**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.

**DEFENDANTS APOTEX INC. AND APOTEX CORP.'S MEMORANDUM IN SUPPORT OF MOTION TO DISMISS PURSUANT TO FED. R. CIV. P. 12(b)(6)**

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## I. INTRODUCTION

Pursuant to Federal Rule of Civil Procedure 12(b)(6), Defendants Apotex Inc. and Apotex Corp. (collectively, "Apotex") move to dismiss the Complaint filed by Plaintiffs Amgen Inc. and Amgen Manufacturing Limited (collectively, "Amgen") for failure to state a claim upon which relief can be granted. Unhappy with the outcome in this Court before Judge Cohn in 2016, this action is Amgen's latest attempt to thwart Apotex from marketing its biosimilar versions of Amgen's Neulasta® and Neupogen® products.

Apotex filed its abbreviated Biologic License Applications ("aBLAs") at the U.S. Food & Drug Administration ("FDA") in 2014 and 2015, upon which Amgen alleged in two prior litigations that Apotex's manufacturing process infringed U.S. Patent No. 8,952,138 ("the '138 patent"). In those prior cases—Nos. 15-61631-CIV-COHN/SELTZER and 15-62081-CIV-COHN/SELTZER (consolidated)—this Court found, and the Federal Circuit affirmed, that Apotex's manufacturing process did not infringe any claims of the '138 patent.

Having lost its infringement case against Apotex on the '138 patent, in 2017 Amgen filed another patent application that issued on January 2, 2018 as U.S. Patent No. 9,856,287 ("the '287 patent"). The '287 patent, which claims priority to the '138 patent, has an identical specification and many of the same claim limitations as the '138 patent. On August 7, 2018, Amgen filed this action, taking the untenable position that Apotex's manufacturing process—the very same process Amgen accused of infringing the '138 patent—now infringes the '287 patent. There can be no dispute concerning the steps Apotex uses in its accused manufacturing process, as Amgen obtained discovery of Apotex's aBLAs in the prior actions. Instead, the sole legal inquiry is whether the claims of the '287 patent can cover Apotex's accused manufacturing process. Dismissal is appropriate because Amgen's Complaint fails to raise any substantive legal question as to whether Apotex's manufacturing process can infringe any claim of the '287 patent.

In general, the claims of the '287 patent relate to unfolding and refolding proteins expressed in bacterial cells in order to obtain properly folded proteins on an industrial scale. More specifically, the claims of the '287 patent require "an amount of oxidant" and "an amount of reductant," that "the amounts of the oxidant and the reductant are related through a thiol-pair ratio and a thiol-pair buffer strength" and that the "thiol-pair buffer strength maintains the solubility of the solution."

Two legal issues lead to a dispositive determination of non-infringement here, both

independently and collectively. The first is prosecution history estoppel, whereby a party is precluded from expanding the scope of a patent's claims to cover subject matter that was surrendered during prosecution of the patent. The second is issue preclusion, whereby a party who argues for and receives a proposed claim construction is collaterally estopped from re-litigating the meaning of that same claim term. Simply put, since this Court adopted Amgen's proposed construction in entering judgment for Apotex that was affirmed on appeal, that legal determination is law of this case. These well-established legal principles demonstrate that Amgen has failed to state a claim for which relief can be granted, and serve as the basis for Apotex's Rule 12(b)(6) motion.

As to the first, during prosecution of the '287 patent, Amgen argued at the U.S. Patent & Trademark Office ("PTO") that the claims of the '287 patent were patentable over a prior art process for protein refolding that utilized an oxidant and reductant. Amgen successfully argued at the PTO that the claims of the '287 patent do not merely require the use of an oxidant and reductant for protein refolding, but rather, require the use of equations whereby the amounts of oxidant and reductant are optimized by calculating a "thiol-pair ratio" and "thiol-pair buffer strength." Having successfully argued at the PTO that the use of the equations relating thiol-pair ratio and thiol-pair buffer strength were critical for patentability, Amgen cannot now allege that Apotex's manufacturing process—which uses no such equations—infringes the '287 patent. Indeed, like the prior art that Amgen overcame during prosecution of the '287 patent at the PTO, Apotex's manufacturing process merely includes an oxidant and reductant but does not rely on any equations that optimize the amounts of oxidant and reductant using a "thiol-pair ratio" or "thiol-pair buffer strength." Thus, Amgen's Complaint fails to state a claim upon which relief can be granted.

