UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF FLORIDA

Case No. 18-61828-CIV-WPD/LSS

AMGEN INC. and AMGEN MANUFACTURING LIMITED,

Plaintiffs,

v.

APOTEX INC. and APOTEX CORP.,

Defendants.

ORDER DENYING
APOTEX INC. AND APOTEX CORP.'S MOTION TO DISMISS

THIS CAUSE is before the Court on Defendants Apotex Inc. and Apotex Corp.'s Motion to Dismiss [DE's 8/9]. The Court has carefully considered the Motion [DE's 8/9], Plaintiffs Amgen Inc. and Amgen Manufacturing Limited's Response [DE 46], Plaintiffs' Reply [DE 50], Plaintiffs' Complaint [DE 1], and documents integral to Plaintiffs' complaint such as the prosecution history of U.S. Patent No. 9,856,287 and is otherwise fully advised in the premises. At the request of both sides, the Court held or oral argument on the Motion on March 19, 2019.

I. BACKGROUND

The parties to this action are Plaintiffs Amgen Inc. and Amgen Manufacturing, Limited (collectively, "Amgen"), and Defendants Apotex Inc. and Apotex Corp. (collectively, "Apotex"). *See* Complaint [DE 1] ¶¶ 1-5.

The controversy between Plaintiffs Amgen Inc. and Amgen Manufacturing Ltd. ("Plaintiffs") and Defendants Apotex Inc. and Apotex Corp. ("Defendants") dates back to December, 2014, when Defendants filed abbreviated Biologics License Applications ("aBLAs")

that seek approval from the United States Food & Drug Administration ("FDA") for filgrastim and pegfilgrastim products, which are biosimilar versions of Plaintiffs' Neupogen® and Neulasta® products, respectively.

Under the statutory scheme established by Congress in the Biologics Price Competition and Innovation Act ("BPCIA"), in August and October, 2015, Plaintiffs sued Defendants in the Southern District of Florida for patent infringement under the BPCIA, the federal Food, Drug and Cosmetics Act ("FDCA"), United States Code, Title 21, and the Patent Act, United States Code, Title 35 (the "Prior Action"),[1] arguing that Defendants' biosimilar products were manufactured by a process that infringed U.S. Patent No. 8,952,138 (the "138 patent"). After a bench trial in July, 2016, the Court concluded that Defendants' manufacturing process for its biosimilar products did not infringe the 138 patent. On November 13, 2017, the United States Court of Appeals for the Federal Circuit upheld this Court's decision that Defendants' manufacturing process did not infringe the 138 patent. *Amgen Inc. et al. v. Apotex Inc. et al.*, 712 Fed.Appx. 985 (Fed. Cir. 2017).

While the Prior Action involving the 138 patent was on appeal, on February 1, 2017, Plaintiffs filed a patent application that issued on January 2, 2018, as U.S. Patent No. 9,856,287 (the "287 patent"). The 287 patent is related to the 138 patent, and, as such, these patents share a common specification or disclosure and include the same figures and drawings.

On August 7, 2018, Plaintiffs instituted this second action for patent infringement against Defendants under the BPCIA, FDCA, and the Patent Act, United States Code, Title 35, alleging that Defendants' manufacturing process for its biosimilar products infringes the 287 patent. *See*

[1] Case No. 15-61631-CIV-COHN/SELTZER (Consolidated with 15-62081-CIV-COHN/SELTZER).

[DE 1]. According to the allegations of the Complaint, which the Court assumes as true for purposes of this motion to dismiss:

Two of Amgen's products are NEUPOGEN® and NEULASTA®. *Id.* ¶¶ 8-13. Both drugs are approved to "decrease the incidence of infection, as manifested by febrile neutropenia, in patients . . . receiving myelosuppressive anticancer drugs." *Id.* "Neutropenia is a deficiency in neutrophils, a condition which makes the individual highly susceptible to infection." *Id.* ¶ 9. "The active ingredient in NEUPOGEN® is filgrastim, a recombinantly expressed . . . protein known as human granulocyte-colony stimulating factor or 'G-CSF.'" *Id.* ¶ 10. "The active ingredient in NEULASTA® is pegfilgrastim, a form of the G-CSF protein" that "requires less frequent administration." *Id.* ¶ 12. G-CSF counteracts neutropenia "by binding to specific receptors on the surface of certain types of cells to stimulate the production of neutrophils." *Id.* ¶ 10. Thus, "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." *Id.* ¶ 13.

