# Biosimilars

*Biossimilares*

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## SUMMARY

Although common themes permeate the environment across continents and particular divergences as to how to proceed exist between different regulatory agencies, it seems that policies are still in flux. Not all polices will suffice to fit all dissimilar biologics, and these in place or being developed may, in turn, change to accommodate new or unexpected developments. Consideration for accelerated approval for those compounds that do not present complex questions should be considered.The regulatory agencies should be more forthcoming, the industry sector exercise social responsibility, and the public should have realistic expectations. Arq Bras Endocrinol Metab. 2011;55(8):669-70


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## RESUMO

Embora haja temas comuns no ambiente dos diferentes continentes e divergências particulares sobre como proceder entre diferentes agências regulatórias, parece que as decisões políticas ainda caminham. Nem todas as políticas serão suficientes para acomodar todos os diferentes produtos biológicos, e as políticas atuais ou em desenvolvimento podem, por sua vez, mudar para acomodar novos e inesperados desenvolvimentos. Deve-se considerar a aprovação mais rápida para aqueles compostos que não apresentem questões complexas. As agências regulatórias deveriam ser mais acessíveis, as indústrias deveriam exercitar sua responsabilidade social e o público deveria ter expectativas realísticas. Arq Bras Endocrinol Metab. 2011;55(8):669-70


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## HOPES

The development of recombinant technology made possible the synthesis of proteins and compounds that due to their complexity or cost synthetic chemistry was not able to provide. The improvement of these during the last 35 years has increased expectations that more compounds will be available and that the costs of those already in the market will decrease when product competition expands. These expectations have not materialized due to many valid scientific reasons, regulatory barriers and strong pressure from innovators that traditionally have tried to limit competition in the marketplace. This short assay will attempt to clarify some of the central issues pertaining to these issues.

A biosimilar product, as it names implies, is a recombinant product that mimics the pharmacological action of a previously existing product that when used affords analogous responses and comparable safety as the original one. The biosimilars may be produced using identical platforms or not (i.e. *E. coli vs.* a mammalian cell line or others) and the goal is that the chemical similarity would be identical to the copied product from the primary to the quaternary structures. Many steps such as the formulation also could differ but the desired final goal is that the biological activity will be alike.

## BARRIERS

In contrast to generic drugs where in most cases the chemical structure can be easily replicated and successfully synthesized, most biological products present structural complexities generating substantial barriers that limit our ability to properly ascertain bioequivalence, unless head to head clinical comparisons are made. The need of clinical studies appears to defeat the purpose of simply copying a product. After all these years of

experience with recombinant technology there is still a high level of insecurity in that the copied product will be as effective as the original and safe as well.

Why is this the case and is the level of uncertainty the same for all products?

Biologicals vary in complexity encompassing from cell therapies, small proteins and large proteins, complex proteins with and without post translational modifications (i.e. glycosylation), monoclonal antibodies, and others. All these require sophisticated platforms for their production and multiple other manufacturing steps that increase, in turn, the complexity; isolating the products from these systems also present barriers limiting sometimes the purity, an essential requirement, to have the desired end product. Systems may lead to aggregation of proteins of peptides and or the production of variants or isoforms that may alter the desired biological action of the required end-product. Additional concerns relate to potential contamination from the cell systems used, as well as pharmaceutical considerations related to formulations that may alter the bioavailability, half life, disposition, immunogenicity and others variables, rendering the desired beneficial effects unfulfilled or increasing the risks for adverse drug related events.

Many concerns regarding biosimilars have emerged but most have centered on the potential to trigger immunogenicity by these products. These issues could be divided into two groups. One relates to acute immune responses leading to the potential triggering from minute allergic reactions to anaphylactic responses. This could be expected also with no biological products. Other concerns relate to immune responses to contaminants and more importantly to the active moiety itself. Any reaction may have wide implications from blocking partially or completely the desired biological activity to the generation of antibodies without any clinical repercussions. The former, if serious, could potentially lead to grave outcomes and/or impose difficult medical managing decisions because patients will not be able to receive or respond to therapy.

## AVENUES FOR DEVELOPMENT

Different regulatory routes to allow for market access have been established in Europe and in the US. In addition, product class-specific guidelines have been developed in Europe where simple bio-equivalence is not sufficient to grant approval. Other variables such as equivalence margins (this mostly pertains to standards of statistic stringency) efficacy, safety and immunogenicity are also required. Finally monitoring on an ongoing basis after approval to continue to assess the benefit-risk ratio is mandatory.

The questions posed by the US regulators follow a similar path but there is also flexibility to exercise judgment in the developmental and approval process. The general goal is to decrease uncertainty. The underlying theme is to try to reach interchangeability, i.e. "that the same product is expected to produce the same clinical result in any given patient and that the risk associated with alternation of switching between the two products is no greater than that involved in continuing the use of the reference product." Currently in the US is attempting to develop standards to ensure that products meet these stringent requirements.

Are biosimilars important in pediatrics?

Considering that the first two products developed using recombinant technology were growth hormone and insulin, it becomes apparent why the availability of biosimilars of these two hormones could impact the access to treatment by reducing their costs. Many health care systems and children that currently cannot afford treatment due to cost will probably benefit from safe and effective products at reduced prices that biosimilars offer.

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