As to the second legal principle, Amgen's Complaint alleges that the amounts of oxidant and reductant used in Apotex's manufacturing process are related through a thiol-pair ratio and thiol-pair buffer strength that is calculated *in the refolding solution*. However, during the prior actions involving the '138 patent, Amgen argued successfully during claim construction that the "thiol-pair ratio" and "thiol-pair buffer" can only be based on the concentrations of reductants and oxidants *in the redox component*. Having argued for the construction of a claim term that was adopted by this Court in prior actions involving the related '138 patent, Amgen is estopped from now arguing for a different construction in this action. Applying Amgen's claim

construction from the prior actions to Apotex's manufacturing process there can be no infringement of the '287 patent as a matter of law, and Amgen's Complaint therefore fails to state a claim upon which relief can be granted.

Apotex was found to not infringe the predecessor '138 patent, and clearly does not infringe the follow-on '287 patent either. Amgen did not file this action on its merits, but rather in order to make it more costly for a biosimilar applicant to offer lower-cost medications to the public. Apotex's motion to dismiss Amgen's Complaint should be granted.

## II. FACTUAL BACKGROUND

### A. The Prior Actions Involving the '138 Patent

This is the second round of litigation filed by Amgen concerning Apotex's aBLAs that seek FDA-approval for biosimilar versions of Amgen's Neulasta® and Neupogen® products. The prior actions were presided over by Judge Cohn in this district, and the Court found that Apotex's manufacturing process for its biosimilar products did not infringe any claims of the '138 patent. *See* Exh. 4. The U.S. Court of Appeals for the Federal Circuit affirmed this Court's ruling. Exh. 1.

Amgen now alleges that Apotex's manufacturing process—the same manufacturing process that Amgen accused of infringing '138 patent in the prior actions—infringes the '287 patent. The '287 patent asserted by Amgen in this action has an identical specification and includes many of the same claim limitations as the '138 patent. Notably, claim 1 of the '138 patent includes the terms "thiol pair ratio" and "redox buffer strength" (i.e., thiol-pair buffer strength):

> 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.

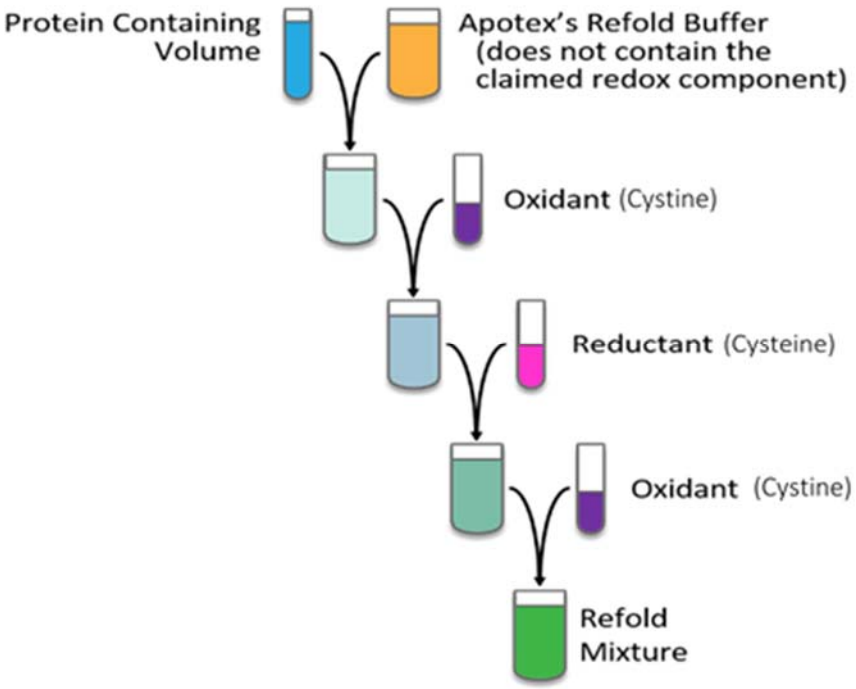
Exh. 11 at 17:47-58.

During claim construction in the prior actions, Amgen argued that the thiol-pair ratio and redox buffer strength (i.e., thiol-pair buffer strength) could only be calculated using the concentrations of reductant and oxidant that are present *in the redox component*:

> The parties dispute how to calculate the values of the concentration of the reductant and the concentration of the oxidant, which values are then used to calculate the "final thiol-pair ratio" and "redox buffer strength" according to Equations 1 and 2, respectively. *Amgen proposes that the values be based on the concentrations of reductants and oxidants in the redox component*, as defined by the equations. Apotex, on the other hand, proposes that the values are based on concentrations of reductants and oxidants in the refold mixture, which is at odds with the language of the claim and the teachings of the specification.