This case relates to Apotex's efforts to make and obtain approval to market "biosimilar" versions of Amgen's NEUPOGEN® and NEULASTA® products. *Id.* ¶¶ 18-24. "Biosimilars" can be analogized to generic drugs, but instead of being copies of so-called "small molecules," biosimilars are "similar" (not identical) to biological products, in recognition of their production from living organisms and attendant natural variation. Until recently, the U.S. Food and Drug Administration ("FDA") licensed biological products "[u]nder the traditional pathway for FDA approval, [whereby] an innovator must demonstrate that its biologic drug is safe, pure, and potent through clinical trials." *Id.* ¶ 14. "The [Biologics Price Competition and Innovation Act (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," *i.e.*, the innovator product licensed by FDA under the traditional regulatory pathway. *Id.* ¶ 14.

"Apotex, seeking the benefits of the subsection (k) pathway with Amgen as the [reference product sponsor]," submitted abbreviated Biologics License Application ("aBLA") Nos. 761026 and 761027. [DE 1] ¶¶ 19, 22. Apotex represented to FDA that its proposed products are biosimilar to Amgen's NEULASTA® and NEUPOGEN® products. *Id.* ¶¶ 19-24. "After Apotex filed each of its aBLAs," the parties "engaged in the information exchange described in the BPCIA." *Id.* ¶ 25. Specifically, Amgen identified U.S. Patent No. 8,952,138 (the "'138 Patent") "as a patent that the Apotex-proposed products would infringe." *Id.* "Following the information exchange, Amgen filed two immediate patent infringement suits against Apotex" pursuant to the BPCIA arising under 35 U.S.C. § 271(e)(2)(C)(i), (a), (b), (c), and/or (g) in this Court asserting the '138 Patent. [DE 1] ¶ 26. These two suits were consolidated. *Id.* ¶ 27. Judge Cohn held a bench trial in July 2016, and issued findings of fact and conclusions of law in September 2016. *Id.* The Court "found that Amgen 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." *Id.* "Amgen appealed the Court's judgment, and the Federal Circuit affirmed." *Id.* "The Federal Circuit mandate for that case issued" in December 2017. *Id.*

On January 2, 2018, the U.S. Patent and Trademark Office issued U.S. Patent No. 9,856,287 (the "'287 Patent") to Amgen. *Id.* ¶ 28. While the '287 Patent shares the same priority and the same specification as the '138 Patent, the '287 Patent necessarily has a different prosecution history than the '138 Patent.

Amgen filed its Complaint in the present action in August 2018, alleging that Apotex's manufacturing process disclosed in its aBLAs infringes one or more claims of the '287 patent. *Id.* Specifically, the Complaint alleges that "Apotex uses the same process to produce the same filgrastim used in its Filgrastim Product and Pegfilgrastim Product." [DE 1] at ¶ 35. Amgen further alleges that "Apotex infringes claims of the '287 Patent, including for example, Claim 16" and that "Each of the elements in at least Claim 16 are satisfied in Apotex's accused process." *Id.* ¶¶ 33-40.

