IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF FLORIDA

AMGEN INC. and AMGEN MANUFACTURING LIMITED, Plaintiff, v. APOTEX INC. and APOTEX CORP., Defendant.	Case No. _____

COMPLAINT FOR PATENT INFRINGEMENT

Plaintiffs Amgen Inc. and Amgen Manufacturing Ltd. (together, "Amgen") for its Complaint against Defendants Apotex Inc. and Apotex Corp. (together, "Apotex") allege as follows:

THE PARTIES

1. Amgen Inc. is a corporation existing under the laws of the State of Delaware, with its principal place of business at One Amgen Center Drive, Thousand Oaks, California 91320. Amgen Inc. discovers, develops, manufactures, and sells innovative therapeutic products based on advances in molecular biology, recombinant DNA technology, and chemistry.

2. Amgen Manufacturing Limited ("AML") is a corporation existing under the laws of Bermuda with its principal place of business in Juncos, Puerto Rico. AML manufactures and sells biologic medicines for treating particular diseases in humans.

3. Apotex Inc. is a corporation existing under the laws of Canada, with its principal place of business at 150 Signet Drive, Toronto, Ontario M9L 1T9, Canada. Upon information and belief, acting in concert with Defendant Apotex Corp., Apotex Inc. is in the business of developing, manufacturing, and marketing biopharmaceutical products that are distributed and

sold throughout the United States and in the State of Florida. *See Amgen Inc. & Amgen Mfg. Ltd. v. Apotex Inc. & Apotex Corp.*, No. 0:15-cv-61631-JIC (consolidated with No. 0:15-cv-62081-JIC), D.E. 47 at 2, 5 (S.D. Fla. Oct. 23, 2015).

4. Apotex Corp. is a corporation existing under the laws of Delaware, with its principle place of business at 2400 North Commerce Parkway, Suite 400, Weston, Florida 33326. Upon information and belief, acting in concert with Defendant Apotex Inc., Apotex Corp. is in the business of developing, manufacturing, and marketing biopharmaceutical products that are distributed and sold throughout the United States and in the State of Florida. Upon information and belief, Apotex Corp. is also the United States agent for Apotex Inc. for purposes including, but not limited to, filing regulatory submissions to and corresponding with the U.S. Food and Drug Administration ("FDA"). *See* No. 0:15-cv-61631-JIC, D.E. 47 at 2 (S.D. Fla. Oct. 23, 2015).

5. Upon information and belief, Apotex Corp. is a wholly owned affiliate of Apotex Inc. Upon information and belief, Apotex Corp. acts at the direction of, under the control of, and for the direct benefit of Apotex Inc. and is controlled and/or dominated by Apotex Inc.

NATURE OF THE ACTION

6. This is an action for patent infringement involving United States Patent No. 9,856,287 ("the '287 Patent"), attached hereto as Exhibit 1, arising under the patent laws of the United States, Title 35, United States Code, including 35 U.S.C. § 271(e)(2)(C)(i), which was enacted in 2010 as part of the Biologics Price Competition and Innovation Act of 2009 ("the BPCIA"), Pub. L. No. 111-148, §§ 7001-7003, 124 Stat. 119, 804-21 (2010) (amending, *inter alia*, 35 U.S.C. § 271 and 42 U.S.C. § 262).

BACKGROUND

A. Amgen's Innovative NEUPOGEN® and NEULASTA® Products

7. Amgen is one of the world's leading biopharmaceutical companies and is dedicated to using discoveries in human biology to invent, develop, manufacture, and sell new therapeutic products for the benefit of patients suffering from serious illnesses. Developing a new therapeutic product from scratch is extremely expensive: studies estimate the cost of obtaining FDA approval of a new biologic product at more than $2.5 billion. *See* DiMasi J.A. *et al*., Innovation in the pharmaceutical industry: New estimates of R&D costs, 47 J. Health Econ. 20, 25-26 (2016), attached hereto as Exhibit 2. Toward that end, Amgen has invested billions of dollars into its research and development efforts.

8. In 1991, after conducting extensive clinical trials and submitting the results of those trials to FDA to prove that NEUPOGEN® is safe, pure, and potent, Amgen first received FDA approval for NEUPOGEN® to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a significant incidence of severe neutropenia with fever. The FDA later approved several additional indications for the therapeutic use of NEUPOGEN®, including the treatment of patients with severe chronic neutropenia, patients with acute myeloid leukemia receiving induction or consolidation chemotherapy, patients receiving bone marrow transplant, and patients undergoing peripheral blood progenitor cell collection and therapy.

9. Neutropenia is a deficiency in neutrophils, a condition which makes the individual highly susceptible to infection. Neutrophils are the most abundant type of white blood cell and form a vital part of the human immune system. Neutropenia can result from a number of causes; it is a common side effect of chemotherapeutic drugs used to treat certain forms of cancer.

10. The active ingredient in NEUPOGEN® is filgrastim, a recombinantly expressed, 175-amino acid form of a protein known as human granulocyte-colony stimulating factor or "G-CSF." NEUPOGEN® is also known as recombinant methionyl human granulocyte-colony stimulating factor. NEUPOGEN® works by binding to specific receptors on the surface of certain types of cells to stimulate the production of neutrophils. NEUPOGEN® thus counteracts neutropenia.

11. In 2002, Amgen received FDA approval for NEULASTA®. As it did for NEUPOGEN®, Amgen conducted extensive clinical trials and submitted the results of those trials to FDA to prove that NEULASTA® is safe, pure, and potent. NEULASTA® is also indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anticancer drugs associated with a significant incidence of severe neutropenia with fever.

