

The Approval Process for Biosimilar Erythropoiesis-Stimulating Agents

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Abstract

A biosimilar drug or follow-on biologic drug is defined by the Public Health Service Act as a product that is “highly similar to the reference product notwithstanding minor differences in clinically active components and there are no clinically meaningful differences between the biologic product and the reference product in terms of the safety, purity and potency of the product.” The advantage of biosimilar drugs is that they are significantly less expensive than the reference products, allowing for increased accessibility and cost savings. Recognizing these advantages, the US Congress passed the Biologics Price Competition and Innovation Act in 2009 as part of health care reform. The Biologics Price Competition and Innovation Act allows sponsors of biosimilar agents to seek approval by showing structural and functional similarity to the reference agent, with the extent of required clinical studies to be determined on the basis of the degree of biosimilarity with the reference product. The goal is to bring biosimilar agents to the market more efficiently while still protecting the safety of the public. The European Union has had such a process in place for a number of years. Two biosimilar epoetin agents have been approved in the European Union since 2007, and their companies are conducting trials to seek approval in the United States, because Amgen’s patent protection for epoetin alfa expires in 2014. Trials completed for European Union approval of both agents showed similar efficacy and safety to the reference epoetin alfa. As with all biologics, immunogenicity concerns may persist because of the fragility of the manufacturing process and the worldwide experience with pure red cell aplasia as a result of epoetin therapy. The uptake of biosimilar epoetins after approval in the United States will depend on the balance of cost advantage against safety concerns. Competition in the marketplace will likely decrease the cost of the reference agent as well.

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Introduction

Biologic drugs are substances made from living organisms or their products used in the prevention, diagnosis, or treatment of diseases. Since the introduction of the first genetically engineered biologic drug (recombinant human insulin) in 1982, these agents have proliferated and been used for a variety of previously untreatable diseases. Indications for currently available biologic drugs include cell therapy for cancer, clotting factors for hemophilia, cytokine or growth factors for cancer and hepatitis C, enzymes for hereditary deficiencies, mAbs for arthritis and cancer, polyclonal antibodies for immunodeficiency, toxins for cosmetic use, and vaccines for influenza and other viruses (1). A biological product has been defined by the Food and Drug Administration (FDA) as a “virus, therapeutic serum, toxin, antitoxin, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product . . . applicable to the prevention, treatment or cure of a disease or condition of human beings” (2). Currently, about 30% of the pharmaceutical industry’s research and development budget is dedicated to the creation of biologics (3). Biologics are much more expensive to develop and produce, because they are significantly more structurally complex than the small-molecule drugs prevalent in the therapeutic marketplace. As a

result, their high cost limits the access of these important agents to many people who truly need them.

The term biosimilar has been loosely used to describe any copy or replica of a biologic drug with a target that is the same as the originator or reference agent. However, that use of the term biosimilar incorrectly includes follow-on biologics that have not proven comparability with the reference drugs, because they been developed for markets that are not highly regulated, such as markets in Asia, Africa, and Central and South America. Many of the countries in these regions do not have a well developed rigorous process for the testing and approval of agents that purport to be similar to their reference compounds. The lesser quality and adverse outcomes that have been reported with agents called biosimilar in these countries have made many health care providers and regulators skeptical as to the safety and efficacy of biosimilar agents in general. However, the correct use of biosimilar is with reference to follow-on biologics that have been approved in highly regulated markets, such as the European Union (EU), the United States, Canada, Japan, Australia, and New Zealand. Such agents must meet strict criteria of quality and comparability with their respective reference biologics, and the track record for such agents after approval in highly regulated markets has been favorable (4). The experience in the EU, which has had a rigorous pathway for the approval

