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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

AMGEN INC. and AMGEN MANUFACTURING LIMITED, Plaintiffs, v. ADELLO BIOLOGICS, LLC, AMNEAL PHARMACEUTICALS LLC, and AMNEAL PHARMACEUTICALS, INC. Defendants	C.A. No. 2:18-cv-03347-CCC-MF **DEFENDANTS' OPENING CLAIM CONSTRUCTION BRIEF**

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I. INTRODUCTION

Defendants Adello Biologics, LLC[1], Amneal Pharmaceuticals LLC and Amneal Pharmaceuticals, Inc.[2] (collectively, "Defendants") respectfully submit this Opening Claim Construction Brief to address disputed terms of the patents asserted by Plaintiffs Amgen Inc. and Amgen Manufacturing Limited (collectively, "Amgen") in this infringement action – U.S. Patent Nos. 8,952,138 ("the '138 patent"), 9,856,287 ("the '287 patent"), 8,940,878 ("the '878 patent"), and 9,643,997 ("the '997 patent") (collectively, the "Patents-in-Suit"). *See* Exs. 1-4.[3]

This lawsuit is but one of Amgen's many attempts to fend off aspiring biosimilar entrants to the filgrastim market. In addition to the Defendants here, Amgen has sued Sandoz, Mylan, Hospira, and Apotex (twice) on one or more of the four Patents-in-Suit. Amgen has yet to prevail on any claim in any forum. It has, however, fully litigated claim construction, including certain of the precise issues now before this Court, before various District Courts, the Federal Circuit, and the Patent Trial and Appeal Board.

Now, because Amgen's own prior positions – and the resulting decisions – cannot sustain a good-faith infringement claim against Kashiv's filgrastim manufacturing processes, Amgen seeks yet another claim construction do-over in this Court. Many of the constructions Amgen

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[1] On January 1, 2019 Adello Biologics, LLC ("Adello") entered into a corporate transaction with Kashiv Pharma, LLC, and the resulting entity was renamed Kashiv BioSciences, LLC ("Kashiv"). Kashiv is now the owner of the Abbreviated Biologics License Application ("aBLA") No. 761082, which is the subject of Amgen's present BPCIA suit. On February 18, 2019, Adello filed notices with the FDA to change the sponsoring entity of aBLA No. 761082 to Kashiv. In light of these transactions, Kashiv's counsel will confer with Plaintiffs' counsel regarding the substitution of Kashiv for Adello as a party to this action. For purposes of this brief, Defendants refer to Kashiv as the owner of the accused Filgrastim Product.

[2] In participating in claim construction, Amneal Pharmaceuticals LLC and Amneal Pharmaceuticals, Inc. reserve, and do not waive, their position that they are not proper parties or defendants in this action.

[3] Cited exhibits are attached to the Declaration of Kevin C. Quigley, filed herewith.

proposes here are irreconcilable with constructions it previously advocated and obtained elsewhere. Amgen's flip-flopping goes beyond mere damage to its credibility (and that of its experts); in many instances, it constitutes textbook collateral estoppel. Moreover, Amgen's litigation-inspired constructions are contrary to the plain language of the asserted claims and the disclosures of the Patents-in-Suit. The Court should reject them.

Defendants' proposed constructions are consistent with the understanding of those skilled in the art, black-letter claim construction law, and prior rulings. Because the Patents-in-Suit consist of two sets of related patents that share specifications – the '138 and '287 patents (directed to protein refolding); and the '878 and '997 patents (directed to protein purification) – the resolution of a disputed term often applies across two patents. In several instances, Defendants submit that a disputed term is not susceptible of any adequate construction and is therefore indefinite under 35 U.S.C. § 112.

