UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF FLORIDA

Case No. 15-61631-CIV-COHN (consolidated with 15-62081-CIV-COHN)

AMGEN INC. and AMGEN MANUFACTURING LIMITED,

Plaintiffs,

v.

APOTEX INC. and APOTEX CORP.,

Defendants.

DEFENDANTS APOTEX INC. AND APOTEX CORP.'S RESPONSIVE CLAIM CONSTRUCTION BRIEF

TABLE OF CONTENTS

Page

I. INTRODUCTION 1
II. ARGUMENT 3
A. The '138 Patent 3
1. "*a protein . . . present in a volume at a concentration of 2.0 g/L or greater*" 3
2. "*refold buffer*" 6
3. "*redox component*" 7
4. "*final thiol-pair ratio*" 8
5. "*redox buffer strength*" 10
6. "*2 mM or greater*" 13
7. "*refold mixture*" 15
B. The '427 Patent 17
1. "*chemotherapeutic agent*" 17
2. "*disease treating-effective amount*" 18
III. CONCLUSION 19

TABLE OF AUTHORITIES

Cases **Page(s)**

Abbott Labs. v. Sandoz, Inc.,
566 F.3d 1282 (Fed. Cir. 2009).....15

AK Steel Corp. v. Sollac & Ugine,
344 F.3d 1234 (Fed. Cir. 2003).....13

Ariad Pharm., Inc. v. Eli Lilly & Co.,
598 F.3d 1336 (Fed. Cir. 2010).....14

Bicon, Inc. v. Straumann Co.,
441 F.3d 945 (Fed. Cir. 2006).....6, 7

Digital-Vending Servs. Int'l v. Univ. of Phoenix, Inc.,
672 F.3d 1270 (Fed. Cir. 2012).....6, 7

O2 Micro Int'l Ltd. v Beyond Innovation Tech. Co.,
521 F.3d 1351 (Fed. Cir. 2008).....13

SmithKline Beecham Corp. v. Apotex Corp.,
403 F.3d 1331 (Fed. Cir. 2005).....5

Texas Instruments Inc. v. U.S. Int'l Trade Comm'n,
988 F.2d 1165 (Fed. Cir. 1993).....15

Statutes

35 U.S.C. § 112.....5, 13, 14

Pursuant to the Court's Supplemental Scheduling Order of November 12, 2015 (D.E. 58), Defendants Apotex Inc. and Apotex Corp. ("Apotex") hereby submit this Brief in response to Plaintiffs' Opening Claim Construction Brief (D.E. 77).

I. INTRODUCTION

Plaintiffs Amgen Inc. and Amgen Manufacturing Limited's ("Plaintiffs" or "Amgen") seek to stretch the plain language of the claims of the patents-in-suit in a manner that flies in the face of the tenets of claim construction. Amgen's proposed claim constructions cannot be correct because they improperly and unnecessarily add limitations to the claims and broaden the scope of the claims in a manner that is inconsistent with the intrinsic record. The Court should deny Amgen's litigation-based attempt to modify the claim scope, and instead construe the disputed claim terms in a manner that is consistent with the specifications of the patents-in-suit and the intrinsic record and with how a person of ordinary skill in the art ("POSA") would interpret the claims. Without its improper claim constructions, Amgen has no reasonable basis to maintain its infringement claim against Apotex.

The disputed terms of the '138 patent: Amgen's proposed construction for the term "a protein . . . present in a volume at a concentration of 2.0 g/L or greater" makes no sense when read in light of the intrinsic record. Both the specification and the prosecution history of U.S. Patent No. 8,952,138 ("the '138 patent") consistently state that the purportedly inventive method is directed to protein refolding at high concentrations, and more particularly to protein refolding in volumes at concentrations of 2.0 g/L and above. Protein refolding occurs exclusively in a refold mixture, which is formed only upon addition of a protein to the refold buffer. Thus, Amgen's proposed construction is contrary to the purpose of the purported invention of the '138 patent and cannot be correct.

Amgen's proposed constructions for the terms "refold buffer" and "redox component" unnecessarily repeat limitations that are already expressly recited in the claim. Thus, Amgen's proposed constructions for these terms are redundant and unnecessary.

Further, Amgen's proposed constructions for the terms "final thiol-pair ratio" and "redox buffer strength" are anything but clear from the plain language of the claims, as Amgen asserts. The claims of the '138 patent do not disclose any specific equations or method for calculating a "final-thiol pair ratio" or "redox buffer strength." Instead, one must consult the '138 patent

specification to retrieve this information. In doing so, it is clear that using only the volume of the redox component, as Amgen contends, would again be inconsistent with the purpose of the purported invention. Indeed, the '138 patent makes clear that one must account for the volumes of both the protein and the refold buffer to determine the correct "final thiol-pair ratio" and "redox buffer strength" for the specific protein that is being refolded.

What is more, Amgen's attempt to rely on the plain and ordinary meaning of the term "2mM or greater" is improper, as the scope of this is clearly in dispute. Indeed, the inventors of the '138 patent clearly ascribed a particular meaning to the term "2mM or greater," as the words "effectively bounded at a maximum of 100 mM" appear repeatedly in the patent specification. Leaving this term unbounded would improperly broaden the claim scope beyond what is described or enabled by the specification of the '138 patent.

The disputed terms of the '427 patent: Amgen's proposed constructions for the two disputed terms of U.S. Patent No. 6,162,427 ("the '427 patent") are not only inconsistent with the definitions provided in the patent specification but also conflict with each other.

First, Amgen would have this Court limit the term "chemotherapeutic agent" to cover only a part of what is disclosed in the patent specification. However, the '427 patent explicitly defines a "chemotherapeutic agent" as including both exogenous substances that can be used to damage or destroy microorganisms, parasites or tumor cells, and therapeutic agents that can open the endothelial barrier. Nowhere during prosecution of the '427 patent did Amgen argue to the Patent Office that "chemotherapeutic agents" should be limited to only a part of this definition, as Amgen now contends.

Second, Amgen would have this Court compound this error through its proposed construction for a "disease treating-effective amount." The term "disease treating-effective amount" modifies the term "chemotherapeutic agent" in claim 1 of the '427 patent. If, as Amgen contends, a "chemotherapeutic agent" only refers to "exogenous substances suited and used to damage or destroy microorganisms, parasites or tumor cells," then the term "disease treating-effective amount" cannot refer to "an amount sufficient to enhance the mobilization of stem cells for recovery from the blood for subsequent peripheral transplantation." Thus, Amgen's constructions of these two terms, when placed together, makes no sense and should be rejected.

For the reasons stated herein, the Court should reject Amgen's proposed constructions of the disputed terms and instead adopt Apotex's proposed constructions, which follow the tenets of claim construction, and are consistent with the intrinsic records and extrinsic evidence.

II. ARGUMENT

A. The '138 Patent

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

Amgen's Proposed Construction	Apotex's Proposed Construction
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

A comparison of the competing constructions above reveals that the sole point of difference between the parties is whether the "2.0 g/L or greater" limitation of claim 1 is in reference to the protein concentration before or after dilution with the refold buffer. Amgen contends that the claim requires a protein concentration of "2.0 g/L or greater" in a "volume" prior to contact with the refold buffer, *i.e.*, prior to refolding. (D.E. 77 at 5-7.) This construction cannot be correct.

In support of its construction, Amgen argues that the specification discloses protein "'present in a volume at a concentration of 10 g/L or greater'" prior to contact with refold buffer. (D.E. 77 at 6 (citing '138 patent at col. 10, ll. 17-22).) Amgen further argues that "[t]his protein-containing volume 'is then contacted with a refold buffer,' representing the combining step that forms the refold mixture." (D.E. 77 at 6 (citing '138 patent at col. 10, ll. 22-23).) Amgen's argument misses the mark. Indeed, it is common sense that a protein concentration of 2.0 g/L or greater during refolding necessarily requires the protein to be at a higher concentration in a "volume" prior to dilution with the refold buffer. However, the protein concentration prior to refolding is plainly irrelevant to what the inventors of the '138 patent deemed as their invention.

As set forth in the specification, the '138 patent purportedly invented a method for "*refolding* proteins in volumes at concentrations of 2.0 g/L and above." (*See* D.E. 76, Exh. A at col. 1, ll. 11-14 (emphasis added).) Thus, the crux of the purported invention concerns protein *refolding* at high concentrations. This is confirmed by both the intrinsic record and extrinsic evidence.

For example, the specification of the '138 patent states that "[a] method of refolding proteins expressed in non-mammalian cells present *in concentrations of 2.0 g/L or higher is disclosed*. The method comprises identifying the thiol pair ratio and the redox buffer strength to achieve conditions under which efficient *folding at concentrations of 2.0 g/L or higher is achieved*." (*See* D.E. 76, Exh. A at Abstract (emphasis added); *see also* Exhibit A, *Declaration of Anne S. Robinson, Ph.D. in Support of Defendants' Responsive Claim Construction Brief* at ¶ 5 [hereinafter Robinson Decl.].) The "Field of the Invention" of the '138 patent continues, "[t]he present invention generally relates to *refolding proteins at high concentrations*, and more particularly *to refolding proteins in volumes at concentrations of 2.0 g/L and above*." (*See* D.E. 76, Exh. A at col. 1, ll. 11-14 (emphasis added); *see also* Robinson Decl. at ¶ 5.) As Amgen aptly notes in its Opening Brief, "[c]laims 'must be construed so as to be consistent with the specification, of which they are part.'" (D.E. 77 at 6 (citing *Phillips v. AWH Corp.*, 415 F.3d 1303, 1316 (Fed. Cir. 2005).) In this case, it is readily apparent that the '138 patent specification explicitly refers to the 2.0 g/L limitation in the context of *folding and refolding* proteins. It is undisputed that the only volume in which refolding occurs is the refold mixture, which is the volume containing the protein combined with the refold buffer.

The prosecution history of the '138 patent further shows why Amgen's proposed construction cannot be correct. During prosecution, the Patent Office rejected the pending claims as anticipated by the prior art. (*See* D.E. 76, Exh. H at 5; D.E. 76, Exh. I at 6; *see also* Robinson Decl. at ¶ 6.) In responding to the Patent Office's rejections, Amgen repeatedly argued that the claims were patentable over the prior art based on "applicants' disclosure that facilitate the ability *to refold proteins at concentrations of 2.0 g/L and greater*." (*See* D.E. 76, Exh. H at 6 (emphasis added); *see also* Robinson Decl. at ¶ 6.) Further, Amgen specifically argued that:

> [N]owhere in this [prior art] document is the *concept of refolding at a concentration of 2.0 g/L or greater disclosed* . . . . Applicants submit that the combined dilution of approximately 250-fold does not lend itself to the creation of a *high concentration refolding mixture*, as recited in applicants' pending claims.

(*See* D.E. 76, Exh. H at 6 (emphasis added); *see also* Robinson Decl. at ¶ 6.) Thus, during prosecution Amgen explicitly stated that the inventive aspect of the claims was the ability to refold proteins at concentrations of 2.0 g/L or greater. Accordingly, Amgen's proposed construction—*i.e.,* a protein concentration of 2.0 g/L or greater *prior* to contact with the refold

buffer—directly conflicts with arguments Amgen made at the Patent Office to distinguish the claims over the prior art. Amgen's proposed construction therefore cannot be correct.

Additionally, Amgen's proposed construction must fail because it would not satisfy the requirements of 35 U.S.C. § 112, second paragraph. Under 35 U.S.C. § 112, second paragraph, the claim, when read in light of the specification, must apprise those skilled in the art of the scope of the claim. *See SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1340 (Fed. Cir. 2005), *reh'g en banc denied*, No. 03-1285, -1313, 2005 U.S. App. LEXIS 14121 (Fed. Cir. June 15, 2005). Here, Amgen's proposed construction does not specify any particular "volume" in which the 2.0 g/L protein concentration is calculated. (D.E. 77 at 5-7.) Rather, Amgen is asking the Court to define the "volume" that contains protein at a concentration of 2.0 g/L or greater as *any* "volume" prior to contact with the refold buffer. (*Id.*) Amgen's construction would render the claim indefinite. Indeed, there are many "volume(s)" in which the protein can be found at a concentration of 2.0 g/L or greater prior to dilution in refold buffer. (*See* Robinson Decl. at ¶ 11.) For example, the "volume" could be the affinity chromatography elution pool (*See* D.E. 76, Exh. A at col. 10, ll. 2-5), the volume situated in a process stream (*Id*. at col. 10, ll. 5-6), or the volume of solubilization buffer. (*See* Robinson Decl. at ¶ 11.) Under Amgen's proposed construction, it is entirely unclear where the 2.0 g/L protein concentration is calculated. (*Id*.) Thus, a POSA would not understand the scope of the claim in light of the specification. Because Amgen's proposed construction would make the claim indefinite, Amgen's proposed construction must fail.

Amgen's proposed construction is also improper because it would place claim 1 directly in the scope of the prior art. The prior art discloses that "[t]he *majority* of the published work on inclusion body protein refolding has used relatively high denaturant . . . and protein (1-10 mg/ml) [*i.e.,* 1-10 g/L] concentrations in the solubilization step." (*See* D.E. 76, Exh. F at 203 (emphasis added); *see also* Exhibit B, R. Rudolph & H. Lilie, "In vitro folding of inclusion body proteins," 10 *FASEB J*. 49, 53 (1996) (disclosing a protein concentration of 5 mg/ml (*i.e.,* 5 g/L) following solubilization of inclusion bodies).) Thus, the prior art clearly discloses protein concentrations of 2.0 g/L or greater in solubilization buffer. (*See* Robinson Decl. at ¶ 9.) And, as described above, under Amgen's proposed construction, the 2.0 g/L or greater protein concentration can exist in *any* volume prior to contact with the refold buffer; ergo, under Amgen's proposed

construction, the 2.0 g/L protein concentration could be in solubilization buffer. Accordingly, under Amgen's proposed construction, claim 1 would fall squarely within the scope of the prior art.

2. "*refold buffer*"

Amgen's Proposed Construction	Apotex's Proposed Construction
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 a biologically active form.

The parties agree that the construction of "refold buffer" should include "a preparation that supports the renaturation of protein to a biologically active form." However, Amgen further contends that the "refold buffer" should be construed to further include: "(1) a redox component and (2) one or more of (i) a denaturant, (ii) an aggregation suppressor, and (iii) a protein stabilizer." (D.E. 77 at 7.)

In support of its construction, Amgen states: "[b]ecause 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." (*Id*.) But that construction would render the entire "redox component . . . and one or more of: (i) a denaturant; (ii) and aggregation suppressor; and (iii) a protein stabilizer" term a meaningless claim limitation that is simply duplicative of the claimed "refold buffer" itself. As the Federal Circuit has explained, it is important to construe claims in light of the surrounding claim language, such that words in a claim are not rendered superfluous. *See Digital-Vending Servs. Int'l v. Univ. of Phoenix, Inc*., 672 F.3d 1270, 1275 (Fed. Cir. 2012) ("If 'registration server' were construed to inherently contain the 'free of content . . .' characteristic, the additional [claim limitation that required said server to be] 'free of content . . .' would be superfluous."); *see also Bicon, Inc. v. Straumann Co*., 441 F.3d 945, 950 (Fed. Cir. 2006) ("claims are interpreted with an eye toward giving effect to all terms in the claim.").

Accordingly, the Court should reject Amgen's proposed construction.

3. "*redox component*"

Amgen's Proposed Construction	Apotex's Proposed Construction
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 agree that the construction of "redox component" should include "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." However, Amgen further contends that the construction should include: "[t]he 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." (D.E. 77 at 8.)

Amgen argues that "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." (*Id*. (emphasis added).) But, much as above, that construction would render the "redox component comprising a final thiol-pair ratio having a range of 0.001 to 100 and a redox buffer strength of 2mM or greater" term a meaningless claim limitation that is simply duplicative of the claimed "redox component" itself. As the Federal Circuit has explained, it is important to construe claims in light of the surrounding claim language, such that words in a claim are not rendered superfluous. *See Digital-Vending Servs.*, 672 F.3d at 1275 ("If 'registration server' were construed to inherently contain the 'free of content . . .' characteristic, the additional [claim limitation that required said server to be] 'free of content . . .' would be superfluous."); *see also Bicon, Inc.*, 441 F.3d at 950 ("claims are interpreted with an eye toward giving effect to all terms in the claim.").

Accordingly, the Court should reject Amgen's proposed construction.

4. "*final thiol-pair ratio*"

Amgen's Proposed Construction	Apotex's Proposed Construction
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: $\frac{[reductant]^2}{[oxidant]}$ where the ratio is the ratio in the refold mixture

The parties agree that in order to calculate the "final thiol-pair ratio," the ratio is based on the concentrations of the reductant and the oxidant in a solution. However, Amgen contends that the relevant solution is the one that contains the redox components alone—that is, the concentration of redox components in solution prior to combination with the refold mixture. Based on the intrinsic evidence, Amgen's proposed construction is incorrect and must fail.

In contrast to Amgen's assertion, nothing in the plain language of the claims supports Amgen's proposed "concentrations are the concentrations in the redox component" limitation. (D.E. 77 at 8-9.) Amgen cannot argue that one need only review claim 1 of the '138 patent to arrive at the equation to calculate the "final thiol-pair ratio." Indeed, the equation is not even provided in claim 1 of the '138 patent; it appears only in the specification. Thus, it follows that one must consult the specification to determine the proper concentration to use when calculating the "final thiol-pair ratio." And, there is no indication whatsoever in the specification or the prosecution history that the patentees intended to limit the "final thiol-pair ratio" to the "concentrations in the redox component" as now proposed by Amgen. To the contrary, it is readily apparent from the intrinsic record that final thiol-pair ratio is calculated in the refold mixture, not in the redox component.

For example, one of the stated goals of the purported invention is to optimize the refold chemistry (*i.e.*, the relationship between final thiol-pair ratio, redox buffer strength, and protein concentration) to facilitate protein refolding at high protein concentrations, such as 2.0 g/L or greater. (*See* D.E. 76, Exh. A at col. 4, ll. 21-24; *see also* Robinson Decl. at ¶ 13.) This goal is exemplified in Figures 1a-1f, where the effect of thiol-pair ratio and thiol buffer strength on the distribution of product-related species (*e.g.*, properly folded versus incorrectly formed protein species) was analyzed. (*See* D.E. 76, Exh. A at col. 8, ll. 44-47; *see also* Robinson Decl. at ¶ 13.) In summarizing the results of these figures, the specification discloses:

> FIGS. **1***a*-**1***f* demonstrate that at a constant 6 g/L protein concentration, *as the thiol-pair buffer strength is increased, the thiol-pair ratio required to achieve a comparable species distribution must also increase* . . . At lower redox buffer strengths, the overall system [*i.e.,* the refold reaction] becomes much more difficult to control. The protein concentration and number of cysteines contained in the protein sequence also relate to the minimum required thiol-pair buffer strength required to control the system. *Below a certain point*, which will vary from protein to protein, *the protein thiol concentration can overwhelm the redox couple chemistry and lead to irreproducible results*.

(*See* D.E. 76, Exh. A at col. 8, l. 53 to col. 9, l. 2 (emphasis added).) It is clear from this disclosure that a change in thiol-pair buffer strength (*i.e.,* redox buffer strength) requires a concomitant change in the thiol-pair ratio to provide a "comparable species distribution." (*See* Robinson Decl. at ¶ 14.) It follows, therefore, that the "final" thiol-pair ratio cannot be calculated in the redox component, as suggested by Amgen, because at that point the redox buffer strength has not been finalized. (*Id*.) Indeed, as explained in detail below, the concentration of the redox buffer strength in the redox component is not final because it will necessarily be diluted when combined with the refold buffer and the protein, *i.e.,* the refold mixture. (*Id.* at ¶ 15.) Accordingly, because of the critical dynamic between the thiol-pair ratio and redox buffer strength, the thiol-pair ratio must be calculated in the refold mixture, the only volume in which the "final" thiol-pair ratio and redox buffer strength can be guaranteed. (*Id*.)

Amgen's proposed construction is also improper based on the following disclosures in the specification:

> 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*."

(*See* D.E. 76, Exh. A at col. 8, ll. 19-36 (emphasis added).) In this case, the specification refers to "the ratio and concentration of the redox couple chemicals" in a "refold solution," not in a component of the refold solution (as proposed by Amgen). (*See* Robinson Decl. at ¶ 16.) The specification further discloses, "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." (*See* D.E. 76, Exh. A at col. 4, ll. 15-20 (emphasis added); *see also* Robinson Decl. at ¶ 17.) Notably, the only "volume" in which the thiol-pair and the protein are ever found concurrently is the refold mixture. (*See* Robinson Decl. at ¶ 17.) Thus, to "control" the thiol-pair buffer strength, in conjunction with the thiol-pair ratio and protein concentration, the final thiol-pair ratio must be calculated in the refold mixture. (*Id.*) Otherwise, this passage would make no sense. (*Id.*)

For at least the above reasons, Amgen's proposed construction is erroneous.

5. "***redox buffer strength***"

Amgen's Proposed Construction	Apotex's Proposed Construction
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 fundamental disagreement between the parties concerning "redox buffer strength" centers again on which solution should be used as the basis for calculating the redox buffer strength. Amgen contends that, much as with final thiol-pair ratio, "redox buffer strength refers to the concentrations of the oxidant and reductant in the redox component." (D.E. 77 at 9-10.) And, as with "final thiol-pair ratio" discussed above, nothing in the plain language of the claims supports Amgen's proposed "concentrations are the concentrations in the redox component" limitation. (*See* Robinson Decl. at ¶ 19.) One must necessarily consult the specification to arrive at the equation and concentration to use in the equation. In doing so, there is no indication in the specification or the prosecution history that the patentees intended to limit the "redox buffer strength" to the "concentrations in the redox component." (*Id.*) To the contrary, the intrinsic record makes clear that redox buffer strength is calculated in the refold mixture, not in the redox component as suggested by Amgen. (*Id.*)

For example, the specification discloses that one of the stated goals of the purported invention is to optimize the refold chemistry (*i.e.,* the relationship between final thiol-pair ratio, redox buffer strength, and protein concentration) to facilitate protein refolding at high protein concentrations, such as 2.0 g/L or greater. (*See* D.E. 76, Exh. A at col. 4, ll. 21-24; *see also*

Robinson Decl. at ¶ 20.) This is exemplified in Figures 1a-1f, where the effect of thiol-pair ratio and thiol buffer strength on the distribution of product-related species (*e.g.*, properly folded versus incorrectly formed protein species) was analyzed. (*See* D.E. 76, Exh. A at col. 8, ll. 44-47; *see also* Robinson Decl. at ¶ 20.) As the specification discloses,

> FIGS. **1***a*-**1***f* demonstrate that at a constant 6 g/L protein concentration, as the thiol-pair buffer strength is increased, the thiol-pair ratio required to achieve a comparable species distribution must also increase. . . . *At lower redox buffer strengths, the overall system* [*i.e.,* the refold reaction] *becomes much more difficult to control*. The protein concentration and number of cysteines contained in the protein sequence also relate to the minimum required thiol-pair buffer strength required to control the system. *Below a certain point*, which will vary from protein to protein, *the protein thiol concentration can overwhelm the redox couple chemistry and lead to irreproducible results*.

(*See* D.E. 76, Exh. A at col. 8, l. 53 to col. 9, l. 2 (emphasis added).) It is clear from this disclosure that the redox buffer strength must be calculated in the refold mixture, the only volume in which the "final" optimized redox buffer strength can be determined. (*See* Robinson Decl. at ¶ 20.) If the redox buffer strength were calculated in the redox component, as suggested by Amgen, this concentration would not reflect the "optimal" redox buffer strength because it would be subsequently diluted by refold buffer. (*Id.*) In fact, under Amgen's proposed construction, the redox buffer strength would be remarkably diluted by the addition of refold buffer and thus would not be expected to provide the same contribution to the refolding process. (*Id.* at ¶ 21.) As explained above, "[a]t lower redox buffer strengths" the refolding reaction is "much more difficult to control," and, in fact, if the redox buffer strength is diluted "[b]elow a certain point" the redox couple chemistry may be "overwhelm[ed]" and "lead to irreproducible results." (*See* D.E. 76, Exh. A at col. 8, l. 62 to col. 9, l. 2; *see also* Robinson Decl. at ¶ 21.) Thus, Amgen's proposed construction cannot be correct in light of these disclosures in the patent specification.

The specification also discloses:

> 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*.

(*See* D.E. 76, Exh. A at col. 8, ll. 19-36 (emphasis added).) The specification further discloses, "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 2g/L or greater, can be achieved." (*Id*. at col. 4, ll. 15-20 (emphasis added); *see also* Robinson Decl. at ¶ 22.) Likewise the specification discloses "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 in the total reaction as well*." (*See* D.E. 76, Exh. A at col. 4, ll. 51-55 (emphasis added); *see also* Robinson Decl. at ¶ 22.) Notably, the only volume in which the thiol-pair and the protein are found concurrently is the refold mixture, *i.e.,* the "total reaction" volume. (*See* Robinson Decl. at ¶ 22.) Thus to "control" the redox buffer strength (a/k/a thiol-pair buffer strength), in conjunction with the thiol-pair ratio and protein concentration, the redox buffer strength must be calculated in the refold mixture. (*Id*.)

Further evidence that Amgen's proposed construction is incorrect is provided in Example 2 of the '138 patent, which identifies refold conditions and redox components. (*See* D.E. 76, Exh. A at col. 13, ll. 60-65; *see also* Robinson Decl. at ¶ 23.) Example 2 discloses: "[t]he thiol-pair ratio and redox buffer strength were determined using an experimental matrix of thiol-pair ratio (0.1 to 100, more typically 1 to 25) versus buffer strength (typically 2 mM to 20 mM, *depending on the protein concentration*, the number of cysteine residues in the protein, and the concentration of reductant used to solubilize the inclusion bodies)." (*See* D.E. 76, Exh. A at col. 14, ll. 30-36 (emphasis added); *see also* Robinson Decl. at ¶ 23.) This passage demonstrates to a POSA that the volume used to calculate the redox buffer strength would account for both the volume of protein and refold buffer (*i.e.,* the refold mixture). (*See* Robinson Decl. at ¶ 23.)

The prosecution history further exemplifies why Amgen's proposed construction is erroneous. For example, Applicants distinguished their invention from the prior art by arguing that

> The disclosure of the balanced relationship of thiol-pair ratio, thiol-pair buffer strength and protein concentration, which is provided in the instant disclosure, was also not previously disclosed. It is the interaction of these properties provided by applicants' disclosure

> that facilitate the ability to refold proteins at concentrations of 2.0 g/L and greater.

(*See* D.E. 76, Exh. H at 6; *see also* Robinson Decl. at ¶ 24.) In light of this disclosure in the prosecution history, a POSA would understand that the only volume in which the protein and redox components "interact" to facilitate refolding is the refold mixture. (*See* Robinson Decl. at ¶ 24.) Thus, the "redox buffer strength" would necessarily be calculated in the refold mixture to ensure a "balanced relationship" and "interaction" between the thiol-pair ratio, thiol-pair buffer strength and protein concentration. (*See id.*)

Accordingly, the Court should reject Amgen's proposed construction.

6. "*2 mM or greater*"

Amgen's Proposed Construction	Apotex's Proposed Construction
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

Amgen's proposed construction of the term "2 mM or greater" is inadequate. *See, e.g.*, *O2 Micro Int'l Ltd. v Beyond Innovation Tech. Co.*, 521 F.3d 1351, 1361 (Fed. Cir. 2008) ("A determination that a claim term 'needs no construction' or has the 'plain and ordinary meaning' may be inadequate . . . when reliance on a term's 'ordinary' meaning does not resolve the parties' dispute.") Further, Amgen's proposed construction does not meet the requirements of 35 U.S.C. § 112, first paragraph. Moreover, the specification supports Apotex's proposed construction.

Amgen contends that "[a POSA] would understand that '2 mM or greater' has a plain meaning, and refers to a redox buffer strength of 2 millimolar or greater." (D.E. 77 at 10.) Amgen's proposed construction would not satisfy the requirements of 35 U.S.C. § 112, first paragraph. The enablement requirement is met "when one skilled in the art, after reading the specification, could practice the claimed invention without undue experimentation." *AK Steel Corp. v. Sollac & Ugine*, 344 F.3d 1234, 1244 (Fed. Cir. 2003) (citing *In re Wands*, 858 F.2d 731, 736-737 (Fed. Cir. 1988)). Amgen's proposed construction would provide a POSA with an unlimited range of redox buffer strengths to assess. Further, given the dynamic between the thiol-pair ratio and redox buffer strength, a POSA would have thousands, if not millions, of possible thiol-pair ratio/redox buffer strength combinations to assess. This is the epitome of undue experimentation. What is more, nowhere does the specification of the '138 patent teach a

POSA how to make and use an unlimited number of redox buffer strengths, *i.e.,* 2 mM *or greater*.

Rather, the specification provides support for an upper limit for the redox buffer strength as proposed by Apotex. For example, the specification explicitly discloses, in five (5) separate places, a thiol-pair buffer strength [*i.e.,* redox buffer strength] equal to or greater than 2 mM, "wherein the thiol-pair buffer strength is effectively bounded at a maximum of 100 mM." (*See* D.E. 76, Exh. A at col. 2, l. 67 through col. 3, l. 4; *id*. at col. 10, ll. 29-33 and 54-64; *id*. at col. 11, ll. 16-20 and 45-49 (emphasis added); *see also* Robinson Decl. at ¶ 26.) Thus, the specification makes it abundantly clear to one skilled in the art that the patent is using the term "2 mM or greater" to describe a redox buffer strength between 2 mM and 100 mM. (*See* Robinson Decl. at ¶ 26.)

The specification of the '138 patent further discloses, "in terms of ranges, the thiol buffer strength [*i.e.,* redox buffer strength] is between 2 and 20 mM." (*See* D.E. 76, Exh. A at col. 10, ll. 34-35 and 64-65; *id*. at col. 11, ll. 20-21 and 49-51; *id*. at col. 3, ll. 4-5; *see also* Robinson Decl. at ¶ 27.) Again, this shows that the "2 mM or greater" redox buffer strength term plainly means that the range of redox buffer strengths is not unlimited. (*See* Robinson Decl. at ¶ 27.) Instead, not only is there a suggested range of redox buffer strengths (*i.e.,* 2 mM to 20 mM), but there are explicit statements within the specification that effectively restrict the range to a maximum of 100 mM. (*Id*.)

Amgen's proposed construction would not satisfy the written description requirement either. Under 35 U.S.C. § 112, first paragraph, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. *See Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). In this case, the '138 patent specification does not show the inventors were in possession of a method of refolding a protein that would encompass the 2 mM *or greater* redox buffer strength limitation of the claims. As described above, the specification of the '138 patent only describes redox buffer strengths in the range of 2 to 20 mM. Moreover, the specification explicitly bounds the maximum redox buffer strength at 100 mM.

For at least these reasons, the Court should reject Amgen's proposed construction.

7. "*refold mixture*"

Amgen's Proposed Construction	Apotex's Proposed Construction
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 the protein and the refold buffer are combined to form the refold mixture. However, Amgen is incorrect that 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." (D.E. 77 at 11.) Instead, Amgen's motive behind this construction is litigation-based, because without it, Amgen cannot prove its infringement case. Amgen should not be allowed to insert a limitation into the claim that is not supported by the intrinsic record and that is contrary to the purpose of the purported invention just because it needs to maintain this action.

Indeed, nothing in the plain language of the claims supports Amgen's proposed "where 'high protein concentration' is at or above about 1 g/L" (D.E. 77 at 11-12). (*See* Robinson Decl. at ¶ 31.) Claim 1 specifically recites, *inter alia*, "A method of refolding a protein . . . present in a volume at a concentration of *2.0 g/L or greater* . . .." (*See* D.E. 76, Exh. A at claim 1 (emphasis added).) To narrow the scope of a claim beyond its plain and ordinary meaning, the terms, claims, specification, or prosecution histories must "clearly indicate that the invention encompasses no more than that confined structure or method." *Abbott Labs. v. Sandoz, Inc.*, 566 F.3d 1282, 1288 (Fed. Cir. 2009) (citation omitted). Here, there is no indication in the specification that the inventors intended their claimed method of refolding proteins to encompass a minimum protein concentration of about 1g/L. Accordingly, Amgen should not be allowed to rewrite the claims of the '138 patent to accommodate their current litigation strategy. *Texas Instruments Inc. v. U.S. Int'l Trade Comm'n*, 988 F.2d 1165, 1171 (Fed. Cir. 1993) (Courts "can neither broaden nor narrow claims to give the patentee something different than what [was] set forth." (citation omitted)).

Amgen contends that "[a] person of ordinary skill would . . . understand from the disclosure in the '138 Patent that the invention 'relates to refolding proteins at high concentrations.'" (D.E. 77 at 11 (citing '138 patent at col. 1, ll. 11-12; col. 2, ll. 22, 24, 28-29; col. 4, ll. 9, 19, 24, 58; Exh. 4 at ¶¶ 38-39).) Amgen's citation, however, conveniently ignores

the rest of the sentence. (*See* Robinson Decl. at ¶ 33.) Specifically, the specification states: "[t]he present invention generally relates to refolding proteins at high concentrations, *and more particularly to refolding proteins in volumes at concentrations of 2.0 g/L and above*." (*See* D.E. 76, Exh. A at col. 1, ll. 11-14 (emphasis added).) In fact, when the '138 patent refers to high protein concentrations, it is generally followed by the phrase 2.0 g/L or greater. (*See* D.E. 76, Exh. A at col. 2, ll. 17-21 ("refolded at high concentrations, *i.e.,* concentrations of 2.0 g/L and higher"); *see also id*. at col. 4, ll. 15-24 ("As described herein . . . 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 . . . protein refolding at high protein concentrations, such as concentrations higher than 2.0 g/L."); Robinson Decl. at ¶ 33.)

Amgen's expert, Dr. Willson, also states "a [POSA] would understand that in the context of protein refolding, the boundary at or above which the protein concentration in a refold mixture would be considered 'high' was about 1 g/l." (*See* D.E. 77, Exh. 4 at ¶ 40.) For the same reasons as discussed above, however, it is clear that the '138 patent refers to protein concentrations of 2.0 g/L or greater in the refold mixture as "high concentrations."

Amgen further contends that "[t]he specification . . . teaches that the protein concentration in the refold mixture can be as low as 1 g/L when practicing the claimed method." (D.E. 77 at 11.) And, Dr. Willson argues that "a [POSA] . . . would understand claim 1 of the '138 Patent to allow for a protein concentration of less than 2 g/l upon formation of the refold mixture, but no less than about 1 g/l." (*See id.* at Exh. 4 at ¶ 50 (emphasis in original).) That is simply not true. None of the disclosures cited by Amgen (*id.* at 11 (citing '138 patent at col. 10, ll. 12-16; col. 12, ll. 40-53; Exhibit 4 at ¶¶ 33-36)) use the language "high protein concentration" when disclosing a range of protein concentrations which encompass 1 g/L or greater. What is more, contrary to Dr. Willson's assertion, a POSA would not understand the refold mixture to allow for a protein concentration between 1-2 g/l. (*See* Robinson Decl. at ¶ 34.) As set forth above, the intrinsic record is clear—the purported invention is directed to refolding proteins at high protein concentrations, *i.e.*, 2.0 g/L or greater. (*See* D.E. 76, Exh. A at Abstract; *see also id*. at col. 1, ll. 11-14; D.E. 76, Exh. H at 6-7, Exh. I at 8; Robinson Decl. at ¶ 34.)

Accordingly, Amgen's proposed construction must be rejected.

B. The '427 Patent

1. "*chemotherapeutic agent*"

Amgen's Proposed Construction	Apotex's Proposed Construction
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

The dispute regarding the proposed constructions centers on whether "chemotherapeutic agent" refers to a substance with a single function, *i.e.,* the ability to damage or destroy, *inter alia*, tumor cells, or with dual functions, *i.e.*, the ability to damage or destroy, *inter alia*, tumor cells and open the endothelial barrier, rendering it permeable for stem cells. Amgen argues that "Apotex seeks to improperly broaden the scope of 'chemotherapeutic agent.'" (D.E. 77 at 13.) That is not true. Apotex's construction comes straight from the '427 patent specification. For example, the '427 patent defines "chemotherapeutic agent" as follows:

> As chemotherapeutic agents in the meaning of the invention those therapeutic agents may be used which open the endothelial, rendering it permeable for stem cells [*i.e.,* enhancing stem cell mobilization]. Hereinbelow, chemotherapeutic agents are understood to be exogenous substances suited and used to damage or destroy microorganisms, parasites or tumor cells.

(*See* D.E. 76, Exh. B at col. 2, ll. 34-39.) The specification further discloses, "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 leukophersis), then performing the antitumor therapy using a cytostatic agent [*i.e.*, a chemotherapeutic agent] or irradiation and subsequently, conducting the peripheral stem cell transplantation." (*See* D.E. 76, Exh. B at col. 3, ll. 24-30.) Thus, the specification makes it clear to one skilled in the art that the '427 patent is using the term "chemotherapeutic agent" to describe to describe *both* therapeutic agents that open the endothelial barrier to enhance stem cell mobilization and exogenous substances that damage or destroy microorganisms, parasites or tumor cells. Amgen cannot explain why it seeks to limit "chemotherapeutic agent" to only part of the definition provided in the specification.

For at least these reasons, the Court should reject Amgen's proposed construction.

2. "***disease treating-effective amount***"

Amgen's Proposed Construction	Apotex's Proposed Construction
An amount sufficient to enhance the mobilization of stem cells for recovery from the blood for subsequent peripheral transplantation.	Indefinite.

Amgen proposes that "disease treating-effective amount" should be construed to mean "[a]n amount sufficient to enhance the mobilization of stem cells for recovery from the blood for subsequent peripheral transplantation." (D.E. 77 at 14-15.) In support of their construction, Amgen cites to disclosures in the specification discussing administration of a chemotherapeutic agent for stem cell mobilization. (*Id.*) However, Amgen fails to note that the specification also describes the ability of a chemotherapeutic agent to damage or destroy tumor cells.

For example, the '427 patent defines "chemotherapeutic agent" as follows:

> As chemotherapeutic agents in the meaning of the invention those therapeutic agents may be used which open the endothelial, rendering it permeable for stem cells [*i.e.*, enhancing stem cell mobilization]. Hereinbelow, *chemotherapeutic agents are understood to be exogenous substances suited and used to damage or destroy microorganisms, parasites or tumor cells*.

(*See* D.E. 76, Exh. B at col. 2, ll. 34-39 (emphasis added).) Further, the patent specification discloses that "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 leukopheresis), then performing the antitumor therapy using a cytostatic agent [*i.e.*, a chemotherapeutic agent] or irradiation and subsequently, conducting the peripheral stem cell transplantation." (*See id.*, Exh. B at col. 3, ll. 24-30.) Thus, 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*.

What is more, the term "disease treating-effective amount" is used to modify the term "chemotherapeutic agent." (*See id.*, Exh. B at claim 1.) And, as discussed above, Amgen themselves define chemotherapeutic agent as an "[e]xogenous substance capable of damaging or destroying . . . tumor cells." (D.E. 77 at 12-13). Thus, based on Amgen's proposed construction of "chemotherapeutic agent," a "disease treating-effective amount" should be the amount of a chemotherapeutic agent capable of, *inter alia*, damaging or destroying tumor cells. However,

Amgen's proposed construction of "disease treating-effective amount" fails to account for their definition of "chemotherapeutic agent." This discrepancy between Amgen's proposed construction of "chemotherapeutic agent" and "disease treating-effective amount" further highlights the indefiniteness of this term.

Amgen also notes that "[t]he specification identifies a dosage range for the chemotherapeutic agent as '0.05-100 mg/kg/day.'" (*Id.* at 14-15 (citing '427 patent at col. 3, ll. 11-12).) Amgen argues that a POSA would understand this dosage range to be "the 'disease treating-effective amount' needed to achieve the goal of enhancing stem cell mobilization." (*Id.* at 15.) However, as Dr. Scadden stated in his Declaration in Support of Defendants' Opening Claim Construction Brief, this dosage range is capable of *both* damaging or destroying tumor cells and opening the endothelial barrier. (*See* D.E. 76, Exh. D at ¶ 50.)

For these reasons, the Court should reject Amgen's proposed construction.

III. CONCLUSION

For the foregoing reasons, Apotex respectfully requests that the Court reject Amgen's proposed constructions of the disputed terms and adopt Apotex's constructions.

Dated: January 8, 2016

Respectfully submitted

By: */s/ Simeon D. Brier*

Simeon D. Brier
Florida Bar No.: 525782
Matthew B. Criscuolo
Florida Bar No.: 58441
COZEN O'CONNOR
One North Clematis Street
Suite 510
West Palm Beach, FL 33401
Telephone: 561-515-5250
Email: sbrier@cozen.com
mcriscuolo@cozen.com

Admitted *Pro Hac Vice*

W. Blake Coblentz
Kerry B. McTigue
Barry Golob
Milton A. Marquis
Aaron S. Lukas
COZEN O'CONNOR
1200 Nineteenth Street, N.W.
Washington, DC 20036
Telephone: 202-912-4800
Email: wcoblentz@cozen.com
kmctigue@cozen.com
bgolob@cozen.com
mmarquis@cozen.com
alukas@cozen.com

Marilyn Neiman
Keri L. Schaubert
COZEN O'CONNOR
277 Park Avenue
New York, NY 10172
Telephone: 212-883-4900
Email: mneiman@cozen.com
kschaubert@cozen.com

Attorneys for Defendants and Counterclaim Plaintiffs Apotex Inc. and Apotex Corp.

CERTIFICATE OF SERVICE

I HEREBY CERTIFY that on this 8th day of January, 2016, I electronically filed the foregoing document with the Clerk of the Court using CM/ECF. I also certify that the foregoing document is being served this day on all counsel of record identified on the attached service list in the manner specified, either via transmission of Notices of Electronic Filing generated by CM/ECF or in some other authorized manner for those counsel or parties who are not authorized to electronically receive Notices of Electronic Filing.

Dated: January 8, 2016

/s/ Simeon D. Brier
Simeon D. Brier

SERVICE LIST

John F. O'Sullivan
Fla. Bar No. 143154
Allen P. Pegg
Fla. Bar No. 597821
HOGAN LOVELLS
600 Brickell Ave., Suite 2700
Miami, FL 33131
Telephone: (305) 459-6500
Facsimile: (305) 459-6550
john.osullivan@hoganlovells.com
allen.pegg@hoganlovells.com

Of Counsel:

Nicholas Groombridge
Catherine Nyarady
Jennifer Gordon
Peter Sandel
PAUL, WEISS, RIFKIND, WHARTON & GARRISON
1285 Avenue of the Americas
New York, NY 10019
Telephone: (212) 373-3000
Facsimile: (212) 757-3990
ngroombridge@paulweiss.com
cnyarady@paulweiss.com
jengordon@paulweiss.com
psandel@paulweiss.com

Wendy A. Whiteford
Lois M. Kwasigroch
Kimberlin Morley
AMGEN INC.
One Amgen Center Drive
Thousand Oaks, CA 91320
Telephone: (805) 447-1000
Facsimile: (805) 447-1010
wendy@amgen.com
loisk@amgen.com
kmorley@amgen.com