Educational Objectives

Goal: The goal of this program is to educate pharmacists and pharmacy technicians about the legal and regulatory pathways for biosimilars approved by the United States Food and Drug Administration, as well as to discuss the biosimilars that are available or will soon be available in the United States. Readers will also gain knowledge of the economic impact of pharmacists and pharmacy technicians, and of the role they can play in the formulary process and education about biosimilars.

After participating in this activity, pharmacists will be able to:
- Describe the legal and regulatory history of the pathway for approval of biosimilars in the United States and Europe.
- Explain FDA requirements for biosimilarity and interchangeability.
- Discuss the potential clinical and economic impact of biosimilars.
- Identify the FDA-approved biosimilars available, or soon to be available, in the marketplace.
- Explain the role of pharmacists in making formulary decisions about biosimilars with healthcare administrators, providers, and patients.

After participating in this activity, pharmacy technicians will be able to:
- Describe the difference between generic equivalents and biosimilars.
- Discuss the potential clinical and economic impacts of biosimilars.
- Identify the FDA-approved biosimilars available, or soon to be available, in the marketplace.
- Explain the role of the pharmacy technician in the procurement, preparation, and distribution of biosimilars.

Abstract

Biologic products have grown in use to treat a variety of diseases and conditions ranging from rheumatologic conditions to cancer. Many of the patents on these original “reference” products are expiring in the near future, leading to the development of a number of biosimilar products. Biosimilars are products intended to be “highly similar to” or “ interchangeable with” the reference product. There are many considerations regarding the manufacturing, testing, approval, clinical use, and safety monitoring of biosimilar products. As more and more biosimilar products enter the market in the United States, healthcare systems, providers, and patients will have many choices to make regarding formularies and treatment choices. Pharmacists will play a large role in the management, procurement, and monitoring of these products. They can also provide objective information to legislators, healthcare administrators, practitioners, and patients.

Faculty: Christopher Niemann, PharmD, BCOP; Jennifer Marshall, PharmD, MBA; and Lauren VanHook, PharmD

Dr. Niemann is a clinical coordinator for Oncology in the Pharmacy Department at UConn Health in Farmington, Conn. Dr. Marshall and Dr. VanHook are PGY1 pharmacy residents at UConn Health in Farmington, Conn.

Faculty Disclosure: Dr. Niemann, Dr. Marshall, and Dr. VanHook have no actual or potential conflict of interest associated with this article.

Disclosure of Discussions of Off-Label and Investigational Uses of Drugs: This activity may contain discussion of unlabeled/unapproved use of drugs in the United States and will be noted if it occurs. The content and views presented in this educational program are those of the faculty and do not necessarily represent those of Drug Topics or University of Connecticut School of Pharmacy. Please refer to the official information for each product for discussion of approved indications, contraindications, and warnings.

Christopher Niemann, PharmD, BCOP
Clinical Coordinator – Oncology, UConn Health, Farmington, Conn.

Jennifer Marshall, PharmD, MBA
PGY1 Pharmacy Resident, UConn Health, Farmington, Conn.

Lauren VanHook, PharmD
PGY1 Pharmacy Resident, UConn Health, Farmington, Conn.
Introduction

Globally, use of biologic products has grown rapidly. These agents are used to treat a wide variety of diseases and conditions ranging from immune diseases to cancer. The expiration of patents for many original (or “reference”) products has opened the door for rapid development of biosimilar products.

Biologic products’ complex research, development, and manufacturing processes often translate to high price tags. The use and cost associated with biologic products in the United States have grown markedly. In 2000, only one of the top 10 drugs based on sales was a biologic product, whereas in 2008, five of the top 10 drugs based on sales were biologic products. In 2011, 10 of the top 15 drugs based on sales were biologic products. Worldwide sales of biologic products in 2015 are expected to top $167 million.1 The Congressional Budget Office predicts that the first approved biosimilar in the United States could save patients and payers roughly $6 billion over the next 10 years due to creating competition.2

In 2000, only one of the top 10 drugs based on sales was a biologic product, whereas in 2008, five of the top 10 drugs based on sales were biologic products. In 2011, 10 of the top 15 drugs based on sales were biologic products. In 2011, 10 of the top 15 drugs based on sales were biologic products.”

