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Biosimilars: Implications for health-system pharmacists

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During the first decade of the 21st century, annual growth rates for U.S. drug expenditures were marked by overall consistent and sustained moderation.1 As an example, within the inpatient nonfederal hospital setting, pharmaceutical spending in the 12 months ending on September 30, 2012, was marked by negative growth (–0.4%), with the most current projections calling for an annual growth rate of −0.5% to 1.5% in 2013.1

While the cost of pharmaceuticals is driven by many elements, the factor most frequently cited as helping to sustain this trend is the introduction of generic alternatives for many commonly prescribed medications.1 At the end of 2010, generic drugs accounted for 78% of all retail prescriptions dispensed in the United States.2 A recent IMS Health report suggested that between 2002 and 2011, the availability and use of generic drugs resulted in a savings of $1 trillion for the U.S. health care system.3 Following the introduction of generic formulations of top-selling products such as enoxaparin, gemcitabine, meropenem, oxaliplatin, and docetaxel in recent years, two additional blockbusters, atorvastatin and clopidogrel, reached the end of their patent protection in 2012.

Although generic competition has moderated expenditures for many

Purpose. An update on scientific and regulatory challenges in the rapidly evolving field of biosimilar product development is presented.

Summary. The U.S. market for biosimilar products (i.e., highly similar "follow-on" versions of approved biological drugs) is expected to expand with establishment of an expedited-approval pathway for biosimilars similar to that implemented in European Union countries eight years ago. In 2012, the Food and Drug Administration (FDA) published draft guidance clarifying the requirements of the biosimilars approval pathway; although no biosimilar has yet been approved via that pathway, FDA is engaged in ongoing meetings with a number of potential applicants. Due to molecular differences between innovator products and biosimilar versions, biosimilars are highly sensitive to manufacturing changes that can potentially have important safety and efficacy implications. Establishing the interchangeability of biosimilar and innovator drugs may be difficult at first, and it is possible that some biosimilars might not carry all the same indications for which the reference drug is approved. Pharmaceutical cost savings attained through the use of biosimilars are expected to average 20–30%. With several top-selling biologicals likely to lose patent exclusivity by 2020, health systems should prepare for the availability of new biosimilars by addressing formulary management and therapeutic interchange issues, pharmacovigilance and patient safety concerns, and related financial and operational issues.

Conclusion. Over the coming years, biosimilars will present opportunities for health care organizations to manage the growth of pharmaceutical expenditures. Pharmacists can play a key role in preparing health systems for projected rapid expansion in the use of biosimilars and associated medication-use policy challenges.
blockbuster small-molecule medications, drug expenditure growth is increasingly associated with biologicals: drug products derived from living organisms. Frequently, these biological medications are more costly than small-molecule drugs and have narrow indications for use in serious and often chronic diseases. Historically in the United States, after expiration of the originator molecule’s patent, biologicals have not been subject to direct competition from alternative suppliers of products approved through an abbreviated approval process like that created 30 years ago to facilitate the marketing of lower-cost generic versions of nonbiological drugs. However, barriers to expedited approval of “follow-on” versions of originator biologicals, commonly referred to as biosimilars, are being removed.

The purpose of this article is to summarize basic information pharmacists and other clinicians need in order to successfully manage the introduction of biosimilars into health systems, including manufacturing, regulatory, and medication-use policy concepts.

The increasing importance of biologicals

Since the introduction of recombinant human insulin in 1982, the use of biological medications (also called therapeutic proteins) has continued to increase. The biological products bevacizumab, epoetin, infliximab, pegfilgrastim, rituximab, and trastuzumab are all among the top 15 medications used in both the hospital and clinic settings. In 2009, global sales of biologicals were $93 billion, and future sales are expected to grow at least twice as fast as those of small molecules. By 2016, 10 of the 20 top-selling drugs globally are expected to be biologicals. Many of these biologicals no longer move through traditional distribution methods but are supplied via specialty pharmacy distribution services. In 2011, this segment of the supply chain grew an estimated 17.1%. The increasing use of existing biologicals, coupled with the presence of numerous biologicals in the investigational drug pipeline, illustrates the increasing impact these products will have on overall pharmaceutical expenditures.

The introduction of lower-cost alternatives for branded small molecules was facilitated by the Drug Price Competition and Patent Term Restoration Act of 1984 (informally known as Hatch–Waxman), which established the abbreviated new drug application (ANDA) pathway for the approval of generic medications. The Hatch–Waxman Act balanced the need for originator-molecule manufacturers to have a meaningful period of patent protection and marketing exclusivity to recover development costs for new pharmaceuticals with the societal expectation of eventual access to less-expensive alternatives. Most important, the legislation allowed ANDA sponsors to seek approval through a demonstration of bioequivalence without the completion of separate clinical trials, thus enabling the marketing of generic medications at substantially discounted prices. However, the Hatch–Waxman Act only applies to small-molecule medications approved under the federal Food, Drug, and Cosmetic Act (FDCA).

The need for a regulatory pathway for copies of biologicals was finally addressed in 2010, when the Biologics Price Competition and Innovation (BPCI) Act was signed into law. The BPCI Act created an abbreviated process for Food and Drug Administration (FDA) approval of copies of a biological that are not developed by the maker of the originator drug. Because biologicals cannot be copied in the precise way a small molecule can be duplicated, the term biosimilar is used for these products. A biosimilar can be simply defined as a copy of a therapeutic protein not developed by the original manufacturer and approved through some abbreviated regulatory process. Formal definitions of biosimilar are available in the BPCI Act, and a consensus definition has been proposed. At the time this article was prepared, no marketing application for a biosimilar had been approved under the BPCI Act provisions, yet the relevant considerations for the appropriate use of these products are becoming clearer.

