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' RESPONSIVE CLAIM CONSTRUCTION BRIEF

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I. Introduction

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 response to the opening claim construction brief of Defendants, Apotex Inc. and Apotex Corp. (collectively "Apotex") (D.E. 76). Accompanying Amgen's responsive brief are (1) the Rebuttal Declaration of Richard C. Willson, Ph.D. Regarding Claim Construction of Shultz et al., U.S. Patent No. 8,952,138 (hereinafter "2d Willson Decl.") (attached hereto as Exhibit 1), rebutting the Declaration of Anne S. Robinson, Ph.D., in Support of Defendants' Opening Claim Construction Brief; and (2) the Rebuttal Declaration of Louis M. Pelus, Ph.D. Regarding Claim Construction of Baumann et al., U.S. Patent No. 6,162,427 (hereinafter "Pelus Decl.") (attached hereto as Exhibit 2), rebutting the Declaration of David T. Scadden, M.D., in Support of Defendants' Opening Claim Construction Brief.

II. Shultz et al., U.S. Patent No. 8,952,138

A. The Invention of the '138 Patent

As addressed in Amgen's opening claim construction brief, U.S. Patent No. 8,952,138 ("the '138 Patent") (D.E. 77-1) discloses and claims methods of refolding proteins that have been produced by non-mammalian expression systems, such as bacteria. Bacteria can be genetically manipulated to produce therapeutically useful proteins, but often these proteins are produced in biologically inactive, misfolded forms or in unusable protein aggregates. They must therefore be artificially unfolded and refolded into unaggregated, biologically-active molecules that can be put to therapeutic use. The '138 Patent provides a redox chemistry-based approach for refolding proteins at high concentration, which in turn allows for more efficient refolding operations at industrial scales.

B. Summary of Argument

As discussed below, Apotex's proposed claim constructions are fundamentally flawed because they ignore the language and logical structure of claim 1, both of which are fully supported by the teachings of the patent specification. Indeed, Apotex would effectively rewrite claim 1 to transfer parameters associated with certain elements of the claim and make them limitations of another element, the refold mixture. Apotex further wishes improperly to read limitations into the claim from the specification. For comparison, claim 1 as written is presented next to claim 1 as Apotex would have it:

Claim 1 of the '138 Patent	Apotex's Rewritten version of claim 1
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.	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~~ **and** ~~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~~;~~ **wherein the refold mixture comprises:** **protein at a concentration of 2.0 g/L or greater;** **a final thiol-pair ratio having a range of 0.001-100; and** **a redox buffer strength of 2 mM to 100 mM;** (b) incubating the refold mixture; and (c) isolating the protein from the refold mixture.

The bolded language in the rewritten version of claim 1, starting with "wherein the refold mixture comprises" illustrates how Apotex's constructions have taken the protein concentration of the protein-containing "volume" prior to contact with the refold buffer, as well as the thiol-pair ratio and redox buffer strength of the "redox component," and made them define the "refold mixture." Apotex has also imposed a 100 mM upper limit on redox buffer strength. Claim 1 of the '138 Patent is simply not written that way, and for this reason alone, Apotex's proposed constructions should be rejected.

Furthermore, as discussed herein and in the accompanying 2d Willson Declaration, neither the specification nor prosecution history support Apotex's wholesale rearrangement of the claim. Apotex's proposed constructions, all of which flow from its altered vision of the claim, as above, where features of other claim elements become associated with the "refold mixture," run counter to the intrinsic evidence in this case. It would be erroneous for the Court to adopt them.

C. Construction of Disputed Claim Terms

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

The parties' key dispute is whether the claim term at issue refers to the concentration of protein before or after forming the refold mixture. Under Amgen's proposed construction, the protein concentration is 2 g/L or greater in a volume before that protein-containing volume is contacted with the refold buffer to form the refold mixture. Under Apotex's proposed construction, the protein concentration is that of the refold mixture, after contacting the protein with a refold buffer. As discussed below, Apotex's proposed construction ignores the claim language, and is at odds with the specification. For these reasons, it should be rejected.

The claim language itself is clear that the protein is "present in a volume at a concentration of 2.0 g/L or greater," and that this protein in a volume is contacted with a refold buffer to form a refold mixture. Thus, the "volume" in the preamble of the claim is not a reference to the refold mixture, but instead a reference to the volume in which the protein exists prior to being contacted with the refold buffer. Repeatedly, throughout the specification, the term "volume" is used in this manner, consistent with Amgen's proposed construction. *See* '138 Patent, 3:19–22, 7:16–19, 10:3–4, 10:19–22; 2d Willson Decl. ¶¶ 17–19.

In support of its construction, Apotex argues, "A protein diluted with the refold buffer is the same as what claim 1 and the specification of the '138 patent refer to as a 'refold mixture,'" and that this is "the 'volume' in which folding and refolding takes place." D.E. 76 at 10. But this would mean that in claim 1, the terms "volume" and "refold mixture" are synonymous, violating the principle that different claim terms should be presumed to have different meanings. *See Becton, Dickinson & Co.* v. *Tyco Healthcare Grp., LP*, 616 F.3d 1249, 1254 (Fed. Cir. 2010) ("In the absence of any evidence to the contrary, we must presume that the use of . . . different terms in the claims connotes different meanings.").

