UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF FLORIDA

CASE NO. 15-61631-CIV-COHN/SELTZER
(CONSOLIDATED WITH 15-62081-CIV-COHN/SELTZER)

AMGEN INC. and AMGEN MANUFACTURING LIMITED,

Plaintiffs,

v.

APOTEX INC. and APOTEX CORP.,

Defendants.
_____/

FINDINGS OF FACT AND CONCLUSIONS OF LAW

THIS CAUSE came before the Court for nonjury trial on July 11, 2016 through July 18, 2016. The parties provided the Court with revised proposed findings of fact and conclusions of law on August 18, 2016 [DE 262–65]. The Court has considered all submissions and the evidence presented at trial, and is otherwise advised in the premises.

Plaintiffs Amgen Inc. and Amgen Manufacturing Limited (collectively, "Amgen") sued Defendants Apotex Inc. and Apotex Corp. (collectively, "Apotex") under the Biologics Price Competition and Innovation Act ("BPCIA") for infringement of U.S. Patent No. 8,952,138 (the "'138 Patent"). Amgen is the owner of all rights, title, and interest in the '138 Patent, which covers a process of protein refolding. Apotex filed abbreviated Biologics License Application ("aBLA") Nos. 761026 and 761027 seeking approval from the U.S. Food & Drug Administration ("FDA") to market biosimilar versions of Amgen's Neulasta (Pegfilgrastim) and Neupogen (Filgrastim) products,

respectively. Amgen alleges that aBLA Nos. 761026 and 761027 infringe the '138 Patent under 35 U.S.C. § 271(e)(2)(C)(i), and also allege that the commercial manufacture, use, sale, offer for sale, or importation of Apotex's Pegfilgrastim and Filgrastim products will infringe the asserted claims of the '138 Patent under 35 U.S.C. § 271(a) and/or (g). Apotex alleges that the process described in its aBLAs falls outside the scope of the asserted claims of the '138 Patent and seeks a declaratory judgment of non-infringement and invalidity for lack of enablement.

For the reasons set forth below, the Court finds that Amgen has not met its burden to prove that Apotex's process for refolding Filgrastim and Pegfilgrastim infringe, either literally or under the doctrine of equivalents, each limitation of the '138 Patent. Additionally, the Court finds that Apotex has established that its process, as described in aBLA Nos. 761026 and 761027, does not infringe the '138 Patent. Having found no infringement, the Court shall dismiss without prejudice Apotex's counterclaim for invalidity. [1]

Pursuant to Federal Rule of Civil Procedure 52, the Court issues the following Findings of Fact and Conclusions of Law.

I. FINDINGS OF FACT

A. The '138 Patent

1. The '138 Patent is entitled "Refolding Proteins Using a Chemically Controlled Redox State." The '138 Patent issued on February 10, 2015, to inventors Joseph Edward Shultz, Roger Hart, and Ronald Nixon Keener, III, was assigned to

[1] Apotex also argued at trial that its Pegfilgrastim product does not infringe the '138 Patent because pegylation of Filgrastim constitutes a "material change" to the claimed process. Because the Court finds no infringement, this argument is now moot.

Amgen Inc. The '138 Patent claims priority to Provisional U.S. Application No. 61/219,257, which was filed on June 22, 2009.

1. The Asserted Claims of the '138 Patent

2. Amgen asserted claims 1–3, 6–7, 13, 15–17, and 22–23 of the '138 Patent against Apotex. Claims 2–3, 6–7, 13, 15–17, and 22–23 depend from claim 1.

3. Claim 1 of the '138 Patent states:

> **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.

4. Claim 2 of the '138 Patent states:

> **2.** The method of claim 1, wherein the final thiol-pair ratio is selected from the group consisting of 0.05 to 50, 0.1 to 50, 0.25 to 50, 0.5 to 50, 0.75 to 40, 1.0 to 50 and 1.5 to 50, 2 to 50, 5 to 50, 10 to 50, 15 to 50, 20 to 50, 30 to 50 or 40 to 50.

5. Claim 3 of the '138 Patent states:

> **3.** The method of claim 1, wherein the thiol-pair buffer strength is selected from the group consisting of greater than or equal to 2.25 mM, 2.5 mM, 2.75 mM, 3 mM, 5 mM, 7.5 mM, 10 mM and 15 mM.

6. Claim 6 of the '138 Patent states:

> **6.** The method of claim 1, wherein the protein is present in the volume in a soluble form.

7. Claim 7 of the '138 Patent states:

> **7.** The method of claim 1, wherein the protein is recombinant.

8. Claim 13 of the '138 Patent states:

> **13.** The method of claim 1, wherein the non-mammalian expression system is one of a bacterial expression system and a yeast expression system.

9. Claim 15 of the '138 Patent states:

> **15.** The method of claim 1, wherein the protein stabilizer is selected from the group consisting of arginine, proline, poly-ethylene glycols, non-ionic surfactants, ionic surfactants, polyhydric alcohols, glycerol, sucrose, sorbitol, glucose, Tris, sodium sulfate, potassium sulfate and osmolytes.

10. Claim 16 of the '138 Patent states:

> **16.** The method of claim 1, wherein the aggregation suppressor is selected from the group consisting of arginine, proline, polyethylene glycols, non-ionic surfactants, ionic surfactants, polyhydric alcohols, glycerol, sucrose, sorbitol, glucose, Tris, sodium sulfate, potassium sulfate and osmolytes.

11. Claim 17 of the '138 Patent states:

> **17.** The method of claim 1, wherein the thiol-pairs comprise at least one component selected from the group consisting of glutathione-reduced, glutathione-oxidized, cysteine, cystine, cysteamine, cystamine and beta-mercaptoethanol.

12. Claim 22 of the '138 Patent states:

> **22.** The method of claim 1, wherein the isolating comprises contacting the mixture with an ion exchange separation matrix.

13. Claim 23 of the '138 Patent states:

> **23.** The method of claim 1, wherein the isolating further comprises a filtration step.