Due to their complexity, biosimilars will require a greater investment of time and clinical resources in support of approval as compared with small-molecule generics, which are adopted for use in health systems with little or no formulary review. All clinicians should familiarize themselves with the inherent differences between generic medications and biologicals and educate themselves on the rapidly expanding clinical literature concerning biosimilars. If the U.S. market is to realize the full financial and clinical benefits of biosimilars, pharmacists will need to take a leadership position in supporting an accurate understanding of these products and creating a clinical environment conducive to their safe and effective use. In addition to summarizing key principles related to the manufacture, regulation, marketing, and formulary management of biologicals and biosimilars, this article provides an outlook regarding the anticipated market in the United States based on the experience in Europe, as well as FDA’s historical approach to the approval of follow-on biologicals.

Differences between small molecules and biologicals

In order to differentiate small-molecule generics and biosimilars, pharmacists must be cognizant of key attributes of the two types of products. Although both categories of products are regulated and approved by FDA, important differences exist in their molecular complexity and manufacturing processes.
Molecular and manufacturing differences. As their name implies, small-molecule drugs are composed of molecular components that are comparatively small in size. They have relatively uncomplicated chemical structures made up of basic atomic units such as carbon, hydrogen, and oxygen.10 The molecular weights of these molecules range from a few hundred daltons (e.g., linezolid, ondansetron) to a few thousand daltons (e.g., daptomycin, enoxaparin).11-14 Small-molecule products are synthesized through predictable chemical processes and can be completely characterized by existing analytical methods, thus allowing for the demonstration that a generic version contains the identical active ingredient contained in the reference innovator product to which it is compared.10 Given their small size, these molecules usually are not immunogenic without binding to a carrier protein.15

In contrast, biologicals are proteins developed from living sources such as bacteria (e.g., *Escherichia coli*), yeast, or mammalian cells (e.g., Chinese hamster ovary cells) and are much larger, usually in the range of 10,000 daltons (e.g., filgrastim, pegfilgrastim) to several hundred thousand daltons, as in the case of monoclonal antibodies such as rituximab and infliximab.10,16-20 The basic components of biologicals are glycoproteins, amino acids, and sugar molecules.10 The unique pharmacologic action of each biological depends on a specific sequence of amino acids.10,21

The manufacturing steps used to create biologicals are often proprietary and involve numerous complex processes, including the isolation of a targeted gene sequence, the cloning of that gene sequence, and the use of a DNA vector to transfer the targeted DNA into an expression system.21 From there, effective manufacturing requires knowledge of cell expansion, filtration, centrifugation, purification, product characterization, and determination of product stability.21 As biologicals are manufactured via the manipulation of living organisms, the resulting purified bulk drug can vary from one production run to the next, and any modification in manufacturing steps can yield a different product.6,10 Biologicals’ primary, secondary, tertiary, and quaternary structures; their tendency to aggregate; and any posttranslational modifications (e.g., glycosylation, oxidation, phosphorylation) can affect their activity profile as well as their capacity to behave in an immunogenic fashion.10,15 Biologicals are readily recognized by the immune system as a result of their size and complexity and can directly induce a range of immunologic responses, some of which can have substantial clinical consequences, including loss of efficacy and the potential for anaphylaxis and infusion reactions.15

Regulatory differences. The regulation of small-molecule drugs is defined by the FDCA, which was first enacted in 1938 and was modified by the Hatch–Waxman Act in 1984 to allow for the approval of generic medications.22 In contrast, biologicals were initially regulated by the Biologicals Act of 1902, which was revised and codified into section 351 of the Public Health Services Act in 1944.23 Just as the Hatch–Waxman Act created an ANDA companion to the previously established new drug application (NDA) process, the BPCI Act created a biosimilar application to accompany the biologics license application (BLA).6,22 (Table 1). The applicable section of the FDCA or Public Health Services Act is often used to identify the type of application. Therefore, product applications submitted for approval under the ANDA program are sometimes referred to as 505(j) applications, while product applications submitted for approval through the biosimilars pathway are called 351(k) applications.

New molecular entities, whether they are small molecules or biologicals, require full clinical evaluations of safety and efficacy via the NDA or the BLA pathway, respectively.23 However, the approval processes for generics and follow-on biologicals—either the 505(j) or ANDA pathway or the 351(k) or biosimilar pathway—vary in terms of the requirements for clinical data.6,22,23 Given that a small molecule can be synthesized and characterized in full, an ANDA filing for a generic medication can be based on the demonstration of bioequivalence, as a bioequivalent agent would be expected to produce the same clinical response as the reference product. A drug approved via the ANDA process must have the same active ingredient, dosage form, route of administration, strength, conditions of use, and labeling as the originator reference product.23

Once approved, the generic medication usually is designated “therapeutically equivalent” through an “A” Orange Book code rating, allowing for pharmacist substitution.7 A generic medication is approved for the same set of indications as the originator reference product and receives the same nonproprietary name, as developed by the United States Adopted Names (USAN) Council,23,24 USAN, which is tri-sponsored by the American Medical Association, the United States Pharmacopeial Convention, and the American Pharmacists Association, works to select simple, informative, and unique nonproprietary names for drugs by establishing logical nomenclature classifications based on pharmacologic or chemical relationships.24 The USAN “one substance, one name” philosophy of generic naming is intended to help clearly identify an active substance across different brand or trade names, formulations, and combination products.24

