Original Article

Biosimilars Are Here: A Hospital Pharmacist's Guide to Educating Health Care Professionals on Biosimilars

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ABSTRACT

Background: Pharmacists are the recognized experts in pharmacotherapy. With the recent introduction of biosimilar agents into the US market, pharmacists are poised to play a pivotal role in evaluating their risks versus benefits within the framework of cost containment.

Purpose: This article provides hospital pharmacists with the necessary information on the principles surrounding the development, approval process, and use of biosimilars.

Methods: Information contained in this article enables hospital pharmacists to identify concerns relating to biosimilars, implement educational components, and successfully evaluate biosimilars for the addition to the formulary. Additionally, this article reviews the European experience with biosimilars, the US Food and Drug Administration approval process, and postauthorization safety and pharmacovigilance programs.

Conclusion: It is important to educate health care providers about the differences between biosimilars and their reference biologics. The adoption of biosimilars is necessary to control long-term costs of biologics, increase patient access to care, and encourage innovation.

Key Words—biosimilars, education, filgrastim, pharmacoeconomics, P&T, *Retacrit*

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The goal of pharmacological treatment is to improve the health and quality of life of patients. With the use of biologic drugs, pharmacological management has become increasingly complex, often requiring the input of a multidisciplinary team to administer and monitor the chosen therapy.¹ Pharmacists are well educated on the chemical characteristics of medicines – their use, nature, and preparation – and the processes and analytical techniques used to determine their purity and strength.² Furthermore, pharmacists are comprehensively trained in pharmacology to achieve an in-depth understanding of a drug's pharmacokinetic (PK) properties. As the acknowledged drug experts, hospital pharmacists must maintain their knowledge by keeping aware of current medical literature.³ With the recent advent of biosimilar agents into the US

market, pharmacists are poised to play a pivotal role in evaluating risk versus benefit within the framework of cost containment. They should be prepared to educate and communicate information regarding the facts about the development of biosimilars and their use to other health care professionals (HCPs) and patients.

The purpose of this article is to provide hospital pharmacists with the necessary information about the principles surrounding the development, approval process, and use of biosimilars. This information will enable hospital pharmacists to uncover HCPs' concerns about biosimilars, implement educational components, and successfully evaluate biosimilars for formulary inclusion. This article will review the recent and expected introduction of biosimilars into the US market, the European experience with biosimilars, the

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US Food and Drug Administration (FDA) approval process, and postauthorization safety and pharmacovigilance programs. Additionally, this article will discuss the importance of prompt and accurate education of staff by shedding light on some of the confusion about the differences between biosimilars and generics and the potential disparities between biosimilars and reference biologics. (See box titled, Biosimilars FAQs for Health Care Professionals.)

BIOLOGICS: LIFESAVING, LIFE CHANGING, AND BUDGET BREAKING

There has been tremendous growth and development of biologic agents in the pharmaceutical industry. This is mainly due to the powerful efficacy exhibited by many of these agents for the treatment

of life-threatening or life-changing conditions. Despite their enormous value, biopharmaceuticals have become a serious financial threat to the health care system. Some of the treatments now available are extraordinarily expensive, and some patients who qualify for treatment are not able to afford the cost of treatment. Such high costs may be expected when the medicine is new and innovative, however it is much harder to sustain when its patent protection expires.⁴

It is estimated that \$67 billion worth of patents on biologic agents will expire before 2020 (Table 1). With the expiration of patents and the recent advancements in bioanalytical techniques, the door has been opened for the development of biosimilar versions of originator agents. According to a statement released by the FDA, "Biosimilars are likely to create greater

BIOSIMILARS FAQs FOR HEALTH CARE PROFESSIONALS³⁷

1. What is a biologic drug?

A biologic medicine is a complex drug produced from a cell or living organism. Because they are made from living organisms, no 2 batches of biologic drugs are exactly alike.^{38,39}

