

CONTINUING EDUCATION STUDY GUIDE

# A Health-System Pharmacist's Guide to Biosimilars: Regulatory, Scientific, and Practical Considerations

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# A Health-System Pharmacist's Guide to Biosimilars: Regulatory, Scientific, and Practical Considerations

## A Discussion Guide for Health-System Pharmacists on Biosimilars

### Continuing Education Study Guide

This Continuing Education Discussion Guide is part of an educational initiative designed to prepare pharmacists for the introduction of biosimilars into clinical practice in the United States. For additional resources on this topic, including an on-demand continuing education activity, visit [www.biosimcentral.org](http://www.biosimcentral.org).

*The estimated time to complete this activity is 90 minutes. This activity is provided free of charge and is available from March 1, 2013, through August 1, 2014.*

### Learning Objectives

After participating in this knowledge-based activity, participants should be able to

1. Describe the legal and regulatory history of the abbreviated pathway for approval of biosimilars by the Food and Drug Administration (FDA), explain FDA requirements for biosimilarity and interchangeability, and discuss the potential clinical and economic impact of biosimilars in the United States.
2. Compare and contrast the size, chemical structure, and manufacturing process for traditional chemical drugs and biological products, and explain how these factors affect product purity, potency, safety, and effectiveness.
3. Describe the review process used by FDA for biosimilar approval and how the European experience with biosimilars is likely to affect the approach used by FDA.
4. Explain factors that affect the immunogenicity of biopharmaceuticals and the importance of postmarketing pharmacovigilance to ensure the safe use of biosimilars.
5. Discuss the role of health-system pharmacists in making formulary decisions about biosimilars, conducting pharmacovigilance activities, and educating health care administrators, providers, legislators, policymakers, payors, and patients about these products.

### Target Audience

This activity was planned to meet the needs of health-system pharmacists who will be in a position to promote the appropriate use of biosimilars and provide education about biosimilars to policymakers, patients, and decision makers in health systems and payor organizations.

### System Requirements

**Web Browser:** Microsoft Internet Explorer, Mozilla Firefox, Apple Safari or Google Chrome.

*Note:* Please disable any "pop-up blocker" features.

**Software:** Adobe Acrobat Reader version 7 or above to view PDF files (If you do not have Acrobat Reader, you can download it for free from [get.adobe.com/reader](http://get.adobe.com/reader)).

**Connection Speed:** Cable, DSL, or better of at least 300 kbps.

## Executive Summary

To improve the affordability of popular but costly biological therapies, an abbreviated pathway for approval by the Food and Drug Administration (FDA) has been established for biological products that are "highly similar" (biosimilar) to or interchangeable with the innovator biological product. Biosimilars are not completely identical to the innovator product because of the large molecular size, complexity and proprietary nature of the manufacturing process, and inherent variability of all biopharmaceuticals. A step-wise approach to evaluating a totality of the evidence from analytical, preclinical, and clinical studies will be used by FDA to evaluate biosimilars. The agency is likely to establish product- and class-specific requirements for data demonstrating biosimilarity, an approach similar to that established by the European Union, where a pathway to biosimilar approval has been implemented. Postmarketing pharmacovigilance is needed for biosimilars because of the potential for a unique adverse effect profile that differs from that for the innovator product. The FDA review process is a work in progress because of unresolved questions about product exclusivity, naming, and other issues. Health-system pharmacists play an important role in making formulary decisions about biosimilars; educating health care administrators, providers, legislators, policymakers, payors, and patients about these products; and conducting pharmacovigilance activities to ensure the safe use of biosimilars in the institution.

## Reviewers and Disclosures

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Ms. Dombrowski declares that she has no relationships pertinent to this activity.

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## Related to Your Practice

1. What biopharmaceuticals are on your institution's formulary?
2. What biological products have you dispensed?
3. During the next year or two, could you be involved in evaluating biosimilars for your formulary?
4. Will you have a role in educating patients and/or other clinicians about biosimilars?
5. Have any serious adverse reactions to biological products been reported at your work place?

## Introduction

Biopharmaceuticals are widely used to treat a variety of common diseases and conditions, including cancer, anemia of chronic renal failure, rheumatoid arthritis, and other immune diseases. The introduction of biopharmaceuticals has had a substantial impact on oncology, nephrology, rheumatology, and other areas of clinical practice. Biological products are expensive because of the high costs for research, development, and manufacturing. The use of and costs associated with biological products have increased markedly in the past decade in the United States. In 2000, only one of the top 10 drug products based on sales was a biopharmaceutical, but five of the top 10 drug products were biopharmaceuticals by 2008.<sup>1</sup> In 2011, biopharmaceuticals comprised 10 of the top 15 drugs used in clinics based on expenditures.<sup>2</sup> Worldwide sales of biopharmaceuticals are expected to increase from \$92 billion in 2009 to more than \$167 billion annually by 2015.<sup>3</sup> Monoclonal antibody products are expected to drive the majority of the growth in the biopharmaceuticals market in the coming years.<sup>3</sup>

The process for obtaining approval for biopharmaceuticals from the Food and Drug Administration (FDA) involves submission of a biologics license application (BLA) supported by extensive clinical trial data that are costly and time consuming to develop. An abbreviated pathway for FDA approval of biological products that are "highly similar" (i.e., biosimilar) to or interchangeable with a biological product was established by the Biologics Price Competition and Innovation Act of 2009 (BPCI Act), which amended the Public Health Service Act and was signed into law in March 2010 as part of the Patient Protection and Affordable Care Act.<sup>4,5</sup> The goal of the BPCI Act is similar to that of the Drug Price Competition and Patent Term Restoration Act of 1984 (known as the Hatch-Waxman Act), which established abbreviated pathways for the approval of small-molecule, chemically-synthesized drug products under the Federal Food, Drug, and Cosmetic Act.<sup>4</sup> In implementing the BPCI Act, FDA seeks to allow the use of established knowledge of a drug, thereby avoiding unnecessary duplication of effort for clinical research and saving time and resources.<sup>4</sup>

Statutory provisions of the BPCI Act establish two separate standards for biosimilarity and interchangeability. A biosimilar product may be approved by FDA if data demonstrate that the product is "highly similar" to the reference (i.e., innovator) product notwithstanding minor differences in clinically-inactive ingredients and there are no clinically-meaningful differences between the biological product and the reference product in safety, purity, or potency.<sup>6</sup> A higher standard was established for interchangeable biosimilar products, which must produce the same clinical results (i.e., neither greater nor lesser effectiveness) as the reference product.<sup>5</sup> When multiple doses are used in a patient, 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.