In arguing that the specification supports its proposed construction, Apotex and Dr. Robinson focus inappositely on passages in the specification which disclose protein

concentrations of 2 g/L or greater, but do not set 2 g/L as the minimum (or "floor") protein concentration in the refold mixture. *See* D.E. 76 at 10–11; D.E. 76-4 ¶¶ 57, 61. Furthermore, several of the passages on which Apotex and Dr. Robinson rely state that protein concentrations of 2 g/L or greater in the refold mixture are exemplary. For instance, at col. 4, ll. 15–24, the '138 Patent states:

> As described herein, by controlling the thiol-pair buffer strength, in conjunction with thiol-pair ratio and protein concentration, the efficiency of protein folding operations can be optimized and enhanced and the refolding of proteins at high concentrations, for example, 2 g/L or greater, can be achieved.
>
> Thus, in one aspect, the present disclosure relates to the identification and control of redox thiol-pair ratio chemistries that facilitate protein refolding at high protein concentrations, such as concentrations higher than 2.0 g/L.

'138 Patent, 4:15–24 (emphasis added); 2d Willson Decl. ¶¶ 13–14. Thus, 2 g/L is not the floor concentration of the refold mixture as Apotex insists.

Moreover, Apotex and Dr. Robinson completely ignore the disclosures in the specification that allow for a dilution of the protein concentration in the initial protein-containing volume to a concentration as low as 1 g/L in the refold mixture. *See* '138 Patent, 10:12–16[1], 12:44–49; 2d Willson Decl. ¶ 12. Apotex fails to explain how its proposed construction could be proper, when its proposed construction would exclude such embodiments from the scope of the claims. *See Phillips* v. *AWH Corp.*, 415 F.3d 1303, 1316 (Fed. Cir. 2005) ("[C]laims must be construed so as to be consistent with the specification, of which they are a part."). In contrast, Amgen's proposed construction encompasses the embodiments in which the protein concentration is as low as 1 g/L after contacting the initial protein-containing volume with a refold buffer to form the refold mixture. Amgen's proposed construction also encompasses the examples cited by Apotex and Dr. Robinson that involve protein concentrations in the refold mixture at 6 g/L or 12 g/L, which would necessarily involve protein concentrations in the initial protein-containing volume above 2 g/L, prior to contact with a refold buffer to form a refold mixture. *See* '138 Patent, 14:57–58, 15:39–40; 2d Willson Decl. ¶¶ 13–15.

Apotex relies on the prosecution history to support its proposed construction, arguing that the patentees distinguished the claimed invention from "the prior art by arguing that the key

[1] "Further combination with protein stabilizers, aggregation suppressors and redox components, at an optimized Thiol-pair ration [sic] and Thiol-pair Buffer Strength, allows for refolding at concentrations of 1-40 g/L, for example at concentrations of 10-20 g/L."

aspect concerned the refolding of proteins at concentrations of 2.0 g/L or greater after dilution in the refold buffer." D.E. 76 at 11 (emphasis in original). Apotex's characterization of the prosecution history is incorrect. In distinguishing the prior art U.S. Patent No. 7,138,370 (the "'370 Patent") cited by the Examiner,[2] the applicants' basic argument was that the large dilution reported in the '370 Patent—i.e., 250-fold—"did not lend itself to a high-concentration refolding mixture, as recited in applicants' pending claims." D.E. 76-13 at 6. Thus, the applicants characterized the refold mixture of the claims as having a "high" protein concentration, which would be understood to mean a protein concentration of about 1 g/L or greater.[3] 2d Willson Decl. at ¶ 24.; *see also* D.E. 77-4 (hereinafter "1st Willson Decl.") at ¶¶ 38–49. Contrary to Apotex's arguments, the applicants did not represent to the Examiner that applicants' pending claims required protein concentrations to be 2.0 g/L or greater in the refold mixture. Instead, they argued that "nowhere in the [relevant section of the '370 Patent] is the concept of refolding proteins at a concentration of 2.0 g/L or greater disclosed." D.E. 76-13 at 6. This is not a characterization of the pending claims, but rather, a correct characterization of the '370 Patent. 2d Willson Decl. at ¶¶ 21–22.

Apotex failed to mention in its opening brief that after the foregoing arguments were made, the Examiner maintained the rejection of the claims over the '370 Patent. It was only after the applicants' attorney substantiated the magnitude of the 250-fold dilution used in the '370 Patent that the Examiner accepted that the '370 Patent did not anticipate then-pending claim 1 (which did not differ from claim 1 as issued). Thus, contrary to what Apotex suggests, it was not an argument that the refold mixture of claim 1 had a protein concentration of 2 g/L or greater that was the basis for allowance. Rather, it was the substantiation that the prior art '370 Patent refolded at a dilute, not a high, protein concentration that got the claim allowed. 2d Willson Decl. at ¶¶ 27–29. In view of the complete prosecution history, there is no basis therein to interpret claim 1 of the '138 Patent as Apotex proposes, i.e. requiring a protein concentration in the refold mixture of 2.0 g/L or higher. Rather, as Amgen proposes, it is the initial protein-containing volume that has a protein concentration of 2.0 g/L or greater.

