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Editorial

Are Biosimilars Identical to the Reference Products?

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Biotechnological drugs have become an essential part of modern pharmacotherapy and are expected to reach a 50% share in the pharmaceutical market in the next few years. The recent and pending patent expirations for a number of biopharmaceuticals (e.g. human growth hormone, erythropoietin, interferons ,etc.) have led to the development of alternative versions of biological products called biosimilars or follow-on biologics (FoB). As with traditional low molecular weight chemically derived pharmaceuticals, this allows the possibility of developing new and cheaper versions of biopharmaceutical products. However, it is important to state that whilst biosimilar products are similar to the original product, they are not exactly the same and may not be biogenerics.

"Interchangeability" is a term used to designate the situation where scientific data convincingly demonstrates that two products with very similar molecular compositions or active ingredient (s) can be safely substituted for one another and have the same biologic response and not create adverse health outcomes. With small molecular products, there is a long history to support the use of various scientific approaches to establish "bioequivalence" between products with the same active ingredient (s) produced by different manufacturers. Bioequivalent products can indeed be expected to behave in a pharmacologically interchangeable manner, when used in patient care.

With protein products, as of today, the FDA has not determined how interchangeability can be established for complex proteins. Different large protein products, with similar molecular composition, may behave differently in people and substitution of one for another may result in serious health outcomes (e.g. generation of a pathologic immune response).

Biosimilars are attempted copies of existing biological medicinal products, but the unique multi-dimensional structure of the proteins and in consequence their complicated mode of action are not easily reproducible. In fact biotechnological medicine, even with the same type of cells or microorganisms, can possess different pharmacokinetic and pharmacodynamic properties. Recombinant proteins are completely different from chemical small molecule drugs in terms of their manufacturing, structure and action. Biotechnological drugs are large molecules with a fragile-3-dimensional structure and are products of living cells and usually contain a mixture of different isoforms. Chemical drugs are more stable, whereas biological drugs are sensitive to change in physical conditions which require not only strict manufacturing processes but also appropriate storage at pharmacies and by the patients. Manufacturing and formulation of protein products is highly complex and lengthy and the manufacturing process is critical in terms of defining the characteristics of the final product. These products are usually much more difficult to characterize than chemically derived ones, and past experiences has shown that even minor differences can have important clinical consequences.

For all these reasons European Agency for the Evaluation of Medical Products (EMEA) has named these products biosimilars, and not generics or biogenerics. As a direct consequence the approval process that is used for generic drugs cannot be applied to drugs claiming similarity to biopharmaceuticals.

The history of the development of regulatory laws in the case of biosimilars is short, due to the fact that expiry of patent protection for major biological medicines took place in the recent years. In fact EMEA is a pioneer in the regulations on biosimilars, since FDA is still working on the guideline on

follow-on biologics. According to the EMEA guidelines, biosimilars manufactures need to identify a single reference product and conduct tests to demonstrate biophysical similarity. It is also obligatory for the manufacturer to provide sufficient non-clinical (in vitro and in vivo pharmacodynamic and toxicological studies) and clinical data to demonstrate the clinical similarity to the reference product.

For example, in the case of erythropoietin for the treatment of renal anemia, in addition to conducting pharmacokinetic and pharmacodynamic studies in healthy volunteers, comparable clinical efficacy between the biosimilars and the reference products will need to be presented in at least two adequately powered randomized, parallel clinical trials. These clinical studies should be conducted in patients with renal anemia, including one titration study in epoetin-naïve patients (chronic kidney disease patients with subcutaneous administration of the drug) and one maintenance study in patients already treated with erythropoiesis stimulating agents (chronic dialysis patients with intravenous administration of the product). Also, a risk management/pharmacovigilance plan with attention paid to potential rare serious adverse events should be presented before approval. Most importantly, the guidance requires immunogenicity data to be provided before approval.

Overall, extensive comparability tests are required to demonstrate that biosimilars have a comparable profiles in terms of quality, safety and efficacy to the reference product. When scientific data establishing pharmacologic interchangeability do not exist, especially with more complicated protein molecules with potential critical immunologic safety issues, it is important that patients and physicians be aware that protein products with a similar molecular composition may indeed not be interchangeable.

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