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Opinion of some Brazilian rheumatologists about biosimilars

Due to the recent expiration of patents of some biologics, studies have been expected to produce alternative versions of those drugs, called biosimilars. The manufacturers of biosimilars will not have access to the manufacturing processes of innovative biologics because such knowledge is exlusive property of innovative companies. Thus, the precise replication of any protein is impossible, in contrast to what happens with the production of generic drugs, which small chemical molecules are identical to the molecules of the original drugs, and which analysis requirements are only based on their chemical composition.

In Brazil, similarly to what already happens in other countries, the next months will witness the opportunity of entrance into the Brazilian market of ENBREL® (etanercept; Pfizer-Wyeth) and MABTHERA® (rituximab; Roche) biosimilars, two known medications that are part of the therapeutic arsenal of rheumatology and other clinical specialties.[1] Like all biologics, the main problem related to the safety of a biosimilar is its immunogenicity. The immunogenicity and efficacy of a biosimilar product can only be properly evaluated from strict clinical trials performed before its approval and through a pharmacovigilance system established after the product commercialization. The entrance in the Brazilian market of biosimilars of the molecules currently prescribed by rheumatologists, known as third-generation biological proteins, requires our proper education and information spread in a transparent and non-biased way, so that the correct decisions on prescribing those drugs are taken.

To objectively evaluate the basic knowledge about the major medical aspects related to biosimilars, a questionnaire was applied to 200 rheumatologists (doctors and resident doctors) during the XXVIII Brazilian Congress of Rheumatology, held at the city of Porto Alegre, from September 18th to 22nd 2010. Such questionnaire consisted of seven multiple-choice questions about the definition of biosimilars, the biotechnological aspects of their production, and the performance of clinical trials related to biocomparability, immunogenicity, pharmacovigilance, and national regulatory aspects. The questionnaire was applied by two medical students of the Universidade Federal do Paraná (UFPR), and each professional had three minutes to fill it in (around 25 seconds per question). The professionals were interviewed in the corridors of the event during the breaks of the academic sessions, and most of them were standing while answering the questions. The size of the sample was randomly defined, considering that it should represent as much as possible the universe of over 1,000 participants in the event. The interviewees did not receive any instruction on how to complete the questionnaire, except for the specification of the time limit and the possibility of choosing more than one answer in each question.

Of the 200 questionnaires applied, 95% were answered and 5% were not returned to the interviewees, and, thus, 189 questionnaires were available for subsequent analysis (Table 1).

Table 1
Questionnaire about biosimilars

1	***Do you know what biosimilars are?***		
	YES	**67%**	(114)
	NO	**33%**	(56)
2	***In case of an affi rmative answer, choose an item that adjusts to your concept of biosimilars:***		
	A biologic that demontrates bioequivalence with the original biodrug and has all preclinical and clinical trials equal to those already performed with the original biodrug. Besides, when approved, it already has a well-defi ned immunogenicity	**34%**	(45)
	A biologic that demonstrates bioequivalence with an original biodrug and does not need clinical trials to be commercialized	**27%**	(35)
	A molecule equal to that of the original biologic but of lower production cost	**20%**	(27)
	An attempt to copy an innovative biodrug and will never be equal to it	**11%**	(14)
	A generic biologic of an already commercialized biodrug	**8%**	(11)

Continue

Table 1
Questionnaire about biosimilars (*Cont.*)

3	***Do you agree with the information that there are already biosimilars in the Brazilian market?***		
	NO	**64%**	(107)
	YES	**36%**	(60)
4	***Are you familiar to RDC 315?***		
	NO	**95%**	(145)
	YES	**5%**	(8)
5	***In your opinion, what are the major problems related to the approval of biosimilars in our country? More than one item can be pointed.***		
	Bioequivalence tests	**19%**	(125)
	Safety	**18%**	(118)
	Bioefficacy	**16%**	(108)
	Assurance that phase III clinical trials will be performed in a sample of the Brazilian population	**10%**	(65)
	Good manufacturing practices and high reputation of the producer	**10%**	(64)
	Maintenance of an adequate national system of pharmacovigilance specific to biosimilars	**9%**	(58)
	Transparency of the Brazilian regulatory system	**9%**	(58)
	Immunogenicity	**7%**	(49)
	Name of the biosimilar equal to that of the innovative biologic	**3%**	(18)
6	***Identify the major problems after the commercialization of a biosimilar.***		
	Maintenance of an adequate national system of pharmacovigilance specific to the biosimilar	**24%**	(77)
	Therapeutic failure	**23%**	(74)
	Efficacy	**23%**	(72)
	Interchangeability between the innovative biologic and the biosimilar	**17%**	(55)
	Immunogenicity	**12%**	(39)
7	***In your opinion, what are the advantages of a biosimilar?***		
	Lower price	**67%**	(130)
	Commercialization approved with initial indication including all diseases previously approved for the use of the innovative biodrug	**16%**	(32)
	Administration route different from that of the original biodrug	**3%**	(6)
	Lower therapeutic dose	**1%**	(2)
	There are no advantages	**13%**	(25)

