IN THE UNITED STATES DISTRICT COURT

FOR THE SOUTHERN DISTRICT OF FLORIDA

AMGEN INC. and AMGEN MANUFACTURING LIMITED, Plaintiffs, vs. APOTEX INC. and APOTEX CORP., Defendants.	Case No. 15-cv-61631-JIC/BSS

PLAINTIFFS AMGEN INC.'S AND AMGEN MANUFACTURING LIMITED'S MOTION FOR PRELIMINARY INJUNCTION AND INCORPORATED MEMORANDUM OF LAW

TABLE OF CONTENTS

TABLE OF AUTHORITIES

CASES

STATUTES

RULES

OTHER AUTHORITIES

Plaintiffs Amgen Inc. and Amgen Manufacturing Limited (together, "Amgen"), pursuant to this Court's October 13, 2015 Order Setting Briefing Schedule [D.E. 41] and Fed. R. Civ. P. 65, respectfully move for a preliminary injunction against Apotex Inc. and Apotex Corp. (together, "Apotex"), and submit this incorporated memorandum of law in support thereof.

PRELIMINARY STATEMENT

Amgen seeks a preliminary injunction to restrain Apotex from any commercial marketing of a "biosimilar" copy of Amgen's NEULASTA® (pegfilgrastim) product until Apotex complies with Federal law by giving Amgen proper notice. That notice must be given at least 180 days before the first commercial marketing of Apotex's product, and may not be given until the product is licensed by the Food and Drug Administration. Apotex refuses to provide that notice.

Apotex has applied to FDA for approval of a "biosimilar" version of Amgen's NEULASTA®, a medication that helps the body fight infection during chemotherapy. "Biosimilars" are like generic drugs, but instead of being copies of so-called "small molecules," biosimilars are instead similar to "biological products," which are themselves complex medicines made from living cells. Apotex submitted its application under the federal biosimilars statute, the Biologics Price Competition and Innovation Act of 2009 (the "BPCIA"), Pub. L. No. 111-148, 124 Stat. 119 (2010). Before 2010, FDA licensed biological products only under the traditional pathway of 42 U.S.C. § 262(a), which typically requires three phases of clinical trials to prove safety and efficacy. The BPCIA created an abbreviated regulatory pathway, codified in 42 U.S.C. § 262(k), for approval of a biological product as "biosimilar to" a "reference product" that has itself already been licensed by FDA under the traditional regulatory pathway. Apotex sought FDA approval under the abbreviated pathway by referencing NEULASTA®. In the vocabulary of the BPCIA, Amgen Inc. is the Reference Product Sponsor (or, "RPS") and Apotex Inc. is the "subsection (k) applicant" (or, "Applicant"). *See* 42 U.S.C. § 262(*l*)(1)(A).

Congress enacted the BPCIA as part of the Affordable Care Act, because it was "the sense of the Senate that a biosimilars pathway balancing innovation and consumer interests should be established." BPCIA, Pub. L. No. 111-148, § 7001(b), 124 Stat. at 804. Prior to the BPCIA, innovators enjoyed permanent and exclusive rights to their clinical trial data and FDA license. In creating the abbreviated regulatory pathway, Congress advanced the public's interest in price competition in part by diminishing these innovators' rights. After an innovator's product has been licensed for four years, biosimilar applicants can now "reference" the innovator's

license pursuant to the BPCIA, and thereby rely on the innovator's prior demonstration of safety and efficacy rather than generate its own clinical trial data, as was traditionally required. After the innovator's product has been licensed for twelve years, and with the benefit of further data accumulated and reported to FDA from the innovator's post-approval experience, FDA may approve the biosimilar product based on this new statutory "referencing" authority. Licensure through the abbreviated biosimilar pathway saves the Applicant significant time, risk, and expense, and lets the Applicant enter a market with established demand for the product.

On the other side of the balance, Congress protected the public's interest in fostering innovation—the purpose of patents—by establishing a mechanism by which the RPS receives information, notice, and a period of time to assess and act on its patent rights, without imposing on the courts for emergency relief to prevent actual injury from patent infringement. Accordingly, the BPCIA has two phases, each directed at the orderly resolution of patent disputes. The "early" phase starts when FDA accepts the Applicant's Biologics License Application (or "aBLA") for review. The Applicant is to provide its aBLA to the RPS along with information about how its proposed product is manufactured. Based on this disclosure, the RPS identifies relevant patents, and the parties exchange detailed contentions about infringement, validity, and enforceability. *See* 42 U.S.C. § 262(*l*)(2)-(3). The parties then create a list of patents for litigation, either by agreement or by a blind exchange of previously identified patents, *see id.* §§ 262(*l*)(4), (5), and an "Immediate patent infringement action" under 42 U.S.C. § 262(*l*)(6) is filed. Apotex and Amgen engaged in the first phase of patent-dispute resolution under 42 U.S.C. § 262(*l*)(2) through (4), and this lawsuit is a paragraph (*l*)(6) lawsuit.

The second phase of the BPCIA process starts when FDA licenses the biosimilar product for commercial marketing. In this later phase, the BPCIA protects the value of patents, including those that may not have become part of the paragraph (*l*)(6) lawsuit, as well as those that are newly issued or licensed after the first phase commences, by preserving the status quo during a limited statutory period. This period occurs between FDA licensure of the biosimilar and its first commercial availability. During that defined statutory window of 180 days, the RPS may seek further discovery as is needed and injunctive relief to maintain the status quo after that 180-day window has closed and until the court finally resolves any patent issues. To that end, 42 U.S.C. § 262(*l*)(8)(A)—the provision at issue on this motion—states as follows:

> *Notice of Commercial Marketing.* –The subsection (k) applicant [here, Apotex] shall provide notice to the reference product sponsor [here, Amgen] not later than 180 days before the date of the first commercial marketing of the biological product licensed under subsection (k).

Paragraph (*l*)(8)(B) authorizes the RPS to commence preliminary injunction proceedings "After receiving the notice under subparagraph (A) and before such date of the first commercial marketing of such biological product." And paragraph (*l*)(8)(C) provides for further, expedited discovery if the RPS seeks a preliminary injunction.