II. LEGAL PRINCIPLES

A. Claim Construction

Claim construction is a matter of law for the Court to decide. *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 391 (1996). The words of a claim "are generally given their ordinary and customary meaning," *i.e.*, the meaning that they "would have to a person of ordinary skill in the art in question at the time of the invention." *Phillips v. AWH* Corp., 415 F.3d 1303, 1312-13 (Fed. Cir. 2005) (*en banc*) (internal citations omitted). "The construction that stays true to the claim language and most naturally aligns with the patent's description of the invention will be, in the end, the correct construction." *Phillips*, 415 F.3d at 1316 (internal citation omitted).

B. Indefiniteness

Indefiniteness presents a question of law which may be decided as part of claim

construction. *See Jazz Pharm., Inc. v. Amneal Pharm.*, LLC, No. 13-0391, 2017 U.S. Dist. LEXIS 183344, at *7-8 (D.N.J. Nov. 6, 2017) (citing *Interval Licensing LLC v. AOL, Inc.*, 766 F.3d 1364, 1368-74 (Fed. Cir. 2014) (affirming the district court's indefiniteness ruling at claim construction post-*Nautilus*)); *Mycone Dental Supply Co. v. Creative Nail Design, Inc.*, No. 11-4380, 2014 U.S. Dist. LEXIS 93051 (D.N.J. July 9, 2014) ("[I]ndefiniteness is a significant issue to be adjudicated at claim construction . . . ."). "[A] patent is invalid for indefiniteness if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 901 (2014).

C. Collateral Estoppel and Prior Constructions

Collateral estoppel may apply to bar a party from advocating claim constructions contrary to those it previously litigated to final judgment in another court. *See Nestlé USA, Inc. v. Steuben Foods, Inc.*, 884 F.3d 1350, 1351-52 (Fed. Cir. 2018). Here, under controlling Third Circuit law, collateral estoppel applies where "(1) the identical issue was previously adjudicated; (2) the issue was actually litigated; (3) the previous determination was necessary to the decision; and (4) the party being precluded from relitigating the issue was fully represented in the prior action." *Jean Alexander Cosmetics, Inc. v. L'Oreal USA, Inc.*, 458 F.3d 244, 249 (3d Cir. 2006) (internal citations omitted).

Even if a prior claim construction is not binding for purposes of collateral estoppel, "district court claim construction decisions will be given careful consideration and considerable deference by later courts unless there is intervening case law or a new party that raises new arguments." *Ravo v. Tyco Healthcare Group LP*, No. 2:11-CV-01637-JCF, 2013 U.S. Dist. LEXIS 91493, at *16-17 (W.D. Pa. Mar. 13, 2013) (summarizing cases). Courts recognize the

"importance of uniformity in the treatment of a given patent" and generally disfavor parties changing positions. *Markman*, 517 U.S. at 390; *see also, e.g., Amgen Inc. v. Mylan, Inc.*, No. 2:17-cv-01235, 2018 U.S. Dist. LEXIS 197482, at *22 (W.D. Pa. Nov. 20, 2018); *LG Display Co. v. AU Optronics Corp.*, 709 F. Supp. 2d 311, 320 (D. Del. 2010).

III. PERSON OF ORDINARY SKILL IN THE ART

The Patents-in-Suit relate to the refolding and purification of proteins synthesized in bacterial host cells ("non-mammalian expression systems"). It is well understood in the art that proteins expressed in a bacterial cell are often misfolded and/or aggregated with other proteins. Accordingly, the proteins must be artificially unfolded ("solubilized") and then refolded in a solution that facilitates their properly folded, biologically active three-dimensional form. The refolded proteins are then "purified," or separated from unwanted components remaining in the refold solution, by well-known processes such as chromatography.[4]

A person of ordinary skill in the art (a "POSA") in 2009 would have at least a Bachelor's degree (or the equivalent) in Chemistry or Biochemistry or Chemical Engineering with several years of experience in biochemical manufacturing, protein purification, protein refolding, and protein chemistry; or, alternatively, an advanced degree (Masters or Ph.D.) in Chemistry or Biochemistry or Chemical Engineering with emphasis in the same areas. Zhou Decl., ¶¶ 12-13.