Exh. 2 at 8 (emphasis added). Amgen's proposed constructions and arguments that the thiol-pair ratio and redox buffer strength can only be calculated *in the redox component* were adopted by this Court in the prior actions involving the '138 patent. Exh. 3 at Appx7-9.

This Court heard extensive testimony in the prior actions concerning Apotex's accused manufacturing process, an overview of which is set forth in the following schematic diagram:



Exh. 4 at Appx20. As shown above, Apotex's manufacturing process refolds the filgrastim protein by way of a step-wise addition of oxidant, reductant, and (again) oxidant to a protein containing volume in order to form a refold mixture.

In the first step, a Refolding Buffer (orange) is created and placed in a refolding vessel, followed by the slow addition of solubilized and reduced inclusion bodies (royal blue) over 90 minutes. *Id.* at Appx21; Exh. 5 at Appx5904-5905; Exh. 6 at 5597-5598.

Then, an oxidant (Cystine Solution, purple) and a reductant (Cysteine Solution, pink) are added to the Refolding Buffer in a stepwise manner. Exh. 4 at Appx21; *see* Exh. 5 at Appx5904-5905; Exh. 6 at Appx5597-5598. According to Apotex's aBLAs:

- First, an oxidant (360 mL of Cystine Solution, purple);
- Second, a reductant (32 mL of Cysteine Solution, pink); and
- Third, an oxidant (80 mL of Cystine Solution, purple),

are added to Apotex's Refolding Buffer. Exh. 4 at Appx21; *see* Exh. 5 at Appx5904-5905; Exh. 6 at Appx5597-5598. Apotex's aBLAs further specify that the oxidant and reductant are added separately and in a stepwise manner to the Refolding Buffer for defined reasons: the first Cystine addition is to "neutralize the DTT[,]" next, Cysteine is added to "break S-H (thiosulfide) bonds[,]" and then the second Cystine addition "reduce[s] the free S moieties so they [are] not available to form intramolecular disulfide bonds after refolding." Exh. 4 at Appx21. After the stepwise addition of the oxidant and reductant (Cystine and Cysteine Solutions, respectively), Apotex incubates the refold mixture for at least 18 hours. *Id.*

In the prior actions, this Court found it was undisputed that Apotex's manufacturing process does not literally include the claimed redox component that has an oxidant (Cystine) and reductant (Cysteine) combined together outside the refold mixture. *Id.* at Appx29.

**B. The Present Action**

Amgen filed the Complaint in the present action on August 7, 2018, which alleges that Apotex's manufacturing process disclosed in its aBLAs infringes at least one claim of the '287 patent. The '287 patent claims priority to the '138 patent, and shares the same specification. The '287 patent issued with 30 claims, with claims 1, 10, 16, and 26 being the independent claims. The claims of the '287 patent are similar to those of the '138 patent, with many of the same limitations. Specifically, each and every claim of the '287 patent requires that "the amounts of the oxidant and the reductant are related through a thiol-pair ratio and a thiol-pair

buffer strength" and that the "thiol-pair buffer strength maintains the solubility of the solution." Exh. 7 at 18:21 – 21:12. The '287 patent specification and arguments Amgen submitted to the PTO during the prosecution of the '287 patent make clear that these claim limitations were essential for patentability over the prior art.

In its Complaint, Amgen specifically addressed claim 16 of the '287 patent, which recites:

> 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.

*Id.* at 19:54 – 20:4.

The '287 patent acknowledges that it was well known in the prior art that when refolding proteins, especially proteins with cysteine residues, "it is often necessary to accomplish the refolding in an environment which allows correct formation of disulfide bonds (e.g., a redox system)." *Id.* at 1:53-57. Further, it is undisputed that protein refolding using a redox system (i.e., an oxidant and reductant) was also well known in the prior art. The '287 patent differentiates the claimed methods from the prior art through the use of equations to calculate a "thiol-pair ratio" and "thiol-pair buffer strength," specifically stating that:

> Until the present disclosure, specific relationships had not been provided for thiol buffer strength, thiol-pair ratio chemistry, and protein concentration with respect to complex proteins that related to efficiency of protein production.

* * *

> Prior to the present disclosure a specific controlled investigation of the independent effects of thiol-pair ratio and thiol-pair buffer strength had not been disclosed for complex proteins.