Apotex purported to give Amgen notice of commercial marketing on April 17, 2015. Notably, because FDA had not approved Apotex's aBLA at that time—indeed, it still has not done so—there was no "product licensed" when Apotex gave notice. Whether an Applicant could give notice before FDA approval was a question then being litigated in a separate lawsuit between Amgen and another company, Sandoz. Apotex gambled that the Federal Circuit would hold that notice of commercial marketing could be given before FDA approval. Apotex lost that bet. In July, the Federal Circuit held that a biosimilar applicant "may only give effective notice of commercial marketing after the FDA has licensed its product." *Amgen Inc.* v. *Sandoz Inc.*, 794 F.3d 1347, 1358 (Fed. Cir. 2015) (emphasis added). Apotex's April notice was ineffective.

Rather than agreeing to give notice after any FDA approval, Apotex now argues that it need not give notice at all, because giving notice is not mandatory. But that argument is foreclosed by the statute and by the same Federal Circuit case. The statute uses the verb "shall," which usually denotes a mandatory obligation. 42 U.S.C. § 262(*l*)(8)(A). And the Federal Circuit squarely rejected the notion that notice is optional: "A question exists, however, concerning whether the 'shall' provision in paragraph (*l*)(8)(A) is mandatory. We conclude that it is." 794 F.3d at 1359. Apotex argues that it is exempt from this mandatory obligation because it has, so far, complied with the provisions of the BPCIA, specifically because it provided Amgen with a copy of its aBLA, *see* 42 U.S.C. § 262(*l*)(2)(A). Apotex seeks to distinguish itself from Sandoz, which did not provide the information called for by paragraph (*l*)(2)(A). But Apotex's compliance with paragraph (*l*)(2)(A) does not excuse it from the notice-of-commercial-marketing provision in paragraph (*l*)(8)(A). The Federal Circuit said so explicitly: "nothing in paragraph (*l*)(8)(A) conditions the notice requirement on paragraph (*l*)(2)(A) or other provisions of subsection (*l*)." *Amgen*, 794 F.3d at 1360. Apotex nevertheless refuses to provide notice under paragraph (*l*)(8)(A).

This is Amgen's motion for a preliminary injunction to compel Apotex to comply with the statute by forbidding Apotex from commencing commercial marketing of its biosimilar product until it has given Amgen at least 180 days' notice of first commercial marketing if, and after, FDA licenses its product.

The parties have cooperated to streamline this motion for the Court, stipulating to the elements of the preliminary-injunction test other than likelihood of success on the merits. What remains, then, is a question of law: Is Amgen likely to succeed in showing that under 42 U.S.C. § 262(*l*)(8)(A), if FDA approves Apotex's aBLA, Apotex must then give Amgen at least 180 days' notice before first commercial marketing of that biosimilar product? For the reasons set forth below, Amgen respectfully submits that such pre-marketing notice is required, and respectfully requests that the Court enter an injunction prohibiting Apotex from any commercial marketing of its biosimilar pegfilgrastim product until it has complied with that requirement.

STATEMENT OF FACTS

Amgen draws these facts from Apotex's Answer to Amgen's Complaint, from public records, and from the accompanying declarations of Robert Azelby, Vice President and General Manager Oncology at Amgen Inc., and Nicholas Groombridge, Amgen's counsel.

Amgen's NEULASTA® (pegfilgrastim) Product

Amgen Inc. discovers, develops, manufactures, and sells innovative therapeutic products based on advances in molecular biology, recombinant DNA technology, and chemistry. (Complaint ¶ 1; Answer ¶ 1.) Amgen Manufacturing Limited manufactures and sells biologic medicines for treating diseases in humans. (Complaint ¶ 2; Answer ¶ 2.)

Amgen's NEULASTA® (pegfilgrastim) is a recombinantly produced protein that stimulates the production of neutrophils, a type of white blood cell. It is used to counteract neutropenia, a neutrophil deficiency that makes a person highly susceptible to life-threatening infections and is a common side effect of certain chemotherapeutic drugs. (Complaint ¶¶ 38-39; Answer ¶¶ 38-39; Azelby Decl. ¶¶ 4-5.)

In 2002, Amgen obtained regulatory approval for NEULASTA® under the traditional biologics regulatory pathway, 42 U.S.C. § 262(a). To do so, Amgen demonstrated to FDA that NEULASTA® "is safe, pure, and potent." 42 U.S.C. § 262(a)(2)(C)(i)(I). Amgen Inc. is the owner of the FDA license for NEULASTA®. (Groombridge Decl. ¶ 9 & Ex. G.)

The value of the biological license for NEULASTA® to Amgen, to would-be Applicants and to society is the direct result of significant investments by Amgen. That is not unusual. Developing innovative pharmaceutical products requires enormous amounts of time, human resources, and money. The average cost to develop a new drug (including the cost of failures) exceeds $1 billion. (Groombridge Decl. ¶ 7 & Ex. H.)

As the BPCIA recognizes, Amgen and other innovative biopharmaceutical companies seek to protect their investments through patenting its inventions. Amgen is asserting two patents here—U.S. Patent Nos. 8,952,138 and 5,824,784—that are directed to pegfilgrastim and to methods of making recombinant proteins like pegfilgrastim.

Apotex's aBLA for Biosimilar Pegfilgrastim

Apotex Inc. develops, manufactures, and sells pharmaceuticals, including generic medicines. (Answer ¶ 3.) Apotex Corp. markets pharmaceuticals in the United States, including generic medicines. (Answer ¶ 4.)

Apotex filed an aBLA under the BPCIA's abbreviated pathway, 42 U.S.C. § 262(k), seeking approval of its biosimilar pegfilgrastim product, designating Amgen's NEULASTA® as the reference product. (Complaint ¶¶ 41-42; Answer ¶¶ 41-42, 44.) Amgen Inc. is therefore the Reference Product Sponsor with respect to Apotex's aBLA. (Groombridge Decl. ¶ 2 & Ex. A.) On December 16, 2014, Apotex notified Amgen that FDA had accepted Apotex's aBLA for review. (Complaint ¶ 46; Answer ¶ 46.) FDA has not yet approved Apotex's aBLA. As set forth in the parties' joint motion to set a briefing schedule, "Apotex asserts that FDA's decision regarding Apotex's aBLA could be issued at any time," and Apotex has agreed to refrain from commercial marketing of its product through only a date certain agreed to in connection with this motion. DE 37 at 2, 3.