For the foregoing reasons, Apotex's proposed construction should be rejected and

[2] The relevant passage of the '370 Patent relied on by the Examiner is column 76 (attached as Exhibit B of 2d Willson Decl.). It reports no protein concentrations, in the refold mixture or otherwise.

[3] The language of then-pending claim 1 was the same as the issued claim 1 of the '138 Patent.

Amgen's proposed construction should be adopted.

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 crux of the parties' dispute is whether the construction should state what the refold buffer comprises. Apotex's brief criticizes Amgen's proposed construction as containing redundant language already in the claim. But, as pointed out in Amgen's opening brief, part (a) of claim 1 contains the term "comprising" twice and Amgen's proposed construction was offered to identify precisely the elements that the refold buffer comprises. Part (a) of claim 1 uses "comprising" twice in a nested fashion, such that one of the elements of which the refold buffer is comprised, the redox component, itself comprises other elements as discussed below. Together, Amgen's proposed constructions of "refold buffer" and "redox component" identify which elements go with which "comprising" as would be understood by a person of ordinary skill in the art. For this reason, Amgen's proposed construction of "refold buffer" should be adopted.

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

As with "refold buffer," one of the parties' disputes with respect to "redox component" centers on whether the construction should state what the redox component comprises. Apotex argues that the portion of Amgen's proposed construction stating what the redox component comprises is unnecessary because the details regarding the thiol-pair ratio and redox buffer strength are already present in the claim. For the reasons just discussed with respect to "refold buffer," Amgen's proposed construction is intended to precisely identify the elements that the

redox component comprises.

There is another difference between the parties' proposed constructions of "redox component." Whereas Apotex's proposed construction fails to mention that the redox component may consist of combinations of thiol-reactive chemicals, Amgen's proposed construction specifies that combinations of thiol-reactive chemicals can be used to form the redox component, consistent with the specification of the '138 Patent. '138 Patent, 6:63–7:2.[4]

Because of the specificity that Amgen's proposed construction provides with respect to the elements that make up the redox component, and because it specifies the use of combinations of thiol-reactive chemicals (consistent with the pairs of thiol-reactive chemicals described throughout the specification),[5] it should be adopted.

4. "final thiol-pair ratio"/ "redox buffer strength"

Claim Term	Amgen's Construction	Apotex's Construction
"final thiol-pair ratio" (claim 1)	Defined by the following equation: $\frac{[\text{reductant}]^2}{[\text{oxidant}]}$, 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
"redox buffer strength" (claim 1)	Also called "buffer thiol strength," "thiol-pair buffer strength," or "thiol-pair strength," defined by the following equation: $2[\text{oxidant}] + [\text{reductant}]$, where the concentrations are the concentrations in the redox component.	$2[\text{oxidant}] + [\text{reductant}]$, where the concentrations are the concentrations in the refold mixture

The terms "final thiol-pair ratio" and "redox buffer strength" are defined mathematically in the specification. The parties agree that the equation used to calculate "final thiol-pair ratio" is Equation 1 at col. 6, ll. 25–27 of the '138 Patent, $[\text{reductant}]^2/[\text{oxidant}]$, and that the equation

[4] "As used herein, the term 'redox component' means any thiol-reactive chemical or solution comprising such a chemical that facilitates a reversible thiol exchange with another thiol or cysteine residues of a protein. Examples of such compounds include, but are not limited to, glutathione-reduced, glutathione-oxidized, cysteine, cystine, cysteamine, cystamine, beta-mercaptoethanol, and combinations thereof." '138 Patent, 6:63–7:2 (emphasis added).

[5] *See, e.g.*, '138 Patent, 12:48–49 ("the redox pair (e.g., cysteine and cystamine)").

used to calculate "redox buffer strength" is Equation 2 at col. 6, ll. 36–38, 2[oxidant]+[reductant]. As is evident, the equations that govern these claim terms have the same variables, "[reductant]" and "[oxidant]." In scientific usage, brackets ("[ ]") signify the concentration of a chemical compound, calculated as amount per volume. 2d Willson Decl. ¶ 33.

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

As set forth previously, claim 1 recites

> 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.

As is evident from the claim language, the "final thiol-pair ratio" and "redox buffer strength" are characteristics of the "redox component" and not the "refold mixture," and it thus follows that the values of the concentrations of oxidants and reductants used in Equations 1 and 2 be based on the volume of the redox component, and not the refold mixture. 2d Willson Decl. ¶¶ 34–36.

Like the claim language itself, the specification uses the terms "final thiol-pair ratio" and "redox buffer strength" in association with the redox component, not the refold mixture:

> The protein is then contacted with a refold buffer comprising a denaturant, an aggregation suppressor, a protein stabilizer and a redox component, wherein the redox component has a final thiol-pair ratio (as defined herein) having a range of 0.001 to 100 . . . and a Thiol-pair [i.e. redox] buffer strength (as defined herein) equal to or greater than 2 mM[.]

'138 Patent, 10:22–30 (emphasis added). Because it is the redox component, not the refold mixture, that has a "final thiol-pair ratio" and a "redox buffer strength," the concentrations of the oxidants and reductants used to calculate these terms should be based on the volume of the redox component, not the refold mixture.