Biologic products versus small molecule drugs

Small molecule drugs are fairly small in size, simple in structure, highly pure and stable, and easily manufactured. Small molecule drugs are produced using organic chemistry reactions with known chemicals and reagents. These predictable, controlled reactions are easily replicated.

In contrast, biologic products are usually large in size, have complex and often folded structures, and are heterogeneous products with impurities (Table 1). Dependent on living systems such as bacteria, viruses, and animal, plant, or human cells, their manufacturing processes are difficult to replicate. Slight differences in manufacturing systems can affect the product’s structure and function. Environmental factors such as light, temperature, and moisture can also influence the manufacturing process and affect product integrity.

| PAUSE AND PONDER |

**How can I as a pharmacist play a key role in the use of biosimilars at my institution?**

The U.S. government defines a biologic product as “any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment, or cure of diseases or injuries of man.”1 Most biologic products are larger in molecular weight and more complex than traditional drugs. Biologic products may vary in size and complexity. Some are fairly small and simple, such as growth hormones or insulin, whereas others such as the monoclonal antibodies rituximab and trastuzumab are more complex.1

This program will discuss the regulations established by the U.S. Food and Drug Administration (FDA) for the approval of biosimilar drugs, discuss important terminology surrounding biosimilar drugs, and review the approval process for biosimilars. It will discuss biosimilar approval process in Europe and biosimilars available for use in Europe. It will also cover the important roles that pharmacists can play in the use of biosimilar drugs in the United States.

**FDA definitions**

Many of the terms, definitions, and verbiage pertaining to biologic products and biosimilars can confuse healthcare providers and patients. As more biosimilars become available on the U.S. market, pharmacists can play key roles in educating other providers and their patients about differences in biologic terms, the processes regarding the development of these products, regulations surrounding the approval of these products, and the interchangeability of biologic products. (Table 2) contains key FDA definitions pertaining to reference products, biosimilars/biosimilarity, and interchangeability.3

**FDA regulations and approval process**

To understand the biosimilar approval process, it is necessary to understand the process innovators follow when they develop a new biologic. A reference (or “innovator”) biologic product’s manufacturer must file a Biologics License Application (BLA) under section 351(a) of the Public Health Service (PHS) Act. The manufacturer has to supply significant data to the FDA, similar to the data provided for a small molecule drug, showing the safety and efficacy of the product. Prior to 2010, the FDA had no established process for biosimilars. Every biosimilar had to navigate the entire BLA process. No abbreviated processes were available.

In March 2010, President Obama signed the Affordable Care Act into law, enacting the Biologics Price Competition and Innovation Act (BPCIA). The goal of the BPCIA is similar to that of the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Act), which established abbreviated pathways for generic drug approval. The BPCIA establishes an abbreviated pathway for the approval of biologic products that are “highly similar” (ie, biosimilars) to or interchangeable with the “reference” biologic product.

Manufacturers of biologic products have three pathways they may choose from for approval. The options are for approval as a biosimilar biologic, an interchangeable biologic, or a noninnovator biologic. Both a biosimilar biologic and an interchangeable biologic use the abbreviated pathway established by the BPCIA, with an interchangeable biologic requiring...
greater supporting data for approval. A noninnovator biologic requires the manufacturer to submit a full BLA to the FDA for approval and has a greater requirement for supporting data than both a biosimilar biologic and an interchangeable biologic.

Biosimilar approval

The simplest process involves biosimilar designation. During the approval process, the FDA compares the biosimilar product with the reference product using data from analytical studies demonstrating high similarity. The FDA uses a stepwise approach in the approval process. This stepwise approach uses structural analyses, functional assays, animal studies, and human studies (Fig. 1). Structural analyses and functional assays demonstrate that the biologic product is highly similar to the reference product notwithstanding minor differences in clinically inactive components. Animal studies are used to assess toxicity and immunogenicity. Human studies are used to assess pharmacokinetics, pharmacodynamics, clinical immunogenicity, safety, and clinical effectiveness.

As part of the approval process for a biosimilar biologic product, a manufacturer must submit a BLA under section 351(k) of the PHS Act. The BLA includes scientific data demonstrating that the biologic product is biosimilar to the reference product and has the same mechanism of action, conditions of use, route of administration, dosage form, and strength. The biosimilar product must also be manufactured, processed, and packed in a facility that meets the standards designed to assure that the product is safe, pure, and potent.