The Parties' Exchanges of Information Pursuant to the BPCIA

The BPCIA established a patent-dispute-resolution regime that includes amendments to Titles 28, 35, and 42 of the United States Code. The BPCIA made submission of an aBLA an artificial act of patent infringement, allowing infringement suits to be filed before FDA approval and before marketing of the biosimilar product. *See* 35 U.S.C. § 271(e)(2)(C), (e)(4). And the BPCIA "established a unique and elaborate process for information exchange between the biosimilar applicant and the RPS to resolve patent disputes." *Amgen*, 794 F.3d at 1352. That process is embodied in 42 U.S.C. § 262(*l*), "Patents." Until quite recently, Amgen and Apotex

had followed that process faithfully. Apotex's refusal to continue to do so is the reason for this motion.

The BPCIA has two phases, each targeted at orderly resolution of patent disputes. The first phase begins (and began here) with FDA's acceptance of the Applicant's aBLA for review. Within 20 days after FDA notifies a biosimilar Applicant that it has accepted the Applicant's aBLA for review, the Applicant gives the RPS a copy of its aBLA and "such other information that describes the process or processes used to manufacture the biological product that is the subject of such application," 42 U.S.C. § 262(*l*)(2)(A); *Amgen*, 794 F.3d at 1352. FDA accepted Apotex's aBLA for its biosimilar pegfilgrastim product on December 15, 2014. Apotex notified Amgen the next day, and thereafter provided its aBLA to Amgen. Apotex did not provide any additional manufacturing information, but Amgen has no basis to contend any such additional manufacturing information existed, and agrees for purposes of this motion that Apotex satisfied paragraph (*l*)(2)(A). Next follows a sequential exchange of "lists of patents for which" the parties "believe a claim of patent infringement could reasonably be asserted by the RPS, as well as their respective positions on infringement, validity, and enforceability of those patents." *Amgen*, 794 F.3d at 1352. The RPS initiates the exchange with a patent list in accordance with 42 U.S.C. § 262(*l*)(3)(A). The Applicant "may" respond with its own list of additional patents that could be infringed, but must provide—"shall provide" —for each listed patent either a statement that it will remain off the market until the patent expires or, on a claim-by-claim basis, a detailed statement of its factual and legal basis for believing that the patent is invalid, unenforceable, or not infringed. 42 U.S.C. § 262(*l*)(3)(B). Finally, the RPS then "shall provide," for the disputed patents, a detailed statement that each patent will be infringed and a response to the Applicant's invalidity and unenforceability contentions. 42 U.S.C. § 262(*l*)(3)(C).

Apotex and Amgen engaged in the exchanges described in paragraph (*l*)(3). The exchange was complete by June 16, 2015. (Complaint ¶¶ 48-50; Answer ¶¶ 48-50.)

The next step in this first phase of the BPCIA is for the parties to attempt to agree, under paragraph (*l*)(4), on which of the patents listed pursuant to paragraph (*l*)(3), if any, should be included in an immediate patent-infringement action and, failing agreement, to follow a dispute-resolution procedure under paragraph (*l*)(5) to identify those patents. Either way, once the parties have arrived at the list of patents on which suit will be brought, the RPS is then directed to bring an "Immediate patent infringement action" on each of the listed patents within 30 days.

42 U.S.C. § 262(*l*)(6). The Applicant must provide the complaint to FDA, which must publish it in the Federal Register. *Id.*

Apotex and Amgen agreed that Amgen would file suit under paragraph (*l*)(6) on two patents, U.S. Patent Nos. 8,952,138 and 5,824,784. (Complaint ¶ 51; Answer ¶ 51.) Amgen did so on August 8, 2015. This is that lawsuit.

Further Steps Under the BPCIA and Pre-Marketing Notice

The RPS's obligation to identify patents does not end with the exchange of patent lists pursuant to paragraph (*l*)(3) or with the filing of an immediate patent litigation under 262(*l*)(6). Instead, if a patent is newly issued to, or exclusively licensed by, the RPS after it has provided its paragraph (*l*)(3)(A) list, the RPS must supplement that list within 30 days. *See* 42 U.S.C. § 262(*l*)(7). Within 30 days thereafter, the Applicant "shall provide" the RPS with a statement in accordance with paragraph (*l*)(3)(B), providing "for each listed patent either a statement that it will remain off the market until the patent expires or, on a claim-by-claim basis, a detailed statement of its factual and legal basis for believing that the patent is invalid, unenforceable, or not infringed." *See* 42 U.S.C. § 262(*l*)(3)(B), (7).

These newly issued or licensed patents, along with patents that were initially listed under paragraph (*l*)(3) but not listed for inclusion in the paragraph (*l*)(6) lawsuit, then become subject to 42 U.S.C. § 262(*l*)(8), entitled "Notice of commercial marketing and preliminary injunction." That paragraph contains the requirement of pre-marketing notice, the provision at issue on this motion, 42 U.S.C. § 262(*l*)(8)(A).

The second phase of the BPCIA's orderly resolution of patent disputes starts at FDA approval of the Applicant's biosimilar product. FDA licensure of the biosimilar product authorizes the Applicant to commercially market the biosimilar in the United States. It also triggers the Applicant's obligation to give the RPS at least 180 days' advanced notice of the date of the first commercial marketing of the licensed biosimilar product. *See* 42 U.S.C. § 262(*l*)(8)(A). As the Federal Circuit stated, "Subsection 262(*l*) also provides that the Applicant give notice of commercial marketing to the RPS at least 180 days prior to commercial marketing of its product licensed under subsection (k), which then allows the RPS a period of time to seek a preliminary injunction based on patents that the parties initially identified during information exchange but were not selected for the immediate infringement action, as well as any newly issued or licensed patents." *Amgen*, 794 F.3d at 1352. Paragraph (*l*)(8) provides:

> (8) Notice of commercial marketing and preliminary injunction
>
> (A) Notice of commercial marketing
>
> 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).
>
> (B) Preliminary injunction
>
> After receiving the notice under subparagraph (A) and before such date of the first commercial marketing of such biological product, the reference product sponsor may seek a preliminary injunction prohibiting the subsection (k) applicant from engaging in the commercial manufacture or sale of such biological product until the court decides the issue of patent validity, enforcement, and infringement with respect to any patent that is—
>
> > (i) included in the list provided by the reference product sponsor under paragraph (3)(A) or in the list provided by the subsection (k) applicant under paragraph (3)(B); and
> >
> > (ii) not included, as applicable, on—
> >
> > > (I) the list of patents described in paragraph (4); or
> > >
> > > (II) the lists of patents described in paragraph (5)(B).