of biosimilar agents since 2005, has shown that savings in cost as well as expansion of access can be achieved without adversely affecting patient outcomes by applying consistent and appropriate scientific regulatory standards to biosimilars exactly as they are applied to the reference biologics. Benefiting from the European experience, the United States enacted the Biologics Price Competition and Innovation Act (BPCIA) in 2009 as part of the Patient Protection and Affordable Care Act to clarify and expedite the approval process for biosimilar agents. In 2009, almost 75% of small-molecule prescriptions in the United States were for generics, and the approval of a generic agent resulted in an average savings of 77% of the product's cost within 1 year (1). Although the cost savings associated with the use of biosimilar drugs would not be as great, the Federal Trade Commission predicted that their availability would significantly reduce the cost of biologics and increase their accessibility (5). For example, the cost of the top three biologics for the treatment of rheumatic disorders worldwide approached \$20 billion annually in 2012 (6). It has been suggested, with minimal supporting data, that the biosimilars approved in the United States and the EU to date have afforded a modest cost savings of 15%–30% over their reference agents (7–10). The savings may ultimately be greater as the reference products lower their prices to compete with the biosimilars. The European Generic Medicines Association has reported that the use of biosimilar agents has generated savings of 1.4 billion euros per year for European health care systems (11). It has been estimated that a 20% reduction in the price of five off-patent biopharmaceuticals would save the US Federal Government \$9–12 billion over the next 10 years (8,12). In the case of erythropoiesis-stimulating agents (ESAs) in the United States, spending has already decreased substantially because of the results of randomized clinical trials showing increased cardiovascular events at higher target hemoglobin (Hb) levels, the FDA black box warning to use the minimal dose required to avoid transfusion, and the Medicare quality incentive program, which financially penalizes a dialysis provider with an excessive percentage of patients receiving ESAs who have an average Hb > 12 g/dl.

Challenges in Producing Biologic and Biosimilar Products

Biologic drugs vary from simple replacement hormones to large complex molecules with extensive post-translational modifications, such as mAbs. Experience has shown that even minor modifications in the manufacturing, packaging, and distribution process, including upscaling to meet increased commercial demand, improving the efficiency of the process, and modernizing the process when major equipment requires replacement or updating, can produce changes in the product molecule, which may adversely affect efficacy, safety, and/or immunogenicity (13). As a result, the FDA has required sponsors of biologic drugs to show that any production change does not have an adverse effect on the identity, strength, quality, purity, or potency of the product as related to the agent's safety and effectiveness. This demonstration is done through appropriate analytic testing, functional assays, and in some cases, animal and/or clinical studies, and it is known as comparability testing. Comparability allows production changes to occur without a completely new product development program. Obviously, the

more extensive the manufacturing change, the more likely a change in product attributes will occur and the more data that the FDA will require to ensure that the resulting product has comparable efficacy and safety with the original compound. Although establishing biosimilarity of a follow-on agent by another manufacturer may represent an extreme form of a comparability assessment, the scientific concept is identical. Showing that a proposed product is biosimilar to a reference product will be more complex than assessing comparability of a product before and after a manufacturing change by the same producer. A manufacturer modifying its own processes has thorough knowledge and information about the product and the current process, including controls and acceptance parameters. The developer of a biosimilar product will likely have different manufacturing procedures (*e.g.*, cell line, raw materials, equipment, processes, process controls, and acceptance criteria) from the reference agent and no direct knowledge of the manufacturing procedures for the reference agent. Therefore, more data and information will be required to establish biosimilarity than establish comparability of a product after a manufacturing change (13). Because the analytic process for biosimilar agents is relatively new and untested, the nature and extent of the additional data and information required will likely evolve and become more clearly established as increasing numbers of agents move through the approval pathway.

Biologic drugs are not homogenous (unlike small-molecule drugs). Because they are produced by biologic systems that are neither perfect nor consistent by nature, biologic drugs invariably will have heterogeneity that results from variability in post-translational processes, and it is compounded by variability from even the highest-quality manufacturing, packaging, and distribution processes. As a result, there can be no perfect copy of a biologic drug (a bioidentical drug), because even the reference agent does not contain all perfect identical molecules. Even native macromolecules may be heterogeneous because of variations in post-translational processes, resulting in glycosylation inconsistencies that do not affect function. Section 351(i)(2) of the Public Health Services (PHS) Act (14) defines biosimilarity to mean “that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity and potency of the product” (14). To meet the higher standard of interchangeability for a biosimilar agent, Section 351(k)(4) of the PHS Act (14) requires an applicant to “provide sufficient information to demonstrate biosimilarity, and also to demonstrate that the biological product can be expected to produce the same clinical results as the reference product in any given patient and, if the biological product is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between the use of the biological product and the reference product is not greater than the risk of using the reference product without such alteration or switch” (14).

