In the News

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The New Biosimilars Frontier *By Sapna W. Palla and Monica A. Kolinsky*

The market for "biosimilars"—generic versions of federal Food and Drug Administration (FDA) approved biological drugs—which is an over $100 billion industry, is rapidly growing. Indeed, it is expected to be the single fastest-growing biologics sector in the next five years. By some accounts, sales of biosimilars are expected to reach $6.22 billion by 2020 from $2.29 billion in 2015. *See* Press Release, Mkts. & Mkts., Biosimilars Market Worth $6.22 Billion by 2020 (July 16, 2015).

The Biologics Price Competition and Innovation Act (BPCIA) was enacted in March 2010 as part of the Patient Protection and Affordable Care Act. 42 U.S.C. § 262. It provides a pathway for the approval of biologics by the FDA based on similarity or interchangeability with a licensed biologic as well as specific procedures for patent dispute resolution and litigation between an innovator (known as the reference product sponsor, or RPS) and a biosimilar applicant. However, the complex and largely untested regulatory scheme under the BPCIA has a number of ambiguities that have left it susceptible to challenge.

This article discusses the BPCIA framework, recent jurisprudence under the BPCIA, and strategies for RPSs and applicants in light of ambiguities in the BPCIA framework.

THE "PATENT DANCE" UNDER THE BPCIA

The BPCIA specifies a complex and lengthy procedure for patent information exchange and litigation often termed the "patent dance."

The statute states that within 20 days after a biosimilar application has been accepted for review, the applicant "shall" provide the RPS its application and a description of its manufacturing process. 42 U.S.C. § 262(l)(2)(A). Within 60 days of receipt, the RPS must provide the applicant with a list of all patents the RPS believes could "reasonably be asserted" against the applicant and identify those patents it would license. 42 U.S.C. § 262(l)(3)(A). Within 60 days of receipt, the applicant may provide its own list of potentially infringed patents that could be asserted by the RPS and must provide either (1) a detailed statement for its basis that the patent(s) cited by the RPS are invalid, unenforceable, or not infringed; or (2) a statement that the applicant will not market its product until the expiration of the listed patent(s). 42 U.S.C. § 262(l)(3)(B).

Within 60 days of receipt of the applicant's statement, the RPS must provide a detailed statement of why it believes the patent(s) will be infringed, as well as a response to the applicant's statements concerning validity and enforceability. 42 U.S.C. § 262(l)(3)(C). After the patent exchange process has been completed, the parties have to engage in negotiations to determine which patents will be litigated. 42 U.S.C. § 262(l)(4). If an

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agreement is reached, the RPS has 30 days to bring suit on the patents agreed to by the parties. If an agreement is not reached, the applicant has to notify the RPS of the number of patents to be litigated. 42 U.S.C. § 262(l)(5)(A). Within five days of notification, the parties have to exchange lists of the patents they believe should be litigated with the limitation that the number of patents submitted by the RPS cannot exceed the number listed by the applicant. If the applicant does not list any patents, the RPS may list only one patent. 42 U.S.C. § 262(l)(5)(B). The RPS has 30 days to bring suit on the patents listed. 42 U.S.C. § 262(l)(6)(B).

The statute also provides for "notice of commercial marketing" where the applicant "shall provide notice to the [RPS] not later than 180 days before the date of the first commercial marketing" of the biosimilar. 42 U.S.C. § 262(l)(8)(A).

CHALLENGING THE "PATENT DANCE": THE *AMGEN V. SANDOZ* FIGHT

Five years after the BPCIA was introduced, the Federal Circuit had its first opportunity to substantively interpret the provisions of the BPCIA in a dispute between Amgen (the RPS) and Sandoz (the applicant). Amgen Inc. v. Sandoz Inc., 794 F.3d 1347 (Fed. Cir. 2015), arose from Sandoz's accepted application for Zarxio®, its biosimilar version of Amgen's Neupogen® (filgrastim), which is used to treat neutropenia-related infection in cancer patients receiving chemotherapy. This was the first time that the Federal Circuit had addressed whether the disclosure and patent exchange provisions (the so-called "patent dance") of the BPCIA are mandatory or whether either party can opt out of the requirements and settle as specified in the statute. The split decision interpreted the "information exchange" and "notice" provisions of the BPCIA.

"Information exchange" provision. Amgen alleged that Sandoz failed to comply with the information exchange provision set forth in paragraph (l)(2)(A) of the BPCIA by opting not to provide Amgen with a copy of the biosimilar application within 20 days of the FDA's notice of acceptance. The U.S. District Court for the Northern District of California agreed with Sandoz's interpretation of this provision, holding that despite the use of "shall," disclosures under the information exchange provision are not intended to be mandatory because the BPCIA expressly provides remedies for the RPS in the event that the applicant does not comply with the disclosures.