Interchangeable status

For an agent to receive approval as an interchangeable biologic, the product must be proven to be “highly similar” to the reference product and must have no clinically meaningful differences from the reference product. Additionally, the product should produce the same clinical results in any given patient, and the risk of switching or alternating must not be greater than the risk of using the reference product consistently.

Noninnovator biologic status

A manufacturer must submit a full BLA instead of following the abbreviated pathway outlined by the BPCIA for a noninnovator biologic product. The noninnovator pathway requires significantly more data for approval than the biosimilar biologic and interchangeable biologic pathways. The noninnovator pathway is the pathway which Teva Pharmaceuticals chose to follow when seeking approval for its product Granix (tbo-filgrastim), a human granulocyte colony-stimulating factor. This product is not considered a biosimilar or interchangeable biosimilar with Amgen’s Neupogen (filgrastim).

The FDA evaluates applications with no defined threshold for the scope or amount of data required for approval. The scope or amount of data may depend on the drug or drug class being evaluated. Because a one-size-fits-all approach cannot be used in the evaluation of biosimilar products, the agency determines on a case-by-case basis which data are required and which are not.

The BPCIA currently does not include regulations regarding substitution of biosimilars that have been approved for use. The FDA has left it to individual states to enact legislation regarding substitutions with biosimilars. Currently, eight states have enacted statutes regarding biosimilars and substitution (Table 3). An application for a biosimilar product may not be submitted to the FDA for four years after the approval of the innovator product. The FDA grants one year of exclusivity for the first interchangeable biosimilar. Manufacturers are granted 12 years of exclusivity for an innovator biologic product, with an additional six months if studies were performed in pediatric patients.

Biosimilars in Europe

The experience Europe has gained with several biosimilars being approved can provide important insight to the FDA. The European process can serve as a model to help refine the approval process in the United States. In Europe, the European Medicines Agency (EMA) oversees the safety of human and veterinary medications. Among many other duties, the EMA is responsible for the scientific evaluation of marketing authorization applications for human and veterinary medication use within the European Union. This allows for a centralized process in which pharmaceutical manufacturers may submit a single application to the EMA which, if accepted by the European Commission, is then valid for all members of the European Union (including Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and the United Kingdom). Marketing authorizations granted by the European Commission are also valid for members of the European Eco-

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Comparison of small molecule drugs and biologic drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHARACTERISTIC</td>
<td>BIOLOGIC PRODUCTS</td>
</tr>
<tr>
<td>SIZE</td>
<td>Large, with large molecular weights</td>
</tr>
<tr>
<td>STRUCTURE</td>
<td>Complex</td>
</tr>
<tr>
<td>MANUFACTURING PROCESS</td>
<td>Complex, uses living systems</td>
</tr>
<tr>
<td>PURITY AND STABILITY</td>
<td>Heterogeneous product with impurities; environmental factors and improper handling may alter product</td>
</tr>
</tbody>
</table>

Source: Ref 1

56 DrugTopics | JANUARY 2016 | DRUGTOPICS.COM
The European Commission (EMA) developed its first guideline on similar biologic medicinal products (biosimilars) in June 2004. After discussion, commentary, and adoption by the EMA’s Committee for Medicinal Products for Human Use (CHMP), the guideline was put into effect on October 30, 2005. This guideline has since been monitored and updated by the Working Party on Similar Biomedical Products, which works in conjunction with the Biologicals Working Party to ensure the high quality of biosimilars in the European Union. This collaboration has allowed the EMA to publish guidelines on nonclinical and clinical aspects of the development of biosimilars, overarching biosimilar guidelines, and product-specific biosimilar guidelines. Currently, the nine product-specific biosimilar areas include alpha interferons, beta interferons, erythropoietins, follicle-stimulating hormones, granulocyte colony-stimulating factors, growth hormones, human insulin and insulin analogs, low-molecular-weight heparins, and monoclonal antibodies.