2. Claim Construction

14. In its Claim Construction Order and Sealed Omnibus Order, the Court construed certain terms of the '138 Patent as follows:

Claim Term	Court's Construction
"a protein . . . present in a volume at a concentration of 2.0 g/L or greater"	A protein as it existed in a volume before contacting the volume with a refold buffer. The protein concentration in the volume is 2.0 g/L or greater.
"refold mixture"	A mixture formed from contacting (1) the volume in which the concentration of protein is 2.0g/L or greater with (2) the refold buffer. The refold mixture has a high protein concentration, where "high protein concentration" is at or above about 1g/L protein.
"refold buffer"	A preparation that supports the renaturation of protein to a biologically active form. The refold buffer comprises (1) a redox component and (2) one or more of (i) a denaturant, (ii) an aggregation suppressor, and (iii) a protein stabilizer.
"redox component"	Any thiol-reactive chemical or combinations of such chemicals, or solution comprising such a chemical or chemicals that facilitates a reversible thiol exchange with another thiol or the cysteine residues of a protein. The redox component comprises a final thiol-pair ratio in the range of 0.001-100 and a redox buffer strength of 2mM or greater.
"final thiol-pair ratio"	Defined by the following equation: $\frac{[reductant]^2}{[oxidant]}$ where the concentrations are the concentrations in the redox component.
"redox buffer strength"	Also called "buffer thiol strength," "thiol-pair buffer strength," or "thiol-pair strength," defined by the following equation: $2[oxidant] + [reductant]$ where the concentrations are the concentrations in the redox component.
"2 mM or greater"	2mM or greater, wherein the redox buffer strength is effectively bounded at a maximum of 100mM.
"protein"	Any chain of at least five naturally or non-naturally occurring amino acids linked by peptide bonds including but not limited to the protein of interest.

B. Apotex's Manufacturing Process

15. Apotex's refolding process for its Pegfilgrastim and Filgrastim products is described in detail in aBLA Nos. 761026 and 761027, respectively (hereinafter "Apotex's aBLAs"). Apotex's aBLAs seek FDA licensure to market biosimilar versions of Amgen's Neulasta (Pegfilgrastim) and Neupogen (Filgrastim) products, respectively.

16. Apotex's refolding process includes an "upstream" process and a "downstream" process. The end product of Apotex's upstream process is inclusion bodies. During the upstream process, Apotex performs multiple washes of the inclusion bodies with a buffer and water. Following each of these washes, the inclusion bodies are centrifuged to separate a wet "pellet" of inclusion bodies from the supernatant (liquid). The wet inclusion bodies are weighed at the conclusion of the upstream process and then frozen. The inclusion bodies remain frozen in storage until they are used in Apotex's downstream process.

17. Apotex's aBLAs specify that between 144 grams (hereinafter "grams" or "g") and 216 grams of inclusion bodies are used to begin Apotex's downstream process. In addition to specifying the wet weight of inclusion bodies carried from the upstream process into Apotex's downstream process, Apotex's aBLAs specify the amount of inclusion bodies as a concentration, as shown in the table below, which is equivalent to 0.9 to 1.4 grams per Liter (hereinafter "Liter" or "L") of Apotex's Refolding Buffer.

Table S.2.2-26: Inclusion Bodies Solubilization Operating Parameters

Operating Parameter	Operating Range	Set Point
IB amount per L of Refolding Buffer (160 L)	0.9 – 1.4 g/L	1.1 g/L
IB Solubilization Buffer volume	5.4 – 5.6 L	5.5 L
Amount of DTT added to solubilized IBs	4.44 – 5.55 g	5.00 g
Mixing time for reduction of solubilized IBs	20 – 40 min	30 min

DTT = dithiothreitol; IB = Inclusion Body

This concentration is determined by dividing the lowest and highest amounts of inclusion bodies—144 g and 216 g, respectively—by the nominal volume of the refold buffer tank, which is 160 L.

18. The first step in Apotex's downstream process is solubilization of the inclusion bodies. After the inclusion bodies are thawed in a small amount of water, they are dissolved in Apotex's solubilization buffer, resulting in a solution having a volume of 7.2 L. The solubilized inclusion bodies are then reacted with dithiothreitol ("DTT") to reduce the proteins into their primary, unfolded structure.

19. According to Apotex's aBLAs specifications, and shown in the table below, the concentration of Filgrastim in the solubilization buffer is 4.24 to 11.80 milligrams (hereinafter "milligrams" or "mg") per milliliter (hereinafter "milliliter" or "mL"), which is the same as 4.24 to 11.80 g/L.

