IN THE UNITED STATES DISTRICT COURT

FOR THE SOUTHERN DISTRICT OF FLORIDA

Case No. 15-cv-61631-JIC/BSS

AMGEN INC. and AMGEN MANUFACTURING LIMITED,

Plaintiffs,

vs.

APOTEX INC. and APOTEX CORP.,

Defendants.

PLAINTIFFS' OPENING CLAIM CONSTRUCTION BRIEF

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Pursuant to this Court's Supplemental Scheduling Order [D.E. 58], Plaintiffs Amgen Inc. and Amgen Manufacturing Limited (collectively "Amgen") respectfully submit this brief in support of their proposed claim constructions for the patents-in-suit in this case. Pursuant to 42 U.S.C. § 262(*l*)(6)(A), the parties agreed that the following three patents owned by Amgen would be the subject of this suit. U.S. Patent No. 8,952,138 ("the '138 Patent") is entitled "Refolding Proteins Using a Chemically Controlled Redox State," and issued on February 10, 2015. It is attached hereto as Exhibit 1. U.S. Patent No. 6,162,427 ("the '427 Patent"), is entitled "Combination of G-CSF with a Chemotherapeutic Agent for Stem Cell Mobilization," and issued on December 19, 2000. It is attached hereto as Exhibit 2. U.S. Patent No. 5,824,784 ("the '784 Patent"), is entitled "N-Terminally Chemically Modified Protein Compositions and Methods," and issued on October 20, 1998. It is attached hereto as Exhibit 3.

I. Introduction

A. Patents-in-Suit

1. The '138 Patent

The use of recombinant DNA technology began in earnest in the early 1980s and was the basis of the biotechnology revolution. For the first time, scientists could harness the natural mechanisms by which bacterial cells make their own proteins and engineer those bacteria to make therapeutically useful non-bacterial proteins. However, while bacteria could be manipulated into producing non-bacterial (usually mammalian) proteins, the proteins so produced were often non-functional. Proteins are usually produced as chains of amino acids, but generally the protein chain must fold into a specific configuration to be functional—a process referred to as "protein folding." In many instances, bacteria can produce non-bacterial protein chains but lack the ability to properly fold those chains. The proteins are misfolded and/or aggregated with other bacterial proteins and must be artificially unfolded and refolded after being separated from the bacteria. The '138 patent is directed to improved methods for refolding proteins made in bacterial or "non-mammalian" cells.[1]

As the patent specification notes, prior means of refolding recombinant proteins generally relied on the use of very dilute protein solutions and thus necessitated the use of very large volumes. '138 Patent, 1:18–67; Ex. 4 at ¶ 24. However, the need to use very dilute solutions

[1] The technical background of the '138 Patent is further discussed in the Declaration of Dr. Richard Willson ("Willson Declaration"), attached as Exhibit 4 to this brief, the contents of which are incorporated herein by reference.

posed a significant limitation on the production of recombinant proteins on an industrial scale, because of the need for huge refolding tanks and the facilities to house them. Ex. 4 at ¶ 24. The inventors of the '138 Patent discovered that efficient refolding of proteins expressed in non-mammalian expression systems is impacted by the protein concentration, and by the particular conditions relating to breaking ("reducing") and forming ("oxidizing") bonds within the protein (referred to as "redox" chemistry in the patent). Ex. 4 at ¶ 25 & n.3. Their patent teaches how to choose these parameters and others (e.g., the inclusion of one or more chemicals that serve as a denaturant, aggregation suppressor, or protein stabilizer) to optimize and enhance the efficiency of refolding proteins at concentrations significantly higher, i.e., significantly less dilute, than those typically employed in the prior art. Ex. 4 at ¶¶ 30–50. The invention claimed in the '138 Patent is, thus, an improved, redox chemistry-based methodology for efficiently refolding proteins at high concentration.

2. The '427 Patent

The '427 Patent discloses and claims methods of treatment of diseases that require peripheral hematopoietic stem cell transplantation. More specifically, the inventors of the '427 Patent discovered that administration of granulocyte colony-stimulating factor ("G-CSF"), followed by a chemotherapeutic agent enhances stem cell mobilization.

