UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF FLORIDA

CASE NO. 15-61631-CIV-COHN/SELTZER

AMGEN, INC., and AMGEN MANUFACTURING LIMITED,,

Plaintiffs,

v.

APOTEX INC. and APOTEX CORP.,

Defendants.
_____/

CLAIM CONSTRUCTION ORDER

THIS CAUSE has come before the Court upon the parties' motions and briefs (DE [76], [77], [82], [83], [89], and [90]) for the construction of certain claim language in U.S. Patents Nos. 8,952,138 (the "'138 Patent") and 6,162,427 (the "'427 Patent").[1] The '138 patent is entitled "Refolding Proteins Using a Chemically Controlled Redox State" and was issued on February 10, 2015. The '427 patent is entitled "Combination of G-SF with a Chemotherapeutic Agent for Stem Cell Mobilization" and was issued on December 19, 2000. The patents are owned by Amgen, Inc., and Amgen Manufacturing Limited (collectively "Amgen").

Amgen develops, manufactures, and markets biologic therapy products including Neulasta (a pegylated filgrastim product) and Neupogen (a filgrastim product). Neulesta and Neupogen are, in the simplest of terms, biologic therapies which consist

[1]A third patent, Patent No. 5,824,784 (the "'784 Patent") has expired and is not considered in this Order.

of bacterial proteins that stimulate production of white blood cells in patients undergoing chemotherapy and/or stem cell transplants. The '138 patent is directed to improved methods for refolding the proteins made in bacterial cells, allowing for industrial scale protein production. The '427 patent provides an improved means of enhancing the mobilization of hematopoietic stem cells in patients undergoing stem cell transplants. Amgen has asserted patent claims against Apotex Inc. and Apotex Corp. (collectively "Apotex") based upon Apotex's filings with the U.S. Food & Drug Administration seeking approval to market biosimilar versions of Amgen's products.

The parties dispute the meaning of several claim terms in the '138 and '427 patents. The Court held a hearing on February 5, 2016, at which both parties presented extensive argument. The parties agreed to rely upon the evidence and affidavits in the record and, therefore, did not present any testimony.

I. LEGAL STANDARD

The fundamental purpose of a patent is to give notice to others of the subject matter as to which the inventor claims exclusive rights. See Oakley Inc. v. Sunglass Hut Int'l, 316 F.3d 1331, 1340 (Fed. Cir. 2003). Thus, the focus of claim construction is ascertaining how one of ordinary skill in the relevant art would have understood the claim language at the time of the invention. See Phillips v. AWH Corp., 415 F.3d 1303, 1312-13 (Fed. Cir. 2005) (*en banc*).

With two exceptions not relevant here, the words used in a patent are evaluated by determining their "ordinary and customary meaning." Id. To ascertain that meaning, the Court "looks to 'those sources available to the public that show what a person of skill in the art would have understood disputed claim language to mean.'" Id. at 1314

(quoting Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc., 381 F.3d 1111, 1116 (Fed. Cir. 2004)). Those sources include "the words of the claims themselves, the remainder of the specification, the prosecution history, and extrinsic evidence concerning relevant scientific principles, the meaning of technical terms, and the state of the art." Phillips, 415 F.3d at 1314 (quoting Innova, 381 F.3d at 1116).

The Court may also rely on expert testimony, which is extrinsic evidence, to determine the state of the art at the time of the invention, and how a person of ordinary skill would have understood certain terms of art at that time. Teva Pharm. USA, Inc. v. Sandoz, Inc., 135 S. Ct. 831, 841 (2015). The Court may then use these factual determinations in its legal determination of how the person of ordinary skill in the art would have understood such terms as used in the patent at issue. Id.

