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Editorial

Biosimilar Drugs, Myths and Reality☆

Mitos y realidades sobre los medicamentos biosimilares

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The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency in June 2013 issued a positive opinion for the approval of Remsima® and Inflectra®, 2 biosimilar Remicade analogs®. Numerous opinions, news and articles in scientific journals and in what is called the trade press have been published over the last year. However, that same month of June, the Spanish Agency for Medicines and Health Products authorized 107 generics with hardly any notice. By the time the positive CHMP opinion on Remsima® and Inflectra® was issued, there were 13 more biosimilar medicines approved by the European Commission. None of these generated as much excitement as the release of the 2 biosimilars. What has motivated, in this past year, the increased news and meetings on biosimilar medicines?

In 2008, 3 of the 10 top-selling drugs in Europe were biologics. Five years later, 8 of the 10 top-selling drugs in Europe are biologics. At the top of them, we find the monoclonal antibodies used in rheumatology, dermatology, inflammatory bowel disease and various cancers. Virtually all of them will lose exclusivity by 2020. A market that, overall, is in the ballpark of 73 billion U.S. dollars (55 000 million euros) according to IMS.[1] This has generated a growing interest in the availability of biosimilars and, in fact, there are 39 biosimilar drugs in various stages of development at this time. But also, as expected, some interest in delaying such availability. This debate often mixes arguments and scientific uncertainties, regulatory positions that necessarily evolve in the light of knowledge, budgetary items, points of interest and disinterested views, ultimately, myths and realities on which we will try to shed some light.

All medications to be approved by drug agencies need to demonstrate quality, safety and efficacy. When the drug is new, this demonstration requires a full development (clinical trials phase I, phase II and phase III).When the drug is known, after the expiry of the periods of patent and data protection to which they are entitled, the development of new drugs with the same active ingredient can rely on the known data from the innovator. For the active ingredients of chemical synthesis, these drugs are called generics and clinical development is sufficient to demonstrate, through bioequivalence studies, that they reach the same plasma concentrations as their innovative counterparts and assume that its efficacy and safety is the same. It is this abbreviated development, and not the application of suboptimal quality standards, which allows them to be marketed at a cheaper price. Although initially they were also the focus of similar scrutiny, no one responsibly disputes today the existence of generic medications.

For biological medicinal products, the comparability exercise is different.[2] A biological medicinal product is a drug that contains one or more active principles produced or derived from a biological source. The active principles of biological medicines are larger and more complex than those of non-biological drugs. It is said that in this case "the process (manufacturing) is the product", trying to indicate that it is the complete combination of data quality, preclinical and clinical results that constitute an individual product. That is why both their complexity and the way they are manufactured may result in some degree of variability in the molecules of the same active ingredient, especially in different batches of the same drug. To get an idea, an innovative drug that has introduced variations in the manufacturing process is required to demonstrate comparability to itself over time to maintain its permits.

A biosimilar are biological drugs that are developed to be similar to other biological drugs that are already authorized and, therefore, base part of their development on what is known as the innovator.[3] A biosimilar drug is not the same as a generic drug, as these drugs have simpler structures and it is easier to ensure that they are identical to that of the reference medicine. However, the active substance of a biosimilar and the reference product is the same biological substance, although there may be minor differences due to their complex nature and mechanisms of production. It should be stressed that this variability exists for both innovative biologics and their biosimilars.

In some emerging countries with laxer regulatory systems than Europe, there has been a proliferation of innovative biological medicines, which has been exploited by opponents of biosimilars to attack those who have been authorized in a more stable and regulated environment. We have all heard of the threat posed by the "Chinese enbrel" (oncologists' Chinese trastuzumab'). It is important to note that we ar4e referring here to such products, but rather of those same authorized products and with those same rules that were applied at the time (and are continuing) to innovative medicines. And manufactured and implanted in the EU by solvent laboratories. Therefore, for a biosimilar drug to be authorized, it has to be proven that the variability inherent

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in any biological medicinal product and other innovative drugs has no different effects on the safety and efficacy of the product. When the biosimilar product is authorized, it is generally used at the same dose and to treat the same diseases as the innovative referenced. If there are special precautions with respect to the innovative drug, these are also applicable to the biosimilar. The requirements for the approval of biosimilars are very strict[4–6] and their own development has made their release much slower than that of other similar innovative medicines.

Therefore, when already authorized, drug agencies ensure that between the innovator and biosimilar drug there are no significant differences in quality, safety or efficacy. In this sense, there is no advantage of one over the other. Obviously, with an abbreviated development, biosimilars can be priced lower than the innovator, and this is the main advantage, to allow price competition which, in most cases, does not occur with drugs that undergo full development.

Once these and some other questions about biosimilars are solved, the biggest stumbling blocks are interchangeability and substitution. What happens to patients who are already treated with a biologic and a biosimilar appears on the market? This is not exactly as a generic, which reasonably assures interchangeability and replacement. Biological drugs are on the list of non-substitutable drugs. Does this mean that you cannot switch from one to another? Not exactly. In fact, doctors change from one biologic to another without any detected associated problems. It happens that this must be done case by case and always with regard to the patient. There is no experience or data on the consequences of abrupt changes or substitutions of some other biological drugs in short periods. However, it is expected that a number of patients with rheumatoid arthritis change treatments over a period of 2 years, ever more toward a biological treatment. This may be, for example, an opportunity for the introduction of biosimilars. At this point common sense must prevail and collaborative work between the different actors within hospitals so that together, on one the hand, do not lose the advantage posed by the development of biosimilars but, on the other, do not generate a replacement policy that may jeopardize the safety and efficacy of the drugs or calls into question the consistency of the system.

The pharmaceuticals sector is a highly regulated industry. The regulation is also as sophisticated as the type of drug produced. In this sense, one can only say that when agencies authorize a drug it is because they guarantee quality, safety and efficacy in the conditions set on the data sheet. The system also has mechanisms to detect and correct problems. Repeating polemics and discussions that ensued with the appearance of generic drugs in the case of biosimilars now would be a mistake for everyone. What is necessary is that patients and professionals better know and understand the rules.

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