12. The active ingredient in NEULASTA® is pegfilgrastim, a form of the G-CSF protein conjugated to a 20 kD monomethoxypolyethylene glycol ("m-PEG" or simply, "PEG"). NEULASTA® counteracts neutropenia by the same mechanism of action as NEUPOGEN®. NEULASTA®, by virtue of the conjugated PEG moiety, has a longer serum half-life than NEUPOGEN® and therefore requires less frequent administration compared to NEUPOGEN®.

13. NEUPOGEN® and NEULASTA® represent major advances in cancer treatment by protecting chemotherapy patients from the harmful effects of neutropenia and by thus facilitating more effective chemotherapy regimes.

B. The BPCIA and the Prior Actions

14. Under the traditional pathway for FDA approval, an innovator must demonstrate that its biologic drug is safe, pure, and potent through clinical trials. *See* 42 U.S.C. § 262(a).

The BPCIA created an abbreviated pathway for the approval of biosimilar versions of approved biologic drugs. 42 U.S.C. § 262(k). The abbreviated pathway (also known as "the subsection (k) pathway") allows a biosimilar applicant (or "subsection (k) applicant") to rely on the prior licensure and approval status of an innovative biological product (a "reference product") that the biosimilar purports to copy. Under the subsection (k) pathway, the biosimilar applicant may rely on its reference product's data rather than demonstrating that the biosimilar product is safe, pure, and potent, as the reference product sponsor ("RPS") did when it filed its Biologics License Application ("BLA") under the traditional 42 U.S.C. § 262(a) pathway.

15. The BPCIA provides for the subsection (k) applicant and the RPS to engage in a series of information exchanges and good-faith negotiations between parties prior to the filing of a patent infringement lawsuit, as set forth in 42 U.S.C. § 262(*l*)(2)-(*l*)(5). This process culminates in an "immediate patent infringement action" pursuant to 42 U.S.C. § 262(*l*)(6).

16. Additionally, under 42 U.S.C. § 262(*l*)(7), if a patent is issued to, or exclusively licensed by, the RPS after the date that the RPS provided the list to the subsection (k) applicant under 42 U.S.C. § 262(*l*)(3)(A), and the RPS reasonably believes that, due to the issuance of such a patent, a claim of patent infringement could reasonably be asserted by the RPS if a person not licensed by the RPS engaged in the making, using, offering to sell, selling, or importing into the United States of the biological product that is the subject of the subsection (k) application, not later than 30 days after such issuance or licensing, the RPS shall provide to the subsection (k) applicant a supplement to the list provided by the RPS under 42 U.S.C. § 262(*l*)(3)(A) that includes such patent. Not later than 30 days after such supplement is provided, the subsection (k) applicant shall provide a statement to the RPS in accordance with 42 U.S.C. § 262(*l*)(3)(B), and such patent shall be subject to 42 U.S.C. § 262(*l*)(8).

17. Under 42 U.S.C. § 262(*l*)(8)(A), a subsection (k) applicant must provide notice of commercial marketing to the RPS not later than 180 days before the date of the first commercial marketing of its biosimilar product.

18. Here, Amgen is the sponsor of two reference products, NEUPOGEN® and NEULASTA® that are approved by FDA for decreasing the incidence of infection in patients receiving myelosuppressive anti-cancer drugs (among other indications in the case of NEUPOGEN®). *See Amgen Inc. v. Apotex Inc.*, 712 F. App'x 985, 986 (Fed. Cir. 2017).

19. Apotex, seeking the benefits of the subsection (k) pathway with Amgen as the RPS, submitted abbreviated Biologics License Application ("aBLA") No. 761026 ("the Apotex Pegfilgrastim aBLA"), which FDA accepted on or about December 16, 2014. *See Amgen*, 712 F. App'x at 986; *see also* No. 0:15-cv-61631-JIC, D.E. 47 at 3, 10 (S.D. Fla. Oct. 23, 2015). Apotex filed the Apotex Pegfilgrastim aBLA under Section 351(k) of the Public Health Service Act to obtain approval to commercially manufacture, use, offer to sell, and sell, and import into the United States the Apotex Pegfilgrastim Product as a biosimilar version of Amgen's NEULASTA®. *See Amgen*, 712 F. App'x at 986; *see also* No. 0:15-cv-61631-JIC, D.E. 47 at 10 (S.D. Fla. Oct. 23, 2015). The Apotex Pegfilgrastim aBLA listed Amgen's NEULASTA® as the reference product. *See Amgen*, 712 F. App'x at 986; *see also* No. 0:15-cv-61631-JIC, D.E. 47 at 9 (S.D. Fla. Oct. 23, 2015).

20. Apotex has represented to FDA that its Pegfilgrastim Product is biosimilar to Amgen's NEULASTA®. As such, the Apotex Pegfilgrastim Product should work by the same mechanism of action as NEULASTA® for the conditions of use prescribed, recommended, or suggested in NEULASTA®'s approved label and the route of administration, the dosage form, and the strength of the Apotex Pegfilgrastim Product are the same as those of Amgen's

NEULASTA®. *See* 42 U.S.C. § 262(k)(2)(A)(i); *see also* No. 0:15-cv-61631-JIC, D.E. 47 at 10 (S.D. Fla. Oct. 23, 2015).

21. In seeking approval for the Apotex Pegfilgrastim aBLA under the subsection (k) pathway, Apotex is able to rely on the clinical data that Amgen generated for NEULASTA® rather than independently demonstrating that the Apotex Pegfilgrastim Product is safe, pure, and potent, as Amgen was required to do to obtain FDA licensure of NEULASTA® under 42 U.S.C. § 262(a). *See* 42 U.S.C. § 262(k); *Sandoz Inc. v. Amgen Inc.*, 137 S. Ct. 1664, 1670 (2017).