Thus far, 19 biosimilars have received marketing authorization approval from the European Commission (Table 4). The first biosimilar, Omnitrope, was approved on April 12, 2006, and remains the only approved biosimilar within the growth hormone class. Omnitrope shares the active ingredient somatropin with its reference product, Genotropin. In 2007, five additional biosimilar products were approved by the European Commission. All five were erythropoietin products. Two of the new biosimilars, Retacrit and Silapo, have the active ingredient epoetin zeta, whereas Abseamed, Binocrit, and Epoetin Alfa Hexal have epoetin alfa as the active ingredient. Nonetheless, all five erythropoietin biosimilars have Eprex/Erypo as the reference product. From 2008 to 2014, eight granulocyte colony-stimulating factor biosimilars received approval: Accofi, Biogranstim, Filgrastim Hexal, Grastofil, Nivestim, Ratiogranstim, Tevagrastim, and Zarzio. All of these products are biosimilars of filgrastim, with Neupogen as the reference product. The first monoclonal antibody biosimilars were approved in 2013: Remsima and Inflectra. Both are infliximab monoclonal antibodies, with Remicade as the reference product. Currently, these are the only approved biosimilars of the monoclonal antibody class. In 2013 and 2014, the European Commission approved two follicle-stimulating hormone biosimilars, Ovaleap and Bemfola, which share the active ingredient follitropinalfa and the reference product GONAL-f. The European Commission also approved Abasaglar in 2014; this agent is the first biosimilar of the insulin analog class, with insulin glargine as the active ingredient and Lantus as its reference product.

The EMA’s evaluation of biosimilars for marketing authorization approval is similar to that employed by the FDA. The EMA requires that pharmaceutical manufacturers conduct well-performed studies with results that clearly demonstrate that the proposed biosimilar medication has no significant differences in quality, safety, or efficacy from the reference medication. Quality may be assessed by comparing the structure and biological activity of the proposed biosimilar with its reference product. Alternatively, safety and efficacy may be evaluated by comparing the benefits and risks of the product, especially in terms of immune-related adverse events, with those of the reference product. Of note, although the EMA is responsible for evaluating biosimilar medications for authorization purposes, it does not provide any recommendations or guidance on the interchangeability of biosimilar products. When a patient is considering the possibility of switching between two or more biosimilar agents, the EMA suggests consultation with the ordering provider and/or pharmacist.

Biosimilars in the United States

The United States lags far behind Europe in the area of biosimilars. As previously mentioned, Europe published and disseminated its first biosimilar guideline in October 2005, with its first biosimilar product approved just six months later. In contrast, the United States had its first formal meeting between FDA members and biosimilar biologic product sponsors or applicants in March 2013. At this point, the European Union already had 12 biosimilars available on the market.

Unlike the 19 biosimilars that have received marketing authorization approval in the European Union, the FDA has approved only one biosimilar agent. On March 6, 2015, Zarxio (filgrastim-snvdz) was announced as the first biosimilar agent to receive FDA approval, with Neupogen as its reference product. Although FDA experts have approved only one biosimilar in the United States thus far, many more

---

**TABLE 2**

<table>
<thead>
<tr>
<th>TERM</th>
<th>DEFINITION</th>
</tr>
</thead>
<tbody>
<tr>
<td>REFERENCE PRODUCT</td>
<td>The biologic product licensed by the FDA under the Public Health Service Act, against which a proposed biosimilar product is evaluated</td>
</tr>
<tr>
<td>BIOSIMILAR OR BIOSIMILARITY</td>
<td>The biologic product is “highly similar” to the reference product notwithstanding minor differences in inactive components. There are no clinically meaningful differences between the biologic product and the reference product in terms of safety, purity, and potency</td>
</tr>
<tr>
<td>BIOSIMILAR BIOLOGIC PRODUCT</td>
<td>A biologic product that has been demonstrated to be biosimilar to the reference product</td>
</tr>
<tr>
<td>INTERCHANGEABLE OR INTERCHANGEABILITY</td>
<td>The biologic product is biosimilar to the reference product and produces the same clinical results as the reference product. The risk of switching between the biosimilar product and the reference product must not be greater than the risk of using the reference product consistently</td>
</tr>
</tbody>
</table>

Source: Ref 3
biosimilars are in research, development, and clinical testing.