IV. THE '138 PATENT

The '138 patent purports to cover methods of refolding proteins at high concentrations using a chemically controlled redox state. Specifically, the '138 patent describes the use of a "redox component" comprising oxidants and reductants ("thiol pairs") that facilitate refolding.[5]

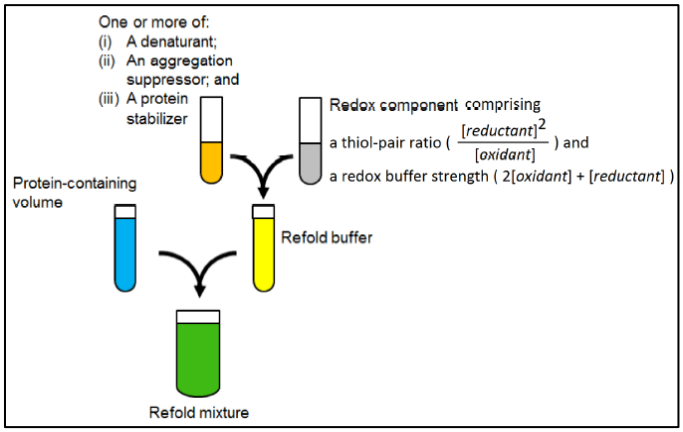
[4] A full background of the relevant technology is provided in the Declaration of Zhaohui Sunny Zhou, Ph.D. ("Zhou Decl."), filed herewith. *See* Zhou Decl., ¶¶ 19-29.

[5] Disulfide bonds between amino acid cysteine residues form a protein's three-dimensional structure. Reductants can break incorrect disulfide bonds; oxidants can form desired bonds.

Claim 1, the sole independent claim of the '138 patent,[6] recites two attributes of the redox component – "thiol-pair ratio" (TPR) and "redox buffer strength" (RBS) – which are calculated using equations set forth in the specification. 6:25-41. The patent asserts that by controlling TPR and RBS according to the parameters set forth in the claim, proteins can be refolded with greater efficiency, at higher concentrations than those previously used in the art.[7]

Below, the language of claim 1 is highlighted to correspond with a graphic[8] depicting the various volumes involved in the claimed method. Disputed claim terms are underlined

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.



A. The Collateral Estoppel Effects of the *Apotex* Court's Decision.

Amgen has already litigated the '138 patent – and each of its five disputed terms – to a final judgment. In *Amgen v. Apotex*, the U.S. District Court for the Southern District of Florida entered findings of fact and conclusions of law of non-infringement in favor of Apotex. Ex. 5. The Federal Circuit affirmed the decision. Ex. 6. Integral to the non-infringement judgment

[6] Amgen asserts only dependent claim 18 (which depends from claim 1) against Defendants. All other claims of the '138 patent were cancelled by the Patent Trial and Appeal Board in *Apotex Inc. et al. v. Amgen Inc. et al.*, IPR No. 2016-01542 (Final Written Decision, February 15, 2018). The parties do not dispute the meaning of any terms of dependent claim 18.

[7] In fact, the patent merely recites methods of refolding proteins that were well-known and understood in the art, as Defendants will separately demonstrate at the appropriate time.

[8] Amgen previously used this identical graphic in the *Apotex* IPR. *See* Ex. 9, p. 12.

were several of the district court's claim construction rulings. Because Amgen had a full and fair opportunity to litigate these issues, the doctrine of collateral estoppel bars any contrary result here. *See Jean Alexander Cosmetics*, 458 F.3d at 249. Indeed, with respect to all but one of the disputed terms, the positions adopted by the *Apotex* court were forcefully advocated by ***Amgen***.

