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Biosimilars

Poised to Turn to Inter Partes Review to Resolve Patent Disputes

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On March 6, 2015, the U.S. Food and Drug Administration (FDA) approved the first biosimilar drug in the U.S., Sandoz's Zarxio™, to treat cancer patients who are at increased risk for infection. A "biosimilar" is a biological product that is highly similar to an existing FDA-approved biological product ("reference product") and exhibits no clinically meaningful differences from the reference product in terms of safety, purity and potency.[1] A biosimilar is sometimes thought of as a "generic" version of its biologic reference product; however, unlike a traditional generic pharmaceutical, a biosimilar is not an exact copy of its reference product due to the fact that biological products are large, complex biomolecular structures made in living cells (e.g., therapeutic recombinant proteins, antibodies, vaccines, antitoxins and blood products). In view of this distinction, the Biologics Price Competition and Innovation Act (BPCIA), part of the Patient Protection and Affordable Care Act of 2009, introduced new patent-related provisions governing the approval of biosimilars. The BPCIA was designed to integrate a defined patent dispute resolution process – addressing the reference product sponsor's claims of patent infringement and the biosimilar applicant's claims of patent invalidity – into the biosimilar approval process, ensuring that full information exchange occurs at relevant and crucial periods during the approval process. Nevertheless, Sandoz has thus far managed to circumvent the patent dispute resolution procedures of the BPCIA. Sandoz and other biosimilar applicants are likely eyeing *inter partes* review as a more favorable option for resolving patent disputes.

The BPCIA provides regulatory exclusivity to biologic reference products for 12 years. After this exclusivity period, and upon demonstration of clinical biosimilarity, the FDA can approve a biosimilar application for safety and efficacy, paving the way for market entry. The FDA's acceptance of a biosimilar application for review commences what is commonly referred to as the "patent dance," a complicated information-exchange process for addressing patent disputes between the biosimilar applicant and the reference product sponsor. The first step in this exchange is for the biosimilar applicant to provide the reference product sponsor with a copy of its application, as well as any other information describing the processes used to manufacture the biosimilar product, within 20 days of the FDA's acceptance of the biosimilar application. The next steps require the parties to "engage in good faith negotiations to agree on which, if any, patents" should be litigated. If agreement is reached, the reference product sponsor has 30 days to bring an action for patent infringement. If no agreement is reached, further rounds of information exchange ensue in an attempt to identify which patents should be the subject of an infringement action. All told, under the BPCIA, the parties can take up to 230 days just to commence litigation. [2]

Notwithstanding the BPCIA's detailed, step-by-step patent dispute resolution procedures, the U.S. District Court for the Northern District of California recently ruled in *Amgen v. Sandoz*[3] that the statute's procedures are optional. Amgen, the company that makes the reference product (Neupogen®) for Sandoz's Zarxio™, sued Sandoz for failing to provide Amgen with a copy of its biosimilar application within 20 days of acceptance by the FDA. Amgen argued, and the district court acknowledged, that the patent dispute resolution procedures of the BPCIA "repeatedly use the word 'shall' to describe the parties' obligations under its prescribed procedures."[4] Nevertheless, the court found that such language does not make the procedures mandatory. Instead, the court adopted a permissive interpretation of the overall statutory scheme, noting in particular that the statute specifically permits a reference product sponsor to bring a patent infringement action immediately if a biosimilar applicant chooses not comply with the BPCIA's disclosure procedures.[5] Amgen appealed and, with FDA approval by then granted, brought a motion for a preliminary injunction to prevent the launch of Zarxio™. The Federal Circuit granted that motion on May 5, 2015, and will hear the appeal on June 3, 2015.

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Similar patent disputes and challenges to the BPCIA are emerging around the country. For example, Janssen Biotech, Inc. recently brought suit against Celltrion Healthcare Co. in the U.S. District Court for the District of Massachusetts, alleging that Celltrion, in seeking approval of its biosimilar, circumvented the information and patent exchange procedures of the BPCIA.[6] Additionally, the U.S. District Court for the Southern District of New York prevented biosimilar applicants from using declaratory judgement to avoid complying with the BPCIA's patent dispute resolution provisions, ruling in two cases that the biosimilar applicants had to follow the BPCIA's statutory procedures.[7]

Clearly, biosimilar applicants are loathe to engage in the "patent dance" set forth in the BPCIA, perhaps due to the time and costs involved, or perhaps because they are reluctant to make the required disclosures. The courts – particularly the Federal Circuit in the upcoming appeal of *Amgen v. Sandoz* – will need to clarify whether biosimilar applicants can "decline to dance." If they can, as the District Court for the Northern District of California ruled, what mechanism will biosimilar applicants use to settle patent disputes with their reference product sponsors? Many believe that the answer to this question is *inter partes* review (IPR), a relatively new type of post-grant patent proceeding implemented in September 2012 under the America Invents Act (AIA).

Biosimilar applicants are loathe to engage in the BPCIA's "patent dance."

IPR is a mechanism for challenging the validity of issued patent claims based on anticipation or obviousness challenges using prior art patents and printed publications. Any party other than the patent owner can petition for IPR. IPR proceedings are administered by the Patent Trial and Appeal Board (PTAB) of the United States Patent and Trademark Office (USPTO), rather than by the courts. The purpose of these proceedings is to provide a petitioner the opportunity to challenge the validity of an issued patent in a timely and cost-effective manner.