To support its argument that "final thiol-pair ratio" and "redox buffer strength" should be calculated using concentrations based on the volume of the refold mixture, Apotex twice relies on the following passage from the '138 Patent:

> The optimal refold chemistry for a given protein represents a careful balance that maximizes the folded/oxidized state while minimizing undesirable product species . . . . One factor that is important in achieving this balance is the redox-state of the refold system. The redox-state is affected by many factors including . . . the ratio and concentration of the redox couple chemicals in the refold solution.

'138 Patent, 8:19–36 (emphasis added). Apotex has incompletely quoted the disclosure at column 8 of the '138 Patent, and, in so doing, has distorted the patent's teachings to leave the incorrect impression that the concentrations of redox chemicals (i.e., oxidants and reductants) used to calculate the thiol-pair ratio and redox buffer strength according to Equations 1 and 2, respectively, are concentrations in the "refold solution," i.e. refold mixture.

The '138 Patent at column 8, lines 19 to 43, actually states the following:

> The optimal refold chemistry for a given protein represents a careful balance that maximizes the folded/oxidized state while minimizing undesirable product species . . . . One factor that is important in achieving this balance is the redox-state of the refold system. The redox-state is affected by many factors, including, but not limited to, the number of cysteine residues contained in the protein, the ratio and concentration of the redox couple chemicals in the refold solution (e.g., cysteine, cystine, cystamine, cysteamine, glutathione-reduced and glutathione-oxidized), the concentration of reductant carried over from the solubilization buffer (e.g., DTT, glutathione and beta-mercaptoethanol), the level of heavy metals in the mixture, and the concentration of oxygen in the solution.
>
> Thiol-pair ratio and thiol-pair buffer strength are defined in Equations 1 and 2, infra [sic, supra], using cysteine and cystamine as an example reductant and oxidant, respectively. These quantities, coupled with protein concentration and reductant carry-over from the solubilization, can be factors in achieving a balance between the thiol-pair ratio and the thiol-pair buffer strength.

'138 Patent, 8:19–46 (emphasis added).

In context, the inventors of the '138 Patent are acknowledging in column 8, as they do

repeatedly throughout the specification (*see, e.g.*, 4:46–58[6]), that numerous factors affect the redox state in the refold mixture where protein refolding takes place, including the "redox couple chemicals" [i.e., the thiol-reactive chemicals of the redox component] as well as the cysteine residues of the protein. But such an acknowledgment is not a teaching that thiol-pair ratio and redox buffer strength are to be calculated based on the concentrations of "redox couple chemicals" and cysteine residues of the protein in the refold mixture. In fact, as is clear from the second paragraph cited above (which Apotex omitted), "these quantities" (i.e., thiol-pair ratio and redox buffer strength) are considered separate and distinct from the other "factors" in the refold mixture. The implication is that they are separately calculated. In essence, the inventors warn that other factors in the refold mixture can affect the "the balance between the thiol-pair ratio and the thiol-pair buffer strength," the elements of which the redox component is comprised. 2d Willson Decl. ¶ 42.

Hence, the '138 Patent teaches an empirical approach to finding optimal redox conditions for refolding any protein by systematically varying parameters within the researcher's control, those being the "final thiol-pair ratio" and "redox buffer strength" of the redox component, and testing whether, once combined with the protein-containing volume to form a refold mixture, other factors in the refold mixture (such as cysteine residues of the protein, carry-over of chemicals from a prior process step, etc.) affect "the balance" between these parameters. For example, the '138 Patent teaches:

> Prior to the present disclosure a specific controlled investigation of the independent effects of thiol-pair ratio and thiol-pair buffer strength had not been disclosed for complex proteins.
>
> * * * *
>
> Thus, in one aspect, the present disclosure relates to the identification and control of redox thiol-pair ratio chemistries that facilitate protein refolding at high protein concentrations, such as concentrations higher than 2.0 g/L. The method can be

[6] "The buffer thiol-pair ratio is, however, only one component in determining the total system thiol-pair ratio in the total reaction. Since the cysteine residues in the unfolded protein are reactants as well, the buffer thiol strength needs to vary in proportion with increases in protein concentration to achieve the optimal system thiol-pair ratio. Thus, in addition to demonstrating that buffer thiol strength interacts with the thiol-pair ratio, it has also been shown that the buffer thiol strength relates to the protein concentration as well. Optimization of the buffer thiol strength and the system thiol pair ratio can be tailored to a particular protein, such as a complex protein, to minimize cysteine mispairing yet still facilitate a refold at a high concentration." '138 Patent, 4:46–58.

> applied to any type of protein, including simple proteins and complex proteins . . . .
>
> * * * *
>
> A mathematical formula was deduced to allow the precise calculation of the ratios and strengths of individual redox couple components to achieve matrices of buffer thiol-pair ratio and buffer thiol strength. Once this relationship was established, it was possible to systematically demonstrate that thiol buffer strength and the thiol-pair ratio interact to define the distribution of resulting product-related species in a refolding reaction.
>
> * * * *
>
> Optimization of the buffer thiol strength and the system thiol pair ratio can be tailored to a particular protein, such as a complex protein, to minimize cysteine mispairing yet still facilitate a refold at a high concentration.
>
> * * * *
>
> Optimization of the redox component[:] Thiol-pair Ratios and Thiol-pair Buffer Strengths can be performed for each protein. A matrix or series of multifactorial matrices can be evaluated to optimize the refolding reaction for conditions that optimize yield and distributions of desired species.