Exh. 7 at 4:18-22 and 27-30. Thus, according to the '287 patent, the alleged novelty of Amgen's invention was the fact that the prior art had not related the concentrations of oxidants and reductants through a "thiol-pair ratio" and "thiol-pair buffer strength."

During prosecution of the '287 patent at the PTO, Amgen also argued that its claims were patentable over the prior art because "the amounts of the oxidant and reductant are related through a thiol-pair ratio and a thiol-pair buffer strength" and because the "thiol-pair buffer strength maintains the solubility of the solution." The PTO initially rejected Amgen's patent application that would eventually issue as the '287 patent as anticipated by U.S. Patent No. 7,138,370 ("Oliner"), which disclosed refolding proteins with an oxidant and reductant (e.g., cysteine and cystamine). Exh. 8 at 2. The PTO rejected the same claims as obvious over U.S. Pub. 2007/02348860 ("Schlegl") in view of Hevehan.[1] *Id.* at 3-4. Schlegl discloses methods for refolding proteins with an oxidant and reductant (e.g., GSSG and GSH). *Id.* Further, Hevehan disclosed methods of refolding proteins with a oxidant and reductant (e.g., GSSH and DTT) and concluded the protein yields strongly depended on thiol concentrations of the renaturation buffer. *Id.*

In response to these rejections, Amgen amended the claims to require that "the amounts of the oxidant and reductant are related through a thiol-pair ratio and a thiol-pair buffer strength" and the "thiol-pair buffer strength maintains the solubility of the preparation." *See, e.g.*, Exh. 9 at 2, claim 25. Amgen acknowledged that Oliner taught a protein refolding process with an oxidant and reductant (i.e., cysteine and cystamine), but argued that amended claim 25 was patentable over Oliner because:

> **Second, Oliner fails to disclose that the thiol-pair buffer strength maintains the solubility of the preparation** and is effected based on a desired amount yield of properly refolded protein.
>
> Moreover, Oliner fails to disclose or suggest that the thiol-pair ratio and thiol-pair buffer strength are such that incubating the refold

[1] Hevehan refers to DL Hevehan & Clark E. De Bernardez, *Oxidative renaturation of lysozyme at high concentrations*, 54 BIOTECHNOL BIOENG. 221-30 (1996).

> mixture results in a consistent yield of the properly refolded proteins. **Thus, as distinguished from 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.

*Id.* at 10-11 (emphasis added). Moreover, concerning the use of equations to calculate a "thiol-pair ratio" and "redox buffer strength," Amgen argued to the PTO that:

> Oliner does not disclose either of the above equations [for thiol-pair ratio and thiol-pair buffer strength]. **Oliner does not even suggest that either equation is used to calculate the thiol-pair ratio value or the thiol-pair buffer strength**. It 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. **Clearly, Oliner did not use the equations to derive the claimed thiol-pair ratio range, or the thiol-pair buffer strength**.

*Id.* at 12 (emphasis added).

Amgen made similar arguments to the PTO in order to overcome the obviousness rejection over Schlegl in view of Hevehan. Specifically, Amgen argued that:

> Schlegl fails to disclose that the amounts of the oxidant and the reductant are related through a thiol-pair ratio and a thiol-pair buffer strength. Also, Schlegl fails to disclose that the thiol-pair buffer strength maintains the solubility of the preparation and is effected based on a desired amount yield of properly refolded protein.
>
> * * *
>
> Hevehan does not disclose that the thiol-pair buffer strength maintains the solubility of the preparation and is effected based on a desired amount yield of properly refolded protein.

*Id.* at 14. Moreover, concerning the use of equations to calculate a "thiol-pair ratio" and "redox buffer strength," Amgen argued to the PTO that:

> Schlegl does not disclose either equation [to calculate a thiol-pair ratio and thiol-pair buffer strength]. Thus, Schlegl does not even suggest that either equation is used in deriving the thiol-pair ratio range or the thiol-pair buffer strength.
>
> Further, the Action relies on portions of both Schlegl and Hevehan as disclosing the claimed thiol-pair ratio range of 0.001 to 100 calculated according to the equation $\frac{[the\ reductant]^2}{[the\ oxidant]}$. However, Hevehan, like Schlegl, also fails to disclose any equation. Further,

> Hevehan, like Schlegl fails to teach the efficient refolding of proteins can be achieved by the thiol-pair ratio and thiol-pair buffer strength.
>
> Significantly, both references instead admittedly rely on trial-and-error to determine redox conditions that can be used for refolding the specifically disclosed proteins. This trial and error contrasts to the methods of claims 34 and 35 (and the other claimed methods herein).

