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OPINION ARTICLE

Biosimilars or Follow-on Biologics in Dermatology

Biosimilares o biosecuelas en Dermatología

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The first generation of biologics produced using recombinant technology appeared in the 1980s, and the patents that protect them are about to expire, despite the fact that some were granted extensions. As is the case with conventional small-molecule drugs, the expiry of patents opens the market to generics, whose main advantage is their low cost, a feature much sought after by insurance companies, governments, and, of course, patients, especially when they pay for the drugs out of their own pocket. The patents for erythropoietin, somatropin, and some beta interferons have already expired. In the field of dermatology, it is worth remembering that those for Humira, Enbrel, and Remicade run out in 2016, 2012, and 2018, respectively.[1]

These biological molecules are complex in that we must take into account several factors: amino acid sequence, tertiary structure, glycosylation (which can modify their efficacy and even render them toxic), and impurities arising from the production process (which can affect immunogenicity, efficacy, and the adverse effects profile when compared with the original molecule). Consequently, the equivalents of generics are known as biosimilars or follow-on biologics. As the clinical properties of these agents depend to a large extent on the production process—surrounded by a veil of secrecy in the absence of a licensing agreement—the classic notion of bioequivalence cannot be applied to generics. Although the requisite laboratory and validation technology to establish biosimilarity is available, comparative clinical trials would be necessary to demonstrate that the efficacy and safety profile of an agent was similar to that of the original biologic.

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In 2003, the European Medicines Agency (EMEA) pioneered the development of guidelines enabling biosimilars to be evaluated and approved. In 2007 (the year the EMEA recommended approval of 3 biosimilar versions of recombinant erythropoietin), the United States Senate Committee on Health, Education, Labor, and Pensions approved legislation permitting the development of guidelines by the United States Food and Drug Administration (FDA). In the federal budget for 2010 (presented in February and passed in April 2009), President Obama included plans for the development of guidelines on fast-track approval of biosimilars. The following week, the shares of the leading biotechnology companies Biogen Idec, Amgen, Celgene, and Genzyme fell by between 12% and 24%,[2] and numerous job offers to be cover the summer of 2009 appeared on the web site of the Center for Biologics Evaluation and Research of the FDA.[3]

In June 2009, the Federal Trade Commission published a report refuting the arguments of the biologics industry in favor of maintaining exclusive marketing rights for at least 14 years. (It must be borne in mind that the owners of the original product will maintain a substantial share of the market after the introduction of a biosimilar, since the drugs will not be freely interchangeable after their introduction.) The Commission preferred that the—ever scarce—funding for research go to developing new medicines rather than confirming the clinical efficacy and safety data of existing drugs. At present, the United States legislative branch is evaluating 2 legal instruments that set the exclusivity limit at 5 years (Waxman bill) and 12 years (Pathway for Biosimilars Act). The Obama government proposes a "generous compromise" (7 years) that would achieve the objective of reforming the United States health system by reducing costs.[4] Furthermore, in June 2009, a bill was

passed (H.R. 1706) prohibiting the practice of compensating generics producers (by the owners of the proprietary name) to delay the launch of their products. A possible negative effect of this legislation is that it could make it difficult to reach out-of-court settlements in actions filed by the owner of the original biologic or drug.[5]

Sooner rather than later, the FDA will establish guidelines for the approval of biosimilars. These will probably require the performance of comparative clinical trials to demonstrate similarity in efficacy and safety, and it seems highly unlikely that it will propose automatic substitution by the pharmacy office (as is the case in some countries in the European Union). Price will be an important driver in this market, although without compromising physicians' freedom to prescribe.

Despite regulatory delays from the FDA and opposition from the owners of the rights to the original molecules, the field of biosimilars is currently the most promising and fastest-developing area in the pharmaceutical industry. The driving force behind this development is the success of monoclonal antibodies, which, at the end of 2007, accounted for sales of around 26 000 million US dollars in the 7 main markets of the world. And this figure could be double in 2013.[6] Biologics currently account for 10% of drug sales, with an annual growth rate (in 2007) of 15%,[7] and the development of biosimilars represents an excellent commercial opportunity that would benefit the same large companies—or their subsidiaries—that introduced the original biologics, since they already have in place the necessary technology, production plants, and sales networks.