Biological product is defined by the U.S. government as "any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment, or cure of diseases or injuries of man."<sup>7</sup> Most biological products are proteins, and these products can be thought of as therapeutic proteins from a medication-use perspective. In fact, the term "proposed therapeutic protein" is used by FDA for a biological product seeking to demonstrate biosimilarity to a reference biological product as part of a marketing application.<sup>8</sup> A variety of terms have been used for biological products that are similar to a reference biological product and approved using an abbreviated regulatory process. These terms include biosimilar, follow-on biologic, follow-on protein, generic biopharmaceutical, biogeneric, comparable biologic, and subsequent-entry biologic.<sup>9</sup> Biosimilar currently is the term used by FDA, and this term is widely accepted across the United States.

## Manufacturing Complexity

Most biological products have a larger molecular weight and more complex three-dimensional structure than traditional drugs (Table 1), although biopharmaceuticals vary in size and complexity.<sup>11</sup> Some biopharmaceuticals (e.g., growth hormone, insulin) are relatively simple, but monoclonal antibody products (e.g., bevacizumab, trastuzumab) are larger, more complex molecules.

TABLE 1

**Differences Between Small-Molecule Drugs and Biopharmaceuticals<sup>10,11</sup>**

CHARACTERISTIC	SMALL-MOLECULE DRUGS	BIOPHARMACEUTICALS
Structure	Simple	Complex
Size	Small, with low molecular weight	Large, with large molecular weight
Ease of characterization	Readily defined	Difficult to fully characterize
Manufacturing process	Straightforward, predictable, controlled, organic chemistry reactions using known chemicals and reagents	Complex, involving living systems
Purity and stability of product	High purity and stability	Heterogeneous product with impurities, vulnerable to environmental factors and improper handling
Immunogenicity	Low	High

Although it is feasible to fully define the structure of and reproduce small-molecule drugs, the larger size and greater complexity of biological products and limitations of currently available analytical techniques make it difficult to fully characterize the chemical structure and physicochemical and biological properties of biological products.<sup>8</sup> Improvements in these analytical techniques have been made, but limitations remain. Small differences in the chemical structure can have substantial effects on the safety, purity, and potency of biological products.<sup>8</sup> These changes could affect the effectiveness and safety of the product.

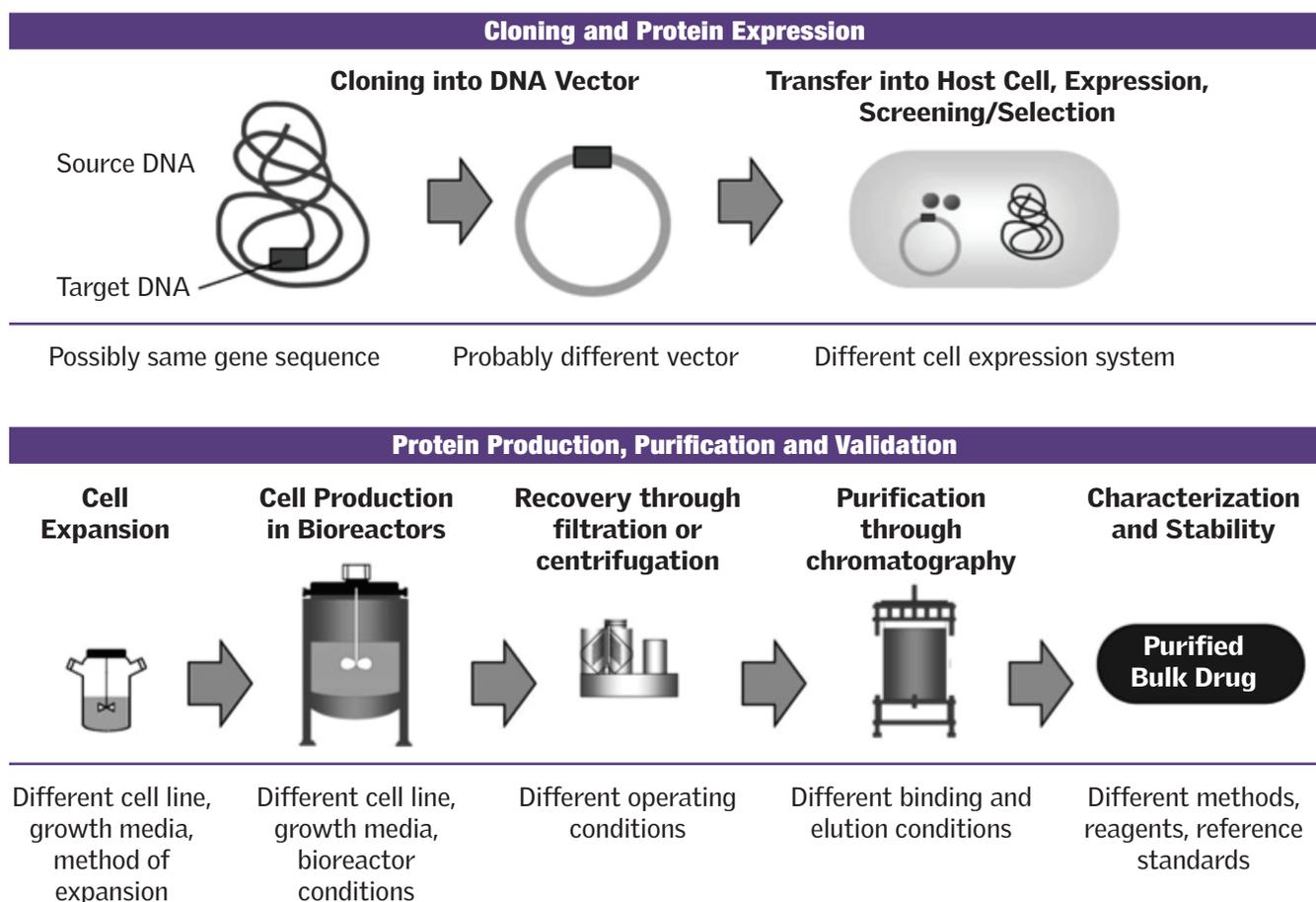
The manufacturing process for biological products is more complex than that for small-molecule drugs, which are produced through chemical reactions that are controlled and predictable. Biological products are produced in living systems, (e.g., bacteria; viruses; plant, animal, or human cells).<sup>5</sup> Biological products are affected by changes to the manufacturing process to a greater extent than are small-molecule drugs.<sup>10</sup> The biological systems in which proteins are produced are inherently variable and can have a substantial effect on the structure and function of the product.<sup>12</sup> Therefore, biological products are characterized by variability, even among different lots of the same product.