The Federal Circuit's majority opinion, authored by Judge Alan Lourie and joined by Judge Raymond Chen, analyzed the language of the information exchange provision in the context of the BPCIA as a whole and concluded that Congress intended "shall provide" to be permissive, not mandatory. The majority's reasoning followed the district court on this issue, in that the BPCIA expressly contemplates an applicant's failure to disclose the application by setting forth consequences for such failure. *Amgen v. Sandoz*, 794 F.3d at 1355.

Judge Pauline Newman dissented from this part of the opinion, asserting that the majority's interpretation of the information exchange provision disrupts the balance of obligations and benefits the BPCIA sets forth for the applicant and the RPS, and noting that the majority did not construe the plain language of the information exchange provision in accordance with established precedent where "shall" is the language of command. *Amgen v. Sandoz*, 794 F.3d at 1366 (Newman, J., dissenting in part).

"Notice" provision. Amgen also argued that the 180-day notice of commercial marketing provided by Sandoz was ineffective under paragraph (l)(8)(A) of the BPCIA because such notice was given before the FDA approved Sandoz's biosimilar product. The district court held that the applicant may give such notice any time after the FDA accepts the biosimilar application for review, in this case prior to FDA approval.

Judge Newman joined Judge Lourie in the majority opinion, concluding that the applicant cannot give effective marketing notice until after the FDA has approved the biosimilar application, thus reversing the district court on this issue. The majority's reasoning focused on ensuring the existence of a "fully crystallized controversy" with respect to the scope of the approved application before injunctive relief could be granted. *Amgen v. Sandoz*, 794 F.3d at 1358.

In addition to providing preapproval marketing notice to Amgen, Sandoz also had given Amgen notice of commercial marketing after it received FDA approval. In accordance with its interpretation of the notice provision, the Federal Circuit enjoined Sandoz from marketing Zarxio® until 180 days after the postapproval notice, giving Amgen a six-month extension of exclusivity. *Amgen v. Sandoz*, 794 F.3d at 1359.

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Judge Chen dissented from the section of the opinion interpreting the term "shall," asserting that the majority construed the information exchange provision in the context of the BPCIA as a whole but construed the notice provision as a standalone provision. The dissent contended that when the notice provision is read in the context of the BPCIA in its entirety, "shall" means "must," just as it does in the information exchange provision. *Amgen v. Sandoz*, 794 F.3d at 1367 (Chen, J., dissenting in part).

After the split decision, both parties requested rehearing en banc but the petitions were denied.

IMPACT OF THE *AMGEN V. SANDOZ* DECISION

The impact of Amgen v. Sandoz is currently playing out in three pending district court cases with claims hinging on the Federal Circuit's interpretation of the BPCIA's information disclosure and notice provisions. The BPCIA-related issue being litigated in the pending cases focuses on the interplay between the "information exchange" provision and the "notice" provision. Specifically, the cases seek clarity as to whether 180-day advance notice to the branded company of commercial marketing of the biosimilar is required, as the Federal Circuit ruled, even when the applicant has engaged in the information exchange, or patent dance, which the Federal Circuit deemed optional.

In *Janssen Biotech, Inc. v. Celltrion Healthcare Co., Ltd.*, No. 1:15-cv-10698 (D. Mass. filed Mar. 6, 2015), Janssen initiated patent infringement litigation to delay Celltrion's biosimilar version of Janssen's Remicade® (infliximab), which is used for the treatment of Crohn's disease, ulcerative colitis, rheumatoid arthritis, and similar indications. There are several outstanding substantive motions, including cross-motions for summary judgment based on the Federal Circuit's ruling in *Amgen v. Sandoz*. Celltrion contends that because it complied with the optional patent dance by disclosing its biosimilar approval application and manufacturing information to Janssen and agreeing that all of the patents identified by Janssen would be the subject of litigation, it is exempt from providing the 180-day notice of commercial marketing. Janssen disagrees and argues that Celltrion did not disclose all of the required manufacturing information and so did not comply with the patent dance. Janssen further contends that the ultimate determination of whether compliance with the patent dance exempts an applicant from providing the 180-day notice of commercial marketing is not relevant in this case because Celltrion did not comply, and thus was required to provide notice to Janssen. A hearing is not yet scheduled.