Certain cancer therapies are so severe that a patient's bone marrow—the source of stem cells that make up our blood and immune system—is destroyed or "ablated." The destruction of the bone marrow can be reversed by reconstituting the bone marrow with transplanted hematopoietic stem cells. Hematopoietic stem cells are the progenitor cells that can differentiate and mature into all of the cells that make up the blood and immune system. To reconstitute the bone marrow, the hematopoietic stem cells must first be mobilized and collected from the patient prior to their undergoing the severe cancer therapy. Before the invention of the '427 Patent, it was known in the art that hematopoietic stem cells could be collected from peripheral blood (i.e., the blood circulating through our veins and arteries) by a process known as leukapheresis. Before the invention of the '427 Patent, it was also known that administering G-CSF alone, a chemotherapeutic agent alone, or a chemotherapeutic agent followed by G-CSF could enhance the mobilization of stem cells from bone marrow to peripheral blood for collection by leukapheresis and subsequent transplantation back to the patient. '427 Patent, 1:32–54.

As the '427 Patent discloses, the prior art approaches typically required several leukapheresis sessions to collect sufficient stem cells for a successful transplantation, and these sessions are extremely stressful for the patient. '427 Patent, 1:24–27, 55–57. However, certain patients fail to mobilize sufficient stem cells necessary for successful transplant using the prior art mobilization approaches. The inventors of the '427 Patent surprisingly discovered that when G-CSF was administered *first* followed by administration of a chemotherapeutic agent, the yield of hematopoietic stem cells in peripheral blood was enhanced compared to the prior art approaches. This, in turn, leads to more efficient collection of stem cells in the run-up to ablative cancer treatment, i.e., fewer leukaphareses, and, consequently, greater patient comfort. Thus, the invention disclosed and claimed in the '427 Patent is an improved method of treating diseases requiring peripheral stem cell transplantation, in which G-CSF and a chemotherapeutic agent (or agents), in that order, are administered to enhance stem cell mobilization.

3. The '784 Patent

The '784 Patent discloses and claims modified forms of G-CSF having polyethylene glycol ("PEG") attached to the N-terminus ("N-terminally pegylated G-CSF"), as well as methods of making such modified proteins.[2]

As discussed in the specification, prior art approaches taught that chemically attaching PEG molecules to proteins, referred to as "pegylation," led to greater stability of the pegylated protein, but that the techniques were non-selective, and could attach PEG molecules to any reactive group on the protein. '784 Patent, 1:20–3:5.

Thus, reaction conditions in the prior art produced heterogeneous populations of pegylated proteins, having multiple states of pegylation at various reactive groups. '784 Patent, 3:5–15. The production of a heterogeneous population of pegylated proteins was a limitation to the use of such proteins in pharmaceutical therapeutic applications, because the lot-to-lot biological activity of such a heterogeneous population was unpredictable. '784 Patent, 3:16–39. The invention disclosed and claimed in the '784 Patent allows the selective pegylation of the N-terminus of the G-CSF protein, minimizing the production of G-CSF pegylated at other reactive sites. *See, e.g.*, '784 Patent, 3:47–4:22, claim 1.

[2] The chemical structure of filgrastim, which is a non-pegylated, recombinant form of human G-CSF, is provided in the Willson Declaration at ¶ 22.

II. Law of Claim Construction

Patent claims define the scope of the patent right. *See Phillips* v. *AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (en banc) ("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.") (internal quotation marks omitted). Claim construction is an issue of law. *Markman* v. *Westview Instruments, Inc.*, 517 U.S. 370, 376 (1996). It begins with consideration of the intrinsic evidence of record: i.e., the text of the claims, the specification, and (if in evidence) the prosecution history. *Phillips*, 415 F.3d at 1313, 1317. Claim terms "are generally given their ordinary and customary meaning," which is "the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention." *Id.*, 415 F.3d at 1312–13.

Claims "must be read in view of the specification, of which they are a part," and the specification is usually "the single best guide to the meaning of a disputed term." *Id.*, 415 F.3d at 1315; *see also Vitronics Corp.* v. *Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996) ("[I]t is always necessary to review the specification to determine whether the inventor has used any terms in a manner inconsistent with their ordinary meaning."). When considering the specification "it is improper to read limitations from a preferred embodiment described in the specification—even if it is the only embodiment—into the claims absent a clear indication in the intrinsic record that the patentee intended the claims to be so limited." *Epos Techs. Ltd.* v. *Pegasus Techs. Ltd.*, 766 F.3d 1338, 1341 (Fed. Cir. 2014).

While the Court can also consider the patent's prosecution history (which is intrinsic evidence), in addition to the specification, the prosecution history is often "less useful for claim construction purposes" than the specification, and because it is an "ongoing negotiation between the PTO and the applicant, rather than the final product of that negotiation, it often lacks the clarity of the specification." *Philips*, 415 F.3d at 1317.