*Id.* at 16-17. Thus, Amgen left no doubt that despite the prior art disclosing a protein refolding process with an oxidant and reductant, it was relating the amounts of the oxidant and reductant through a thiol-pair ratio and thiol-pair buffer strength using the equations disclosed in the '287 patent, and specifically controlling these parameters, that distinguished the claimed invention from the prior art.

And it was relating the amounts of the oxidant and reductant through a thiol-pair ratio and thiol-pair buffer strength using the equations disclosed in the '287 patent that led the PTO to allow the claims of the '287 patent. The Notice of Allowability states that: "[t]he following is an examiner's statement of reasons for allowance: 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." Exh. 10 at 2. Thus, to state a valid claim against Apotex, Amgen must allege that Apotex's manufacturing process relates to the critical "thiol-pair ratio or strength" used to maintain solubility, as set forth in the '287 patent. Because Amgen has not (and cannot) assert such allegations against Apotex, the Complaint should be dismissed with prejudice.

## III. ARGUMENT

This Court should dismiss this case at the pleading stage because it does not state a plausible infringement claim. Taking into account Amgen's arguments made in the prior actions, this Court's factual findings in the prior actions concerning Apotex's aBLAs, and Amgen's arguments to the PTO concerning the patentability of the '287 patent—all of which the Court can consider in deciding this motion—Apotex's accused manufacturing process does not infringe the '287 patent as a matter of law.

### A. Legal Principles

To withstand a motion to dismiss under Rule 12(b)(6), a complaint must contain "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). Although a complaint "does not need detailed factual allegations," it must provide "more than labels and conclusions, and a formulaic recitation of the elements of a cause of action will not do . . . ." *Id.* at 555; *see Ashcroft v. Iqbal,* 556 U.S. 662, 678 (2009) (explaining that Rule 8(a)(2)'s pleading standard "demands more than an unadorned, the-defendant-unlawfully-harmed-me accusation"). In the same vein, a complaint may not rest on "'naked assertion[s]' devoid of 'further factual enhancement.'" *Iqbal,* 556 U.S. at 678 (quoting *Twombly,* 550 U.S. at 557 (alteration in original)). "Factual allegations must be enough to raise a right to relief above the speculative level . . . ." *Twombly*, 550 U.S. at 555. These elements are required to survive a motion brought under Rule 12(b)(6), which requests dismissal for "failure to state a claim upon which relief can be granted."

When reviewing a motion under Rule 12(b)(6), a court, as a general rule, must accept the plaintiff's allegations as true and evaluate all plausible inferences derived from those facts in favor of the plaintiff. *See Miccosukee Tribe of Indians of Fla. v. S. Everglades Restoration All.*, 304 F.3d 1076, 1082-88 (11th Cir. 2002); *AXA Equitable Life Ins. Co. v. Infinity Fin. Grp., LLC*, 608 F. Supp. 2d 1349, 1353 (S.D. Fla. 2009). However, this tenet does not apply to legal conclusions, and courts "are not bound to accept as true a legal conclusion couched as a factual allegation." *Twombly,* 550 U.S. at 555 (quoting *Papasan v. Allain*, 478 U.S. 265, 286 (1986)); *see Iqbal,* 556 U.S. at 678; *Thaeter v. Palm Beach Cty. Sheriff's Office*, 449 F.3d 1342, 1352 (11th Cir. 2006). Importantly, a court ruling on a Rule 12(b)(6) motion may consider not just the complaint itself, but also such documents integral thereto. *See, e.g., AstraZeneca Pharm. LP v. Apotex Corp.*, 669 F.3d 1370, 1378 n.5 (Fed. Cir. 2012); *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) ("[A] document outside the four corners of the complaint may still be considered if it is central to the plaintiff's claims and is undisputed in terms of authenticity.") (citing *Horsley v. Feldt*, 304 F.3d 1125, 1135 (11th Cir. 2002)).

A court ruling on a Rule 12(b)(6) motion may also consider the prosecution history of the patent-in-suit. *See Genetic Techs. Ltd. v. Bristol-Myers Squibb Co.*, 72 F. Supp. 3d 521, 526 (D. Del. 2014) ("A court may also take judicial notice of the prosecution histories, which are 'public records.'"), *aff'd sub nom., Genetic Techs. Ltd. v. Merial L.L.C.*, 818 F.3d 1369 (Fed. Cir. 2016).