In *Amgen Inc. v. Apotex Inc.*, No. 0:15-cv-61631 (S.D. Fla. filed Oct. 5, 2015), Amgen's patent infringement suit against Apotex's biosimilar version of Amgen's Neulasta® (pegfilgrastim), used to treat neutropenia in cancer patients, includes a claim that Apotex violated the BPCIA's notice provision. Apotex provided its biosimilar application and manufacturing information to Amgen, and agreed that all of the patents identified by Amgen would be the subject of litigation. Amgen does not dispute that Apotex complied with the patent dance. Prior to the Federal Circuit's decision in *Amgen v. Sandoz*, and before Apotex's biosimilar was approved by the FDA, Apotex provided Amgen with notice of commercial marketing. In light of the decision in *Amgen v. Sandoz*, Amgen now contends that Apotex's notice was ineffective under the Federal Circuit's interpretation of the notice provision. Apotex argues that because it complied with the patent dance, it may opt out of providing notice in this case. Trial is scheduled for July 11, 2016. The court granted Amgen's motion for preliminary injunction after a December 3, 2015, hearing. A week later, Apotex appealed to the Federal Circuit, which appeal was pending at the time of publication.

In *Amgen Inc. v. Hospira, Inc.*, No. 1:15-cv-00839 (D. Del. filed Sept. 18, 2015), Amgen is also squaring off against Hospira for its biosimilar version of Amgen's Epogen®, used to treat anemia in patients with cancer or chronic kidney disease. Hospira provided its biosimilar application but allegedly did not fully disclose its manufacturing information. Hospira agreed that the patents listed by Amgen that could be asserted would be the subject of litigation. Similar to Amgen's case against Apotex, prior to the Federal Circuit's decision in Amgen v. Sandoz, and before Hospira's biosimilar was approved by the FDA, Hospira provided Amgen with notice of commercial marketing. Amgen contends that Hospira's notice was ineffective under the Federal Circuit's finding in Amgen v. Sandoz that notice of commercial marketing is mandatory and must be provided after FDA approval of the biosimilar. Hospira argues that notice is not required in this case

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because it complied with the information disclosure provision.

HOW CAN RPSS AND APPLICANTS WORK AROUND THE "PATENT DANCE"?

While the BPCIA framework is here to stay in the near future, as can be seen from recent jurisprudence, both the applicant and the RPS can take advantage of it and operate outside its regulatory framework to obtain early resolution of patent infringement, validity, and enforceability issues.

The *Amgen v. Sandoz* decision makes clear that the BPCIA does not mandate disclosure of the biosimilar application, allowing applicants to forgo the patent dance. The decision also may extend an RPS's exclusivity by six months, given that the 180-day notice of commercial marketing must be communicated after FDA approval. The fact that there is no automatic stay under the BPCIA increases the likelihood that applicants will introduce their products while still "at risk"; for example, they might launch before any litigation is resolved. As the *Amgen v. Sandoz* decision shows, particularly where the applicant's commercial launch might occur before the completion of the underlying litigation, preliminary injunction motions must be taken into consideration. Thus, the absence of an automatic stay emphasizes the importance of preliminary injunction motions.

Furthermore, despite the complex presuit dispute resolution process, it appears that an RPS can still bring suit before completion of the dispute resolution process. Therefore, applicants should be prepared to face the possibility of a patent infringement suit on patents outside the framework of the negotiation process envisioned by the BPCIA. An applicant should also carefully consider which patents should be put on the patent lists provided under the BPCIA because the applicant may be subject to a patent infringement suit on these patents regardless of the negotiation process.

Early claim construction to obtain clarity on patent infringement positions could be very advantageous for both the applicant and the RPS. Given that the Supreme Court has recently ruled, in *Teva Pharmaceuticals USA, Inc. v. Sandoz, Inc.,* 135 S. Ct. 831 (2015), that more deference should be accorded on appeal to factual findings on claim construction issues, it is important to consider when and where (in district court, the International Trade Commission, or the Patent Trial and Appeal Board) such determinations should be made.

STRATEGIES FOR DISCOVERY

The scope and expense of discovery in matters invoking the BPCIA could potentially be very expensive, intrusive, and lengthy. Both applicants and RPSs need to consider, before even engaging in the patent dance, what strategies they can use to protect themselves. An applicant may create a voluminous number of documents over the course of research and development leading to the biosimilar or interchangeable biological product and may also develop its own patent portfolio surrounding its biological product. Thus, assessment of discovery needs, including the scope of potentially responsive documents and witnesses who may be deposed, should be done at an early stage, preferably prior to filing of the biosimilar application. This is important to ensure readiness to respond to any patent litigation.

AVOID POTENTIAL LITIGATION BETWEEN APPLICANTS

In developing a biosimilar product, an applicant may develop its own intellectual property and obtain patents on its proprietary intellectual property. This may lead to one applicant facing an infringement suit from another applicant after it has launched its biological product. Therefore, it is advisable for applicants to carefully monitor the patent activities of their competitors, as well as to seek timely patent protection of their intellectual property.

CONCLUSION

Given the complex and often inconsistent regulatory framework for the approval of biological products under the BPCIA, both applicants and RPSs are likely to encounter many issues as the legislation is interpreted and enforced by the courts. As discussed above, both applicants and RPSs will have to engage in careful strategic and innovative thinking to determine how they can best protect the intellectual property related to their biological products.

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