22. Apotex also submitted aBLA No. 761027 ("the Apotex Filgrastim aBLA"), which FDA accepted on or about February 13, 2015, seeking the benefits of the subsection (k) pathway with Amgen as the RPS. *See Amgen*, 712 F. App'x at 986; *see also* No. 0:15-cv-61631-JIC, D.E. 64 at 3, 9–10 (S.D. Fla. Dec. 1, 2015). Apotex filed the Apotex Filgrastim aBLA under Section 351(k) of the Public Health Service Act to obtain approval to commercially manufacture, use, offer to sell, and sell within the United States, and import into the United States the Apotex Filgrastim Product, which is a biosimilar of Amgen's NEUPOGEN®. *See Amgen*, 712 F. App'x at 986; *see also* No. 0:15-cv-61631-JIC, D.E. 64 at 9-10 (S.D. Fla. Dec. 1, 2015). The Apotex Filgrastim aBLA listed Amgen's NEUPOGEN® as the reference product. *See Amgen*, 712 F. App'x at 986; *see also* No. 0:15-cv-61631-JIC, D.E. 64 at 9 (S.D. Fla. Dec. 1, 2015).

23. Apotex has represented to FDA that its Filgrastim Product is biosimilar to Amgen's NEUPOGEN®. As such, the Apotex Filgrastim Product should work by the same mechanism of action as NEUPOGEN® for the conditions of use prescribed, recommended, or suggested in NEUPOGEN®'s approved label and the route of administration, the dosage form, and the strength of the Apotex Filgrastim Product are the same as those of Amgen's

NEUPOGEN®. *See* 42 U.S.C. § 262(k)(2)(A)(i); *see also* No. 0:15-cv-61631-JIC, D.E. 64 at 9–10 (S.D. Fla. Dec. 1, 2015).

24. In seeking approval for the Apotex Filgrastim aBLA under the subsection (k) pathway, Apotex is able to rely on the clinical data that Amgen generated for NEUPOGEN® rather than independently demonstrating that the Apotex Filgrastim Product is safe, pure, and potent, as Amgen was required to do to obtain FDA licensure of NEUPOGEN® under 42 U.S.C. § 262(a). *See* 42 U.S.C. § 262(k); *Sandoz Inc. v. Amgen Inc.*, 137 S. Ct. at 1670.

25. After Apotex filed each of its aBLAs, Apotex and Amgen engaged in the information exchange described in the BPCIA. In particular, under 42 U.S.C. § 262(*l*)(3), "Amgen identified [United States Patent No. 8,952,138 ("the '138 Patent")] as a patent that the Apotex-proposed products would infringe, and Apotex replied by sending Amgen a detailed statement describing, claim by claim, the factual and legal basis for its opinion that it did not infringe. Amgen responded with its contrary, detailed view of infringement." *See Amgen*, 712 F. App'x at 986–87.

26. Following the information exchange, Amgen filed two immediate patent infringement suits against Apotex pursuant to 42 U.S.C. § 262(*l*)(6)—one for each of Apotex's aBLAs—arising under 35 U.S.C. § 271(e)(2)(C)(i), (a),(b), (c), and/or (g) in this Court. *See id.*; *see also* No. 0:15-cv-61631-JIC, D.E. 1 (S.D. Fla. Aug. 6, 2015); *Amgen Inc. & Amgen Mfg. Ltd. v. Apotex Inc. & Apotex Corp.*, No. 0:15-cv-62081-JIC, D.E. 1 (S.D. Fla. Oct. 2, 2015). Those lawsuits asserted the '138 Patent. Amgen also identified and asserted U.S. Patent No. 6,162,427 ("the '427 Patent") and U.S. Patent No. 5,824,784 ("the '784 Patent"). *See* No. 0:15-cv-61631-JIC, D.E. 1 at 2 (S.D. Fla. Aug. 6, 2015); No. 0:15-cv-62081-JIC, D.E. 1 at 2 (S.D. Fla. Oct. 2,

2015). The Court later entered a Joint Stipulation of Dismissal of the '427 Patent and the '784 Patent. *See* No. 0:15-cv-61631-JIC, D.E. 179 (S.D. Fla June 15, 2016).

27. Amgen's two immediate patent infringement suits against Apotex pursuant to 42 U.S.C. § 262(*l*)(6) "were consolidated. [This Court] held a bench trial in July 2016, and it issued findings of fact and conclusions of law [and final judgment] on September 6, 2016. The [Court] found that Amgen had failed to prove that Apotex's proposed commercial marketing of the two products, pursuant to [the Apotex aBLAs], would infringe the '138 patent, either literally or under the doctrine of equivalents." *See Amgen*, 712 F. App'x at 987; *see also* No. 0:15-cv-61631-JIC, D.E. 267 (S.D. Fla. Sep. 6, 2016); No. 0:15-cv-61631-JIC, D.E. 268 (S.D. Fla. Sep. 6, 2016). Amgen appealed the Court's judgment, and the Federal Circuit affirmed. *See Amgen*, 712 F. App'x at 987. The Federal Circuit mandate for that case issued on December 12, 2017. *See* No. 0:15-cv-61631-JIC (S.D. Fla.), D.E. 292 (Mandate).

C. This Action

1. U.S Patent No. 9,856,287

28. Following the issuance of the Federal Circuit mandate for the appeal from the prior patent infringement actions, the U.S. Patent and Trademark Office issued the '287 Patent to Amgen on January 2, 2018. A true and correct copy of the '287 Patent is attached as Exhibit 1.

29. Amgen is the owner of all rights, title, and interest in the '287 Patent.

30. AML holds an exclusive license to the '287 Patent.

31. The '287 Patent is titled "Refolding Proteins Using a Chemically Controlled Redox State." The '287 Patent was duly and legally issued on January 2, 2018 by the United States Patent and Trademark Office ("USPTO"). The inventors of the '287 Patent are Joseph Edward Shultz, Roger Hart, and Ronald Nixon Keener III.