Many biological products are proteins that are similar or identical to human proteins and developed

through recombinant DNA technology. Proteins can vary in the primary amino acid sequence, modifications made to the amino acid chain (e.g., pegylation, glycosylation, or addition of other side chains to form a secondary structure), and the higher order structure of the protein (e.g., folding to form a tertiary structure, more complex interactions to form a quaternary structure).<sup>8</sup> Proteins typically are stabilized by weak bonds and vulnerable to environmental factors (e.g., light, temperature, moisture) that can compromise the structural integrity of the protein.<sup>8,11</sup>

Figure 1 illustrates the steps in recombinant protein manufacture and sources of variability. The human DNA sequence that encodes the desired protein is identified, isolated, inserted into a vector, and incorporated into the genome of a suitable host cell (e.g., bacterium, mammalian cell).<sup>11,13</sup> Bacterial host cells are inexpensive, easy to grow, and generate high product yields, but they cannot be used to produce large, complex proteins.<sup>14</sup> By contrast, mammalian cells can be used to produce large, complex proteins, but they are costly and generate low product yields.<sup>14</sup> A master cell bank with identical cells that produce the desired protein is established through cell screening and selection. The master cell bank is then used to culture additional cells on a large-scale basis under strictly-defined conditions that optimize the production of the protein. In the purification step,

FIGURE 1

**Recombinant protein production: sources of variation between manufacturers<sup>13</sup>**

Mellstedt H, Niederwieser D, Ludwig H, *Annals of Oncology*, 2008, 19, 412 by permission of Oxford University Press.

undesired proteins and other impurities are removed from the culture medium. The harvested protein is analyzed for uniformity in its three-dimensional structure and potency using a variety of analytical tools, including physicochemical and biological tests. The protein is then formulated by adding excipients (e.g., antioxidants, osmotic agents, buffers), placed into containers and packages, and stored and shipped under appropriate environmental conditions.

Modification of any of the steps in the manufacture of biological products (e.g., use of a different vector to create a host cell, system for screening and selection to establish a master cell bank, culture medium, method for protein production or purification, or excipients) has the potential to alter the effectiveness and safety of the product.<sup>11,13,15</sup> Therefore, a manufacturer may be required by FDA to assess the effects of changes to its processes

for manufacturing a protein using appropriate analytical tests, functional assays, and animal and clinical studies to ensure that the change does not adversely affect the identity, quality, purity, potency, safety, or effectiveness of the product.<sup>8</sup> In many cases involving a change by the innovator to its own processes, nonclinical and clinical safety and efficacy data are not needed because analytical testing and functional assays suffice.<sup>12</sup>

The manufacturing process and environmental conditions used for the innovator product usually are difficult for a different manufacturer to duplicate because of their proprietary nature and complexity. Therefore, biosimilars are highly unlikely to be completely identical to innovator products. Whether minor differences in the product affect potency, safety, or purity is the question addressed by regulatory agencies evaluating biosimilars for approval.

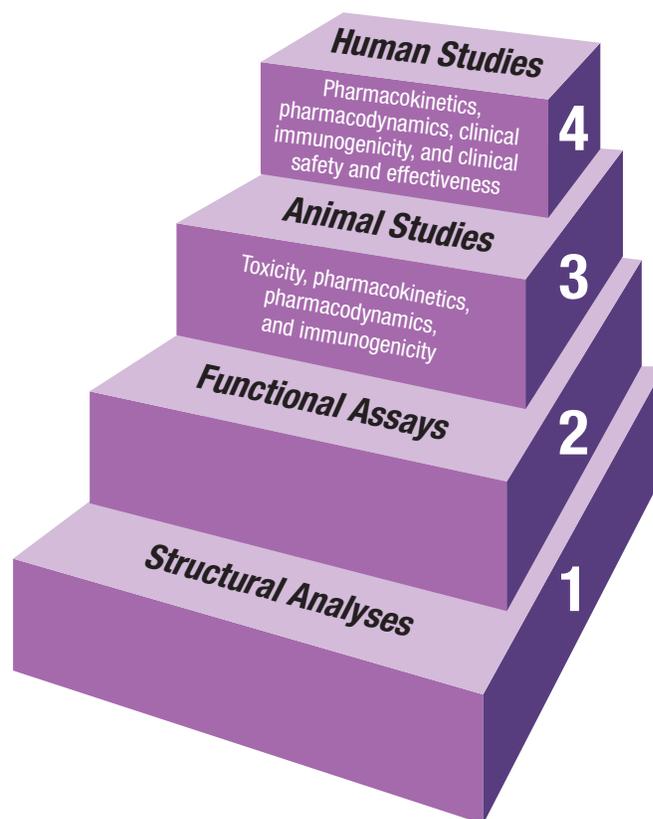
## FDA Review Process

Because biosimilars are not the same as the innovator product, the FDA approval process used for generic small-molecule drugs, which entails demonstration of pharmaceutical equivalence and bioequivalence through analytical testing (i.e., identical active ingredients) and comparative bioavailability studies, is inadequate for biosimilars.<sup>15,16</sup> The FDA approval process for biosimilars is governed by the Public Health Service Act. It involves comparison of biosimilars with the innovator product using data derived from analytical studies demonstrating high similarity of the proposed therapeutic protein to the reference product (notwithstanding minor differences in clinically-inactive components), animal studies (including assessment of toxicity), and clinical studies (including assessment of immunogenicity and pharmacokinetics or pharmacodynamics).<sup>8</sup> These data must be sufficient to demonstrate safety, purity, and potency in conditions of use for which the reference product is licensed and the biosimilar is intended to be used.<sup>8</sup> A step-wise approach to demonstrating biosimilarity and interchangeability, starting with structural and functional characterization and proceeding to animal studies (toxicity, pharmacokinetics, pharmacodynamics, and immunogenicity), and human studies (pharmacokinetics, pharmacodynamics, clinical immunogenicity, and clinical safety and effectiveness), is recommended by FDA (Figure 2) because the findings at each step may help guide subsequent testing.<sup>8</sup> The agency has the discretion to determine that some requirements are not needed and recognizes that a one-size-fits-all approach to evaluating data is not practical.<sup>17</sup> A totality-of-the-evidence approach to evaluating data will be used by FDA, with no defined threshold for the scope or amount of data required. The data required by FDA will vary by the drug and drug class.<sup>17</sup>

To strike a balance between improving the affordability of biological products and fostering innovation by manufacturers, the BCPI Act established 12 years of exclusivity for an innovator biological product, with an additional 6 months if studies in pediatric patients are conducted.<sup>6</sup> An application for a biosimilar product may not be submitted to FDA for 4 years after approval of the innovator product. One year of exclusivity is granted for the first interchangeable biosimilar.