**Biosimilars in the pipeline**

The biosimilar pipeline has many agents in research and development, most of which are monoclonal antibodies for oncologic or immunologic indications. With the increased use of these biologic agents and the recent expiration of many major patents, larger pharmaceutical companies including Sandoz, Amgen, and Pfizer are taking advantage of the opportunity to diversify their portfolio and get their piece of the biosimilar pie.\(^{15-17}\) Many pharmaceutical companies are testing potential biosimilars for the immunologic monoclonal antibodies Humira (adalimumab), Rituxan (rituximab), Remicade (infliximab), and Enbrel (etanercept). Additionally, many of the same pharmaceutical companies are developing oncologic monoclonal antibody biosimilars for Herceptin (trastuzumab), Avastin (bevacizumab), and Erbitux (cetuximab). Although the aforementioned oncologic and immunologic monoclonal antibodies make up a large majority of the biosimilar pipeline, other types of biosimilars are in development as well, including biosimilars for Xgeva/Prolia (denosumab), Actemra (tocilizumab), Simponi (golimumab), Stelara (ustekinumab), and Neulasta (pegfilgrastim).\(^ {18}\)

**Naming of biosimilars**

There has been great debate on how to name biosimilar products. Unlike small molecule drugs, which use the same nonproprietary name as the branded product, biosimilar products are not identical to the reference product. Giving the biosimilar product the same nonproprietary name would be misleading. However, giving a biosimilar product a branded name and a new nonproprietary name could lead to confusion for consumers, resulting in slower uptake rates and hindering competition.\(^ {19}\) Some discussion has centered on the idea of adding a prefix or suffix to the nonproprietary name. Sandoz chose to use a four-letter suffix after the nonproprietary name when naming its biosimilar product filgrastim-sndz (Zarxio). The FDA hopes to issue guidance on the naming of biosimilars in the near future.

**Extrapolation**

Extrapolation is the approval of biosimilars for multiple indications without the need for additional research. Extrapolation is controversial, as some question its safety and efficacy. The FDA has allowed extrapolation for Zarxio (filgrastim-sndz), the first biosimilar approved in the United States, but it will analyze each future biosimilar on a case-by-case basis. FDA guidance states, “If the proposed product meets the statutory for licensure as a biosimilar under section 351(k) of the PHS Act based on data derived from a clinical study sufficient to demonstrate safety, purity, and potency in an appropriate condition of use, the potential exists for the biosimilar product to be licensed for one or more additional conditions of use for which the reference product is licensed.”\(^ {20}\)

**How many biosimilars are currently approved by the FDA in the United States?**

**Reimbursement**

As more biosimilars hit the U.S. market, questions are being raised regarding whether third-party payers and insurance companies will accept biosimilars as treatment options and offer reimbursement. The Centers for Medicare and Medicaid Services has issued several guidelines on biosimilar reimbursement. In March 2015, CMS stated that reimbursement for biosimilars would be the average sale price in addition to 6% of the average sale price of the innovator drug in order to reduce incentives for prescribing more expensive biologic products under Medicare Part B.\(^ {20}\)

**The pharmacist’s role**

Pharmacists will play a vital role in their communities and healthcare institutions as the biosimilar market continues to expand and more agents gain FDA approval. Regardless of specialty or practice site, pharmacist roles pertaining to biosimilars will involve four major areas: education, leadership, dispensing, and post-market reporting/pharmacovigilance.

**Education**

First, pharmacists have the responsibility of educating themselves on the complexities of biosimilars and the special legislation that regulates them. In addition to staying updated on the latest approved biosimilar agents, pharmacists need to make sure they understand the science, product variability, and approval processes...
CONTINUING EDUCATION

LAW: PRIMER ON BIOSIMILAR AGENTS

for biosimilars and biologic products. Having knowledge about these details, as well as about the unique naming protocols and definitions of different classes of approved agents, will better prepare pharmacists as members of the healthcare team to effectively and objectively educate providers. The pharmacist’s ability to provide objective information about biosimilars to providers will be an integral part of their role. Pharmacists should be aware of targeted marketing strategies and be prepared to answer questions from providers as the biosimilar industry establishes itself and moves forward.