Courts 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.*

Claims must "particularly point[] out and distinctly claim[] the subject matter which the

applicant regards as [the] invention." 35 U.S.C. § 112, ¶ 2 (2006).[3] This affords "clear notice of what is claimed, thereby 'appris[ing] the public of what is open to them.' " *Nautilus, Inc.* v. *Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2129 (2014) (quoting *Markman*, 517 U.S. at 373). The Supreme Court has held that Section 112, second paragraph, requires that claims must, when read "in light of the specification and prosecution history, inform those skilled in the art about the scope of the invention with reasonable certainty," or be invalid for indefiniteness. *Id.* "A determination of indefiniteness is a legal conclusion that is drawn from the court's performance of its duty as the construer of claims." *Datamize, LLC* v. *Plumtree Software, Inc.*, 417 F.3d 1342, 1347 (Fed. Cir. 2005).

III. Construction of Disputed Terms

A. '138 Patent

1. "a protein . . . present in a volume at a concentration of 2.0 g/L or greater"

Claim Term	Amgen's Construction	Apotex's Construction
"a protein . . . present in a volume at a concentration of 2.0 g/L or greater" (claim 1)	A protein as it exists in a volume before contacting the volume with a refold buffer. The protein concentration in the volume is 2.0 g/L or greater.	A protein . . . present at a concentration of 2.0 g/L or greater after dilution in a refold buffer

Amgen's proposed construction reflects the clear language of claim 1, set forth below:

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.

'138 Patent, claim 1 (emphasis added).

[3] The pre-America Invents Act statutory provisions apply to the patents-in-suit, as they were filed before September 16, 2012. Leahy-Smith America Invents Act, Pub. L. No. 112-29, § 9(e), 125 Stat. 284, 297 (2011).

Claim 1 clearly recites a "volume" that contains the protein at a concentration of 2.0 g/L or greater. The claim also recites a "refold buffer," comprising several elements. These are "contacted" with one another, or combined, to form the "refold mixture." Prior to formation of the refold mixture, the volume containing the protein at 2.0 g/L or greater is necessarily separate from the refold buffer, otherwise it would not need to be "contacted" with the refold buffer. Amgen's proposed construction matches this logical necessity; Apotex's proposed construction does not.

The specification fully supports Amgen's proposed construction. In one instance, "a protein is expressed in a non-mammalian expression system" and is further processed to be "present in a volume at a concentration of 10 g/L or greater." '138 Patent, 10:17–22. This results in a protein-containing volume, with a protein concentration of 2.0 g/L or greater, prior to any combining step—consistent with Amgen's proposed construction. This protein-containing volume "is then contacted with a refold buffer," representing the combining step that forms the refold mixture. '138 Patent, 10:22–23. As noted by Prof. Willson, the protein concentration in the initial volume, as well as the concentrations of the components of the refold buffer, become diluted when contacted with one another. Ex. 4 ¶ 30. The specification twice discloses that after such a dilution, the protein concentration in the *refold mixture* can be as low as 1 g/L ('138 Patent, 12:40–53, 10:12–16), further condemning Apotex's proposed construction, which is inconsistent with these passages of the specification.

The specification contains another, similar disclosure, where "a protein is expressed in a non-mammalian expression system and is present in a volume at a concentration of 2.0 g/L or greater." '138 Patent, 11:6–20. This protein is then "contacted with a refold buffer," and "[a]fter the protein has been contacted," the resulting "refold mixture is then incubated." '138 Patent, 11:9, 64–67; *see also* '138 Patent, 14:66–15:8 (describing the combination of the refold buffer and an elution volume containing the protein to form a "diluted mixture"); 15:4762 (describing the combination of a volume of solubilized inclusion bodies and a refold buffer to form a "diluted mixture"). Thus, consistent with the logical import of the claim language, the specification repeatedly describes one volume having a protein concentration of 2.0 g/L or greater *prior to* being combined with the refold buffer, to form the refold mixture. Claims "must be construed so as to be consistent with the specification, of which they are a part." *Phillips*, 415

F.3d at 1316. The Court should, therefore, adopt Amgen's proposed construction, which directly mirrors this disclosure.

2. "refold buffer"

Claim Term	Amgen's Construction	Apotex's Construction
"refold buffer" (claim 1)	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.	A preparation that supports the renaturation of protein to biologically active form