FIGURE 2

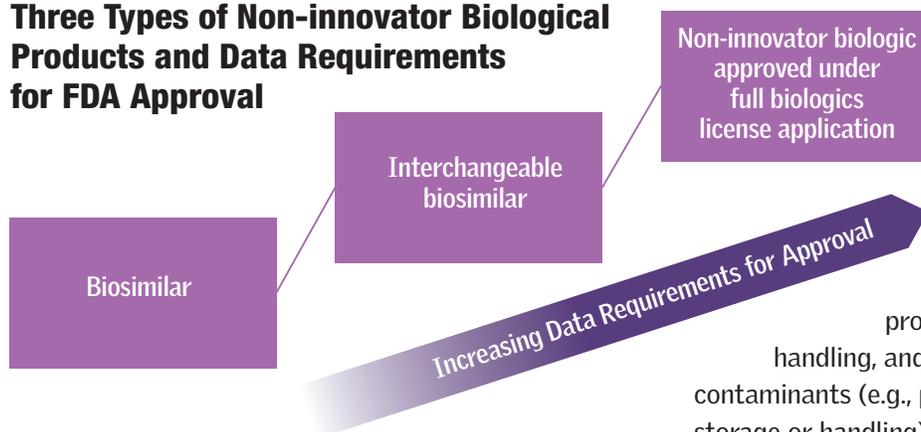
### FDA Step-Wise Approach to Demonstrating Biosimilarity and Interchangeability<sup>8</sup>



Manufacturers of non-innovator products may submit a full BLA to FDA instead of following the abbreviated pathway established by the BPCI Act, although the requirements for supporting data are greater. This approach has the potential to create a third type of non-innovator biological product on the U.S. market in addition to biosimilars and interchangeable biosimilars (Figure 3). Approval by FDA of tbo-filgrastim, a human granulocyte colony-stimulating factor produced through recombinant DNA technology, in August 2012 is an example of such a product.<sup>18</sup> It was approved based on data obtained from clinical efficacy and safety studies of tbo-filgrastim, not data extrapolated from the innovator filgrastim product (Neupogen, Amgen). The agency does not consider this product biosimilar to or interchangeable with Neupogen.<sup>19</sup>

FIGURE 3

### Three Types of Non-innovator Biological Products and Data Requirements for FDA Approval



### Safety

Infections and immune system disorders are the most common safety problems associated with biopharmaceuticals.<sup>20</sup> Because biopharmaceuticals are produced in living organisms, both innovator and biosimilar products are inherently heterogeneous and can elicit an immune reaction.<sup>15</sup> Immune reactions to biopharmaceuticals are potentially serious and life-threatening, although allergy, anaphylaxis, and serum sickness are now rare because of improvements in the purity of biopharmaceuticals.<sup>21</sup>

There are two types of immune reactions to biopharmaceuticals: classical reactions and the breakdown of immune tolerance. Classical reactions are the result of exposure to antigens perceived as foreign (e.g., replacement clotting factors in patients with inherited deficiencies, products from animal or plant sources).<sup>21</sup> Neutralizing antibody formation and the loss of product efficacy typically occurs quickly and persists. Increasing the dose may partly overcome the loss of efficacy.

Breakdown of immune tolerance may develop after administration of recombinant human proteins due to the presence of impurities or aggregates.<sup>21</sup> Although these proteins are not perceived as foreign, antibodies form that bind the impurities or protein aggregates.<sup>21</sup> The breakdown of immune tolerance is less common than classical reactions. It usually is slow to develop. The binding antibodies may disappear during or after discontinuation of treatment.

Various product- and patient-related factors contribute to the immunogenicity of biopharmaceuticals.<sup>11,21,22</sup> Product-related factors include structural properties (e.g., amino acid sequence, glycosylation), processing, formulation, storage, handling, and the presence of impurities or contaminants (e.g., protein aggregates due to improper storage or handling).<sup>11,21</sup> Patient-related factors include genetic background, immune status, and route and duration of administration.<sup>11,21</sup> Immunogenicity is lower in immunocompromised patients than immunocompetent patients because of impaired antibody formation.<sup>11</sup> Intramuscular and subcutaneous injections are more immunogenic than intravenous injection.<sup>11</sup> Topical administration is less immunogenic than all three types of injection. A long duration of administration is associated with high immunogenicity.<sup>11,21</sup>

The immunogenicity of biopharmaceuticals is difficult to predict because of the limitations in available immunogenicity assays.<sup>11</sup> The potential for immunogenicity when switching between an innovator and biosimilar is a concern.<sup>23</sup> Data from crossover (i.e., switching) studies in which patients switch from the innovator to a biosimilar or vice versa are particularly useful for demonstrating the safety of biosimilars.<sup>9</sup>

Postmarketing pharmacovigilance is needed to detect and assess immunogenicity and other safety problems with all biological products. Rare but potentially serious adverse events are unlikely to be detected before marketing.<sup>23</sup> The extent to which the safety profile of biosimilars is similar to that of the innovator product will be unclear at the time of approval. Adverse events unique to biosimilars (i.e., not associated with the innovator product) could be observed because of minor differences between products, although the risk for serious new adverse events is lower for biosimilars than when an innovator product containing a new substance is first introduced into the market.<sup>23</sup> The adverse effect profiles of biosimilars and innovator biological products could differ in clinically-important ways.