Because biologicals are more complex than small-molecule drugs, subject to variation in manufactur-
ing, and difficult to characterize, it would be inappropriate to apply the term generic—or even biogenic. Instead, these follow-on versions of biologicals are more correctly described as biosimilars: “highly similar” products approved on the basis of detailed structural and functional characterizations and clinical trial information.26 According to the BPCI Act, a biosimilar is a product for which “a clinical study or studies” are sufficient “to demonstrate safety, purity, and potency for one or more appropriate conditions of use for which the referenced product is licensed.”8 However, the indications for which a biosimilar is approved do not necessarily include all of the licensed uses of the innovator reference product but could vary depending on each biosimilar sponsor’s application and the extent to which the clinical trial information supports extrapolation across multiple indications.25 Also, the BPCI Act included a separate, more rigorous designation of “interchangeability.” Only interchangeable biosimilars are substitutable by a pharmacist without the intervention of the prescriber.8 FDA has yet to define the additional level of evidence required to achieve this higher standard; however, the agency has indicated that it is unlikely that a designation of interchangeability would be granted at the time of initial approval.25 The labeling of biosimilars must state whether or not they have been deemed interchangeable with the reference product.26 It is unclear how aggressively biosimilar product sponsors will seek that designation.

Given the inherent variability in the active ingredient of all biologicals, it is uncertain as to whether or not FDA will conclude that biosimilars should receive the same proprietary name as the reference product. Current American Society of Health-System Pharmacists (ASHP) guidelines state that generic drugs deemed bioequivalent by FDA do not generally require a review by institutional pharmacy and therapeutics (P&T) committees.27 As biosimilars will not be deemed bioequivalent and could vary from reference drugs in terms of labeled indications and even naming, health care institutions will need to develop policies and conduct detailed evaluations prior to formulary inclusion of biosimilar agents.18

### Historical lessons from Europe (and the United States)

Although the formal biosimilars approval pathway is still under development in the United States, biosimilars are well established in other parts of the world, most notably the European Union (EU), which accounts for 80% of the global spending on these molecules.28 The EU regulatory pathway for biosimilars was established in 2005, and the first biosimilar, a version of human growth hormone (somatropin), was approved in 2006.10,23 The EU approval pathway is governed by an overarching “Guideline on Similar Biological Medicinal Products” that provides general guidelines on quality, safety, and efficacy as well as product-specific class requirements for insulins, somatropin, granulocyte colony-stimulating factors (G-CSFs), erythropoietic-stimulating agents (ESAs), interferons, low-molecular-weight heparins, and, most recently, monoclonal antibodies.4 Until recently, the biosimilars approved in Europe were all versions of somatropin, G-CSFs, and ESAs.29 While they are large-molecule drugs, these products are considered relatively less complex biologicals. On September 10, 2013, the profile of biosimilars approved in the EU changed when final marketing authorization was granted to Inflectra (infliximab, Hospira).30 While remaining patients and marketing exclusivities will determine exactly when this product can be sold within the EU, its approval represents a substantial step as the first European monoclonal antibody (a class comprising agents of greater complexity).30,31

The uptake of biosimilars varies across the countries in Europe depending on differences in local pricing and reimbursement policies,
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stakeholder influence, and perceptions regarding use. 28 Germany and France together account for the majority of the market share in the region, 34% and 17%, respectively, although usage in Spain and the United Kingdom has started to increase. 28 Biosimilar G-CSFs appear to have achieved the highest level of within-class uptake, accounting for 25% of all European G-CSF sales. 28 Overall, a 30% price reduction with biosimilar versus reference products has been observed across Europe, as compared to the 70–80% decrease typically associated with small-molecule generics. 28

With nearly a decade of experience, clinicians and regulators in Europe have identified barriers to biosimilars adoption and possible solutions to address potential concerns. The Working Party on Similar Biological Medicinal Products (BMWP) of the European Medicines Agency (EMA) recently published an article addressing many of the perceptions that have limited the use of biosimilars. 32 The authors stated that “a clear understanding of the scientific principles of the biosimilar concept and access to unbiased information on licensed biosimilars” are important for prescribers “to make informed and important treatment choices for their patients.” This article and several other recent publications are highly recommended as additional reading for health professionals preparing for growth in the biosimilars market. 4,10,32,33

At the time of writing, an officially recognized biosimilar had not been approved in the United States via the 351(k) pathway, but FDA has experience approving copies of complex molecules. 33 These approved products have been either follow-on versions of relatively simple recombinant agents such as somatropin, calcitonin salmon, and glucagon hydrochloride or medications derived from naturally occurring sources, as in the case of enoxaparin, which is made from porcine intestines. 33 However, none of these agents should be considered biosimilars, as the originator reference products against which they were compared were initially approved via an NDA rather than a BLA. Follow-on recombinant somatropin, calcitonin salmon, and glucagon were all approved via a 505(b)(2) application. 33 The 505(b)(2) pathway provides a middle ground between an NDA and an ANDA filing. Like a product approved via the ANDA pathway, a 505(b)(2) product is a version of a previously approved drug. 34 However, in contrast to the ANDA pathway, the 505(b)(2) application allows for the approval of a modification to a previously approved drug product, including a change in dosing regimen, a new active ingredient, or a new indication for use. 34 Although it may be a new formulation, the 505(b)(2) product can be approved on the basis of clinical data on the originator product, and its manufacturer is not required to repeat patient studies. 34 In the case of enoxaparin, follow-on versions of the product were approved by the ANDA pathway instead of via a 351(k) application. Therefore, subsequent versions of enoxaparin are true generic medications with the same active ingredient, dosage form, route of administration, and indications as the branded product and for which direct substitution as an A-rated therapeutic equivalent is allowed. 33

Pharmacists should be cognizant of the fact that subsequent versions of biological medications can be approved via different pathways in the United States, depending on the application type governing approval of the originator reference product (i.e., NDA or BLA). Pharmacists also should be cognizant that biological product regulation varies from country to country. For example, while regulated as small-molecule products in the United States, both somatropin and enoxaparin are covered under the EMA’s class-specific guidance for biosimilars; therefore, literature referring to these agents as biosimilars would be accurate for EU-marketed products but incorrect for products currently approved in the United States.