2. What is a biosimilar?

A biosimilar is a biologic medicine that has been proven, through a rigorous regulatory process, to be highly similar to a marketed biologic drug whose patent has expired.^{6,40} Because biosimilars are designed to be similar to a biologic drug already on the market, they are less costly to develop and require less development time.^{6,39,41} However, the estimated costs of developing a biosimilar product for highly-regulated markets such as Europe or the US still ranges from \$75 to \$250 million.⁴² Biosimilars deliver comparable clinical, safety, and efficacy results as the originator drug. Prior to receiving FDA approval, manufacturers of biosimilars must provide substantial data showing the biosimilar has a highly comparable chemical structure as well as comparable clinical safety and efficacy outcomes compared to the reference biologic drug. Post-marketing surveillance data (ie, adverse event reporting) from Europe is also analyzed. As is the practice today in Europe, once approved, companies will continue monitoring the safety of their biosimilar products through pharmacovigilance programs.²²

3. Which current biologic drugs are most likely to be impacted by competition from biosimilars?

The first biologic drugs expected to come off patent protection and most likely to face competition from biosimilars in the United States include⁴¹:

1. *Neupoge* (filgrastim) – approved March 2015
2. *Epoge* (epoetin alfa)
3. *Synagi* (palivizumab)
4. *Avonex/Rebif* (interferon beta-1a)
5. *Neulasta* (pegfilgrastim)

4. How much will biosimilars cost?

Biosimilars are projected to cost at least 20% to 30% less than reference biologics and are estimated to save \$250 billion in the United States by 2024.^{39,43}

Table 1. Expirations and costs of selected biologics^{44,45}

Biologics	Dose	Cost/year AWP	Expected patent expiration	
			Europe	US
<i>Avastin</i> (bevacizumab)	10 mg/kg every week	\$21,174	Jan 2022	July 2019
<i>Herceptin</i> (trastuzumab)	6 mg/kg every 3 weeks	\$116,777	Expired	June 2019
<i>Humira</i> (adalimumab)	40 mg every other week	\$45,452	April 2018	Dec 2016
<i>Synagis</i> (palivizumab)	9 kg infant, 15 mg/kg, 5 doses/year	\$30,500	Feb 2015	Dec 2018
<i>Erbix</i> (cefuximab)	LD 400 mg/m ² ; MD 250 mg/m ² weekly	\$81,900	Expired	Feb 2016
<i>Remicade</i> (infliximab)	5 mg/kg, 11 doses/ year	\$49,011	Feb 2015	Sep 2018
<i>Rituxan</i> (rituximab)	375 mg/m ² , cost/year represents 8 cycles	\$45,111	Expired	Sep 2016
<i>Aranesp</i> (darbepoetin)	2.25 mcg/kg weekly/8 weeks/year	\$25,937	July 2016	May 2024
<i>Avonex</i> (interferon beta-1a)	30 mcg weekly	\$297,772	2015	2015
<i>Enbrel</i> (etanercept)	50 mg weekly for RA	\$46,388	Feb 2015	Nov 2028
<i>Epogen</i> (epoetin alfa)	40,000 units once weekly/8 weeks/year	\$5,556	Expired	Expired
<i>Neulasta</i> (pegfilgrastim)	6 mg once	\$8,932	Aug 2017	Oct 2015
<i>Neupogen</i> (filgrastim)	5-10 mcg/kg/day for 14 days	\$10,104	Expired	Expired
<i>Lantus</i> (insulin glargine)	0.2 units/kg/day for type 2 diabetes	\$1,741	Expired	Expired
<i>Lovenox</i> (enoxaparin)	1.5 mg/kg/day for 7 days for DVT/PE	\$1,043	Expired	Expired

Note: AWP = average wholesale price based on 80 kg person, 1.73 m²; DVT = deep vein thrombosis; LD = loading dose; MD = maintenance dose; PE = pulmonary embolism; RA= rheumatoid arthritis.

competition in the medical marketplace. This could not only increase treatment options for patients, but also lead to less expensive alternatives to comparable products. With an increasing number of biosimilars on the market, consumers should expect to get equally safe and effective treatment, but at lower costs.”⁵

