering from such a condition.

In view of the above, there is no doubt that the pharmaceutical industry, *a priori*, would have no interest in the development of drugs for the treatment of rare diseases. This constitutes a major obstacle to the protection of the health of such patients (21-24), which is why the regulations provide for the establishment of incentives for the marketing of orphan drugs (25).

There are also many other examples of orphan drugs that have not been financed by the Spanish National Health System: (a) tobramycin; antibiotic of the aminoglycoside group used in the treatment of cystic fibrosis, or infections by the bacterium *Pseudomonas aeruginosa*, in its pharmaceutical form of hard capsule for inhalation; (b) ataluren; drug used in the treatment of a highly debilitating type of muscular dystrophy, whose patients have a life expectancy of no more than thirty years.

On the other hand, it should be noted that there is no mention in our domestic legislation of the bioethical criteria for the adoption of decisions on the public financing of drugs, which, according to various authors (16) -especially the principle of justice, which *roughly speaking* consists of "treating equals equally and unequal unequally" (26) and can be interpreted as meaning that people's needs must be duly met (27) —should be taken into consideration in order to ensure access to medicines under equitable conditions— that is, to

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guarantee impartiality in the distribution of these resources (28), a position that seems to us to be more than coherent. In this respect, Sanchez-Caro states, "the integration of ethics in healthcare organizations is profitable" (27).

Notwithstanding the above, the Spanish Bioethics Committee issued in 2017 a report on the public funding of a certain drug, at the request of the General Directorate of Public Health, Quality and Innovation of the General Secretariat of Health and Consumption of the Ministry responsible for health at the Spanish level, in accordance with the provisions of Article 78. 1 a) of Law 14/2007, of July 3, 2007, on Biomedical Research, according to which the aforementioned Committee is empowered to "issue reports, proposals and recommendations to the public authorities at the state and autonomous community level on matters with relevant bioethical implications" (29).

Likewise, due to the limitation of health resources —for example, drugs— destined to the improvement or restoration of health by the population, it seems clear that state intervention on the industrial sales prices of drugs for human use is more than justified (13,18). In this regard, it is worth highlighting, among other initiatives, the need to establish an efficiency threshold in the public financing of medicines (30) —for example, through the establishment of maximum expenditure ceilings—.

4. Essential medicines

4.1. Concept

In recent decades, the pharmaceutical industry has been marketing a broad pharmacotherapeutic arsenal in a market with an asymmetrical and atypical relationship between the different agents involved in it. Since in the case of the drugs included in the pharmaceutical provision of the National Health System, the consumer —patient and/or user— neither decides nor pays for the drug in full; the

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prescriber neither pays for it nor consumes it; and whoever finances it —the public administration— neither prescribes it, nor does he/she consume it (31). From the above it can be seen that, within the framework of the rational use of health resources in general, and of drugs in particular, it seems clear that it is necessary to select the drugs with the best cost-effectiveness ratio, in order to guarantee their access to the population.

According to Mahler, essential medicines constitute "one of the elements of Primary Health Care, to ensure that all people could have an economically and socially productive life" (32). Unfortunately, more than one third of the world's population is unable to access such products (33).

The concept of essential medicines was coined by WHO in 1977 to designate those products that meet the basic health needs of most of the population. For this reason, these drugs should be available in all countries in sufficient quantities.

Although it is true that the classification of drugs as essential is criticized by some authors, who argue that there could be drugs that are necessary for the population but are not recognized as such by the WHO (16). It is considered appropriate for an international organization to establish, by means of a non-binding document, a list of drugs for which a continuous and sufficient supply should be guaranteed for the population, given the limited health resources. Similarly, several authors have criticized the WHO list of essential drugs because the procedure for selecting and including drugs prioritizes economic criteria over therapeutic ones (34).

Unfortunately, universal and equitable access to medicines can be considered a utopia. There is no doubt about the difficulty of access by the population of developing countries to the drugs required to meet the demand for medicines by these societies (7,14,18,31,35,36). Medicines are essential to the lives of citizens (37), given their link to the right to life and health protection.

Particularly significant is the traditional problem of antiretroviral drugs (38), used in therapy for the treatment of human immunodeficiency virus infection, since, on the one hand, they are difficult to

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access and, on the other, a message of monogamy or sexual abstinence is conveyed to these populations (39).

Recently, the problem related to vaccination coverage against COVID-19 can be cited (40-42). In Spain, the population has been stratified into groups according to priorities, and it is also worth considering whether, once a certain level of vaccination coverage has been reached, these resources could be distributed to developing countries to ensure more equitable access, or whether the maximum vaccination quota could be reached (43,44). The development of new formulations of these vaccines, either original drugs or biosimilar drugs that may be developed in the future, would contribute significantly to improving universal access.