Understanding the BPCI Act and FDA guidance documents

As previously mentioned, the BPCI Act created the 351(k) pathway, allowing FDA to approve biosimilars, including interchangeable biosimilars. It also defined additional parameters of approval for biosimilars, including the timing of application submission and the duration of marketing exclusivity for originator reference products. According to the BPCI Act, FDA cannot accept an application for a biosimilar until 4 years after the licensure of the originator reference product and cannot approve a biosimilar until 12 years after the reference product was approved. 8 The BPCI Act also defines the circumstances in which marketing exclusivity can be extended for the originator reference product based on the completion of pediatric or orphan drug studies. 8 In addition, the first interchangeable biosimilar approved is to be assigned a 12-month exclusivity period during which no other related biosimilar could be designated as interchangeable. 8 Perhaps of greatest importance regarding the ultimate use of the biosimilar-approval pathway, the BPCI Act defines a formal resolution process for the negotiation of patents. 6,8

According to the BPCI Act, within 20 days of FDA acceptance of an application for approval of a biosimilar, the applicant must also share its application with the sponsor of the originator reference product so that the latter party’s work to identify, negotiate, and (if necessary) litigate patent infringement disputes can begin. 8 There have been some suggestions that such disclosure of confidential information may limit the number of suppliers willing to
pursue this route to approval and instead prompt applicants to seek the approval of biosimilars via a BLA.35 The actual extent of use of the 351(k) pathway remains to be determined as the industry and FDA gain greater experience.

FDA published additional guidance concerning the biosimilar-approval pathway on February 9, 2012, in the form of three draft documents, two of which respectively address scientific and quality considerations in demonstrating biosimilarity to an originator reference product and one of which provides answers to key questions applicants have posed regarding implementation of the BPCI Act.25,26,36 The draft guidance revealed key principles that FDA is using to implement the approval pathway.

Throughout the guidance, FDA emphasized it will use a “totality of the evidence” approach in reviewing all of the information submitted in support of a biosimilar agent’s approval, including the results of detailed analytical testing, clinical immunogenicity evaluation, animal studies, and human clinical trials.26 In addition, FDA encouraged sponsors to use a stepwise process for the development of biosimilars.26 At each step of the development process, FDA advised, sponsors should identify the extent of remaining uncertainty regarding the demonstration of biosimilarity and use subsequent development steps to address those residual concerns.26 Advances in analytical and manufacturing technology should enable applicants to characterize a proposed biosimilar more accurately.26

The draft FDA guidance noted that the foundation for a biosimilar-development program will be the availability and quality of comparative analytical data.26 Sponsors must be able to demonstrate the comparability of the proposed biosimilar agent and the reference product in terms of primary structure (i.e., amino acid sequence), higher-order structures, enzymatic posttranslational modifications such as glycosylation and phosphorylation, other potential variants such as protein deamidation and oxidation, and intentional chemical modifications.26 Applicants must demonstrate that the mechanism of action of the proposed product is the same as that of the reference protein product. FDA will require applicants to use endpoints and study populations that are clinically relevant and sensitive in detecting meaningful differences in safety and efficacy.26

According to the draft guidance, FDA will allow the sponsor of a biosimilar application to pursue all or only a subset of the indications, routes of administration, and product presentations (e.g., strengths, delivery devices, container closure systems) associated with the originator’s reference product.25 Also, FDA will allow the sponsor to use comparator data involving a non-U.S.-licensed product in support of the overall application.25 However, this allowance would not eliminate the need for clinical data comparing the proposed biosimilar with the originator’s U.S.-licensed product.25

FDA is currently finalizing these guidance documents. The February 2012 guidance did not address biosimilars naming or requirements to achieve an interchangeability approval. In addition to these remaining regulatory issues, other decisions by FDA will continue to shape the biosimilar approval pathway, including a pending response to a citizen’s petition filed by AbbVie Inc. concerning the scope of the approval pathway for biosimilar versions of biologicals approved prior to enactment of the BPCI Act.27 Pharmacists must be aware of these developing regulatory decisions.

Before biosimilarity, there was comparability

Biosimilarity may appear to be a new concept to pharmacists and other practitioners. In fact, it is an extension of a well-defined process established by regulatory organizations such as FDA and EMA and accepted within the pharmaceutical industry.3,33 Given that biologicals derive from living organisms, the resulting end products can vary from production batch to production batch. In addition, over the life cycle of a biological, originator companies implement manufacturing changes to scale up production and may even relocate production facilities.4,10 Any such process modification can result in product variations.

Therefore, originator-molecule manufacturers must evaluate their products before and after a manufacturing change to ensure there are no differences in clinical efficacy or safety. To support such evaluations, FDA developed the concept of “comparability” in the 1996 guidance document “Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products.”34 This concept has since been incorporated into International Conference on Harmonisation (ICH) guidance Q5E, “Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process,” for use in Europe, Japan, and the United States.38 ICH is a global initiative involving regulatory authorities and pharmaceutical industry experts in Europe, Japan, and the United States.38 The intent of ICH in this area is to discuss the scientific and technical aspects of pharmaceutical product registration to eliminate the duplication of testing involved in the development of new medications.38 ICH guidance Q5E was the basis for the development of the EU approval pathway for biosimilars.35

According to ICH guidance Q5E, the demonstration of comparability does not necessarily require that the quality attributes of a given product before and after a manufacturing
change be identical. Instead, a determination of comparability means that the products are highly similar, and sufficient knowledge is provided to ensure that if differences in quality attributes exist, they do not result in an adverse impact on the safety or efficacy of the drug; such a determination can be based on analytical testing, biological assays, and, possibly, nonclinical and clinical data. However, rarely does a comparability determination require a manufacturer to conduct clinical trials. Manufacturers have never been required to conduct “switching” studies, wherein patients are alternated between therapy with agents produced before and after a manufacturing change in order to assess the products’ relative safety and efficacy.

