



## BIOSIMILARS

By: Alexander Reger, Legislative Analyst II

### BIOSIMILARS

- Biosimilars are medicines designed to be similar to another biologically derived medicine.
- Unlike many traditional generic medicines, biosimilars are not identical to their reference drug.
- The FDA has not yet approved any biosimilar medicines for use and is currently revising guidelines for the approval and application process.

### QUESTION

This report answers several questions pertaining to the use and regulation of biosimilar medicines. The questions and answers are listed individually below.

#### ***1. What are biologics and biosimilars?***

A biologic or biopharmaceutical is a medicine generally derived from living cells or organisms by using biotechnology, including DNA engineering, synthetic production, or extraction from naturally produced sources. A biosimilar (also called a follow-on protein product or a subsequent entry biologic (SEB)) is a biopharmaceutical produced using a similar or identical process and originating material as the original biopharmaceutical drug ([Food and Drug Administration, "Biosimilar Biological Products," 2012](#)).

Three characteristics make reproducing biological medicines more difficult than making other generic drugs, leading to potential differences between the biosimilar and the reference drug. First, the biological organisms from which the biosimilar and the reference drug are derived may not be identical. Second, the production process is more complex than for non-biologic generic drugs. Finally, parts of the production process may remain confidential even after the patent covering the process expires ([Simoens, "Biosimilar Medicines and Cost-Effectiveness," 2011](#)). As a result, the biosimilar and the original biopharmaceutical are not exact duplicates. The biosimilar may have different medical effects or combinations of effects.

## **2. Are there federal regulations governing biosimilars?**

The Food and Drug Administration (FDA) regulates biosimilars. Under federal [guidelines](#) adopted after the [Biologics Price Competition and Innovation Act \(2009\)](#), to gain FDA approval for a biosimilar, a company must provide information to the FDA proving that the product (1) works in the same fashion as the reference drug; (2) has labeled conditions of use that have been previously approved for the reference product; (3) is administered in the same form and dose as the reference drug; (4) is “highly similar” to the reference product; and (5) has no clinically meaningful difference from the reference product. “Biosimilarity” is then determined by the FDA based on an overall assessment of the evidence. Among other elements, evidence includes clinical trials and animal studies ([Food and Drug Administration, “Biosimilar Biological Products,” 2012](#)).

A biosimilar may be considered “interchangeable” and substituted for the original biopharmaceutical without prior authorization from the health provider if the FDA determines it is a biosimilar that (1) can be expected to produce the same clinical result as the reference product in any patient and (2) has similar safety risks as the reference product ([Food and Drug Administration, “Biosimilar Biological Products,” 2012](#)).

A “period of exclusivity” exists during which biosimilars may not be approved. According to the FDA, no application may be submitted until four years and approved until 12 years after the reference product is originally licensed ([Food and Drug Administration, “Biosimilar Biological Products,” 2012](#)).

According to the FDA Center for Biologics Evaluation and Research, no biosimilar medicines have been approved for use in the United States. Guidelines for the approval and application process are currently in revision. In addition, the agency [tracks](#) only the number of biosimilar applications it receives (five for FY 2013). It does not appear that the use and prescription rate of biosimilar drugs is tracked.

## **3. Are there cost savings associated with biosimilars compared to their reference drugs?**

Although biosimilars usually retail for a much higher percentage of the original cost of their reference drug than regular generics, according to research from outside the United States, they nevertheless represent a cost savings over their original counterparts ([Mellstedt et al. “The Challenge of Biosimilars,” 2008](#)). While the difference in price between generic medicines and their reference drugs can be as high as 80%, the difference between a biosimilar and its reference drug typically ranges from 15%-30% (Simoens 2011). This is due to the costs and length of the approval and development processes.

According to Amgen, a biopharmaceutical company, the cost of producing a biosimilar from inception to approval can range from \$75 - \$250 million, in contrast to \$2 - \$3 million for a generic ([Amgen, "Biologics and Biosimilars: An Overview" 2012](#)). According to Simoens, the clinical trials required to receive approval for biosimilars can cost between \$10 and \$40 million, with the manufacturing process requiring an investment of between \$250 and \$450 million. While generic medicines require about three years of development, biosimilars usually require between six and nine years (Simoens 2011).

#### **4. Have states adopted legislation on biosimilars?**

According to [Nature Biotechnology](#), five states had passed legislation involving biosimilar medicines as of November 2013. The states are Florida, North Dakota, Oregon, Utah, and Virginia.