Table S.2.2-27: Inclusion Bodies Solubilization Performance Parameters

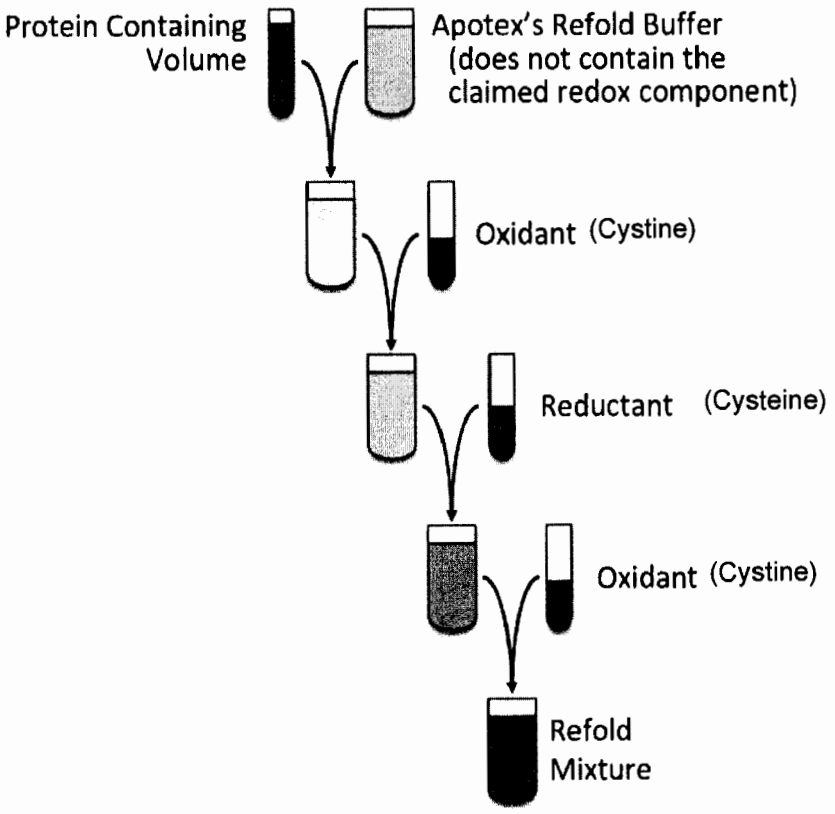
Performance Parameter	Categorization	Acceptance Criterion	Expected Range
Solubilized IB purity by UPLC M1	CPP	≥ 75%	--
Solubilized IB rHu-met-GCSF Concentration by UPLC M1	KPP	--	4.24 – 11.80 mg/mL*
Solubilized IB Endotoxin (Post-filtration)	CPP	NMT 500 EU/mg	--
Solubilized IB Bioburden (Post-filtration)	CPP	NMT 1 CFU/10 mL	--
*Based on the ranging studies that were carried out using a Design of Experiments (DoE) approach, the qualified upper limit for the concentration of protein entering the refolding unit operation is 11.8 mg/mL.			

20. Apotex's specification for the concentration of Filgrastim in the solubilization buffer limits the concentration of Filgrastim that is present in subsequent manufacturing processes. For example, the upper limit of the Filgrastim concentration in Apotex's refold mixture is 0.531 g/L. This upper limit is determined by taking the highest possible concentration of Filgrastim in the solubilization buffer—11.80 mg/mL

(or 11.80 g/L)—and multiplying by the volume of the solubilization buffer, which is 7.2 L, and then dividing by the volume of the refold mixture, which is 160 L.

21. As further shown in Table S.2.2-27: Inclusion Bodies Solubilization Performance Parameters, *supra*, Apotex's aBLAs specify that in the solubilization buffer at least 75 percent of the total protein present must be Filgrastim. This specification for the Filgrastim purity limits the amount of total protein in Apotex's refold mixture to a maximum of 0.708 g/L. This total protein amount is calculated by dividing the maximum Filgrastim concentration by 0.75 (or dividing by 75 percent).

22. Turning to Apotex's refolding process, the following schematic is illustrative:



23. The composition and quantity of ingredients in Apotex's Refolding Buffer, Cystine Solution, and Cysteine Solution are shown below in Table S.2.2-33.

Table S.2.2-33: Refolding – Solution Composition

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

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

24. The first step in Apotex's refolding process is to create Apotex's Refolding Buffer (the orange container in the schematic) and to add it to the refolding vessel. Solubilized and reduced inclusion bodies (royal blue) are then slowly added to Apotex's Refolding Buffer over 90 minutes.

25. After the solubilized and reduced inclusion bodies are added to Apotex's Refolding Buffer, the Cystine Solution (purple) and Cysteine Solution (pink) are added in a stepwise manner. According to the aBLAs, first 360 mL of the Cystine Solution (purple) is added to Apotex's Refolding Buffer to "neutralize DTT." Next, 32 mL of the Cysteine Solution (pink) is added to Apotex's Refolding Buffer to "break S-H (thiosulfide) bonds." Finally, 80 mL of Cystine Solution is added to "reduce the free S moieties so they were not available to form intramolecular disulfide bonds after refolding."

26. After the stepwise addition of the Cystine and Cysteine Solutions, Apotex incubates the refold mixture for at least 18 hours. Then, Apotex isolates the Filgrastim protein using a series of isolation steps.

27. The protein that results from Apotex's manufacturing process is Filgrastim Critical Intermediate ("Filgrastim CI"), which is both the starting material for Apotex's Filgrastim product and the critical intermediary for its Pegfilgrastim product.

C. Apotex Does Not Infringe the Asserted Claims of the '138 Patent.

28. As discussed in detail below, Amgen has not met its burden to show that Apotex's refolding process, as defined by Apotex's aBLAs, infringes the asserted claims of the '138 Patent, either literally or under the doctrine of equivalents. Specifically, Amgen has not established by a preponderance of the evidence that Apotex's process has: (1) a "high protein concentration" at or above about 1g/L; and (2) a redox component having a redox buffer strength of 2 to 100 mM.

29. Moreover, Apotex has shown that its manufacturing process, both as defined in its aBLAs and in practice, does not infringe the '138 Patent.

1. Apotex's Refolding Process Does Not Include a Refold Mixture Having a Protein Concentration At or Above about 1 g/L.

30. Each asserted claim of the '138 Patent requires a "refold mixture" having "a high protein concentration, where 'high protein concentration' is at or above about 1g/L protein." Amgen asserts that Apotex's refolding process literally meets this claim element, and did not allege infringement of this element under the doctrine of equivalents.

31. As discussed in detail below, Amgen did not meet its burden to show by a preponderance of the evidence that Apotex's refolding process literally uses a protein concentration in Apotex's refold mixture that is "at or above about 1 g/L." To the contrary, the Court finds that Apotex's aBLAs require a total protein concentration in

Apotex's refold mixture that is well below "at or above about 1 g/L." Therefore, the Court finds that Apotex's aBLAs do not define an infringing process.

32. The Court finds that Amgen's failure to prove that Apotex's refolding process literally infringes the asserted claims of the '138 Patent is established by: (i) the testimony of Amgen's expert Dr. Richard C. Willson, III and Apotex's experts Dr. Jason Dowd and Dr. Anne S. Robinson that Apotex's inclusion bodies are not wholly protein; (ii) Dr. Dowd's and Dr. Robinson's testimony that Apotex's aBLAs specifications for the amount of inclusion bodies of 0.9 to 1.4 g/L is not reliable for determining protein concentration in the refold mixture because the inclusion bodies are wet at the time of weighing and are mostly water; (iii) the fact that Dr. Willson's opinion that the washed inclusion bodies are almost entirely pure protein did not account for the water present in those inclusion bodies; and (iv) Amgen's lack of evidence that the actual protein concentration in Apotex's refold mixture is "at or above about 1 g/L."