'138 Patent, 4:12–15, 4:20–58, 9:20–24 (emphasis added). These and other passages of the '138 Patent emphasize a controlled, systematic approach for evaluating "precisely" calculable thiol-pair ratios and redox buffer strengths. What would be within a researcher's control, and the only thing that would form the basis of "precise calculations" are the concentrations of oxidants and reductants in the redox component. These are the solutions that a researcher can prepare by weighing out precise amounts of oxidants (e.g., cystamine) and reductants (e.g., cysteine) and adding them to a volume of liquid to make up the redox component. Thus, it is consistent with these teachings that the concentrations of these thiol-reactive chemicals in the volume of the redox component be used to calculate the final thiol-pair ratio and redox buffer strength according Equations 1 and 2, respectively, in column 6 of the '138 Patent. Calculations based on the other, less controllable, and even unknown, thiol-reactive chemicals in the refold mixture would not be precise. 2d Willson Decl. ¶¶ 42–45.

Furthermore, both Equations 1 and 2 are presented in the patent with a "side equation" that illustrates what the inventors intended to go into the calculation of the thiol-pair ratio and redox buffer strength. Specifically Equation 1 is presented as:

$$\text{Buffer TPR} = \frac{[\text{reductant}]^2}{[\text{oxidant}]} = \frac{[\text{cysteine}]^2}{[\text{cystamine}]}$$

And Equation 2 is presented as:

$$\text{Thiol-pair Buffer Strength} = 2[\text{oxidant}] + [\text{reductant}] = 2[\text{cystamine}] + [\text{cysteine}]$$

Notably, neither "side equation" includes thiol-reactive cysteine residues of the protein or other thiol-reactive chemicals within the refold mixture (e.g., chemicals carried over from solubilization). This too, supports Amgen's proposed construction that these calculated claim terms are based on concentrations of oxidants and reductants that one would use to prepare the redox component, not the total mix of thiol-reactive chemicals present in the refold mixture. 2d Willson Decl. ¶ 46–48.

Although Apotex's expert, Dr. Robinson, asserts at paragraphs 75 and 82 of her declaration that, "the inventors clearly intended that the 'total reaction,' protein and all, be included when calculating the final thiol-pair ratio" and that "[t]he inventors clearly intended that the 'total reaction,' protein and all, be included when calculating the redox buffer strength," there is no support in the specification for these assertions. The inventors never report calculating thiol-pair ratio and redox buffer strength in this fashion or how one would go about doing so. 2d Willson Decl. ¶ 40.

For all the foregoing reasons, the Court should adopt Amgen's proposed constructions for the terms 'final thiol-pair ratio' and 'redox buffer strength,' and should reject Apotex's proposed constructions.

5. "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"

The phrase "2 mM or greater" modifies the term "redox buffer strength" in claim 1 of the '138 Patent. Apotex's proposed construction would tack on to the plain language of the claim an additional phrase "wherein the redox buffer strength is effectively bounded at a maximum of 100 mM" for the uncompelling reason that this phrase appears in several locations in the specification. In effect, Apotex is proposing an upper limit on the redox buffer strength such that "2 mM or greater" is actually a range of 2 mM to 100 mM, and presumably (although neither Apotex nor its expert Dr. Robinson explicitly say so) Apotex wants this concentration range to be based on the volume of the refold mixture (which would be consistent with Apotex's proposed construction of "redox buffer strength").

With no justification, Apotex's proposed construction improperly reads a limitation into the claim from certain portions of the specification and ignores the rest of its teachings. Reading in such limitations is improper, even when, as here, the specification discloses several embodiments that include the limitation that is, nonetheless, absent from the claims. *See Epos Techs. Ltd.* v. *Pegasus Techs. Ltd.*, 766 F.3d 1338, 1343–44 (Fed. Cir. 2014) (rejecting claim constructions that improperly included limitations that were repeatedly disclosed in the specification, where the specification did not clearly indicate that the claims should include such limitations). There is every indication (including the claim language itself) that the inventors did not intend to place a 100 mM upper limit on redox buffer strength, and so, none should be read into the claim.

The examples in the specification repeatedly indicate that, during the initial testing to identify the optimal redox buffer strength, a sufficiently large range of redox buffer strengths may be tested. *See, e.g.*, '138 Patent, 9:20–34 (noting that one can "optimize the refolding reaction" by "systematically evaluat[ing] redox chemistries, Thiol-pair ratios, Thiol-pair Buffer Strengths" using conditions that vary each component "over a range of at least three concentration or pH levels"); *see also* '138 Patent, 10:54–11:5, 11:54–63. The patentees clearly disclosed that optimal redox conditions would have to be determined empirically for a given protein. *See, e.g.*, '138 Patent, 9:20–34, 10:54–11:5, 11:54–63; 2d Willson Decl. ¶ 51. It would be initially unknown whether the redox buffer strength needed to exceed 100 mM, and thus the claim allows for the possibility that it might. Apotex's improper effort to read such limitations from the specification into the claims should be rejected, and Amgen's proposed construction should be adopted.