Biosimilar ESAs

Epoetin alfa, a form of recombinant human erythropoietin (rHuEPO) developed by Amgen and introduced in

1989 (15), is a biologic agent that is nearing the end of its patent life in the United States. Amgen's strong patent protection for this agent has successfully kept all biologic ESAs by other manufacturers out of the United States market, despite a number of legal challenges. In other parts of the world, Amgen's patent life and patent protection were not as robust as in the United States, and a number of alternate biologic and biosimilar ESAs have been in use for many years. All rHuEPOs have the same amino acid structure, but rHuEPOs made in different cell lines can differ in their carbohydrate structure, which may affect their pharmacokinetics (PK) and potency. The World Health Organization recommended assigning a different Greek letter identifier to distinguish epoetin molecules differing in carbohydrate structure (16); however, interpretation of this rule by sponsors of biosimilar products has been voluntary and inconsistent. One of two biosimilar ESAs approved in the highly regulated EU market, HX575, uses the international nonproprietary name epoetin alfa. The other biosimilar ESA approved in the EU, SB309, uses the international nonproprietary name epoetin-zeta. Sandoz, the applicant for HX575 approval in the United States, uses the brand name Binocrit; Hospira, the applicant for SB309 approval in the United States, uses the brand name Retacrit.

There are causes for concern on the basis of historical events regarding the immunogenicity of ESAs after a manufacturing change or with the use of biosimilar agents. Most of these concerns relate to the development of pure red cell aplasia (PRCA), a rare condition that leads to severe anemia. Several case reports of an antibody-mediated form of PRCA associated with epoetin therapy appeared in the mid-1990s, but this complication did not receive considerable notice until an epidemic of epoetin-associated PRCA occurred between 1998 and 2002. In 1998, the manufacturer of Eprex (a brand of epoetin alfa) altered the stabilizing agent from HSA to polysorbate 80 and glycine. It is theorized that the polysorbate 80 interacted with leachates from the uncoated rubber stoppers in the Eprex prefilled syringes to induce increased immunogenicity of the agent, which resulted in the increased incidence of PRCA only when the substance was administered subcutaneously (sc). After the cause of the problem was identified, the manufacturer of Eprex coated the rubber stoppers in the prefilled syringes with latex, and the PRCA epidemic subsided. The patients affected with PRCA showed neutralizing antibodies to epoetin that cross-react with endogenous erythropoietin. Patients in the United States were not affected by this PRCA epidemic, because Eprex is not marketed in the United States. In December of 2002, European health authorities officially contra-indicated sc administration of Eprex for patients with CKD (17).

In 2011, Praditpornsilpa *et al.* (18) described the experience in Thailand with follow-on biosimilar (using the loose definition of the term; see above) epoetins. The first biosimilar epoetin alfa became available in 1997 in Thailand, and as of 2009, 14 biosimilar epoetins were licensed in Thailand that were manufactured in Argentina, China, South Korea, and India. Concomitant with the increased penetration of biosimilar epoetins in the Thai market, Praditpornsilpa *et al.* (18) noted an alarming increase in the prevalence of PRCA and sought to more systematically diagnose the disorder and characterize the epidemic. They were able to confirm that 23 of 30 patients referred because of loss of epoetin efficacy

had antibodies to erythropoietin, consistent with PRCA (18). All of these patients received the biosimilar epoetin sc, confirming previous observations that the interaction between an ill-defined alteration in the erythropoietin molecule and sc injection of the agent is a prerequisite for the development of PRCA (18).

Fortunately, antibody-mediated PRCA, although serious, is not usually fatal and generally resolves after withdrawal of the offending ESA, immunosuppressive therapy, and multiple transfusions until endogenous red blood cell production resumes. Peginesatide, which has been withdrawn from the United States market but may be available for compassionate use in this setting, has been shown to be effective in the treatment of 13 of 14 patients with PRCA caused by antierythropoietin antibodies (19).

None of the studies with intravenously (iv) administered HX575 (Binocrit) or SB309 (Retacrit) has reported the presence of neutralizing anti-epoetin antibodies or any signs or symptoms consistent with immune-mediated PRCA. HX575 is currently indicated in the EU only for iv use in patients with CKD on or not on dialysis, anemia of cancer chemotherapy, and autotransfusion in anticipation for major surgery, reflecting the lack of a successfully completed comparator study using the sc route. The Study to Evaluate the Efficacy, Safety, and Immunogenicity of Subcutaneous HX575 in the Treatment of Anemia Associated with Chronic Kidney Disease randomized 337 ESA-naïve predialysis patients to receive either HX575 or Erypro (the branded form of epoetin alfa available in Germany and Austria) through the sc route (20). Two patients in the HX575 arm developed neutralizing anti-epoetin antibodies. Bone marrow biopsy confirmed PRCA in one patient; the other patient died of a myocardial infarction before bone marrow examination could be performed. Root analysis of this result suggested that contamination by tungsten during manufacturing of the prefilled syringes may have led to protein denaturation and aggregation of HX575 batches, which might have been responsible for the increased immunogenicity reported in this study (21).

