FDA Approves First Biosimilar, Zarxio

An alternative version of filgrastim opens the door to competition and potential savings for cancer patients

The FDA's recent approval of Sandoz's biosimilar filgrastim-sndz (Zarxio), for treating neutropenia in cancer patients, may herald a new era of competition and eventually result in lower-cost alternatives for cancer patients taking expensive biologic drugs.

The agency's decision follows the advice of its Oncologic Drugs Advisory Committee, which unanimously recommended approval of Zarxio for all indications currently approved for Amgen's Neupogen (filgrastim). Neupogen lost patent protection at the end of 2013. Zarxio, a recombinant human granulocyte colony-stimulating factor marketed in Europe as Zarzio, is the first biosimilar to be approved for entry into the U.S. market since the Biologics Price Competition and Innovation (BPCI) Act was signed into law in 2010, creating a regulatory pathway for biosimilars.

Biosimilars differ from generic drugs in that they are not exactly identical to corresponding brand-name drugs. Whereas small-molecule drugs are relatively simple to copy, it is impossible to precisely replicate biologic drugs, which are synthesized from living organisms. Unlike generics, biosimilars must be prescribed by name and cannot be directly substituted for brand-name drugs without a physician's approval.

"With today's powerful analytical tools, you will always find differences between biologics," says Emily Shacter, PhD, an independent consultant with ThinkFDA in Takoma Park, MD, who previously served as chief of the Laboratory of Biochemistry, Division of Therapeutic Proteins, at the FDA's Center for Drug Evaluation and Research (CDER). "But the big challenge is knowing how big the differences are, do they matter, and how do you know and show if they matter or not."

The FDA requires biosimilar manufacturers to perform an extensive biologic analysis during the review process to show that the products are "highly similar," and to conduct confirmatory clinical studies demonstrating that any differences between the biosimilar and the original drug are not "clinically meaningful," says Leah Christl, PhD, associate director for therapeutic biologics at CDER's Office of New Drugs.

Sandoz submitted comparative data for Zarxio demonstrating equivalent pharmacokinetic and pharmacodynamic profiles. The company also supplied data from a randomized clinical trial demonstrating that Zarxio is as effective as Neupogen in preventing severe neutropenia in patients with breast cancer who are undergoing chemotherapy.

Biosimilars have been selling in Europe for 30% to 40% less than the original products, and similar savings are possible in the United States, according to a recent analysis by the RAND Corporation (available at www.rand.org). The report estimates that biosimilars will result in a savings of $44.2 billion on biologics over the next decade.

Sandoz, a unit of Novartis, soon could face price competition in the United States from other companies developing their own versions of filgrastim. Last month, Apotex filed an application with the FDA for approval of its filgrastim biosimilar, Grastofil, and is awaiting approval of its version of Amgen's Neulasta, a longer-acting formulation of Neupogen. Other filgrastim biosimilars, such as Hospira's Nivestim, are already on the market in Europe.

In addition, Teva's tbo-filgrastim (Granix) was approved in the United States in 2012, before the regulatory pathway for biosimilars had been established. Although the drug is a biosimilar for filgrastim and is currently marketed as such in Europe under the brand name Tevagrastim, the company had to file a standard biologics license application with the FDA and demonstrate the safety and efficacy of the drug in several clinical trials.

Biosimilars for other biologics are in the pipelines of several major pharmaceutical companies as patents on the brand-name versions expire. For example, Amgen and Pfizer are developing versions of Genentech's trastuzumab (Herceptin), a monoclonal antibody that inhibits the HER2/neu receptor in breast cancer; Genentech's patent expired last year in Europe and will run out in 2019 in the United States. Other Genentech drugs set to lose patent protection over the next few years include bevacizumab (Avastin), an angiogenesis inhibitor (U.S. patent expires in 2019); and rituximab (Rituxan), an anti-CD20 drug (U.S. patent expires in 2016). Amgen and others are working on a version of bevacizumab while Pfizer and others are developing a biosimilar for rituximab.

The flurry of interest in filgrastim may be due to the drug's relatively simple structure, which makes it easier to copy compared with some other drugs, says Shacter.

"Filgrastim is a relatively small, nonglycosylated protein with a single mechanism of action and a well-defined pharmacodynamic endpoint (*in vivo* activity), so it can be more easily analyzed and evaluated compared with some larger, more complicated glycoprotein products like monoclonal antibodies, such as infliximab and rituximab," she explains. "Many monoclonal antibodies not only bind to their target but also have multiple Fc effector activities, so you have several very significant functional domains in the molecule that are responsible for the drug doing what it has to do."

Legal issues surrounding patents can complicate the process of bringing biosimilars to market, says Shacter. Last fall, Amgen filed a patent lawsuit claiming that Sandoz did not meet deadlines for disclosing its manufacturing plans for Zarxio, as required by the BPCI Act. If successful, Amgen's move could delay Zarxio's launch.

Biosimilar makers have to honor patents not only on the drug itself but also on the processes involved in manufacturing it, Shacter explains. "Some of the brand-name drug formulations may also be patented."

While the path to approval can be lengthy for biosimilars, the eventual result will likely benefit patients, says Christl.

"Biological products are the fastest growing market of prescription products," she says. "The new biosimilar approval pathway can create more competition in the marketplace and will provide consumers with access to safe, effective biological products." –*Janet Colwell* ■

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