The Biologics Price Competition and Innovation Act: Commercial Marketing in the Spotlight

By: Hunter Malasky

I. Introduction and Background

The Biologics Price Competition and Innovation Act (BPCIA) was enacted by Congress in 2010 as part of the Affordable Care Act. [1] The BPCIA was intended to help innovators and pharmaceutical drug developers by streamlining the regulation of biologics, much as the Hatch-Waxman Act of 1984 did with respect to small molecule generic drugs. [2] Unlike the Hatch-Waxman Act however, which *only* covered small molecule generic drugs, the BPCIA regulates large molecule drugs with "no clinically meaningful difference" to the reference product. [3]

Biologics, under the BPCIA, are complex molecules such as viruses or therapeutic serums produced for the purpose of preventing, treating, or curing human diseases or conditions. [4] In enacting the BPCIA, Congress sought to facilitate the development and marketing of biosimilars and increase competition amongst drug developers as well as provide a specific process for potential patent infringement claims. [5] Biosimilars are biologics that are "highly similar" to a reference product with no clinically meaningful difference between the biosimilar and the reference product in terms of "safety, purity, and potency of the product." [6]

Recognizing biosimilars as a separate class of products allows drug development companies to produce a drug that is clinically equivalent to a drug already patented and on the market, thus spurring innovation and competition between drug developers and pharmaceutical companies. [7] Because the biosimilar has a reference drug, under the BPCIA, the developer of the biosimilar is able to use clinical data already collected for the reference drug and apply that data for approval from the FDA for their biosimilar. [8] Since the biosimilar developer, referred to as a subsection (k) applicant in 42 USC § 262, does not have to compile its own clinical data

regarding the safety, purity, and potency of its drug, the path towards FDA approval is consequently faster, more certain, and less expensive. [9] However, as a result of this streamlined process, the BPCIA also raises issues involving patent infringement and patent litigation, as several cases have been filed primarily concerning the interpretation of the BPCIA and its specific biosimilar approval process requirements. [10]

II. The Patent Dance

The major change brought about by the BPCIA was creating a process by which a biosimilar developer and its reference product sponsor (the reference product developer) resolve instances of patent infringement. [11] This process has become known as the "patent dance." [12] 42 USC § 262(l) describes the process through which a biosimilar developer can negotiate possible patent infringements and disputes with the reference product sponsor. [13] This process includes the biosimilar developer providing the reference product sponsor with notification of FDA review as well as a copy of the submitted application to the FDA and the manufacturing process of the biosimilar. [14] The reference product sponsor can then reply by providing a list of patents the sponsor believes the biosimilar is infringing, which is then followed by a response from the biosimilar developer identifying which patent infringements may be reasonably asserted. [15]

While the BPCIA patent dance is far more complex than just described, this article is limited to a discussion of recent court decisions interpreting provisions of the BPCIA. [16] Because of the length and novelty of the BPCIA, specific provisions of the statute remain unclear and thus have been the focus of recent litigation. [17] In light of the fact that only four

biosimilars (Amjevita, Erelzi , Zarxio , and Inflectra) have been approved to date, the process under the BPCIA is very much still in its infant years. [18]

This article focuses on recent cases involving the interpretation of paragraph (l)(8)(A) of 42 USC § 262 concerning notice of FDA approval and the commercial marketing of a biosimilar.