Amgen alleges that, as claimed in the 287 patent, "Apotex expresses the filgrastim protein used in its Pegfilgrastim Product and Filgrastim Product in a nonmammalian expression system: *E. coli* (bacterial) cells." *Id.* ¶ 36. Amgen also specifically alleges that "Apotex refolds the filgrastim contained in Pegfilgrastim Product and Filgrastim Product using a refolding solution" as claimed in the '287 Patent. *Id.* ¶ 37. In addition, Amgen identifies the components that comprise the refolding solution as claimed by the 287 patent: at least the filgrastim protein, at least one component selected from the group consisting of a denaturant, an aggregation suppressor and a protein stabilizer (arginine and sorbitol); an amount of oxidant (cystine); and an amount of reductant (cysteine). *Id.* ¶ 38. Further, Amgen alleges that the "the amounts of oxidant (cystine) and reductant (cysteine) 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." *Id.* ¶ 39. Amgen alleges that "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%.'" ¶ 40.

Finally, Amgen's Complaint alleges that Apotex seeks "FDA approval to engage in the commercial manufacture" and/or "sale of each of the Apotex Pegfilgrastim Product and the Apotex Filgrastim Product," biosimilar versions of Amgen's NEUPOGEN® and NEULASTA®. ¶¶ 44, 69, 84. Under the BPCIA, Apotex's submissions of the Pegfilgrastim aBLA and the Filgrastim aBLA are each "an act of infringement under 35 U.S.C. § 271(e)(2)(C)(i)." ¶¶ 42-43, 71-72, 86-87. And, under the Declaratory Judgment Act, Apotex's statements that it "intends to launch" its products "upon FDA approval" give rise to an actual controversy between the parties regarding infringement of the '287 Patent. ¶¶ 48, 76-81, 92-96.

On December 10, 2018, Defendants filed their Motion to Dismiss Plaintiffs' Complaint Pursuant to Fed. R. Civ. P. 12(b)(6). *See* [DE's 8, 9]. Defendants assert that Plaintiffs' infringement claims are barred under the doctrine of collateral estoppel and/or prosecution history disclaimer.

II. LEGAL STANDARD

Rule 8(a)(2) requires "a short and plain statement of the claim showing that the pleader is entitled to relief." FED. R. CIV. P. 8(A)(2). Under Rule 12(b)(6), a motion to dismiss should be granted only if the plaintiff is unable to articulate "enough facts to state a claim to relief that is plausible on its face." *Bell Atl. Corp. v. Twombly*, 550 U.S. 544, 570 (2007). "A claim has facial plausibility when the plaintiff pleads factual content that allows the court to draw the reasonable inference that the defendant is liable for the misconduct alleged." *Ashcroft v. Iqbal*, 556 U.S. 662, 678 (2009) (citing *Twombly*, 550 U.S. at 556). "[A] court must view a complaint in the light most favorable to the plaintiff and accept all of the plaintiff's well-pleaded facts as true." *Am. United Life Ins. Co. v. Martinez*, 480 F.3d 1043, 1066 (11th Cir. 2007).

However, the court need not take allegations as true if they are merely "threadbare recitals of the elements of a cause of action, supported by mere conclusory statements." *Iqbal*, 556 U.S. at 678. "Mere labels and conclusions or a formulaic recitation of the elements of a cause of action will not do, and a plaintiff cannot rely on naked assertions devoid of further factual enhancement." *Franklin v. Curry*, 738 F.3d 1246, 1251 (11th Cir. 2013) (internal quotation marks omitted). "[I]f allegations are indeed more conclusory than factual, then the court does not have to assume their truth." *Chaparro v. Carnival Corp.*, 693 F.3d 1333, 1337 (11th Cir. 2012). In sum, "[t]he plausibility standard 'calls for enough fact to raise a reasonable expectation that discovery will reveal evidence' of the defendant's liability." *Miyahira v. Vitacost.com, Inc.*, 715 F.3d 1257, 1265 (11th Cir. 2013) (quoting *Twombly*, 550 U.S. at 556).

For any legal issues that are particular or unique to patent cases, this Court applies the law of the United States Court of Appeals for the Federal Circuit. *See Aspex Eyewear, Inc. v. Marchon Eyewear, Inc*., 672 F.3d 1335, 1341 n. 1 (Fed. Cir. 2012) ("[T]he question whether a particular claim in a patent case is the same as or separate from another claim has special application to patent cases, and we therefore apply our own [Federal Circuit] law to that issue"); *see also Patent Holder LLC v. Lone Wolf Distributors, Inc*., No. 17-23060-CIV-SCOLA, 2017 WL 5032989, at *2 (S.D. Fla. Nov. 1, 2017).