## Europe as a Model

A regulatory framework for approval of biosimilars was established in 2005 by the European Medicines Agency (EMA), the FDA counterpart in the European Union (EU), and the first biosimilar (somatropin) was approved by EMA in 2006. Numerous biosimilars, including filgrastims and epoetins, have since been approved for use in the EU, although approval has been denied for some products (e.g., an interferon product).<sup>23</sup> The experience in Europe can provide important insights and may serve as a model for efforts to refine the FDA biosimilar approval process and resolve unanswered questions pertaining to biosimilars in the United States. An EMA-FDA biosimilar "cluster" has been established to facilitate communication between the agencies about the development of biosimilars.<sup>23</sup>

In the EU, biosimilar is defined as a copy version of an already authorized biological medicinal product with demonstrated similarity in physicochemical characteristics, efficacy, and safety based on a comprehensive comparability exercise.<sup>15</sup> Biosimilars must be shown to be of a "similar nature in terms of quality, safety, and efficacy" compared with the innovator.<sup>24</sup>

In the EU, 10–11 years of exclusivity are provided to manufacturers of innovator biological products after which time manufacturers of biosimilars may submit applications for marketing approval to EMA.<sup>25</sup> Preclinical and clinical testing, with special attention to immunogenicity and postmarketing testing and surveillance, are required for all biosimilars approved for use in the EU. Biosimilar approval decisions by EMA are made on a totality-of-the-evidence basis, using a step-wise approach to demonstrate biosimilarity based on data from preclinical and clinical testing.<sup>23</sup> This step-wise approach and totality-of-evidence basis for biosimilar approval are the model for what will be implemented in the United States. Product- and class-specific guidelines outlining preclinical and clinical data requirements for biosimilars have been established by EMA for various biopharmaceuticals (e.g., recombinant human insulin) along with overarching guidelines for all biosimilars.<sup>24,26,27</sup> The product- and class-specific requirements vary considerably. The term used by EMA in its guidelines is "similar biological medicinal product", although biosimilar is commonly used instead. The EMA guide-

lines were developed by expert committees, national authorities, members of the scientific community, and industry representatives, with input from the public. The guidelines and information on the documentation submitted in support of a specific biosimilar application are made available to the public by EMA. Prescribing information for biosimilars provides information about the biosimilar nature of the product and directs readers to the EMA web site for additional details. A similar approach with the creation of product- and class-specific guidance to industry probably will be used by FDA because of the unique considerations in approving biosimilars for specific drugs and drug classes.

A risk management plan for postmarketing surveillance and pharmacovigilance is routinely required by EMA for all newly-approved medications, including biosimilars.<sup>9,23,28</sup> The EU recently implemented new legislation strengthening its pharmacovigilance system for all medical products.<sup>29</sup> Proactive and proportionate risk management, a higher quality of safety data, stronger link between safety assessments and regulatory action, and improved transparency, communication, and patient involvement are elements of the pharmacovigilance system improvements. Clear tasks and responsibilities for all parties (e.g., EMA, manufacturers), improved EU decision-making procedures, and efficient use of resources are other components of the new legislation. A new scientific committee at EMA (the Pharmacovigilance Risk Assessment Committee) has been established to assess and monitor medication safety issues.

The extensive product approval process in the EU establishes the therapeutic equivalence and interchangeability of a biosimilar for the innovator biological product.<sup>28</sup> However, substitution of biosimilars for the innovator product is not addressed in the guidelines.<sup>28</sup>

## Economic Impact

The patents on a large number of costly biopharmaceuticals will expire in the near future.<sup>30</sup> The introduction of biosimilars is expected to increase competition among manufacturers, reduce prices, and improve patient access to these products.<sup>31</sup> The cost savings are likely to be smaller on a percentage basis than those realized from the use of generic small-molecule products instead of the innovator product, which can amount to 75% to

80%.<sup>9,10</sup> Cost savings of up to 40% are projected from use of biosimilars instead of the innovator product in the United States.<sup>31</sup> In the EU, price discounts of up to 35% have been realized from such substitutions.<sup>32</sup> A savings of approximately \$25 billion in expenditures for biologics is anticipated in the United States over the period from 2009 to 2018 from the introduction of biosimilars.<sup>31</sup>

Although the introduction of biosimilars is expected to improve the affordability of treatment for cancer and other common diseases, coverage and reimbursement policies of payors for biosimilars remain to be determined and could affect patient access to these products.<sup>10</sup> Payors could deny reimbursement for biosimilars used for off-label indications because of a lack of efficacy and safety data.<sup>10</sup> Alternatively, payors could require the use of biosimilars instead of the innovator for off-label indications despite the lack of clinical data to reduce costs.<sup>10</sup> Such requirements are not necessarily inappropriate if extrapolation of data obtained from use of the product for approved indications is judged reasonable based on scientific considerations (e.g., mechanism of action, receptor, immunogenicity, safety profile).<sup>23</sup>

## Role of the Pharmacist

Health-system pharmacists should take a leadership role in a multidisciplinary effort to evaluate biosimilars for use in the institution through the formulary process. Because biosimilars are not completely identical to the innovator product, an objective analysis of comparative data demonstrating the efficacy and safety (especially immunogenicity) of a biosimilar for specific patient populations treated at the institution is needed. This evaluation should be conducted by the pharmacy and therapeutics (P&T) committee. The formulary evaluation process may be used to add a biosimilar to the formulary as an alternative to or replacement for an innovator product. The formulary process also may be used to establish therapeutic equivalence of products not deemed biosimilar but in the same class (e.g., epoetin alfa and darbepoetin alfa). In many health systems, a specific immune globulin i.v. product has been designated the preferred formulary agent, despite differences among products. Use of an alternative agent is permitted for patients with problems

(e.g., infusion reactions) with the preferred product. A similar approach to that used by the P&T committee to establish the therapeutic equivalence of immune globulin IV products may be used to establish the therapeutic equivalence of biosimilars and innovator biological products.

Cost advantages of biosimilars may enter into formulary decisions. However, cost should not be the primary consideration in formulary decisions.

The FDA provides guidance to industry about the types of data required from manufacturers to establish biosimilarity and interchangeability.<sup>8</sup> This guidance is relevant to health-system pharmacists and other members of the P&T committee contemplating use of biosimilars in the institution.

The FDA-approved labeling for biosimilars will explicitly state whether the product is biosimilar to the reference product for specific FDA-approved indications and whether it is deemed interchangeable.<sup>17</sup> A biosimilar might be approved by FDA for only some but not all of several FDA-approved indications of the innovator product (e.g., erythropoiesis-stimulating agents for treatment of anemia of chronic kidney disease but not cancer chemotherapy-induced anemia). Use of the biosimilar for the other indications for which it is not explicitly approved (i.e., indications that are off-label for the biosimilar but not the innovator product as well as indications that are off-label for both the innovator and biosimilar products) is controversial because of the lack of clinical data.<sup>10</sup> Biosimilar manufacturers may not be required by FDA or have the financial incentive to conduct studies of use of their product for off-label indications. The validity of extrapolating data from the innovator product to the biosimilar requires careful evaluation of the available data, especially immunogenicity data.<sup>23</sup> Health-system pharmacists can provide valuable input into decisions about use of biosimilars in the institution based on available clinical data.