Two recent publications described how this process works in the current marketplace. One article discussed the product variations seen secondary to manufacturing changes involving darbepoetin sourced in the EU. In this analysis of product sourced over a 2.5-year period, capillary zone electrophoresis revealed differences in levels of sialic acid, the presence of which is responsible for the extended half-life of darbepoetin. From November 2008 to April 2011, the relative content of darbepoetin isoforms containing different amounts of sialic acid appeared to change noticeably, likely as a result of a modification in the manufacturing process. Similar examples of this type of variation have been reported for etanercept and infliximab. While manufacturers periodically implement such changes, the product label is not altered to reflect these modifications. The postmanufacturing formulation retains the same name as the original version and both products are allowed to remain on the market at the same time.

In its guidance documents, FDA acknowledged that some of the scientific principles described in ICH Q5E may also apply to the demonstration of biosimilarity. However, the agency also stated that as biosimilar sponsors will be using different cell lines, raw materials, equipment, processes, and process controls, the amount of data and information required to establish biosimilarity will be greater than what is required to determine comparability after an originator’s manufacturing change. Still, the concept of establishing the similarity of biologicals manufactured via modified processes is not new to the pharmaceutical industry or FDA.

Putting biosimilar safety into context

A primary concern regarding biosimilars is the potential for small differences in the manufacturing or formulation of a biosimilar relative to an innovator product to affect the clinical profile of the product, especially with regard to safety considerations. Concerns exist that biosimilar versions may be associated with unique adverse events not seen with the innovator drug. A frequently cited set of events that occurred in the EU over a decade ago involving a manufacturing change and an associated outbreak of a rare anemia syndrome, pure red-cell aplasia (PRCA), illustrated the potential clinical consequences of small changes in the manufacture and formulation of any biological drug. PRCA is characterized by a low reticulocyte count, the absence of erythroblasts in the bone marrow, resistance to recombinant human erythropoietin, and neutralizing antibodies to erythropoietin.

The events that led to the PRCA outbreak began in 1998, when Johnson & Johnson reformulated its European version of epoetin (Eprex) due to concerns that the product’s stabilizing agent, human serum albumin, could transmit a variant of Creutzfeldt–Jakob disease. The human serum albumin component was replaced with polysorbate 80. In the 10 years prior to this change, 1988–98, PRCA had been reported in only three patients receiving recombinant human erythropoietin. From January 1998 to April 2004, 175 cases of PRCA were reported in patients receiving Eprex. Multiple factors have been proposed regarding why this increase in PRCA events occurred, including an increase in subcutaneous administration of epoetin (a more immunogenic route than i.v. administration), failure to maintain the product under appropriate storage conditions, and potential interactions between the new stabilizer (polysorbate 80) and the uncoated rubber stoppers used in Eprex syringes. To address the increased frequency of PRCA, health authorities recommended adherence to storage and handling requirements and mandated i.v. administration of Eprex for patients with chronic kidney disease. Johnson & Johnson replaced the uncoated rubber stoppers with Teflon-coated plungers. The frequency of PRCA events has since declined, although the specific cause of the surge in PRCA cases continues to be debated. However, this example is consistently referenced in the clinical literature as a warning about the potential safety considerations of biosimilars, even though Eprex was and remains a fully licensed innovator biological.

This milieu of uncertainty surrounding biosimilars is further clouded by the availability of alternative biologicals marketed incorrectly as biosimilars in the developing world, where regulatory standards are less robust than those in Europe and those being developed in the United States. Additional incidents of PRCA and substantial variability in the active-ingredient content of ESAs have been reported with these non-biosimilar alternative biologicals. Due to the potential for confusion, EMA’s BMWP has proposed a more precise terminology to differentiate biological products (Table 2). Under this proposed classification,
only products with demonstrated similarity in physicochemical characteristics, efficacy, and safety would be labeled as biosimilar.9 The frequency of adverse events associated with the use of biosimilars has not increased in highly regulated markets such as the EU.53 A recently published review evaluated the EMA dossiers and journal publications on the follow-on epoetins licensed in Europe, including two products approved as biosimilars and one product that, although going through a full development program, is usually classified as a biosimilar.48 The review revealed that the follow-on agents had an overall safety profile consistent with available safety data on epoetin alfa and ESAs. A review of the biosimilar G-CSFs licensed in Europe similarly concluded that what is known about originator filgrastim in general can be extended to the biosimilar versions of this product.49 Another review, focused on the medical literature for EU-marketed human growth hormone, ESAs, and G-CSFs, revealed no safety issues associated with switching among products, including switching among innovator products within the same product class and switching to and from biosimilars.50 Analyses of the active-ingredient content of multiple ESAs marketed in the EU have found content consistency for biosimilars equal to if not greater than that seen for innovator products.53,55

Appropriate monitoring for adverse events, including immunogenicity-related reactions, is important with the use of all biologicals, both innovator products and biosimilars. Although abbreviated processes, the EU and U.S. regulatory pathways for biosimilars approval are stringent and require thorough evaluation of safety and efficacy. As with all biologicals, appropriate postmarketing pharmacovigilance will be critical to the appropriate use of biosimilars.56

The anticipated biosimilars market in the United States

In addition to the differences described above, the market for biosimilars will vary substantially from that for traditional generics. Although the approval process for biosimilars is abbreviated, sponsors must still make a substantial investment in complex manufacturing processes and clinical trial expenses and anticipate the costs of patent litigation. Some estimates suggest that the development cost for a biosimilar ranges from $100 million to $400 million.28 In comparison, the cost of developing a small-molecule generic is estimated to range from $1 million to $4 million.28 Therefore, discounts associated with biosimilars are expected to be only 20–30%, much less than the price decreases frequently seen with generic

Table 2.