33. Further, the Court finds that Apotex's non-infringement is established by: (i) Apotex's aBLAs that require a specific protein concentration range in the refold mixture that is outside the range of "at or above about 1 g/L"; and (ii) Apotex's batch records, which show that the protein concentration in the refold mixture of actual manufactured batches is outside the range of "at or above about 1 g/L."

a. Amgen did not prove that Apotex's specification for inclusion bodies defines the protein concentration in the refold mixture.

34. Amgen's theory of infringement of the protein concentration limitation requires a finding that the inclusion bodies in Apotex's downstream process are primarily pure protein. Specifically, Amgen maintains that the 0.9 to 1.4 g/L inclusion

body concentration specification in Apotex's aBLAs is roughly equivalent to the total protein concentration.

35. The Court does not find that Apotex's inclusion bodies are substantially pure protein. In reaching this conclusion, the Court credits the testimony of Apotex's experts, Dr. Dowd and Dr. Robinson, that Apotex's inclusion bodies are composed of approximately two-thirds water at the time of weighing.

36. Amgen's theory that Apotex's inclusion body specification defines the protein concentration, as explained by Dr. Willson, does not sufficiently account for the water weight present in the inclusion bodies at the time of weighing.

37. Additionally, no evidence affirmatively shows that Apotex's centrifugation process removes water from Apotex's inclusion bodies. Dr. Willson's testimony that Apotex "pours off the liquid containing the stuff that got washed off" during centrifugation speaks to the amount of liquid on the outside of the inclusion bodies, but it does not establish how much liquid remains in them.

38. In light of Dr. Robinson's deposition testimony describing the inclusion bodies after centrifugation and at the time of weighing as a "wet pellet" and the specifications in Apotex's batch records (described in the following section), Amgen knew or should have known that the inclusion bodies contained water.

39. Apotex's pre-litigation letters to Amgen, which incorrectly equate the inclusion body concentration with protein concentration, are not probative on the issue of protein concentration. Statements in the pre-litigation letters are not binding on Apotex, and the Court credits Dr. Dowd's testimony that the statements at issue in these letters are factually incorrect.

40. Based on the above, the Court finds that Apotex's aBLAs specifications of 0.9 to 1.4 g/L merely require an amount of inclusion bodies to be used as an input in Apotex's refolding process, but do not specify the amount of protein present in those inclusion bodies. Thus, the Court finds that Amgen has failed to meet its burden to show by a preponderance of the evidence that Apotex's refolding process literally infringes the protein concentration claim limitation.

b. Apotex's aBLAs specify a protein concentration separate from an inclusion body concentration.

41. The maximum concentration of total protein in Apotex's refold mixture process is limited by Apotex's aBLAs specifications to 0.708 g/L. The Court credits the opinions and calculations of Dr. Dowd and Dr. Robinson in reaching this conclusion.

42. Apotex's aBLAs specify the concentration of Filgrastim in Apotex's solubilization buffer, and this specification limits the concentration of Filgrastim that is present in subsequent manufacturing steps.

43. As shown in Table S.2.2-27: Inclusion Bodies Solubilization Performance Parameters, *supra*, Apotex's aBLAs restrict Apotex's process from exceeding 11.80 g/L of Filgrastim in 7.2 L of solubilization buffer.

44. The upper limit of the Filgrastim concentration in Apotex's refold mixture is 0.531 g/L. This is determined by taking the highest possible concentration of Filgrastim in the solubilization buffer—11.80 g/L—and multiplying by the volume of the solubilization buffer, which is 7.2 L, and then dividing by the volume of the refold mixture, which is 160 L.

45. As further shown in Table S.2.2-27: Inclusion Bodies Solubilization Performance Parameters, *supra*, Apotex's aBLAs also specify that in the solubilization

buffer at least 75 percent of the total protein present must be Filgrastim. This specification for the Filgrastim purity effectively limits the amount of total protein in Apotex's refold mixture to a maximum of 0.708 g/L. This is calculated by dividing the maximum Filgrastim concentration in the refold mixture—0.531 g/L—by 0.75 (or dividing by 75 percent).

46. If Apotex's manufacturing process was to deviate from the amount and quantity of Filgrastim specified in the Apotex aBLAs submitted to the FDA, Apotex would be required to discard that batch. The Court credits the testimony of Dr. Dowd in reaching this conclusion.

47. Amgen cited no evidence to contradict that Apotex's aBLAs specifications limit the maximum protein concentration in Apotex's refold mixture to 0.708 g/L. Evidence that Apotex advertised that it uses a bioreactor capable of utilizing a higher protein concentration is irrelevant to the infringement inquiry because this bioreactor is used for protein synthesis and is not involved in any way in Apotex's refolding process for Filgrastim.

48. Because Apotex's aBLAs limit the amount of total protein in Apotex's refold mixture to a maximum of 0.708 g/L, the Court finds that Apotex's aBLAs specifications directly address the infringement inquiry and define a protein refolding process having a total protein concentration less than "at or above about 1 g/L protein." For these reasons, the Court finds that Apotex's refolding process does not infringe the asserted claims.

c. Batch records show that the products that Apotex will likely market are manufactured by a non-infringing process.

49. Apotex's batch records, which were submitted to the FDA with Apotex's aBLAs, show that Apotex's protein refolding process, in practice, has not and will not use a protein concentration in Apotex's refold mixture that is within the scope of "at or above about 1 g/L protein," as required by claim 1 of the '138 Patent.