**B. The Complaint Fails to State a Claim for Infringement**

The claims of the '287 patent are directed to methods of refolding proteins that require

amounts of an oxidant and a reductant to be related through a thiol-pair ratio and thiol-pair buffer strength, and that the thiol-pair buffer strength maintains the solubility of the solution. As explained above, Amgen accuses Apotex's manufacturing process of infringement. However, for Apotex's manufacturing process to infringe, Apotex's aBLAs must relate the amounts of oxidant and reductant by calculating a thiol-pair ratio and thiol-pair buffer strength, and must use the thiol-pair buffer strength to maintain the solubility of the refold mixture solution. As Apotex's aBLAs and this Court's findings from the prior actions make clear, Apotex's aBLAs describe a manufacturing process that includes no such reliance on any of Amgen's equations for "thiol-pair ratio" or "thiol-pair buffer strength," or that Apotex maintains "the solubility of the refold mixture using a thiol-pair buffer strength." Thus, Apotex's manufacturing process does not literally infringe any claims of the '287 patent.

Moreover, Amgen is estopped from broadening the claims of the '287 patent to cover Apotex's manufacturing process because of arguments and claim amendments that Amgen made during prosecution of the '287 patent, and because broadening the claims to cover Apotex's manufacturing process would improperly ensnare the prior art. Thus, Apotex's manufacturing process cannot infringe any claims of the '287 patent under the doctrine of equivalents.

**1. Apotex's Manufacturing Process Does Not Relate an Oxidant and Reductant Through a Thiol-Pair Ratio and Thiol-Pair Buffer Strength or Maintain the Solubility of the Solution Through a Thiol-Pair Buffer Strength**

Apotex's manufacturing process cannot infringe any claim of the '287 patent because Apotex's aBLAs do not rely on any equations that determine the amounts of oxidant and reductant using a "thiol-pair ratio" or "thiol-pair buffer strength," and Apotex's manufacturing process therefore "does not maintain the solubility of the refold mixture using a thiol-pair buffer strength." *See* Exhs. 5-6. Amgen cannot now argue otherwise, as Amgen had access to Apotex's aBLAs and manufacturing information in the prior actions, and Amgen's Complaint even cites to the publicly available documents from Apotex's aBLAs. *See* D.E. 1 at ¶¶ 38-39. During the prior actions involving the '138 patent, Amgen admitted that Apotex's accused manufacturing process does not literally include a "redox component" or "redox buffer strength," and instead relied on an infringement theory under the doctrine of equivalents. *See* Exh. 4 at Appx28-29. Thus, there can be no dispute that Apotex's aBLAs do not rely on any of the equations required by the '287 patent to determine oxidant and reductant concentrations by

calculating a "thiol-pair ratio" or "thiol-pair buffer strength," or rely on Amgen's equations in order to maintain the solubility of the refold mixture using a thiol-pair buffer strength. Consequently, Amgen's case is limited to infringement under the doctrine of equivalents.

As a matter of law, Amgen is barred from alleging Apotex's manufacturing process infringes any claim of the '287 patent under the doctrine of equivalents. During prosecution of the '287 patent, Amgen faced rejections from the PTO over prior art references (*i.e.,* Oliner, Schlegl, and Hevehan) that used a protein refolding process with an amount of an oxidant and reductant, similar to Apotex's manufacturing process. *See* Exh. 8. Amgen distinguished the '287 patent from the prior art by amending its claims and arguing that the prior art did not relate the amounts of oxidant and reductant by calculating a "thiol-pair ratio" and "thiol-pair buffer strength." *See* Exh. 9. Indeed, Amgen specifically argued that it was improper for the PTO to use hindsight gleaned from Amgen's invention "to select data from a single example in Oliner, and insert that data into the claimed equations [of the '287 patent] in an attempt to show the claimed thiol-pair ratio range." *Id.* at 12. There can be no dispute that, like the Oliner prior art, Apotex's aBLAs do not rely on any of the equations required by the '287 patent to determine oxidant and reductant concentrations by calculating a "thiol-pair ratio" or "thiol-pair buffer strength." Therefore, Amgen's infringement claims against Apotex are impermissibly based upon similarly selecting data from Apotex's aBLAs, "and insert[ing] that data into the claimed equations [of the '287 patent] in an attempt to show the claimed thiol-pair ratio range." *Id*. In other words, for the very same reasons that Amgen previously argued that the claims of the '287 patent were patentable over the prior art, Apotex's manufacturing process does not satisfy the limitations of any claim of the '287 patent.