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<th>Term(s)</th>
<th>Definition</th>
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<td>biosimilar</td>
<td>Copy version of an already authorized biological medicinal product with demonstrated similarity in physicochemical characteristics, efficacy and safety, based on a comprehensive comparability exercise.</td>
<td>Only very small differences between biosimilar and reference with reasurance that these are of no clinical relevance. Extrapolation of clinical indications acceptable if scientifically justified.</td>
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<td>Me-too biological/biologic</td>
<td>Biological medicinal product developed on its own and not directly compared and analyzed against a licensed reference biological. May or may not have been compared clinically.</td>
<td>Unknown whether and which physicochemical differences exist compared to other biological of the same product class. Clinical comparison alone usually not sensitive enough to pick up differences of potential relevance. Therefore, extrapolation of clinical indications problematic.</td>
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<tr>
<td>Noninnovator biological/biologic</td>
<td>Biological medicinal product developed on its own and not directly compared and analyzed against a licensed reference biological. May or may not have been compared clinically.</td>
<td>Only very small differences between biosimilar and reference with reasurance that these are of no clinical relevance. Extrapolation of clinical indications acceptable if scientifically justified.</td>
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<td>Second-generation (next-generation) biological/biologic</td>
<td>Biological that has been structurally and/or functionally altered to achieve an improved or different clinical performance.</td>
<td>Usually stand-alone developments with a full development program. Clear (and intended) differences in the structure of the active substance, and most probably different clinical behavior due to, for example, different potency or immunogenicity. From a regulatory perspective, a claim for “better” would have to be substantiated by data showing a clinically relevant advantage over a first- or previous-generation product.</td>
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small-molecule drugs. However, given the comparatively high overall expense associated with the use of biologicals and traditional resistance to targeting them for cost management strategies such as therapeutic interchange, prior authorization, and discounted contract pricing, even these relatively modest savings will still be of substantial value and interest to hospitals and clinics, payers, and group purchasing organizations (GPOs).

Unlike the current pharmaceutical manufacturing landscape, where suppliers primarily focus solely on branded or generic products, biosimilars will be produced by a blended array of manufacturers. Suppliers traditionally identified as “generic companies,” such as Teva Pharmaceuticals Industries Ltd., Hospira, Inc., and Sandoz (a division of Novartis AG), are expected to compete directly with originator companies such as Genentech, Inc. Companies known as makers of branded drugs, such as Merck & Co., Inc., and Pfizer Inc., may make competing versions of other originator companies’ molecules. Amgen Inc. recently announced that while it is working to defend its epoetin and filgrastim franchises, it too will pursue development of biosimilar versions of products such as bevacizumab, infliximab, and adalimumab with hopes of launching some of these agents by 2017. Multiple collaborations between generic and branded-drug manufacturers specifically for the purpose of participating in the biosimilars market have already been announced. These organizations and collaborative groups appear to be targeting many of the same molecules for initial biosimilars development as innovator drug patents reach or approach expiry.

It is expected that the initial products marketed will be versions of less-complex molecules such as filgrastim and epoetin, with more-complex biologicals (e.g., monoclonal antibodies) becoming available only toward the latter part of this decade (Table 3).

Also in contrast to the traditional small-molecule market, the uptake of biosimilars will be much more influenced by the availability of clinical information espousing positions both in support of and against their use. Originator companies may create marketing messages challenging the extent to which a different manufacturing process can truly yield a comparable or highly similar product and whether a biosimilar can be considered to provide an equivalent level of safety, purity, and potency. Such messages can already be seen in the clinical literature directed specifically at nephrologists, dermatologists, diabetologists, hematologists, and oncology physicians as well as health care providers in general. Recent assessments of clinician understanding regarding biosimilars suggest that these messages have the potential to influence perceptions substantially.

For example, in a survey of 277 clinicians conducted by the National Comprehensive Cancer Network (NCCN) in 2011, over half of respondents, including physicians, nurses, and pharmacists, stated they were not at all familiar (36%) or only slightly familiar (19%) with recent developments pertaining to biosimilars. However, a recent Internet survey of 376 physicians yielded different results. The survey, reported in August 2012, was conducted for the Alliance for Safe Biologic Medicines, an organization whose membership includes Amgen, Genentech, and the Biotechnology Industry Organization and which advocates for the use of unique nonproprietary names for biosimilars and has expressed concerns regarding biosimilars interchangeability. In its survey, 24% of respondents stated that they were very familiar with or had a complete understanding of biosimilars, while 54% indicated some familiarity or a basic understanding. The survey also characterized the respondents’ feelings toward biosimilars naming and interchangeability and the ability to maintain “dispense as written” authority for biosimilars.

Based on these survey results, it appears that there are varying levels of perceived understanding of the biosimilars market. Both the manufacturers of the originator reference products and their biosimilars industry counterparts will be working to fill in the current educational gaps, an area where the branded-drug suppliers would appear to have the resource advantage. As drug information experts, pharmacists...
will have a critical role in leveling the playing field to support an accurate perspective on biosimilars within their institutions. Pharmacists will also need to use resources developed by professional and business-related organizations such as NCCN, ASHP, and GPOs, which will be expected to provide additional educational materials and information about biosimilars. One excellent resource for pharmacists is a website hosted by ASHP Advantage (www.biosimcentral.org) that offers on-demand educational activities, a continuing-education discussion guide, and quarterly newsletters on the latest legislative and regulatory trends related to biosimilars development.