HX575 (Binocrit)

HX575 was approved for use in the EU in 2007. It has the same amino acid sequence as epoetin alfa (22,23). In a PK study comparing HX575 with branded epoetin alfa enrolling 80 healthy men, the pharmacodynamic (PD) results for the two agents were similar. However the PK results found the area under the curve for HX575 to be 18% lower than for epoetin alfa after a single dose and 10% lower after multiple administrations (24). The 10% lower exposure to HX575 to achieve similar Hb results supports the concept that PK profile alone is insufficient to support similar safety and efficacy to the reference agent. In practice, clinicians may need to monitor Hb levels and modify the dose of HX575 when switching patients who are stable on epoetin alfa.

In a maintenance study of 478 clinically stable adult patients on dialysis who were randomized to iv HX575 or epoetin alfa in a 2:1 ratio for 28 weeks and then treated with HX575 for an additional 28 weeks, the two agents were deemed to be clinically equivalent (25). As part of the post-authorization pharmacovigilance program required by the EU, an open-label, single-arm study of iv HX575 was conducted on >1500 patients with CKD. Safety was reported to

be consistent with expectations, with no patient developing PRCA (26). Another study of HX575 showed a difference in potency depending on the manufacturing site. HX575TT, which is manufactured at a different site from HX575, had an area under the curve 15% > HX575, although the two agents had comparable PD responses. This finding again emphasizes the importance of monitoring Hb levels and adjusting the ESA dose accordingly, even when switching to a different version of the same agent (27).

SB309 (Retacrit)

SB309 (epoetin-zeta) was the second biosimilar to receive EU approval. It has the same amino acid sequence as epoetin alfa (24). Two bioavailability studies comparing SB309 with epoetin alfa revealed slightly lower bioavailability for SB309 on a molecular-weight basis, but this result may be because of the greater protein content of reference epoetin alfa (23). In a trial by Krivoshev *et al.* (28) comparing correction of anemia in dialysis patients with iv SB309 with epoetin alfa over 24 weeks, there was no difference in the Hb level achieved, but the mean epoetin dose during the last 4 weeks of treatment was approximately 10% higher with SB309 than with epoetin alfa. A maintenance study by Wizemann *et al.* (29) randomized patients to receive epoetin alfa or SB309 for 12 weeks and then crossed them over to receive the other agent for an additional 12 weeks. Switching from epoetin alfa to SB309 increased the dose required by 10%–15% and transiently decreased the Hb level by about 5%. Switching from SB309 to epoetin alfa reduced the dose required by approximately 10% and increased the Hb by about 10%. Applying the correction factor for the difference in protein content between the two agents placed the differences

within a modified *post hoc* acceptance range from the studies by both Krivoshev *et al.* (28) and Wizemann *et al.* (29). The long-term safety of SB309 was assessed by examining combined outcomes of 745 chronic hemodialysis patients who received the agent in the correction and maintenance studies noted above (28,29). Patients were followed for 56 or 108 weeks to obtain individually-determined, stable Hb target values of 10.5–12.5 g/dl with constant epoetin doses. SB309 maintained target Hb levels with a constant dose. Approximately 5% of the adverse events were considered to be related to the study treatment, and they were consistent with those previously reported with all ESAs (30). In a *post hoc* analysis of the three studies above comparing SB309 with epoetin alfa, the incidence of adverse events was not significantly different between the two treatments (31). In a 28-week study comparing sc SB309 ($n=232$) and epoetin alfa ($n=230$) in chronic hemodialysis patients, there was no statistically significant difference in efficacy between the two agents. There were also no differences in tolerability, and no patient developed anti-epoetin antibodies or PRCA (32).

Retacrit is approved in the EU for iv or sc administration, and it has similar therapeutic indications as epoetin alfa and HX575 described above.

