IN THE UNITED STATES DISTRICT COURT
FOR THE 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.

AMGEN'S MEMORANDUM OF LAW IN OPPOSITION TO APOTEX INC. AND APOTEX CORP.'S MOTION TO DISMISS PURSUANT TO FED. R. CIV. P. 12(b)(6)

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I. INTRODUCTION

This is a patent infringement case arising under the Biologics Price Competition and Innovation Act of 2009 (the "BPCIA") involving Defendants Apotex Inc. and Apotex Corp.'s (collectively, "Apotex") pursuit of U.S. Food and Drug Administration ("FDA") approval for biosimilar versions of Amgen's NEULASTA® and NEUPOGEN® products under 42 U.S.C. § 262(k). DE 1 ¶¶ 6, 19, 22. Under the BPCIA, Apotex's submissions of abbreviated Biologics License Application Nos. 761026 and 761027 (the "Pegfilgrastim aBLA" and the "Filgrastim aBLA")—and any amendments thereto—are each "an act of patent infringement under 35 U.S.C. § 271(e)(2)(C)(i)." *Id.* ¶¶ 42–43, 71–72, 86–87. And Apotex's statements that "it intends to launch each of its [proposed biosimilar products] upon FDA approval" give rise to an actual controversy between the parties as to patent infringement under the Declaratory Judgment Act, 28 U.S.C. § 2201. *Id.* ¶¶ 48, 77–81, 92–96. Thus, Amgen filed a Complaint on August 7, 2018, alleging that Apotex infringed or will infringe Amgen's U.S. Patent No. 9,856,287 ("the '287 Patent").

Amgen's Complaint is supported by detailed factual averments: the Complaint identifies, as an example, each limitation of Claim 16 of the '287 Patent, and then shows how "[e]ach of the elements in at least Claim 16 are satisfied in Apotex's accused process" based "on the information contained in the publicly available portions of the Apotex Pegfilgrastim aBLA and Apotex Filgrastim aBLA." DE 1 ¶¶ 33–40. These statements must be accepted as "true" and all plausible inferences derived from those facts evaluated in favor of Amgen in deciding Apotex's Motion to Dismiss. *Spanakos v. Aronson*, No. 17-cv-80965-MIDDLEBROOKS/Brannon, 2018 WL 2392011, at *2 (S.D. Fla. Apr. 2, 2018) (citing *Ashcroft v. Iqbal*, 556 U.S. 662, 678 (2009) and *Bell Atl. Corp. v. Twombly*, 550 U.S. 544, 554–5 (2007)). Thus, Amgen's Complaint states a plausible claim for patent infringement against Apotex.

Despite these detailed allegations, Apotex moves to dismiss based on the doctrines of collateral estoppel and prosecution history estoppel, raising arguments that go well beyond the four corners of Amgen's Complaint. Each argument fails. Fundamentally, Apotex's Motion contends that Amgen is asserting the same infringement theories as in the prior litigation between Amgen and Apotex, and therefore Apotex must prevail. But that premise is wrong because the claims of the '287 Patent are materially different from those of U.S. Patent No. 8,952,138 (the "'138 Patent") that was at issue in the earlier case. This is apparent from the

following side-by-side comparison with emphasis added to the claim elements on which Apotex relies:

'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.

And, in the earlier case, Amgen argued infringement under the so-called doctrine of equivalents, a legal theory that applies only when the claims of the patent at issue do not on their face cover the allegedly infringing activity. Here by contrast, Amgen asserts that each of the elements in at least Claim 16 of the '287 Patent is met; this states at least literal infringement claims which, as the name suggests, apply when the patents claims literally do cover what is alleged to infringe.

First, Apotex's Motion fails because the parties have claim construction disputes that cannot be resolved on the pleadings. Apotex relies on collateral estoppel to argue that the Court's claim constructions in the prior case on the '138 Patent are controlling here as to the

meaning of "thiol-pair ratio" and the "thiol-pair buffer strength" in the '287 Patent.[1] This is incorrect because the issues in the prior litigation were not "identical" to the issues here or actually litigated, and the prior court's construction of the '138 Patent's thiol-pair terms in the '138 Patent was not a "critical and necessary" aspect of the prior judgment. *FTC v. Nat'l Urological Grp., Inc.*, 785 F.3d 477, 482 (11th Cir. 2015). As shown in the chart above, one of the key ways in which the claim language of the '287 Patent differs from that of the '138 Patent is in how the "thiol pair ratio" and "thiol pair buffer strength" are determined. Specifically, Apotex argues here that there can be no infringement based on a ratio and buffer strength that are measured in a "redox component." Apotex Br. at 11, 14. The "redox component" of the '138 Patent is a pre-existing mixture of some but fewer than all of the components ultimately used to make the solution in which refolding takes place: in essence, the '138 Patent requires that some components be pre-mixed before they are added to this solution. The '287 Patent includes no such requirement. Its claims do not mention a "redox component," and instead recite a ratio and buffer strength that are measured in either "a preparation" or "a solution." Thus, it is improper to incorporate constructions of '138 Patent terms into the '287 Patent claims. Instead, the Court will need to conduct a new claim construction analysis. But, as the Federal Circuit recently held in *Nalco Co. v. Chem-Mod, LLC*: resolution on the pleadings is not appropriate when the "proper scope" of an asserted claim is disputed; it is also not appropriate when factual findings are required. 883 F.3d 1337, 1348-49 (Fed. Cir. 2018).