For biosimilar applicants, IPR offers a number of advantages over the BPCIA and subsequent litigation. Importantly, IPR offers faster and earlier resolution of patent issues. The entire IPR process from petition to final written decision by the PTAB takes no more than 24 months. This means that biosimilar applicants could gain earlier market entry and avoid full-blown litigation costs. An accelerated timeline also makes it more likely that courts will grant a stay of patent litigation pending the outcome of the IPR. Moreover, in contrast to the BPCIA, biosimilar applicants would not necessarily need to wait until they have filed an FDA application to petition for IPR.[8]

Another benefit of IPR for biosimilar applicants is that claims are construed according to a "broadest reasonable interpretation standard" in USPTO proceedings. This usually results in broader claim construction than in district court, which makes invalidating claims easier. There is also a lower burden for proving invalidity in IPR proceedings than in district court litigation. The presumption of patent validity does not apply in IPR. Invalidity need be proved only by a "preponderance of the evidence" in IPR proceedings, as opposed to "clear and convincing evidence" in civil litigation. Finally, IPR proceedings are decided by administrative patent judges, most of whom have a technical science background and are likely to be better suited than district court judges to understand the complex technology surrounding biologic products.

IPR proceedings are also subject to some restrictions, however, that biosimilar applicants should keep in mind. Notably, IPR is limited to validity challenges based on anticipation (35 U.S.C. § 102) or obviousness (35 U.S.C. § 103) shown using patents or printed publications. Other bases of invalidity, such as lack of enablement or lack of written description, and other evidentiary sources, such as offers of sale or public use, cannot be presented in an IPR proceeding. In addition, IPR is only available for a one-year time period after a patent infringement suit is filed against the would-be petitioner. A petition for IPR also cannot be filed after the petitioner has filed a declaratory judgement action challenging the patent's validity. In order to commence IPR, a petitioner must establish a reasonable likelihood that it will prevail on at least one of the claims being challenged. IPR petitioners are also estopped in later litigation or USPTO proceedings from relying on prior art that was raised or reasonably could have been raised during IPR, although this estoppel does not attach until the PTAB issues a final written decision.[9]

While IPR has not been used as often in the biotech/pharma sector as in other technologies,[10] its use in that sector is on the upswing. In particular, IPR is increasingly being used by generic drug companies as a powerful settlement tool in litigation involving brand companies' patents. Moreover, IPR is proving to be an extremely effective mechanism for invalidating patent claims. Statistics across all technology sectors have shown that in about 80 percent of IPR proceedings to date, every claim for which a PTAB trial was instituted was eventually invalidated. This alarmingly high "kill rate" for patent claims led former Federal Circuit Chief Judge Rader to refer to the administrative patent judges of the PTAB as "death squads, killing property rights."[11]

Whether IPR proceedings will continue to result in such a high invalidation rate and whether these general statistics will apply to biotech/pharma cases in particular remains to be seen. The clout of the BPCIA, soon to be decided by the Federal Circuit, is also likely to impact the popularity of IPR among biosimilar drug companies. It is clear, however, that IPR is an attractive option for biosimilar applicants, presenting favorable odds for challenging reference product sponsors' patents and gaining early market entry. Likewise, reference product sponsors should be aware of IPR as a threat to their patent portfolios and should place a premium on prosecuting strong patents.

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1. 42 U.S.C. § 262(k)(2)(A)(i)(I).

2. *See id.*, § 262(l)(2)-(9).

3. *Amgen Inc. v. Sandoz Inc.*, 2015 U.S. Dist. LEXIS 34537 (N.D. Cal. Mar. 19, 2015).

4. *Id.* at *16.

5. *Id.* at *16-*20.

6. *See* Complaint, *Janssen Biotech, Inc., et al. v. Celltrion Healthcare Co., Ltd., et al.*, Case No. 1:15-cv-10698 (D. Mass. 2015).

7. *See Celltrion Healthcare Co. v. Kennedy Trust for Rheumatology Research*, Case No. 1:14-cv-02256-PAC (S.D.N.Y. 2014); *Hospira, Inc. v. Janssen Biotech, Inc., et al.*, Case No. 1:14-cv-7079-PAC (S.D.N.Y. 2014).

8. In an earlier litigation between the same parties regarding a different drug, *Sandoz, Inc. v. Amgen, Inc.* 773 F.3d 1274 (Fed. Cir. 2014), the Federal Circuit held that Sandoz was not entitled to seek declaratory judgement that its proposed biosimilar product would not infringe Amgen's patents for Enbrel®, since Sandoz had not yet filed an application for FDA approval of the product and had only begun required testing, and it was unknown whether the testing would be successful or the product would be approved.

9. *See* 35 U.S.C. §§ 311-319.

10. For fiscal year 2015, approximately 8 percent of IPR petitions have been filed in the bio/pharma sector, compared to 63 percent in the electrical/computer arts. See Patent Trial and Appeal Board AIA Progress Statistics (as of 04/09/2015), http://www.uspto.gov/sites/default/files/documents/aia_statistics_04-09-2015.pdf (viewed May 14, 2015).

11. Bloomberg BNA, "Rader Regrets CLS Bank Impasse, Comments on Latest Patent Reform Bill" (Oct. 28, 2013).