Automatic substitution of generic small-molecule drugs without prior approval from the prescriber is permitted by law in most states based on published bioequivalence data.<sup>17</sup> This practice probably will not be permitted by state law for biosimilars, regardless of an FDA determination of interchangeability because state laws were developed years before the interchangeable

biosimilar designation was established by FDA.<sup>10</sup> In the future, state laws could be developed to address the substitution of biosimilars. Health-system pharmacists should provide input into the state legislative process and board of pharmacy actions pertaining to biosimilar substitution.<sup>17</sup>

Clinics, hospitals, and other health systems will be free to establish formal written agreements authorizing the therapeutic interchange of biosimilars for innovator biological products (i.e., automatic substitution of a formulary biosimilar for a non-formulary or non-preferred innovator product without contacting the prescriber).<sup>17,33</sup> Policies, procedures, and treatment algorithms based on these agreements should include opt-out provisions and provide guidance on dose conversion when switching between products. Strategies to avoid or minimize confusion when switching between products at transitions of care are needed. Questions have been raised about whether informed consent should be required from patients for substitution of biosimilars for innovator products, but this requirement is unnecessary because of the protection afforded by the FDA biosimilar approval process.<sup>23</sup>

## Education

Health-system pharmacists can play an important role in educating health-system administrators, physicians, other health care providers, legislators, policymakers, payors, and patients about the inherent variability of biopharmaceuticals, differences between innovator biological products and biosimilars, FDA approval process for biosimilars, and need for postmarketing pharmacovigilance.<sup>10</sup> Acceptance and use of biosimilars hinges on the comfort level of clinicians and payors after evaluating comparative data.<sup>17</sup> A 2011 survey by the National Comprehensive Cancer Network of conference attendees revealed that many respondents were not at all familiar with biosimilars legislation.<sup>10</sup> Physicians and nurses were less familiar with biosimilars than were pharmacists. Interest in using biosimilars was high among physicians, but a substantial percentage of physicians required additional information to make a decision about biosimilar use. Although many patients have assumed responsibility for and a large role in their own health care, patient interest in biosimilars probably will be strongly influenced by advice from

physicians.<sup>30</sup> Patients may not be aware of whether they are receiving an innovator or biosimilar. Payors are likely to feel economic pressure to use biosimilars, although assurance of clinical efficacy and safety will be required.<sup>30</sup> Awareness of the scientific and quality considerations associated with biosimilars can help legislators and policymakers weigh various stakeholders' competing interests, including the need for new product development, affordability, access to medications, and protection of public safety.<sup>10</sup>

## Pharmacovigilance

Health-system pharmacists play a vital role in the pharmacovigilance needed to detect, assess, and prevent adverse effects and other drug-related problems from biopharmaceuticals. A variety of methods may be used for pharmacovigilance, including prospective patient registries and data mining of billing claims databases and electronic health records.<sup>10</sup> Prospective patient registries are complex, cumbersome, and costly to implement.<sup>34</sup> Data mining is less burdensome and costly because it relies on routinely collected data, but it is not proactive.<sup>34</sup>

If risk evaluation and mitigation strategies (REMS) are required by FDA for innovator products, REMS are likely to also be required for biosimilars. These REMS requirements may provide a proactive strategy for managing safety concerns surrounding biosimilars. If possible, standardized processes should be developed to fulfill REMS requirements for the innovator and biosimilars (and to the extent possible, for all biological products in a therapeutic class) instead of REMS customized for each product.<sup>10,35</sup> The use of standardized REMS is likely to be the most cost-effective strategy for postmarketing pharmacovigilance by health-system pharmacists because it optimizes efficiency while fulfilling FDA requirements.

A system for linking adverse events to a specific biological product is needed for pharmacovigilance purposes.<sup>10</sup> The use of a related but unique nonproprietary name for biosimilars instead of the same nonproprietary name as the innovator product has been suggested to provide traceability.<sup>10,34</sup> Ideally the lot number of the product also would be documented at the time of administration.<sup>10,23</sup> Potential disadvantages of the use of unique nonproprietary names for

biosimilars include confusion and misconceptions among prescribers about the comparability and interchangeability of products, unintentional product substitution, and prescribing and administration errors.<sup>10</sup> A decision about biosimilar naming has not yet been made by FDA. In Europe, the International Nonproprietary Name (INN) system developed by the World Health Organization (WHO) is used for naming small-molecule and biological products.<sup>23</sup> Use of the unique proprietary (i.e., brand) name, manufacturer name, lot number, and country of origin is relied on for tracing biosimilars by WHO, which recommended against assigning unique INNs to biosimilars.<sup>36</sup>

## Conclusion

The FDA pathway to biosimilars approval was developed to improve affordability of and access to biological therapies, but it remains a work in progress because unresolved issues remain. Concerns about safety must be addressed through postmarketing pharmacovigilance. Health-system pharmacists can play an important role in ensuring the safe, effective, and cost-effective use of biosimilars in health systems.

## Accreditation for Pharmacists



The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This activity provides 1.5 hours (0.15 CEUs) of continuing pharmacy education credit (ACPE activity #0204-0000-13-418-H01-P).

## To Receive Continuing Pharmacy Education Credit

Once you have read the discussion guide, click on the link below to take the online assessment test (minimum score 70%) and complete the activity evaluation. Participants may print their official statements of continuing education credit immediately.

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**Please Note:** To claim CPE credit, you must have your NABP e-Profile ID, birth month, and birth day. If you do not have an NABP e-Profile ID, go to [www.MyCPEMonitor.net](http://www.MyCPEMonitor.net) for information and to apply.

## Assessment Test

This assessment test is provided as a study aid only. Follow the instructions above to complete your assessment test and evaluation online to obtain CE credit for this activity.