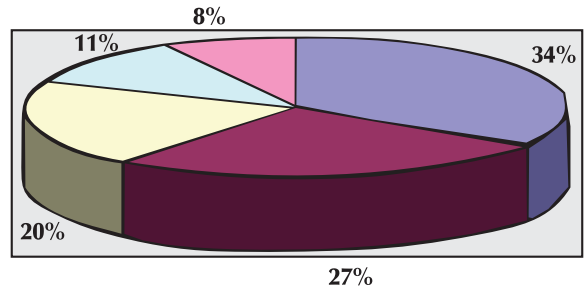
Eighty-nine interviewees were female and 111 were male. Thirty-six resident doctors (18%) answered the questionnaire. One hundred and fourteen interviewees (60%) reported knowing what biosimilars were, 56 (30%) denied knowing the subject, and 19 (10%) did not answer the question (Figure 1). The interviewees were instructed to complete the questionnaire only if the answer to the first question was affirmative. Nevertheless, regardless of answering affirmatively or negatively to the first question, most interviewees (78%) completed the questionnaire.

Only 70% of the interviewees have answered to the question about the definition of the most appropriate concept of a biosimilar. Of those answering that question, 34% chose the item that defined a biosimilar as a biologic that demontrates bioequivalence with the original biodrug, has all preclinical and clinical trials equal to those already performed with the original biodrug, and that, when approved, already has a well-defined immunogenicity; 27% answered that a biosimilar is a biologic that demonstrates bioequivalence with an original biodrug and does not need clinical trials to be commercialized; 20% anwered that a biosimilar is a molecule equal to that of the original biologic, but of lower production cost. Only 11% answered that biosimilars are an attempt to copy innovative biodrugs and will never be equal to them, while 8% of the interviewees answered that a biosimilar is a generic biologic of an already commercialized biodrug (Figure 1).

Around one third of the interviewees (32%) agreed that biosimilars already exist in the Brazilian market, while more than half (56%) did not agree with that statement, and 12% of the interviewees did not answer that question. When asked if they knew RDC 135, only 4% answered affirmatively, 77% answered negatively, and 19% did not answer the question.

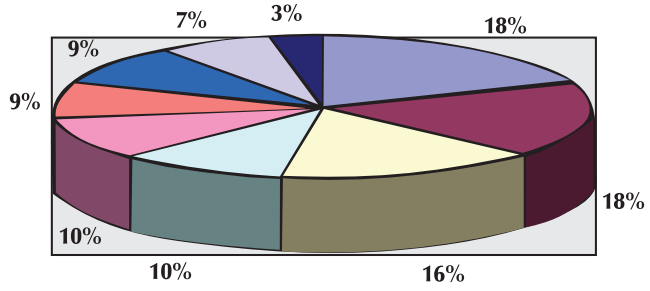
The interviewees also had to point out the major problems related to the approval of biosimilars in Brazil (phase prior to commercialization), and they could choose more than one alternative. Most interviewees (19%) pointed out that the limitation of bioequivalence tests is the major problem; 18% pointed out the safety matter; 16% indicated the establishment of bioefficacy; 10% indicated good manufacturing practices and the high reputation of the manufacturer as fundamental requirements; 10% pointed out the assurance that phase III clinical trials be performed in a sample of the Brazilian population; only 9% indicated the lack of transparency in the approval process of biosimilars by the Brazilian regulatory system as a problem; 9% indicated the importance of maintaining an adequate national system of pharmacovigilance specific for biosimilars; 7% pointed out the immunogenicity problem; and 3% indicated as the major problem the fact that a biosimilar has the same name of an innovative biologic (Figure 2).

