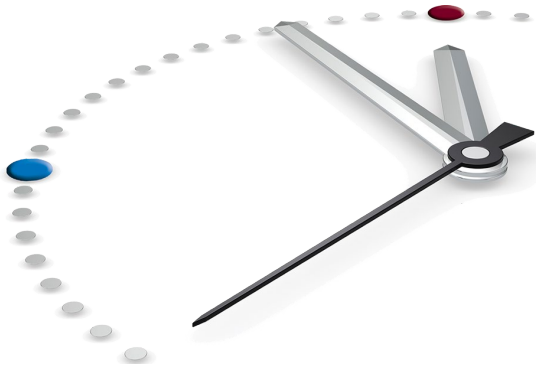
Biosimilars

The Time Is Now: Challenges and Opportunities for Pharmacists



Recent FDA Developments

Two recent developments by the Food and Drug Administration (FDA) are noteworthy because they relate to biosimilars. At the end of March, FDA issued a draft guidance for industry on labeling for biosimilar products. The agency recommends that biosimilar product labeling incorporate relevant data and information from the reference product labeling, with appropriate product-specific modifications. Biosimilar product labeling should include a description of the clinical data that supported safety and efficacy of the reference product as described in the FDA-approved product labeling for the reference product. The relevant data and information from the reference product labeling that should be incorporated into the biosimilar product labeling will depend on whether the biosimilar is approved for some or all of the same indications as the reference product.

In early April, FDA approved Inflectra (infliximab-dyyb), 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. The naming convention of using the suffix "dyyb" appears to be consistent with FDA's current draft guidance on biosimilar naming in that it is four letters, lowercase, unique, and devoid of meaning (i.e., it is not an abbreviation of the manufacturer's name).

Inflectra is the second biosimilar product and the first biosimilar monoclonal antibody product approved by FDA. It is approved for the same indications and has the same warnings as Remicade, except Inflectra is not approved for pediatric patients with ulcerative colitis due to market exclusivity for Remicade for that indication.

Approval of infliximab-dyyb by the agency was based on a review of evidence that included structural and functional characterization, animal study data, human pharmacokinetic and pharmacodynamics data, clinical immunogenicity data, and other clinical safety and effectiveness data that demonstrate biosimilarity. Approval was neither sought nor granted for interchangeability, and FDA has yet to issue interchangeability guidance. When Inflectra will be marketed in the United States is uncertain because Johnson & Johnson has filed a lawsuit against Celltrion and Pfizer based on patent infringement.

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Other Learning Opportunities Available Through this Educational Initiative

- Biosimilars—The Time Is Now: Challenges and Opportunities for Pharmacists (1.5 hours CPE, designated as pharmacy law)
- Ask the Experts: Incorporating Biosimilars in the Medication-use Process (1 hour CPE)
- Engaging the Experts: Faculty interviews with William A. Zellmer
- e-Newsletter, March 2016 issue

Formulary Decision Making

Decisions about inclusion of a biosimilar in the health-system formulary require consideration of a wide variety of factors related to its efficacy and safety, the manufacturer and product, and the facility and patients that it serves. The patient populations studied and clinical data submitted to the FDA when the product was approved, indications for use (especially whether the biosimilar will be used for some or all of the indications for which the reference product is approved), availability of a biomarker to assess efficacy and safety, and immunogenicity concerns when switching from the reference product to a biosimilar are among the efficacy and safety considerations in adding a biosimilar to the formulary.

The immunogenicity concerns associated with biosimilars differ in patients for whom use is *de novo* (i.e., patients who have never received the biosimilar or reference product) and patients who have already begun treatment with the reference product. The extrapolation of data from a clinical trial of a reference biological product in patients with one disease to support use of a biosimilar for patients with other diseases is one of the contentious issues related to biosimilars. A 2014 review article by Weise et al. provides a framework for making extrapolation decisions that considers clinical experience with the reference product and the mechanism of action, target receptors, molecular structure, pharmacokinetics, and immunogenicity profile of the biosimilar.

In the on-demand activity, "Biosimilars—The Time Is Now: Challenges and Opportunities for Pharmacists," faculty member James D. Stevenson identifies some of the operational challenges that pharmacists must consider when biosimilars are included in the formulary. For example, one challenge is the need to differentiate biosimilars from reference products in computerized prescriber order entry, electronic medical record, electronic medication administration record, and pharmacy information systems. Differentiation is necessary regardless of what products are included in the formulary because of the need to document whether the patient received a nonformulary product in another setting. Careful medication reconciliation at the time of hospital admission and discharge is important because of the potential for immunogenicity concerns when switching between the reference product and a biosimilar and the need for accurate information when reporting adverse events for pharmacovigilance purposes.