The BPCIA

In 2009, as part of health care reform, the US Congress enacted the BPCIA, which gives the FDA the authority to approve any biosimilar drug for which the reference product is a previously licensed biologic approved through a biologic license application (BLA). The BPCIA offers 12 years exclusivity to biologics, meaning that the FDA cannot

Table 1. Food and Drug Administration pathways available for the approval of biosimilar drugs

Act	United States Drug Approval Statutes
Food Drug and Cosmetic Act	
505(b)(1) NDA	Full stand-alone NDA. Approval process typically used for new chemical entities. Sponsor-produced preclinical and clinical data are used to support approval.
505(b)(2) NDA	Abbreviated licensure pathway. Allows sponsor to rely partially on existing publically available pharmacology, safety, and efficacy data on molecule. Typically, the approval process for a new dosage form, new indication, or new delivery system. Process established by Hatch–Waxman Act of 1984.
505(j) ANDA for generic agents	Abbreviated application for generic drugs. Identical active ingredient, dosage, form, and route of administration as reference licensed drug. Sponsor shows PK bioequivalence to reference product in healthy subjects. Application references safety and efficacy data from licensed drug. Process established by Hatch–Waxman Act of 1984.
Public Health Services Act	
351(a) BLA	Full standalone application for biologic drugs. Sponsor-generated data from preclinical and clinical programs are used to support approval.
351(k) BLA for biosimilar agents	Abbreviated licensure pathway for follow-on biologic products shown to be highly similar to an FDA-licensed reference biologic. Extensive analytical testing and tailored clinical comparison with reference biologic are needed to support approval. Process established by the Biologic Price Competition and Innovation Act of 2009.
NDA, new drug application; ANDA, abbreviated new drug application; BLA, biologics license application; PK, pharmacokinetics; FDA, Food and Drug Administration.	

approve a biosimilar until 12 years after it approves the reference product (33). However, the developer of a biosimilar agent may submit a 351(k) application as soon as 4 years after the approval of the reference product. The historical approval pathways for biosimilar agents are summarized in Table 1. Before the BPCIA, there was no abbreviated pathway for the approval of follow-on biologics with a reference product that was approved through the BLA pathway. Follow-on versions of drugs must be approved through the same pathway as the reference product. A handful of biologics, such as insulin and human growth hormone, have been approved over the years through the Food, Drug, and Cosmetic Act. Follow-on versions of these drugs are approved through the 505 pathway. If it is an abbreviated application, it would be either a 505(b)(2) or an abbreviated new drug application 505(j). As of 2011, the FDA has approved eight biosimilars in the 505(b)(2) category and three biosimilars as abbreviated new drug applications (3). Most biologics, including epoetin, filgrastim, and mAbs, have been approved through the PHS Act 351(a). The BPCIA established the abbreviated pathway, 351(k), to streamline the approval of biosimilars of reference products that were approved through a full 351(a) BLA. This pathway allows the FDA to designate the biosimilar as interchangeable, if appropriate, with the reference product. The 351(k) pathway is based on the principle of comparability after a manufacturing change for a biologic agent, which is an international standard described in the International Conference on Harmonization Q5E (34), part of a library of documents developed by the International Conference on Harmonization regarding biotechnology. The process begins with structural and functional characterization of the biosimilar and reference products. The more rigorous the analysis and the fewer the differences between the agents, the less additional testing will be required. The goal is to generate fingerprint-like analysis algorithms, which include elements listed in Table 2. One can argue that, because this process is relatively new, there is currently little standardization for assay type, materials, and methods, leaving much latitude for the

manufacturer of a biosimilar agent to decide which assays to submit to the FDA. However, most of the elements in Table 2 are clear cut, and it is primarily the functional assays that are at issue. It is anticipated that the FDA will proceed cautiously in this area, with public safety as its paramount consideration. There must be sufficient knowledge of the mechanism of action of the agent to predict the clinical relevance of any observed structural differences. Animal data to assess toxicity, immunogenicity, and PK/PD may be required if safety uncertainties remain before human testing of the biosimilar. The extent of required human testing will depend on the congruence of the structural/functional analysis, the knowledge base regarding the reference agent and its safety issues, and any residual concerns from the previous steps. Generally, human PK/PD testing will be required, but there should be little need to establish safety and efficacy independently for the biosimilar agent unless significant residual concerns persist. Immunogenicity studies, including assessment of binding antibodies and neutralizing antibodies, may be required. The FDA will then make its determination regarding approval on the basis of the “totality of the evidence” (italics added by the FDA) (14). It is anticipated

