

Biosimilars require scientifically reliable comparative clinical data

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In Brazil, the Law 9787 of February 10, 1999, authorized the commercialization by any pharmaceutical company of drugs, whose patent protection expired, in a standardized packaging with a yellow band and a 'G' of 'generic'. Generic drugs are usually cheaper, because, after the expiration of the patent protection of their brand-name pharmaceutical products, manufacturers need neither to invest in clinical research, nor to redo the trials that confirm the efficacy and safety of a certain drug. Such costs are inherent to certain phases of the process of research and discovery of new pharmaceutical drugs, and have already been conducted by the innovator company that had first obtained patent on a certain drug. Thus, manufacturers of generic drugs can sell their copies with the same quality of the brand-name pharmaceutical product at a lower price. However, biological drugs differ between themselves regarding complexity and cannot be approved in the same way of synthetic generic drugs or with the same criterion used for synthetic generics.¹

There is worldwide consensus that a similar biotherapeutic product is a biopharmaceutical product approved via a regulatory pathway, which comprises biological and clinical comparison with the brand-name product counterpart, in addition to a strict assessment of its immunogenic potential.² These requirements for a biological molecule to be named 'similar biotherapeutic product' is included in the World Health Organization (WHO) guidelines on evaluation of similar biotherapeutic products, and are considered the minimum conditions required for approval for market and selling.^{2,3}

Similarly to other emerging countries, from the economic viewpoint, Brazil has a promising market of similar biotherapeutic products to manufacturers and/or traders of copies, patients and payers, including the Federal Government. However, the approval for marketing and selling similar biotherapeutic products, unlike generic drugs, without the conduction of quality clinical trials, represents a real threat to patients. The Brazilian Sanitary Surveillance Agency (ANVISA) has established a review of its previous normalization to approve similar

biotherapeutic products by use of the RDC 55, published at the end of 2010.⁴ However, that normalization diverges in certain aspects from the WHO guidelines, particularly in establishing two regulatory pathways for approval, individual and comparative, in the extrapolation of therapeutic indications and in differences in the emphasis given to the design and statistical considerations of the trials; nevertheless, the practical application of the latter has not yet been completely clarified by that agency to the scientific community.⁵

An interesting exercise recently published in the medical literature, and conducted in a meeting sponsored by the WHO in Seoul, South Korea, illustrates the relevance of the need for a case-to-case approach when comparing clinical data between similar biotherapeutic products and their brand-name pharmaceutical counterparts.⁶ That is the only way to ensure the adequate efficacy and safety of similar biotherapeutic products to any studied indication.

The fact that small biochemical and biological differences might cause significant clinical differences makes us believe that one biosimilar product must at least be as effective and safe as its brand-name pharmaceutical counterpart. Comparative randomized clinical trials are currently considered the best experimental design to assess treatment-related questions.

In a phase 3 study, a similar biotherapeutic product can be assessed by use of statistical designs, such as the equivalence and non-inferiority approaches comparing them with controls. The former has the greatest affinity with the nature of the biosimilarity process (to ensure that a similar biotherapeutic product is neither more nor less effective than a brand-name pharmaceutical product counterpart at the same dose and for the same route of administration).⁷ Non-inferiority studies are justified and accepted mainly when the innovative product already has a large safety margin, and they are aimed at determining whether the similar biotherapeutic product is at least as effective as its brand-name pharmaceutical product counterpart, or even a little less effective, but within a certain

pre-established limit, that is, within an acceptable range.⁸ In addition, one copy might have a better efficacy profile, above that range, but the non-inferiority result will be equally valid. Theoretically, a similar biotherapeutic product could be better assessed by use of equivalence studies, which are more restrict, implying that neither better nor worse results should exist within the pre-established range. The non-inferiority margin is based on previous studies performed with the brand-name pharmaceutical product counterpart, preferably in comparison with a placebo.

It is worth noting that in the non-inferiority study, the populations studied and the outcomes should be equal to those of the study providing the characteristics of the brand-name pharmaceutical product counterpart. Superiority studies, as shown in Figure 1, are not meant to comparison between biological innovations and copies, but might be used to demonstrate the better efficacy profile of molecules known as biobetters. Another important aspect relates to the size of the sample that should be included in the comparative study between an innovation and its copy. That sample size will depend mainly on the value stipulated for the non-inferiority margin and data variability.⁹ Very wide non-inferiority or equivalence margins usually require small sample sizes, while narrower margins require a larger number of patients. Unfortunately, so far the sample sizes of non-inferiority or equivalence studies involving similar biotherapeutic products have been very small. In addition, it is worth noting that occasional losses of patients per group in a study, mainly due to flaws in the interpretation of tests and patient's withdrawal, should be replaced to maintain the statistical power of the project. In Brazil, copies of recombinant erythropoietin have been approved after an open study with 25 patients in phase 1–2a studies.¹⁰ Studies like those would not be adequate for the current approval of copies of fusion proteins or monoclonal antibodies, whose patents expire.

The choice of a clinical trial design depends on several factors, and the specific design selected for a particular trial should be explicitly justified in the protocol of that trial. The selection of the endpoints of primary efficacy and of the statistical design of the main study, as well as the calculation of the appropriate sample size to ensure statistical power, is a multi-step process. To be properly assessed, that process

requires clear understanding of the comparability margins (sometimes called comparability limits or, simply, margins) for a certain endpoint, which ultimately translates better efficacy. According to the WHO, the selected margin should represent the largest difference in efficacy/safety that matters in clinical practice.

Similarly, regarding the treatment of individuals with rheumatoid arthritis, only margins properly defined to detect significant differences between a certain anti-TNF biosimilar and its brand-name pharmaceutical product counterpart, based on the efficacy measured by the impact of both treatments on the ACR20 index, could be accepted. By definition, any difference in result contained within that variation would have no clinical relevance. By nature, the comparability margins for a certain endpoint result from clinical reasoning, being frequently neither well established nor universally accepted. Thus, the choice of the sample size should be well justified by the sponsors of the study, being usually a combination of the opinion of experts and previously published analyses.

In addition, ANVISA representatives should also agree with those margins before the study is initiated. Thus, it is understandable that experts of the Brazilian Society of Rheumatology, with a large experience in managing patients with rheumatoid arthritis and spondyloarthritis, be previously consulted by the sponsors of the study to provide an opinion about and agree on the size of those margins, in cases in which the endpoints are related to rheumatic disorders. The combination should not be based on 'guesses', requiring a deep search in the literature about the most impacting clinical outcomes related to the current treatment of rheumatic disorders.

The scientific community of Brazilian rheumatology waits for the results of high-quality clinical trials developed by manufacturers responsible for new biosimilars of biological molecules used in their clinical practice.

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