Biosimilar Formulary Considerations

Efficacy and Safety	Manufacturer	Product	Facility and Patients
» Clinical data » Range of indications » Immunogenicity concerns » Potential for therapeutic interchange » Number of similar agents on formulary » Pharmacovigilance requirements	» Supply reliability » History of drug shortages » Supply chain security » Anti-counterfeit measures » Patient assistance programs » Reimbursement support	» Product packaging and labeling » Bar coding » Compatibility with closed system transfer devices and robotics » Product preparation and administration processes » Storage requirements	» Economic considerations » Facility » Payers » Patients » Payer policies » Transitions of care » Information technology and medication system requirements » Staff and patient educational requirements

Source: Griffith N, McBride A, Stevenson JG, Green L. Formulary selection criteria for biosimilars: considerations for US health-system pharmacists. *Hosp Pharm.* 2014; 49:813-25.

Interchangeability and State Substitution Laws

Substitution of generic small-molecule drugs without prior approval from the prescriber is a common practice in pharmacy and is permitted by law in all 50 states. However, biosimilars are not regulated as generic products because, unlike generics, the active ingredient in a biosimilar is not completely identical to the reference product due to the large molecular size and the complexity and proprietary nature of the manufacturing process for all biologicals. Minor changes in the manufacturing process can affect immunogenicity and safety.

FDA considers biosimilar products interchangeable if they produce the same clinical result as the reference product in any given patient and the risk of harm or diminished efficacy due to alternating or switching between the biosimilar and the reference product is no greater than that from using the reference product consistently. While still in the process of developing guidance related to interchangeability, FDA has noted that an interchangeable product will be appropriate to be "substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product." Thus, state biosimilar substitution laws have linked product selection criteria to those deemed "interchangeable" by the FDA.

According to the National Conference of State Legislatures, new legislation related to biologics or biosimilars has been filed in at least 31 states since 2013, with legislation enacted in 19 states and Puerto Rico. As of April 2016, bills were pending in 12 states.

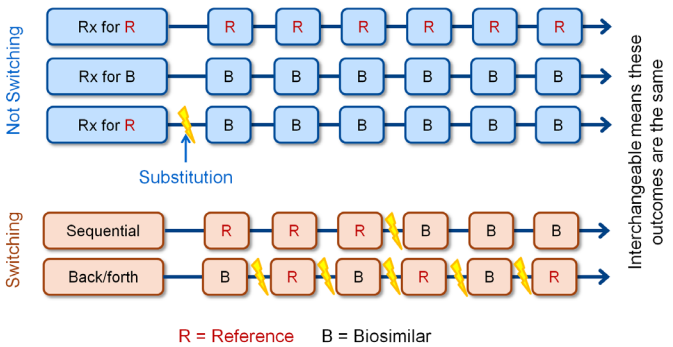
All of the state substitution laws for biosimilars require that the biosimilar be deemed interchangeable by FDA. The agency created the "Purple Book" to help healthcare professionals understand the approval status of reference biologics, biosimilars, and interchangeable biosimilars. Other typical features of state legislation related to the substitution of biosimilars are as follows:

- The prescriber can prevent substitution with "dispense as written" or "brand medically necessary;"
- The prescriber must be notified of the substitution;
- The patient must be notified of the substitution and in some states, prior patient consent is required; and
- Records of the substitution must be retained by the pharmacist and physician.

Some state legislation requires the pharmacist to explain the cost or price of the biologic and the interchangeable biosimilar. Legislation in some states provides immunity for pharmacists who make a substitution in compliance with state law.

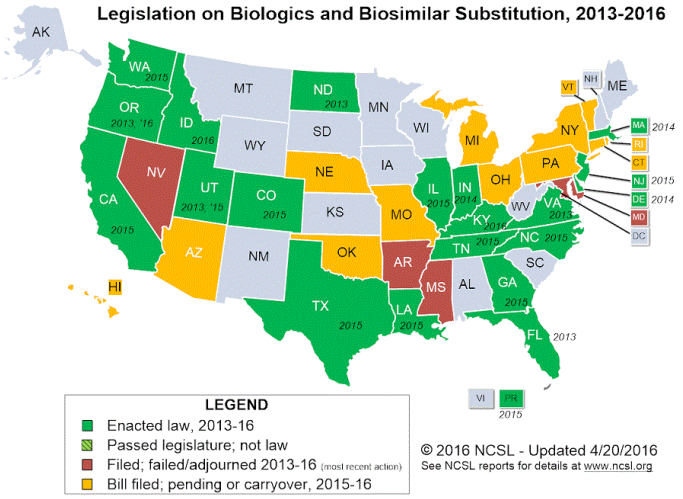
Because laws and regulations pertaining to biosimilar substitution are subject to change in many states, pharmacists should consult their state boards of pharmacies for the current status of legislation. Pharmacists can also use their unique insight, education, and training to provide input into the state legislative process.

Framework for Switching Reference Product and Biosimilar



Interchangeable means that the outcomes are the same regardless of whether (a) switching between reference product and biosimilar or (b) substitution of biosimilar for reference product occurred.