"It is a 'bedrock principle' of patent law that 'the claims of a patent define the invention to which the patentee is entitled the right to exclude.'" Phillips, 415 F.3d at 1312 (quoting Innova, 381 F.3d at 1115). Because the Court must examine the patent as a whole, there is a presumption that claim terms normally will be used consistently throughout a patent, such that "the usage of a term in one claim can often illuminate the meaning of the same term in other claims." Id. at 1314. Terms also must be construed in light of the entirety of the patent, not just in the context of the particular claim(s) in which they appear. Phillips, 415 F.3d at 1313. The claim language must be read in conjunction with the description in the specification. "'Usually, [the specification] is dispositive; it is the single best guide to the meaning of a disputed term.'" Id. at 1315 (quoting Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582 (Fed. Cir. 1996)).

Even so, the Court must be careful not to import limitations from the specification's embodiment(s) into the claims. Phillips, 415 F.3d at 1319-20.

II. ANALYSIS

A. The '138 Patent

The parties identified seven disputed claim terms in the '138 Patent. The terms appear in claim 1, which reads as follows:

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

The first term at issue is "*a protein . . . present in a volume at a concentration of 2.0g/L or greater. . . .*" Amgen's construction is: "A protein as it exists in a volume before contacting the volume with a refold buffer. The protein concentration in the volume is 2.0g/L or greater." Apotex's construction is: "a protein . . . present at a concentration of 2.0g/L or greater after dilution in a refold buffer." The sole point of difference between the parties is whether the concentration of the protein is determined before or after it is contacted with the refold buffer.

The Court agrees with Amgen that the concentration of the protein is determined *before* it is contacted with the refold buffer. This construction is consistent with the language of the claim itself, as well as the specification. *Phillips*, 415 F.3d at 1316.

Under the terms of the claim, the protein which is being refolded, is "expressed in a non-mammalian expression *and* present in a volume at a concentration of 2.0g/L or greater. . . ." DE [77-1] '138 Patent 2:52-54 (emphasis added). The specification makes clear that the protein in a volume at a concentration of 2.0g/L or greater "is contacted with a refold buffer . . . " '138 Patent 11:6-9. This is also consistent with the Background of the Invention, which states that "[u]ntil the present disclosure, these types of complex molecules could not be refolded at high concentrations, i.e., concentrations of 2.0g/L and higher, with any meaningful degree of efficiency on a small scale, and notably not on an industrial scale." DE [77-1], '138 Patent 2:17-21. Accordingly, the Court construes the claim term "*a protein . . . present in a volume at a concentration of 2.0g/L or greater. . . .*" as "A protein as it existed in a volume before contacting the volume with a refold buffer. The protein concentration in the volume is 2.0g/L or greater."

The second disputed claim term is "refold buffer." Amgen's construction is: "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." Apotex's construction is: "A preparation that supports the renaturation of protein to a biologically active form." Apotex argues that the components of the refold buffer are already expressly recited as limitations within claim 1, and so their inclusion in the construction of "refold buffer" is redundant and unnecessary.

The Court finds that Amgen's construction of the claim term "refold buffer" is consistent with the language of the claim and the principles of English grammar, and

that Apotex's proposed construction could lead to the creation of a refold buffer that does not contain the components required by the claim itself. This would be improper. Gillette Co. v. Energizer Holdings, Inc., 405 F.3d 1367, 1372-74 (Fed. Cir. 2005) (the word "comprising" indicates that the recited feature includes at least the listed elements). For this reason, the Court construes the term "refold buffer" as "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."

The third disputed claim term is "redox component." Amgen construes this term to mean "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." Apotex's construction is: "Any thiol-reactive chemical or solution comprising such a chemical that facilitates a reversible thiol exchange with another thiol or the cysteine residues of a protein."

Again, Apotex argues that Amgen's construction is redundant, because it contains terms already expressed in the claim itself. As stated above, the construction offered by Amgen is consistent with the terms of the claim and reflects the express claim language. Amgen's construction does not render any other portion of the claim superfluous. Accordingly, the Court construes the term "redox component" as "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."