In addition to facts set forth in Plaintiffs' complaint, in reviewing Defendants' Motion this Court may also consider documents integral to the complaint, such as the prosecution history of the 287 patent and portions of Defendants' aBLAs that were attached to the complaint. *See, e.g., Wilchombe v. TeeVee Toons, Inc*., 555 F.3d 949, 959 (11th Cir. 2009); *Maxcess, Inc. v. Lucent Techs., Inc*., 433 F.3d 1337, 1340 n.3 (11th Cir. 2005); *Genetic Techs. Ltd. v. Bristol-Myers Squibb Co*., 72 F. Supp. 3d 521, 526 (D. Del. 2014) *aff'd sub nom., Genetic Techs. Ltd. v.*

Merial L.L.C., 818 F.3d 1369 (Fed. Cir. 2016).

III. DISCUSSION

Apotex asserts that Amgen's Complaint should be dismissed for two reasons: first, based on the prior case involving the 138 patent, Amgen is estopped from alleging that the thiol-pair ratio and thiol-pair buffer strength are calculated in Apotex's refold mixture, called "solution" in the claims of the 287 patent; and second, prosecution history disclaimer bars Amgen from asserting that Apotex's process infringes the 287 patent. The Court first addresses Defendants' collateral estoppel argument, and then addresses the Defendants' arguments concerning prosecution history disclaimer. While Apotex may ultimately win this case as to one or both of these arguments, the Court finds that the instant motion is due to be denied at this stage of the litigation.

A. Collateral Estoppel

First, Defendants move to dismiss the Complaint for failure to state a claim based on principles of collateral estoppel, alleging that they are protected from re-litigating issues that were resolved against Plaintiffs in the Prior Action.

Collateral estoppel applies where the issues are identical; the issues were actually litigated; the issues were a "critical and necessary" aspect of the prior judgment; and the allegedly estopped party had a full and fair opportunity to litigate. *FTC v. Nat'l Urological Grp., Inc.*, 785 F.3d 477, 482 (11th Cir. 2015).

The Complaint identifies Defendants' "refolding solution" as containing "amounts of oxidant (cysteine) and reductant (cystine) [that] 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." [DE 1] at p. 12. In the Prior Action, the

Court adopted Plaintiffs' proposed constructions for the claim terms "thiol-pair ratio" and "thiol-pair buffer strength" (also called "redox buffer strength"), finding that these values were calculated in "the redox component." *See Amgen, Inc. et al. v. Apotex Inc. et al*., No. 15-61631-CIV-COHN/SELTZER, 2016 WL 1375566, at *3-4 (S.D. Fla. April 7, 2016). Defendants contend that Plaintiffs' infringement claims are precluded by claim constructions for "thiol-pair ratio" and "thiol-pair buffer strength" that Plaintiffs advocated for and that the Court adopted in the Prior Action. Particularly, Defendants argue that Plaintiffs are collaterally estopped from alleging infringement in this action based on the "thiol-pair ratio" and "thiol-pair buffer strength" being calculated in Apotex's "refolding solution." *See* [DE 1] at 12.

Plaintiffs argue that collateral estoppel does not apply because the issues in the Prior Action were not identical to those here, and because the constructions for these claim terms in the 138 patent were not critical and necessary to the Court's prior judgment. Further, Plaintiffs argue that claim construction is necessary in this action because the claim terms at issue can, and do, have different meanings in the context of the claims of the 287 patent. *See id*.