The parties agree that the "refold buffer" is "a preparation that supports the renaturation of protein to a biologically active form," which is taken directly from the specification. *See* '138 Patent, 1:46–47. Because step (a) of claim 1 contains the word "comprising" twice, the second sentence of Amgen's proposed construction actually reiterates the claim language itself to emphasize which elements the refold buffer comprises, specifically a redox component,[4] and one or more of a denaturant, an aggregation suppressor and a protein stabilizer. '138 Patent, claim 1. This construction is consistent with principles of English grammar. *See Kruse Tech. P'ship* v. *Volkswagen AG*, 544 F. App'x 943, 949 (Fed. Cir. 2013) ("[A] claim must be read in accordance with the precepts of English grammar." (quoting *In re Hyatt*, 708 F.2d 712, 714 (Fed. Cir. 1983))). To the extent that Apotex's proposed construction would not require the refold buffer as recited in claim 1 to comprise the specific elements listed above, it would be improper because it would contradict the express claim language. "In the patent claim context the term 'comprising' is well understood to mean 'including but not limited to.' " *Cias, Inc.* v. *All. Gaming Corp.*, 504 F.3d 1356, 1360 (Fed. Cir. 2007); *see also Gillette Co.* v. *Energizer Holdings, Inc.*, 405 F.3d 1367, 1372–74 (Fed. Cir. 2005) (noting that "comprising" indicates that the recited feature includes at least the listed elements).

[4] As discussed below, the redox component "comprises" its own elements.

3. "redox component"

Claim Term	Amgen's Construction	Apotex's Construction
"redox component" (claim 1)	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 2 mM or greater.	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

The parties at least agree that the "redox component" 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," as set forth in the specification. *See* '138 Patent, 6:63–66. Amgen's proposed construction further reflects that thiol-reactive chemicals may be used in combination, as indicated by the specification. *See* '138 Patent, 6:66–7:2, 11:57–63 (noting the recited compounds or "combinations thereof" could make up the redox component); *see also* '138 Patent, 3:38–42, 8:30–33, 10:53–54, and 12:49. Furthermore, to ensure that the second use of the term "comprising" in step (a) is clear, the second sentence of Amgen's proposed construction reiterates the claim language itself to explicitly note that it is the "redox component" that comprises the "final thiol-pair ratio" and the "redox buffer strength," two calculated terms as discussed below. Amgen's proposed construction reflects this express claim language, and should therefore be adopted. *See Cias, Inc.*, 504 F.3d at 1360; *see also Gillette Co.*, 405 F.3d at 1372–74.

4. "final thiol-pair ratio"

Claim Term	Amgen's Construction	Apotex's Construction
"final thiol-pair ratio" (claim 1)	Defined by the following equation: $\frac{[reductant]^2}{[oxidant]}$, where the concentrations are the concentrations in the redox component.	The relationship of the reduced and oxidized redox species used in the refold buffer as defined in Equation 1: $\frac{[\text{reductant}]^2}{[\text{oxidant}]}$, Where the ratio is the ratio in the refold mixture

The parties agree the final thiol-pair ratio is defined by Equation 1 set forth at column 6, lines 23–28, but they dispute whether the final thiol-pair ratio refers to a ratio of concentrations

of the oxidant and reductant in the redox component, as in Amgen's proposed construction, or in the refold mixture, as in Apotex's proposed construction. The plain language of claim 1 recites a redox component that is not initially part of the refold mixture, and in that context, the claim recites the final thiol-pair ratio as being an element of the redox component. *See Phillips*, 415 F.3d at 1314 ("[T]he context of the surrounding words of the claim also must be considered in determining the ordinary and customary meaning of those term."). Thus, the plain language of claim 1 recites the final thiol-pair ratio of the redox component *prior* to the formation of the refold mixture. Amgen's proposed construction mirrors this plain language of the claim. The specification also recites the final thiol-pair ratio of the redox component *prior* to the formation of the refold mixture, consistent with Amgen's proposed construction. *See, e.g.*, '138 Patent, 11:64–67 ("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."); *see also* '138 Patent, 10:24–30, 11:11–17, 11:40–46. Apotex's construction requires that the final thiol-pair ratio is that *after* formation of the refold mixture. This improperly contradicts the plain language of the claim.

5. "redox buffer strength"

Claim Term	Amgen's Construction	Apotex's Construction
"redox buffer strength" (claim 1)	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."	$2[oxidant] + [reductant]$, where the concentrations are the concentrations in the refold mixture

The parties agree the redox buffer strength is defined by Equation 2 set forth at column 6, lines 35–38, but they dispute whether the redox buffer strength refers to concentrations of the oxidant and reductant in the redox component, as in Amgen's proposed construction, or in the refold mixture, as in Apotex's proposed construction. The plain language of claim 1 recites a redox component that is not initially part of the refold mixture, and in that context, the claim recites the redox buffer strength as being an element of the redox component. *See Phillips*, 415 F.3d at 1314 ("[T]he context of the surrounding words of the claim also must be considered in determining the ordinary and customary meaning of those term."). Thus, the plain language of claim 1 recites the redox buffer strength of the redox component *prior* to the formation of the refold mixture. Amgen's proposed construction mirrors this plain language of the claim. The

specification also recites the redox buffer strength of the redox component *prior* to the formation of the refold mixture, consistent with Amgen's proposed construction. *See, e.g.*, '138 Patent, 11:64–67 ("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."); *see also* '138 Patent, 10:24–30, 11:11–17, 11:40–46. Apotex's construction improperly contradicts the plain language of the claim.