Pharmacists will also play an important role in educating patients about the difference between biosimilars and biologics. Patients currently being treated with innovator biologic products and those initiating treatment with biologic therapies will likely be affected, as insurance companies, third-party payers, and patients look to save money through the use of lower-priced biosimilars. These patients may approach their local pharmacists with questions about the new medications following physician visits or advertisements from various media sources. Pharmacists should be prepared for these questions and do their best to answer them in a way that is comprehensible to the patient. It will be especially important to maintain open communication among pharmacists, patients, and prescribers as more patients are switched to biosimilar therapy in the future and biosimilar substitution policies expand.

Pharmacists can also serve as educators to administrators, policy makers, payers, and legislators on various aspects of biosimilars such as the FDA approval process, product variability, pharmacovigilance, and post-market surveillance processes.

Leadership
Pharmacists should assume leadership roles in a multidisciplinary effort to evaluate biosimilars for use through the formulary process. It is essential for pharmacists to take the lead within Pharmacy and Therapeutics committees (P&T committees). They must conduct objective analyses of comparative data demonstrating the safety and efficacy of biosimilars before adding an agent to the formulary and/or replacing innovator products. The formulary process may also be used to establish therapeutic equivalence of products not officially deemed to be biosimilar or interchangeable, yet in the same class. Pharmacists and P&T committees must remain objective in their evaluations of biosimilar products, as discussions regarding cost advantage will inevitably enter into the decision-making process. Cost advantages can be discussed and considered but should never be the primary concern or given priority over patient care.

Pharmacists can serve as leaders within their own departments or stores, educating fellow pharmacists about biosimilar agents through continuing education and clinical pearl activities. Pharmacists can also assist in the development of hospital and corporate policies concerning biosimilars both in and outside of the pharmacy department. Similarly, many important legislative decisions regarding biologic product

### Table 4: Biosimilars available in Europe

<table>
<thead>
<tr>
<th>MEDICATION NAME</th>
<th>ACTIVE INGREDIENT</th>
<th>REFERENCE PRODUCT</th>
<th>DATE OF AUTHORIZATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>RETACRIT</td>
<td>Epoetin zeta</td>
<td>Eprex/Erypo</td>
<td>12/18/2007</td>
</tr>
<tr>
<td>SILAPAZ</td>
<td>Epoetin zeta</td>
<td>Eprex/Erypo</td>
<td>12/18/2007</td>
</tr>
<tr>
<td>ACCOFIL</td>
<td>Filgrastim</td>
<td>Neupogen</td>
<td>9/18/2014</td>
</tr>
<tr>
<td>BIOGRASTIM</td>
<td>Filgrastim</td>
<td>Neupogen</td>
<td>9/15/2008</td>
</tr>
<tr>
<td>FILGRASTIM HEXAL</td>
<td>Filgrastim</td>
<td>Neupogen</td>
<td>2/6/2009</td>
</tr>
<tr>
<td>GRASTOFIL</td>
<td>Filgrastim</td>
<td>Neupogen</td>
<td>10/18/2013</td>
</tr>
<tr>
<td>NIVESTIM</td>
<td>Filgrastim</td>
<td>Neupogen</td>
<td>6/8/2010</td>
</tr>
<tr>
<td>RATIOGRASTIM</td>
<td>Filgrastim</td>
<td>Neupogen</td>
<td>9/15/2008</td>
</tr>
<tr>
<td>TEVAGRASTIM</td>
<td>Filgrastim</td>
<td>Neupogen</td>
<td>9/15/2008</td>
</tr>
<tr>
<td>ZARZIO</td>
<td>Filgrastim</td>
<td>Neupogen</td>
<td>2/6/2009</td>
</tr>
<tr>
<td>BEMFOLA</td>
<td>Follitropin alfa</td>
<td>GONAL-f</td>
<td>3/27/2014</td>
</tr>
<tr>
<td>OVALEAP</td>
<td>Follitropin alfa</td>
<td>GONAL-f</td>
<td>9/27/2013</td>
</tr>
<tr>
<td>INFLECTRA</td>
<td>Inflimab</td>
<td>Remicade</td>
<td>9/10/2013</td>
</tr>
<tr>
<td>REMSIMA</td>
<td>Inflimab</td>
<td>Remicade</td>
<td>9/10/2013</td>
</tr>
<tr>
<td>ABASAGLAR (PREVIOUSLY ABASRIA)</td>
<td>Insulin glargine</td>
<td>Lantus</td>
<td>9/9/2014</td>
</tr>
<tr>
<td>OMNITROPE</td>
<td>Somatropin</td>
<td>Genotropin</td>
<td>4/12/2006</td>
</tr>
</tbody>
</table>

Source: Ref 10
substitution will be decided in the future by individual states. This is another area in which informed pharmacists can serve as valuable resources of objective information.