One fundamental issue resolved by the *Apotex* court applies across numerous claim terms, so Defendants address it here before proceeding to the individual constructions. At Amgen's urging, the *Apotex* court held that thiol-pair ratio and redox buffer strength are calculated using concentrations of reductant and oxidant in the ***redox component*** volume – as opposed to the refold mixture (which was Apotex's contention). Ex. 7. As the court explained, the plain language of the claim compels this result:

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

Ex. 7, pp. 7-8. The court also relied on Amgen's expert, Richard C. Willson, who opined: "a POSITA would understand that TPR and RBS are based on concentrations of oxidant and reductant in the redox component and not, as [Apotex's expert] suggests, in the refold mixture." Ex. 8, ¶ 42.[9] The *Apotex* court's construction proved necessary to the ultimate judgment of non-infringement, because it found that the buffer strength of Apotex's accused process – calculated using concentrations in the redox component – exceeded the scope of the claim. Ex. 5, pp. 16-19.

Amgen now proposes constructions of "redox component," "thiol-pair ratio," and "redox

[9] *See also id.* at ¶ 44 ("It makes sense that the concentrations of oxidants and reductants used to calculate TPR and RBS should be based on the redox component, because the researcher would have both precise knowledge of and control over these concentrations (and would have neither precise knowledge of, nor control over, the composition of the refold mixture).")

buffer strength" which pointedly omit language specifying that the relevant concentrations of reductant and oxidant are calculated in the redox component. That is because Amgen's infringement contentions for the '138 and '287 patents in this case are based upon concentrations in the ***refold mixture*** of Kashiv's process – precisely the opposite of its position in *Apotex*. *See* Ex. 33. As the *Apotex* court correctly decided, the position Amgen advocated in that case was supported by both the claim language and the specification. Amgen may not escape the constraints of collateral estoppel in order to strategically preserve ambiguity for another day. This Court should adopt constructions that are consistent with – indeed, compelled by – the constructions Amgen itself previously advocated and obtained in *Apotex*.[10]

B. The Disputed Terms.

1. "a redox component"

Amgen's Proposed Construction	Defendants' 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."	"A single volume consisting of a combination of reductant and oxidant that facilitates a reversible thiol exchange between thiols or with 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."

The '138 patent specification defines "redox component" as "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." 6:63-66. Thus, the patent teaches that the key function of a redox component is that it "facilitates a reversible thiol exchange with another thiol or the cysteine residues of a protein." *Id.* at 65-66. The parties agree on this point.

The broad, functional definition of "redox component" in the specification, however, is

[10] In fact, Amgen also advocated and received a construction requiring TPR and RBS to be calculated in the redox component in the *Apotex* IPR. *See* Ex. 9, pp. 10-12; Ex. 10, p. 18 n.4, 20 n.5; Ex. 11, pp. 10-11.

limited in several important ways by the plain language of the claim itself. Defendants' construction accurately incorporates those limitations; Amgen's does not. *See* Zhou Decl., ¶¶ 39-44.

First, consistent with the express language of the claim and Amgen's prior positions, Defendants' proposed construction explicitly notes that the "redox component" itself comprises the "final thiol-pair ratio" and the "redox buffer strength." The *Apotex* court, at Amgen's urging, included this very same language in its construction of "redox component." Ex. 7, pp. at 6-7 ("[T]he construction offered by Amgen is consistent with the terms of the claim and reflects the express claim language. [It] does not render any other portion of the claim superfluous."). Indeed, as explained above, Amgen is collaterally estopped from arguing otherwise.

Second, by requiring that the "redox component" of the claims "compris[e] a final thiol-pair ratio" with a value greater than zero, the method claimed by the '138 patent necessarily requires the use of at least two (*i.e.*, a pair of) thiol-reactive chemicals in the redox component – specifically, a reductant and an oxidant, the components of the "thiol-pair ratio." *See, e.g.*, 6:25-28 (providing that thiol-pair ratio equals "[reductant]^2/[oxidant]"). Defendants' proposed definition clarifies – that the "redox component" must contain this combination of reductant and oxidant. This would be plain and unambiguous to a POSA. *See* Zhou Decl., ¶ 42.