Second, Apotex argues that the Complaint should be dismissed based on the doctrine of prosecution history estoppel, without the benefit of claim construction or discovery. Apotex Br. at 1–2. This fails because Amgen, as noted above, 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." DE 1 ¶¶ 33–40; *see id* at ¶¶ 69–73, 84–88. Amgen also alleges how each element of Claim 16 is met in Apotex's process, which states a claim of literal infringement. Prosecution history estoppel does not bar claims of literal infringement. *See, e.g., AccuScan, Inc. v. Xerox Corp.*, 76 F. App'x 290, 291 (Fed. Cir. 2003).

[1] With respect to buffering component, the '138 Patent uses the term "redox buffer strength" while the '287 Patent uses a different term, "thiol-pair buffer strength." Apotex asserts without explanation that the two are synonymous. Apotex Br. at 3. Whether the two terms in fact have the same meaning is an issue that will have to be addressed in this case but it is not necessary to the resolution of Apotex's Motion.

In any event, Amgen states more than a plausible claim for infringement under the doctrine of equivalents. The prosecution statements on which Apotex relies were made with respect to ***specific dependent claims***, *i.e.*, those claims that explicitly recite that the thiol-pair ratio and thiol-pair buffer strength are "calculated"—and not ***all claims***. *See* Apotex Br. Ex. 9 at 12 (discussing only then-claims 34 and 35). Thus, those statements do not give rise to prosecution history estoppel for all of the asserted claims. Nor do those statements evince a clear and unmistakable surrender of claim scope as to the dependent claims, which were amended to overcome the Examiner's rejection; the Examiner then issued the amended claims without any further narrowing of claim scope as a result of Amgen's statements during prosecution.

Third, Apotex asserts that its Motion should be granted, relying on *Amgen Inc. v. Coherus Biosciences, Inc.*, No. 17-cv-546-LPS-CJB, DE 72 (D. Del. Mar. 26, 2018). Apotex Br. at 15–16. But a different court's decision on a ***different*** patent in a ***different*** case with a ***different*** manufacturing process does not (and cannot) provide any guidance here. The Delaware court was not asked to decide (and did not decide) whether the Apotex manufacturing process literally satisfied the '287 Patent claims. Indeed, another district court has declined to follow the *Coherus* court's decision on the same patent as in the *Coherus* case. *See* Ex. 1 (Order on Defendants' Motion for Judgment on the Pleadings, *Amgen Inc. v. Mylan Inc.*, No. 2:17-cv-01235 (W.D. Pa. Nov. 15, 2018)).

Accordingly, Amgen respectfully requests that the Court deny Apotex's Motion.

II. STATEMENT OF FACTS

"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 benefits of patients suffering from serious illnesses." DE 1 ¶ 7. Two of its 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. DE 1 ¶¶ 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, 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 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 42 the subsection (k) pathway with Amgen as the [reference product sponsor]," submitted two abbreviated Biologics License Application ("aBLA") Nos. 761026 and 761027. DE 1 ¶¶ 19, 22. "Apotex represented to FDA that its [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 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 ¶ 26. These two suits were consolidated. *Id.* ¶ 27. Judge James I. Cohn of this Court "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.*

"Following the issuance of the Federal Circuit mandate for the appeal," the U.S. Patent and Trademark Office, having considered materials from the litigation during prosecution, "issued the '287 Patent to Amgen on January 2, 2018." DE 1 ¶ 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. Further, the '287 Patent claims are materially different from the claims of 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. DE 1. Amgen seeks a bench trial in the present action, DE 42, and intends to seek a jury trial should FDA approve, and Apotex launch, one or both of its proposed biosimilar products.