The fourth disputed claim term is "final thiol-pair ratio." Amgen's construction is: "Defined by the following equation:

$$\frac{[reductant]^2}{[oxidant]}$$

where the concentrations are the concentrations in the redox component." Apotex's construction is: "The relationship of the reduced and oxidized redox species used in the refold buffer as defined in Equation 1:

$$\frac{[reductant]^2}{[oxidant]}$$

where the ratio is the ratio in the refold mixture." The parties agree that the final thiol-pair ratio is based on the concentrations of the reductant and the oxidant in a solution, as defined by Equation 1 set forth at column 6, lines 23-28, but they disagree as to whether the ratio applies to the redox component (Amgen) or the refold mixture (Apotex).

Again, the plain language of the claim reveals that the redox component is comprised of a final thiol-pair ratio and one or more listed elements, combined "to form a refold mixture." This indicates that the ratio applies to the redox component and not to the refold mixture. The specification supports this conclusion as well, where it states: "After the protein has been contacted with a redox component having the recited thiol-pair ratio and redox buffer strength to form a refold mixture, the refold mixture is then incubated for a desired period of time." DE [77-1], '138 Patent 11:64-67. For this

reason, the Court constructs the term "final thiol-pair ratio" to mean "Defined by the following equation:

$$\frac{[reductant]^2}{[oxidant]}$$

where the concentrations are the concentrations in the redox component."

The fifth disputed claim term is "redox buffer strength." Amgen's construction is: "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." Apotex's construction is: "2[oxidant] + [reductant] where the concentrations are the concentrations in the refold mixture." The parties agree on the equation for defining the redox buffer strength, but dispute which solution (the redox component or the refold mixture) should be used as the basis for calculating the redox buffer strength.

The Court finds that the plain language of claim 1 recites the redox buffer strength of the redox component prior to the formation of the refold mixture; the claim language is careful to say which value is measured at which stage. Adopting Apotex's proposed construction would require the Court to re-write the claim. Additionally, Apotex's proposed construction is contradicted by the teachings of the specification and the rebuttal declaration of Richard C. Willson, Ph.D DE [83-1]. The values of the concentrations of oxidants and reductants used in the equations in the specification are based on the volume of the redox component, and not the refold mixture. Accordingly, based upon the language of the claim and the specification, the Court construes the term "redox buffer strength" as follows: "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."

The sixth claim term in dispute is the term "refold mixture." Amgen's construction is: "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." Apotex's construction is: "A mixture formed from contacting the protein and the refold buffer." Apotex's proposed construction of the term "refold mixture" derives from its proposed construction that the term "*a protein . . . present in a volume at a concentration of 2.0g/L or greater. . . .*" is "a protein . . . present at a concentration of 2.0g/L or greater after dilution in a refold buffer." The Court has rejected that construction and rejects Apotex's construction of the term "refold mixture" as well. The language of the claim, the specification and the state of the prior art support the conclusion that the refold mixture of claim 1 of the '138 Patent would be interpreted by a person of ordinary skill in the art to have a minimum or "floor" concentration at or above about 1g/L. Thus, the Court constructs the term "refold mixture" as "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."

The seventh, and last, disputed claim term of the '138 Patent is the term "2mM or greater." Amgen's construction is: "No construction necessary. The term should be given its plain and ordinary meaning." Apotex's construction is: "2mM or greater, wherein the redox buffer strength is effectively bounded at a maximum of 100mM."

Apotex argues that the specification repeatedly states that the "thiol-pair buffer strength is effectively bounded at a maximum of 100mM" and, therefore, "the specification makes it abundantly clear to one skilled in the art that the patent is using the term '2mM or greater' to describe a redox buffer strength between 2mM and 100mM." DE [76, p. 19]. To the contrary, Amgen argues that the maximum of 100mM referred to in the specification is merely an embodiment, which does not impose a limitation on the language of the claim. Thus, argues Amgen, the term "2mM or greater" means what it says, with no limitation.