Another major problem is the lack of treatments for the so-called "neglected diseases" (24,45), mainly due to the absence of promoters, since they mainly affect developing countries. Existing treatments for such pathologies suffer from severe problems of effectiveness, for example, the emergence of resistance, or safety, i.e., they are highly toxic.

While it is true that privately owned pharmaceutical laboratories are the main investors in the research and development of new drugs, given that this is their main economic activity, their invaluable contribution to the development of drugs for human use for the treatment and/or prevention of neglected diseases should be emphasized, so that the financing of such activities comes mainly from public institutions (45).

Essential drugs should not only be available in sufficient quantity to meet the health demands of the population. They should also meet the following requirements: a) be in the appropriate pharmaceutical form; b) satisfy adequate health guarantees, quality, efficacy, identification, information, and safety; c) be available at a price that can be afforded by the payer, e.g., the patient, the public health system, etc.

Due to the particularities of pediatric medicines, three decades later the list of essential medicines for exclusive use in humans up to twelve years of age was published independently.

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The lists of essential drugs published by the WHO are not legally binding for the different countries, i.e. they have the character of recommendations and are therefore not valid worldwide. Their usefulness lies in the fact that they are a fundamental tool for the health planning of national territories. States must therefore draw up their own lists of essential drugs, based on the list defined by the WHO, considering the specific health needs of the population whose right to health protection must be satisfied, and ensure an adequate level of access to the drugs. The selection of biosimilar drugs by states can contribute significantly to the rationalization of the costs associated with medical treatments without reducing the quality of healthcare, and without the need to limit access to biological therapies.

Initially, the WHO list of essential medicines contained two hundred and forty-three active ingredients in twenty-seven pharmacological groups. This list has been revised every two years since then, the list of essential drugs for pediatric use only is revised at the same frequency. In 2021, five hundred and sixty-four drugs are incorporated into the general list; and three hundred and forty-eight drugs are incorporated into the list of pediatric drugs.

4.2. Classification

In turn, within the list of essential drugs, for each pharmacological group, one or two categories can be distinguished. On the one hand, a basic list, which includes only those, drugs necessary to cover the basic health needs of the population. These are, by definition, those that have demonstrated the greatest efficacy and safety, and those that present the best cost-effectiveness ratio for the priority disorders, that is, those most relevant in relation to public health, and the potential safety and cost-effectiveness of the treatment.

On the other hand, a complementary list will be established, which incorporates second-choice drugs for the treatment of priority disorders, in which any of the following circumstances are present: a) a specialized diagnosis is required, b) specific monitoring facilities, c) assistance by a specialist, d) reasons related to price cost

https://doi.org/10.36105/mye.2023v34n2.05

or cost-effectiveness ratio less favorable with respect to the drugs on the main list.

4.3. Addition of biological drugs

In the latest WHO general list of essential drugs (2021), sixty of them are of a biological nature, while the number of essential drugs for the pediatric population is smaller, at forty-two.

With respect to the general list and as can be seen in Table 1, fourteen essential drugs with biological active ingredients were initially incorporated (1977). In the revisions carried out during the last decades of the 20th century, the introduction of biological drugs in these lists has been discrete: five in 1979, one in 1984, two in 1987, one in 1991, one in 1993, and three in 1999. In total, twenty-six biological drugs were designated as essential until 1999. Although in the three subsequent revisions (2001, 2003 and 2005) no biological drugs were incorporated. In the current century an important turning point is observed, since, unlike what happened at the beginning of the 21st century, thirty-five biological drugs have been incorporated: eight in 2008, one in 2009, one in 2011, one in 2011, three in 2013, seven in 2015, six in 2017, nine in 2019, and one in 2021.

Table 1. Essential medicines (2021) of a biological nature for which authorized presentations of biosimilar medicines exist in the EU.

Name of the active substance	**General list / Pediatric medication list**
Bevacizumab	Yes (2013) / No
Enoxaparin	Yes (2015) / Yes (2015)
Filgastrim	Yes (2015) / No
Rituximab	Yes (2015) / Yes (2015)
Trastuzumab	Yes (2015) / No
Erythropoiesis-stimulating agent (epoetin alfa, epoetin beta, epoetin beta methoxy polyethylene glycol, epoetin zeta)	Yes (2017) / Yes (2017)

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Adalimumab	Yes (2019) / Yes (2019)
Etanercept	Yes (2019) / No
Infliximab	Yes (2019) / No
Long-acting insulin (insulin glargine)	Yes (2021) / Yes (2021)

Source: prepared by the authors.