42 U.S.C. § 262(*l*)(8)(A), (B). "The purpose of paragraph (*l*)(8)(A) is clear: requiring notice of commercial marketing be given to allow the RPS a period of time to assess and act upon its patent rights." *Amgen*, 794 F.3d at 1360.

On April 17, 2015, Apotex purported to provide notice of commercial marketing to Amgen. (Groombridge Decl. ¶ 2 & Ex. A.) Amgen responded on May 8, 2015, asserting that paragraph (*l*)(8)(A) notice cannot be given until FDA approves the Applicant's aBLA, among other things because the statute refers to "the biological product licensed under subsection (k)," and there is no product licensed prior to FDA approval. (*Id.* at ¶ 3 & Ex. B.)

Limitations on Declaratory Judgments

The BPCIA borrows from the Hatch-Waxman Act and prohibits gaming the system by placing limits on "any" actions for declaratory judgments with respect to patents that do not make the list, pursuant to either paragraph (*l*)(4) or (*l*)(5), for the immediate patent infringement action under paragraph (*l*)(6), plus later-issued or -licensed patents under paragraph (*l*)(7). That

prohibition ends when the Applicant gives at least 180 days' advance notice of first commercial marketing of the licensed biosimilar product. Thus, paragraph (*l*)(9) provides:

> (9) Limitation on declaratory judgment action
>
> (A) Subsection (k) application provided—If a subsection (k) applicant provides the application and information required under paragraph (2)(A), neither the reference product sponsor nor the subsection (k) applicant may, prior to the date notice is received under paragraph (8)(A), bring any action under section 2201 of title 28 for a declaration of infringement, validity, or enforceability of any patent that is described in clauses (i) and (ii) of paragraph (8)(B).

Deferring the availability of declaratory judgment actions until the Applicant provides the notice of commercial marketing benefits both the Applicant and the RPS by ensuring that both parties earnestly engage in the first phase of the BPCIA's patent-resolution process. If the Applicant fails to complete a required action, the statute maintains the bar to declaratory judgments for the Applicant but lifts it with respect to the RPS:

> (B) Subsequent failure to act by subsection (k) applicant—If a subsection (k) applicant fails to complete an action required of the subsection (k) applicant under paragraph (3)(B)(ii), paragraph (5), paragraph (6)(C)(i), paragraph (7), or paragraph (8)(A), the reference product sponsor, but not the subsection (k) applicant, may bring an action under section 2201 of title 28 for a declaration of infringement, validity, or enforceability of any patent included in the list described in paragraph (3)(A), including as provided under paragraph (7).
>
> (C) Subsection (k) application not provided—If a subsection (k) applicant fails to provide the application and information required under paragraph (2)(A), the reference product sponsor, but not the subsection (k) applicant, may bring an action under section 2201 of title 28 for a declaration of infringement, validity, or enforceability of any patent that claims the biological product or a use of the biological product.

42 U.S.C. § 262(*l*)(9)(B), (C).

The *Amgen* v. *Sandoz* Case

The *Amgen* v. *Sandoz* decision from the Federal Circuit provides more than controlling precedent here. It also provides context to explain some of Apotex's actions. A brief overview of the case is therefore warranted:

Sandoz sought (and eventually received) FDA approval to market a biosimilar version of Amgen's NEUPOGEN® (filgrastim), a biological product that has similarity to the pegfilgrastim

product at issue here.[1] On July 8, 2014, Sandoz notified Amgen that it had filed an aBLA for its filgrastim product, that it believed the application would be approved in the first half of 2015, and that Sandoz "intended to launch its biosimilar product immediately upon FDA approval." *Amgen*, 794 F.3d at 1352-53. Sandoz deemed that to be notice under paragraph (*l*)(8)(A) even though FDA had not yet approved its aBLA. Further, Sandoz informed Amgen that Sandoz had chosen not to provide its aBLA and manufacturing information as contemplated by paragraph (*l*)(2)(A).

Amgen sued Sandoz in the Northern District of California for patent infringement, and sought a preliminary injunction to compel Sandoz to provide the aBLA and manufacturing information called for by paragraph (*l*)(2)(A) and to compel Sandoz to provide at least 180 days' notice of first commercial marketing after, but only after, FDA approval of Sandoz's application.

While the motion was pending in the district court, on March 6, 2015, FDA approved Sandoz's aBLA. That day, Sandoz again provided 180 days' notice of commercial marketing, maintaining that its July 2014 notice had been effective but nevertheless giving "a 'further notice of commercial marketing' to Amgen on the date of FDA approval." *Id.* at 1353.

The district court denied Amgen's motion, finding that neither provision of the aBLA and manufacturing information under paragraph (*l*)(2)(A) nor pre-marketing notice under paragraph (*l*)(8)(A) is mandatory, and that Sandoz had thus complied with the BPCIA.

Amgen appealed. Under the four-factor test for injunctive relief, the Federal Circuit granted Amgen's motion for an injunction pending appeal, and enjoined Sandoz from "marketing, selling, offering for sale, or importing into the United States its FDA-approved ZARXIO® biosimilar product until this Court resolves the appeal." (Groombridge Decl. ¶ 6 & Ex. E.) *See also Amgen*, 794 F.3d at 1362.

After receiving full briefing and hearing oral argument, the Federal Circuit affirmed in part and reversed in part. Judge Lourie wrote the Panel opinion, but was joined in different parts of that opinion by Judges Newman and Chen, who each dissented in part as well.

Regarding paragraph (*l*)(2)(A), Judges Lourie and Chen held that the Applicant is not required to provide its aBLA and manufacturing information, and that if it fails to do so, the

[1] Apotex has also submitted an aBLA seeking FDA approval of its own biosimilar filgrastim product. That product is the subject of a second lawsuit that Amgen has commenced against Apotex in this District, Case No. 15-62081, filed on October 2, 2015.

RPS's sole remedy is to commence a declaratory judgment action under paragraph (*l*)(9)(C) or a patent-infringement action under 35 U.S.C. § 271(e)(2)(C)(ii). *See Amgen*, 794 F.3d at 1354-56. From this, Judge Newman dissented, and would have held that providing the aBLA and manufacturing information is mandatory. *Id.* at 1364 (Newman, J., dissenting in part).