6. "2 mM or greater"

Claim Term	Amgen's Construction	Apotex's Construction
"2 mM or greater" (claim 1)	No construction is necessary. The term should be given its plain and ordinary meaning.	"2 mM or greater, wherein the redox buffer strength is effectively bounded at a maximum of 100 mM"

A person of ordinary skill in the art at the time of the invention would understand that "2 mM or greater" has a plain meaning, and refers to a redox buffer strength of 2 millimolar or greater. "[W]ords of a claim are generally given their ordinary and customary meaning" which is "the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention." *Phillips*, 415 F.3d at 1312 (internal quotation marks omitted). The Court should, therefore, apply this plain meaning to the term "2 mM or greater."

The Court should reject Apotex's proposed construction because it reads in the limitation "redox buffer strength is effectively bounded at a maximum of 100 mM" from the specification, which is improper. *See Epos Techs. Ltd.*, 766 F.3d at 1341. Rather than representing intentional limits on the scope of the claim, the embodiments that describe upper limits on the redox buffer strength are merely demonstrative of particular conditions used in the examples, and not an absolute limit on range of concentration. *Phillips*, 415 F.3d at 1323 ("One of the best ways to teach a person of ordinary skill in the art how to make and use the invention is to provide an example of how to practice the invention in a particular case."). The specification explains that the method can be applied to "any type of protein," '138 Patent, 4:23–24, and that the "[o]ptimization of the buffer thiol strength and system thiol pair ratio can be tailored to a particular protein." '138 Patent, 4:55–58; 9:10–30. This indicates to a person of ordinary skill in the art that, depending on the protein to be refolded, the optimal redox buffer strength will need to be determined empirically, and need not be effectively bounded at a maximum of 100 mM, as Apotex suggests. Thus, a person of ordinary skill in the art would appreciate that the optimal

redox buffer strength for refolding a particular protein can be determined empirically, according to the teachings in the specification, without a strict upper bound of redox buffer strength.

7. "refold mixture"

Claim Term	Amgen's Construction	Apotex's Construction
"refold mixture" (claim 1)	A mixture formed from contacting (1) the volume in which the concentration of protein is 2.0 g/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 1 g/L protein.	A mixture formed from contacting the protein and the refold buffer

The parties agree that two components are combined to form the refold mixture, the volume containing the protein, and the refold buffer. As explained in the accompanying Declaration of Richard C. Willson, (attached hereto as Exhibit 4), it follows, therefore, that in the method of claim 1, the protein concentration will be diluted from its starting point once combined with the refold buffer to form the refold mixture. Ex. 4 at ¶ 30. Based on the disclosure of the '138 Patent (*see* Ex. 4 at ¶¶ 31–39) and the state of the art at the time of the invention (*see* Ex. 4 at ¶¶ 40–48), a person of ordinary skill in the art would have understood that the refold mixture of claim 1 would have a minimum protein concentration of about 1 g/L. *See* Ex. 4 at ¶¶ 37, 49–50.

As the specification explains, prior art approaches involved protein concentrations in refolding mixtures of "typically 0.01-0.5 g/L." '138 Patent, 1:52–54; Ex. 4 at ¶ 32. The patentees thus distinguished the refolding protein concentration of the claimed invention from the dilute concentrations used in the prior art. Ex. 4 at ¶ 32. The specification also teaches that the protein concentration in the refold mixture can be as low as 1 g/L when practicing the claimed method. *See* '138 Patent 10:12–16, 12:40–53; Ex. 4 at ¶¶ 33–36. Based on these disclosures, the person of ordinary skill in the art would understand that the protein concentration of the refold mixture can be less than 2 g/L, including 1 g/L, but not the dilute protein concentrations of the prior art. Ex. 4 ¶ 37, 49-50.

A person of ordinary skill would further understand from the disclosure in the '138 Patent that the invention "relates to refolding proteins at high concentrations." '138 Patent, 1:11–12, 2:22, 24, 28–29, 4:9, 19, 24, 58; Ex. 4 at ¶¶ 38–39. At the time of the invention, the state of the art of protein refolding was such that a person of ordinary skill in the art would have understood

that protein concentrations of about 1 g/L in a refold mixture was a boundary at or above which the concentration would be considered "high." Ex. 4 at ¶¶ 40–48. A person of ordinary skill in the art would, therefore, understand that refolding protein at a concentration at or above about 1 g/L in the refold mixture is within the scope of claim 1. Ex. 4 ¶ 49.

