Biologicals play a vital role in treating many chronic diseases, and these therapies can cost tens of thousands, in some cases hundreds of thousands, of dollars per year per patient. Biologicals and specialty products—many of which are biological products—are the fastest growing pharmaceutical expense in the United States. According to a 2015 report in The Economist, biologics accounted for 22% of sales for big pharmaceutical companies in 2013, and this is expected to increase to 32% by 2023. It has been noted that one in three drugs in the pharmaceutical research and development pipeline is a biological product. Considering that this is expected to increase by 20% annually, by the year 2025 three of four new drug approvals will be biological products.

The effect of biologicals on hospital drug budgets is already being felt. Biological products accounted for 9 of the top 15 medication expenditures in U.S. hospitals in 2014, according to the most recent drug expenditure forecast published in the American Journal of Health-System Pharmacy.

Biosimilars have the potential to mitigate the growth in expenditures on biological products because of price competition with the reference (i.e., brand name) product. According to a 2014 report by Express Scripts, in the European Union the sales prices of biosimilars have been approximately 30% lower than the reference product. Previously Express Scripts projected a cost savings of $250 billion in the United States over a 10-year period from the introduction of the 11 biosimilar products most likely to enter the market. The potential for growth in sales of biosimilars is large in the European Union and United States because of upcoming patent expirations.

Pharmacists, policymakers, patient advocacy groups, and payers in the United States have been closely monitoring the experience with biosimilars in the European Union. After much speculation about the implications for the United States, the first biosimilar product—Sandoz' filgrastim-sndz (Zarxio)—was approved by the Food and Drug Administration (FDA) in March 2015, and it is anticipated that this is the first of many biosimilars that will be approved by FDA. Filgrastim-sndz shares five indications with the reference product, Amgen’s Neupogen. FDA has not yet issued guidance on what evidence needs to be submitted for a biosimilar to be designated as interchangeable with the reference product.

A biosimilar form of Johnson & Johnson’s Remicade (infliximab) made by South Korea-based Celltrion, Inc. and licensed to Pfizer Inc. in the United States is likely to be the second biosimilar product approved by FDA. In a 21-to-3 vote, an FDA advisory committee in February 2016 recommended approval of this biosimilar infliximab product for the same indications as the reference product (i.e., Crohn’s disease, ulcerative colitis, rheumatoid arthritis in combination with methotrexate, ankylosing spondylitis, and psoriatic arthritis). Dissenting votes were related to concerns about the proposed indications for use based on extrapolation of clinical data from the reference product to the biosimilar, as well as concerns about the immunogenicity and long-term safety of the biosimilar. If approved, this biosimilar infliximab product will be the first biosimilar monoclonal antibody approved in the United States.

The approval by FDA of the first biosimilar was hailed by consumer groups as good news because of price competition, although the cost savings are not expected to be as great as with small-molecule generic drugs. As noted in a recent ASHP Pharmacy News report, members of the U.S. Congress have expressed frustration with the slow pace of approval of biosimilars by FDA.
Patent cliff and growth potential for biosimilars market.
www.gabionline.net/Biosimilars/General/Top-8-blockbuster-biologicals-2013

Interest in Biosimilars Sparked by Curiosity Coupled with Necessity

Faculty member James Stevenson’s interest in and knowledge of biosimilars arose during his former tenure as chief pharmacy officer of a large university hospital as a result of attempts to control institutional drug costs and improve patient access to costly drug therapies at a time when the role of biologics in therapeutics was increasing. “I was aware that biosimilars were available in the European Union, and I thought we had a lot to learn from the European experience,” Dr. Stevenson told William A. Zellmer during a recent Engaging the Experts interview. A regulatory pathway to biosimilar approval was established in the European Union in 2005, and the first biosimilar product was approved in 2006. Dr. Stevenson recognized that the European experience had important implications for the pathway to approval of biosimilars by the U.S. Food and Drug Administration established as part of the Patient Protection and Affordable Care Act signed into law by President Obama in 2010.

<table>
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<th>Initiative Faculty</th>
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| **Edward C. Li**, Pharm.D., M.P.H., BCOP, *Activity Chair*  
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Department of Pharmacy Practice  
University of New England College of Pharmacy  
Portland, Maine |
| **James G. Stevenson**, Pharm.D., FASHP  
Professor, Department of Clinical Pharmacy  
University of Michigan College of Pharmacy  
President, Hospital and Health System Services  
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The Affordable Care Act also was the introductory point to biosimilars for fellow faculty member Edward Li, who was then working on policy issues at the National Comprehen-
sive Cancer Network (NCCN). Sparked by a hallway discussion, he and colleagues did more investigation and recognized the potential transformative impact of biosimilars on oncology practice once the FDA approval pathway was established and biosimilar products became available. They convened a work group of stakeholders, including members of the pharmaceutical industry, payers, and healthcare providers, to identify and address issues related to biosimilars. The group’s efforts culminated in publication of a white paper in 2011 (J Natl Compr Canc Netw. 2011; 9(suppl 4):S1-22) that included survey results demonstrating a need for education of healthcare professionals about biosimilars.

Dr. Li’s personal experience underscores the need for healthcare professionals to learn about biosimilars. He noted, “My education level about biosimilars has increased markedly from initially not knowing much about them and feeling hesitant about their use to being knowledgeable and comfortable with these products now.”

To hear Drs. Stevenson and Li discuss important issues related to integrating biosimilars into the medication-use process from their respective perspectives as a pharmacy manager and oncology pharmacist, listen to the complete Engaging the Experts interview (presented in two segments) or subscribe to the ASHP Advantage podcast series in iTunes. Topics range from the European Union experience and the FDA review process to formulary considerations and state substitution laws.