Turning to 180 days' notice under paragraph (*l*)(8)(A)—the provision at issue here—the Panel unanimously held that to be effective, notice may be given only after FDA approval:

> We therefore conclude that, under paragraph (*l*)(8)(A), a subsection (k) applicant may only give effective notice of commercial marketing after the FDA has licensed its product. The district court thus erred in holding that a notice of commercial marketing under paragraph (*l*)(8)(A) may effectively be given before the biological product is licensed, and we therefore reverse its conclusion relating to its interpretation of § 262(*l*)(8)(A) and the date when Sandoz may market its product.

Id. at 1358 (majority opinion). The Panel then considered the impact of that decision on the facts of the case before it. Judges Lourie and Newman held that the requirement of notice under paragraph (*l*)(8)(A) is mandatory: "A question exists, however, concerning whether the "shall" provision in paragraph (*l*)(8)(A) is mandatory. We conclude that it is." *Id.* at 1359. They extended the injunction pending appeal until only September 2, 2015, exactly 180 days after Sandoz gave post-FDA-approval notice of commercial marketing.

Judge Chen dissented in this part, and would have held that because Sandoz did not provide its aBLA and manufacturing information under paragraph (*l*)(2)(A), none of the subsequent provisions, including paragraph (*l*)(8)(A), applied to the dispute between Amgen and Sandoz: when "the (k) applicant fails to comply with (*l*)(2), the provisions in (*l*)(3)-(*l*)(8) cease to matter." *Id.* at 1367 (Chen, J., dissenting in part).

Each of Amgen and Sandoz petitioned the Federal Circuit to re-hear, en banc, the aspects of the opinion on which the other prevailed. The Federal Circuit denied those petitions today. (Groombridge Decl. ¶ 11 & Ex. I.)

Apotex's Newfound Position Regarding Notice Under Paragraph (*l*)(8)(A)

The Federal Circuit's decision in *Amgen* renders Apotex's April 17, 2015 notice of commercial marketing ineffective, because that notice was given before FDA approval of Apotex's application. The Federal Circuit held that an Applicant "may only give effective notice of commercial marketing after the FDA has licensed its product." *Amgen*, 794 F.3d at 1359.

On August 24, 2015, Apotex's counsel wrote to Amgen's counsel to assert that, under *Amgen* v. *Sandoz*, Apotex believed that it was not required to give 180 days' notice under paragraph (*l*)(8)(A), because Apotex—unlike Sandoz—had provided its aBLA under paragraph (*l*)(2)(A). Apotex asserted that "because Apotex followed the pathway and provided Amgen with its application and manufacturing information, providing a notice of commercial marketing is not mandatory." (Groombridge Decl. Ex. D.)

This Motion for a Preliminary Injunction

By this motion, Amgen seeks a preliminary injunction restraining Apotex from commercial marketing of its biosimilar pegfilgrastim product on any license issuing from its pending aBLA until it provides 180 days' notice after FDA approval of that product. The parties agree that whether Amgen is likely to succeed in showing that the BPCIA requires Apotex to give that notice is a question of law. And the parties have stipulated, to the fullest extent possible, to the other elements of the test for preliminary injunctive relief. (*See* Groombridge Decl. ¶ 7 & Ex. F.)

Irreparable Harm: The parties stipulated that "Solely for the purposes of Amgen's motion for a preliminary injunction, Apotex will not dispute that Amgen would be irreparably harmed if Apotex were to commence commercial marketing of its biosimilar pegfilgrastim product without providing notice under 42 U.S.C. § 262(*l*)(8)(A) after FDA approval of the product and at least 180 days prior to commencing such commercial marketing." (Groombridge Decl. Ex. F.)

Balance of Hardships: The parties stipulated that "because the question of whether Apotex is required to provide notice under 42 U.S.C. § 262(*l*)(8)(A) after FDA approval of the product and at least 180 days prior to commencing such commercial marketing is a matter of statutory interpretation, the parties agree that, if the Court finds in favor of Amgen regarding likelihood of [success on] the merits, the balance of hardships favors Amgen." *Id.*

The Public Interest: The parties stipulated that "[b]ecause the public interest favors compliance with federal statutes as properly interpreted, Apotex agrees that should the Court find in favor of Amgen regarding likelihood of [success on] the merits, it will not dispute that the public interest favors the issuance of an injunction barring Apotex from commercially marketing its biosimilar pegfilgrastim product without providing notice under 42 U.S.C. § 262(*l*)(8)(A)

after FDA approval of the product and at least 180 days prior to commencing such commercial marketing." *Id.*

The parties further stipulated to a briefing schedule for this motion, and Apotex agreed to refrain from commercial marketing until a date certain (assuming FDA approval) to give the Court time to consider this motion. (Groombridge Decl. ¶ 8 & DE 38, DE40.)

ARGUMENT

Amgen is entitled to a preliminary injunction if it demonstrates (1) a substantial likelihood of success on the merits; (2) that it will suffer irreparable injury unless the injunction issues; (3) that the threatened injury to Amgen outweighs the threatened harm the injunction may cause to Apotex; and (4) that the injunction will not disserve the public interest. *Bryan* v. *Hall Chem. Co.*, 993 F.2d 831, 835 (11th Cir. 1993); *see also Winter* v. *Natural Res. Def. Council, Inc.*, 555 U.S. 7, 20 (2008); *Aevoe Corp.* v. *AE Tech Co.*, 727 F.3d 1375, 1381 (Fed. Cir. 2013).

I. Likelihood of Success on the Merits: The BPCIA Requires Apotex to Provide At Least 180 Days' Notice of Commercial Marketing After FDA Approval

The parties agree that the sole likelihood-of-success issue here is a question of law: does the BPCIA require Apotex to provide Amgen with at least 180 days' notice of the first commercial marketing of its biosimilar pegfilgrastim product after FDA approves Apotex's aBLA? The statute itself answers that question in the affirmative, as does the Federal Circuit's decision in *Amgen Inc.* v. *Sandoz Inc.*, 794 F.3d 1347 (Fed. Cir. 2015).