At present, China and India are free ports for the production of low-cost drugs (copies or generics), and they are the natural location to develop biosimilars. In fact, for some time now, the Chinese company 3Sbio[8] has been producing for its home market a version of Amgen's erythropoietin—which Amgen never bothered registering in China for some inexplicable reason—under the name EPIAO, with the approval of the Chinese equivalent of the FDA. The company's portfolio also includes a recombinant interferon alpha-2a (Intefen) and a recombinant interleukin 2 (Inleusin). Even at a very low price, the profit margin of these products is approximately 90%.[9] However, despite having the advantage of a huge market, China is disadvantaged by its poor reputation in terms of quality control (eg, toxic toys, melamine in food products). The potential advantage of India is that it is home to larger companies, such as Ranbaxy and Dr. Reddy's, which are used to negotiating with the EMEA and the FDA and are prepared to meet the clinical development costs and perform the necessary trials to obtain final approval for a biosimilar. Although the cost of producing biologics is high, huge factories are not necessary; a few bioreactors are all it takes, and suitably trained technical staff are available. Chris Zhisheng Chen—the operations manager of Shanghai Celgen Bio-Pharmaceutical Co. Ltd, whose main product is a biosimilar of etanercept—obtained a doctorate in chemical engineering from the University of Delaware. He then worked for 5 years as Manager of Bioprocess Technology at Merck and for 3 years as Director of Production, Biotechnology at Lilly, before returning to China.[10] The development of this biosimilar of etanercept is an exemplary case that was discussed at a conference in September 2009 in Beijing,[11] at which the technical aspects of biopharmacology (cell culture lines, culture media, analytical and quality control, regulatory matters) were covered. The conference was attended by representatives from the leading pharmaceutical companies (Merck, Pfizer, Bayer Healthcare), which may be thinking of outsourcing future production of biosimilars. Given that there are more than 40 companies developing biosimilars in the United States alone, and that the main players include Teva, Sandoz, Mylan, Momenta, and even giants such as Merck and Pfizer (who have just bought Schering-Plough and Wyeth, respectively), the notion of market exclusivity does not seem to be very popular, not even among at least part of the pharmaceutical industry.

Biosimilars came onto the European market in 2006 and now include various proteins (eg, somatropin, erythropoietin, and various colony growth factors), with a 20%-30% discount on the original molecule. Although there is no biosimilar of a monoclonal antibody on the European market today, the European Commission has given the go-ahead for the formation of a joint venture between Teva (a specialist in generics with an interest in the biosimilars market) and Lonza (a biotechnology company that produces reactors, media, and other cell culture materials on request), and there is talk that their portfolio would include etanercept and rituximab.[12]

In October 2005, the directive on similar biological medicinal products came into force.[13] This directive defines the applicable regulatory framework and guidelines for comparative studies in terms of quality, safety, and efficacy that determine the evaluation and final approval of a biosimilar. In principal, a biosimilar must have the same pharmaceutical form, strength, and route of administration as the reference biologic (previously authorized in the European Union). The directive on quality[14] develops the requisites for demonstrating comparability. The biosimilar is compared to the reference biologic by applying suitably validated analytical methods that make it possible to establish the physicochemical properties, biological activity, and purity and impurities of the biosimilar (even under stress conditions that can affect the stability of the product, taking into account degradation pathways and potential post-translation modifications). The directive admits the possibility of bioprocessing-related differences whose impact should be confirmed by appropriate studies (clinical or nonclinical) that are set out in the relevant directive.[15] Finally, the requisites for comparability with regard to immunogenicity are set out in the appropriate directive,[16] to which an appendix—currently being prepared—on monoclonal antibodies will be added.[17]

In summary, the development of biologics has engendered a new paradigm in our specialty and revolutionized the pharmaceutical industry: the "blockbusters" designed to provide a moderate benefit to a large part of the population have been replaced by biologics as the driver of marketing strategies. Furthermore, market forces and cost control during a period of recession are promoting the development of biosimilars, whose regulation was pioneered by the EMEA (the directives have been adopted in countries

such as Australia). The requirements for demonstrating biosimilarity in terms of quality, activity, efficacy, safety, and immunogenicity are strict, although they do make it possible to obtain biosimilars inexpensively. This will bring the therapeutic benefits of these drugs to a greater number of patients and will encourage innovative companies to allocate research resources to the study of new pathogenic pathways and disease mechanisms. Dermatologists will play an important role in the development of both new biologics and biosimilars, and we can consider ourselves extremely fortunate to be able to meet these new challenges in the course of our professional life.

Conflicts of Interest

The author declares no conflicts of interest.

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