Fundamentally, there is a factual dispute between the parties whether the concentration at which proteins are refolded according to the method of claim 1 of the '138 Patent is 2.0 g/L or greater, as Apotex maintains,[5] or about 1 g/L or greater, as Amgen maintains. Prof. Willson has provided his testimony that shows that Amgen's proposed construction is the correct one. It is supported by the specification and accurately reflects the interpretation of a person of ordinary skill in the art, based on the state of the art at the time of the invention. Ex. 4 ¶¶ 2650. *See Teva Pharm. USA*, 135 S. Ct. at 841 (courts can consider expert testimony to resolve factual disputes underlying claim interpretation).

B. '427 Patent

For ease of reference, claims 1 and 4 of the '427 Patent 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 endothelial barrier of the patient to render the endothelial barrier permeable for stem cells.

1. "chemotherapeutic agent"

Claim Term	Amgen's Construction	Apotex's Construction
"chemotherapeutic agent" (claim 1)	Exogenous substance capable of damaging or destroying microorganisms, parasites or tumor cells.	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.

[5] *See* Apotex's proposed construction of "a protein . . . present in a volume at a concentration of 2.0 g/L or greater," *supra*.

There is little dispute that a "chemotherapeutic agent" within the meaning of claim 1, is an exogenous substance which can "damage or destroy microorganisms, parasites or tumor cells." *See* '427 Patent, 2:37–39. Amgen's proposed construction defines "chemotherapeutic agent" as a generic term based on function, without specifying a possible mechanism of action—a feature that is expressly recited in claim 4, which depends on claim 1.

Apotex seeks to improperly broaden the scope of "chemotherapeutic agent" by defining it to include an alternative, specifically, the "or" of its "and/or" construction. Apotex's construction encompasses all "therapeutic agents which open the endothelial barrier, rendering it permeable for stem cells," regardless of whether such substances can "damage or destroy microorganisms, parasites or tumor cells." Such a construction is wrong, and ignores the specification and dependent claim 4. Nothing in the specification supports Apotex's construction that a therapeutic agent's ability to open the endothelial barrier *alone* is sufficient to make such an agent a "chemotherapeutic agent" within the meaning of claim 1.

The specification states that "[a]s chemotherapeutic agents in the meaning of the invention[,] those therapeutic agents *may be used* which open the endothelial barrier, rendering it permeable for stem cells." '427 patent, 2:34–36 (emphasis added). *See Phillips*, 415 F.3d at 1316 ("[C]laims must be construed so as to be consistent with the specification, of which they are a part."). In other words, a chemotherapeutic agent within the scope of claim 1 may possess the ability to open the endothelial barrier, or it may not. That is why this proposed mechanism of action is presented in a dependent claim, as a subset of chemotherapeutic agents that damage or destroy micro-organisms, parasites or tumor cells. To the extent Apotex suggests by the "and" of its "and/or" construction, that it would be proper to limit claim 1 to only those chemotherapeutic agents which have both properties (i.e., opening the endothelial barrier and damaging/destroying cells), they are wrong. By principles of claim differentiation, claim 1 should not be so limited, given that dependent claim 4 narrows claim 1 to agents that damage/destroy cells by the specific mechanism of opening the endothelial barrier. *AllVoice Computing PLC* v. *Nuance Commc'ns, Inc.*, 504 F.3d 1236, 1247–48 (Fed. Cir. 2007).

2. "disease treating-effective amount"

Claim Term	Amgen's Construction	Apotex's Construction
"disease treating-effective amount" (claim 1)	An amount sufficient to enhance the mobilization of stem cells for recovery from the blood for subsequent peripheral transplantation.	Indefinite[6]

The term "disease treating-effective amount" is not indefinite and would be understood by a person of ordinary skill in the art based on the specification of the '427 Patent. Amgen's proposed construction correctly reflects that understanding, as informed by the specification, and should be adopted.

The preamble of claim 1 identifies the claimed method as "treating a disease requiring peripheral stem cell transplantation." The amount of administered chemotherapeutic agent(s) would be understood to be an amount sufficient to serve this purpose.

