Biosimilars and drug development in allergic and immunologic diseases

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After the first approval of a recombinant insulin in 1982, the number of biologic drugs has shown a continuous and exponential increasing trend, which is expected to soon cross over the progressively decreasing trend of the number of chemical drugs. For instance, in the period 2011-2016, 85 biologics were approved by the US Food and Drug Administration (FDA), and 109 biologics were approved by the European Medicines Agency (EMA), with 14 (12.8%) among these last 109 having single (n = 9) or multiple (n = 5) indications in allergic and immunologic diseases.[1,2]

This changing attitude in drug development is having effects on health care, the pharmaceutical industry, regulators, and payers.[3,4] In fact, the higher costs for the development of biologics and their indications frequently confined to selected small populations have produced a significant increase in total drug expenditure that is often not sustainable for many national health services. As a consequence, instead of increasing the quality of health care, the progress in drug development produced the paradoxical effect of reducing it because of impaired access of patients to safe and effective but expensive medicines. This also led to an increased risk for pharmaceutical companies to make huge investments without any certainty for financial return.

Biosimilars have been considered a remedy to this phenomenon because of their potential to significantly reduce the costs of the many biologics with an expired patent, including most of those at the top of the lists for sales and costs at well over the $1 billion of the "old-style" blockbusters.[5] However, the hope to produce global savings ranging from €11.8 to €33.4 billion in 8 European Union countries by 2020 (http://www.medicinesforeurope.com/2016/02/22/test-article-t/) is at present not fully realized.

Biosimilars (also known as similar biological medicinal products or follow-on biologics) are in fact defined by the EMA as biological medicinal products that contain a version of the active substance of an already authorized original biological medicinal product (reference medicinal product). Similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety, and efficacy based on a comprehensive comparability exercise needs to be established (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf).

Biosimilars include products derived from recombinant DNA technology (ie, mAbs) and potentially all biologics, such as vaccines, cytokines, hormones, clotting factors, tissue-engineered products, and gene and cell therapies. Biosimilars cannot be considered generics because they have a high molecular weight and a complex heterogeneous structure, are produced through processes strongly dependent on specific experimental conditions, and are usually immunogenic (Fig 1). Therefore the comparison of biosimilars with their reference products is more complex than that required for chemical drugs and implies an accurate comparative assessment of their quality and clinical features, which is known as a "comparability exercise."

Europe has led the pace for the development of biosimilars, with 31 products having received a positive opinion from the EMA (26 with a valid marketing authorization, 2 products waiting for the European Commission decision, and 3 withdrawn by the manufacturers). Somatropin (Omnitrope; Sandoz, Princeton, NJ) was the first product approved as a biosimilar in 2006, whereas the first mAb (infliximab; Remsima [Napp Pharmaceuticals, Cambridge, United Kingdom] or Inflectra [Hospira, Lake Forest, Ill]) was authorized in 2013.[1]

Biosimilars represent an argument of high interest for allergists and clinical immunologists because 7 (22%) of 31 of the products that received a positive opinion from the EMA Committee on Medicinal Products for Human Use have an indication for allergic and immune diseases (Table I). Furthermore, in view of the upcoming expiration of patents and intellectual property rights of several biologics of interest in allergy and clinical immunology, a high number of biosimilars is at present under development or review. For instance, a phase II/III trial was completed in May 2016 by Sorrento Therapeutics/Mabtech for omalizumab, patents of which will expire in June 2017 in the United States and August 2017 in Europe.