Other Learning Opportunities Available Through this Educational Initiative

» Biosimilars—The Time Is Now: Challenges and Opportunities for Pharmacists (1.5 hours CPE, qualifies for pharmacy law CE, available now)
» Ask the Experts: Incorporating Biosimilars in the Medication-use Process (1 hour CPE, available mid April 2016)
» Engaging the Experts: Faculty interviews with William A. Zellmer

We’re Talking about Biosimilars, but What Are They?

The definitions of biosimilar from FDA and European Medicines Agency (EMA), the regulatory equivalent of FDA in Europe, are essentially the same:

» U.S. Food and Drug Administration: A biological product that is highly similar to a U.S.-licensed reference biological product notwithstanding minor differences in inactive components and for which there are no clinically meaningful differences in safety, purity, or potency of the product.

» European Medicines Agency: …structurally highly similar versions of an already authorized biological medicinal product (the reference product) with demonstrated similarity in physicochemical characteristics, efficacy, and safety based on a comprehensive comparability exercise.

Despite their similarities, the EMA definition is more specific. The FDA definition focuses on the end result of comparisons between reference products and biosimilars (safety, purity, and potency). By contrast, by also specifying comparison of physicochemical characteristics as a process for making comparisons, the EMA definition may be more useful.

Human Erythropoietin
165 amino acids
MW ~ 34,000 Da

Cisplatin
(NH₄)₂PtCl₂
MW ~ 300 Da

Structure of a biological product (left) compared with a small-molecule drug.
Illustration courtesy of Olgun Guvench, M.D., Ph.D., University of New England College of Pharmacy.

Notice that both definitions state that a biosimilar is a biological product, and perhaps that should be defined, as well. FDA defines biological products, or biologics, as medicinal products that are made from a variety of natural sources (human, animal, or microorganism). Biologics have a high
molecular weight and have a complex and heterogeneous structure that cannot be characterized fully. Biologics are highly sensitive to external conditions and manufacturing changes and have relatively high immunogenicity.

This is in contrast to small-molecule drugs, which have a relatively low molecular weight, can be characterized fully, and are stable. The final structure of small-molecule drugs is independent of the manufacturing process. Unlike biological products, small-molecule drugs are mostly non-immunogenic.

What’s in a Name?

The naming of biological products is an ongoing controversial issue. In August 2015, FDA released a draft guidance with proposed naming of biological products, including biosimilars, using a suffix with four lower case letters added to a core nonproprietary name. This approach was designed to address safety concerns related to immunogenicity, the need for pharmacovigilance of specific products (i.e., traceability during postmarketing surveillance), and the potential for inadvertent switching of products not deemed interchangeable by FDA. Pharmacovigilance is needed for all biological products regardless of whether they are reference or biosimilar products because of their immunogenicity. Since differences in manufacturing processes can affect immunogenicity, the immunogenicity of a biosimilar may be higher or lower than the reference product. Assessing immunogenicity is a challenge.

Critics of the FDA approach to naming biological products note that the four-letter suffix should not be necessary for products that are deemed interchangeable and indeed could inhibit interchange. They argue that the more complex naming system increases the likelihood that errors could occur, actually harming pharmacovigilance. Traceability could be provided by documenting the lot number of the product dispensed.

The FDA’s four-letter suffix was intended to be devoid of meaning, but filgrastim-sndz was used to name the first biosimilar product approved by FDA in the United States (Sandoz’ product).

In November 2015, the following policy on Nonproprietary Naming of Biological Products was approved by the ASHP inaugural virtual House of Delegates:

To advocate that originator biological products, related biological products, and biosimilar products share the same global nonproprietary name as defined by the United States Adopted Name Council, the World Health Organization Programme on International Nonproprietary Names, and United States Pharmacopeial Convention; further, to oppose unique nonproprietary naming for originator biological products, related biological products, and biosimilar products.

The virtual House of Delegates is a secure online voting platform designed to create professional policies to address rapidly evolving developments in patient care and pharmacy practice. At the virtual House of Delegates, policy recommendations must be approved by at least 85% of delegates to become ASHP policy, and any recommendations not reaching that level of consensus are considered by the House of Delegates when it convenes at the ASHP Summer Meetings. Nearly 93% of state delegates participated in voting in the ASHP virtual House of Delegates to approve the new biosimilars naming policy.

The World Health Organization (WHO) has proposed a naming convention involving the voluntary use of a biological qualifier (BQ) that will likely solidify the proposed naming put forward by FDA last year. A BQ would be a random alphabetic and digital code used in conjunction with the International Nonproprietary Name (INN), not a constituent part of the INN. According to WHO, “the availability of a single global scheme would better harmonize international pharmacovigilance efforts and will avoid proliferation of separate and distinct national qualifier systems.”

More information:


In January 2016, the FDA Center for Drug Evaluation and Research announced its agenda for publishing new or revised draft guidances on various topics, including biosimilarity. Three aspects of biosimilarity will be addressed:

» Considerations in demonstrating interchangeability with a reference product,
» Labeling for biosimilar products, and
» Statistical approaches to evaluation of analytical similarity data to support a demonstration of biosimilarity.

These guidances should provide important insight into FDA requirements for biosimilars and are expected to be highly relevant to pharmacists, especially since state biologic substitution laws are linked to FDA's interchangeability designation. Further, the labeling of biosimilar products will affect how pharmacy and therapeutics committees review the product for formulary consideration at their institutions.

More information: