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' REPLY CLAIM CONSTRUCTION BRIEF

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I. Shultz et al., U.S. Patent No. 8,952,138 ("the '138 Patent")

A. Preliminary Statement

The parties dispute the construction of each claim term in the Joint Claim Construction Statement ("JCCS"). D.E. 69. Major disagreements have crystallized around the parties' differing views of the "refold mixture" element of claim 1, specifically, what its minimum protein concentration is and what role it plays in the calculation of the mathematically defined claim terms, "final thiol-pair ratio" and "redox buffer strength."

The dispute about the minimum protein concentration in the refold mixture reduces to a handful of questions:

- Is the "volume" referred to in the preamble of claim 1, which contains protein at a concentration of 2.0 g/L or greater, separate and distinct from the "refold mixture" referred to in the body of the claim?
- Does the claim language allow for dilution of the protein in the "volume" when it is contacted with the refold buffer to form the refold mixture, and thus allow for a minimum protein concentration in the refold mixture less than 2.0 g/L?
- Would it be understood by skilled artisans that the protein concentration in the refold mixture is high, and thus would include protein concentrations at or above 1 g/L?

The answers bear not only on the term "refold mixture" but also on the term "a protein . . . present in a volume at a concentration of 2.0 g/L or greater." The answer to each question, Amgen submits, is "yes," based on both the intrinsic and extrinsic evidence of record.

As to the role of the refold mixture in the calculation of "final thiol-pair ratio" and "redox buffer strength," Amgen submits that these mathematically derived values should not be based on the concentrations of oxidants and reductants in the refold mixture, but rather on the concentration of oxidants and reductants in the "redox component," the element of the claim with which they are associated. Apotex, in effect, seeks to rewrite the claim, making the "final thiol-pair ratio" and the "redox buffer strength" attributes of the refold mixture, so as to use the volume of the refold mixture in its calculations. *See* D.E. 83 at 2. Apotex is impermissibly rewriting the claim for some other advantage.

Furthermore, Apotex, through its expert Dr. Robinson, has modified its calculations, further straining the constructions of "final thiol-pair ratio" and "redox buffer strength." Apotex wishes to use the volume of the refold mixture in its calculations, at the same time excluding

certain oxidants and reductants present in the refold mixture from the calculation of these claim terms. Apotex's proposed constructions of "final thiol-pair ratio" and "redox buffer strength" are contrary to the claim language, mathematically incoherent and driven not by the intrinsic record but a desire to evade the claim. They should be rejected.

B. Construction of Disputed Claim Terms

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

The parties' dispute addresses the word "volume" in the preamble of claim 1. Apotex asserts that "volume" is synonymous with "refold mixture," and thus that the "2.0 g/L or greater" protein concentration referred to in the preamble becomes that of the refold mixture, and that the minimum protein concentration of the refold mixture becomes 2.0 g/L. As discussed below, Apotex is wrong as to each part of this syllogism.

In view of the intrinsic record, a skilled artisan would not understand "volume" and "refold mixture" in claim 1 to mean the same thing, as Amgen's opening and responsive claim construction briefs explained. (D.E. 77 at 5–6; D.E. 83 at 3). As Dr. Willson testified at his recent deposition, "[t]he spec does not use the word "volume" for the refold mixture. It explicitly uses the word 'volume' for things other than the refold mixture." Deposition of Richard C. Willson, Ph.D. at 81:4–6, attached hereto as Exhibit 1. Apotex's expert, Dr. Robinson, conceded that the '138 Patent specification uses the word "volume" to describe protein preparations that are not refold mixtures. *See* Deposition of Anne S. Robinson, Ph.D. at 110:19–22; 123:14–17, attached hereto as Exhibit 3.

Dependent claims 4 and 5 of the '138 Patent drive home the point that the word "volume" in the preamble of claim 1 is not being used to signify the refold mixture. Collectively, claims 4 and 5 specify that the volume in the preamble of claim 1 is a non-native limited solubility form and more specifically, an inclusion body: the very volume that Dr. Robinson conceded was not a refold mixture. *Id.* Consequently, Apotex's equating "volume" with "refold mixture" is flatly wrong, as is its position that the protein concentration of "2.0 g/L or greater" in the preamble is that of the refold mixture.

Amgen's proposed construction of "a protein . . . present in a volume at a concentration of 2.0 g/L or greater" is that this is a reference to an initial protein-containing volume, with a concentration of 2.0 g/L or greater, before it is contacted with a refold buffer. The contacting of this initial protein-containing volume with the refold buffer necessarily dilutes the protein and

thus, what was a 2.0 g/L or greater protein concentration in the initial volume becomes more dilute when the refold mixture is formed. *See, e.g.*, Willson Depo. 40:14–20. Dr. Robinson admitted that before a protein is in the refold mixture, it is in an initial volume that gets contacted with a refold buffer. *See* Robinson Depo. 127:21–128:3.

She further conceded that one of the initial protein-containing "volumes" described in the patent, a solubilization pool, was the type of volume that can be contacted with a refold buffer to form a refold mixture. *See* Robinson Depo. 125:5–9. Dr. Robinson further testified that pools of solubilized inclusion bodies can contain protein concentrations of 2 g/L or greater. Robinson Depo. 121:16–20. Though Dr. Robinson maintained that 2.0 g/L or greater protein concentration in the preamble of claim 1 would be interpreted to mean the protein concentration in the refold mixture, her concessions above are inconsistent with this position. The language of claims 1, 4 and 5, the specification, and the testimony of both Drs. Willson and Robinson, far better support the view that "volume" and "refold mixture" are distinct things that should not be conflated. The "volume" is an initial protein-containing volume with a protein concentration of 2.0 g/L or greater that gets contacted with, and diluted by, a refold buffer to form a refold mixture with a protein concentration necessarily more dilute than that of the initial protein-containing volume.

Lastly, contrary to Apotex's belatedly offered view that Amgen's proposed construction would render the claim term "volume" indefinite (*see* D.E. 82-2, hereinafter "2d Robinson Decl." at ¶¶ 10–11), the patent provides several examples of "volumes." *See* '138 Patent at 9:63–10:6. Thus, the "volume" of claim 1 is not "*any* 'volume' prior to contact with the refold buffer," as Dr. Robinson suggests (*see* 2d Robinson Decl. at ¶ 10), but rather the types of initial volumes with proteins in a misfolded or aggregated state that require refolding. Because the scope of claim 1 is entirely clear under Amgen's proposed construction, it cannot be indefinite.

2. "refold buffer"/"redox component"

Apotex complains that Amgen's proposed constructions of "refold buffer" and "redox component" are redundant, that the claim already recites what the refold buffer comprises and what the redox component comprises. This would suggest that there is no disagreement about what the refold buffer and the redox component comprise. Yet inexplicably, Apotex does not want this Court to explicitly itemize what makes up the refold buffer and the redox component. As discussed below, Apotex is attempting to have "final thiol-pair ratio" and "redox buffer strength" <u>calculated on the basis of the volume of the refold mixture</u> without accounting for all

the oxidant and reductant species present in the refold mixture. Perhaps Apotex seeks to avoid a construction of "redox component" that exposes the inappropriateness of calculating the final thiol-pair ratio and redox buffer strength based on the volume of the refold mixture.

In any event, given the importance of the concept of a redox component to the practice of the invention, adopting Amgen's proposed constructions, that spell out what the redox component comprises and which element of the claim comprises the redox component, will assist the Court and a jury to better understand the metes and bounds of the claimed invention. It should also be noted that Apotex's expert, Dr. Robinson, agreed that the redox component can comprise combinations of thiol-reactive chemicals. *See* Robinson Depo. 55:19–56:18.

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

The terms "final thiol-pair ratio" and "redox buffer strength" are defined mathematically in the specification. The parties agree that the equations used to calculate these terms are Equations 1 and 2 in column 6 of the '427 Patent. These equations have the same variables, "[reductant]" and "[oxidant]." However "reductant" and "oxidant" do not refer to specific compounds, but rather to categories of compounds that serve to donate electrons or accept electrons, respectively. Notably, a refold mixture is an extremely complex composition with numerous known and unknown oxidant and reductant species, whereas a redox component is a solution of known composition, the oxidant and reductant content of which a scientist can control. 2d Willson Decl. at ¶¶ 42–45.

The parties dispute how to calculate the values of the concentrations of the reductants and the oxidants, which values are then used to calculate the "final thiol-pair ratio" and "redox buffer strength." Amgen has consistently proposed that the values be based on the concentrations of reductants and oxidants <u>in the redox component</u>, which the scientist can precisely control.

Apotex, on the other hand, has shifted its position. Apotex previously argued that all the contents of the refold mixture (i.e. the complex mix of oxidant and reductant species, "protein and all") should form the basis of the calculations of final thiol-pair ratio and redox buffer strength. *See* D.E. 76 at 13–16; D.E. 82 at 8–13; D.E. 76-4 (hereinafter "1st Robinson Decl.") at ¶¶ 74–77, 81–84. Dr. Robinson opined that Apotex's construction was correct, in part, because it accounted for the patent's statement that the cysteine residues in the unfolded protein are also reactants in the refold mixture. *Id.* at ¶¶ 75, 82 (quoting '138 Patent at 4:48–51). Apotex repeated these arguments in its responsive claim construction brief, as did Dr. Robinson in her

second declaration. *See* D.E. 82 at 9–12; 2d Robinson Decl. at ¶¶ 13–17, 19–20, 22–23. Thus, Apotex's arguments have rested (improperly, in Amgen's view) on the alleged need to calculate the "final thiol-pair ratio" and "redox buffer strength" in "conjunction with . . . protein concentration."

Yet now, as revealed by Dr. Robinson's testimony at her deposition, Apotex argues for the first time (shifting its initial position), that its proposed construction merely means that the calculations of the "final thiol-pair ratio" and "redox buffer strength" use the volume of the refold mixture to determine the concentrations of the oxidant and reductant contributed to the refold mixture by the redox component, while ignoring the contribution of other oxidants and reductants in the refold mixture (such as the same "cysteine residues in the unfolded protein" originally so important to Apotex). Dr. Robinson's testimony confirmed that Apotex's initial arguments did attempt to account for the constituents of the refold mixture. *See* Robinson Depo. 72:8–73:2. But she then testified that Apotex simply meant that only the volume of the refold mixture should be used to calculate "final thiol-pair ratio" and "redox buffer strength," without accounting for the other constituents of the refold mixture. Robinson Depo. 80:21–81:12; *see also* Robinson Depo. 82:13–83:21.

At worst, this testimony is part of an improper attempt by Apotex to shift its claim construction positions at the eleventh hour. At best, it demonstrates the lack of clarity of Apotex's position. In either case, this Court should reject Apotex's confusing construction, and adopt Amgen's proposed constructions (based on the concentrations of the oxidants and reductants in the redox component), which are clear, supported by the specification and the claim language (as explained in Amgen's prior briefs and accompanying declarations of its expert Dr. Willson) and have remained consistent through these proceedings.

4. "2 mM or greater"

Claim 1 calls for a redox buffer strength of "2mM or greater." Apotex wants "2 mM or greater" to be construed as having an upper boundary of 100 mM. Amgen believes "2mM or greater" requires no construction, much less the insertion of a limitation from the patent specification into the claim.

The patentees clearly knew how to include claim limitations regarding the redox buffer strength. Dependent claim 3 adds a series of lower boundaries for redox buffer strength that are higher than the 2 mM lower boundary recited in claim 1. *See* claim 3; Willson Depo. 229:15–

231:10. Had the patentees intended to include an upper limit on redox buffer strength, they could have done so, but did not. Given the patent's teachings to optimize redox buffer strength for a given protein, the inventors left open the possibility of using a redox buffer strength greater than 100 mM.

As it does on other occasions, Apotex argues that Amgen's view of this claim term will render the claim invalid under 35 U.S.C. § 112, and that, therefore, Amgen's proposed construction cannot be right. The suggestion that Amgen is pursuing claim constructions that would render its patents' claims invalid and that Apotex is interested in constructions that preserve the validity of Amgen's claims is ludicrous on its face. Apotex's proposed construction of "2 mM or greater" as requiring a 100 mM upper boundary should be rejected.

5. "refold mixture"

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 minimum protein concentration in the refold mixture is lower than 2.0 g/L, and should be interpreted to be about 1 g/L protein. Apotex's proposed construction of "a protein . . . present in a volume at a concentration of 2.0 g/L or greater," effectively makes "2.0 g/L or greater" the minimum protein concentration in the refold mixture. Thus, while the parties and their experts agree that protein concentration in the refold mixture is high, (1st Willson Decl. ¶¶ 38–50; 1st Robinson Decl. ¶ 60; D.E. 76 at 10; D.E. 77 at 20, 11–12) they disagree on where "high" begins, at about 1 g/L (Amgen) or at 2 g/L (Apotex).

Apotex's proposed construction would exclude from the scope of claim 1 embodiments that unambiguously allow for a protein concentration in the refold mixture of as low as 1 g/L. *See* '138 Patent, 10:12–16 ("refolding at concentrations of 1–40 g/L); *see also* '138 Patent 12:44–49 ("protein concentration in the range of 1 to 15 g/L"). In her second declaration, Dr. Robinson appears to argue that a person of ordinary skill would not conclude from these portions of the specification that the refold mixture could contain protein concentrations as low as 1 g/L because the patent does not describe the above-quoted ranges as "high protein concentrations." 2d Robinson Decl. ¶ 32. Yet in that same declaration, responding to Dr. Willson's first declaration, Dr. Robinson never disputed that there is an art-recognized boundary between low and high protein concentrations for protein refolding, and that that boundary is at about 1 g/L.

Moreover, as Dr. Willson noted during his deposition (*see* Willson Depo. at 71:1–13), Dr. Robinson cites a reference that includes 1 g/L as the lower end of the range of high protein concentrations (*see* 2d Robinson Decl. at ¶ 9) which undercuts her opinion that 1 g/L would not be within the range of "high protein concentration" as understood by a person of ordinary skill in the art.

II. Baumann et al., U.S. Patent No. 6,162,427 ("the '427 Patent")

A. Preliminary Statement

As of the priority date of the '427 Patent, methods of treating diseases requiring peripheral stem cell transplantation existed. Typical protocols included the following steps: (1) administration of an agent or agents to mobilize stem cells from the bone marrow to the peripheral blood; (2) collection of stem cells from the peripheral blood by a process such as leukapheresis, (3) administration of high-dose radiation or cytotoxic agents to reduce the number of cells, including cancerous cells, in the bone marrow to ready it for the transplant, and (4) reinfusing the collected peripheral blood stem cells back into the patient to restore the hematopoietic function.

As of the priority date of the '427 Patent, GCSF was used to mobilize stem cells in the first step of the protocol described above. Chemotherapeutic agents, used for treating cancer, had been observed to mobilize stem cells, and were also used in transplantation protocols at the stem cell mobilizations step. Combinations of chemotherapeutic agents and GCSF (administered in that order) were also used for stem cell mobilization in transplantation protocols.

What Baumann et al. surprisingly discovered was that by reversing the order of administration of mobilizing agents, i.e., administering GCSF first and then a chemotherapeutic agent or agents, the mobilization of stem cells was enhanced. *See, e.g.*, '427 Patent 1:62–65; 2:8–11. Giving the mobilization agents in this specific order resulted in more cells to collect from the peripheral blood, leading to fewer leukaphereses and greater comfort for patients.

Skilled artisans reading claim 1 of the '427 Patent in view of the specification would understand that the inventors were claiming an improved method for treating diseases requiring peripheral stem cell transplantation and that the improvement resided in the stem cell mobilization step of the protocol. Put differently, no skilled artisan would conclude that Baumann et al. had invented a new use of anti-tumor chemotherapeutic agents for the third step of the transplantation protocol outlined above, where high-dosage chemotherapy may be given to

kill cancer cells and ready the bone marrow to receive the transplant.

Against this backdrop, there would be no confusion for a skilled artisan about the meaning of "chemotherapeutic agent" or "disease treating-effective amount" in claim 1 of the '427 Patent, although Apotex tries mightily to create it. The invention of the '427 Patent resides in the administration of GCSF followed by a chemotherapeutic agent to enhance stem cell mobilization. The chemotherapeutic agents used in the Baumann et al. method are described (and would be recognized) as ones that can (and did at the time) serve the purpose of damaging or destroying cells. They are also used in the claimed method to enhance stem cell mobilization, regardless of the mechanism by which they mobilize those stem cells.

Moreover, there is nothing indefinite about the term "disease treating-effective amount." With a clear understanding of the purpose for which the chemotherapeutic agent is being used, the skilled artisan similarly would understand that the amount to be administered is one that results in enhanced mobilization of stem cells, so that more cells are collected for subsequent transplantation, improving the efficiency with which the disease requiring peripheral stem cell transplantation is treated. As of the priority date of the '427 Patent, skilled artisans were capable of selecting dosages of chemotherapeutic agents that would enhance the number of stem cells mobilized from bone marrow to peripheral blood.

B. Construction of Disputed Claim Terms

1. "chemotherapeutic agent"

To reach a construction of "chemotherapeutic agent," the first inquiry should be: for what purpose is the chemotherapeutic agent being used in claim 1? As discussed above, a skilled artisan would understand from reading the '427 Patent that the chemotherapeutic agent was being used in combination with GCSF to enhance stem cell mobilization.

The next inquiry is, what does the '427 Patent teach about specific chemotherapeutic agents that can be used for this purpose? At col. 2, lines 41–54, the patent identifies numerous, specific chemotherapeutic agents and categories into which they fall, regardless of their mechanism of action.

The last inquiry is, does the '427 Patent identify a genus into which these chemotherapeutic agents fall? The answer is yes. At col. 2, lines 37–39, the patent teaches that the compounds listed in col. 2, lines 41–54 "damage or destroy microorganisms, parasites or tumor cells." Amgen proposes its construction ("exogenous substance capable of damaging or

destroying microorganisms, parasites or tumor cells") based on this language, because this is how the patent generically identifies the chemotherapeutic agents that can be used for stem cell mobilization in the practice of the claimed invention.