The marketing authorization of biosimilars in Europe is granted through a centralized procedure by the European Commission, following the opinion of the EMA Committee on Medicinal Products for Human Use supported by the Biosimilar Medicine Working Party and the Biologics Working Party. The EMA has published several documents to regulate the requirements for approval of biosimilars, including an overarching guideline defining principles, general guidelines on quality and nonclinical and clinical aspects to define safety and efficacy, and guidelines for specific products, such as insulin, somatotropin, granulocyte colony-stimulating factor, epoetin, IFN-α, low-molecular-weight heparins, and mAbs.[1] The EMA also provides scientific advice that has been shown to be extremely useful for

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Chemical drugs/Generics	Biologics/Biosimilars
• Low Molecular weight	• High molecular weight
• Simple structure	• Complex structure
• Chemically produced	• Produced by living cells
• Standardized manufacturing process	• Specialized manufacturing process
• Possible to obtain exactly the same molecule	• Possible variability among different batches (as for biologics)
• Stable	• Sensitive to storage and handling
• Non immunogenic	• Immunogenic
• Bioequivalence	• Complex comparability exercise

FIG 1. The molecular structure of a chemical drug (cetirizine) and a biologic (infliximab) as examples to highlight the differences between generics and biosimilars in replicating reference medicines.

a correct implementation of the guidelines and a successful outcome of the applications.

According to EMA guidelines, quality assessment is the primary fundamental step in the evaluation of biosimilars. The reference product should be approved in the European Union, even if pivotal data from comparison with comparators authorized in regulated countries might be accepted under certain conditions. Nonclinical tests are usually based on *in vitro* assays that are preferred to studies in animal models.

With reference to clinical aspects, a biosimilar is intended to be used at the same posology and dosing regimen or regimens as those of the reference products to treat the same disease or diseases. End points for clinical comparability might be different from those used to show efficacy of the originator. However, phase III studies of biosimilars should contain common end points with the pivotal studies of the originator. If justified by using a common mechanism, indications for a biosimilar can be extended to all those of the originator, even if not tested in authorization studies. Equivalence designs should be preferred, but noninferiority designs might be acceptable. Interestingly, superiority of the biosimilar versus the originator is not acceptable.

Immunogenicity is a major safety concern for products that can elicit specific antibodies potentially responsible for hypersensitivity reactions and severe adverse events (as in the case of the pure red-cell aplasia induced by epoetin α),[6] as well as for inhibition of the drug effect. Different methods are available for testing the production of antibodies against biosimilars. However, there is no evidence of a higher risk of immunogenicity for biosimilars compared with that of the reference products.

Pharmacovigilance for biosimilars should not be less than for the originator. Therefore a risk management plan is requested, and traceability should be guaranteed. The same registry used for the originator can be used. Up to now, however, in 10 years of experience, the EMA has not identified any safety signal or adverse drug reaction that is new, more frequent, or more severe for biosimilar products compared with their reference medicines.

The drug development of biosimilars is not confined to Europe but represents a worldwide phenomenon. Biosimilar products are available to patients in more than 60 countries around the world. At the end of 2014, we counted 53 biosimilars approved in all countries. However, it is very difficult to keep this number updated because it increases almost on a daily basis.

In the United States the first biosimilar (filgrastim-sdnz [ZARXIO, Sandoz] clinically comparable to Neupogen [Amgen, Thousand Oaks, Calif] and with the same 5 indications) was approved by the FDA in March 2015 according to the Biologics Price Competition and Innovation Act passed by the Congress in 2009 as part of the Affordable Care Act.[7] This authorized the FDA to oversee an "abbreviated pathway" for approval of biosimilars, which stimulated a high number of applications currently at different stages of the marketing authorization process. One of the major topics of debate in the United States at the moment is whether biosimilars should have the same International Nonproprietary Name as the originator and criteria for an interchangeable designation. Substitution of the originators with the biosimilar products (interchangeability) is in fact a general matter of extensive discussion that mainly depends on national decisions.[8]

In Canada, regulatory and clinical guidelines of biosimilars, named in this country subsequent entry biologics, have been recently reviewed, also focusing on requirements for extrapolation (the granting of indication approved for the reference biological to the subsequent entry biologic without conducting clinical trials for that indication).[9]

In Argentina, Cuba, and Mexico copies of biologics were not originally registered as biosimilars because in the 1980s, there were no patent laws in Latin American countries. When Venezuela and Brazil first and then other countries (Mexico in