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Perspective

# The Emerging Role of Biosimilar Epoetins in Nephrology in the United States

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Biologic drugs, including epoetin, continue to play an important role in the management of medical conditions. However, biologics are costly and soon many of the patents on these drugs will expire, making way for non–brand name products (ie, biosimilars). It is only by introducing competition to the marketplace that costs will de-escalate. In Europe, a specific regulatory pathway for approving biosimilars has been in place since 2005. A similar review pathway in the United States has been developed by the US Food and Drug Administration. These guidelines for approving biosimilars are stringent, requiring preclinical pharmacodynamic and toxicologic studies, clinical studies to demonstrate bioequivalence and efficacy, and long-term postmarketing studies to monitor drug safety. Biosimilar epoetin has been used in Europe since 2007, and a wealth of data has been collected. These studies and reports indicate that the efficacy and safety profiles of biosimilar epoetin are similar to those of originator epoetin alfa. Biosimilars of epoetin alfa are expected to be among the first biosimilar agents to be approved for use in the United States. The availability of lower cost epoetins may have significant impact on the treatment of anemia of chronic kidney disease.
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***INDEX WORDS:*** Biologic; biosimilar; bioequivalent drug; epoetin; epoetin alfa; epoetin zeta; recombinant human erythropoietin (rHuEPO); erythropoiesis-stimulating agent (ESA); anemia; chronic kidney disease (CKD); economics; safety; Retacrit.

The number of people diagnosed with kidney disease in the United States has doubled during each of the last 2 decades, with approximately 26 million Americans exhibiting some evidence of chronic kidney disease (CKD).[1] Erythropoiesis-stimulating agents continue to have an important role in the treatment of anemia of CKD, with new agents emerging into the market (Table 1[2-6]). Epoetin alfa is used in a majority of patients with dialysis-dependent CKD and in many individuals with non–dialysis-dependent CKD, and its high cost is a significant proportion of the total expense of treating patients with CKD. Consequently, epoetin alfa poses a substantial burden to both the patient and society.[7]

In the United States, the patent on epoetin alfa (Epogen/Procrit; Amgen) was scheduled to expire in 2014. When this occurs, it is expected that biosimilar epoetins, which have been available in Europe for 7 years (the European patent for epoetin alfa expired in 2004), will be marketed in the United States. As in Europe, biosimilar epoetin alfa may assist in controlling health care costs for patients with end-stage renal disease while maintaining high-quality anemia therapy.

## INTRODUCTION TO BIOLOGICS AND BIOSIMILARS

Biologic drugs are defined as compounds made by or derived from living organisms and include epoetin, monoclonal antibodies, interferons, and human insulin. Unlike traditional drugs, biologic drugs have complex molecular structures, exhibit heterogeneity, and vary with respect to higher order structure or posttranslational modifications. Another challenge to uniformity is that the manufacture of all biologics is characterized by batch-to-batch variability of the product, which some evidence suggests is considerable.

A non–brand name copy of a biologic drug, or biosimilar, is defined by the US Food and Drug Administration (FDA) as a biological product that is highly similar to the reference product, even if there are minor differences in clinically inactive components.[8] Also, the biosimilar can have no clinically meaningful differences to the reference product in terms of safety, purity, and potency. Due to the structural complexity and heterogeneity of biologic drugs, demonstrating high similarity to the reference product is more difficult for biosimilars than for other drugs, and the FDA has established a distinct regulatory pathway for biosimilars to encourage market

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**Table 1.** Antianemia Agents

| Agent | Active Compound | Manufacturing Process | Year Licensed/Stage of Development |
|---|---|---|---|
| Erythropoiesis-stimulating agents | | | |
| Epoetin alfa/beta (Epogen, Eprex, Erypo, NeoRecommon) | rHuEPO | Recombinant DNA technology; *EPO* cDNA–transfected CHO cells | 1989 (Epogen, US); 1990 (Eprex/Erypo/NeoRecommon, Europe) |
| Epoetin delta (Dynepo) | rHuEPO | Recombinant DNA technology; *EPO* cDNA–transfected CHO cells | 2006 (outside of US); product withdrawn by Shire in 2009 |
| Biosimilar epoetins (Binocrit, Retacrit, Silapo, Eporatio) | rHuEPO | Recombinant DNA technology; *EPO* cDNA–transfected CHO cells | 2007 (Europe); 2015 in US? |
| Darbepoetin alfa (Aranesp) | Hyperglycosylated rHuEPO analogue | Recombinant DNA technology; mutated *EPO* cDNA–transfected CHO cells | 2001 (US and Europe) |
| C.E.R.A. (Mircera) | Pegylated rHuEPO analogue | | 2009 (outside of US) |
| Peginesatide (Omontys) | Dimeric pegylated peptide | Synthetic peptide chemistry | 2013; withdrawn by Affymax and Takeda in 2013 |
| Novel agents | | | |
| HIF stabilizers | Prolyl hydroxylase inhibitor | Chemical synthesis | |
| GSK1278863 | | | Phase 2 |
| AKB-6548 | | | Phase 2 |
| AKB-6899 | | | Preclinical testing |
| Roxadustat, FG-4592, ASP1517 | | | Phase 3 |
| Hepcidin modulators | Various | Various | Phase 1 planning? |
| GATA-2 inhibitors | Small molecule | Chemical synthesis | Unknown |
| *EPO* gene therapy (EPODURE) | Skin cells (microdermis) transfected with *EPO* gene | Biopump technology, harvesting skin biopsies and using adenovirus as vector | Phase 2 |

Abbreviations: cDNA, complementary DNA; C.E.R.A., continuous erythropoietin receptor activator; CHO, Chinese hamster ovary; *EPO*, erythropoietin; GATA-2, GATA binding protein 2; HIF, hypoxia inducible factor; rHuEPO, recombinant human erythropoietin; US, United States.

References[2-6] provided the information presented in this table.

competition and innovation.[8] Biosimilars licensed under this new regulatory framework are likely to reach the US market as soon as 2015. Biosimilar forms of recombinant human erythropoietin (rHuEPO) for the treatment of anemia of CKD are likely to be among the first approved. A summary of facts pertinent to biosimilars, and specifically biosimilar epoetin, is presented in Box 1.

## EUROPEAN REGULATORY PATHWAYS AND CLINICAL EXPERIENCE WITH BIOSIMILAR EPOETINS

The European Medicines Agency (EMA) was the first major authority to identify and institute an abbreviated approval pathway for biosimilar medications in efforts to increase patient access to medications, reduce the cost of treatment, and encourage innovation. Subsequently, the World Health Organization (WHO) developed guidelines for the evaluation of similar biotherapeutic proteins that were formally adopted in 2009.[9] The EMA and WHO guidelines have since been used by several other countries to provide a basis for the development of their own regulatory processes.

EMA guidelines specify that modern state-of-the-art analytical techniques should be used to assess the physiochemical properties of biosimilars and that biological assays should be performed to assess their biological activity compared to the reference drug. The purity and impurity profiles of both the active substance and the final medicinal product must be assessed qualitatively and quantitatively. Since the expiration of patent protection for epoetin alfa in Europe in 2004, a number of biosimilar epoetins have been approved for use in the European Union.

### Efficacy

Multiple efficacy studies have compared biosimilar epoetin (SB309/epoetin zeta [Hospira]) with its reference product (epoetin alfa [Epogen]) for intravenous and subcutaneous administration in the correction and maintenance phases of treating the anemia of CKD.[10]