Amgen is therefore estopped from relying upon the doctrine of equivalents to expand the scope of the claims of the '287 patent to cover subject matter that was surrendered during prosecution of the '287 patent. *See*, *e.g.*, *Trading Techs. Int'l, Inc. v. Open E Cry, LLC*, 728 F.3d 1309, 1323 (Fed. Cir. 2013); *Conoco, Inc. v. Energy & Envtl. Int'l, L.C.*, 460 F.3d 1349, 1363 (Fed. Cir. 2006) (explaining that prosecution history estoppel can arise either through an amendment to the claim or through argument); *Texas Instruments, Inc. v. U.S. Int'l Trade Comm'n*, 988 F.2d 1165, 1174-75 (Fed. Cir. 1993) ("By expressly stating that claim 12 was patentable because of the opposite-side gating limitation, particularly in light of their previous admission that same-side gating was known in the art, the inventors unmistakably excluded the

same-side gating as an equivalent."); *see also Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722 (2002).

Amgen is similarly barred from broadening the claims of the '287 patent to encompass any process that, like the prior art Amgen overcame during prosecution, merely discloses amounts of oxidant and reductant but fails to relate those amounts using a "thiol-pair ratio" or "thiol-pair buffer strength." *See Intendis GMBH v. Glenmark Pharm. Inc., USA*, 822 F.3d 1355, 1363 (Fed. Cir. 2016) ("A patentee may not assert 'a scope of equivalency that would encompass, or ensnare, the prior art.'" (quoting *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d. 1314, 1322 (Fed. Cir. 2009))); *see also Wilson Sporting Goods Co. v. David Geoffrey & Assocs.*, 904 F.2d 677, 684 (Fed. Cir. 1990) ("[S]ince prior art always limits what an inventor could have claimed, it limits the range of permissible equivalents of a claim.")). Indeed, the prior art references that Amgen overcame during prosecution of the '287 patent all disclosed a protein refolding process with an amount of an oxidant and reductant. *See* Exh 8.

To be clear, in its Complaint, Amgen does not and cannot point to anywhere in Apotex's aBLAs where Apotex relates the oxidant and reductant used in its stepwise refolding method through a "thiol-pair ratio" or "thiol-pair buffer strength," or maintains the solubility of its refolding mixture using a thiol-pair buffer strength. *See* D.E. 1 at ¶¶ 38-39. As discussed above, Apotex's manufacturing process discloses nothing more than an amount of an oxidant and reductant used in its stepwise protein refolding method. Indeed, this is exactly the portion of Apotex's aBLA that Amgen points to for infringement. *See* D.E. 1 at ¶¶ 37-39. This is improper. In doing so, Amgen has improperly broadened the claims of the '287 patent to ensnare the very prior art it overcame during prosecution.

**2. Amgen Is Estopped from Alleging That the Thiol-Pair Ratio and Thiol-Pair Buffer Strength Are Calculated in Apotex's Refold Mixture**

Even if it were proper to look at just the amounts of oxidant and reductant in Apotex's manufacturing process to calculate the thiol-pair ratio and thiol-pair buffer strength, Amgen still cannot establish that Apotex's process infringes any claim of the '287 patent. In its Complaint, Amgen's allegations that Apotex's manufacturing process includes the required "thiol-pair ratio" and "thiol-pair buffer strength" rely solely on the concentrations of oxidant and reductant in Apotex's *refold mixture*. *See* D.E. 1 at ¶¶ 38-39 ("In . . . *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." (citing Exh. 5 at Appx5904–5907). These allegations in Amgen's Complaint directly contradict its position in the prior actions concerning the '138 patent, in which Amgen argued successfully that the "thiol-pair ratio" and "thiol-pair buffer strength" can only be calculated *in the redox component*.

A party is 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. *See Nestle USA, Inc. v. Steuben Foods, Inc.*, 884 F.3d 1350, 1352 (Fed. Cir. 2018); *see also SightSound Techs., LLC v. Apple Inc.*, 809 F.3d 1307, 1316 (Fed. Cir. 2015) ("Where multiple patents 'derive from the same parent application and share many common terms, we must interpret the claims consistently across all asserted patents.'" (quoting *NTP, Inc. v. Research In Motion, Ltd.*, 418 F.3d 1282, 1293 (Fed. Cir. 2005))).

During claim construction in the prior actions involving the '138 patent, Amgen argued extensively that the patent specification did not support Apotex's proposed construction that the thiol-pair ratio and thiol-pair buffer strength are calculated in the refold mixture. *See* Exh. 2 at 7-12. Instead, Amgen argued a claim construction where the thiol-pair ratio and thiol-pair buffer strength are calculated in the redox component. The court adopted Amgen's construction.