Biosimilar Development: Comparability Analysis

The FDA approval process directly correlates to the approval processes of the European Medicines Agency (EMA) and Health Canada. The Biologics Price Competition and Innovation Act (BPCI Act) of 2009 was signed into law in March 2010. The BPCI Act establishes an abbreviated approval pathway for biological products that are “highly similar” (biosimilar) to an FDA-approved biological (reference) product.⁶ A “reference” product may be defined as

a biologic drug that was patented when it was first developed, but has since lost its patent protection. (See **Appendices A and B.**)

It may seem as if biosimilars are simply generic versions of biological products. With nonbiologic agents, the production of bioequivalent generic products is readily possible, because such molecules can be produced molecularly homogeneous, thus becoming exact molecular copies of the reference product. In contrast, because all biologics (including biosimilars) are considerably larger and significantly less stable than nonbiologic agents and because all biologicals are isolated from living organisms, the production of a homogeneous set of molecularly identical molecules is not possible. Thus, the reference products are molecularly heterogeneous to a well-defined certain degree, and this heterogeneity varies from batch to

batch within certain limits. Therefore, biosimilars are highly similar to the reference product they are compared to, but have allowable differences, as is the case for batch-to-batch consistency of a biological reference product. On the other hand, biosimilars must be proven to exhibit no clinically meaningful differences in terms of safety, purity, and potency from the reference product.⁷

It is important to understand the fundamental differences between FDA data requirements for a new drug approval and that of a biosimilar drug approval. Because a new drug molecule has never been used in humans, approval is based on the efficacy and safety observed during clinical trials. Biosimilars are approved based on extensive physicochemical characterization that ensures the reference and biosimilar molecules are similar. Advanced, state-of-the-art bio-analytical techniques that may have been unavailable when the originator product was developed ensure that the biosimilar molecule quality attributes and relevant mechanisms of action (MOAs) match those of the originator.⁸

The FDA will only approve a biosimilar product if it has the same mechanism of action, route of administration, dosage form, and potency as its reference product. FDA has issued guidelines requiring a stepwise process to demonstrate biosimilarity, beginning with comprehensive structural and functional analyses, followed by preclinical animal studies to assess toxicity and clinical studies on pharmacokinetics, pharmacodynamics, and immunogenicity. Each step removes uncertainty when conducted with rigor (**Figure 1**). Once a biosimilar has been approved by the FDA, patients and HCPs will be able to rely upon its safety and effectiveness just as they would for the reference product to which the biosimilar is compared.^{7,9}

The quality controls imposed for both innovator biologics and biosimilars ensure that these products are created within an acceptable range of variability and do not have any significant differences in clinical efficacy.^{10,11} Therefore, because the approval of biosimilars leverages the clinical evidence of their reference products, the clinical trial programs of biosimilars serve to confirm the totality of the comparability of biosimilarity evidence. After the FDA concludes that an approved biosimilar product is structurally very similar to its reference product, the FDA may grant approval for certain indications based on the extrapolation of clinical efficacy and safety data conducted from one disease state to another. A biosimilar can only be approved for indications and conditions of use that have been previously approved for the reference product.

Formation of antidrug antibodies (ADAs) in patients is a significant issue that must be evaluated for all biologics – both originator products and biosimilars – before they enter the market. Binding antibodies may affect the PK, and neutralizing antibodies can lead to loss of efficacy. Therefore, it is important to identify immunogenicity and other immunological reactions, for example, infusion and hypersensitivity reactions, during the development of a biosimilar.¹² Immunogenicity may be influenced by patient-, disease-, or product-related factors. Patient- and disease-related factors of the originator product are already known. The FDA carefully evaluates the biosimilar on its potential product-related factors, such as structural alterations (eg, aggregation, which has been implicated in the immunogenicity of epoetins) or impurities/contaminants, most of which are readily detected by state-of-the-art analytical methods.¹² Knowing that the presence of aggregates may increase the immunogenicity, their levels should be

Figure 1. Biosimilar development steps.⁴⁶ PD = pharmacodynamic; PK = pharmacokinetic.

similar (or lower) in a biosimilar compared with its reference product. This usually can be determined by analytical methods. Human immunogenicity data are required and provided by a phase III clinical study before the FDA grants approval to exclude an increase in immunogenicity of the biosimilar compared with the reference product.¹²

