Biologic Products and Biosimilars: The Basics

What are Biologic Products and Biosimilars?

Biologic products are pharmacologic agents produced in living cell cultures or through genetic engineering of proteins. Therapeutic biologic products work by a variety of mechanisms including replacing missing enzymes (e.g., cerezyme), enhancing normal regulatory processes (e.g., epoetin alpha, filgrastim or peg-filgrastim), altering the immune response (e.g., infliximab, ipilumumab), or modulating the neoplastic process (e.g., rituxumab, bevaziumab, or trastuzumab). *Biosimilars* are biologic products that are produced by a company and/or method that differs from the reference product. Importantly, biosimilars are not the same thing as generic drugs. Generic drugs are chemically synthesized small molecules that can be reliably reproduced in large quantities with easily standardized processes. In contrast, biosimilars and other biologic products are large, complex proteins produced in living cell cultures. These cell cultures cannot be standardized and are proprietary. Small changes in the production process may, or may not, have substantial clinical impact.

Common Questions and Controversies Surrounding Biosimilars

Will use of biosimilars result in the same clinical outcomes for my patients?
This is the most challenging question that clinicians will face. The answer is currently unknown. If the production methods result in an altered immunogenicity profile, changes in efficacy or toxicity may result. Alternatively, alterations in immunogenicity may have no impact in therapeutic effects. We do have an example of an unexpected toxicity profile for a biosimilar arising from an altered manufacturing process. One of the biosimilar epoetin agents produced in Europe was found to cause red blood cell aplasia in more than 500 patients when the manufacturing process was altered.

Are Biosimilars Interchangeable with the Reference Product?
Our current experience with hematopoietic growth factors illuminates how this question could be relevant. Filgrastim and sargramostim are both FDA approved to reduce the incidence of neutropenia following cytotoxic chemotherapy. However, they stimulate different cell lines, resulting in different clinical effects and toxicity profiles. Several years ago, some hospitals tried to implement an automatic substitution of sargramostim for filgrastim in order to reduce costs. These programs have largely been stopped due to physician recognition that the clinical outcomes were not equivalent. If the FDA decides that a biosimilar is considered interchangeable with a reference product, then pharmacists in most states would be able to substitute the biosimilar product for a reference product without notifying the prescribing physician.

When are the first biosimilars expected to hit the U.S. market?

Based on current patent timing, the entry for biosimilars is expected in 3-5 years. Biosimilars have been commercially available in Europe for approximately five years. The first products available in the U.S. will be smaller molecule drugs such as erythrocyte-stimulating agents and hematopoietic growth factors. The first monoclonal antibody to reach patent expiration in the U.S. will be rituximab. Generic manufacturers in the U.S., China and India are preparing to enter the biosimilar market.

Will the use of biosimilars result in significant cost savings?

Utilizing traditional generic compounds can result in savings of 75-80% when compared to the originator compound. However, due to the more stringent requirements for the production of biosimilars, the cost savings will likely not be as substantial. In Europe, pricing for biosimilars is approximately 30% less than the originator product. There are currently more than 140 proprietary biologic products FDA approved in the U.S. The cost for a single dose of some of these agents can easily exceed $10,000. Even a 30% reduction in price could result in substantial savings for health systems or physician practices.

The Future and Biosimilars

At the present time, the FDA is formulating its regulatory recommendations for the approval of biosimilar products. The recently passed Patient Protection and Affordable Care Act of 2010 allows for an expedited approved process for biosimilar products. Within the next three years, clinicians must familiarize themselves with biosimilars. Clinicians will also be needed to participate in post-marketing surveillance programs (known as “pharmacovigilence”) in order to determine the long term efficacy and toxicity profiles of these emerging agents.

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