6. "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' dispute about the construction of "refold mixture" is related to their dispute about the meaning of "a protein . . . present in a volume at a concentration of 2.0 g/L or greater,"

discussed above. According to Amgen's proposed construction, because the claim allows for dilution upon formation of the refold mixture, the floor of the protein concentration in the refold mixture is lower than 2.0 g/L, and should be interpreted to have a floor of about 1 g/L protein. Although its proposed construction for "refold mixture" does not so state, based on Apotex's proposed construction of "a protein . . . present in a volume at a concentration of 2.0 g/L or greater," Apotex effectively proposes that the floor protein concentration in the refold mixture is 2.0 g/L. Where the parties are in agreement, however, is that the protein concentration in the refold mixture is "high." As discussed in Amgen's opening claim construction brief and supporting declaration of Dr. Willson (D.E. 77 at 11–12; 1st Willson Decl. ¶¶ 36–50), the focus of the invention in the '138 Patent is on refolding proteins at high concentrations. Apotex's expert, Dr. Robinson, agrees and characterizes the claimed invention of the '138 Patent as pertaining to protein refolding at high concentrations. *See, e.g.*, D.E. 76-4 ¶ 60.

As the claim language clearly indicates, the protein "present in a volume at a concentration of 2.0 g/L or greater" is contacted with a refold buffer to form the refold mixture, thus allowing for some dilution. Because the claimed method is directed to high protein concentration refolding, the dilution called for by the claim language must result in a concentration of protein in the refold mixture that remains high, and distinct from the dilute protein refolding conditions of the prior art. Since it was understood in the art that protein refolding at "high" concentrations meant at or above a protein concentration of about 1 g/L or greater (*see* D.E. 77 at 11–12; 1st Willson Decl. ¶¶ 36–50) 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 of about 1 g/L.

In support for its proposed construction, Apotex asserts that Amgen's proposed lower limit of "at or above about1 g/L" "is unsupported by any of the intrinsic evidence." D.E. 76 at 18. Apotex is flatly incorrect. As mentioned above in Section II.C.1, the specification teaches in multiple places that the concentration of the refold mixture can be as low as 1 g/L. *See* '138 Patent, 10:12–16, 12:44–49; 2d Willson Decl. ¶ 12. Apotex has ignored those sections of the specification entirely. Similarly, Apotex's expert, Dr. Robinson, also ignores the disclosures in the specification that allow for protein concentration as low as 1 g/L in the refold mixture. *See* D.E. 76-4 ¶¶ 57–61. Apotex's argument therefore fails, for lack of consideration of the clear intrinsic evidence supporting Amgen's proposed construction. *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."). Furthermore, as discussed by Dr. Willson in his first declaration, the state of the art at the time of the invention was such that claim 1 would be understood to have a refold mixture in which the protein concentration was high, that is, with a protein concentration at or above about 1 g/L. 1st Willson Decl. ¶¶ 36–50.

Thus, based on both intrinsic and extrinsic evidence, Amgen's proposed construction should be adopted.

III. Baumann et al., U.S. Patent No. 6,162,427

A. The Invention of the '427 Patent

U.S. Patent No. 6,162,427 ("the '427 Patent") (D.E. 77-2) discloses and claims methods of treatment of diseases that require peripheral hematopoietic stem cell transplantation. At the time of the invention of the '427 Patent, a typical protocol for treating a patient in need of a peripheral stem cell transplant entailed (1) administering an agent or agents to the patient that would mobilize stem cells from bone marrow to peripheral blood; (2) collecting the stem cells from peripheral blood by leukapheresis; (3) storing the collected stem cells; (4) irradiating, or administering high doses of cytotoxic agents to, the patient, to obliterate cells in bone marrow, preparing it to accept the transplant;[7] and (5) reinfusing the patient with the previously collected and stored peripheral stem cells, which home to bone marrow and restore the hematopoietic system of the patient. Pelus Decl. ¶¶ 26–28.

Whereas G-CSF alone, chemotherapeutic agents alone, and combinations of a chemotherapeutic agent and G-CSF (in that order) had been administered to patients in the prior art for purposes of stem cell mobilization (step (1) in the protocol above), the inventors of the '427 Patent discovered that administering G-CSF followed by administration of a chemotherapeutic agent surprisingly resulted in enhanced stem cell concentrations in peripheral blood, improving the efficiency of collection. *See* '427 Patent, 1:62–65; Pelus Decl. ¶¶ 32–33. Based on this discovery, the inventors claimed a method of treating a disease requiring peripheral stem cell transplantation that features their novel approach—the administration of G-CSF followed by administration of a chemotherapeutic agent to enhance stem cell mobilization.

[7] The '427 Patent refers to this step of the protocol as "myeloablative or myelotoxic therapy," 1:57–58, or "antitumor therapy," 3:25. This step may also be referred to as "cytoreductive conditioning," meaning that the number of cells ("cyto") is being reduced in the bone marrow by virtue of being killed by the radiation or cytotoxic agents. Pelus Decl. ¶ 26.

