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Biosimilars in pediatrics

Paulo Cáceres Guido[1], *Julieta González*[1]

ABSTRACT

Biosimilars are highly similar versions of already authorized biological drugs. A notable benefit of these is their significantly lower price compared to innovator drugs, which frees up healthcare resources and improves affordability. Leading regulatory agencies approve biosimilars after rigorous comparability studies, ensuring that there are no significant differences in quality, safety, and effectiveness. Currently, the structural and functional equivalence of biosimilars to originators may be sufficient evidence, together with post-marketing experience, to support their safe and effective use in pediatrics. Although the extrapolation of indications and interchangeability continues to be debated, research continues to support the use of biosimilars. However, challenges remain, such as regulatory heterogeneity and mistrust due to misinformation. Continuing education and clear public policies are essential to maximize their adoption and access to vulnerable populations such as children.

Keywords: *pharmaceutical biosimilars; pediatrics; drug interchangeability; drug costs.*

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[1] *Hospital Pediátrico Prof. Dr. Juan P. Garrahan, Autonomous City of Buenos Aires, Argentina.*

Correspondence to *Paulo Cáceres Guido: caceresguido@gmail.com*

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INTRODUCTION

The emergence of biological medicines has radically transformed the management of multiple chronic and complex diseases in both adult and pediatric populations. However, the high cost associated with these drugs has been a significant barrier to their affordability worldwide. This is where similar biological medicines (biosimilars) emerge as a promising option by joining the pharmacotherapeutic arsenal.

Biosimilars, while not identical copies of the original biological product, are highly similar in quality, purity, potency, safety, and effectiveness, and do not show clinically significant differences from the already authorized innovative product. Unlike chemically synthesized drugs, they are usually derived from biotechnological processes developed in living systems (e.g., human cells, animals, and microorganisms), which explains why it is impossible to replicate their complex chemical structure with complete accuracy.[1,2]

Regulatory framework and current status

Since the approval of the first biosimilar in Europe in 2006 (somatropin), the number of products of this type has grown significantly worldwide (*Table 1*).[3] This expansion has not only broadened the therapeutic options available but also encourages competition, which translates into greater availability and affordability for patients.[1,2]

The approval of a biosimilar is based on a rigorous comparability process using a "totality of evidence" approach. This process involves comprehensive analytical characterization, preclinical studies, and comparative clinical trials, including pharmacokinetic and pharmacodynamic analyses.[2] Leading global regulatory agencies, such as the FDA (U.S. Food and Drug Administration) and the EMA (European Medicines Agency), have established clear and strict guidelines for the development and approval of biosimilars, facilitating their entry into the global market.[4,5] Within this framework, currently, the analytical evaluation that examines structure and function is considered as sensitive as clinical studies in detecting clinically relevant differences between a biosimilar and its original.[2]

Table 1. Biosimilars approved by the EMA/FDA for each biological drug

Biological drug	Approved indications	Biosimilar approval (EMA/FDA) *
Somatropin	Growth hormone deficiency	2006/ #
Epoetin	Anemia	2007/2018
Filgrastim	Neutropenia	2008/2015
Follitropin alfa	Anovulation	2013/ -
Infliximab	Immune-mediated inflammatory diseases	2013/2016
Glargine insulin	Diabetes	2014/2015
Etanercept	Immune-mediated inflammatory diseases	2016/2016
Enoxaparin	Venous thromboembolism	2016/ -
Adalimumab	Immune-mediated inflammatory diseases	2017/2016
Trastuzumab	Breast and gastric cancer	2017/2017
Teriparatide	Osteoporosis	2017 / -
Bevacizumab	Cancer (colorectal, breast, lung, ovarian, renal, and others)	2018/2017
Rituximab	Immune-mediated inflammatory diseases, hematological cancers	2017/2019
Ranibizumab	Retinopathy	2021/2021
Omalizumab	Asthma, chronic urticaria	2020/2025
Natalizumab	Multiple sclerosis	2023/2023
Tocilizumab	Immune-mediated inflammatory diseases	2023/2023
Aflibercept	Retinopathy	2023/2024
Eculizumab	Paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome	2023/2024
Ustekinumab	Immune-mediated inflammatory diseases	2024/2023
Denosumab	Osteoporosis - Malignant bone neoplasms	2024/2024

** Year in which the first biosimilar was approved for each biological product; #It was also approved by the FDA in 2006, but not as a biosimilar, but as a biological product (at that time, the specific regulatory category identified by that name did not yet exist for the FDA).*

EMA: European Medicines Agency; FDA: Food and Drug Administration.

Benefits, safety, clinical equivalence, and extrapolation of indications

A key benefit of biosimilars lies in reducing the prices of high-cost biological medicines, thereby increasing their affordability. Their use can generate significant savings, as they are typically priced at least 25% lower than the innovator product and can even exceed that percentage by a wide margin.[6] This frees up resources that can be used for other healthcare interventions, which is crucial, particularly in pediatrics, where chronic diseases often require costly and prolonged treatments.[7]

About safety, the primary concern has been immunogenicity, i.e., the ability of a biological drug to induce an immune response in the patient. While this is a key consideration for all biologics (including reference products), comparative studies must ensure that the immunogenicity profile of the biosimilar is similar to that of the original.[1] For vulnerable populations such as children, whose immune systems are still developing, active post-marketing pharmacovigilance (phase IV) is of vital importance, including accurate product traceability for the correct attribution of any potential adverse events.

