The US Food and Drug Administration (FDA) could approve the first biosimilar drug for use in dialysis patients later this year, a prospect that could shake up the market with an alternative to Amgen’s dominant anemia biologic drug Epogen (epoetin alfa) that has been used in Europe for several years.

Biosimilars are essentially the generic versions of biologic drugs, which are compounds that are made by or derived from living organisms rather than manufactured like most drugs. Because biologics—which include compounds such as the erythropoiesis-stimulating agent (ESA) epoetin, monoclonal antibodies, interferons, and human insulin—are derived using organic processes, they cannot be duplicated exactly. They show much more heterogeneity, batch-to-batch variability, and other variations compared with generic drugs, which merely require replication of the chemical formula in a controlled manufacturing process.

As patents on the first biologics began to expire, enabling companies to consider the creation of drugs based on similar principles to compete with them, the need arose for a pathway to approve these biosimilars. Because their equivalence is not as obvious as that of a generic drug, regulators wrestled with the question of what standards would be reasonable to meet without going through the approval process for a brand new drug. The European Union put such a pathway in place in 2005.

In the US, a provision of the Affordable Care Act called the Biologics Price Competition and Innovation Act of 2009 empowered the FDA to implement an abbreviated regulatory approval process for biosimilars. A manufacturer must provide clinical studies showing that a product has no meaningful differences in terms of safety, purity, and potency in comparison to a “reference product”—a specific FDA-approved biologic.

After several years of working out the details, the FDA approved its first biosimilar drug in March—Sandoz’s Zarxio (filgrastim-sndz), a biosimilar to Amgen’s cancer drug Neupogen (filgrastim). The biosimilar widely considered to be next in the pipeline for approval is Hospira’s epoetin zeta, a competitor to Amgen’s epoetin alfa, used to treat anemia in patients with chronic kidney disease (CKD).

A dominant drug
“Epoetin alfa is used in a majority of patients with dialysis-dependent CKD and in many individuals with non-dialysis-dependent CKD,” study says

On October 1, 2015, US healthcare providers will transition to the tenth version of ICD-10, the World Health Organization (WHO) disease classification system. Approved by WHO in 1990, ICD-10 is now used by more than 115 countries to record morbidity and mortality statistics, and more than 20 countries incorporate ICD-10 into their reimbursement processes. The US version, modified by the National Center for Health Statistics (NCHS) and the Centers for Medicare and Medicaid Services (CMS), includes ICD-10 Clinical Modification (ICD-10-CM), comprising 68,000 codes for use in clinical settings, and the ICD-10 Procedure Coding System (ICD-10-PCS), comprising an additional 75,000 procedure codes.

Methods of disease classification developed in England and France in the 17th and 18th centuries remain the foundation for systems used today to classify morbidity and mortality (1). The United States adopted the World Health Organization (WHO) Manual of the International Statistical Classification of Diseases, Injuries
Biosimilar Drug

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cient CKD), and its high cost is a significant proportion of the total expense of treating patients with CKD,” Steven Fishbane, MD, and Hitshe H. Shah, MD, wrote in an article, “The Emerging Role of Biosimilar Epoetins in Nephrology in the United States,” in the American Journal of Kidney Disease. Epoetin alfa dominates the market that it is Medicare’s single largest drug expenditure, some $2 billion in 2010. The five-year-head start in Europe allows US healthcare providers to benefit from the European experience. “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,” Fishbane and Shaw said. And many studies have found significant cost savings from the use of biosimilars, similar to the use of generics compared with brand-name drugs. How readily the US medical market will accept biosimilars remains to be seen. Many specialists tend to be conservative and slow to replace tried-and-true therapies, but the special circumstances of the dialysis market could make it more open to change, according to a study by the Marwood Group, a healthcare policy consulting firm. (ASN is a client of the Marwood Group and receives healthcare advisory services.) Marwood researchers conducted in-depth interviews with decision-makers at dialysis clinics to gauge their attitudes about biosimilars.

“Marwood believes that physicians will generally take a cautious approach to switching patients over from branded products to biosimilars,” the report says. “However, in the case of erythropoiesis-stimulating agents, the drug reimbursement methodology for dialysis clinics has the potential to drive a more rapid adoption. Dialysis is one of the few areas of therapy where care is reimbursed at a bundled rate, which in this case includes the cost of anemia drugs such as Epoetin. As a result, those in the business of running dialysis clinics are aware of the fixed payments they receive from Medicare and work to maximize quality of care while also likely trying to maximize profit. The more they can lower their cost to deliver care, the more likely they will increase their margins in each dialysis treatment.”

“A lot of clinics are facing economic pressure,” study author Stephen Williams, MD, told Kidney News. “They see this as a good way to save some money for a product that is essentially almost identical to the branded product.”