B. Summary of Argument

Reading the specification of the '427 Patent leaves no doubt that the chemotherapeutic agent referred to in claim 1 is being administered for the purpose of enhancing stem cell mobilization (step (1), above) and not for the purpose of obliterating cells within the bone marrow, readying it for the transplant (step (4), above). Pelus Decl. ¶¶ 66–68. It would also be understood that the chemotherapeutic agent was being given in an amount that serves the purpose of enhanced stem cell mobilization, so that more stem cells are in the peripheral blood and can be more efficiently collected for subsequent transplantation back into the patient in need of such treatment. Pelus Decl. ¶¶ 68–71. It is also abundantly clear that the inventors did not intend the chemotherapeutic agent of claim 1 to be (1) limited to only those agents that mobilize stem cells by one specific mechanism of action, viz., opening the endothelial barrier rendering it permeable to stem cells or (2) inclusive of agents that work by the foregoing mechanism of action regardless of whether they damage or destroy cells. Rather, the genus of chemotherapeutic agents of claim 1 are those that function to damage or destroy cells, a subset of which agents may achieve stem cell mobilization by opening the endothelial barrier, rendering it permeable to stem cells. Pelus Decl. ¶¶ 41–61.

Whereas Apotex's approach to claim construction for the '138 Patent was to re-write the claim, its strategy for the '427 Patent is to unnecessarily cause confusion. Apotex has proposed a construction for "chemotherapeutic agent" that obfuscates the scope of claim 1, while ignoring the teachings of the specification and the import of dependent claims. And, in arguing that "disease treating effective-amount" is indefinite, Apotex attempts to introduce ambiguity where none exists. Both of Apotex's arguments should be rejected.

C. Construction of Disputed Claim Terms

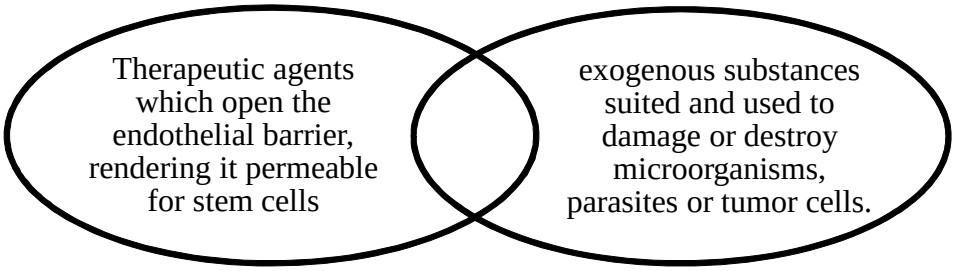
For context, the language of claim 1 of the '427 Patent reads as follows, with the disputed terms underlined:

> 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.

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.

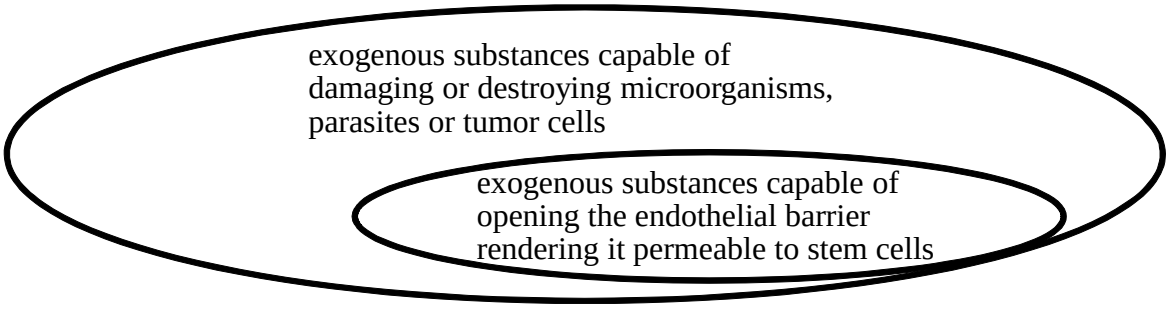
Apotex's proposed construction with its use of "and/or" confusingly encompasses alternative and overlapping genuses. As described in the accompanying declaration of Amgen's expert, Dr. Pelus, Apotex's proposed construction can be represented by a Venn diagram:



Pelus Decl. ¶¶ 46–48. Apotex, however, cannot point to anything in the specification that supports its interpretation of "chemotherapeutic agent" as including agents that only open the endothelial barrier, rendering it permeable for stem cells, but do not serve to damage or destroy cells. The portion of the specification Apotex cites at col. 2, ll. 34–39[8] merely indicates that, for stem cell mobilization purposes, agents which open the endothelial barrier may be a useful subset of exogenous substances that damage or destroy cells. Pelus Decl. ¶¶ 49–53. Moreover, because dependent claim 4 specifies the particular mechanism of action of opening the endothelial barrier to render it permeable to stem cells, the basic principles of claim differentiation would indicate that the chemotherapeutic agent of claim 1 is not limited to this or any other particular mechanism of action. *See Philips*, 415 F.3d at 1315 ("[T]he presence of a dependent claim that adds a particular limitation gives rise to a presumption that the limitation in question is not present in the independent claim."). Given the teachings of the '427 Patent specification and the inclusion of dependent claim 4, the term "chemotherapeutic agent" as used

[8] "As 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. Hereinbelow, chemotherapeutic agents are understood to be exogenous substances suited and used to damage or destroy microorganisms, parasites or tumor cells." '427 Patent, 2:34–39 (emphasis added).

in claim 1 would be understood by a person of ordinary skill in the art to mean, as Amgen proposes, a genus of "exogenous substances capable of damaging or destroying microorganisms, parasites or tumor cells," within which would be a subgenus of such substances that are capable of mobilizing stem cells by opening the endothelial barrier, rendering it permeable to stem cells. Pelus Decl. ¶¶ 49–53. This may be illustrated as follows:



The aspect of Apotex's proposed construction that would require the chemotherapeutic agents of claim 1 to work only according to the particular mechanism of action of opening the endothelial barrier would also run counter to the knowledge in the art at the time of the invention. At that time, the exact mechanism of action by which particular chemotherapeutic agents contributed to stem cell mobilization was not clear, and thus a person of ordinary skill in the art would not have understood claim 1 to be limited to a particular mechanism of action, and certainly not to one that had not been scientifically proven. Pelus Decl. ¶¶ 54–60.