32. The ’287 Patent covers improved redox chemistry-based methodologies for efficiently refolding cysteine-containing proteins expressed in non-mammalian cells at high protein concentrations.

33. Apotex infringes claims of the ’287 Patent, including for example, Claim 16.

34. Claim 16 recites:

> A method of refolding proteins expressed in a nonmammalian expression system, the method comprising:
> preparing a solution comprising:
> the proteins;
> at least one ingredient selected from the group consisting of a denaturant, an aggregation suppressor and a protein stabilizer;
> an amount of oxidant; and
> an amount of reductant,
> wherein the amounts of the oxidant and the reductant are related through a thiol-pair ratio and a thiol-pair buffer strength,
> wherein the thiol-pair ratio is in the range of 0.001-100, and
> wherein the thiol-pair buffer strength maintains the solubility of the solution; and
> incubating the solution so that at least about 25% of the proteins are properly refolded.

Claim 16 is infringed based at least on the information contained in the publicly available portions of the Apotex Pegfilgrastim aBLA and Apotex Filgrastim aBLA.

35. As an initial matter, Apotex uses the same process to produce the same filgrastim used in its Filgrastim Product and Pegfilgrastim Product:

> Filgrastim is manufactured by IPL as a Drug Substance for the commercial product, Filgrastim Drug Product, as well as a Critical Intermediate, as an input for the pegylated Apo-Filgrastim DS. Both Filgrastim Critical Intermediate and Filgrastim Drug Substance are the same, however depending on the final fate of Filgrastim; these are identified as either Filgrastim Drug Substance (used to manufacture Filgrastim Drug Product) or Filgrastim Critical Intermediate (used as an input to manufacture by pegylation, pegylated Apo-Filgrastim DS)

Amgen Inc. v. Apotex Inc., No. 2017-1010, Non-Confidential Joint Appendix Vol. III at Appx5556 n.1, D.E. 42-3 (Fed. Cir. Feb. 7, 2017) (“Non-Confidential Joint Appendix”).

36. Each of the elements in at least Claim 16 are satisfied in Apotex's accused process. In Apotex's accused process, Apotex expresses the filgrastim protein used in its Pegfilgrastim Product and Filgrastim Product in a nonmammalian expression system: *E. coli* (bacterial) cells:

> Apotex's filgrastim critical intermediate is a "recombinant protein composed of the mature and unmodified form of human granulocyte colony stimulating factor (G-CSF). The recombinant protein is expressed by *Escherichia coli* (*E.coli*) as a single continuous polypeptide consisting of 175 amino acid residues." The filgrastim critical intermediate is used as the starting material in the "Pegylated Apo-Filgrastim Drug Substance manufacturing process."

Id. at Appx7396 n.90 (internal citations omitted).

37. In Apotex's accused process, Apotex refolds the filgrastim contained in its Pegfilgrastim Product and Filgrastim Product using a refolding solution:

Table S.2.2-33: Refolding – Solution Composition

Solution	Component	Quantity
Refolding Buffer, pH 9.0 ± 0.2, Conductivity 17.5 ± 1.5 mS/cm	Arginine base	16.8 ± 0.02 kg
	Tris base	1940.00 ± 0.02 g
	Sorbitol	8.0 ± 0.8 kg
	EDTA disodium dihydrate	118.80 ± 0.02 g
	WFI Ph. Eur., IP, USP	q.s. to 168.0 kg
Cystine Solution	Cystine	13.2 ± 3.6 g
	0.2 N Hydrochloric Acid	440 ± 4 mL
Cysteine Solution	Cysteine	2.500 ± 0.025 g
	WFI Ph. Eur., IP, USP	32.00 ± 0.32 mL

Tris = Tris (hydroxymethyl) aminomethane; WFI = Water for Injection; USP: United State Pharmacopoeia

See No. 2017-1010, Non-Confidential Apotex Responsive Brief at 8, D.E. 32, (Fed. Cir. Jan. 17, 2017) ("Non-Confidential Apotex Brief"); Non-Confidential Joint Appendix at Appx5906.

38. In Apotex's accused process, Apotex's refolding solution comprises:

- a protein: at least the filgrastim protein (*see* Non-Confidential Joint Appendix at Appx5904–5907, Appx7150, Appx7397, Appx7448; *see also* Non-Confidential Apotex Brief at 7–8 (Fed. Cir. 2017));
- at least one ingredient selected from the group consisting of a denaturant, an aggregation suppressor and a protein stabilizer: arginine and sorbitol (Non-

Confidential Joint Appendix at Appx5904–5907, Appx7150; '287 Patent, 3:41-50);

- an amount of oxidant: cysteine (Non-Confidential Joint Appendix at Appx5904–5907, Appx7150, Appx7397, Appx7448; Non-Confidential Apotex Brief at 7–8; '287 Patent, 3:51-54);

- an amount of reductant: cystine (Non-Confidential Joint Appendix at Appx5904–5907, Appx7150, Appx7397, Appx7448; Non-Confidential Apotex Brief at 7–8; '287 Patent, 3:51-54).

39. In Apotex's accused process, the refolding solution that Apotex prepares, the amounts of oxidant (cysteine) and reductant (cystine) are related through a thiol-pair ratio and a thiol-pair buffer strength, wherein the thiol-pair ratio is in the range of 0.001-100 and the thiol-pair buffer strength maintains the solubility of the solution. *See* Non-Confidential Joint Appendix at Appx5904–5907.