III. 42 USC § 262 (l)(8)(A) – Notice of Commercial Marketing and Preliminary Injunction

Thus far, the major interpretive cases of the BPCIA have centered on the interpretation of § 262 (l)(8)(A), "Notice of Commercial Marketing and Preliminary Injunction." [19] Paragraph (8)(A) establishes that the biosimilar developer "shall provide notice to the reference product sponsor not later than 180 days before the date of the first commercial marketing of the biological product licensed under subsection (k)." [20] The purpose behind this notice is to give the reference product sponsor as well as the court a defined statutory window during which parties can assess any rights to the biosimilar product prior to its commercial launch. [21] This obviates the need for the reference product sponsor to rush to make a decision on whether to request a preliminary injunction and whether a court should issue such an injunction. [22] In the first case that addressed this particular issue, Amgen, Inc. v. Sandoz, Inc., the court determined that even if the biosimilar developer does not follow the patent dispute process laid out in paragraph (l)(2)(A), the biosimilar developer is still required to file notice of commercial marketing with the reference product sponsor 180 days before the date of first commercial marketing. [23] While the court established that the notice is mandatory when a biosimilar does not comply with the process illustrated in (l)(2)(A), Sandoz did not address the question of whether a biosimilar developer who complies with paragraph (2)(A) is subsequently required to comply with paragraph (8)(A). That unresolved question is what ultimately led to the case of Amgen, Inc. v. Apotex, Inc. [24]

IV. Amgen, Inc. v. Apotex, Inc.

a. Facts and Background

Amgen is a pharmaceutical company that developed the FDA-approved cancer therapy Neulasta, which is currently on the market. [25] Neulasta's active ingredient is pegfilgrastin. [26] Apotex developed a biosimilar to Amgen's Neulasta, which it used as its reference product in order to take advantage of the streamlined biosimilar process set out in the BPCIA. [27] Apotex complied with paragraph (2)(A) of the BPCIA by filing the abbreviated application for approval of its biosimilar to both the FDA and Amgen. [28] Amgen claims that Apotex infringed two of its method patents, U.S. Patents No. 8,952,138 and 5,824,784. [29] Apotex later notified Amgen that it did not plan on informing Amgen in the event the FDA approved its biosimilar, and thus would not provide the 180 day notice of commercial marketing as dictated in 42 USC § 262(l)(8). [30] Amgen filed their claim requesting injunctive relief in the form of an order requiring Apotex to comply with § 262(l)(8), notifying Amgen of FDA approval and refraining from marketing the product for 180 days after providing notice. [31]

The question before the court was whether the 180-day notice dictated by paragraph (8)(A) is required for biosimilar developers who comply with paragraph (2)(A) of the BPCIA. [32] Even though one of the patents in dispute, Patent '784, expired on October 20, 2015, well before the proceedings of the case, its expiration did not affect the issue of statutory interpretation before the court. [33]

b. Procedural History

Amgen sought injunctive relief to compel Apotex to 1) notify Amgen if and when the FDA approved Apotex's biosimilar and 2) to refrain from marketing the biosimilar until at least 180 days after the notice. [34] The district court focused on the text of paragraph (8)(A) to

determine whether or not the notice and 180-day period was required for developers that followed the BPCIA patent exchange process. [35] In relevant part, paragraph (8)(A) states that the biosimilar applicant "shall provide notice to the reference product sponsor..." [36] The court was thus tasked with interpreting the meaning of the word "shall" as used in the statute. [37] The court referenced the decision in Sandoz, where the Federal Circuit determined that "shall" with respect to Paragraph (8)(A) was mandatory language, even though "shall" in paragraph (2) was interpreted as not being mandatory. [38]

Apotex contended that the Sandoz decision should be limited to mean that only biosimilar developers who did not comply with paragraph (2) are required to file the 180-day notice. [39] The court rejected Apotex's claim, asserting that not requiring the 180-day notice in all scenarios would result in confusion and inconsistency, and therefore the 180-day notice requirement should not depend on whether the biosimilar developer complies with paragraph (2). [40] The court's reasoning is grounded in the purpose of paragraph (8)(A), which is to provide a defined statutory window in which the reference product sponsor can evaluate patent claims and afford courts adequate time to grant potential injunctions. [41]

Apotex also argued that requiring the 180-day notice would effectively extend the FDA granted 12-year exclusivity period of Amgen's product by 180 days. [42] The court noted that this was a peculiar situation because one of the Amgen patents, patent '784, was due to have its exclusivity period expire at the time Apotex filed the biosimilar notice. [43] Therefore if Apotex is required to refrain from marketing its product for 180-days after notice, that decision effectively gives Amgen product exclusivity past the granted 12-year period. [44] The court noted although the exclusivity period would be extended in this case, the statute must be interpreted as it was enacted, not in light of the peculiar facts of any one case. [45] Furthermore,

on balance, the 180-day period is unlikely to negatively impact Apotex, while still serving its intended function of allowing Amgen adequate time to solidify patent infringement claims. [46]