Looking towards biosimilar experience in Europe, in several large multicenter studies, some biosimilars, such as infliximab (*Inflectra*; Hospira), displayed nearly identical immunological responses to their reference drugs (in this case, *Remicade* [Janssen]).^{13,14} Other studies indicate that with the current knowledge about immunogenicity concerns with the reference products and by utilizing advanced technology, the development of biosimilars with lower aggregation and/or immunogenicity than the reference products may be possible.^{15,16}

Postauthorization Safety and Pharmacovigilance

Biosimilars have been marketed in Europe and Canada for years. They have demonstrated similar safety and efficacy to their reference products. In the European Union, the first patents on biopharmaceuticals expired in 2001, and the first biosimilar medicines were approved by European Medicines Agency (EMA) in 2006. In Canada, the first biosimilar product was approved in 2009.^{4,17}

Most European Union countries, in cooperation with the World Health Organization (WHO) resources, have developed postmarketing pharmacovigilance programs enabling HCPs to report any unanticipated adverse events (AEs) and/or lack of efficacy for a particular biosimilar. These programs are a series of organized scientific and data collection activities related to the detection, assessment, understanding, prevention, and communication of potential safety concerns with drug products. The goal is to promptly identify and evaluate safety signals so that risks can be appropriately managed. Using the totality of evidence gained with the originator drug, AE monitoring may be more focused. Therefore, AEs specific to the reference biologic will be closely monitored for the biosimilar on a long-term basis and in large cohorts of patients.

The steadily increasing exposure of patients in Europe to biosimilars has enabled the FDA and hospital pharmacists to examine pharmacovigilance data to ascertain the safety of the biosimilars. For example, when considering filgrastim-sndz, the FDA reviewed the postmarketing experience outside of the United States.¹⁸ Filgrastim biosimilars are licensed in

all countries of the European Economic Area (30 full member states, 1 provisional member state) and have been on the market since 2009. European postmarketing experience represented approximately 7 million patient-days of exposure at the time of review. This significant experience results in a deep understanding of the safety profile of the biosimilar. The postmarketing surveillance program demonstrated no new important safety signals of concern, including immunogenicity, or any significant changes in the safety profile of the biosimilar compared to the reference product. It can be concluded that according to postmarketing data, the safety profiles of the biosimilar and the reference product are similar.¹⁸ The benefit/risk assessment is considered favorable.^{19,20}

Retacrit (epoetin; Hospira) is a biosimilar to epoetin alfa (reference product, *Eprex*; Janssen-Cilag GmbH) in Europe, and Hospira is expected to market a biosimilar to epoetin alfa in the United States (reference product, *Epogen*; Amgen) in the near future. Prior to the approval of *Retacrit* in the European Union, Hospira developed a comprehensive risk management plan that included postauthorization safety surveillance to identify potential safety concerns for that drug. All AEs reported from December 2007 through May 2015 were compiled from Hospira's safety database of *Retacrit*. The estimated total cumulative exposure during this time period was approximately 120 million patient-days (WHO daily defined dose of 1,000 IU).²¹ The number of AEs, including immunogenicity, reported did not indicate any significant increase when compared with cumulative experience of the biosimilar and the reference products, and thus there were no new safety signals identified.²¹

As is the practice today in Europe, the FDA will typically require manufacturers to continue monitoring the safety of their biosimilar products once approved. In the February 2012 guidance to the biosimilars industry, the FDA stated that monitoring the safety of biosimilar drugs would be an important component ensuring the safety and effectiveness of biological products.²² However, to effectively and efficiently track and monitor biosimilars, there must be a predetermined naming scheme to differentiate biosimilars from the reference products.