50. Apotex's batch records document the way in which Apotex has made its Filgrastim and Pegfilgrastim products. Apotex's batch records report both the amount of wet inclusion bodies that are used to begin Apotex's refolding process, as well as the total amount of protein present in those inclusion bodies. Apotex's batch records also confirm that the total wet weight of the inclusion bodies are used to calculate the 0.9 to 1.4 g/L inclusion body concentration in the refold mixture.

51. Apotex's batch records reflect that inclusion bodies from Apotex's upstream process are weighed wet prior to being placed into cold storage for up to 90 days. That Apotex's inclusion bodies are frozen suggests that water is present with the inclusion bodies.

52. After the inclusion bodies have been solubilized, Apotex measures the total protein concentration using an optical density measurement at 280 nanometers, also referred to as "OD280." Apotex uses the OD280 measurement in the solubilization buffer to calculate the total amount of protein that was present in Apotex's inclusion bodies and records this amount in its batch records.

53. The batch records show that, in the 91 times that Apotex has run its manufacturing process, the average protein content in Apotex's inclusion bodies has been 36 percent, with the balance of Apotex's inclusion bodies—on average, 64 percent

by weight—being water. Further, in the 91 times that Apotex has run its manufacturing process, the highest protein concentration in the refold mixture has been 0.56 g/L, which is well below the claimed "at or above 1 g/L." The Court credits Dr. Dowd's testimony in reaching these findings.

54. In addition to measuring the protein concentration in the solubilization buffer, Apotex measures the protein concentration in its refold mixture using the OD280 measurement. However, this second measurement of protein concentration (taken in the refold mixture) reports an artificially higher amount of protein because cysteine and cystine are present at high concentrations, and both absorb light at 280 nanometers. Although the measurement of protein concentration in the refold mixture is not a reliable indicator of protein concentration, a clear explanation exists for the difference between the OD280 measurements from the solubilization buffer and the refold mixture. Thus, the higher OD280 measurement of protein concentration in the refold mixture does not render unreliable the OD280 measurement in the solubilization buffer.

55. For these reasons, the Court finds that Apotex's batch records provide an accurate record of Apotex's manufacturing process, which does not literally infringe any of the asserted claims of the '138 Patent.

2. Apotex's Refolding Process Does Not Include a Redox Component Having a Redox Buffer Strength of 2 to 100 mM or Its Equivalent.

56. Each of the asserted claims of the '138 Patent requires a "redox component comprising . . . a redox buffer strength of 2 mM or greater," wherein the redox buffer strength is effectively bounded at a maximum of 100 mM.

57. The claim specifies a minimum redox buffer strength because, as the Patent states, "[a]t lower redox buffer strengths, the overall system becomes much

more difficult to control." The imposition of an effective maximum redox buffer strength is to address solubility limitations.

58. Apotex's process does not literally include the claimed redox component that has an oxidant (cystine) and a reductant (cysteine) combined together outside of the refold mixture. Nor does Apotex's process literally include the claimed redox buffer strength. These conclusions are not in dispute.

59. Instead, Amgen argues that Apotex's process has (1) an equivalent redox component (2) that equivalently satisfies the buffer strength limitation.

60. The Court will assume, without deciding, that the Cysteine and Cystine Solutions added in a stepwise manner in Apotex's refolding process is the equivalent of the claimed redox component.

61. The Court does find, however, that Amgen has failed to meet its burden to prove that the hypothetical redox component in Apotex's process—the combination of Apotex's Cysteine and Cystine Solutions in a hypothetical volume—satisfies the redox buffer strength claim limitation under the doctrine of equivalents.

62. Specifically, Amgen has not proven by a preponderance of the evidence that the redox buffer strength of Apotex's hypothetical redox component is insubstantially different from the claimed redox buffer strength of 2 to 100 mM.

63. The maximum possible combined volume of Apotex's Cystine and Cysteine Solutions is 476.32 mL (444 mL of Cystine Solution plus 32.32 mL of Cysteine Solution). Thus, the maximum possible volume of Apotex's hypothetical redox component is 476.32 mL.

64. The redox buffer strength of Apotex's hypothetical redox component ranges from 214 to 340 mM.

65. Thus, Apotex's process uses a smaller volume of more concentrated redox component than is claimed in the '138 Patent to achieve its desired redox conditions.

66. According to Dr. Willson, when using a redox component with a redox buffer strength of 100 mM (within the limitation of the claim), one would need to practice the claimed method with a total volume of 1.0 L to 1.6 L of such a redox component to deliver the same number of molecules of cystine and cysteine to the refold mixture as in Apotex's process.

67. A volume of 1 to 1.6 L is two to three times greater than the volume of the hypothetical redox component.

68. The difference between a redox component in a 476.32 mL volume and a 1 to 1.6 L volume, particularly when its components are added in a stepwise manner, is substantial. The Court credits Dr. Robinson's opinion in reaching this conclusion.

69. Amgen's evidence is insufficient that simply increasing the redox component volume will serve substantially the same function in substantially the same way to achieve substantially the same result as practicing a volume with the claimed redox component strength. Dr. Willson did not specify what liquid would be used to increase the volume of the hypothetical redox component in Apotex's process to achieve the desired redox buffer strength. Dr. Willson also acknowledged that he did not know where equivalence would be lost by increasing the volume of the redox component volume. Additionally, Dr. Willson did not perform any experiments or

present any evidence that increasing the volume of the redox component would result in an insubstantial difference.

70. Additionally, Apotex's aBLAs specify the volume of each Cystine and Cysteine Solution allowed in its manufacturing process. A batch utilizing combined redox chemical solutions with a volume of 1 to 1.6 L is not possible under Apotex's aBLAs. Apotex's process does not, and cannot, meet the claim requirement of a redox buffer strength effectively bounded at a maximum of 100 mM.

II. CONCLUSIONS OF LAW

Amgen has not met its burden to prove that Apotex's process for manufacturing its Filgrastim and Pegfilgrastim products meets each and every claim limitation of the '138 Patent. Specifically, Amgen has not proven by a preponderance of the evidence that Apotex's process literally meets the protein concentration claim limitation or equivalently meets the redox buffer strength claim limitation. Thus, no finding of infringement is warranted. Apotex, however, is entitled to a judgment of non-infringement because it has proven that its manufacturing process does not satisfy at least one of the Patent's claim limitations.