40. In Apotex's accused process, Apotex incubates the refolding solution so that at least about 25% of the filgrastim protein it uses in its Pegfilgrastim Product and Filgrastim Product is properly refolded: the "Expected Range" of the "Refolding Step Yield" is "≥ 60%." *Id.* at Appx7361.

2. Apotex's Submissions to FDA of its Pegfilgrastim aBLA and Filgrastim aBLA

41. Apotex caused the submission of the Apotex Pegfilgrastim aBLA, which FDA accepted on or about December 16, 2014, for the purpose of obtaining FDA approval to engage in the commercial manufacture, use, or sale of the Apotex Pegfilgrastim Product. Apotex caused the submission of the Apotex Filgrastim aBLA, which FDA accepted on or about February 13, 2015, for the purpose of obtaining FDA approval to engage in the commercial manufacture, use, or sale of the Apotex Filgrastim Product.

42. This infringement action follows under 35 U.S.C. § 271(e)(2)(C)(i), which provides that "[i]t shall be an act of infringement to submit—with respect to a patent that is

identified in the list of patents" described in 42 U.S.C. § 262(*l*)(3)(A) "an application seeking approval of a biological product" for the purpose of obtaining FDA approval to engage in commercial manufacture, use, or sale. Under 42 U.S.C. § 262(*l*)(7), the RPS may supplement the 42 U.S.C. § 262(*l*)(3)(A) list with a patent issued to the RPS after the date the RPS provided the 42 U.S.C. § 262(*l*)(3)(A) list to the subsection (k) applicant.

43. On January 31, 2018, Amgen supplemented each of the lists that Amgen provided to Apotex under 42 U.S.C. § 262(*l*)(3)(A) for the Apotex Pegfilgrastim aBLA and the Apotex Filgrastim aBLA to include the '287 Patent; and Apotex provided Amgen with its statements under 42 U.S.C. § 262(*l*)(3)(B) on March 2, 2018 regarding the '287 Patent. Accordingly, Apotex has committed an act of infringement under 35 U.S.C. § 271(e)(2)(C)(i) with respect to the '287 Patent as to each of the Apotex Pegfilgrastim aBLA and Apotex Filgrastim aBLA submissions.

44. Upon information and belief, Apotex is continuing its efforts to obtain FDA approval to engage in the commercial manufacture, use, or sale of each of the Apotex Pegfilgrastim Product and the Apotex Filgrastim Product. *See* Apobiologix, R&D Overview, http://www.apobiologix.com/rd/default.asp (last visited on Aug. 1, 2018) (indicating that the "Development Progress" of the Apotex Pegfilgrastim Product (Lapelga™) and the Apotex Filgrastim Product ("Grastofil™") are currently "Filed" with "Marketed" as the next step in the United States). Upon information and belief, Apotex has committed further acts of infringement with respect to each of the Apotex Pegfilgrastim Product and the Apotex Filgrastim Product since the '287 Patent issued.

45. For an act of infringement under 35 U.S.C. § 271(e)(2), the Court may grant injunctive relief and damages or other monetary relief. 35 U.S.C. § 271(e)(4)(B)-(C).

46. Unless enjoined by this Court, upon information and belief, Apotex will infringe one or more claims of the '287 Patent under 35 U.S.C. § 271(a), (b), (c), and/or (g) by making, using, offering to sell or selling within the United States, or importing into the United States the Apotex Pegfilgrastim Product, which Apotex makes by a process covered by the '287 Patent, before the expiration of the '287 Patent.

47. Unless enjoined by this Court, upon information and belief, Apotex will infringe one or more claims of the '287 Patent under 35 U.S.C. § 271(a), (b), (c), and/or (g) by making, using, offering to sell or selling within the United States, or importing into the United States the Apotex Filgrastim Product, which Apotex makes by a process covered by the '287 Patent, before the expiration of the '287 Patent.

48. Apotex's infringement of the '287 Patent under 35 U.S.C. § 271(a), (b), (c), and/or (g) is a substantial controversy "of sufficient immediacy and reality to warrant the issuance of a declaratory judgment" under 28 U.S.C. § 2201. *See Medimmune, Inc. v. Genentech, Inc.*, 549 U.S. 118, 127 (2007) (quoting *Md. Cas. Co. v. Pac. Coal & Oil Co.*, 312 U.S. 270, 273 (1941)). Upon information and belief, Apotex intends to launch each of its Pegfilgrastim Product and Filgrastim Product upon FDA approval. Apotex publicly states that the next step in the development process for its Pegfilgrastim Product and Filgrastim Product is to market it. *See* Apobiologix, R&D Overview, http://www.apobiologix.com/rd/default.asp (last visited on Aug. 1, 2018).

JURISDICTION AND VENUE

49. This action arises under the patent laws of the United States, Title 35 of the United States Code, and under the Declaratory Judgment Act of 1934 (28 U.S.C. §§ 2201-2202), Title 28 of the United States Code.

50. This Court has subject matter jurisdiction pursuant to 28 U.S.C. §§ 1331 and 1338(a).

51. Venue is proper in this Court pursuant to 28 U.S.C. §§ 1391(b) and (c), and 28 U.S.C. § 1400(b).

A. Apotex Inc.

52. Apotex Inc. develops, manufactures, seeks regulatory approval for, markets, distributes, and sells biopharmaceuticals for sale and use throughout the United States, including in the State of Florida. *See* No. 0:15-cv-61631-JIC, D.E. 47 at 5 (S.D. Fla. Oct. 23, 2015); No. 0:15-cv-61631-JIC, D.E. 64 at 4–5 (S.D. Fla. Dec. 1, 2015).