Here, upon careful consideration, the Court determines that it is inappropriate to apply collateral estoppel at this stage of the proceedings to prohibit Amgen from arguing a different meaning for the terms thiol-pair ratio and thiol-pair buffer strength in the 287 patent than it did in the prior actions for the 138 patent. The fact that the 287 patent is related to the 138 patent does not necessarily mean that collateral estoppel applies. *See e.Digital Corp. v. Futurewei Techs., Inc.*, 772 F.3d 723, 727 (Fed. Cir. 2014) ("[A] court cannot impose collateral estoppel to bar a claim construction dispute solely because the patents are related."); *Purdue Pharma L.P. v. Mylan Pharms. Inc.*, No. 15-cv-1155-RGA-SR, 2017 WL 784989, at *3-5 (D. Del. Mar. 1, 2017), *adopted by* 2017 WL 2569604 (D. Del. June 13, 2017). Even though the 287 patent and

the 138 patent have the same specification, potential differences in claim language is critical because claims define the invention. *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1347 (Fed. Cir. 2010) (*en banc*); *see In re Hiniker Co.*, 150 F.3d 1362, 1369 (Fed. Cir. 1998). Here, Claim 1 of the 138 patent and Claim 16 of the 287 patent do not contain the identical language:

138 patent, Claim 1	**287 patent, Claim 16**
1. A method of refolding a protein expressed in a non-mammalian expression system and present in a volume at a concentration of 2.0 g/L or greater comprising: (a) contacting the protein with a refold buffer comprising ***a redox component comprising a final thiol-pair ratio having a range of 0.001 to 100 and a redox buffer strength of 2 mM or greater*** and one or more of: (i) a denaturant; (ii) an aggregation suppressor; and (iii) a protein stabilizer, to form a refold mixture; (b) incubating the refold mixture; and (c) isolating the protein from the refold mixture.	16. A method of refolding proteins expressed in a non-mammalian 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.

138 patent, Claim 1 (emphases added); 287 patent, Claim 16 (emphases added).

This Court has not yet construed the claims of the 287 patent and would need to conduct a new claim construction analysis to resolve the issues that Apotex raises in its motion. Until the Court conducts a *Markman* hearing and properly construes the claims of the 287 patent, the

Court cannot determine whether there are material differences in the claim terms that were not previously litigated. *See, e.g., Purdue Pharma*, 2017 WL 784989, at *5-6 (denying motion to dismiss on collateral estoppel grounds, explaining: "At this stage of the proceedings, defendants have failed to establish that the invalid claims of the previously-litigated low-ABUK patents are sufficiently identical to the disputed claims of the '933 patent. The claims of the '933 patent contain limitations not set forth in the low-ABUK patents, but whether these limitations are material to the patentability of the '933 patent is a question of fact to be reserved for a later stage of the proceedings."). Accordingly, the Court declines to apply collateral estoppel to dismiss the Complaint at this stage of the proceedings.

B. Prosecution History Disclaimer

Defendants also move to dismiss Plaintiffs' complaint for failure to state a claim based on the principle of prosecution history disclaimer[2], alleging that claim amendments and arguments made by Plaintiffs during prosecution of the 287 patent preclude Plaintiffs' infringement allegations as a matter of law.

Under the doctrine of prosecution history disclaimer, a patentee is precluded from "recapturing through claim interpretation specific meanings disclaimed during prosecution." *Omega Engineering, Inc v. Raytek Corp*., 334 F. 3d 1314, 1323 (Fed. Cir. 2003) (citing *Schriber-Schroth Co. v. Cleveland Trust Co*., 311 U.S. 211 (1940)). In order for disclaimer to apply, the