Dispensing
This role is a given for pharmacists; however, it is important to keep in mind the particular responsibilities that accompany being the gatekeeper to products such as biosimilars. As the FDA has yet to offer guidance on a naming system for biosimilars, educating technicians and pharmacists who will fill and dispense these agents will reduce confusion. Pharmacists should always be aware of the products kept in the pharmacies at which they work and educate themselves on each unique product's appropriate storage, monitoring, transportation, and disposal requirements. Policies should be implemented to prevent possible medication errors between classes of biologics; these policies may include adequate signage and strategic placement of look-alike, sound-alike products. Dispensing pharmacists also have the responsibility of knowing and following specific legislation regarding biosimilars.

Pharmacists should also educate themselves and other healthcare providers about the FDA's “Purple Book.” Many pharmacists are very familiar with the “Orange Book,” which identifies drug products (small molecule drugs) approved by the FDA and discusses the safety, efficacy, and interchangeability of these agents. The Purple Book is a similar publication about biologic products. It contains information about all biologic products, including biosimilar and interchangeable biologic products licensed by the FDA under the PHS Act. This book includes information about the date that a biologic product was licensed under 351(a) of the PHS Act and whether the FDA evaluated the biologic product for reference product exclusivity under section 351(k) of the PHS Act. The Purple Book enables healthcare providers to determine whether the FDA has determined a biologic product to be biosimilar or to interchangeable with a reference product. Biosimilar and interchangeable biologic products licensed under 351(k) will be listed under the reference product to which biosimilarity or interchangeability has been demonstrated.

Postmarket reporting/pharmacovigilance
As biosimilars become more integrated into the healthcare system and their use in patients increases, it is important for pharmacists to remember that their role does not end with education and dispensing of the medication. As they are at the front line of patient care, pharmacists play a key role in reporting adverse events and therapeutic outcomes related to biosimilar therapy just as they currently do for other drug therapies. The FDA will undoubtedly keep a close eye on postmarket reports regarding biosimilars due to the production and long-term safety controversies that surround them and the abbreviated pathways through which they are approved. As more biosimilars are approved by the FDA and put into large-scale production, pharmacists should maintain constant pharmacovigilance over the quality and observed effects of these agents to ensure optimal patient safety.

As the medication experts of the healthcare field, pharmacists have a professional responsibility to themselves, their patients, and the rest of the healthcare team to take on the roles described above. The first biosimilar has been officially approved by the FDA, so these proposed roles are actively becoming less of a proposal and more of a reality for many practitioners.

Conclusion
The use and development of biologics within the United States have increased substantially over the past decade. With the FDA’s approval of the first biosimilar Zarxio (filgrastim-sndz), this is a new and exciting time in pharmacy. It is also a time for pharmacists to familiarize themselves with the special considerations associated with these agents. Biosimilars are, as a whole, complex agents that are unlikely to be identical to the innovator products they are attempting to mimic because of the intricacies of biologic production processes. As most of these agents will gain FDA approval via the abbreviated pathway granted by the BCPIA of 2010, the role of the pharmacist is extremely important in the evaluation of biosimilar products and their adoption onto formularies. Even though the groundwork for the biosimilar industry has been laid out, there are still many areas of uncertainty as the FDA monitors postmarket surveillance reports and states individually decide on product substitution policies. In the meantime, pharmacists should do their best to educate themselves and provide objective information to providers and patients while keeping patient safety as the number one priority.