III. ARGUMENT

In addressing a motion to dismiss, "the Court's consideration is limited to the four corners of the complaint." *Apotex, Inc. v. UCB, Inc.*, No. 12-cv-60706-MIDDLEBROOKS/ BRANNON, 2013 WL 12091641, at *2 (S.D. Fla. Jan. 17, 2013) (citing *St. George v. Pinellas Cty.*, 285 F.3d 1334, 1337 (11th Cir. 2002)). This Court can grant a motion to dismiss under Rule 12(b)(6) only if, after accepting all well-pleaded allegations in the complaint as true, and viewing them in the light most favorable to plaintiff, plaintiff has not stated a plausible claim for relief. *See, e.g.*, *Twombly*, 550 U.S. at 570; *see Spanakos*, 2018 WL 2392011, at *2 (citing *Iqbal*, 556 U.S. at 678 and *Twombly*, 550 U.S. at 554-55). A patentee should be allowed an opportunity to show evidence to support its case. *Advanced Cardiovascular Sys., Inc. v. SciMed Life Sys., Inc.*, 988 F.2d 1157, 1160-61 (Fed. Cir. 1993) (vacating dismissal of patent infringement claim).

A. Amgen's Complaint States More Than a Plausible Claim for Relief for Patent Infringement

1. Amgen's Complaint Contains Detailed Allegations of Patent Infringement

Patent infringement is a question of fact. *See Vanda Pharm. Inc. v. W.-Ward Pharm. Int'l Ltd.*, 887 F.3d 1117, 1125 (Fed. Cir. 2018). The infringement inquiry here pursuant to 35 U.S.C. § 271(e)(2) and the Declaratory Judgment Act is focused on a comparison of the asserted patent claims against the accused process for the product that is likely to be sold following FDA approval. *Id.* This comparison involves the "two-step process of 'construing the claims and comparing the properly construed claims to the accused [process]." *Tinnus Enters., LLC v.*

Telebrands Corp., 846 F.3d 1190, 1203 (Fed. Cir. 2017) (quoting *Advanced Steel Recovery, LLC v. X–Body Equip., Inc.*, 808 F.3d 1313, 1316 (Fed. Cir. 2015)).

Claim construction is a question of law for which "courts may have to resolve subsidiary factual disputes." *Teva Pharms. USA, Inc. v. Sandoz, Inc.*, ___ U.S. ___, 135 S. Ct. 831, 838 (2015). The Court has not yet construed the claims of the '287 Patent, and discovery has not yet commenced in this action. Thus, Amgen's Complaint compares the claims of the '287 Patent as issued to the information that Apotex has publicly disclosed about its process. The last regulatory correspondence that Apotex has publicly disclosed is from February 2015.[2] Amgen's detailed allegations comparing the patent claims to Apotex's publicly-available disclosures from its 2014 and 2015 aBLA submissions about its process state more than a plausible claim for relief for patent infringement here. *See, e.g.*, *Nalco*, 883 F.3d at 1350; *Spanakos*, 2018 WL 2392011.

Specifically, 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®. DE 1 ¶¶ 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)." *Id.* ¶¶ 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. DE 1 ¶¶ 48, 77-81, 92-96. The Complaint also alleges that "Apotex uses the same process to produce the same filgrastim used in its Filgrastim Product and Pegfilgrastim Product." *Id.* ¶ 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. For example, 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. And Amgen specifically alleges that "Apotex refolds the filgrastim contained in Pegfilgrastim Product and

[2] *See* Ex. 2, APOBIOLOGIX NEWS, *Apotex Announces FDA Has Accepted for Filing its Biosimilar Application for Filgrastim (Grastofil™)*, available at http://www.apobiologix.com/news/20150213.asp (last accessed Jan. 18, 2019).

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 (cysteine); and an amount of reductant (cystine). *Id.* ¶ 38.

2. The Parties' Claim Construction Disputes Cannot Be Resolved on a Motion to Dismiss

The parties' claim construction disputes are not "suitable for resolution on a motion to dismiss." *Nalco*, 883 F.3d at 1349*; see In re Bill of Lading Transmission and Processing Sys. Patent Litig.*, 681 F.3d 1323, 1343 n.13 (Fed. Cir. 2012) (citation omitted) (claim construction at the pleading stage is inappropriate). In *Nalco*, the Federal Circuit reversed a district court's dismissal of Nalco's infringement claims because that dismissal required resolution of a claim construction dispute, which "was inappropriate at the Rule 12(b)(6) stage of the proceedings." *Id.* at 1349. Similarly, district courts have denied motions to dismiss because it "would be premature to engage in [claim construction] at the motion to dismiss stage." *Spanakos*, 2018 WL 2392011, at *5; *see Automated Transaction Corp. v. Bill Me Later, Inc.*, No. 09-cv-61903, 2010 WL 1882264 (S.D. Fla. May 11, 2010) ("absent agreement of the parties that claim construction should be done now, prior to discovery, the Court will defer its claim construction to a later date in this case."). Indeed, as plaintiff in another case, Apotex successfully argued to this court that "Claim Construction is Inappropriate at the Motion to Dismiss Stage."[3] *See Apotex*, 2013 WL 12091641, at *1–2 & n.4 (denying motion to dismiss in part "because Plaintiffs have not had an opportunity for discovery, nor have the claims in the Patent been construed").