The clinical equivalence between a biosimilar and its reference product is established through comparability studies, which demonstrate that there are no clinically significant differences in terms of effectiveness and safety. It is essential to emphasize that, although they are not exact copies, biosimilars are highly similar to the innovator product, equivalent in terms of ensuring the expected clinical response without increasing the risk of immunogenicity, loss of efficacy, or adverse effects.[2,8]

A cornerstone of biosimilar development is the extrapolation of indications. This allows a biosimilar formally approved for a specific indication to demonstrate equivalence with the reference product, but for other indications, without the need for additional clinical trials for each one, provided that the justification is robust.[1,2] This principle, supported by many leading regulatory agencies, has generated debate, particularly in pediatrics, where extrapolating data from adults is not always directly applicable. However, evidence within this age group is constantly growing and continues to support the use of biosimilars extrapolated to an increasing number of conditions.

By the mid-2010s (2015-2020), key research on biosimilars in adults and pediatrics marked a milestone in their global adoption. Studies focusing on certain drugs such as infliximab and etanercept, used to treat conditions such as Crohn's disease, ulcerative colitis, juvenile idiopathic arthritis, and pediatric psoriasis, generated robust evidence that directly impacted regulatory decisions. This period consolidated the integration of biosimilars into pediatric clinical protocols and public health policies on an international scale.[8-10]

Global challenges and regional context, economic impact, and outlook

The adoption of biosimilars worldwide is uneven. Barriers remain in Latin America, although their potential to improve the affordability and sustainability of health systems is recognized. These barriers include the lack of harmonized regulatory frameworks between countries, misinformation, and, as a result, occasional mistrust among professionals and the general public.[6] For example, Argentina's National Administration of Medicines, Food, and Medical Technology (ANMAT), in its Provision 1741/2025, incorporated a Comparability Guide that recognizes a product as a biosimilar if it has the same dose and form of administration as the original, with no differences that affect its safety or improve its effectiveness.

The switching of an original biological product with its biosimilar remains a controversial issue, especially if it does not require the intervention of the prescriber, with its adoption varying according to national or local regulations. In clinical practice, this decision is strongly influenced by the dissemination of information by the various actors involved in these issues (laboratories, researchers, clinicians, and regulators), which affects prescribers' confidence. Only biosimilars with an interchangeability designation can be automatically substituted at the pharmacy (without prescriber intervention), provided that local regulations allow it. For example, to demonstrate interchangeability, the FDA requires comparative analytical studies (and generally no longer specific clinical studies) confirming the safety and effectiveness of biosimilars, with no clinically relevant differences.[2]

In addition, current evidence (including dozens of reports since 2019) indicates that even switching from one biosimilar to another does not affect therapeutic response or increase adverse events.[11] However, as part of good

clinical practice, it is always advisable to monitor the patient's response after any brand switch, whether biological or chemically synthesized (original, generic, or similar), especially in sensitive populations such as pediatrics.

The economic impact of biosimilar use is undeniable, even when analyzing studies in the pediatric population, allowing for significant savings that translate into greater access to treatment for a larger number of patients.[4,6,8] However, despite the benefits, acceptance of biosimilars by healthcare professionals has been variable. Factors such as a lack of clear information, doubts about the quality of approval processes in some countries, and the absence of specific guidelines for pediatric use have contributed to this reluctance.[1,6,8] Continuing education, access to transparent information, and evidence-based communication are crucial to improving confidence and acceptance. In turn, complexities in procurement, dispensing, and sometimes dependence on the provider or payer limit effective access.[6]

In light of these challenges, it is imperative to strengthen public policies that promote the adoption of biosimilars whenever evidence supports it, educating professionals and patients to ensure the traceability of these products. Collaboration between regulatory agencies and alignment with international guidelines could facilitate more equitable and safe access. Local production, together with regulatory harmonization, also represents a valuable strategy for ensuring supply and reducing dependence on imports, a crucial aspect in the face of potential global supply crises.[6]

CONCLUSIONS

The use of biosimilars is undeniably set to expand in patients of all ages as patents on the original biologics expire. Although there is still a need to strengthen the evidence in the pediatric population, not all leading regulatory agencies worldwide require specific information for this population. Similarly, despite the intrinsic complexity associated with pediatric research, and strengthening the scientific basis for this type of patient, more studies specifically designed for this group are needed, along with active pharmacovigilance and collaborative actions between hospitals, research institutes, and scientific societies. It should also be noted that, to date, the structural and functional equivalence demonstrated between biosimilars and their reference biologics, together with the absence of significant clinical differences with adults and post-marketing experience in pediatric populations, supports their safe and effective use in pediatrics, as well as fairer and more equitable management because of more efficient reallocation of healthcare resources.

Growing competition and falling prices for advanced biologic medicines are occurring in a context where regulation is evolving alongside evidence to speed access. It is essential that physicians and other healthcare professionals, as well as regulatory agencies and the scientific community at large, continue to collaborate to ensure the safe and effective implementation of biosimilars, maximizing their potential to improve global health, particularly in highly vulnerable populations such as pediatrics. ■

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