It is expected that FDA will release additional guidance information concerning the outstanding issues of biosimilars naming and interchangeability. In addition, several states have adopted or are considering legislation to address the prescribing and dispensing of biosimilars. Primary aims of state legislation include ensuring that pharmacists do not automatically substitute noninterchangeable biosimilars, that appropriate notification is given to prescribers when interchangeable biosimilars are substituted, and that pharmacists obtain patient consent for biosimilar substitution in some cases. As of the time of writing, North Dakota, Oregon, Virginia, and Utah had adopted such legislation; however, with the exception of North Dakota’s, the legislation in these states includes sunset provisions. Efforts to enact similar bills in states such as Colorado, Illinois, Indiana, Maryland, Mississippi, Nevada, Texas, and Washington have failed. The impact of biosimilars-focused state laws and regulations on inpatient practice is uncertain. Still, health-system pharmacists whose practice settings include outpatient environments should be aware of their state’s pharmacy requirements concerning biosimilars.

Also, it is important to keep in mind that the central underlying premise of biosimilars development is that a highly similar product of comparable safety and efficacy can be manufactured at a lower cost. Therefore, the payer community is expected to be a source of information and support concerning the adoption of biosimilars. A recent online survey of 102 health plans revealed that 49% of respondents currently plan to place biosimilars at a lower cost-sharing tier than branded specialty drugs, while 64% envision restricting the use of biosimilars through “step edits” (a process by which a prescription history of the use of specific alternative preferred agents is verified before coverage is provided).

**Formulary management strategies for biosimilars**

Even in the event that FDA or state regulation does not permit automatic substitution of products, health systems may still consider using the formulary tool of therapeutic interchange. Defined as the authorized exchange of therapeutic alternatives in accordance with previously established and approved written guidelines or protocols within a formulary system, therapeutic interchange is a powerful formulary management tool. Under a therapeutic interchange program, mechanisms are established with the approval of the medical staff of an organized health system to substitute one product for another once the organization has determined that they are therapeutically equivalent; often this is done to streamline the formulary and to create financial savings.

Criteria for an effective therapeutic interchange program include the inclusion of products that can be considered therapeutically equivalent in their efficacy and safety, the potential for savings through the use of one product over another, the development of a clear process for interchange, sufficient knowledge and understanding of the products by prescribers within the system, the ability to “opt out” under specific circumstances, and, ideally, the ability to assess the outcomes of therapy with the agents. In many health systems, therapeutic interchange programs are already in place for a variety of biological agents. Typically in such programs, there is an established primary agent within a therapeutic category, and automatic conversion to this agent—except in situations defined by very specific criteria—is approved by the medical staff. For example, with regard to ESAs, there are often automatic interchange programs that convert orders for multiple ESA products to orders for a single ESA as a way of simplifying the formulary and consolidating the market share of one product in order to improve contracting and lower overall costs. Similar types of programs have been employed with other biological agents such as human insulin and i.v. immune globulin. It is likely that health systems will take similar approaches to consolidate the use of biosimilar agents within their formularies.

Pharmacists will be expected to provide leadership and guidance in balancing the financial and clinical issues associated with formulary decisions on biosimilars and the selection and use of these products. It is clear that there will be significant financial pressures and opportunities to utilize biosimilar products to effect savings, but this must be done in a way that protects the quality of care, safety, and medication-use outcomes. This is a role that pharmacists have fulfilled historically through P&T committees and the formulary process.

Use of sound principles of formulary management will be critical in providing objective and rational analyses to assure the appropriate utilization of biosimilar medicines. Included in such analyses will be the consideration of factors including data on efficacy and safety, the range of indications for use, the...
potential for immunogenicity, safe use through appropriate naming and labeling of the products within the medication-use system, an effective pharmacovigilance plan, economic considerations (from both health-system and patient perspectives), appropriate and effective interchange processes (particularly at transitions of care), and the need for provider and patient education. ASHP has published a policy statement supporting this approach.68

It is unlikely that FDA will declare any of the early biosimilar products to be automatically interchangeable by pharmacies, although that designation exists in the BPCI Act. State pharmacy practice acts have provisions for the oversight of pharmacy-level substitution practices, and some states have implemented different approaches to substitution. Pharmacists will need to be aware of both FDA and state regulations when determining what levels of interchange or substitution may be permissible during the use of biosimilars. However, regardless of any regulations on automatic substitution, health systems will likely be allowed to set up therapeutic equivalence programs within the framework of their own formulary systems, as approved by the medical staff.

One area that will likely be particularly challenging for pharmacists and health-system P&T committees relates to transitions of care. As mentioned previously, payers undoubtedly will provide significant incentives to use biosimilar medicines to reduce or control costs.63 These efforts could include prior authorization of biosimilars or the imposition of substantial copayment or coinsurance premiums for the use of the originator product when a biosimilar medicine is available. Pharmaceutical industry contracting with health systems could involve significant discounts to encourage the health systems to continue to use the originator product even when biosimilar products are available. This will create a dilemma regarding whether to forgo these discounts in order to minimize switching among similar products at transitions of care or to ensure that the financial impact on patients is minimized when they are discharged from the hospital.