Recognizing that its motion to dismiss is coming before this Court's claim construction ruling (and even the parties' proposed constructions, let alone argument on those issue), Apotex urges the Court to simply adopt the constructions given for the different '138 Patent in the parties' prior case. According to Apotex, "[t]he claim terms of the '287 patent that are relevant to this motion were construed by this Court in the prior actions according to Amgen's proposed constructions." Apotex Br. at 15. This is incorrect. No court has ever construed the claims of the '287 Patent, which issued after the Federal Circuit closed the prior case. Further, this Court

[3] Plaintiffs' Memorandum of Law In Opposition to Defendants' Motion to Dismiss, *Apotex, Inc. v. UCB, Inc.*, No. 12-cv-60706 -MIDDLEBROOKS/BRANNON (S.D. Fla. July 17, 2012).

is not bound by the construction of the '138 Patent in the prior action. *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.").

While the Court need not reach this issue to resolve Apotex's Motion, *Nalco*, 883 F.3d at 1349, it would be error for the Court to adopt the same constructions for the thiol-pair terms in the '287 Patent as in the '138 Patent. The '138 Patent has different claim language than the '287 Patent, including because the thiol-pair terms are part of a "redox component" in the '138 Patent whereas the thiol-pair terms are part of a "solution" or "preparation" in the '287 Patent. This difference is meaningful to Apotex's non-infringement argument, which depends on the highlighted terms below having the same meaning in the '138 Patent and the '287 Patent.

'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.

According to Apotex, because its process does not literally include a "redox component" or a "redox buffer strength," as those terms have been construed in the '138 Patent, its process cannot include amounts of oxidant and reductant "related through a thiol-pair ratio and a thiol-

pair buffer," as those terms are used in the '287 Patent. Apotex Br. at 11-12. This misses the point. That Apotex's process does not literally have a "redox component" (highlighted yellow in the table above) is inconsequential because having a "redox component" is not a limitation of the '287 Patent claims. Further, Apotex apparently assumes that the "thiol-pair buffer strength" of the '287 Patent claims (highlighted in blue) is measured in a redox component because the "redox buffer strength" of the '138 Patent claims (highlighted in green) is measured in a redox component. *See* Apotex Br. at 11. But the '287 Patent claims do not even mention a redox component. Properly construed, the "thiol-pair buffer strength" of the '287 Patent claims (highlighted in blue) is ***not*** measured in a redox component.

3. Discovery Should Proceed as to Apotex's Process

Apotex asserts that there "can be no dispute concerning the steps Apotex uses in its accused manufacturing process" because "Amgen obtained discovery of Apotex's aBLAs in the prior actions." Apotex Br. 1, 15. Based on the information about Apotex's manufacturing process that was publicly known prior to the filing of this action, there can be no doubt that Amgen has plausibly alleged infringement. But Apotex's aBLAs were filed in 2014 and fact discovery in the prior case closed in March 2016, and Amgen has not been provided with information about Apotex's aBLAs since that time. Ex. 3 (Scheduling Order, No. 15-cv-61631-JIC (S.D. Fla. Aug. 28, 2015)). Apotex's submissions prior to 2016 (including its 2014 aBLAs) have not been approved by FDA, and in the multiple years that have elapsed since fact discovery in the prior litigation, Amgen has not been provided information regarding the process(es) of manufacture of Apotex's proposed biosimilars; nor has Amgen been provided Apotex's correspondence with FDA about these proposed biosimilars and their process(es) of manufacture. [4]

Apotex argues that additional discovery is unnecessary because it believes this lawsuit can be resolved with reference to the 2014 aBLAs alone. Apotex Br. at 15. Apotex cannot prematurely end this case by declining to provide discovery on its present submissions to FDA. Indeed, it has been publicly reported that FDA rejected Apotex's originally-filed aBLAs by

[4] On its website, Apotex states that "The FDA is actively reviewing [its] applications for both [its] biosimilar to Neulasta® and [its] biosimilar to Neupogen® for use in the United States." *See* Ex. 4 (http://www.apobiologix.com/rd/default.asp).

sending what are known as "Complete Response Letters" to Apotex.[5] Discovery should proceed so that Amgen can obtain information concerning FDA's communications with Apotex, including FDA's rejections in the Complete Response Letters and Apotex's responses to FDA or any resubmissions or amendments to the aBLAs.

B. Each of Apotex's Arguments That Amgen's Complaint Should Be Dismissed Based on Collateral Estoppel and Prosecution History Estoppel Fails

1. There is No Collateral Estoppel From the Prior Case Involving the Different '138 Patent

Apotex asserts that "Amgen is collaterally estopped from arguing a different meaning for the terms thiol-pair ratio and thiol-pair buffer strength in the '287 Patent then [sic] it did in the '138 Patent." Apotex Br. at 14. This fails. Collateral estoppel applies only where the issues are identical; they 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*, 785 F.3d at 482.