"Patent infringement, whether literal or by equivalence, is an issue of fact, which the patentee must prove by a preponderance of the evidence." Siemens Med. Sols. USA, Inc. v. Saint-Gobain Ceramics & Plastics, Inc., 637 F.3d 1269, 1279 (Fed. Cir. 2011). Determining infringement requires a two-step analysis: (1) the patent claims must be construed to ascertain their scope and meaning; and (2) the claims, as properly construed, must be compared to the accused method or product. SmithKline

Diagnostics, Inc. v. Helena Labs. Corp., 859 F.2d 878, 889 (Fed. Cir. 1988). The Court previously construed the asserted claims, leaving the issue of infringement for trial.

To prove infringement, the patentee must show that an accused method meets each and every limitation of a claim, either literally or under the doctrine of equivalents. Deering Precision Instruments, L.L.C. v. Vector Distrib. Sys., Inc., 347 F.3d 1314, 1324 (Fed. Cir. 2003). "To show literal infringement of a patent, a patentee must supply sufficient evidence to prove that the accused product or process meets every element or limitation of a claim." Rohm & Haas Co. v. Brotech Corp., 127 F.3d 1089, 1092 (Fed. Cir. 1997) (citing Lemelson v. United States, 752 F.2d 1538, 1551 (Fed. Cir. 1985)). Under the doctrine of equivalents, a "process that does not literally infringe upon the express terms of a patent claim may nonetheless be found to infringe if there is 'equivalence' between the elements of the accused . . . process and the claimed elements of the patented invention." Warner-Jenkinson Co. v. Hilton Davis Chem. Co., 520 U.S. 17, 21 (1997) (citation omitted). Because Amgen has conceded that Apotex's process does not literally satisfy some limitations of claim 1 of the '138 Patent, Amgen proceeds on a theory of infringement by equivalence.

A dependent claim "incorporate[s] by reference all the limitations of the claim to which it refers." 35 U.S.C. § 112. If an independent claim is not infringed, then each corresponding dependent claim cannot be infringed. See Wahpeton Canvas Co., Inc. v. Frontier, Inc., 870 F.2d 1546, 1553 (Fed. Cir. 1989) ("It is axiomatic that dependent claims cannot be found infringed unless the claims from which they depend have been found to have been infringed . . . .").

A. Amgen Has Not Met Its Burden to Prove Literal Infringement of the Protein Concentration Claim Limitation.

Amgen did not meet its burden to show by a preponderance of the evidence that Apotex's refolding process literally uses a protein concentration in Apotex's refold mixture that is "at or above 1 g/L." Nor did Amgen proffer evidence or assert that Apotex's refolding process meets this limitation under the doctrine of equivalents.

Under the BPCIA, the "submission" of an aBLA to the FDA, which seeks approval to commercially market a biosimilar biologic product, is an act of infringement of the patents identified by the parties during the BPCIA information exchange process. 35 U.S.C. § 271(e)(2)(C)(i); Amgen Inc. v. Apotex Inc., 2016 WL 3606770, at *4. Similar to the Hatch-Waxman Act (which is analogous to the BPCIA in some respects, see Amgen Inc. v. Sandoz Inc., 794 F.3d 1347, 1351 (Fed. Cir. 2015)), the ultimate infringement question, however, is determined by traditional patent law principles. See Sunovion Pharmaceuticals, Inc. v. Teva Pharmaceuticals USA, Inc., 731 F.3d 1271, 1278 (Fed. Cir. 2013). If the process that an aBLA applicant is asking the FDA to approve falls within the scope of an asserted patent claim, a judgment of infringement must necessarily ensue. Id.

To determine infringement, a court compares the patent claim to the aBLAs specification, which is "what [the applicant] has asked the FDA to approve as a regulatory matter." Id.; see also Abbott Labs. v. TorPham, Inc., 300 F.3d 1367, 1373 (Fed. Cir. 2002) ("Because drug manufacturers are bound by strict statutory provisions to sell only those products that comport with the ANDA's description of the drug, an ANDA specification defining a proposed generic drug in a manner that directly addresses the issue of infringement will control the infringement inquiry."). If the aBLA

applicant has asked the FDA to approve a process within the scope of the claim, it is an infringement as a matter of law. See Sunovion, 731 F.3d at 1280. Manufacturing guidelines, batch records, product samples, and certifications pledging not to infringe cannot be used to overcome that infringement. See id. at 1278–80. This other evidence is considered only if the aBLA is "silent" with respect to the claim limitations of the patents-in-suit. See Meds. Co. v. Mylan Inc., 72 F. Supp. 3d 837, 887 (N.D. Ill. 2014) (citing Ferring B.V. v. Watson Labs., Inc.-Fla., 764 F.3d 1382, 1387 (Fed. Cir. 2014)). It is the burden of the patentee to prove by a preponderance of the evidence that the alleged infringer will likely market an infringing product, and that burden is never shifted to the alleged infringer. See Glaxo, Inc. v. Novopharm, Ltd., 110 F.3d 1562, 1568–70 (Fed. Cir. 1997).

Here, Amgen asserts that Apotex's aBLAs speak directly to the issue of infringement because Apotex's aBLAs contain process specifications for inclusion bodies. However, Amgen has not established that Apotex's specification for inclusion bodies defines a protein concentration in the refold mixture. Instead, the Court finds extensive evidence that Apotex's inclusion bodies are wet at the time they are weighed and are on average about two-thirds water. Further, whether Apotex refers to the inclusion bodies as a "pellet" or a "paste," does not change the fact that water constitutes the majority of Apotex's inclusion bodies at the time of weighing. Nor is this finding changed because Apotex's pre-litigation letters under 42 U.S.C. § 262(l)(3)(B) incorrectly referred to the inclusion body concentration as the protein concentration. These letters were not part of Apotex's aBLAs, were never filed with the FDA, do not impact the process and product approved by the FDA, and are not controlling. See

Takeda Chem. Indus., Ltd. v. Mylan Labs., Inc., 549 F.3d 1381, 1390–91 (Fed. Cir. 2008) ("It is clear from the district court's opinion that it . . . [did not] limit the filers to the theories raised in their certification letters.").