Legislation in all five states allows a patient to use a biosimilar if the (1) biosimilar is FDA-approved and designated interchangeable; (2) patient's doctor does not specify that the original brand is medically necessary; and (3) patient is informed of the substitution and does not refuse. Four states (North Dakota, Oregon, Utah, and Virginia) require the pharmacist to notify the prescribing doctor that a substitution has occurred. Three states (Oregon, Utah, and Virginia) include sunset clauses linked to certain reporting provisions. In addition, Utah requires the patient to undergo counseling on use of the biosimilar and Virginia requires the retail cost of both the biosimilar and reference drug be included on the label. Table 1 lists the states that had passed biosimilar legislation as of November 2013.

As of November 2013, at least 13 other states had recently considered but failed to pass legislation or had pending legislation on biosimilars ([Biosimilars Legislation State by State, 2013](#)).

#### **5. Are biosimilars used in other countries?**

According to the research organization Pharmaceutical Product Development, at least 11 countries and the European Union (E.U.) allow, regulate, or are currently conducting clinical trials of biosimilars, as of March 2013. As of February 2012, the E.U. had approved at least 14 biosimilar medicines. Table 1 displays the countries by region.

**Table 1: A Glimpse of Biosimilar Global Use**

<b>Region</b>	<b>Countries</b>
North America	Canada
Europe	E.U. (including U.K.)
Asia and Pacific	China, India, Singapore, South Korea, Taiwan
Central and South America	Argentina, Brazil, Mexico
Eastern Europe	Russia, Turkey

Source: Pharmaceutical Product Development. "[Developing Biosimilars in Emerging Markets: Regulatory and Clinical Considerations, 2013](#)"

## **RESOURCES**

1. Rachel Sherman, Associate Director for Medical Policy, "Biosimilar Biological Products," *Biosimilar Guidance Webinar*, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, February 15, 2012. Available: <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm292463.pdf>
2. Steven Simoens, "Biosimilar Medicines and Cost-Effectiveness" *ClinicoEconomics and Outcomes Research* 2011:3. Available: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3169973/pdf/ceor-3-029.pdf>
3. Mellstedt et al., "The Challenge of Biosimilars," *Annals of Oncology* 2008: 19. Available: <http://annonc.oxfordjournals.org/content/19/3/411.full>
4. *Nature Biotechnology* 31(11). Available: <http://www.nature.com/nbt/journal/v31/n11/full/nbt1113-947.html>
5. Amgen, "Biologics and Biosimilars: An Overview," 2012. Available: [http://www.amgen.com/pdfs/misc/Biologics\\_and\\_Biosimilars\\_Overview.pdf](http://www.amgen.com/pdfs/misc/Biologics_and_Biosimilars_Overview.pdf)
6. "Developing Biosimilars in Emerging Market: Regulatory and Clinical Considerations" *PPDI White Paper*, March 2013. Available: <http://www.healthtrustpg.com/biosimilars/pdf/ppd.pdf>

7. Florida statute: Fl. Stat. Ann. § 465.0252, § 465.019. Available:  
[http://www.leg.state.fl.us/statutes/index.cfm?mode=View%20Statutes&SubMenu=1&App\\_mode=Display\\_Statute&Search\\_String=biosimilar&URL=0400-0499/0465/Sections/0465.0252.html](http://www.leg.state.fl.us/statutes/index.cfm?mode=View%20Statutes&SubMenu=1&App_mode=Display_Statute&Search_String=biosimilar&URL=0400-0499/0465/Sections/0465.0252.html)
8. North Dakota statute: N.D. Code 19-02.1-14.3. Available:  
<http://www.legis.nd.gov/cencode/t19c02-1.pdf?20140214131510>
9. Oregon statute: Or. Rev. Stat. § 689.522. Available:  
[http://www.oregonlegislature.gov/bills\\_laws/lawsstatutes/2013ors689.html](http://www.oregonlegislature.gov/bills_laws/lawsstatutes/2013ors689.html)
10. Utah statute: Utah Code Ann. § 58-17b-605.5. Available:  
[http://le.utah.gov/code/TITLE58/htm/58\\_17b060505.htm](http://le.utah.gov/code/TITLE58/htm/58_17b060505.htm)
11. Virginia statute: Va. Code Ann. § 54.1-3408.04. Available:  
<http://leg1.state.va.us/cgi-bin/legp504.exe?000+cod+54.1-3408.04>

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