Further, it is undisputed that the '138 and '287 patents share an identical specification and common claim terms. Indeed, the claims of both patents require a "thiol-pair ratio," "thiol-pair buffer strength" (i.e., redox buffer strength), and "refolding at protein concentrations of 2.0 g/L or greater." *Compare, e.g.*, Exh. 7 ('287 patent), claims 16 and 18, *with* Exh. 11 ('138 patent), claim 1.

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 it did in the prior actions for the '138 patent. Thus, Amgen is estopped from arguing that the thiol-pair ratio and thiol-pair buffer strength are calculated in Apotex's refold mixture. Because Amgen's only allegation is that Apotex's manufacturing process infringes the claims of the '287 patent because it relates the oxidant and reductant through a thiol-pair ratio and thiol-pair buffer strength in the refold mixture (called refold solution in the Complaint), Amgen cannot establish infringement. *See* D.E. 1 at ¶¶ 38-39. Consequently, Amgen fails to state a claim for infringement for this additional reason.

**C. The Court Can Grant Apotex's Motion Now**

This motion can and should be decided now. First, Amgen needs no additional discovery. Amgen received Apotex's full aBLAs and manufacturing information during the course of the prior actions. Indeed, Amgen's Complaint cites to portions of Apotex's aBLAs that became publicly available during the prior actions. *See id.* at ¶¶ 35-40. These aBLA documents describe Apotex's manufacturing process in sufficient detail to establish, as a matter of law, that there can be no infringement of the '287 patent. And it is Apotex's aBLAs that control the infringement inquiry. *See*, *e.g.*, 42 U.S.C. § 262 (*l*)(3)(A)(i) (addressing possible infringement through the unlicensed "making, using, offering to sell, selling, or importing in the United States of the biological product that is the subject of the subsection (k) application"); 35 U.S.C. §§ 271(e)(2), (e)(2)(C)(i) (filing an aBLA "shall be an act of infringement").

Second, there is no need to wait for the claim construction process in this case. The 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. As described above, it is Amgen's amendments and arguments during prosecution of the '287 patent and Amgen's adopted claim construction arguments in the prior actions that serve as the basis for this motion.

Third, at least one court has granted a motion to dismiss that involved similar circumstances. In *Amgen v. Coherus*, the district court granted Coherus's motion to dismiss for failure to state a claim in an action where Amgen alleged that Coherus's filing of an aBLA to market a biosimilar version of Amgen's Neulasta® product infringed another patent that is related. *See Amgen Inc. v. Coherus Biosciences, Inc.*, No. 17-546-LPS-CJB, D.I. 72 (D. Del. Mar. 26, 2018) (adopting report and recommendation (D.I. 50, 59)). In granting Coherus's motion, the court found that Amgen could not broaden its claims through the doctrine of equivalents to cover Coherus's manufacturing process because of argument based prosecution history estoppel. *Id.* at 12-17. Moreover, the court held that it could take into account the contents of Coherus's aBLA, as well as portions of the prosecution history of the patent in question. *Id.* at 6.

There is even more reason to grant Apotex's motion to dismiss in this case. Whereas the court in *Coherus* found Amgen was estopped from broadening the claims based on argument based prosecution history estoppel, in this case, Amgen should be estopped from broadening the claims of the '287 patent based on both amendment and argument based prosecution history

estoppel. What is more, in the *Coherus* case, Amgen gained access to Coherus's aBLA through the exchange of information pursuant to the Biologics Price Competition and Innovation Act ("BPCIA"). In this case, Amgen had full discovery into Apotex's aBLAs and manufacturing process in the prior actions, including document discovery, fact depositions, expert reports, etc. Despite this, Amgen cannot make a plausible case of infringement.

Finally, there is no reason to allow Amgen to amend its Complaint. No amendment to the Complaint could undo the prosecution history estoppel and collateral estoppel that precludes Amgen from making an infringement claim in this case.

## IV. CONCLUSION

For the foregoing reasons, Apotex's motion to dismiss should be granted.

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Respectfully submitted

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**CERTIFICATE OF SERVICE**

I HEREBY CERTIFY that on December 10, 2018, I electronically filed the foregoing document with the Clerk of the Court using CM/ECF. I also certify that the foregoing document is being served this day on all counsel of record identified on the attached Service List in the manner specified, 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 electronically receive Notices of Electronic Filing.

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