Regarding the questions related to the major problems after commercialization of the biosimilars, 24% of the interviewees



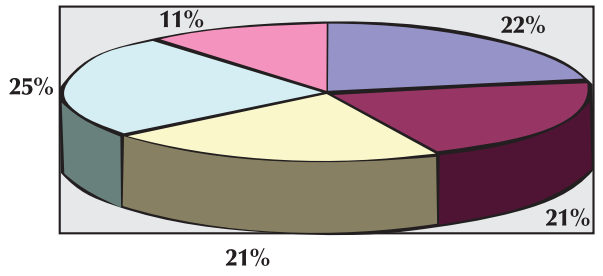
- A biologic that demontrates bioequivalence with the original biodrug, has all preclinical and clinical trials equal to those already performed with the original biodrug, and that, when approved, already has a well-defined immunogenicity;
- A biologic that demonstrates bioequivalence with an original biodrug and does not need clinical trials to be commercialized;
- A molecule equal to that of an original biologic, but of lower production cost;
- An attempt to copy an innovative biodrug and that will never be equal to it;
- A generic biologic of an already commercialized biodrug.

Figure 1
Concepts on biosimilars.



- Bioequivalence tests;
- Safety;
- Bioefficacy;
- Assurance that phase III clinical trials be performed in a sample of the Brazilian population;
- Good manufacturing practices and high reputation of the producer;
- Maintenance of an adequate national system of pharmacovigilance specific to the biosimilar;
- Transparency of the Brazilian regulatory system;
- Immunogenicity;
- Name of the biosimilar equal to that of the innovative biologic.

Figure 2
Major problems related to the approval of biosimilars in Brazil.



- Maintenance of an adequate national system of pharmacovigilance specific to the biosimilar;
- Therapeutic failure;
- Efficacy;
- Interchangeability between the innovative biologic and the biosimilar;
- Immunogenicity.

Figure 3
Major problems after commercialization of biosimilars.

stated that the creation and maintenance of an adequate national system of pharmacovigilance specific to biosimilars was fundamental; 23% pointed out the problem of efficacy; other 23% indicated the problem of therapeutic failure; 17% indicated the problem of interchangeability between the innovative biologic and the biosimilar; and 12% indicated the immunogenicity problem (Figure 3).

Regarding the advantages provided by the entrance of biosimilars in the Brazilian market, a question in which more than one alternative could be indicated, the most chosen one was the smallest price, accounting for 67% of the answers; 16% of the interviewees pointed out as advantageous the fact that the commercialization be approved with initial indication including all diseases previously approved for the use of the

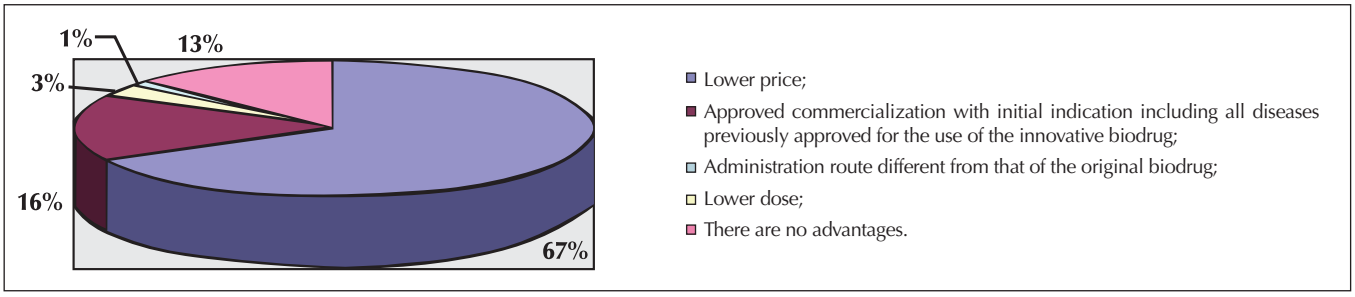


Figure 4
Advantages of the entrance of biosimilars in the Brazilian market.

innovative biodrug; 3% answered as advantageous the fact that a biosimilar has a route of administration different from that of the original; and 1% chose the fact that the biosimilar has a smaller therapeutic dose. Finally, 13% of the interviewees, on choosing the last item, believe there is no advantage in commercializing biosimilars (Figure 4).

At first, we understand that the use of simple and easily applicable questionnaires, like the one suggested, may contribute to mapping the current phase of the knowledge of rheumatologists and other health professionals about the main issues involved in the approval processes of the use of biosimilars for treating autoimmune diseases, in addition to encouraging other productions about that subject in other countries.

One third of the professionals reported not being familiar to what biosimilars were, what seems reasonable, since the subject is relatively new to rheumatologists, although biosimilars, specially insulins and erythropoietins, are already available in the Brazilian market.

The loss of patent protection for the biologics used in the treatment of rheumatic diseases in Brazil will begin this year. The Brazilian Unified Health System (SUS – from Portuguese, *Sistema Único de Sáude*) is the major buyer of those molecules, and the protocols of the Clinical and Therapeutic Guidelines of the Brazilian Ministry of Health include all TNF inhibitors for the treatment of patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis.