Third, the claim recites "*a* redox component" (emphasis added) – *i.e.*, a single volume rather than multiple volumes. That is, the amounts of reductant and oxidant are combined together in a single "redox component" volume before that volume is combined with the other components of the refold buffer and the refold mixture. The *Apotex* court made this very observation. *See* Ex. 5, ¶ 58 ("Apotex's process does not literally include the claimed redox component that has an oxidant (cystine) and a reductant (cysteine) combined together outside of the refold mixture"). Any other interpretation would read the singular qualifier "a" out of the claim altogether. *See* Zhou Decl., ¶ 43.

2. "final thiol-pair ratio having a range of 0.001 to 100"

Amgen's Proposed Construction	Defendants' Proposed Construction
"The relationship of the reduced and oxidized redox species used in the redox component of the refold buffer as defined by the equation [*reductant*]^2/[*oxidant*], having a range of 0.001 to 100."	Indefinite. *Alternatively*: Defined by the following equation: [*reductant*]^2/[*oxidant*], where the concentrations are the concentrations in the redox component.

Again, Amgen is precluded from arguing for a construction contrary to the construction adopted by the *Apotex* court: "Defined by the following equation: [*reductant*]^2/[*oxidant*], where the concentrations are the concentrations in the redox component."

Even accepting this construction, however, there is a fundamental problem with this term that was not raised before the *Apotex* court: because neither the claim nor the specification provides a ***unit*** of concentration for the thiol-pair ratio, the term is indefinite. *See* Zhou Decl., ¶¶ 45-52. In fact, it is mathematically impossible to calculate thiol-pair ratio without knowing the applicable unit. This deficiency is not cured by Amgen's proposed construction, nor can it be cured by any construction. It is fatal to the claim. *See Nautilus*, 572 U.S. at 901.

The thiol-pair ratio equation ([*reductant*]^2/[*oxidant*]) was well-known in the art prior to 2009 as a way to observe the relationship between the concentrations of reductant and oxidant in a redox system. Zhou Decl., ¶ 48 (citing references). Importantly, however, the prior art always specified the unit of concentration (molarity) used in the calculation and applicable to the result.[11] Some references used molar (**M**); others used millimolar (**mM**); still others used micromolar (**µM**). *See* Zhou Decl., ¶ 48 (providing examples using each unit of concentration).

The '138 patent, by contrast, does not provide any unit for the claimed range of 0.001-100

[11] Regardless of the unit of concentration used in measuring [*reductant*] and [*oxidant*], the result of the [*reductant*]^2/[*oxidant*] equation must have the same unit. That is because the squared term in the numerator ([*reductant*]^2) squares both the numerical value and the unit. Only one instance of the unit in the numerator is cancelled out by the unit in the denominator. *See* Zhou Decl., ¶ 50.

in Claim 1. Nor does it provide a unit at any other place in the specification that refers to the results of the thiol-pair ratio equation. *See, e.g.*, Figs. 1a-1f; 2:63-66; 10:25-60; 11:11-45. The failure to specify the unit also renders the claimed range (0.001 to 100) meaningless. The units of concentration used by persons of skill in the art vary by factors of a thousand. 1 M equals 1,000 mM, and 1 mM = 1,000 µM. When using the same concentrations of reductant and oxidant, but merely expressing those concentrations using different units, the results of the [reductant]^2/[oxidant] equation vary dramatically.[12] *See* Zhou Decl., ¶ 49-51.

Thus, the absence of a unit renders the "thiol-pair ratio" equation both incomplete and useless and, therefore, indefinite. *See Teva Pharm. USA, Inc. v. Sandoz, Inc.*, 789 F.3d 1335, 1344-45 (Fed. Cir. 2015) (claim indefinite where patent failed to indicate the proper unit of measurement of "molecular weight," where unit of measurement could be M_p, M_n, or M_w).

3. "redox buffer strength"

Amgen's Proposed Construction	Defendants' Proposed Construction
"2[*oxidant*] + [*reductant*]"	"Defined by the following equation: 2[*oxidant*] + [*reductant*], where the concentrations are the concentrations in the redox component."