[2] Apotex argued in its opening brief that "Amgen's case is limited to infringement under the doctrine of equivalents" and that prosecution history *estoppel* prevents Amgen from alleging infringement under the doctrine of equivalents as to the '287 Patent claim terms "thiol-pair ratio" and "thiol-pair buffer strength." *See* [DE 9] at 11-13. However, Amgen has alleged that the term is literally met, and prosecution history estoppel does not apply to literal infringement claims. *AccuScan, Inc. v. Xerox Corp.*, 76 F. App'x 290, 291 (Fed. Cir. 2003) (non-precedential); *Peach State Labs., Inc. v. Envtl. Mfg. Sols., LLC*, No. 6:09-cv-395, 2011 WL 13141167, at *4 n.4 (M.D. Fla. Dec. 29, 2011) ("[I]t is well settled that 'prosecution history estoppel [is] inapplicable to literal infringement.'") (quoting *Ballard Med. Prods. v. Allegiance Healthcare Corp.*, 268 F.3d 1352, 1358 (Fed. Cir. 2001)). Thus, Apotex's reply brief acknowledges that Amgen alleges literal infringement and argues that Amgen's infringement claim is also barred by prosecution disclaimer. *See* [DE 50] at 2. At the March 15, 2019 hearing, counsel for both sides had full opportunity to argue their positions on prosecution history disclaimer, and did so robustly.

disavowal of claim scope must be unambiguous. *See id*. at 1324-25. *See also Ecolab, Inc. v. Envirochem, Inc*., 264 F.3d 1358, 1368 (Fed. Cir. 2001) ("[A]ll express representations made by or on behalf of the applicant to the examiner to induce a patent grant limit the interpretation of the claims so as to exclude any interpretation that may have been disclaimed or disavowed during prosecution in order to obtain claim allowance.") (citation omitted).

Defendants argue that the Complaint must be dismissed because the doctrine of prosecution history disclaimer bars Plaintiffs from alleging infringement by a protein refolding method that does not use or rely on the claimed thiol-pair ratio or buffer strength. During prosecution of the 287 patent, Patent Office rejected the pending claims over several prior art references that disclosed methods of protein refolding using an amount of an oxidant and an amount of a reductant. *See* [DE 9-8]. In response to these prior art rejections, Plaintiffs added the phrase "wherein the amounts of oxidant and reductant are related through a thiol-pair ratio and a thiol pair buffer strength" to the independent claims of the 287 patent. Further, Plaintiffs submitted that "as distinguished from [prior art] Oliner, the presently claimed method advantageously controls parameters, via the claimed thiol-pair ratio range and the thiol-pair buffer strength, to consistently yield at least about 25% properly refolding protein." *See* [DE 9-9] at 12. Concerning dependent claims 34 and 35, Plaintiffs also submitted that "[i]t appears that the Office Action simply used hindsight gleaned from the claimed present invention to select data from a single example in Oliner, and insert that data into the claimed equations in an attempt to show the claimed thiol-pair ratio range." *See* [DE 9-9] at 13. In finding the claims of the 287 patent patentable over the prior art, the Patent Office, in pertinent part, stated that "the claims are allowable because the most pertinent prior art neither teaches nor suggests the final thiol-pair ratio or strength as set forth in claims 34, 35, 56-57, 65-67 and 72." *See* [DE 9-10] at 3.

Upon a careful review of the prosecution history of the '287 Patent, the Court finds that the prosecution statements cited by Apotex, as set forth *supra*, do not "evince[] a clear and unmistakable surrender of subject matter" as the law requires, to permit the Court to apply prosecution history disclaimer at this early juncture. *See Intendis GMBH v. Glenmark Pharms. Inc., USA*, 822 F.3d 1355, 1365 (Fed. Cir. 2016); *Omega Eng'g, Inc, v. Raytek Corp.*, 334 F.3d 1314, 1324-26 (Fed. Cir. 2003). The Court may revisit these arguments at a later stage of the proceedings following claim construction and discovery.

IV. CONCLUSION

Based on the foregoing, it is **ORDERED AND ADJUDGED** that Defendants Apotex Inc. and Apotex Corp.'s Motion to Dismiss Pursuant to Fed. R. Civ. P. 12(b)(6) [DE's 8, 9] is hereby **DENIED**. Apotex shall file its Answer on or before April 18, 2019.

DONE AND ORDERED in Chambers at Fort Lauderdale, Broward County, Florida, this 4th day of April, 2019.

WILLIAM P. DIMITROULEAS
United States District Judge

Copies furnished to

Counsel of Record