"It is the claims that define the metes and bounds of the patentee's invention. Phillips, 415 F.3d at 1313. The patentee is free to choose a broad term and expect to obtain the full scope of its plain and ordinary meaning unless the patentee explicitly redefines the term or disavows its full scope." Thorner v. Sony Computer Entm't Am. LLC, 669 F.3d 1362, 1367 (Fed. Cir. 2012). "[O]ne purpose for examining the specification is to determine if the patentee has limited the scope of the claims." Scimed Life Sys., Inc. v. Advanced Cardiovascular Sys., Inc., 242 F.3d 1337,1341 (Fed. Cir. 2001) (quoting Watts v. XL Sys., Inc., 232 F.3d 877, 882 (Fed. Cir. 2000)). The Court finds that the specification does, indeed, impose an upper limit of 100mM on the thiol-pair buffer strength. The Court is particularly convinced by the fact that the specification repeatedly sets forth a suggested range of redox buffer strengths, yet each time specifically limits the possible ranges, "wherein the thiol-pair buffer strength is effectively bounded at a maximum of 100mM." Accordingly, the Court constructs the claim term ""2mM or greater" to mean "2mM or greater, wherein the redox buffer strength is effectively bounded at a maximum of 100mM."

B. The ’427 Patent

The parties identify two disputed claim terms in the ’427 Patent. They are located in claims 1 and 4, which are set forth below:

> 1. A method of treating a disease requiring peripheral stem cell transplantation in a patient in need of such treatment,
>
> comprising
>
> administering to the patient a hematopoietic stem cell mobilizing-effective amount of G-CSF; and
>
> thereafter administering to the patient a disease treating-effective amount of at least one chemotherapeutic agent.
>
> 4. The method of claim 1, wherein the at least one chemotherapeutic agent opens the enothelial barrier of the patient to render the endothelial barrier permeable for stem cells.

The first term in dispute in the ’427 Patent is “chemotherapeutic agent” as found in claim 1. Amgen’s construction is: “Exogenous substance capable of damaging or destroying microorganisms, parasites or tumor cells.” Apotex’s construction is: “Therapeutic agents which open the endothelial barrier, rendering it permeable for stem cells and/or exogenous substances suited and used to damage or destroy microorganisms, parasites or tumor cells.” The Court concludes, based upon claim 1 and the dependent claim 4, as well as the use of the term “chemotherapeutic agent” in the specification, that the term “chemotherapeutic agent” in claim 1 is not limited to therapeutic agents which open the endothelial barrier. Accordingly, the Court constructs the claim term “chemotherapeutic agent” to mean “Exogenous substance capable of damaging or destroying microorganisms, parasites or tumor cells.”

The final term in dispute in the '427 Patent is the phrase "disease treating-effective amount." Apotex argues that this term is indefinite, thus invalidating the patent. Amgen's construction is: "An amount sufficient to enhance the mobilization of stem cells for recovery from the blood for subsequent peripheral transplantation."

The specification explains that the treatment covered by the claim is for diseases that require stem cell transplantation and that the treatment "depends on the mobilization of the bone marrow stem cells . . . ." The specification also provides a dosage range for the chemotherapeutic agent of "0.05 - 100 mg/kg/day." Accordingly, the Court agrees with Amgen that "[a] person of ordinary skill in the art would understand that a dose of chemotherapeutic agent within this range, when administered after G-CSF, would be the "disease treating-effective amount" needed to achieve the goal of enhancing stem cell mobilization for recovery from blood and subsequent transplantation." DE [77], p.19. Thus, the Court constructs the term "disease treating-effective amount" to mean "[a]n amount sufficient to enhance the mobilization of stem cells for recovery from the blood for subsequent peripheral transplantation."

It is so **ORDERED.**

DONE AND ORDERED in Chambers, Fort Lauderdale, Florida, this 7th day of April, 2016.

JAMES I. COHN
United States District Judge

Copies provided to:

Counsel of record via CM/ECF