53. This Court has personal specific jurisdiction over Apotex Inc. because Apotex Inc. has committed, or aided, abetted, contributed to and/or participated in the commission of, the tortious act of patent infringement that has led to foreseeable harm and injury to Amgen. In particular, Apotex Inc. collaborates with Apotex Corp. to develop, manufacture, seek approval for, and sell the disputed biosimilar products, which will cause tortious injury to Plaintiffs.

54. Moreover, upon information and belief, Apotex Inc., following any FDA approval of the biosimilar product, will sell the Apotex Pegfilgrastim Product and the Apotex Filgrastim Product that is the subject of the patent infringement claims in this action in Florida and throughout the United States.

55. This Court has personal general jurisdiction over Apotex Inc. by virtue of, *inter alia*, its having conducted business in this District, having availed itself of the rights and benefits of Florida law, and having engaged in substantial and continuing contacts with Florida. Upon information and belief, Apotex Inc. has regular and continuous commercial business dealings

with representatives, agents, distributors, and customers located in Florida and in this District, including with its subsidiary, Apotex Corp.

56. Upon information and belief, Apotex Inc. exercises considerable control over Apotex Corp. with respect to biosimilar products and approves significant decisions of Apotex Corp., including designating Apotex Corp. as the agent for Apotex Inc. in connection with preparing and filing the Apotex aBLAs.

57. Apotex Inc. submitted to the jurisdiction of this Court in the prior actions between Amgen and Apotex regarding the Apotex aBLAs. No. 0:15-cv-61631-JIC, D.E. 47 at 5–6 (S.D. Fla. Oct. 23, 2015); No. 0:15-cv-61631-JIC, D.E. 64 at 4–6 (S.D. Fla. Dec. 1, 2015).

58. In addition, Apotex Inc. previously submitted to the jurisdiction of this Court and previously availed itself of this Court by filing suit in this jurisdiction and/or by asserting counterclaims in other civil actions initiated in this jurisdiction. *See, e.g.*, *Apotex, Inc. et al v. Mylan Pharmaceuticals, Inc.*, Case No. 12-cv-60704 (S.D. Fla. Apr. 20, 2012). Further, Apotex Inc.previously admitted that this Court has personal jurisdiction over both Apotex Corp. and Apotex Inc. *See Alcon v. Apotex Inc. & Apotex Corp.*, C.A. No. 1:06-cv-01642, D.E. 23 at 7 (S.D. Ind. Dec. 13, 2006) ("Plaintiffs could have brought this action in the S.D. Fla. because the S.D. Fla. has personal jurisdiction over both Defendants. Apotex Corp. has a principal place of business in Weston, Florida, while Apotex Inc. is a Canadian corporation that regularly conducts business in Florida. Thus, venue in the S.D. Fla. would also be proper.").

59. In the alternative, should Apotex Inc. contest jurisdiction in this forum, this Court has personal jurisdiction over Apotex Inc. under Fed. R. Civ. P. 4(k)(2) because, on information and belief, Apotex Inc. "is not subject to jurisdiction in any state's courts of general jurisdiction," and because "exercising jurisdiction is nevertheless consistent with the United States

Constitution and laws" given that Apotex Inc. has filed the Apotex aBLAs in the United States for a product that it intends to market in the United States.

B. Apotex Corp.

60. This Court has personal jurisdiction over Apotex Corp. by virtue of the fact that, *inter alia*, Apotex Corp. has a principle place of business within this judicial district, in Weston, Florida. *See* No. 0:15-cv-61631-JIC, D.E. 47 at 6 (S.D. Fla. Oct. 23, 2015); No. 0:15-cv-61631-JIC, D.E. 64 at 6 (S.D. Fla. Dec. 1, 2015).

61. Apotex Corp. develops, manufactures, seeks regulatory approval for, markets, distributes, and sells biopharmaceuticals for sale and use throughout the United States, including in the State of Florida. *See* No. 0:15-cv-61631-JIC, D.E. 47 at 6 (S.D. Fla. Oct. 23, 2015); No. 0:15-cv-61631-JIC, D.E. 64 at 6 (S.D. Fla. Dec. 1, 2015).

62. This Court has personal specific jurisdiction over Apotex Corp. because Apotex Corp. has committed, or aided, abetted, contributed to and/or participated in the commission of, the tortious act of patent infringement that has led to foreseeable harm and injury to Amgen. In particular, on information and belief, Apotex Corp. collaborated with Apotex Inc. to develop, manufacture, and seek approval for the disputed biosimilar products, and on information, ApoBiologix®, a division of Apotex Corp., will market the disputed biosimilar products in the United States, which will cause tortious injury to Plaintiffs.

63. This Court has personal general jurisdiction over Apotex Corp. by virtue of, *inter alia*, its having conducted business in this District, having availed itself of the rights and benefits of Florida law, and having engaged in substantial and continuing contacts with Florida. Upon information and belief, Apotex Corp. has regular and continuous commercial business dealings with representatives, agents, distributors, and customers located in Florida and in this District.

64. Apotex Corp. submitted to the jurisdiction of this Court in the prior actions between Amgen and Apotex regarding the Apotex aBLAs. No. 0:15-cv-61631-JIC, D.E. 47 at 6–7 (S.D. Fla. Oct. 23, 2015); No. 0:15-cv-61631-JIC, D.E. 64 at 6–7 (S.D. Fla. Dec. 1, 2015).

65. In addition, Apotex Corp. has previously submitted to the jurisdiction of this Court and has previously availed itself of this Court by filing suit in this jurisdiction and/or by asserting counterclaims in other civil actions initiated in this jurisdiction. *See, e.g., Apotex, Inc. et al v. Mylan Pharms., Inc.*, No. 0:12-cv-60704 (S.D. Fla., Apr. 20, 2012). Further, Apotex previously admitted that this Court has personal jurisdiction over both Apotex Corp. and Apotex Inc. *See Alcon v. Apotex Inc. & Apotex Corp.*, No. 1:06-cv-01642, D.E. 23 at 7 (S.D. Ind. Dec. 13, 2006) ("Plaintiffs could have brought this action in the S.D. Fla. because the S.D. Fla. has personal jurisdiction over both Defendants. Apotex Corp. has a principal place of business in Weston, Florida, while Apotex Inc. is a Canadian corporation that regularly conducts business in Florida. Thus, venue in the S.D. Fla. would also be proper.").