As an initial matter, the law of the Eleventh Circuit applies to the collateral estoppel issues raised by Apotex as collateral estoppel is not an issue that is unique to patent law. Apotex never states or applies the Eleventh Circuit standard in its brief, instead citing two Federal Circuit cases that did not arise out of the Eleventh Circuit. Apotex Br. at 14.

First, the '287 Patent infringement issues here are not "identical" to the '138 Patent infringement issues in the prior case, and thus not actually litigated in the prior case. *See FTC*, 785 F.3d at 482. In patent infringement actions, the issues are not identical where a contextual difference "modifies, clarifies, or even informs the construction of the [claim] limitation." *e.Digital*, 772 F.3d at 726; *Yodlee, Inc. v. Plaid Techs., Inc.*, No. 14-cv-1445-LPS, 2016 WL 204372, at *4 (D. Del. Jan. 15, 2016) (no collateral estoppel where prior construction's issues were "somewhat different"). Collateral estoppel thus does not apply where, as here, a patent includes new, material claim terms that were not previously litigated. *See Purdue Pharma L.P.*

[5] *See, e.g.*, Ex. 5, Sue Sutter, *US Biosimilars: 40% First-Cycle Approval Rate Leaves Room for Improvement*, PHARMA INTELLIGENCE (July 7, 2017), available at https://pharmaintelligence.informa.com/resources/product-content/first-cycle-approval-rate (last accessed Jan. 18, 2019); Ex. 6, Stanton Mehr, *Pegfilgrastim: 0 for 3 on Biosimilars at FDA*, BIOSIMILARS REVIEW & REPORT (June 13, 2017), *available at* https://biosimilarsrr.com/2017/06/13/pegfilgrastim-0-for-3-on-biosimilars-at-fda/ (last accessed Jan. 18, 2019).

v. Mylan Pharms. Inc., No. 15-cv-1155-RGA-SR, 2017 WL 784989, at *5 (D. Del. Mar. 1, 2017), *adopted by* 2017 WL 2569604 (D. Del. June 13, 2017) (denying motion to dismiss because collateral estoppel did not apply where "[t]he claims of the '933 patent contain limitations not set forth in the [previously-construed] patents" and on the pleadings it was unclear "whether these limitations are material"); *Personalized Media Commc'ns, LLC v. Apple Inc.*, No. 2:15-cv-1366, 2016 WL 5719701, at *2 (E.D. Tex. Sept. 13, 2016), *adopted by* 2016 WL 5475798 (E.D. Tex. Sept. 28, 2016) (denying motion to dismiss because collateral estoppel did not apply where new patent contained a new claim term); *cf. ArcelorMittal Atlantique et Lorraine v. AK Steel Corp.*, 908 F.3d 1267, 1275–1276 (Fed. Cir. 2018) (vacating grant of motion to dismiss and explaining that "Differences with respect to the claimed limitations constitute changes in controlling facts, such that collateral estoppel does not apply").

Here, as discussed above, the thiol-pair terms in the '287 Patent appear in a different operative context than in the '138 Patent, presenting new factual disputes that were not resolved by the '138 Patent claim construction in the prior case. *See e.Digital*, 772 F.3d at 727 ("[A] court cannot impose collateral estoppel to bar a claim construction dispute solely because the patents are related.); *Purdue*, 2017 WL 784989, at *3-5; *Yodlee*, 2016 WL 204372, at *3–4 (no collateral estoppel despite prior construction of "identical" terms because issues were "somewhat different" in the prior case). Specifically, Amgen alleges in its Complaint that the "thiol-pair ratio" and "thiol-pair buffer strength" are calculated in the "solution" for claim 16—not in a "redox component." DE 1 ¶ 39. The prior case did not involve, address, or resolve this issue because the '138 Patent claims did not include a "preparation" or "solution." *See* Apotex Br. Ex. 3 (Claim Construction Opinion). This is a new issue requiring new analysis which was not actually litigated in the prior case. And Amgen did not have an opportunity to litigate these issues in the prior case because the '287 Patent had not issued and was not asserted there.

Second, there is no collateral estoppel because the construction of the thiol-pair terms in the '138 Patent was not a "critical and necessary" aspect of the judgment in the prior case. *FTC*, 785 F.3d at 482. Even where a prior court construed certain terms, collateral estoppel will not apply if the movant does not show that those constructions were a "critical and necessary" aspect of the judgment in the prior litigation. *Voter Verified, Inc. v. Election Sys. & Software LLC*, 887 F.3d 1376, 1383–84 (Fed. Cir. 2018); *Blitzsafe Texas, LLC v. Honda Motor Co., Ltd.*, No. 2:15-cv-1274-JRG-RSP, 2016 WL 4762083, at *6 (E.D. Tex. Sept. 13, 2016). Here, Apotex has

failed to allege, let alone prove, that the construction of the thiol-pair terms was a "critical and necessary" aspect of the prior judgment. Indeed, the Federal Circuit affirmed the prior judgment without any discussion of the thiol-pair terms. *See Amgen Inc. v. Apotex Inc.*, 712 F. App'x 985 (Fed. Cir. 2017); *see also* Apotex Br. Ex. 4 (findings of fact and conclusions of law do not discuss the "thiol-pair" terms).