In their AJKD article, Fishbane and Shah said: “Availability of biosimilars in the United States is predicted to significantly reduce the cost of biologics and increase their availability, as has been the case in Europe, where cost analyses have reported substantial economic benefits.”

Epoetin zeta
Hospira launched epoetin zeta under the brand name Retacrit in Europe in 2008 and in Australia in 2011, and the company has several other biosimilars in these markets. “Hospira has delivered more than 5 million doses of biosimilars to patients in Europe and Australia over the past five years, with no concerning reporting of unusual or unexpected adverse events,” according to the company’s website. Nothing in the European experience indicates that there will be a problem in getting the epoetin zeta approved in the US.

Hospira presented a pair of randomized clinical studies at the National Kidney Foundation spring meeting that evaluated the pharmacokinetic and pharmacodynamics of epoetin zeta with Amgen’s EpoGen reference product in healthy volunteers. Both studies were consistent with a finding of biosimilarity between the products, according to a Hospira press release. The FDA’s goal is to complete its review of most biosimilar applications within 10 months of acceptance of the filing, a standard it met with approving Sandoz’s Zarxio. Hospira submitted its epoetin zeta application in December 2014, so it could receive approval later this year.

Sandoz also has an EpoGen biosimilar in development. It has been on the market in Europe for several years under the brand name Binocrit and has generated more than 160,000 patient-years of clinical experience. According to the company, Binocrit is the leading epoetin biosimilar in Europe. It has been in phase 3 clinical trials for some time, but Sandoz has not as yet filed for approval with the FDA.

Legal issues could cause delays
Legal issues surrounding expiring patents could delay a biosimilar’s introduction into the market long after its approval by the FDA, said Kim Vukhac, who also worked on the Marwood Group study. Although the FDA has approved Sandoz’s Neupogen-equivalent, it is available in more than 60 countries worldwide, patent litigation has evidently prevented its US launch.

An established process governs the introduction of generic versions of brand-name drugs. Brand name manufacturers must publish the patents protecting their drugs, so it is easy to know when the patents relate to a drug expire. But no such directory exists for biologics. A company working to introduce a biosimilar is supposed to work with the company that makes the reference drug in a process that has come to be called the “patent dance,” Vukhac said.

“It is a series of steps, a back and forth process, where the biosimilar company submits information to the reference brand company, and they are supposed to work out what patents they will be litigating,” she said. But Sandoz decided that it is not going to follow this patent dance for its newly approved biosimilar to Neupogen. The drug is not launching because Amgen and Sandoz are in court arguing over whether Sandoz needs to follow the patent dance. The two companies “are not even litigating at this point actual the patents, they are litigating how to litigate,” Vukhac said.

Because these are the first products setting precedents for what could turn out to be a complicated legal process, even if an EpoGen biosimilar is approved soon, “it is very possible we don’t see a launch,” Vukhac said.
“If there are patents still in existence around Epogen that Amgen decided to try to enforce, that could obviously delay things,” Williams added. “It is not always easy to figure out what patents are out there, and it is different from the small molecule drugs, where you essentially know what [the patents] are because companies have to list them. In this case you don’t actually have to list them, so finding them is more difficult than it might seem.”

Another potential stumbling block that apparently will not affect clinics’ adoption of a biosimilar is the experience with the failed anemia drug, Omontys (peginesatide). The FDA approved Omontys to treat anemia in adult dialysis patients with CKD in 2012. The drug offered an alternative to Epogen for less than a year. The manufacturer recalled all lots of the drug because some patients had severe hypersensitivity reactions, including anaphylaxis, that resulted in some deaths.

Dialysis clinic leaders indicated to the Marwood researchers that the Omontys experience would not affect their attitude toward biosimilars. Perhaps because Omontys was a synthetic peptide, not a biologic drug or a biosimilar. “They saw it as an unfortunate incident specific to that product, not an issue that should be extrapolated to other products,” Vukhac said.

**History of use**

Clinic leaders appear more likely to look to the European experience. “There is a history of successful use of Epogen-like products outside the US in sophisticated healthcare markets,” Williams said. “I think that is helpful to the way that people think about these things. The products that are coming into the US are essentially the same ones that they are using in Europe today. It is the same companies, and the same processes that they are using to make these biosimilars, so it is not like we are totally starting from scratch here with the Epogen-like products.”

Vukhac added that doctors are often seen as resistant to change, but the representatives of dialysis clinics interviewed indicated that they are open to switching. “They change their protocols fairly often, so they are pretty adaptive, which may be different from other specialties,” she said.