Legislation on Biologics and Biosimilar Substitution, 2013-2016



Source: National Conference of State Legislatures. http://www.ncsl.org/research/health/state-laws-and-legislation-related-to-biologic-medications-and-substitution-of-biosimilars.aspx (accessed 2016 May 4). Used with permission.

Education as Key to Success

Both Drs. Li and Stevenson believe that pharmacists can feel confident about the FDA approach to approving biosimilars based on the experience in the European Union, where a regulatory pathway to approval of biosimilars was established in 2005 and the first biosimilar product was approved in 2006. Early concerns about the safety of complex biosimilar molecules have been allayed because approximately 20 biosimilars currently are available in the European Union, and none of these products has been removed from the market due to regulatory or safety concerns. The approach by FDA is conservative and appropriate to ensure the safe and effective use of biosimilars.

Industry analysts have noted that in the European Union education about the efficacy and safety of biosimilars played a vital role in their successful incorporation into the medication-use process. Comprehensive, unbiased education was provided early after the introduction of biosimilars, and similar efforts are needed in the United States.

According to results of an outcome survey of participants in the December 2015 educational activity (now available on demand), "Biosimilars—The Time Is Now: Challenges and Opportunities for Pharmacists," pharmacists recognize the need for education about biosimilars and are taking a leadership role in educating other health professionals in their health systems. Two months after attending the symposium, 75% of survey respondents already had or planned to provide education about biosimilars for their pharmacist, physician, and nurse colleagues.

Since FDA has not yet published criteria for biosimilar interchangeability or resolved issues related to the naming of biosimilars and pharmacovigilance, pharmacists need to remain abreast of new developments pertaining to biosimilars and advise their colleagues about the implications.

More information:

Stanton D. Greater education efforts needed to aid biosimilars in US, say developers. BioPharma-Reporter. November 13, 2015. http://www.biopharma-reporter.com/Markets-Regulations/Greater-education-efforts-needed-to-push-biosimilars-in-US-developers (accessed 2016 May 4).

FDA Education on Biosimilars Basics

An online educational program , "FDA Overview of Biosimilar Products," for pharmacists, physicians, nurses, nurse practitioners, and physician assistants defines biosimilars and describes the legislation that granted FDA the legal authority that led to the abbreviated regulatory pathway to approval of biosimilars. The complexity of biological product manufacturing and the rigorous and science-based approach the agency has taken to support biosimilar product development are discussed. The program, which is accredited for 1.5 hours of continuing pharmacy education, is designed to help healthcare professionals make informed decisions when prescribing, dispensing, or administering biosimilar products.

Progression from Education to Practice

In addition to educating colleagues about biosimilars, how else did participants in the Midyear symposium put the information they learned into practice? Perhaps their responses can serve as fodder for initiatives you can take in your health system:

- Develop a policy to standardize evaluation of biosimilar products for formulary inclusion.
- Review a newly approved biosimilar product for formulary inclusion.
- Develop strategies to address pharmacist substitution and interchange of biosimilars for reference products.
- Develop a process for addressing transitions of care when patients are receiving biological products that have multiple manufacturers.
- Develop a plan for maintaining and identifying specific biological products within the health system's electronic medical record system.

Get started by checking out the educational resources at www.ashpadvantage.com/BiosimsNow.

Anticipated Development of Biosimilars in the U.S. in Next Two or Three Years

Brand Name (U.S. or EU)	International Nonproprietary Name	Manufacturer	aBLA submitted	FDA approval
Zarxio (U.S.)	filgrastim-sndz	Sandoz	Jul 2014	Mar 2015
Inflectra (U.S.)	infliximab-dyyb	Celltrion	Aug 2014	Apr 2016
	pegfilgrastim	Apotex Sandoz	Dec 2014 Nov 2015	
Retacrit (EU)	epoetin zeta	Hospira	Jan 2015	
Grastofil (EU)	filgrastim	Apotex	Feb 2015	
	etanercept	Sandoz	Oct 2015	
	adalimumab	Amgen	Nov 2015	

aBLA = abbreviated Biologic License Application, EU = European Union, FDA = Food and Drug Administration.

Selected Resources on Biosimilars

Websites

- » ASHP Resource Center on Biosimilars
- » American Journal of Managed Care Resource Center
- » Food and Drug Administration – Information on Biosimilars
- » Food and Drug Administration – Biosimilarity Guidances

Key Articles

- » Li E, Ramanan S, Green L et al. Pharmacist substitution of biological products. *J Manag Care Spec Pharm.* 2015; 21:532-9.
- » Lucio SD, Stevenson JG, Hoffman JM. Biosimilars: implications for health-system pharmacists. *Am J Health-Syst Pharm.* 2013; 70:2004-17.
- » Weise M, Kurki P, Wolff-Holz E et al. Biosimilars: the science of extrapolation. *Blood.* 2014; 124:3191-6.
- » Zelenetz AD, Ahmed I, Braud EL et al. NCCN biosimilars white paper. *J Natl Compr Canc Netw.* 2011; 9(suppl 4):S1-22.

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