The FDA has not yet issued guidance on how current and future biosimilar products will be named, but it is important for hospital pharmacists to understand the issues that surround the naming of biosimilars. The International Nonproprietary Name (INN) is the official generic name given to a pharmaceutical's active ingredient by the WHO, and it applies to each

product globally. Thus, products with the same active ingredient have always shared the same INN, even in different countries. The WHO INN expert group recommended that the current INN system should be maintained, so that physicians and regulatory authorities around the world will be familiar with the active ingredients in all medicines.²³ The current system gives the same INN to different products from different manufacturers, even if there are slight differences. Some argue that a biosimilar that is designed to be chemically and pharmacologically highly similar to the reference product should not have a different INN. Others express the desire for unique INNs for biosimilars on the basis that this may theoretically improve the effectiveness of postmarketing pharmacovigilance requested by the FDA.²⁴

Assuring Quality Across the Continuum of Patient Care: Supply and Switching Considerations

The approval of a biosimilar means that it has been demonstrated to be highly similar to the reference product with no clinically meaningful differences. Although the FDA currently does not specifically require studies evaluating the safety and efficacy of switching from the reference product to a biosimilar, these studies may be available. For example, multiple studies suggest that patients receiving stable epoetin maintenance therapy may be switched to biosimilar epoetin without any clinically significant alteration in efficacy, tolerability, or dose.²⁵⁻²⁷ A post hoc analysis of data from 3 published prospective clinical trials was conducted.²⁷⁻³⁰ In total, 481 patients had switched treatments. In those patients, mean hemoglobin (Hb) concentration was maintained at target levels (10.5-12.5 g/dL) throughout the switch, and the 95% confidence intervals (CIs) of the mean difference in weekly epoetin dose after switch remained within prespecified equivalence margins (± 45 IU/kg/week).²⁵ Additionally, a small single-center observational study noted that switching of 43 patients from other erythropoiesis-stimulating agents (ESAs) to biosimilar epoetin could be achieved while maintaining Hb levels, with no significant change in ESA dose. When product switching does occur, all product details must be recorded to enable accurate patient follow-up.²⁷

The approval of a biosimilar may or may not mean that the biosimilar is interchangeable with the reference product. FDA approval of a biosimilar product guarantees equivalence of the biosimilar with respect to the mechanism of action, the route of

administration, the dosage form, and the strength of the product. An interchangeable biological product, in addition to meeting the biosimilarity standard, is expected to produce the same clinical result as the reference product in any given patient and for a product that is given to a patient more than once. Additionally, it must be demonstrated that the risk in terms of safety and effectiveness of alternating or switching between the interchangeable and the reference product is not greater than the risk of using the reference product without alternating or switching.³¹

The decision about whether to substitute may depend on indications and clinical decisions when there is not a plethora of clinical evidence. These decisions will impact patients who may be admitted to a facility already on a biologic product or who may leave using a biologic product.

When making the decision regarding interchanging or substituting products, there are many factors for hospital pharmacists to consider:

- Specific agent
- Acute vs chronic therapy
- Treatment indication
- Therapeutically naïve patients vs patients already receiving the particular medication
- Equivalence
- Efficacy/safety
- Published studies
- Cost advantage

The decision may be influenced in part by regulatory bodies. State law may establish procedures for how biosimilars substitution may be carried out in the ambulatory setting and detail requirements for informing the patient and the prescribing physician and for record keeping when an interchangeable biosimilar is substituted for a prescribed originator biological.³²

Although state and federal legislatures may support biosimilar substitution in the United States, the requirements may impose burdensome and potentially costly constraints on retail pharmacists when they dispense biosimilar drugs already approved as interchangeable by FDA.³² However procedures that use monitoring software to inform patients and the prescribing physician and to track and trace use may already be in place at the hospital pharmacy level. In a recent survey conducted by The Academy of Managed Care Pharmacy, the American Pharmacists Association, and the American Society of Health-System Pharmacists, approximately

75% of pharmacists indicated that they would be confident or very confident in substituting an interchangeable biosimilar with the reference product if the biosimilar shared the same active ingredient or nonproprietary name of the reference biological.³³

Pharmacy and Therapeutics (P&T) Committee

Biosimilars will impact many settings, such as hospitals, ambulatory centers, specialty pharmacies, and health plans. The HCPs most impacted by formulary decisions may not be well versed with drug status and therapeutic interchange. Because of the information and marketing efforts presented by the manufacturers of patent-expired biologics, it is important for hospital pharmacists to perform academic detailing and educate the P&T committee on the basics of biosimilars. This will enable the committee to make informed decisions.