Apotex, however, did prove that its aBLAs specify a protein concentration separate from an inclusion body concentration. Based on the highest allowable Filgrastim concentration required by Apotex's aBLAs, the maximum total protein concentration allowable in Apotex's refold mixture is restricted at 0.708 g/L. Therefore, Apotex's aBLAs specifications directly show that the total protein concentration in Apotex's refold mixture is outside the "at or above about 1 g/L protein" range required by the Court's construction of the claim element "refold mixture." Amgen cited no relevant evidence contradicting that Apotex's aBLAs specifications effectively limit the maximum protein concentration in Apotex's refold mixture to 0.708 g/L. As a result, the Court finds that Apotex's aBLAs specifications directly address the infringement inquiry and define a protein refolding process having a total protein concentration less than "at or above about 1 g/L protein." See Sunovion, 731 F.3d at 1279–80 (citing Bayer, 212 F.3d at 1250) ("In Bayer, we upheld a summary judgment of no literal infringement because the generic manufacturer's ANDA specification itself required that the proposed product have a specific surface area outside of the range claimed by the innovator's asserted patent."). For at least these reasons, the Court finds that Apotex's refolding process does not infringe the asserted claims.

Furthermore, even if Apotex's aBLAs had been silent on the issue of protein concentration, Apotex's batch records show that the drug products it intends to market are manufactured by a non-infringing process. In the 91 times that Apotex has run its

manufacturing process, the highest protein concentration in the refold mixture has been 0.56 g/L, which is well below the claimed "at or above about 1 g/L" limitation. Apotex submitted its batch records, which include an outline for each step in the manufacturing process with operating parameters, to the FDA along with the aBLAs, and there is no evidence that the FDA has questioned the accuracy of Apotex's measurements. Thus, Apotex's batch records support a finding that judgment of non-infringement is proper because Apotex's refolding process for the drugs it intends to market does not infringe any asserted claim of the '138 Patent under 35 U.S.C. § 271(e)(2). See Glaxo, 110 F.3d at 1568–70.

B. Amgen Has Not Met Its Burden to Prove Equivalent Infringement of the Redox Buffer Strength Claim Limitation.

Amgen has not proven that Apotex's protein refolding process infringes the redox buffer strength claim limitation of the '138 Patent under the doctrine of equivalents. A patent is infringed under the doctrine of equivalents if the difference(s) between a claim limitation and the corresponding element in the accused process is "insubstantial" ("insubstantial differences" test). See Warner-Jenkinson, 520 U.S. at 39–40 (1997). Alternatively, an element in the accused process is equivalent to a claim limitation only if it performs substantially the same function, in substantially the same way, to yield substantially the same result ("function-way-result" test). See id. at 38–40 (citing Union Paper-Bag Mach. Co. v. Murphy, 97 U.S. 120, 125 (1877)). Which test to apply depends on the facts of the case, because "[d]ifferent linguistic frameworks may be more suitable to different cases, depending on their particular facts." Warner-Jenkinson, 520 U.S. at 40.

"What constitutes equivalency must be determined against the context of the patent, the prior art, and the particular circumstances of the case." Graver Tank & Mfg. Co. v. Linde Air Products Co., 339 U.S. 605, 609 (1950). The doctrine of equivalents "must be applied to individual elements of the claim, not to the invention as a whole." Warner-Jenkinson, 520 U.S. at 29. The patentee must demonstrate that a claim element is found equivalently in the accused product or process by a preponderance of the evidence. Id., 520 U.S. at 37. The equivalence must have been known at the time of the alleged infringement to a person having ordinary skill in the art. Graver Tank, 339 U.S. at 609.

In addition to Amgen's failure to prove that Apotex's protein refolding process literally satisfies the protein concentration limitation, Amgen has not established that Apotex's process equivalently satisfies the limitation of a "redox buffer strength of 2mM or greater." Assuming without deciding that Apotex's hypothetical redox component is equivalent to the claimed redox component, the redox buffer strength of this hypothetical redox component would be 214 to 340 mM. This value is more than two to three times greater than the maximum redox buffer strength of 100 mM permitted under the Court's claim construction. Amgen has established neither that this is an insubstantial difference nor that a redox buffer strength of 214 to 340 mM performs substantially the same function, in substantially the same way, to yield substantially the same result as the claimed redox buffer strength in the redox component.

The relevant inquiry is whether a redox component with a redox buffer strength of 214 to 340 mM is insubstantially different from a redox component with a redox buffer strength of 100 mM. To demonstrate equivalence, Dr. Willson adjusted the volume of

the hypothetical redox component from approximately 472 mL to 1.0 to 1.6 L, adding an unspecified liquid, in an effort to make the redox buffer strength of Apotex's hypothetical redox component meet the redox buffer strength claim limitation. In other words, Amgen attempts to show equivalence by significantly altering Apotex's process. This cannot be done. Apotex is bound by the specifications in its aBLAs and cannot, in practice, increase the volume of its redox component to a volume of 1.0 to 1.6 L without facing serious legal penalties. Moreover, adjusting the volume of the hypothetical redox component to reach a desired redox buffer strength that is not actually utilized in Apotex's process renders meaningless the maximum limit of 100 mM because one could simply adjust the volume of any redox component with a redox component greater than 100 mM to make it fall within the claimed limitation. See Warner-Jenkinson, 520 U.S. at 29 ("It is important to ensure that the application of the doctrine [of equivalents], even as to an individual element, is not allowed such broad play as to effectively eliminate that element in its entirety.").