In addition to these formulary management considerations, many operational and educational issues will need to be addressed by health systems prior to the introduction of biosimilars (Table 4).27,67 Given the possibility of biosimilar drugs having different nonproprietary names than the originator, health systems must ensure that processes exist to distinguish biosimilars throughout all components of the medication management continuum, including the electronic medical record, the medication administration profile, the order-entry interface, pre-defined order sets, care paths, and protocols—extending through final

### Table 4. Educational and Operational Issues Related to Adoption of Biosimilars

<table>
<thead>
<tr>
<th>Medication Management Process Areas</th>
<th>Key Preparatory Steps for Health Systems</th>
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<tbody>
<tr>
<td>Formulary analysis</td>
<td>1. Understand approval history of biosimilar, labeled and off-label indications, brand and nonproprietary names, clinical safety and efficacy information, dosage forms, use in special patient populations, and economic aspects.</td>
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<td>2. Determine if multiple versions of same biological will be on formulary; if so, determine criteria for use of each product (e.g., indication, patient age).</td>
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<td>3. Determine if therapeutic interchange programs will be implemented; if used, obtain P&amp;T committee approval.</td>
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<td></td>
<td>4. Devise a plan for transitions of care, including implications of patient’s insurance coverage.</td>
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<tr>
<td>Order management and information systems</td>
<td>1. Differentiate biosimilar and originator product in computerized order-entry systems, electronic medication records, medication administration profiles, order sets, and protocols.</td>
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<td>Inventory management</td>
<td>1. Ensure pharmacy buyer has adequate information (e.g., NDC number, wholesaler order number) to purchase biosimilar.</td>
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<td>2. If pharmacy will maintain both biosimilar and originator products, establish par levels for each product.</td>
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<tr>
<td>Financial analysis</td>
<td>1. Identify base price, contract price, and reimbursement for biosimilar versus originator product.</td>
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<td>2. Determine financial impact from health-system and patient perspectives.</td>
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<td></td>
<td>3. Consider availability of patient assistance programs.</td>
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<tr>
<td>Education</td>
<td>1. Provide biosimilars drug information and other education resources to pharmacy, physician, and nursing audiences.</td>
</tr>
<tr>
<td></td>
<td>2. Develop appropriate patient educational materials.</td>
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*P&T = pharmacy and therapeutics, NDC = National Drug Code.
product labeling and even bedside bar-coding.\textsuperscript{69} Inventory management systems including automated dispensing devices and associated software, as well as purchasing systems, must reflect biosimilars in a way that allows for their accurate identification by technicians, pharmacy buyers, and all personnel who manage the pharmacy supply chain.

In order to support appropriate pharmacovigilance, health systems must ensure that mechanisms are in place to track the potential for unique adverse events associated with biosimilars that are not observed with the innovator drug.\textsuperscript{69} This preparation includes an accurate understanding of the baseline adverse-event rate with the use of the originator product in each organization.

Most patients have a reasonable understanding of the concept of generic medications. However, substantial education will be required to assist patients in understanding the differences between generics and biosimilars.\textsuperscript{10} Pharmacists, physicians, and nurses will need access to drug information on biosimilars, including content appropriate for patient audiences, to address the numerous questions that will arise as these products come to market.

**Putting knowledge into practice: The first noninnovator biological**

On August 29, 2012, FDA approved tbo-filgrastim (Granix), Teva’s version of filgrastim (previously only marketed as Neupogen by Amgen).\textsuperscript{70} Although tbo-filgrastim was previously approved as a biosimilar in Europe, Teva filed a BLA for the drug in November 2009—prior to enactment of the BPCI Act—and the application was subsequently approved. The settlement terms of a patent infringement suit brought by Teva against Amgen provided that Teva not market its product before November 2013.\textsuperscript{71} Although tbo-filgrastim is not a biosimilar by U.S. standards (i.e., the product was approved through the BLA pathway as opposed to the 351(k) pathway), the drug’s approval was a significant milestone in the advancement of U.S. biosimilars marketing; it also provides a representative example of how pharmacists will need to evaluate and manage similar follow-on biologicals.

Although the dosage and frequency of administration of filgrastim and tbo-filgrastim are the same, the Teva product was not approved with all the indications for which the Amgen product is approved.\textsuperscript{16,72} Tbo-filgrastim is approved for use in patients with cancer receiving myelosuppressive chemotherapy but not for other indications such as use in patients with cancer receiving bone marrow transplants or patients undergoing peripheral blood progenitor-cell collection and therapy.\textsuperscript{72} As a result, once this product comes to market, pharmacists and their P&T committees will have to make decisions regarding whether or not the mechanism of action and the associated clinical evidence support the use of the product outside of the labeled indications. The names of the Amgen and Teva products differ but are still quite similar. Therefore, should a health care organization choose to use the Teva product, steps must be taken to ensure that all order-entry processes, including protocols, and care paths, as well as electronic medication administration records and representations of the product on the displays of automated dispensing devices, reflect the correct agent.

As the biosimilars market continues to develop, so will the diversity in the processes manufacturers choose to use in seeking approval of their products. Some suppliers may file for approval via the BLA pathway, as in the case of tbo-filgrastim, whereas others will choose the biosimilar-specific review process. Others will seek to characterize their products as “biobetters”: biologicals engineered to achieve an improved or different clinical performance.\textsuperscript{7} In addition, there are biological molecules approved through the 505(b)(2) pathway; these must not be confused with biosimilars. Pharmacists will need to understand the differences in all of the approval pathways to educate physicians and other clinicians on the labeling associated with each medication and the manner in which it should be used.

**Conclusion**

Over the coming years, biosimilars will present opportunities for health care organizations to manage the growth of pharmaceutical expenditures. Pharmacists can play a key role in preparing health systems for projected rapid expansion in the use of biosimilars and associated medication-use policy challenges.

**References**