Finally, Apotex claimed that requiring compliance with paragraph (8)(A) rendered paragraph (9) unnecessary. [47] Paragraph (9) provides remedies for the reference product sponsor in the event that the biosimilar developer does not comply with the provisions set forth in § 262. [48] Such remedies include filing for a declaratory judgment action for failure to comply with paragraph (8)(A). [49] The court, referring to Sandoz, rejected Apotex's claim on the grounds that paragraph (9) only sets out exemplary and not exclusive remedies for noncompliance. [50]

For these reasons, the district court granted Amgen's motion for preliminary injunction, requiring Apotex to file notice with Amgen once FDA approval is received. [51] Apotex was also ordered to refrain from marketing the product for 180 days after giving notice to Amgen. [52]

c. Appeal to The Federal Circuit

Following the district court's ruling, Apotex appealed to the Federal Circuit. [53] The Federal Circuit affirmed the ruling of the district court stating that regardless of whether the biosimilar developer complied with paragraph (2), a notice of FDA approval must always be sent to the reference product sponsor, and the biosimilar cannot be marketed within 180 days of that notice. [54] With this decision, paragraph (8)(A) has been interpreted to require any biosimilar developer to provide notice of FDA approval regardless of whether or not the developer has complied with any other aspect of the BPCIA. [55]

The Federal Circuit emphasized the purpose of paragraph (8)(A) in its decision, namely to allow all parties time to assess their rights prior to launch of the biosimilar product and

minimize the potential for rushed decision-making. [56] The Federal Circuit reasoned that this interpretation of paragraph (8)(A) was in line with the overall objective of the BPCIA as a means to reduce uncertainties and deficiencies commonly associated with requests for restraining orders and preliminary injunctions in patent infringement cases. [57]

The Federal Circuit also affirmed the dismissals of Apotex's two other claims regarding 1) the extension of the mandated 12-year exclusivity period and 2) that paragraph (9) established a sole remedy for noncompliance. [58] The Federal Circuit goes on to extend the reasoning behind paragraph (9) as an unsatisfactory remedy for noncompliance, particularly with regards to noncompliance of paragraph (8)(A). [59] The court reasoned that if a biosimilar developer fails to provide the approval and marketing notice, then the reference product sponsor will only find out about the product once the product is already on the market. [60] In such an event, the reference product sponsor will almost certainly rush to court and file for immediate relief, in accordance with paragraph (9)(B), in order to avoid any further harm. [61] This is precisely the type of practice that the BPCIA is meant to discourage, and moreover, the remedy listed in paragraph (9)(B) is not always an appropriate remedy as the harm in this case would already have occurred. [62] For this reason, the Federal Circuit held that the preliminary injunction enforcing Apotex's compliance with paragraph (8)(A) was appropriate. [63]

V. Consequences and Conclusions

While the primary intent of the BPCIA was to streamline the biosimilar patent infringement process and increase competition amongst drug developers, recent litigation under the BPCIA has focused on the interpretation of the statute's provisions detailing the necessity to disclose FDA approval and commercial marketing delays. These passages have been scrutinized because of the major disruption a biosimilar drug would have by suddenly hitting the market and

competing with a drug that has held market exclusivity for up to 12 years. Recent litigation has therefore been necessary to clarify the rights of the parties on both sides of the patent infringement case in understanding what aspects of the BPCIA are mandatory.

The immediate impact of the Apotex and Sandoz decisions are that § 262 (l)(8)(A) requiring notice of FDA approval and 180-day refrain of commercial marketing are always mandatory for any biosimilar product, regardless of compliance with other standards set forth in the BPCIA. The court's decision certainly gives the reference product sponsor as well as the court system some breathing room. Because paragraph (8)(A) is always mandatory, the reference product sponsor will have time to assess its rights as far as potential patent infringements and request any preliminary injunctions. The court in turn gets some reprieve by not feeling rushed to make a decision on whether or not to grant injunctive relief.