For all of the reasons above, judgment of no infringement under the doctrine of equivalents is appropriate because Amgen has failed to prove by a preponderance of the evidence that a redox buffer strength 214 to 340 mM in the redox component is insubstantially different from the claimed redox buffer strength. Because the process defined in Apotex's aBLAs does not infringe claim 1, dependent claims 2, 3, 6, 7, 13, 15, 16, 17, 22, and 23 that depend from claim 1 similarly are not infringed. See Teledyne McCormick Selph, 558 F.2d at 1004.

C. Apotex's Invalidity Counterclaim Shall Be Dismissed.

Having found that the manufacturing process defined in Apotex's aBLAs does not infringe the '138 Patent, the Court declines to render an opinion as to whether the '138 Patent is invalid for lack of enablement. The Federal Circuit has indicated that "a district court can dismiss an invalidity counterclaim when it finds noninfringement or dismisses an infringement claim with prejudice." AstraZeneca LP v. Breath Ltd., 542 F. App'x 971, 981 (Fed. Cir. 2013), as amended on reh'g in part (Dec. 12, 2013) (citing Liquid Dynamics Corp. v. Vaughan Co., Inc., 355 F.3d 1361, 1371 (Fed. Cir. 2004) ("A district court judge faced with an invalidity counterclaim challenging a patent that it concludes was not infringed may either hear the claim or dismiss it without prejudice, subject to review only for abuse of discretion."); Nystrom v. TREX Co., Inc., 339 F.3d 1347, 1351 & n. * (Fed. Cir. 2003) ("[T]he district court could have dismissed the counterclaim without prejudice (either with or without a finding that the counterclaim was moot) following the grant of summary judgment of non-infringement."); Phonometrics, Inc. v. N. Telecom Inc., 133 F.3d 1459, 1468 (Fed. Cir. 1998) ("We have previously held that a district court has discretion to dismiss a counterclaim alleging that a patent is invalid as moot where it finds no infringement.")). "Where . . . non-infringement is clear and invalidity is not plainly evident, it is appropriate to treat only the infringement issue." Leesona Corp. v. United States, 530 F.2d 896, 906 n.9 (Ct. Cl. 1976) (citation omitted). Even after the invalidity counterclaim has been tried, the district court may dismiss the invalidity counterclaim without prejudice where "the non-infringement judgment firmly and clearly resolves the case, and [the defendant] has not shown how a judgment of

invalidity would provide any additional benefit." AstraZeneca LP, 542 F. App'x at 981–82.

Here, a judgment of Apotex's non-infringement firmly and clearly resolves this case. Apotex has not shown how a finding of invalidity of the '138 Patent would provide any additional benefit beyond a judgment of non-infringement. Moreover, unlike Apotex's non-infringement, the issue of invalidity is not plainly evident to the Court based on the evidence presented at trial. Accordingly, the Court defers judgment on the issue of invalidity of the '138 Patent and will dismiss the invalidity counterclaim without prejudice.

D. This Is Not an Unusual Case Warranting an Attorneys' Fee Award.

Under 35 U.S.C. § 271(e)(4), a court may award reasonable attorneys' fees under 35 U.S.C. § 285 to the prevailing party in exceptional cases. An exceptional case is "simply one that stands out from others with respect to the substantive strength of a party's litigating position (considering both the governing law and the facts of the case) or the unreasonable manner in which the case was litigated." Octane Fitness, LLC v. ICON Health & Fitness, Inc., 134 S. Ct. 1749, 1756 (2014); see also ILOR, LLC v. Google, Inc., 631 F.3d 1372, 1380 (Fed. Cir. 2011) (reversing district court finding that case was exceptional where neither plain language of claim, specification, nor prosecution history showed that patentee's claim construction "was so unreasonable that no reasonable litigant could believe it would succeed"). Attorneys' fees are limited to exceptional cases "in order to avoid penalizing a party for merely defending or prosecuting a lawsuit, and are awarded to avoid a gross injustice." Revlon, Inc. v.

Carson Prod. Co., 803 F.2d 676, 679 (Fed. Cir. 1986) (internal citations and quotations omitted).

Determining whether a case is "exceptional" is a case-by-case exercise that should consider the totality of the circumstances. Id. "The determination whether a case is 'exceptional' is indisputably committed to the discretion of the district court." Lumen View Tech. LLC v. Findthebest.com, Inc., 811 F.3d 479, 482 (Fed. Cir. 2016) (citing Highmark Inc. v. Allcare Health Mgmt. Sys., Inc., 134 S. Ct. 1744, 1749 (2014)).

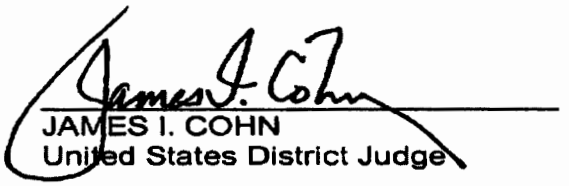
The Court does not find this case "exceptional." Amgen's actions in asserting its patent rights were reasonable. The Court has no reason to doubt that Amgen brought this case upon a good faith belief that Apotex's process practices each claim of the '138 Patent. The substantive strength of Amgen's litigating position certainly was not so weak that no reasonable litigant would think its claims could succeed. To the contrary, Amgen advanced a cogent argument for a finding of infringement, and it should not be penalized simply because the Court found Apotex's evidence and arguments more convincing. Furthermore, Amgen litigated this case in a reasonable and professional manner. No manifest injustice will result if attorneys' fees are not awarded.

III. CONCLUSION

For the foregoing reasons, it is **ORDERED AND ADJUDGED** that a separate Final Judgment will be entered in favor of Defendants Apotex Inc. and Apotex Corp. and against Plaintiffs Amgen Inc. and Amgen Manufacturing Limited on the issue of infringement consistent with the Findings of Fact and Conclusions of Law herein.

DONE AND ORDERED in Chambers at Fort Lauderdale, Broward County,

Florida, this 6th day of September, 2016.



JAMES I. COHN
United States District Judge

Copies provided to:
Counsel of record via CM/ECF