Most interviewees who stated knowing what biosimilars were answered that the immunogenicity of those molecules is perfectly known on the occasion of their approval, and, of those interviewees, only a small number pointed out the immunogenicity matter as one of the major problems related to their approval. Furthermore, most interviewees indicated the low price as an undeniable advantage of biosimilars. Indeed, many authors have stated that biosimilars enable a less expensive medical prescription, which may result in reduced health costs.[2,3] They have also claimed that those molecules may provide the population with greater access to unconventional innovative therapies due to their low added value and lower cost compared with those of innovative biodrugs. However, it is important to emphasize that this promise may not be fulfilled in case there is no total transparency of all parties involved in both the regulation and approval processes of those therapies. It is known that, taking into account the complexity of the biomolecules and their intricate manufacturing process, the structure of biosimilars will not be identical to that of the original biologics, and, therefore, their efficacy and safety profiles should be extensively discussed among prescribing doctors. Moreover, rheumatologists should acknowledge that pharmacovigilance measures that ensure equivalence in the safety of biosimilars as compared with the original biologics are indispensable to patients' safety.

The processes involved in manufacturing biologic drugs easily demonstrate the complexity of the production of these target-proteins from living cells, as any manufacture alteration may result in wrong acid-base quantities and emergence of glycosylation variants, causing conformational changes in these proteins, worsening their final functionality.[4] The process begins with DNA cloning by use of a vector, such as plasmid, and transference of the cloned DNA to a cell that will later express the desired protein. After this basic step, protein production, purification and validation will occur. The monoclonal antibodies and fusion proteins are recognized as third-generation biologics. The first generation is represented by biologics that were identical copies of the proteins produced by the human body, in other words, replacement proteins, such as recombinant insulin and blood factors. The second generation is represented by biologics developed as modified proteins or analogues, such as erythropoietins zeta and alpha.

Differently from generic drugs, biosimilars cannot fall into the same classification – two independent cell lines used in their production cannot be considered identical.[5] There are many examples showing that small alterations in the production process of biologics can lead to serious health problems.[6,7] Furthermore, it is clear that, although still being developed, the analytical methods currently employed to check similarity between highly complex molecules of high molecular weight, such as those of monoclonal antibodies and certain fusion proteins, are still limited.[4]

Only 4% of the interviewees who reported knowing what biosimilars were also claimed to know RDC 135, the major resolution for approval and commercialization of biologics in effect since 2005.[8] In 2010, Brazilian National Health Surveillance Agency (ANVISA) also established a public consultation, in which all sectors of the organized civil society could express their opinion on the subject. The revision of that resolution was concluded and the amendment (RDC55/10) was published at the end of the same year. Prescribing doctors should know at least the major aspects of that resolution, which defines conditions for registration of those biologics and the way their commercialization should be followed up in the Brazilian market.

Regarding the approval of a biosimilar, few professionals considered important that a biosimilar had a different nomenclature from that of its original model (innovative biologic). However, that has been the subject of intense discussion in the international scientific community, because the international nomenclature (INN – International Nonproprietary Name) is properly used for small and easily recognizable molecules, but has limited validity for more complex molecules. Moreover, well-established differences in this nomenclature can easily distinguish biosimilars from innovative biologics for the purpose of prescription exchange and pharmacovigilance follow-up.[9–11]

The fact that few professionals mentioned as an extra advantage of biosimilars the different routes of administration and/or dosages clearly demonstrates the total lack of knowledge on the subject. Most synthetic medications are orally ingested, while almost all biologics are subcutaneously or intravenously injected or even inhaled, because, being proteins, they are also very sensitive to enzymatic degradation in the gastrointestinal tract.[12] The concept of a biosimilar includes its use at the same dosages of the innovative product in efficacy tests, as well as its administration by the same introduction route.

It is obvious that doctors can only make decisions about the precription of biosimilars if they are sufficiently informed on the fundamental differences between these copy molecules and their original and innovative molecules. Any and all poorly founded decision may affect their patients' treatment. Considering biosimilars as new drugs with different structures from those of innovative biodrugs, it seems reasonable to expect different therapetic outcomes and adverse effects.

In general, this research evidences the lack of information about the subject and need for systematic discussions in Brazil and other countries, especially among rheumatologists, who prescribe third-generation biologics. Although those discussions have not been carried out with specialists of other areas who also prescribe biologics, we believe they should be encouraged particularly among dermatologists, oncologists, neurologists, nephrologists, endocrinologists and gastroenterologists.

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