1. **Which of the following laws established the abbreviated pathway for approval of biosimilars in the United States?**
  - a. Biologics Price Competition and Innovation Act.
  - b. Public Health Service Act.
  - c. Drug Price Competition and Patent Term Restoration Act.
  - d. Federal Food, Drug, and Cosmetic Act.
2. **Which of the following statements about the FDA standard for interchangeability is correct?**
  - a. The innovator and biosimilar product must be evaluated for the same indications.
  - b. The innovator and biosimilar product must have the same chemical structure, purity, and stability.
  - c. The effectiveness of the biosimilar product must be the same as that of the innovator product.
  - d. The risk for harm must not increase when switching between the innovator and biosimilar product.
3. **Compared with traditional drugs, biopharmaceuticals are more:**
  - a. Homogenous.
  - b. Stable.
  - c. Immunogenic.
  - d. Simple in structure.
4. **The process for manufacturing biopharmaceuticals is:**
  - a. Straightforward but costly.
  - b. Straightforward and readily reproducible.
  - c. Complex but predictable.
  - d. Complex and costly.
5. **Which of the following will be required by FDA for biosimilars approval?**
  - a. A comprehensive approach with analytical, preclinical, and clinical evidence that exceed a threshold designed to ensure patient safety.
  - b. A totality-of-the-evidence approach with no defined threshold for evidence because the agency may determine that some requirements are not needed.
  - c. A standardized approach with analytical, preclinical, and clinical evidence to ensure fairness among market competitors.
  - d. A step-wise approach with progressively greater requirements for analytical, preclinical, and clinical evidence.
6. **Which of the following statements about the adverse effect profiles of biosimilars and innovator biological products is correct?**
  - a. They will be highly similar.
  - b. They will be identical.
  - c. They could differ in clinically-important ways.
  - d. They could differ but not in clinically-important ways.
7. **Which of the following is an aspect of the pathway for biosimilars approval by the European Union that has been or is likely to be adopted by FDA?**
  - a. Assignment of unique nonproprietary names.
  - b. Establishment of criteria for automatic substitution.
  - c. Establishment of product- and class-specific data requirements.
  - d. Granting 10–11 years of exclusivity before acceptance of biosimilars applications for marketing approval.

- 8. The projected cost savings from the use of biosimilars instead of the innovator product in the United States are as high as:**
- 20%.
  - 40%.
  - 60%.
  - 80%.
- 9. Based on a survey by the National Comprehensive Cancer Network, which of the following statements about the educational needs of physicians, nurses, pharmacists, and patients on biosimilars is correct?**
- Physicians and nurses are not as aware of biosimilars as pharmacists are, and education of physicians, nurses, and patients is needed.
  - Physicians and nurses are as aware of biosimilars as pharmacists are, and education is not needed.
  - Physicians and nurses are as aware of biosimilars as pharmacists are, but education of patients is needed.
  - Physicians are as aware of biosimilars as pharmacists are, but education of patients is needed.
- 10. Which of the following postmarketing pharmacovigilance activities is the most cost-effective, prospective strategy used by health-system pharmacists to assess the safety of biosimilar use in the health system?**
- Standardized REMS.
  - Customized REMS.
  - Data mining of billing claims databases.
  - Patient registries.

## Appendix. Biosimilars Resources

### American Society of Health-System Pharmacists

[www.ashp.org](http://www.ashp.org)

- *Preparing for biosimilars: scientific, regulatory, and practice management issues for pharmacists* initiative with learning opportunities designed to prepare pharmacists for the introduction of biosimilars into clinical practice in the U.S. ([www.biosimcentral.org](http://www.biosimcentral.org))
- ASHP policy 1218 on approval of biosimilar medications ([www.ashp.org/DocLibrary/Policy/HOD/OfficialLang2012Policies.aspx](http://www.ashp.org/DocLibrary/Policy/HOD/OfficialLang2012Policies.aspx))
- ASHP guidelines on the pharmacy and therapeutics committee and the formulary system ([www.ashp.org/DocLibrary/BestPractices/FormGdlPTCommFormSyst.pdf](http://www.ashp.org/DocLibrary/BestPractices/FormGdlPTCommFormSyst.pdf))

### European Medicines Agency

[www.emea.europa.eu/ema/index.jsp?curl=pages/regulation/general/general\\_content\\_000408.jsp&mid=WC0b01ac058002958c](http://www.emea.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp&mid=WC0b01ac058002958c)

- Overarching, product-specific, and other guidelines relevant to biosimilars
- Concept papers on biosimilars

### International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

[www.ich.org](http://www.ich.org)

- Guideline on Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process ([www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Quality/Q5E/Step4/Q5E\\_Guideline.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5E/Step4/Q5E_Guideline.pdf))
- Other quality, safety, and efficacy guidelines

### U.S. Food and Drug Administration

[www.fda.gov](http://www.fda.gov)

- Web page on biologics ([www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/default.htm](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/default.htm))
- Draft guidance for industry on scientific and quality considerations in demonstrating biosimilarity to a reference product
- Fact sheet on issuance of draft guidance for industry ([www.fda.gov/drugs/developmentapprovalprocess/howdrugsare-developedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/ucm291197.htm](http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsare-developedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/ucm291197.htm))