A. The BPCIA Provides That Apotex Must Give 180 Days' Notice

"[A]ll statutory construction cases . . . begin with the language of the statute." *Momenta Pharms., Inc.* v. *Amphastar Pharms., Inc.*, 686 F.3d 1348, 1353-54 (Fed. Cir. 2012). "The 'first step in interpreting a statute is to determine whether the language at issue has a plain and unambiguous meaning with regard to the particular dispute in the case.'" *Id.* at 1354 (*quoting Robinson* v. *Shell Oil Co.*, 519 U.S. 337, 340 (1997)); *see also Intellectual Ventures II LLC* v. *JPMorgan Chase & Co.*, 781 F.3d 1372, 1375-77 (Fed. Cir. 2015).

Paragraph (*l*)(8)(A) is clear: "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)." 42 U.S.C. § 262(*l*)(8)(A) (emphasis added). The verb "shall" presumptively signals a statutory requirement. *See, e.g.*, *Nat'l Ass'n of Home Builders* v. *Defenders of Wildlife*, 551 U.S. 644, 661-62 (2007); *Lopez* v.

Davis, 531 U.S. 230, 241 (2001); *Lexecon, Inc.* v. *Milberg Weiss Bershad Hynes & Lerach*, 523 U.S. 26, 35 (1998); Antonin Scalia & Bryan A. Garner, READING LAW: THE INTERPRETATION OF LEGAL TEXTS 114 (2012) ("[W]hen the word *shall* can reasonably read as mandatory, it ought to be so read."). Nothing in the statute suggests that "shall" in subsection (*l*)(8)(A) is anything but a mandatory command.

Paragraph (*l*)(9)(A) further confirms that an Applicant must give pre-marketing notice under paragraph (*l*)(8)(A). That paragraph provides the "Limitation on declaratory judgment action[s]" where, as here, the Applicant provides its aBLA and manufacturing information to the RPS under paragraph (*l*)(2)(A). Its prohibition ends only when the Applicant gives notice under paragraph (*l*)(8)(A), explicitly contemplating that such notice will be given:

> If a subsection (k) applicant provides the application and information required under paragraph (2)(A), neither the reference product sponsor nor the subsection (k) applicant may, prior to the date notice is received under paragraph (8)(A), bring any action under section 2201 of Title 28, for a declaration of infringement, validity, or enforceability of any patent that is described in clauses (i) and (ii) of paragraph (8)(B).

42 U.S.C. § 262(*l*)(9)(A).

B. Requiring Notice Accords With the Statutory Purpose, While Rendering Notice Optional Frustrates That Purpose

The Federal Circuit, in a unanimous portion of its opinion, recognized the importance of the notice under paragraph (*l*)(8)(A). That notice "allows the RPS to effectively determine whether, and on which patents, to seek a preliminary injunction from the court." *Amgen*, 794 F.3d at 1358. The Federal Circuit rejected the idea that notice could be given before FDA approval, because pre-approval notice would leave the RPS "to guess the scope of the approved license and when commercial marketing would actually begin." *Id.* On the other hand, requiring notice to be given after FDA approval "crystallize[s]" the controversy for the court and avoids needless litigation:

> We believe that Congress intended the notice to follow licensure, at which time the product, its therapeutic uses, and its manufacturing processes are fixed. When a subsection (k) applicant files its aBLA, it likely does not know for certain when, or if, it will obtain FDA licensure. The FDA could request changes to the product during the review process, or it could approve some but not all sought-for uses. Giving notice after FDA licensure, once the scope of the approved license is known and the marketing of the proposed biosimilar product is imminent, allows

> the RPS to effectively determine whether, and on which patents, to seek a preliminary injunction from the court.
>
> Requiring that a product be licensed before notice of commercial marketing ensures the existence of a fully crystallized controversy regarding the need for injunctive relief. It provides a defined statutory window during which the court and the parties can fairly assess the parties' rights prior to the launch of the biosimilar product.

Id. Apotex's position is directly at odds with these statutory purposes. If Apotex were correct and an Applicant could, at its whim, eliminate the notice period by "choosing" not to provide notice under paragraph (*l*)(8)(A), then the "RPS would be left to guess . . . when commercial marketing would actually begin," *id.*, and would have to monitor public sources even to find out when FDA approves the Applicant's aBLA, would have to sprint to court to seek a temporary restraining order just to secure time to seek a preliminary injunction, and would present the court far less than a "fully crystallized controversy" and deprive the court of the "defined statutory window" in which to "fairly assess the parties' rights prior to the launch of the biosimilar product." *Id.* Instead of an ordered, timed process, the result would be chaos, and the careful balance represented by paragraph (*l*)(8)(A) would topple in the Applicant's favor.

C. *Amgen* Confirms That Notice Is Required

For these reasons, the Federal Circuit held in *Amgen* v. *Sandoz* that notice under paragraph (*l*)(8)(A) is mandatory. It did so explicitly, rejecting Sandoz's argument that notice is optional: "A question exists . . . concerning whether the 'shall' provision in paragraph (*l*)(8)(A) is mandatory. We conclude that it is." *Id.* at 1359.

That holding forecloses Apotex's argument. Apotex therefore argues that the Federal Circuit did not mean what it said, and that it actually held that notice is required only where an Applicant—like Sandoz, but not like Apotex—fails to provide the RPS with a copy of its aBLA and manufacturing information under paragraph (*l*)(2)(A). Thus, in its August 24, 2015 letter, Apotex plucked these words out of the middle of a sentence in the Federal Circuit's opinion: " . . . paragraph (*l*)(9)(B) specifies the consequence for a subsequent failure to comply with paragraph (*l*)(8)(A) after the applicant has complied with paragraph (*l*)(2)(A)," thus suggesting that Apotex need not comply with paragraph (*l*)(8)(A) and that Amgen's only remedy is to seek a declaratory judgment under paragraph (*l*)(9)(B). (Groombridge Decl. Ex. D at 1, *quoting* 794 F.3d at 1359.)

But the Federal Circuit's holding that "paragraph (*l*)(8)(A) is mandatory" contains no exception for Applicants who comply with paragraph (*l*)(2)(A), and in fact the court clearly held that "Paragraph (*l*)(8)(A) is a standalone notice provision," and that "nothing in paragraph (*l*)(8)(A) conditions the notice requirement on paragraph (*l*)(2)(A) or other provisions of subsection (l)." *Amgen*, 794 F.3d at 1359-60. Thus, Apotex's provision of the disclosures called for by paragraph (*l*)(2)(A) does not drive the outcome here; Apotex must still give notice under paragraph (*l*)(8)(A) once FDA approves its aBLA. Amgen is entitled to enforce that obligation, just as the Federal Circuit enforced it against Sandoz in granting an injunction pending appeal under Fed. R. App. P. 8A and then extending that injunction until September 2, 2015, precisely 180 days after Sandoz provided post-FDA-approval notice of commercial marketing under paragraph (*l*)(8)(A). (Groombridge Decl. ¶ 6 & Ex. E; *see also Amgen*, 794 F.3d at 1360.)