Apotex cites *Nestle USA, Inc. v. Steuben Foods, Inc.*, 884 F.3d 1350 (Fed. Cir. 2018) for the proposition that a party such as Amgen is always "collaterally estopped from re-litigating the meaning of the same claim term in two related patents where the patents derive from the same patent application and share common terms." Apotex Br. at 14. This fails to compel a finding of collateral estoppel. *Nestle* was an appeal from the Patent Trial and Appeals Board's ("PTAB") construction of the term "aseptic" that differed from the Federal Circuit's construction of "aseptic" in a related patent. 884 F.3d at 1352. The Federal Circuit reversed the PTAB's inconsistent construction, because both patents used the claim term "in a similar fashion" and, "critically, the two patents also provide identical lexicography for the term 'aseptic' in their specifications." *Id.* at 1351-1352. *Nestle* does not apply here. First, the '138 and '287 Patents do not use the thiol-pair terms "in a similar fashion"—one claims a thiol-pair ratio and buffer strength in the "redox component," the other in the "solution" (*see, e.g.*, claim 16) or the "preparation" (*see, e.g.*, claim 1). Second, unlike "aseptic," the thiol-pair terms cannot be construed by simple reference to a "lexicography" within the specification. Rather, they must be construed with reference to the surrounding claim terms—and those differ between the '138 and '287 Patents. *See, e.g.*, Apotex Br. Ex. 3 at 7–8 (construing "thiol-pair ratio" with reference to surrounding claim terms).

2. Prosecution History Estoppel Does Not Apply to Amgen's Literal Infringement Claims, and Does Not Bar Amgen's Infringement Claims Under the Doctrine of Equivalents

Apotex asserts that Amgen cannot allege infringement under the doctrine of equivalents as to the '287 Patent claim terms "thiol-pair ratio" and "thiol-pair buffer strength" based on prosecution history estoppel. Apotex Br. at 11–13. This fails because Amgen asserts that "each of the elements in at least Claim 16 are satisfied in Apotex's process" (DE 1 ¶¶ 33–40), which states a claim of literal infringement that cannot be barred by prosecution history estoppel. *AccuScan, Inc.*, 76 F. App'x at 291; *Peach State Labs., Inc. v. Envtl. Mfg. Sols.*, 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)). Specifically, the Complaint cites a portion of Apotex's aBLA stating that 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." DE 1 ¶ 39 (discussing, as an example, independent claim 16).

Despite the literal infringement allegations in Amgen's Complaint that each element of Claim 16 is satisfied in Apotex's process (DE 1 ¶¶ 33–40), Apotex asserts that "Amgen's case is limited to infringement under the doctrine of equivalents." Apotex Br. at 12. To the extent that Apotex is challenging the sufficiency of Amgen's factual allegations of literal infringement, this too fails. Apotex Br. at 11. As discussed above, this Court is not bound to adopt—and should not adopt—the claim constructions given for the different '138 Patent in the parties' earlier case. Further, contrary to Apotex's assertion, the parties dispute whether Apotex's aBLAs "rely on any of the equations required by the '287 patent to determine oxidant and reductant concentration by calculating a 'thiol-pair ratio' or 'thiol-pair buffer strength.'" Apotex Br. at 11–12. This question of fact is not suitable for resolution on the pleadings. *Nalco*, 883 F.3d at 1349-50.

In any event, Apotex's prosecution history estoppel arguments fail even as to Amgen's infringement allegations under the doctrine of equivalents. Apotex argues that the claims of the '287 Patent require Apotex's aBLAs to "rely" on the equations of the '287 Patent specification for thiol-pair ratio and thiol-pair buffer strength even though such "reliance" is not a claim limitation. *See* Apotex Br. at 12. Specifically, Apotex points to the arguments Amgen made during prosecution on July 17, 2017, in its Response to April 17, 2017 Non-Final Office Action, where Amgen distinguished prior-art references that did not disclose the use of the equations "to calculate the thiol-pair ratio value or the thiol-pair buffer strength," and (in the case of two of the three prior-art references identified by the patent examiner) instead "rely on trial-and-error to determine redox conditions." Apotex Br. Ex. 9 at 12, 16–17.