Apotex's expert, Dr. Scadden, confirmed at his deposition that the chemotherapeutic agents listed in col. 2, lines 41–54 were known to skilled artisans and would be recognized as agents being used to treat cancer, among other purposes. David T. Scadden. M.D. Depo. at 48:25–49:18, attached hereto as Exhibit 4. He also testified that at the time of the invention, the agents being used for stem cell mobilization were in use to treat cancer. Scadden Depo. 36:13–37:2.

It is clear that the inventors of the '427 Patent were identifying the chemotherapeutic agents useful for stem cell mobilization in their claimed method to be chemotherapeutic agents otherwise known for their ability to damage or destroy cells. In view of the teachings of the '427 Patent col. 2, lines 37–54 and consistent with Dr. Scadden's testimony, it is completely appropriate to define a "chemotherapeutic agent" that will be used to enhance stem cell mobilization as a substance capable of damaging or destroying microorganisms, parasites, or tumor cells, as Amgen proposes.

As discussed in Amgen's responsive claim construction brief, Apotex's proposed construction includes a subgenus of compounds that open the endothelial barrier <u>but do not</u> damage or destroy cells. This is not supported by the specification. While Dr. Scadden attempted to "fill in" this category at his deposition, the '427 Patent does not specifically identify the particular substances Dr. Scadden referenced. Scadden Depo. 57:3–23. More fundamentally, the '427 Patent's definitional language at col. 2, lines 37–39 ("Hereinbelow, chemotherapeutic agents are understood to be exogenous substances suited and used to damage or destroy microorganisms, parasites or tumor cells.") cannot be overridden or extended by expert testimony. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1318 (Fed. Cir. 2005) (noting that courts "should discount any expert testimony that is clearly at odds with" the intrinsic record).

There is no question that the specification discloses that compounds which <u>may</u> work by opening the endothelial barrier to render it permeable to stem cells may find application in the claimed invention. But there is no reason to read that or any mechanism of action into claim 1, especially when this specific mechanism of action is recited in dependent claim 4.

2. "disease treating-effective amount"

The term "disease treating-effective amount" in claim 1 of the '427 Patent is not indefinite. It informs the skilled artisan with reasonable certainty about the scope of the claim, and would be understood, as Amgen proposes, to mean "an amount sufficient to enhance the mobilization of stem cells for recovery from blood for subsequent peripheral transplantation."

Apotex's argument relies on the premise that "in the process of 'treating a disease requiring peripheral stem cell transplantation,' a chemotherapeutic agent is used initially to mobilize stem cells and later as an antitumor therapy." D.E. 82 at 18 (emphasis in original).

Because, according to Apotex, the claimed method calls for a "disease treating-effective amount" of a chemotherapeutic agent, the amount might be for stem cell mobilization purposes, for anti-tumor purposes, or both. According to Apotex, a skilled artisan would not understand for what purpose the chemotherapeutic agent was being used, and would, therefore, be unable to determine a disease treating-effective amount of it to use. Apotex is wrong.

First, Apotex's premise is false, because in a transplantation protocol, a chemotherapeutic agent is not necessarily being used for the "anti-tumor therapy" step. Radiation can be used, as Dr. Scadden agreed. Scadden Depo. 78:15–21. More importantly, as discussed above and by Amgen's expert, Dr. Louis M. Pelus, Ph.D. (*See, e.g.*, D.E. 83-6 ("Pelus Decl.") at ¶¶ 68–70; Pelus Depo. 63:20–23, attached hereto as Exhibit 2) a skilled artisan reading the '427 Patent would have no difficulty understanding that the chemotherapeutic agent administered after GCSF in the claimed method is for the purpose of stem cell mobilization. Dr. Scadden agrees. *See* Scadden Depo. 67:2–10. Consequently, the skilled artisan would understand that the amount of chemotherapeutic agent to be given is one that enhances stem cell mobilization, because an increase in the number of stem cells mobilized, collected and reinfused back into the patient more effectively treats the disease requiring the transplant. Given the level of skill in the art, and the guidance on dosage ranges provided by the patent (*see* '427 Patent, 3:11–12), a skilled artisan could readily determine a "disease treating-effective amount" of a given chemotherapeutic agent. *See* Pelus Decl. at ¶ 71; Scadden Depo. 73:21–74:12.

CONCLUSION

For the foregoing reasons, Amgen respectfully requests that the Court adopt its proposed constructions set forth in the JCCS (D.E. 69).

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CERTIFICATE OF SERVICE

I HEREBY CERTIFY that on January 27, 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.

By: */s/ John F. O'Sullivan*____

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