Nor does paragraph (*l*)(9)(B) change the analysis. Paragraph (*l*)(9)(B) is a prohibition on the Applicant seeking a declaratory judgment. As regards the provision of notice under paragraph (*l*)(8)(A), however, paragraph (*l*)(9)(B) offers the RPS no remedy at all because the RPS may seek a declaratory judgment whether or not the Applicant timely provides notice. That is, the Applicant's timely provision of notice under paragraph (*l*)(8)(A) lets both the Applicant and the RPS commence declaratory judgment actions under paragraph (*l*)(9)(A). On the other hand, if the Applicant "fails to complete an action required of" it under paragraph (*l*)(8)(A), then the prohibition against declaratory judgments persists for the Applicant but is lifted for the RPS by paragraph (*l*)(9)(B). Either way, the RPS is permitted to bring a declaratory judgment action.

Apotex also cited to Judge Chen's dissent. (*See* Groombridge Decl. Ex. D.) Judge Chen's and Judge Lourie's disagreement is principally about whether an Applicant that refuses to provide its aBLA and manufacturing information—like Sandoz but not like Apotex—is excused from providing notice of commercial marketing. Judge Chen viewed the provisions of paragraphs (*l*)(2) through (*l*)(8) as an "integrated litigation management process," with all of the steps in paragraphs (*l*)(3) through (*l*)(8) "contingent on the (k) applicant's performance of the first 'shall' step in (*l*)(2)." *Amgen*, 794 F.3d at 1367 (Chen, J., dissenting in part). To Judge Chen, once an Applicant like Sandoz "fails to comply with (*l*)(2)," "the provisions in (*l*)(3)-(*l*)(8) cease to matter." *Id.*

Judge Lourie disagreed and, specifically addressing the facts of Sandoz's refusal to provide its aBLA and manufacturing information, concluded that "where, as here, a subsection

(k) applicant completely fails to provide its aBLA and manufacturing information to the RPS by the statutory deadline, the requirement of paragraph (*l*)(8)(A) is mandatory. Sandoz therefore may not market Zarxio before 180 days from March 6, 2015 [the date Sandoz gave post-FDA-approval notice], *i.e.* September 2, 2015." *Id.* at 1360 (majority opinion).

The converse is not true, however. The Panel majority did not hold or even imply that an Applicant like Apotex that provides its aBLA and any manufacturing information is excused from providing pre-marketing notice. On the contrary, the Panel held that "Paragraph (*l*)(8)(A) is a standalone notice provision," and that "nothing in paragraph (*l*)(8)(A) conditions the notice requirement on paragraph (*l*)(2)(A) or other provisions of subsection (*l*)." *Id.* at 1359-60.

That decision makes complete sense given the purpose of the BPCIA. As the unanimous Federal Circuit panel concluded, requiring notice of commercial marketing after FDA approval "provides a defined statutory window during which the court and the parties can fairly assess the parties' rights prior to the launch of the biosimilar product." *Id.* at 1358. That goal is not altered, and the importance of that defined window is not lessened, because an Applicant like Apotex provides its aBLA and any manufacturing information. The provision of that information allows for the exchange of infringement, validity, and enforceability contentions under paragraph (*l*)(3), but it does not protect the RPS or the court from the crush of a hectic preliminary injunction motion and a temporary restraining order in the days following FDA approval. Rather, that protection comes from the 180-day window called for by paragraph (*l*)(8)(A). That is why the Federal Circuit majority held that notice of commercial marketing is mandatory under that provision.

That decision controls here. This Court should therefore hold that Amgen has a "substantial likelihood"—indeed, it has more than a substantial likelihood—of prevailing on its claim that notice under paragraph (*l*)(8)(A) is mandatory.

II. Irreparable Harm: Apotex's Premature Entry Into the Market Would Irreparably Harm Amgen, as Apotex Concedes

Premature entry by a generic challenger causes price erosion and works irreparable harm. The cases so holding are legion. *See, e.g.*, *Abbott Labs.* v. *Sandoz Inc.*, 544 F.3d 1341, 1361-62 (Fed. Cir. 2008); *Sanofi-Synthelabo* v. *Apotex, Inc.*, 470 F.3d 1368, 1381 (Fed. Cir. 2006). Indeed, in the dispute between Amgen and Sandoz, the Federal Circuit inherently recognized that Sandoz's premature entry into the short-acting filgrastim market would irreparably harm Amgen,

as a showing of irreparable harm is one of the requirements for an injunction pending appeal under Federal Rule of Appellate Procedure 8, and the Federal Circuit granted Amgen's motion for a Rule 8 injunction. (Groombridge Decl. ¶ 6 & Ex. E.)

Here, Robert Azelby, Amgen's Vice President and General Manager Oncology, has testified that Apotex's premature entry into the long-acting filgrastim market will severely and permanently harm Amgen through price erosion. (Azebly Decl. ¶ 12.) He testified: "Amgen currently manufactures and supplies NEULASTA® to meet the entire United States demand for long-acting filgrastim, and is prepared to continue to do so. There is no significant un-met medical need for pegfilgrastim." (*Id.* at ¶ 11.) Sales of Apotex's biosimilar pegfilgrastim product would therefore necessarily erode Amgen's sales. (*Id.*) If, as expected, Apotex prices its product below Amgen's price for NEULASTA®, Amgen could be forced to lower its prices to maintain its market share. (*Id.* at ¶ 12.) Because of Medicare reimbursement formulas, as Mr. Azelby explains, Amgen would not be able to restore its prices if Apotex were later found to have prematurely and wrongly entered the market. The erosion of prices would be permanent. (*Id.*)

Notably, Apotex has stipulated that Amgen would be irreparably harmed if Apotex were to enter the long-acting pegfilgrastim market without providing Amgen the at-least-180 days' notice of paragraph (*l*)(8)(A). Case law permits the parties to stipulate to this aspect of the test for injunctive relief, subject to the Court's independent review to ensure that the stipulation is not collusive. *See WIT Wälchli Innovation Techs.* v. *Westrick*, 12-CIV-20072, 2012 U.S. Dist. LEXIS 7933, at *10 (S.D. Fla. Jan. 24, 2012) (Cohn, J.). The case law recognizing irreparable harm in the context of premature entry by a generic manufacturer (and, in the case of *Amgen v. Sandoz*, a biosimilar manufacturer) supports the parties' stipulation here.