In addition to the P&T committee, all pharmacy, medical, and nursing staffs should receive education on biosimilars. If possible, this should be completed before the originator companies begin detailing their opposition to biosimilar innovation and competition. Some topics to cover in biosimilar education include:

- Differences between biosimilars and generics
- Potential disparities between biosimilars and reference biologics
- FDA approval process of biosimilars
- European and Canadian experience of biosimilars
- Pharmacoeconomic information
- Pharmacovigilance plans

Hospital pharmacists can correct potentially misleading information about regulatory approval, extrapolation, and immunogenicity. They can also identify opposition to biosimilar innovation and competition that is led by manufacturers of patent-expired biologics.³⁴

CONCLUSION

Reduction in the cost of biologics should be a priority for our health care system. The adoption of biosimilars is necessary to control long-term costs of biologics, increase patient access to care, and encourage innovation.

Pharmacists must lead the way by understanding the issues surrounding the biosimilar development and approval process. Hospital pharmacists are

uniquely qualified to comprehensively educate other HCPs. P&T committees should use a nontraditional approach to formulary review, with an emphasis on comparability studies versus clinical trials.

At the time of writing this article, the first biosimilar has been approved in the United States and several more have been marketed for years in Europe,³⁵ Canada,¹⁷ and Japan.³⁶ Hospital pharmacists have a duty to examine whether biosimilars are safe and efficacious for patient use. These drugs can curtail the exploding cost of biologics to the US health system and encourage innovation of new biologics. If biosimilars are not adopted, then current biologics essentially will be “forever” patent-protected, possibly stagnating the future research of biologic therapy, hindering discovery of novel therapies, and limiting patients’ access to medications.

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APPENDIX A

US Food and Drug Administration: Statement on Biosimilars

The Patient Protection and Affordable Care Act (Affordable Care Act), creates “an abbreviated licensure pathway for biological products that are

demonstrated to be ‘biosimilar’ to or ‘interchangeable’ with an FDA-licensed biological product. This pathway is provided in the part of the law known as the Biologics Price Competition and Innovation Act (BPCI Act). Under the BPCI Act, a biological product may be demonstrated to be ‘biosimilar’ if data show that, among other things, the product is ‘highly similar’ to an already-approved biological product.

A biosimilar product is a biological product that is approved based on a showing that it is highly similar to an FDA-approved biological product, known as a reference product, and has no clinically meaningful differences in terms of safety and effectiveness from the reference product. Only minor differences in clinically inactive components are allowable in biosimilar products.

An interchangeable biological product is biosimilar to an FDA-approved reference product and meets additional standards for interchangeability. An interchangeable biological product may be substituted for the reference product by a pharmacist without the intervention of the health care provider who prescribed the reference product.

FDA requires licensed biosimilar and interchangeable biological products to meet the Agency’s rigorous standards of safety and efficacy. That means patients and health care professionals will be able to rely upon the safety and effectiveness of the biosimilar or interchangeable product, just as they would the reference product.”

Source: US Food and Drug Administration. Biosimilars. <http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/default.htm>. Accessed July 8, 2015.

APPENDIX B

First biosimilar approved in the United States

On March 6, 2015, the US Food and Drug Administration approved *Zarxio* (filgrastim-sndz, Sandoz) as the first biosimilar in the United States. It is approved as a biosimilar product and not as an interchangeable product. *Zarxio* is biosimilar to *Neupogen* (filgrastim; Amgen) and is approved for the same indications as *Neupogen*. The FDA’s approval of *Zarxio* is based on 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 *Zarxio* is biosimilar to *Neupogen*. The FDA has designated a placeholder nonproprietary name for this product as “filgrastim-sndz.” The FDA has not yet issued draft

guidance on how current and future biological products marketed will be named.

Source: US Food and Drug Administration. *Zarxio* (filgrastim-sndz). March 2015. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm436648.htm>. Accessed August 31, 2015. ■