For the foregoing reasons, Apotex's proposed construction should be rejected. Amgen's proposed construction, in contrast, is entirely supported by the specification, the claims, and the state of the art at the time of the invention, and should be adopted.

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[9]

The parties dispute the definiteness of the claim term "disease treating-effective amount"

[9] 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 failed 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.

in claim 1 of the '427 Patent, and thus, more is at stake than the meaning of the claim term, but rather, the very validity of the claim itself. Definiteness under 35 U.S.C. § 112, ¶ 2, requires that "a patent's claims, viewed in light of the specification and prosecution history, inform those skilled in the art about the scope of the invention with reasonable certainty." *See Nautilus, Inc.* v. *Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2129 (2014). As discussed below, claim 1 of the '427 Patent satisfies this requirement.

Apotex's argument is that, because "disease treating-effective amount" modifies "chemotherapeutic agent," the former term "could mean the amount of a chemotherapeutic agent necessary to: (1) enhance mobilization of stem cells, (2) damage or destroy tumor cells; and/or (3) enhance stem cell mobilization and damage or destroy tumor cells," and is therefore indefinite. D.E. 76 at 20 (emphasis added). Notably, Apotex did not challenge the definiteness of "chemotherapeutic agent" even though it proposed an "and/or" construction of that term. The sheer inconsistency of Apotex's positions is reason enough to reject its indefiniteness argument.

Apotex relies on the following passage from the '427 Patent for its argument:

> In addition, administration of G-CSF and a chemotherapeutic agent in the run-up to a, e.g., antitumor therapy offers the opportunity of recovering the stem cells mobilized in large amounts from the blood with higher efficiency (e.g., using leukapheresis), then performing the antitumor therapy using a cytostatic agent or irradiation and subsequently, conducting the peripheral stem cell transplantation.

'427 Patent, 3:24–30. A person of ordinary skill in the art would understand from this passage that the chemotherapeutic agent being administered after G-CSF is for the purpose of enhancing mobilization of stem cells to "recover[] the stem cells mobilized in large amounts from the blood with higher efficiency," and not for "antitumor therapy," the term that the '427 Patent uses for the step in a transplant protocol in which the cellular components of the bone marrow are obliterated by irradiation or cytotoxic agents. Pelus Decl. ¶¶ 63–66. This understanding is reinforced by the numerous other passages in the '427 Patent which also explain that the chemotherapeutic agent is being given for the purpose of enhancing mobilization of hematopoietic stem cells prior to recovery or collection by leukapheresis. For example, the abstract of the '427 Patent recites:

> The invention relates to the use of G-CSF in combination with a chemotherapeutic agent (in particular, cyclophosphamide) to produce a pharmaceutical preparation for boosting the mobilization of hematopoietic stem cells from bone marrow in the treatment of diseases requiring peripheral stem cell

> transplantation. The claimed combination results in more efficient leukapheresis, e.g., before myeloblative or myelotoxic therapy.

'427 Patent, abstract (emphasis added); s*ee also* '427 Patent, 1:5–7, 1:67–2:15; Pelus Decl. ¶¶ 67–68.

Contrary to Apotex's argument, a person of ordinary skill in the art would understand that the specific amount of the chemotherapeutic agent would be one that was effective to enhance mobilization of stem cells for collection by leukapheresis. Pelus Decl. ¶¶ 67–70. The '427 Patent provides a dosage range of 0.05–100 mg/kg/day within which to work. *See* '427 Patent, 3:11–12; Pelus Decl. ¶ 69. Identifying an effective dose would have been within the ability of a person of ordinary skill in the art at the time of the invention. Pelus Decl. ¶ 70. Since a person of ordinary skill in the art would understand the purpose for which the chemotherapeutic agent was being given (stem cell mobilization) and could determine a disease treating-effective dose to enhance stem cell mobilization, the term "disease treating-effective amount" is not indefinite. Rather, the term fully complies with 35 U.S.C. § 112, ¶ 2, and meets the legal standard established in *Nautilus*.

For the foregoing reasons, Apotex's argument should be rejected, and Amgen's proposed construction should be adopted.

IV. Kinstler et al., U.S. Patent No. 5,824,784

Apotex has not proposed constructions or any counter-argument as to Amgen's proposed constructions, and therefore Amgen offers no response here. Amgen respectfully reserves the right to reply to any later-added proposed constructions or counter-arguments as to Amgen's proposed constructions that may be presented by Apotex. *See* D.E. 77 at 15 n.7.

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 January 8, 2016, 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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