CLIENT ALERT

Three Take-Aways from Novartis' Historic First U.S. Biosimilar Approval

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Zarxio, Novartis AG's version of Amgen Inc.'s cancer drug Neupogen®, recently won approval from the U.S. Food and Drug Administration (FDA), marking the first time that the FDA has approved a biosimilar for sale in the United States.

The approval process for biosimilars is governed by the Biologics Price Competition and Innovation Act of 2009 (BPCI Act), which was part of the Affordable Care Act that President Obama signed into law in March 2010 to foster competition in high-priced biologics. The BPCI Act created an abbreviated licensure pathway for biological products shown to be "biosimilar" to or "interchangeable" with an FDA-licensed biological product, called the "reference product." Since then, the FDA has issued draft guidelines and held meetings with pharmaceutical manufacturers to provide some direction regarding the expected approval pathway, but many questions remained unanswered. On January 14, 2015, a FDA panel of experts issued a ringing endorsement of Zarxio. As promised, the FDA moved quickly to give the first U.S. biosimilar final approval.

To obtain approval for a biosimilar product under the BPCI Act, the applicant must show that it is highly similar to an already-approved biological product, known as a reference product. Furthermore, the applicant must demonstrate that the biosimilar also has no meaningful clinical differences in terms of safety and effectiveness from the reference product. Minor differences are acceptable, though.

Biological products differ from small molecule drugs in two important ways. First, biological products are generally derived from a living organism. Second, only a biological product that has been approved as an "interchangeable" under the BPCI Act may be substituted for the reference product without the intervention of the prescribing health care provider and only if permitted under the relevant state law. Zarxio was not approved as "interchangeable," meaning that it cannot be substituted without the intervention of the health care provider.

Zarxio was developed by Novartis's Sandoz unit and was determined by the FDA to be highly similar to Amgen's Neupogen®, but not "interchangeable." Neupogen® is designed to increase white blood-cell counts, and lower infection rates, mostly in patients getting chemotherapy and other treatments. The FDA approved the biosimilar Zarxio for all five of the brand-name drug's indications. According to a statement issued by the FDA, Novartis agreed to delay selling Zarxio in the U.S. until a motion for preliminary injunction in a lawsuit with Amgen is resolved or until April 10, whichever is earlier.

There are many lessons to be learned from this watershed event. But here are three take-aways from the FDA's first approval of a biosimilar.

First: An EU Approval and Track Record Helps

The European Union has been approving biosimilars since 2006. And while the FDA has been heavily criticized for moving slowly on biosimilars, one by-product of the slow pace is that many biosimilars have an EU track record of safety and effectiveness. Zarxio was approved by the EU in 2009. This allowed Novartis's Sandoz to tell the FDA that Zarxio had been sold for years in

Europe, pointing to real-world experiences with the drug including, "in excess of 7.5 million days of patient exposure, demonstrating its clinical safety and efficacy," as Sandoz told the FDA advisory committee. Given that the European Medicines Agency has approved 26 biosimilars, there are many more drugs that can follow in Novartis's footsteps.

Second: The Biosimilar Naming Protocol Remains Murky

FDA's approval of Zarxio did not end the heated, and so-far unsettled, debate over what names should be used for biosimilars. Brand manufacturers contend that drug names should be different for biosimilars because, unlike small-molecule generics, they are similar to, but not the same as, the brand-name biologic. Biosimilar manufacturers argue that the name should be the same to avoid patient and physician confusion, as well as to promote substitution of less expensive biosimilars for brand-name biologics. The FDA took a middle ground as an interim approach. The active ingredient in Neupogen® is filgrastim and the FDA required Zarxio's name to be "filgrastim-sndz." How the FDA ultimately decides the naming issue could go a long way to determining how successful biosimilars are in penetrating the market and reducing healthcare costs.

Third: The Pathway Is Clarified, but by No Means Clear

Without a doubt, the substantial EU track record of Zarxio made the FDA's job of approving the drug for U.S. sale much easier. However, the pathway to approval for future biosimilars referencing drugs without prior EU approval remains untested. Soon, biosimilars without prior overseas approvals will come to the FDA. The level of information necessary to provide comfort to the FDA sufficient for approval of such drugs is still not clear. Moreover, as a large molecule drug, Neupogen® is a relatively simple molecule. More complex molecules, such as monoclonal antibodies, a class of biologics that include some of the best-selling blockbuster drugs, such as Herceptin and Humira, may present a greater regulatory approval challenge.

What's Next for the First U.S. Biosimilar?

Despite its historic approval, the timing of Sandoz bringing Zarxio to market still remains up in the air. On March 13, 2015, the Northern District of California will hear arguments on the parties' cross motions for judgment on the pleadings in *Amgen v. Sandoz*, Case No. 3:14-cv-04741-RS, regarding the parties' disputes over the disclosure requirements imposed by the new biosimilar pathway. At the same time, the court will decide whether to grant Amgen's request for a preliminary injunction to restrain Novartis's Sandoz from selling Zarxio. In the meantime, Novartis has agreed to delay Sandoz's U.S. launch of Zarxio until the earlier of the court's decision on Amgen's request for a preliminary injunction or April 10, 2015.

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