Of the list of essential drugs for 2021, there are currently commercial presentations of biosimilar drugs in the EUA for ten of them, drugs containing enoxaparin are authorized at the level of each Member State, and this figure is expected to increase in the coming years, due to the expiration of the patent of the reference biological drugs. For example, the patent of the reference drug whose active ingredient is cetuximab expired in 2014; and in 2022 this will happen in the case of eculizumab (46). Denosumab biosimilar drugs are currently in the clinical research phase (47).

In November 2021 there were ninety commercial presentations of biosimilar drugs considered essential available in Spain. These data highlight the undoubted relevance of biosimilar drugs in therapeutics worldwide.

There is no doubt that biosimilar drugs are essential for the world's population, since their cost-effectiveness ratio is considerably higher than that of reference biological drugs, without there having been any reduction in the health guarantees.

Biosimilar drugs provide accessibility not only from the economic point of view, but also because the laboratories responsible for the manufacture of such products also introduce improvements at the pharmacotechnical level, for example, formulation and pharmaceutical form (48).

5. Biosimilar drugs: key to equitable access

Biosimilar drugs would make it possible to offer state-of-the-art treatments —biologics— to a greater number of patients if they were

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used to replace the respective original drugs. They would also allow earlier initiation of treatment with biologic drugs at the same cost, which is an undoubted benefit for the protection of patients' health. It is for these reasons that biosimilar drugs are said to improve the accessibility of biologic therapies to patients (49), by presenting an optimal cost-effectiveness ratio, as well as by introducing pharmacotechnical improvements.

According to Sánchez-Caro, no reproach can be made from an ethical point of view to medical practitioners who prescribe biosimilar drugs (27), since these have been shown to satisfy the due health guarantees and a relationship of sufficient similarity with the original or reference biologic drugs, in accordance with the application *guidelines*. In this way, not only the principle of justice would be respected —since equitable access would be favored— but also the principle of beneficence, since "health care can be presumed to be correct and for the benefit of the patient" (27).

In any case, the right to health protection, specifically to obtain the most appropriate therapeutic alternative, prevails over the policy of rationalization of pharmaceutical expenditure. In this sense, see the Judgment of the First Section of the Social Chamber, of the High Court of Justice of the Basque Country no. 244/2015, of February 3, 2015. In other words, under no circumstances is it a question of absolutely restricting the use of reference drugs in favor of generic drugs or biosimilars, as the clinical characteristics of the patient and the Hippocratic principle of *primum non-nocere* in medical care must be taken into consideration.

Based on the above, although biosimilar drugs share the same therapeutic indications as the reference drug, medical professionals must take into consideration scientific and ethical criteria when establishing pharmacological treatments, so that neither an excessive prescription with original biological drugs is intended. This would lead to an overwhelming and unnecessary pharmaceutical expenditure —and an inappropriate degree of penetration of biosimilar drugs—, nor inappropriate prescribing of biosimilar drugs for economic reasons —for example, it could happen that a given patient

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does not respond satisfactorily to the biosimilar drug but does respond satisfactorily to the reference biologic drug—.

In this regard, prescribing must be efficient. To this end, the transmission of sufficient therapeutic information must be guaranteed, as well as respect for the bioethical principles of non-maleficence, justice and beneficence, and patient autonomy (50).

In this scenario, the policies to promote the use of generic drugs and biosimilars to reduce their prices, as well as the induction in the price of reference drugs, should also be highlighted. This being the case, in April 2019 the Ministry with health competencies at the Spanish level has published, to date, two versions of the "action plan to promote the use of market regulatory drugs in the National Health System: biosimilar drugs and generic drugs" (51,52).

There is no doubt that biosimilar drugs facilitate equitable access to biological therapies, as they have a more favorable cost-effectiveness ratio compared to reference biological drugs, but it is no less true that not all active ingredients of a biological nature are classified as essential by the WHO. For example, follitropin alfa, somatropin and teriparatide, either because of the existence of more efficient or safer therapeutic alternatives, or because they are intended for the treatment of diseases that are not considered a priority in a public health context.

In short, the therapeutic decisions adopted by physicians must take into consideration the scientific evidence, as reflected, among other documents, in the WHO lists of essential drugs. If the use of biologic drugs is required, biosimilar drugs should be considered, since they constitute an option compatible with the sustainability of economic resources, given that their cost is lower than that of the original or reference biologic drugs.

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