## References

- Blackstone EA, Fuhr JP Jr. Innovation and competition: will biosimilars succeed? The creation of an FDA approval pathway for biosimilars is complex and fraught with hazard. Yes, innovation and market competition are at stake. But so are efficacy and patient safety. *Biotechnol Healthc.* 2012; 9:24-7.
- Hoffman JM, Li E, Doloresco F et al. Projecting future drug expenditures—2012. *Am J Health-Syst Pharm.* 2012; 69:405-21.
- International Market Analysis & Research Consulting. Global biopharmaceutical market report (2010-2015). October 2010. [www.imarcgroup.com/global-biopharmaceutical-market-report-2010-2015/](http://www.imarcgroup.com/global-biopharmaceutical-market-report-2010-2015/) (accessed 2013 Jan 2).
- U.S. Food and Drug Administration. Implementation of the Biologics Price Competition and Innovation Act of 2009. [www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm215089.htm](http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm215089.htm) (accessed 2013 Jan 2).
- U.S. Food and Drug Administration. Draft guidance for industry. Biosimilars: questions and answers regarding implementation of the Biologics Price Competition and Innovation Act of 2009. February 2012. [www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM273001.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM273001.pdf) (accessed 2013 Jan 2).
- U.S. Congress. Sections 7001-7003 (Biologics Price Competition and Innovation Act of 2009) of the Patient Protection and Affordable Care Act (Public Law 111-148). [www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM216146.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM216146.pdf) (accessed 2013 Jan 2).
- U.S. Code of Federal Regulations. Biological products (21CFR600.3). April 1, 2012. [www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=600.3](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=600.3) (accessed 2013 Jan 2).
- U.S. Food and Drug Administration. Draft guidance for industry: scientific considerations in demonstrating biosimilarity to a reference product. February 2012. [www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf) (accessed 2013 Jan 2).
- Hirsch BR, Lyman GH. Biosimilars: are they ready for primetime in the United States? *J Natl Compr Canc Netw.* 2011; 9:934-43.
- Zelenetz AD, Ahmed I, Braud EL et al. NCCN biosimilars white paper: regulatory, scientific, and patient safety perspectives. *J Natl Compr Canc Netw.* 2011; 9(suppl 4):S1-22.
- Crommelin D. Pharmaceutical evaluation of biosimilars: important differences from generic low-molecular-weight pharmaceuticals. *Eur J Hosp Pharm Science.* 2005; 1:11-7. Available at: <http://archive.eahp.eu/Media/Home-page/EJHP-BMJ/EJHP-Science-archive/Issue-1-2005/Scientific-commentary/Pharmaceutical-evaluation-of-biosimilars-important-differences-from-generic-low-molecular-weight-pharmaceuticals>.
- U.S. Food and Drug Administration. Draft guidance for industry: quality considerations in demonstrating biosimilarity to a reference protein product. February 2012. [www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf) (accessed 2013 Jan 2).
- Mellstedt H, Niederwieser D, Ludwig H. The challenge of biosimilars. *Ann Oncol.* 2008; 19:411-9.
- Johnson PE. Implications of biosimilars for the future. *Am J Health-Syst Pharm.* 2008; 65(suppl 6):S16-22.
- Weise M, Bielsky MC, De Smet K et al. Biosimilars—why terminology matters. *Nat Biotechnol.* 2011; 29:690-3.
- U.S. Food and Drug Administration. Guidance for industry bioavailability and bioequivalence studies for orally administered drug products—general considerations. March 2003. [www.fda.gov/downloads/Drugs/.../Guidances/ucm070124.pdf](http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070124.pdf) (accessed 2013 Jan 2).
- Li E, Hoffman JM. Implications of the FDA draft guidance on biosimilars for clinicians: what we know and don't know. *J Natl Compr Canc Netw.* In press.
- Tbo-filgrastim prescribing information. North Wales, PA: Teva Pharmaceuticals USA; 2012 Aug. Available at: [www.accessdata.fda.gov/drugsatfda\\_docs/label/2012/125294s0000lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/125294s0000lbl.pdf) (accessed 2013 Jan 2).
- U.S. Food and Drug Administration. FDA approves new treatment for severe neutropenia in certain cancer patients. August 31, 2012. [www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm317392.htm](http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm317392.htm) (accessed 2013 Jan 2).
- Giezen TJ, Mantel-Teeuwisse AK, Straus SM et al. Safety-related regulatory actions for biologicals approved in the United States and the European Union. *JAMA.* 2008; 300:1887-96.
- Schellekens H. Factors influencing the immunogenicity of therapeutic proteins. *Nephrol Dial Transplant.* 2005; 20(suppl 6):vi3-9.
- Mukovozov I, Sabljic T, Hortelano G et al. Factors that contribute to the immunogenicity of therapeutic recombinant human proteins. *Thromb Haemost.* 2008; 99:874-82.

23. Weise M, Bielsky MC, De Smet K et al. Biosimilars: what clinicians should know. *Blood*. 2012; 120:5111-7. Available at: <http://bloodjournal.hematologylibrary.org/content/120/26/5111.full.pdf+html>.
24. European Medicines Agency Committee for Medicinal Products for Human Use. Guideline on similar biological medicinal products. October 30, 2005. [www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC500003517.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003517.pdf) (accessed 2013 Jan 2).
25. European Medicines Agency. EMA procedural advice for users of the centralized procedure for generic/hybrid applications. January 2012. [www.ema.europa.eu/docs/en\\_GB/document\\_library/Regulatory\\_and\\_procedural\\_guideline/2009/10/WC500004018.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004018.pdf) (accessed 2013 Jan 2).
26. European Medicines Agency Committee for Medicinal Products for Human Use. Guidelines on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. February 22, 2006. [www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC500003920.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003920.pdf) (accessed 2013 Jan 2).
27. European Medicines Agency Committee for Medicinal Products for Human Use. Guidelines on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues. February 22, 2006. [www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC500003953.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003953.pdf) (accessed 2013 Jan 2).
28. Ebbers HC, Crow SA, Vulto AG et al. Interchangeability, immunogenicity and biosimilars. *Nat Biotechnol*. 2012; 30:1186-90.
29. European Commission. The EU pharmacovigilance system. [http://ec.europa.eu/health/human-use/pharmacovigilance/index\\_en.htm](http://ec.europa.eu/health/human-use/pharmacovigilance/index_en.htm) (accessed 2012 Nov 16).
30. IMS Health. Shaping the biosimilars opportunity: a global perspective on the evolving biosimilars landscape. December 2011. [www.imshealth.com/ims/Global/Content/Home%20Page%20Content/IMS%20News/Biosimilars\\_Whitepaper.pdf](http://www.imshealth.com/ims/Global/Content/Home%20Page%20Content/IMS%20News/Biosimilars_Whitepaper.pdf) (accessed 2013 Jan 2).
31. U.S. Congressional Budget Office. Cost estimate S. 1695 Biologics Price Competition and Innovation Act of 2007. June 25, 2008. [www.cbo.gov/sites/default/files/cbofiles/ftpdocs/94xx/doc9496/s1695.pdf](http://www.cbo.gov/sites/default/files/cbofiles/ftpdocs/94xx/doc9496/s1695.pdf) (accessed 2013 Jan 2).
32. Reinke T. Biosimilars might not measure up to health plan expectations. *Managed Care*. October 2012. [www.managedcaremag.com/archives/1210/1210.medmgmt.html](http://www.managedcaremag.com/archives/1210/1210.medmgmt.html) (accessed 2013 Jan 2).
33. American Society of Health-System Pharmacists. ASHP guidelines on the pharmacy and therapeutics committee and the formulary system. *Am J Health-Syst Pharm*. 2008; 65:1272-83.
34. Hennessy S, Leonard CE, Platt R. Assessing the safety and comparative effectiveness of follow-on biologics (biosimilars) in the United States. *Clin Pharmacol Ther*. 2010; 87:157-9.
35. Johnson PE, Dahlman G, Eng K et al. NCCN oncology risk evaluation and mitigation strategies white paper: recommendations for stakeholders. *J Natl Compr Canc Netw*. 2010; 8(suppl 7):S7-27.
36. World Health Organization. Guidelines on evaluation of similar biotherapeutic products. October 2009. [www.who.int/biologicals/areas/biological\\_therapeutics/BIOOTHERAPEUTICS\\_FOR\\_WEB\\_22APRIL2010.pdf](http://www.who.int/biologicals/areas/biological_therapeutics/BIOOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf) (accessed 2013 Jan 2).