66. On information and belief, following FDA approval of the Apotex Pegfilgrastim aBLA, Apotex Corp. will sell the Apotex Pegfilgrastim Product, which is the subject of the infringement claims in this action in the State of Florida and throughout the United States. *See* Apobiologix, R&D Overview, http://www.apobiologix.com/rd/default.asp (last visited on Aug. 1, 2018); *Amgen Inc. v. Apotex Inc.*, No. 16-1308, D.E. 25 at 3–4 (Fed. Cir. Dec. 22, 2015); No. 0:15-cv-61631-JIC, D.E. 55 at 14–15 (S.D. Fla. Nov. 6, 2016).

67. On information and belief, following FDA approval of the Apotex Filgrastim aBLA, Apotex Corp. will sell the Apotex Filgrastim Product, which is the subject of the infringement claims in this action in the State of Florida and throughout the United States. *See* Apobiologix, R&D Overview, http://www.apobiologix.com/rd/default.asp (last visited on Aug.

1, 2018); No. 16-1308, D.E. 25 at 3-4 (Fed. Cir. Dec. 22, 2015); No. 0:15-cv-61631-JIC, D.E. 55 at 14–15 (S.D. Fla. Nov. 11, 2016).

FIRST COUNT
(INFRINGEMENT OF THE ’287 PATENT (PEGFILGRASTIM))

68. The allegations of paragraphs 1-67 are incorporated herein by reference.

69. On information and belief, by its aBLA submissions to FDA, Apotex seeks FDA approval under Section 351(k) of the Public Health Service Act (42 U.S.C § 262(k)) to engage in the commercial manufacture and/or sale of the Apotex Pegfilgrastim Product as a biosimilar version of Amgen’s NEULASTA®.

70. On information and belief, Apotex intends to manufacture, use, sell, offer for sale, and/or import the Apotex Pegfilgrastim Product prior to the expiration of the ’287 Patent.

71. The submission of the Apotex Pegfilgrastim aBLA, including on information and belief, any amendments thereto, is an act (or acts) of infringement of one or more claims of the ’287 Patent under 35 U.S.C. § 271(e)(2)(C)(i).

72. Apotex Corp.’s participation in, contribution to, inducement of, aiding or abetting the submission of the Apotex Pegfilgrastim aBLA and amendment(s) thereto constitutes direct, contributory, or induced infringement of one or more claims of the ’287 Patent under 35 U.S.C. § 271(e)(2)(C)(i).

73. On information and belief, the manufacture, use, sale, offer for sale, and/or importation of the Apotex Pegfilgrastim Product will infringe one or more claims of the ’287 Patent.

74. Amgen will be irreparably harmed if Apotex is not enjoined from infringing or actively inducing or contributing to infringement of one or more claims of the ’287 Patent.

Amgen is entitled to injunctive relief under 35 U.S.C. § 271(e)(4)(B) preventing Apotex from any further infringement. Amgen does not have an adequate remedy at law.

75. To the extent Apotex commercializes its product prior to the expiration of the ’287 Patent, Amgen will also be entitled to damages under 35 U.S.C. § 284.

SECOND COUNT
(DECLARATORY JUDGMENT OF INFRINGEMENT OF THE ’287 PATENT (PEGFILGRASTIM))

76. The allegations of paragraphs 1-75 are incorporated herein by reference.

77. On information and belief, Apotex seeks FDA approval under Section 351(k) of the Public Health Service Act (42 U.S.C § 262(k)) to manufacture and sell the Apotex Pegfilgrastim Product, a biosimilar version of Amgen’s NEULASTA®.

78. Upon information and belief, Apotex intends to, and will, manufacture, use, offer to sell, or sell within the United States, or import into the United States, the Apotex Pegfilgrastim Product immediately upon FDA licensure of the Apotex Pegfilgrastim aBLA, which FDA accepted on or about December 16, 2014. Apotex publicly lists the status of its Pegfilgrastim Product as “Filed,” with “Marketed” as the next step.

79. If Apotex manufactures, uses, offers to sell, or sells within the United States, or imports into the United States, the Apotex Pegfilgrastim Product prior to the expiration of the ’287 Patent, Apotex will infringe one or more claims of the ’287 Patent under 35 U.S.C. § 271(a), (b), (c), and/or (g).

80. An actual controversy has arisen and now exists between the parties concerning whether the Apotex Pegfilgrastim Product will infringe one or more claims of the ’287 Patent.

81. Amgen is entitled to a declaratory judgment that Apotex will infringe one or more claims of the ’287 Patent by making, using, offering to sell, or selling within the United States,

or importing into the United States, the Apotex Pegfilgrastim Product prior to the expiration of the ’287 Patent.

82. Amgen is entitled to injunctive relief preventing Apotex from making, using, offering to sell, or selling within the United States, or importing into the United States, the Apotex Pegfilgrastim Product prior to the expiration of the ’287 Patent. Amgen does not have an adequate remedy at law.

THIRD COUNT
(INFRINGEMENT OF THE ’287 PATENT (FILGRASTIM))

83. The allegations of paragraphs 1-82 are incorporated herein by reference.

84. On information and belief, by its aBLA submissions to FDA, Apotex seeks FDA approval under Section 351(k) of the Public Health Service Act (42 U.S.C § 262(k)) to engage in the commercial manufacture and/or sale of the Apotex Filgrastim Product, a biosimilar version of Amgen’s NEUPOGEN®.