Currently both Sandoz and Apotex are pending *certiorari* with the United States Supreme Court. Both cases are appealing the question of whether paragraph (8)(A) is a standalone requirement, regardless of compliance with other BPCIA provisions. Therefore, it is certainly possible that the Federal Circuit's decisions will be reconsidered. Because of the similarity of questions between both Sandoz and Apotex, if the Supreme Court grants *certiorari* to one case, it will likely hear the other as well. Amicus briefs have already been filed for the cases with The Biosimilars Council and major pharmaceutical company Mylan both advocating for reversal of the decisions.

If the Supreme Court grants *certiorari* and reverses Sandoz and Apotex, a different interpretation of paragraph (8)(A) will have to be established. If this occurs, the most likely interpretation will be one in line with the interpretation of paragraph (2) given by the Federal Circuit in Sandoz, where the court established that the provision is not a requirement. While

there is a clear argument in favor of requiring compliance with paragraph (8)(A) as illustrated by the Federal Circuit decision, a decision by the Supreme Court not requiring compliance could actually increase competition among drug developers by increasing the importance of commercial marketing to consumers and the pricing strategy used by the drug owners. Such an interpretation of paragraph (8)(A) could therefore still be in-line with the purposes of the BPCIA by furthering price competition and innovation.

The recent United States elections that occurred on November 8, 2016 also have direct implications for the BPCIA. The BPCIA was passed as part of the Affordable Care Act under President Barack Obama. With the major shift in political power in Washington, D.C., there is a strong coalition to repeal the Affordable Care Act (ACA). While specifics regarding a repeal have yet to be thoroughly discussed, it will depend on whether the government under President-elect Donald Trump decides to fully repeal and replace the ACA or repeal and replace it only in part. If there is a full repeal of the ACA, the BPCIA will also be a part of the repeal, completely eliminating the biosimilar process that was established. Thus, the future existence of the ACA and the BPCIA is unclear at best.

Assuming the BPCIA is not repealed, the biosimilar market will continue to expand, which will likely generate even more litigation as drug developers grapple with interpreting what exactly the BPCIA requires of them. In the meanwhile, competition is likely to continue to intensify as drug developers begin to manufacture more biosimilars and compete for consumers. As cases relating to the BPCIA are brought before courts, it is crucial to remember the purposes of the BPCIA and balancing the twin goals of providing greater affordable life-saving treatments for consumers and serving the private interests of the drug developers.

ENDNOTES:

[1] *See* 42 USC § 262.
[2] *See id*.; 21 USC § 355.
[3] *See* Dhavan, Gauri M., Mahn, Terry G. *Biosimilars vs. Generics – Major Differences in the Regulatory Model. Pharmaceutical Compliance Monitor*. March 13, 2012.
[4] *See* 42 USC § 262.
[5] *See Amgen, Inc. v. Sandoz, Inc.*, 794 F.3d 1347, 1360 (Fed. Cir. 2015)(*Sandoz, Inc.)*.
[6] *See id.*
[7] *See Emerging Health Care Issues: Follow-On Biologic Drug* Competition. FTC Report. June 2009.
[8] *See id.*
[9] *See id.*
[10] *See Amgen, Inc. v. Apotex*, *Inc.* 827 F.3d 1052 (Fed. Cir. 2016)(*Apotex, Inc.)*; *Amgen, Inc.*, 794 F.3d 1347; *Sandoz Inc. v. Amgen Inc.*, 773 F.3d 1274 (Fed. Cir. 2014)(*Amgen, Inc.)*.
[11] *See* Dhavan, Gauri M., Mahn, Terry G. *Biosimilars vs. Generics – Major Differences in the Regulatory Model. Pharmaceutical Compliance Monitor*. March 13, 2012.
[12] *See* Fogel, Louis E. et al. *The Biosimilar Regulatory Pathway and the Patent Dance*. Jenner and Block.
[13] *See* 42 USC § 262(l).
[14] 42 U.S.C. § 262(l)(2)(A) "Not later than 20 days after the Secretary notifies the subsection (k) applicant that the application has been accepted for review, the subsection (k) applicant--(A) shall provide to the reference product sponsor a copy of the application submitted to the Secretary under subsection (k), and such other information that describes the process or processes used to manufacture the biological product that is the subject of such application."
[15] *See id.*
[16] *See* Dhavan, Gauri M., Mahn, Terry G. *Biosimilars vs. Generics – Major Differences in the Regulatory Model. Pharmaceutical Compliance Monitor*. March 13, 2012.
[17] *See eg. Apotex, Inc.*, 827 F.3d 1052; *Sandoz, Inc.*, 794 F.3d 1347; *Amgen, Inc.*, 773 F.3d 1274.
[18] Center for Drug Evaluation and Research. *List of Licensed Biological Products with (1) Reference Product Exclusivity and (2) Biosimilarity or Interchangeability Evaluations to Date*. Updated October 23, 2016.
[19] *See* 42 USC § 262 (l)(8)(A) "The subsection (k) applicant shall provide notice to the reference product sponsor not later than 180 days before the date of the first commercial marketing of the biological product licensed under subsection (k)." *Apotex*, *Inc.*, 827 F.3d 1052; *Sandoz, Inc.*, 794 F.3d 1347; *Amgen, Inc.*, 773 F.3d 1274;
[20] *See* 42 USC § 262(l)(8)(A).
[21] *See Sandoz, Inc.*, 794 F.3d 1347, 1360.
[22] *See id.*
[23] *See id.* at 1359.
[24] *See Apotex, Inc.*, 827 F.3d 1052.

[25] *See Amgen, Inc. v. Apotex, Inc*., 2015 WL 11198250 at 2 (S.D. Fl. 2015).
[26] Amgen. *Neulasta*. https://www.neulasta.com/.
[27] *See* 42 USC § 262; *Amgen*, 2015 WL 1119820 at 2.
[28] *See Apotex*, *Inc.*, 2015 WL 1119820 at 2.
[29] Brinkerhoff, Courtenay C. *Amgen and Apotex do the Biosimilar Patent Dance*. PharmaPatents: Timely Insight on Emerging Legal Developments. August 27, 2015. Available at https://www.pharmapatentsblog.com/2015/08/27/amgen-fills-out-biosimilar-patent-dance-card/; U.S. Patent No. 8,952138; U.S. Patent No. 5,824,784.
[30] *Id.*
[31] *See id.*
[32] *See Apotex*, *Inc.,* 2015 WL 1119820 at 2.
[33] U.S. Patent No. 5,824,784 (Filed October 1994).
[34] *See Apotex, Inc.*, 2015 WL 1119820 at 2.
[35] *See Apotex, Inc.*, 2015 WL 1119820 at 2.
[36] 42 USC § 262.
[37] *See Apotex, Inc.*, 2015 WL 1119820 at 3.
[38] *See id.*
[39] *See id.*
[40] *See id.*
[41] *See id.*
[42] 42 USC § 262(k)(7)(A); *See Apotex*, 2015 WL 1119820 at 3.
[43] *See Apotex, Inc.*, 2015 WL 1119820 at 3.
[44] *See id*.
[45] *See id.*
[46] *See id.*
[47] *See id.*
[48] *See id.*
[49] *See id.*
[50] *See id.*
[51] *See id.*
[52] *See id.*
[53] *See id.*
[54] *Apotex, Inc.*, 827 F.3d at 1052.
[55] *See Apotex*, *Inc.*, 827 F.3d at 1066; *Sandoz*, 794 F.3d at 1369.
[56] *See Apotex*, *Inc.*, 827 F.3d at 1066.
[57] *See id.* at 1059.
[58] *See id.* at 1063.
[59] *See id.* at 1064.
[60] *See id.* at 1065.
[61] *See id.* at 1064.
[62] *See id.*
[63] *See id.*