How fast a biosimilar might penetrate the market is another open question. The Marwood report says: “According to SEC filings, DaVita has a contract with Amgen which runs through the end of 2018 stipulating that it will use Amgen’s product for 90% of its ESA needs. This represents approximately one-third of the dialysis market. Fresenius is not bound by a similar contract, but is likely to take a measured approach as it has done previously with Omontys.”

The report postulates that smaller- and medium-sized dialysis organizations will be the most receptive to cost savings that could accrue from biosimilar ESAs. “Smaller clinics have been under quite a bit of financial pressure. There have been cuts to the bundle over the last few years, so I think that finding ways to manage those cuts becomes top of mind,” Williams said.

Dialysis clinics will no doubt welcome the availability of alternative drugs and suppliers that address one of their major costs, and while many questions remain, it appears to be only a matter of time until alternatives are available.

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**ICD-10 Coding Switch**

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and Causes of Death in 1948. The ninth version of this manual (ICD-9) was approved by WHO in 1975, and a version modified for the American hospital system was adopted in 1979. In the US, providers use Current Procedural Terminology (CPT) codes, updated yearly by the American Medical Association, to document and bill for specific medical procedures and services. ICD-9 disease classifications began to be harmonized into claims processing in the 1980s.

**Why switch?**

Since the adoption of ICD-9 in 1979, an explosion of new technologies, new procedures, and new quality measures has produced more detail than can be supported by the current system and codes. Moreover, today’s healthcare is global, and it is becoming increasingly difficult to share data critical to public health and research when classification systems are out of sync. According to the American Health Information Management System, ICD-9 “can’t take healthcare into the future” (2).

Many experts speculate that the increased specificity of ICD-10 codes will reduce the need for repetitive exchanges between providers and insurance companies regarding claims, and ultimately reduce the incidence of rejected claims. In addition, large and small healthcare providers may be able to use the increased specificity such as the coding for underlying causes and comorbidity, to improve patient outcomes and better allocate internal resources.

**No pain, no gain?**

Success of transitions to ICD-10 will depend on many organizations, not just providers: electronic health record (EHR) vendors, insurance companies, and others must also convert their systems. Worst-case scenarios for physicians practices during the transition include slowed productivity, higher percentages of rejected claims, and short-term increases in unbillable revenues.

To support the transition, on June 6, 2015, CMS and AMA issued a joint statement highlighting efforts to help physicians make the switch (http://cms.gov/Medicare/ Coding/ICD10/Downloads/AMA-CMS-press-release-letterhead-07-05-15.pdf). CMS and AMA will provide educational support before the transition; to address questions post-transition, CMS will set up a communications center and support an ICD-10 ombudsman, and for 12 months post-transition, CMS will allow flexibility in claims and quality reporting.

Many of the new codes relate to the musculoskeletal system, with significant expansions in coding fractures, so some areas of practice will experience more change than others. Nephrology is not anticipating the same level of change as orthopedics but all coders, physicians, and insurance companies must learn the new chapter organization, new codes, and adapt to providing more, and different kinds of, documentation. Combination codes that include acuity or severity will impact nephrology coding, especially chronic kidney disease (CKD). Diseases closely associated with kidney disease, such as diabetes and hypertension, will add to the learning curve for kidney physicians and staff. Several of the resources listed below focus on the impact of the conversion to ICD-10 on nephrology.

Within and outside the clinic setting, the conversion to ICD-10 may require efforts not yet fully anticipated. The General Equivalence Mappings (GEM) that support the transition from ICD-9 coding to ICD-10 coding in the clinic and hospital settings may not provide comparability ratios for tracking longitudinal data (3). New ICD codes must be incorporated into reporting of quality measures: for example, each AHRQ quality indicator technical specification with ICD-9 CM codes must be converted to ICD-10 CM/PCS codes. After October 1, challenges may arise when ICD-10 codes cannot be used: for instance, in the US, the workers’ compensation auto insurance claims are not required to incorporate ICD 10 coding.

While the headaches are predictable, the increased precision of these classifications, the improved integration with electronic health records, and the ability to convey more detailed data about patient outcomes, may prove great aids to nephrologists and others in their ongoing efforts to evolve and improve patient care.

**Resources**

- • AMA Support for ICD 10 Transition: http://www.ama-assn.org/ama/wire/blog/ICD-10_Monthly_Primer/1


- • Road to 10: The Small Physician Practice’s Route to ICD-10 (CMS) http://www.marco10.org/


- • ICD 10 Crosswalk for Nephrology http://nephrologypracticesolutions.com/icd-10-crosswalk

- • How to document and code for hypertensive diseases in ICD 10 http://www.aapf.org/jpm/2014/0300/pj5.html (includes information specific to hypertension and CKD)


**References**