The specification explains that the enhancement of the mobilization of stem cells is part of—and crucial to—the effective treatment of the underlying disease that requires peripheral stem cell transplantation. '427 Patent, 1:5–9 ("The present invention relates to the novel use of G-CSF and a chemotherapeutic agent or a combination of chemotherapeutic agents to produce a pharmaceutical preparation for enhanced mobilization of hematopoietic stem cells in the treatment of diseases requiring peripheral stem cell transplantation."); *see also* '427 Patent, 1:28–31 ("The success of *treatment* crucially depends on the *mobilization of the bone marrow stem cells*, the subsequent return of which permitting to achieve reconstitution of a functioning hematopoietic system." (emphasis added)), 3:15–16. Therefore, a "disease treating-effective amount" is the amount that is sufficient to enhance the mobilization of stem cells for recovery from the blood for subsequent peripheral transplantation.

Paralleling the language of claim 1, the specification contains multiple descriptions of first administering an amount of G-CSF, and subsequently administering an amount of a chemotherapeutic agent, for the purpose of enhancing mobilization of stem cells for collection by leukapheresis prior to transplantation back to a patient, after such patient has undergone ablative anti-tumor therapy. *See* '427 Patent, 2:8–15, 3:4–17, 3:24–30, 3:37–41. The specification identifies a dosage range for the chemotherapeutic agent as "0.05-100 mg/kg/day." *See* '427

[6] Amgen notes that in its pre-suit statement pursuant to 42 U.S.C. § 262(*l*)(3)(B) dated June 29, 2015, Apotex failed to provide any invalidity analysis with respect to the '427 Patent; therefore, Apotex's statement fails to state that Apotex considers "disease treating-effective amount" to be an indefinite claim term. Amgen, accordingly, reserves the right to challenge the propriety of Apotex's litigation-induced change of position.

Patent, 3:11–12. 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. Amgen's construction is consistent with the claim language itself, and is fully supported by the specification. *See Phillips*, 415 F.3d at 1316 ("[C]laims must be construed so as to be consistent with the specification, of which they are a part."). Contrary to Apotex's assertion that the term is indefinite, Amgen's proposed construction, when read in light of the claims and specification, would inform those skilled in the art about the scope of the asserted claims with reasonable certainty. *See Nautilus*, 134 S. Ct. at 2129.

C. '784 Patent[7]

1. "substantially homogenous"

Claim Term	Amgen's Construction	Apotex's Construction
"substantially homogenous" (claims 1, 7, 8)	Homogenous enough to display the advantages of a homogenous preparation, e.g., ease in clinical application and in predictability of lot to lot pharmacokinetics.	No construction proposed

Amgen's proposed construction restates the meaning of this term as it is expressly set forth in the patent specification. '784 Patent, 5:30–35 ("The present 'substantially homogenous' N-terminally pegylated G-CSF preparations provided herein are those which are homogenous enough to display the advantages of a homogenous preparation, e.g., ease in clinical application [and] in predictability of lot to lot pharmacokinetics."). As used in claims 1, 7 and 8, the term "substantially homogenous" modifies several G-CSF preparations, specifically, "preparation of

[7] Amgen notes that Apotex has declined to propose constructions as to each of the terms to be construed for the '784 Patent. Although Apotex explains that it provides no constructions for the '784 Patent because it expired on October 20, 2015 (*see* Parties' Joint Claim Construction Statement [D.E. 69] at n.1), Amgen's suit seeks remedies for all infringing acts that occurred prior to the expiration of the '784 Patent. Apotex has been on notice of the allegations of infringement of the '784 Patent since its receipt of Amgen's listing of patents pursuant to 42 U.S.C. § 262(*l*)(3)(A) (dated February 27, 2015), Amgen's complaint in this matter [D.E. 1] (dated August 6, 2015), as further informed by Amgen's infringement contentions (dated October 5, 2015). Amgen has not withdrawn these allegations, and continues to seek discovery on and remedies for acts of infringement that may have occurred prior the expiration of the '784 Patent. The '784 Patent, therefore, remains at issue in this litigation. Because Apotex has declined to propose constructions for the terms of the '784 Patent, the Court should find that it has waived any argument contesting Amgen's proposed construction. *See Eli Lilly & Co.* v. *Aradigm Corp.*, 376 F.3d 1352, 1360 (Fed. Cir. 2004) (finding waiver of claim construction argument where party never requested that the district court construe terms and never proposed a construction of terms); *accord Syngenta Seeds, Inc.* v. *Monsanto Co.*, 231 F. App'x 954, 960 (Fed. Cir. 2007) (finding waiver for a party's failure to propose construction to district court).

N-terminally pegylated G-CSF" (claim 1), "preparation of N-terminally monoPEGylated G-CSF" (claim 7), and "preparation of monoPEGylated G-CSF"[8] (claim 8).