85. On information and belief, Apotex intends to manufacture, use, sell, offer for sale, and/or import the Apotex Filgrastim Product prior to the expiration of the ’287 Patent.

86. The submission and filing of the Apotex Filgrastim aBLA, including on information and belief, any amendments thereto is an act (or acts) of infringement of one or more claims of the ’287 Patent under 35 U.S.C. § 271(e)(2)(C)(i).

87. Apotex Corp.’s participation in, contribution to, inducement of, aiding or abetting the submission of the Apotex Filgrastim aBLA and amendment(s) thereto constitutes direct, contributory, or induced infringement of one or more claims of the ’287 Patent under 35 U.S.C. § 271(e)(2)(C)(i).

88. On information and belief, the manufacture, use, sale, offer for sale, and/or importation of the Apotex Filgrastim Product will infringe one or more claims of the ’287 Patent.

89. Amgen will be irreparably harmed if Apotex is not enjoined from infringing or actively inducing or contributing to infringement of one or more claims of the ’287 Patent. Amgen is entitled to injunctive relief under 35 U.S.C. § 271(e)(4)(B) preventing Apotex from any further infringement. Amgen does not have an adequate remedy at law.

90. To the extent Apotex commercializes its product prior to the expiration of the ’287 Patent, Amgen will also be entitled to damages under 35 U.S.C. § 284.

FOURTH COUNT
(DECLARATORY JUDGMENT OF INFRINGEMENT OF THE ’287 PATENT (FILGRASTIM))

91. The allegations of paragraphs 1-90 are incorporated herein by reference.

92. On information and belief, Apotex seeks FDA approval under Section 351(k) of the Public Health Service Act (42 U.S.C § 262(k)) to manufacture and sell the Apotex Filgrastim Product, a biosimilar version of Amgen’s NEUPOGEN®.

93. Upon information and belief, Apotex intends to, and will, manufacture, use, offer to sell, or sell within the United States, or import into the United States, the Apotex Filgrastim Product immediately upon FDA licensure of the Apotex Filgrastim aBLA, which FDA accepted on or about February 13, 2015. *See* No. 16-1308, D.E. 25 at 3–4 (Fed. Cir. Dec. 22, 2015); No. 0:15-cv-61631-JIC, D.E. 55 at 14–15 (S.D. Fla. Nov. 11, 2016). Apotex publicly lists the status of its Filgrastim Product as “Filed,” with “Marketed” as the next step.

94. If Apotex manufactures, uses, offers to sell, or sells within the United States, or imports into the United States, the Apotex Filgrastim Product prior to the expiration of the ’287 Patent, Apotex will infringe one or more claims of the ’287 Patent under 35 U.S.C. § 271(a), (b), (c), and/or (g).

95. An actual controversy has arisen and now exists between the parties concerning whether the Apotex Filgrastim Product will infringe one or more claims of the ’287 Patent.

96. Amgen is entitled to a declaratory judgment that Apotex will infringe one or more claims of the ’287 Patent by making, using, offering to sell, or selling within the United States, or importing into the United States, the Apotex Filgrastim Product prior to the expiration of the ’287 Patent.

97. Amgen is entitled to injunctive relief preventing Apotex from making, using, offering to sell, or selling within the United States, or importing into the United States, the Apotex Filgrastim Product prior to the expiration of the ’287 Patent. Amgen does not have an adequate remedy at law.

PRAYER FOR RELIEF

WHEREFORE, Amgen respectfully requests that this Court enter judgment in its favor against Apotex and grant the following relief:

A. a judgment that Apotex has infringed directly, contributed to, or induced the infringement of one or more claims of the ’287 Patent under 35 U.S.C. § 271(e)(2)(C)(i) by submitting to FDA the Apotex Pegfilgrastim aBLA and amendment(s) thereto;

B. a judgment that Apotex has infringed directly, contributed to, or induced the infringement of one or more claims of the ’287 Patent under 35 U.S.C. § 271(e)(2)(C)(i) by submitting to FDA the Apotex Filgrastim aBLA and amendment(s) thereto;

C. a preliminary and/or permanent injunction that enjoins Apotex, its officers, partners, agents, servants, employees, attorneys, affiliates, divisions, subsidiaries, other related business entities, and those persons in active concert or participation with any of them from infringing the ’287 Patent, or contributing to or inducing anyone to do the same, by acts including the manufacture, use, offer to sell, sale, distribution, or importation of any current or future versions of a product that infringes, or the use or manufacture of which infringes the ’287 Patent;

D. a judgment declaring that the manufacture, use, offer to sell, sale, distribution, or importation of the products described in the Apotex Pegfilgrastim aBLA would constitute infringement of one or more claims of the ’287 Patent, or inducement of or contribution to such conduct, by Apotex pursuant to 35 U.S.C. § 271(a), (b), (c), and/or (g);

E. a judgment declaring that the manufacture, use, offer to sell, sale, distribution, or importation of the products described in the Apotex Filgrastim aBLA would constitute infringement of one or more claims of the ’287 Patent, or inducement of or contribution to such conduct, by Apotex pursuant to 35 U.S.C. § 271(a), (b), (c), and/or (g);

F. a judgment compelling Apotex to pay to Amgen damages adequate to compensate for Apotex’s infringement, in accordance with 35 U.S.C. § 284;

G. a declaration that this is an exceptional case and an award to Amgen of its attorneys’ fees and costs pursuant to 35 U.S.C. § 285; and

H. such other relief as this Court may deem just and proper.

Dated: August 7, 2018

By: */s/ John F. O’Sullivan*

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