The prosecution statements cited by Apotex do not give rise to prosecution history estoppel as to any of the asserted claims because those statements—directed at certain dependent claims—do not "evince a clear and unmistakable surrender of subject matter." *Intendis GMBH v. Glenmark Pharms. Inc., USA*, 822 F.3d 1355, 1365 (Fed. Cir. 2016). Amgen submitted the

application for the '287 Patent to the Patent Office on February 1, 2017. *See* Ex. 7 at 1. On April 17, 2017 the Patent Office Examiner issued a Non-Final Rejection of all claims as anticipated under 35 U.S.C. § 102(b), obvious under 35 U.S.C. § 103(a), and invalid for nonstatutory obviousness-type double patenting. *Id.* at 122-128. Amgen responded on July 17, 2017, making remarks responding to the rejections and also amending both the independent and dependent claims. *Id.* at 152–169 (Response to April 17, 2017 Non-Final Office Action). The Examiner responded on August 22, 2017 by withdrawing the rejections based on anticipation and obviousness, including its rejection of the dependent claims in view of Oliner prior art "In light of Applicants' amendment to the claims." *Id.* at 840–842 (Non-Final Office Action, 2). The Examiner also raised two non-final rejections: nonstatutory obviousness-type double patenting over the '138 Patent, and lack of written description under 35 U.S.C. § 112. *Id.* at 842-844. Amgen responded on September 8, 2017, again amending and making remarks about both the independent and dependent claims and also submitting a Terminal Disclaimer over the '138 Patent. *Id.* at 875–886 (Response to August 22, 2017 Non-Final Office Action). The amended claims were then allowed, and the '287 Patent issued. *Id.* at 939 (Issue Notification (Jan. 2, 2018)) .

Apotex now argues that Amgen's statements in the July 17, 2017 response as to dependent claims then-numbered 34 and 35 bar Amgen from asserting infringement under the doctrine of equivalents of all claims because Apotex does not "calculat[e]" or "rely on" certain equations. Apotex Br. at 11–12. This is incorrect. In its July 17, 2017 response Amgen first addressed reasons why the independent claim (then-claim 25) overcomes the prior art, Apotex Br. Ex. 9 at 10–11, and Amgen then specified that the dependent claims are also patentable for "additional reasons," *id.* at 11. Only then did Amgen make the arguments (specific to then-numbered claims 34 and 35) regarding "calculating" that Apotex points to. *See* Apotex Br. at 12. The statements on which Apotex relies are thus additional reasons for patentability rather than the only reasons why the '287 Patent dependent claims issued over the prior art. Further, in the July 17, 2017 response to the Examiner's rejection that dependent claims 34, 35, 45, and 46 were anticipated by Oliner, Amgen amended those dependent claims to require that the thiol-pair ratio or thiol-pair buffer strength be "calculated, and thus derived" from equations. *See* Apotex Br. Ex. 9 at 3–6. Apotex ignores the amendment (and the Examiner's withdrawal of its rejection in view of the amendment), and focuses on Amgen's statement in the same response that the Oliner

reference "does not disclose either of the above equations. Oliner does not even suggest that either equation is used to calculate the thiol-pair ratio value or the thiol-pair buffer strength." Apotex Br. at 8.

With respect to the independent claims, Amgen's July 2017 statements concerning the use of equations addressing only certain dependent claims are not a clear and unmistakable surrender of the scope of all claims. Because the statements that Apotex cites regarding equations concerned only the pending ***dependent*** claims, those statements have no bearing on the scope of the '287 Patent's ***independent*** claims. Amgen did not make any statements during prosecution suggesting that use of the equations is required to practice the methods of the independent claims. Rather, for the independent claims, Amgen overcame the April 2017 rejection for other reasons that have nothing to do with calculating the thiol-pair ratio or thiol-pair buffer strength according to the equations. *See* Apotex Br. Ex. 9 at 2, 10–11, 13–15.

With respect to the dependent claims (then-numbered 34 and 35), Amgen's statements are not a "clear and unmistakable" surrender of claim scope. Amgen responded to the April 2017 rejection by doing several things: it made amendments and arguments with respect to the independent claims, it amended the dependent claims to include the limitation that the thiol-pair ratio or thiol-pair buffer strength is "calculated, and thus derived,"[6] and it made remarks specific to the dependent claims. *See* Apotex Br. Ex. 9. The Examiner then withdrew the rejections to both the independent and the dependent claims "in light of Applicants' amendment to the claims." Ex. 7 at 842. In these circumstances, Apotex cannot assert that Amgen's remarks regarding the dependent claims "clearly and unmistakably surrender" the scope of any claims, particularly because Amgen overcame the prior art on other grounds. Further, the prosecution history is clear that the "thus derived" limitation (as opposed to the calculated limitation) was not necessary to overcome Oliner and to issue the claims because the Examiner allowed the dependent claims to ultimately issue even after that "thus derived" language was removed in Amgen's September 2017 amendments. *See* Ex. 7 at 877–8; '287 Patent.

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[6] For example, then-claim 34 was amended as follows (emphasis added): "The method of claim 25, wherein the thiol-pair ratio is calculated, ***and thus derived***, according to the following equation:

$$\frac{[the\ reductant]^2}{[the\ oxidant]}$$."