III. Balance of Hardships: The Threatened Injury to Amgen From the Denial of an Injunction Exceeds the Injury to Apotex If One Is Granted, As Apotex Concedes

In deciding whether to issue a preliminary injunction, courts balance the threatened injury to the movant if no preliminary injunction is issued against the threat to the non-movant of an injunction. *See Bryan*, 993 F.2d at 836. The threat to Amgen of the denial of an injunction dovetails with the irreparable harm Amgen faces and that Mr. Azelby explains. And here, too, Apotex has stipulated, agreeing that the balance of hardships favors Amgen if the Court finds that Amgen is likely to succeed on the merits of its claim. *See WIT Wälchli Innovation Techs.*, 2012 U.S. Dist. LEXIS 7933, at *10.

IV. Public Interest: The Public's Interest Is Served By Assuring That Parties Comply With Federal Law

Amgen spent significant amounts of money to develop and obtain the biological license for NEULASTA®. The prescribing information for NEULASTA® reports "seven randomized clinical trials" from which safety data are drawn. (Azelby Decl. ¶ 2; http://pi.amgen.com/united_states/neulasta/neulasta_pi_hcp_english.pdf at § 6.1.) In addition to clinical development and clinical trials, Amgen also incurred the expense and effort to obtain and maintain regulatory approval for facilities to manufacture NEULASTA®. (Groombridge Decl. Ex G.) The public interest supports—indeed, it depends on—innovators like Amgen making such investments. There is therefore a strong public interest in encouraging investment in drug development, and ensuring that the BPCIA protects innovators and further ensuring that parties follow the law serves the public interest. That interest is not outweighed by the fact that a biosimilar may enter the market and sell its product at a lower price.

In this regard, Apotex has stipulated that if the Court finds that Amgen is likely to succeed on the merits, it will not challenge that the public interest is best served by an injunction.

V. Amgen Should Have to Post at Most a Nominal Bond

Amgen respectfully submits that either no bond, or at most a nominal bond, be required to secure any injunction. The Court has wide discretion in setting a bond amount, including requiring "no security at all." *BellSouth Telecomms., Inc.* v. *MCImetro Access Transmission Servs.*, 425 F.3d 964, 971 (11th Cir. 2005). A bond is generally not required where the party seeking the injunction has a high probability of succeeding on the merits of the claim. *See, e.g.*, *Univ. Books & Videos, Inc.* v. *Metro. Dade Cnty.*, 33 F. Supp. 2d 1364, 1374 (S.D. Fla. 1999). And the bond requirement may be waived if not requested or if no evidence is presented that a party will suffer damages from the issuance of an injunction. *Tancogne* v. *Tomjai Enters. Corp.*, 408 F. Supp. 2d 1237, 1252 (S.D. Fla. 2005). Apotex, as the party seeking security, would bear the burden of demonstrating "a rational basis for the amount of the proposed bond." *Cont'l Group, Inc.* v. *KW Prop. Mgmt., LLC*, Case No. 09-60202, 2009 U.S. Dist. LEXIS 101448, at *19 (S.D. Fla. Oct. 30, 2009) (*quoting Int'l Equity Investments, Inc. v. Opportunity Equity Partners, Ltd.*, 441 F. Supp. 2d 552, 556 (S.D.N.Y. 2006)). Moreover, if the Court agrees with Amgen, then Apotex will be required to refrain from commercial marketing only for as long as Congress required Apotex and all Applicants to do so under the BPCIA. Just as the Federal

Circuit, after full briefing on the issue, held that Amgen should not have to post any bond to secure an injunction while Sandoz complied with paragraph (*l*)(8)(A), this Court should hold that no bond, or at most a nominal bond, is required

CONCLUSION

Amgen respectfully requests that the Court enter a preliminary injunction as set forth in Amgen's accompanying proposed order, specifically enjoining Apotex and those acting in concert with it from any commercial marketing of its biosimilar pegfilgrastim product, including selling that product or offering it for sale for use in the United States, until Apotex gives Amgen proper notice, at least 180 days before first commercial marketing but not before its pegfilgrastim biosimilar product is licensed by FDA, and the 180-day notice period is exhausted.

Dated: October 16, 2015

By: */s/ John F. O'Sullivan*
John F. O'Sullivan
Fla. Bar No. 143154
Allen P. Pegg
Fla. Bar No. 597821
HOGAN LOVELLS US LLP
600 Brickell Ave., Suite 2700
Miami, FL 33131
Telephone: (305) 459-6500
Facsimile: (305) 459-6550
john.osullivan@hoganlovells.com
allen.pegg@hoganlovells.com

Of Counsel:

Nicholas Groombridge
Catherine Nyarady
Eric Alan Stone
Jennifer Gordon
Peter Sandel
PAUL, WEISS, RIFKIND, WHARTON
& GARRISON LLP
1285 Avenue of the Americas
New York, NY 10019
Telephone: (212) 373-3000
Facsimile: (212) 757-3990
ngroombridge@paulweiss.com
cnyarady@paulweiss.com

estone@paulweiss.com
jengordon@paulweiss.com
psandel@paulweiss.com

Wendy A. Whiteford
Lois M. Kwasigroch
Kimberlin Morley
AMGEN INC.
One Amgen Center Drive
Thousand Oaks, CA 91320
Telephone: (805) 447-1000
Facsimile: (805) 447-1010
wendy@amgen.com
loisk@amgen.com
kmorley@amgen.com

Attorneys for Plaintiffs
Amgen Inc. and Amgen Manufacturing Limited

CERTIFICATE OF SERVICE

I HEREBY CERTIFY that on October 16, 2015, I electronically filed the foregoing with the Clerk of the Court by using the CM/ECF system which will send a notice of electronic filing to counsel and that a true and correct copy was served via electronic mail on all counsel of parties of record.

By: */s/ John F. O'Sullivan*____
John F. O'Sullivan
Fla. Bar No. 143154
john.osullivan@hoganlovells.com