Are we prepared to prescribe biosimilars?

Biodrugs are recombinant proteins used in the treatment of several diseases. Monoclonal autoantibodies and fusion proteins currently being used in the treatment of autoimmune diseases are examples of biodrugs. Contrary to synthetic molecules, with simpler structures and low molecular weight, which are obtained exclusively by chemical methods, biodrugs are very heterogeneous, more unstable compounds, with tridimensional structure and high molecular weight (100 to 1,000 times larger than synthetic molecules), obtained through complex methodologies that include from the initial production in genetically modified living cell organisms (bacteria, fungus, or mammal cells) to processing using fermentation and purification methods, among others.[1-4] It is well-known that the development of these molecules in the decade of 1980 revolutionized the way physicians treated their patients, especially those with diseases for which an effective treatment or even therapies were not yet available.

Synthetic drugs can be completely characterized by their atomic structure, more than by the processes used to obtain them and those characteristics allow the manufacturers, theoretically, to produce bioequivalent copies of original synthetic molecules in terms of mechanism of action, efficacy, safety, administration routes and quality, and, therefore, they can be characterized as generic drugs.[3,5] After bioequivalence is observed, commercialization of those substances is authorized, as a rule, after the same clinical trials performed with the original synthetic molecules have been carried out.

However, differently from inorganic drugs, the possibility of an identical copy of an innovative biodrug is not really possible. Those drugs that are called biosimilar are, in fact, an attempt to copy them because two independent cell lines used in the production cannot be considered identical.[6,7] Small distinctions between cell lines, at any stage of the manufacturing process of biomolecules and even in the form of patient administration , can result in a great difference regarding adverse effects (two biosimilar drugs can trigger different immunogenic answers in humans). Additionally, as a consequence of those differences, the substitution among biologicals (especially among innovative molecules and biosimilars) can have clinical consequences and even generate public health problems.[7] This does not mean that biosimilars are not safe, considering that, as a rule, they are subject to an approval process, which require substantial additional data in relation to those required for generics by the regulating authorities.

The international nomenclature (International Nonproprietary Name – INN) currently used for synthetic molecules, which is based on well-defined and easily characterized molecular differences, does not seem appropriate for the use intended to the nomenclature of molecules obtained by biotechnological methods, as the different available methods of structure analysis are not sensitive when applied for the characterization of biomolecules. It would be time to rethink a new specific and independent nomenclature for biomolecules.[8,9]

The inadvertent substitution of an innovative molecule by a biosimilar is another problem, considering this ambiguity regarding the name of biodrugs, especially considering that a distinct trustworthy pharmacovigilance system is necessary for these compounds. A valuable lesson regarding the way that small changes in the manufacturing process among biologicalswas given by epoetins. Between 1998 and 2001, a mild increase in the number of cases of pure red cell aplasia (PRCA) after treatment with subcutaneous epoetins, a very rare complication, was observed. Epoetins have been used to treat anemia associated with renal failure, HIV, cancer, and preoperative conditions. The cases described seemed to be related to the use of EPREX® (alpha epoetin; Johnson & Johnson). The increase in this incidence coincided with the change of polysorbate 80 of the human albumin in the formulation of the product.[2] In addition to these cases, small traces of contaminants or impurities have been implicated in a higher incidence of development of antibodies produced by insulin and growth hormone biosimilars.

The process of formulation of biosimilar drugs is critical for the stability of the protein molecule and maintenance of its structural integrity (preventing, for instance, the formation of aggregates) and also for its biological activity, which goes from

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Correspondence to: Ricardo Fuller. Av. Brigadeiro Luiz Antonio, 2.466, conjs. 93-94. São Paulo – SP – Brazil. CEP 01402-000.

the type of administration to the final use by the patient. Both companies that manufacture biosimilar and those that originated the innovative molecules should acknowledge those differences clearly and publicly, as well as any possible harmful effects caused by them, in addition to the need for different nomenclature or prescription systems, uniting efforts to ensure that the distinction be made among those substance in all phases (prescription, dispensation, and administration).[2,4]

Patents of many innovative biodrugs are expiring and this has generated a legitimate opportunity for several manufacturers to develop biosimilars. In Brazil, as well as in other nations, in the next few months the opportunity for the introduction of biosimilar drugs of ENBREL® (etanercept; Pfizer-Wyeth), followed by MABTHERA® (rituximab; Roche), two known drugs that are part of the therapeutic arsenal in rheumatology and other clinical specialties, will appear. Rationally, we should recognize that the opportunity to use biosimilars will come for all immunobiologicals of which patents expire.[10]

The problem related to the prescription of biosimilars is complex and call our attention! European regulating authorities recognized the fact that a specific legislation for the approval of biosimilars was necessary and, in 2004, the EMEA (European Medicines Agency) determined a specific set of rules.[11] In accordance with this legislation, until the beginning of last year more than 10 biosimilars had been approved by the European Union. On the other hand, in the greatest market of biologicals in the world, the USA, biosimilars are recognized as follow-on biologicals and the legislation pertinent to the approval of those products is still being debated, despite the effort of the American senate for a regulatory unification. Recently, the Barack Obama administration brought the debate back into public focus with its fight for the approval of the new health legislation. In Brazil, ANVISA adopted the technical regulation for authorizing registration, post-registration alterations and revalidation of the registration of biologicals through the Resolution of the Collegiate Board (RDC, from the Portuguese) number 315 of 2005. Concerned about the different diversification of immunobiologicals in the different nations, the World Health Organization, in Geneva, is finalizing a new group of guidelines for similar biotherapeutic agents. It is hoped that those documents prepared by committees consisting of specialists on biological standardization can circulate among national regulatory agencies, manufacturers, and other interested parts between 2010 and 2011.[9,12]

Why have biosimilars attracted the interest of public and private financial agents all over the world? Due to the fact that they offer a potential reduction of 30% in the costs of innovative products for health systems.[10] We, health care professionals, should understand that based on this economic-financial question, the manufacturing of biosimilars will continue and it should occupy a good proportion of the market of innovative molecules.

We hope that governments use clear scientific justifications to support the authorization of biosimilars: in addition to the analytical evaluation in relation to the reference product, hard clinical evaluations should be undertaken. It seems rational that comparisons among routes of administration and other efficacy parameters should also be scientifically evaluated in clinical studies.

Finally, our role as prescribing physicians assumes great importance, as the exchange between innovative molecules and biosimilars is our final responsibility, as well as our being capable of promptly communicating the loss of efficacy or signs that indicate differences in immunogenicity.[13] The safe application of biologicals depends on their informed and appropriate use by health care professionals.

Valderilio Feijó Azevedo
Rheumatology Professor of UFPR, Master's Degree and PhD Student in Health Sciences, and student at the Biotechnology Specialization Course of PUC-PR.

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