Finally, as discussed above, the Court need not reach this issue to resolve Apotex's Motion. Given the disputes between the parties as to the import of statements made during the prosecution of the '287 Patent, proceeding through the "fact intensive framework" of determining the existence and scope of any estoppel is better suited for claim construction—when the Court already must consider the full prosecution history—than on the pleadings. *See Amgen Inc. v. Alkem Laboratories Ltd.*, No. 17-cv-815-GMS, 2017 WL 6493150, at *2–3 (D. Del. Dec. 19, 2017) (citing *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co*, 344 F.3d 1359, 1366-67 (Fed. Cir. 2003)) (denying motion for judgment on the pleadings based on prosecution history estoppel where "there are material disputes of fact between the parties concerning the prosecution history").

3. *Coherus* Is Inapposite

Apotex asserts that the outcome here should be informed by a recent decision in a Delaware case between Amgen and Coherus, a different biopharmaceutical company with a different manufacturing process. Apotex Br. at 15. This is incorrect. *Coherus* does not govern here because it is factually and legally distinct. In *Coherus*, Amgen argued that the salts Coherus uses in its manufacturing process infringe the claims of yet another patent—U.S. Patent 8,273,707—*solely* under the doctrine of equivalents.[7] *See* Memorandum Order, *Amgen Inc. v. Coherus Biosciences Inc.*, C.A. No. 17-cv-546-LPS-CJB (D. Del. Mar. 26, 2018) (attached as Ex. 8) at 6–8. The district court in Delaware found that prosecution history estoppel barred this claim. *Id*. That ruling is currently on appeal before the Federal Circuit. No. 18-1993 (Fed. Cir. 2018). Apotex argues that the Delaware court's ruling impels this Court to dismiss Amgen's Complaint. Apotex Br. at 15. But Amgen alleges literal infringement of the '287 Patent, as discussed above, and thus prosecution history estoppel does not apply.

Further, a court's infringement determination is specific to the device or process before that court and requires determination on its own facts. *See Del Mar Avionics, Inc. v. Quinton Instrument Co.*, 836 F.2d 1320, 1324 (Fed. Cir. 1987); *A.B. Dick Co. v. Burroughs Corp.*, 713 F.2d 700, 704 (Fed. Cir. 1983). A finding in one case that prosecution history estoppel prevents a patent holder from asserting infringement under the doctrine of equivalents against an accused

[7] Apotex wrongly asserts the Coherus case involved "another patent that is related." Apotex Br. at 15. There is no relationship between the '287 Patent and the patent at issue in the Coherus litigation beyond the fact that both are owned by Amgen.

process does not preclude a finding of infringement under the doctrine of equivalents for a different process in a later case, even when the same patent and claim terms are at issue in both cases. *See Pfaff v. Wells Elec., Inc.*, 5 F.3d 514, 519–20 (Fed. Cir. 1993). Here, the same patent is not even at issue.

Moreover, Apotex fails to mention that another district court expressly declined to rule on the argument that prosecution history estoppel barred Amgen from asserting infringement of the patent at issue in *Coherus* under the doctrine of equivalents. *See* Ex. 1 (Order on Defendants' Motion for Judgment on the Pleadings, *Amgen Inc. v. Mylan Inc.*, No. 2:17-cv-01235, DE 170 (W.D. Pa. Nov. 15, 2018)). Instead, that court has agreed to construe the terms of the '707 Patent independently because, in that case, the allegedly infringing process is different than the *Coherus* process and Amgen asserted a different theory of liability—literal infringement. So too here, Apotex practices a different process than in *Coherus*; and Amgen alleges literal infringement. The situation before this Court is factually and legally distinct from *Coherus* so the *Coherus* decision should have no bearing on this Court's decision.

IV. REQUEST FOR HEARING

Amgen respectfully requests oral argument of this Motion before the Court. Oral argument would offer the opportunity for Amgen to discuss in greater detail why Apotex's arguments as to collateral estoppel and prosecution history estoppel fail; and also why the parties have claim construction disputes as to the '287 Patent terms and discovery is needed as to Apotex's process beyond what Apotex produced in the parties' prior case before March 2016. Amgen estimates that 45 minutes would be required.

V. CONCLUSION

Amgen respectfully requests that the Court deny Apotex's Motion to Dismiss.

Dated: January 23, 2019

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CERTIFICATE OF SERVICE

I HEREBY CERTIFY that on January 23, 2019, a true and correct copy of the foregoing was electronically filed with the Clerk of the Court using CM/ECF. Copies of the foregoing document will be served upon interested counsel either via transmission of Notices of Electronic Filing generated by CM/ECF or in some other authorized manner for those counsel or parties who are not authorized to receive electronically Notices of Electronic Filing.

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