Biosimilars: Opportunities and Challenges for Nurse Practitioners

Martha M. Rumore, PharmD, JD, Elizabeth Cobb, PharmD, Maureen Sullivan, PharmD, and Deborah Wittman, PharmD, BCACP

ABSTRACT

The science, regulatory, and pharmacovigilance processes for biosimilars are evolving. The Biologics Price Competition and Innovation Act created an abridged approval pathway for biosimilars. The first biosimilar was Food and Drug Administration approved in 2015 with others currently pending approval. As biosimilars become marketed, nurse practitioners will be faced with many challenges, including patient questions regarding them. Nurse practitioners have an important role in the identification of possible safety profile differences between biosimilars and innovator biologicals, especially for immunogenicity. A number of practical considerations need to be addressed including substitutability; off-label prescribing; patient-specific record keeping; and computerized prescriber order entry, education, and reimbursement.

Keywords: biosimilar, biologic, biologics, Food and Drug Administration, interchangeability, substitution

Biologics have revolutionized the treatment of many debilitating and life-threatening diseases such as cancers, rheumatoid arthritis, Crohn disease, ulcerative colitis, multiple sclerosis, and Gaucher disease. Biologics such as cytokines, hormones, clotting factors, monoclonal antibodies, and vaccines have become an essential part of modern pharmacotherapy.[1] In 2013, United States biological sales were $66.3 billion.[2] In 2014, 7 of the top 10 drugs were biologics: adalimumab (Humira, Abbvie, Inc., North Chicago, IL), insulin gargine (Lantus, Sanofi-Aventis, Paris, France), entanercept (Enbrel, Amgen, Thousand Oaks, CA) infliximab (Remicade, Janssen Biotech, Inc., Horsham, PA), rituximab (Rituxan, Genentech, Inc., San Francisco, CA), pegfilgrastim (Neulasta, Amgen, Thousand Oaks, CA), and bevacizumab (Avastin, Genentech, Inc., San Francisco, CA).[3] By 2016, it is predicted that the top 10 drugs worldwide will be mostly biologics.[4]

A biosimilar is a copy of a commercially available biologic that has gone off patent. Biosimilars have been marketed in the European Union (EU), Japan, Australia, and other countries for over 9 years. Over a dozen biosimilar versions of erythropoietin, somatrope (human growth hormone, German Labs, GmbH, Dusseldorf, Germany), and filgrastim (granulocyte colony-stimulating factor [G-CSF]) are marketed in the EU.[5] Last year, the EU approved the first biosimilar insulin, glargine,[6] and in China, over 20 interferon alpha products are marketed.[7] In the United States, the Biologics Price Competition and Innovation Act (BPCIA) created an abbreviated Biologic License Application (aBLA) pathway under so-called §351(k) applications for submission and approval of biosimilars.[8]

Biosimilars are similar, but not identical to, an already Food and Drug Administration (FDA)-approved biologic product known as a biologic reference product. Biosimilars must show no analytic or clinically significant differences from the reference product. Strength and dosing should be identical. Although there must be no clinically meaningful difference from the reference product in terms of purity, safety, and potency, minor differences in inactive ingredients are permitted. Table 1 provides a comparison of the possible differences between biosimilars and the reference product.[2,9] Despite differences, the similarities result in the protein

Table 1. Comparison of Biosimilars and Reference Biologic Products

Similarities	Differences
Exact same primary structure	Minor structural variations (eg, glycosylation patterns); amino acid sequence
Bioequivalency in comparative clinical trials	Manufacturing processes (eg, cell lines, cell culture, purification)
Strength and dose	Inactive ingredients/formulation
Purity, safety, potency	Naming conventions (eg, suffix)
Biologic activity, no clinically meaningful difference	No biogenerics, only "interchangeable" upon FDA determination
Mechanism of action	12 years exclusivity for reference drug; none for biosimilar
Indications (BUT biosimilar may be approved for fewer than all reference product indications)	Packaging and delivery systems may differ
Route of administration (BUT biosimilar may be approved for less routes of administration than reference product)	Stability and expiration dating
	Storage requirements
	Costs

FDA = Food and Drug Administration.

functioning in a similar way to the reference product; hence, the term "biosimilar." Currently, biosimilars are recombinant proteins, not blood or plasma-derived products, immunologicals, or gene and cell therapies. However, these groups of biologics fall within the BPCIA scope and are not precluded from future biosimilar approval.

As patents for many expensive biologicals expire, lower-cost biosimilars are poised to change the pharmaceutical landscape. In hospitals, the biologic intravenous immunoglobulin is often the largest budgetary medication expenditure for the pharmacy department.[10] In outpatient settings, patient adherence issues currently exist with biologics where out-of-pocket expenses result in patients not receiving therapy or filling prescriptions. A key goal of the BPCIA is improving patient affordability and access to biologics.

The RAND Corporation and Congressional Budget Office (Santa Monica, CA) cost savings estimates from biosimilars range from approximately $25 to 44 billion over 10 years.[11] Lower-cost biosimilars may present an opportunity to improve patient access without compromising patient outcomes. A group of biopharmaceutical manufacturers have formed the Biosimilars Forum, a nonprofit organization dedicated solely to improving patient access to biosimilars in the US. Despite the obvious benefits of biosimilars, barriers exist to impede biosimilar adoption. These barriers include ambiguities such as unclear nomenclature; payer, prescriber, and patient acceptance; requirements for clinical data; financial considerations such as research and development costs and patent litigation; and regulatory and legal hurdles such as state biosimilar substitution laws and onerous regulatory requirements for approval including public disclosure of proprietary data (Table 2).

UNDERSTANDING THE TERMINOLOGY

Table 3 provides a glossary relevant to the BPCIA (eg, the term "interchangeable").[8] A biosimilar is not synonymous with an "interchangeable" product.

Table 2. Barriers Impeding US Biosimilar Adoption

- Naming conventions with different nonproprietary names
- Patient and/or prescriber caution
- Payer reimbursement uncertainties
- Unclear requirements for clinical data
- Costs associated with biosimilar development
- Patent litigation delaying biosimilar entrants
- Onerous 351(k) applicant regulatory requirements for interchangeability
- Public disclosure of proprietary data
- Patchwork of individual state substitution laws