References are available online at www.drugtopics.com/cpe.
### TEST QUESTIONS

**1.** Which of the following represents the only biosimilar currently available in the United States?
   - a. Biogestim
   - b. Tevagrestim
   - c. Grastofill
   - d. Zaxio

**2.** Which of the following agencies is responsible for the scientific evaluation of marketing authorization applications for biosimilar agents in the European Union?
   - a. European Commission
   - b. European Medicines Agency
   - c. European Monitoring Centre for Drugs and Drug Addiction
   - d. European Centre for Disease Prevention and Control

**3.** Oncologic biosimilars that are currently in the development pipeline of many major pharmaceutical manufacturers include all of the following except:
   - a. Pertuzumab
   - b. Trastuzumab
   - c. Bevacizumab
   - d. Cetuximab

**4.** Remsima and Inflectra are European biosimilars with which of the following active ingredients?
   - a. Etanercept
   - b. Adalimumab
   - c. Infliximab
   - d. Golimumab

**5.** In Europe, approved biosimilars are available for each of the following classes with the exception of:
   - a. Monoclonal antibodies
   - b. Low-molecular-weight heparins
   - c. Follicle-stimulating hormones
   - d. Granulocyte colony-stimulating factors

**6.** Who has the FDA left in charge of deciding biosimilar product substitution policies?
   - a. Pharmacists
   - b. Third-party payers
   - c. Individual states
   - d. FDA

**7.** Which is not a role of the pharmacist in the area of biosimilars?
   - a. Leadership
   - b. Pharmacovigilance
   - c. Education
   - d. Prescribing

**8.** Whom can the pharmacist help educate on biosimilars?
   - a. Prescribers
   - b. Patients
   - c. Legislators
   - d. All of the above

**9.** Which reference can be used by healthcare providers to determine whether a biosimilar is interchangeable with a reference product?
   - a. Manufacturer’s package insert
   - b. Orange Book
   - c. Purple Book
   - d. Red Book

**10.** The Biologics Price Competition and Innovation Act (BPCIA) was enacted in March 2010 as part of which of the following acts?
   - a. Hatch-Waxman Act
   - b. Affordable Care Act
   - c. Drug Price Competition and Patent Term Restoration Act
   - d. None of the above

**11.** For an agent to receive approval as an “interchangeable biologic,” the following has to be proven:
   - a. The product is highly similar to the reference product
   - b. There is no clinically meaningful differences between the product and the reference product
   - c. The risk of switching or alternating is not greater than the risk of using the reference product consistently
   - d. All of the above

**12.** A biologic product can be approved by which pathway?
   - a. Biosimilar biologic
   - b. Interchangeable biologic
   - c. Noninnovator biologic
   - d. All of the above

**13.** Which pathway for approval requires the manufacturer to supply the most data for approval?
   - a. Biosimilar biologic
   - b. Interchangeable biologic
   - c. Noninnovator biologic
   - d. Small molecule generic drug

**14.** Under which section of the Public Health Service Act does a manufacturer need to file a Biologics License Application for a biosimilar product?
   - a. 351(a)
   - b. 351(k)
   - c. 350(b)
   - d. None of the above

**15.** Under which section of the Public Health Service Act does a manufacturer need to file a Biologics License Application for an innovator product?
   - a. 351(a)
   - b. 351(k)
   - c. 350(b)
   - d. None of the above

**16.** A manufacturer is granted how many years of exclusivity for an innovator biologic product?
   - a. Ten years
   - b. 12 years, plus an additional six months if studies are done in pediatric patients
   - c. Six years
   - d. One year

**17.** The stepwise approach the FDA uses for approval of biosimilar products includes:
   - a. Structural analyses
   - b. Animal studies
   - c. Human studies
   - d. All of the above

**18.** As part of the approval process for a biosimilar biologic product, a manufacturer must submit a Biologics License Application under section 351(k) of the Public Health Service Act with scientific data demonstrating that the biologic product:
   - a. Is biosimilar to the reference product
   - b. Has the same mechanism of action
   - c. Has the same dosage form and strength
   - d. All of the above

**19.** Human studies are used in the approval process of biosimilars to determine information about:
   - a. Pharmacodynamics
   - b. Pharmacokinetics
   - c. Immunogenicity
   - d. All of the above

**20.** The following is true regarding FDA regulations for the naming of biosimilar biologic products:
   - a. Must use nonproprietary name of the innovator product
   - b. Must use a suffix attached to the nonproprietary name of the innovator product
   - c. Must use a suffix attached to the nonproprietary name of the innovator product
   - d. The FDA currently has no regulation for the naming of biosimilar products
References