2. "the sequence identified in SEQ. ID No. 1"/"the amino acid sequence identified in SEQ. ID No. 1"

Claim Term	Amgen's Construction	Apotex's Construction
"the sequence identified in SEQ. ID No. 1" (claim 6)	The amino acid sequence identified in SEQ. ID No. 2.	No construction proposed
"the amino acid sequence identified in SEQ. ID No. 1" (claim 7)	The amino acid sequence encoded by SEQ. ID No. 1; or, in the alternative, the amino acid sequence identified in SEQ. ID No. 2.	No construction proposed

Amgen's proposed constructions merely provide the meaning that a person of ordinary skill in the art would apply to the claimed sequences recited in dependent claims 6 and 7. Claims 6 and 7 both depend from claim 1, and respectively are directed to an N-terminally pegylated G-CSF as in claim 1, where "said G-CSF has the sequence identified in SEQ. ID No. 1" (claim 6) and where "said G-CSF has the amino acid sequence identified in SEQ. ID No. 1" (claim 7). It is beyond reasonable debate that a person of ordinary skill in the art would readily understand that, where claim 1 recites a G-CSF protein, the plainly intended meaning of the phrase "said G-CSF has the sequence identified in SEQ. ID NO. 1" in dependent claim 6 is a reference to the amino acid sequence of the G-CSF protein, which is presented in SEQ. ID NO. 2. It is also beyond reasonable debate that a person of ordinary skill in the art would readily understand that the plainly intended meaning of the phrase "said G-CSF has the amino acid sequence identified in SEQ. ID No. 1" in dependent claim 7 is a reference to the amino acid sequence encoded by the nucleic acid (cDNA) sequence in SEQ. ID NO. 1, or alternatively, the amino acid sequence identified in SEQ. ID NO. 2. The specification also explicitly draws this distinction, noting that the examples used a recombinant G-CSF "having the amino acid sequence (encoded by the DNA sequence) shown below (Seq. ID Nos. 1 and 2)." '784 Patent, 12:50-57. SEQ. ID NO. 1 defines a cDNA sequence that encodes the amino acid sequence (identified in SEQ. ID NO. 2) of the G-CSF protein. When, as here, the intended meaning harmlessly departs from the literal text of the

[8] Claim 8 contains additional limitations that clarify that the G-CSF is "monopegylated" at the N-terminus.

term and the intended meaning is not subject to reasonable debate, Courts unquestionably have the authority to adopt the intended meaning of a term. *See Hoffer* v. *Microsoft Corp.*, 405 F.3d 1326, 1331 (Fed. Cir. 2005); *Novo Indus., L.P.* v. *Micro Molds Corp.*, 350 F.3d 1348, 1356–57 (Fed. Cir. 2003).

3. "pH sufficiently acidic to selectively activate the alpha amino group"

Claim Term	Amgen's Construction	Apotex's Construction
"pH sufficiently acidic to selectively activate the alpha amino group" (claim 10)	A pH at which conjugation of the polymer with the protein (e.g., G-CSF and analogs thereof) predominantly takes place at the N-terminus of the protein and no significant modification of other reactive groups, such as the lysine side chain amino groups, occurs.	No construction proposed

Amgen's proposed construction restates the explanation of this claim term provided by the specification. '784 Patent, 8:9–25. "Alpha amino group" is a term of art that refers to the amino group that defines the N-terminus of a protein, as distinguished from the ε-amino groups on the side chain of the amino acid lysine. *See* '784 Patent, 8:18–19. The specification explains that prior art reactions involved attaching PEG molecules to various reactive groups found on a protein including amino groups. '784 Patent, 1:64–67. A person of ordinary skill in the art would understand from the specification that alpha amino groups at the N-terminus and ε-amino groups of lysine, for example, exhibit "pKa differences." '784 Patent, 8:16–19; 9:23–30. A person of ordinary skill in the art would understand from the teachings of the specification that different amino groups within a protein become reactive at different pH levels, and that, by choosing a pH of the pegylation reaction such that the N-terminal alpha amino group is selectively reactive, the N-terminal alpha amino group can be selectively pegylated, while leaving the other amino groups (such as the ε-amino groups on the side chain of lysine) within the protein unchanged. '784 Patent, 8: 13–25; 9:19–29. The specification would thus inform a person of ordinary skill in the art of the meaning of this claim term.

CONCLUSION

For the foregoing reasons, Amgen respectfully requests that the Court adopt its proposed constructions set forth above.

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CERTIFICATE OF SERVICE

I HEREBY CERTIFY that on December 11, 2015, I electronically filed the foregoing with the Clerk of the Court by using the CM/ECF system which will send a notice of electronic filing to counsel and that a true and correct copy was served via electronic mail on all counsel of parties of record.

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