Table 2. Structural and functional comparison between a biosimilar drug and a reference drug (10)

- Identical primary amino acid sequence (minor N- or C-terminal truncations may be allowed that do not affect safety or effectiveness)
- Primary, tertiary, and quaternary structure
- Post-translational modifications (glycosylation and phosphorylation)
- Other potential variants (protein deamidation, oxidation, and aggregation)
- Intentional chemical modifications (PEGylation)
- Lot-to-lot variability
- Functional assays: bioassays, biologic assays, binding assays, and enzyme kinetics

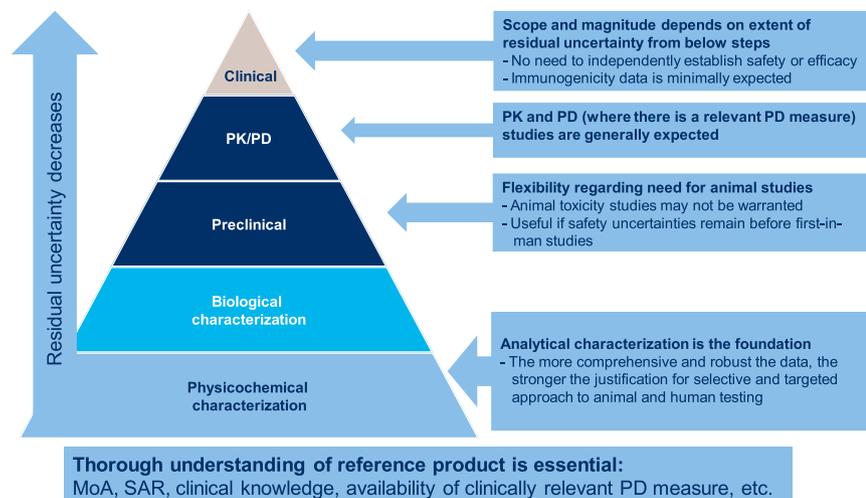


Figure 1. | Overview of Food and Drug Administration (FDA) approach to biosimilarity. MoA, mechanism of action; PD, pharmacodynamics; PK, pharmacokinetics; SAR, structure-activity relationship.

that the FDA will work with the biosimilar agent's sponsor at each step of the evaluation process to customize an approval pathway that serves the public interest to protect its safety while lowering overall health care costs, which is the intention of the BPCIA. The FDA has acknowledged that it will treat each application on a case-by-case basis and avoid a "one size fits all" approach to biosimilar agent approval (Figure 1).

If the proposed agent fulfills the statutory requirements for licensure as a biosimilar product under the BPCIA on the basis of, among other items, data derived from a clinical study that shows safety, purity, and potency in an appropriate condition of use, the potential exists for the proposed agent to be licensed for one or more additional indications of use for which the reference product is licensed. However, the sponsor must provide sufficient scientific justification for extrapolating clinical data to support a determination of biosimilarity for each indication of use for which licensure is sought. Finally, a postmarketing safety program is required for every biologic agent and must be specified in the application for the agent's approval. This requirement is on the basis of the understanding and experience that unanticipated adverse reactions may become apparent only after patient exposure increases exponentially after approval.

Conclusions

The appropriate regulation and approval of biosimilar agents has already brought benefit to patients in the EU through increased accessibility and lower acquisition costs. The BPCIA should decrease the timeline for approval of biosimilar agents, such as ESAs, and the potential for interchangeability of a biosimilar agent with its reference product will facilitate cost savings. Amgen's patent protection in the United States for epoetin alfa will expire in 2014. The manufacturers of two biosimilar ESAs that have been successfully used in the EU are actively working toward submitting studies for evaluation by the FDA. Despite concerns regarding the immunogenicity of ESAs, which may rarely lead to PRCA, the candidate biosimilars seem to be safe, with similar efficacy to epoetin alfa. When and if these agents are approved, the price competition will likely decrease the cost of Amgen's epoetin alfa, and therefore, there will be cost savings, even if a provider does not switch to the lower-priced biosimilar agent. The uptake by the nephrology community of biosimilar ESAs will depend on the balance between cost savings and any residual concerns regarding their safety.

Disclosures

J.B.W. has received compensation for services on advisory boards for Hospira (manufacturer of SB309) and Sandoz (manufacturer of HX575). J.B.W. has no ongoing consulting relationship with either company. Neither Hospira nor Sandoz had a role in the writing of this article.

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