LOS ANGELES
Daily Journal
www.dailyjournal.com
FRIDAY, MARCH 13, 2015

Biosimilar approval a groundbreaking step

By Michelle Rhyu and Susan Krumplitsch

On March 6, nearly five years after the Biologics and Price Control and Innovation Act (BPCIA) was enacted, the federal Food and Drug Administration took a groundbreaking step: It approved the first biosimilar drug for use in the United States. The drug is Sandoz's Zarxio, a white blood cell growth factor primarily used to help prevent infections in cancer patients receiving chemotherapy. Zarxio is a close copy of Amgen's blockbuster biologic, Neupogen (filgrastim), which generated an estimated $1.2 billion in sales for Amgen in 2014.

Biologics are strikingly more complex than small molecule pharmaceuticals, which can be synthesized using conventional and predictable chemical methods. For example, small molecule drugs are typically comprised of 50 to 100 atoms, while biologic drugs are comprised of thousands to tens of thousands of atoms. Biologics are typically produced in living organisms, such as genetically engineered yeast or bacterial cells. Even a minor change in conditions under which the recombinant cells are grown may cause a modification to the resulting biologic. Sensitive biomanufacturing requirements of these drugs may lead to variations in the biologic drug, and as a result, a copycat version of a biologic may be highly similar to the original, but not identical. In contrast, the active ingredients in small molecule pharmaceuticals can be precisely duplicated, resulting in identical generic copies of the original drug.

The BPCIA created an abbreviated regulatory pathway for biologic products demonstrated to be "biosimilar" to or "interchangeable" with already licensed biologics. It was enacted as part of the 2010 Affordable Care Act by adding Section 351(k) to the Public Health Service Act (PHSA). Biosimilar applications made under the rubric of the BPCIA are known as "Section 351(k) applications."

This first-ever approval of a biosimilar under the BPCIA is a significant milestone, and provides important insights into how biosimilars will be evaluated at the FDA. Zarxio was approved as a biosimilar for all of the same indications listed in Neupogen's label. To be deemed biosimilar, Sandoz had to demonstrate that Zarxio is highly similar to the reference product, Neupogen, notwithstanding minor differences in clinically inactive compounds and that there were no clinically meaningful differences between the Zarxio and Neupogen in terms of safety, purity and potency. Zarxio has been marketed in Europe since 2009, and Sandoz was able to rely, in part, on this vast amount of efficacy and safety data in its U.S. biosimilar application.

The FDA has not yet released any guidance on how biosimilar products sold in the U.S. should be named. It gave Zarxio the nonproprietary name "filgrastim-sndz," with the suffix standing for Sandoz The FDA described this as an agency-designated "placeholder," that is not reflective of a larger, comprehensive naming policy for biosimilars.

Zarxio was not designated as interchangeable, which would have allowed for automatic substitution at the pharmacy. Under the BPCIA, to be considered interchangeable, the proposed biologic product must be biosimilar to the reference product and can be expected to produce the same clinical result as the reference product, in any patient. If the biosimilar is given in multiple doses, there must be sufficient data to demonstrate there is no safety risk or reduced efficacy that would result from switching from the reference product. Exactly what companies must demonstrate to meet the interchangeable designation remains unclear, as the FDA has not yet released any draft guidance on this topic.

In addition to the abbreviated regulatory pathway for biosimilars, the BPCIA also establishes a complex scheme for handling patent disputes. The BPCIA has been analogized to the 1984 Hatch-Waxman Act, which provides a litigation framework for generic small molecule drugs. In contrast to Hatch-Waxman, however, the BPCIA contains a complicated and novel litigation framework involving patent exchanges and multiple waves of litigation.

For example, in Hatch-Waxman litigation, the patents covering a particular small molecule drug (including the drug compound, drug formulation and method of using the drug) are published and publicly available on the FDA's website. In contrast, there is no publicly available list of applicable patents covering a biologic drug. Instead, the BPCIA has created a series of pre-litigation exchanges that includes a patent negotiation process, in which the parties privately exchange lists of patents they believe are potentially infringed by the biosimilar applicant. If the parties agree on the list of patents, the branded biologic company shall bring an infringement suit on each patent within 30 days. If the parties do not agree on the list of appropriate patents, there are additional patent lists exchanged, and the branded company shall bring an infringement suit within 30 days on each patent on each list. If the branded company fails to sue within the 30-day deadline, any damages that may result from actual infringement will be limited to a reasonable royalty.

This initial wave of litigation was designed to be resolved long before FDA approval of the biosimilar application. A second phase of litigation is triggered by the biosimilar applicant's obligation to provide 180-day notice of intent to launch. None of the patents litigated in the first phase may be re-litigated in the second phase. Preliminary injunction is available only for patents initially identified by the parties, but not litigated in the first phase.

The litigation provisions of the BPCIA are now being tested in federal court. Thus far, no parties have utilized the information exchange provisions described above. Prior to filing Section 351(k) applications with the FDA, a few biosimilar applicants filed declaratory judgment actions, seeking declarations of noninfringement and invalidity of the branded biologic company's relevant patents. None succeeded as all four cases were eventually dismissed. It now appears settled that a biosimilar applicant cannot preempt the BPCIA litigation provisions by filing a declaratory judgment action prior to filing its biosimilar application with the FDA.

In October 2014, Amgen sued Sandoz in U.S. District Court in the Northern District of California after Sandoz refused to provide Amgen with a copy of Sandoz's Zarxio biosimilar application and manufacturing information as mandated by the BPCIA. This case directly addresses whether the information disclosures mandated by the statute are mandatory. See *Amgen Inc. v. Sandoz Inc.*, 14-04741 (N.D. Cal.). Amgen is seeking declaratory and injunctive relief, and filed a motion for preliminary injunction just prior to FDA's approval of Zarxio. A hearing on Amgen's preliminary injunction motion is set for Friday.

The BPCIA is a complex statute with unique provisions rife with ambiguities. With the FDA's approval of Zarxio and other biosimilars in line for approval, the abbreviated pathway of the BPCIA is here to stay and will likely be active area of life science patent litigation for the foreseeable future.

Michelle Rhyu *is is a partner in Cooley LLP's intellectual property group in the litigation department.*

Susan Krumplitsch *is an associate in the intellectual property litigation practice group and a member of Cooley LLP's litigation department.*

MICHELLE RHYU
Cooley LLP

SUSAN KRUMPLITSCH
Cooley LLP

Cooley