Defendants' proposed construction is identical to the one Amgen advocated, and the *Apotex* court adopted. This construction comports with the plain language of the claim, which recites a "redox component comprising … a redox buffer strength of 2 mM or greater," and the specification, which associates both TPR and RBS with the redox component. 10:22-30; 11:40-

[12] Take, for example, a redox component with concentrations of 18 mM reductant and 3 mM oxidant. Said differently, the concentrations are 0.018 M reductant and 0.003 M oxidant, or 18,000 µM reductant and 3,000 µM oxidant. When using the M unit, the equation results in a thiol-pair ratio of **0.108 M** ([0.018 M]^2/[0.003 M]) – which is squarely within the claimed range of 0.001 to 100. However, when using mM, the result is **108 mM** – which is outside the claimed range of 0.001 to 100. And, when using µM, the result is **108,000 µM** -- dramatically outside the claimed range. *See* Zhou Decl., ¶ 51.

46; *see also* Ex. 7, p. 8 ("[T]he claim language is careful to say which value is measured at which stage. Adopting [a construction permitting the use of concentrations in the refold mixture] would require the Court to re-write the claim.").

4. "2 mM or greater"

Amgen's Proposed Construction	Defendants' Proposed Construction
"greater than or equal to 2 mM"	"2 mM or greater, wherein the redox buffer strength is effectively bounded at a maximum of 100 mM"

The claims require a "redox buffer strength of 2mM or greater." Defendants' proposed construction of "2 mM or greater" was correctly adopted by the *Apotex* court. Ex. 7, pp. 9-10. In rejecting Amgen's insistence that no construction was necessary, the *Apotex* court was "particularly convinced by the fact that the specification repeatedly sets forth a suggested range of redox buffer strengths, yet each time specifically limits the possible ranges, 'wherein the thiol-pair buffer strength is effectively bounded at a maximum of 100 mM.'" *Id.* at 10.

The specification clearly supports Defendants construction. Specifically, in every instance the specification provides possible ranges for the thiol-pair buffer strength (*i.e.,* redox buffer strength), it states that "***the thiol-pair buffer strength is effectively bounded at a maximum of 100 mM.***" *See* 2:67-3:4; 10:29-33; 10:54-64; 11:16-20; 11:45-49 (emphasis added). Also, all exemplary embodiments of the '138 patent also show that "in terms of ranges, the thiol buffer strength is between 2 and 20 mM" (10:34-35 and 64-65; 11:20-21 and 49-51) or between 5 and 20 mM (Figs. 1a-1f). Thus, the '138 patent defines "a redox buffer strength of 2 mM or greater" as a redox buffer strength of 2 mM to 100 mM. *See SciMed Life Sys. v. Advanced Cardiovascular Sys., Inc.*, 242 F.3d 1337, 1342-45 (Fed. Cir. 2001) (specification instructive as to scope of claim); *Perkinelmer Health Scis., Inc. v. Agilent Techs., Inc.*, 962 F. Supp. 2d 304, 309 (D. Mass. 2013) (rejecting construction that "greater than 5000" has no upper limit where

"the intrinsic evidence presented here implies the existence of some upper limit"); *Roche Diagnostics Operations, Inc. v. Abbott Diabetes Care*, 667 F. Supp. 2d 429, 436 (D. Del. 2009) (requiring upper limit provided by the specification).

In *Apotex*, the 100 mM limitation proved necessary to the judgment of non-infringement, as the redox buffer strength of Apotex's process was 214-340 mM. Ex. 5,¶ 64. The *Apotex* court's decision was correct, and Amgen now is estopped from arguing otherwise. *See Aspex Eyewear, Inc. v. Zenni Optical LLC*, 713 F.3d 1377, 1381-82 (Fed. Cir. 2013) (plaintiff estopped from re-litigating construction it argued and lost in previous suit).

5. "refold mixture"

Amgen's Proposed Construction	Defendants' Proposed Construction
"A mixture formed from contacting (1) the protein with (2) a refold buffer."	"A mixture formed from contacting (1) the entire volume in which the concentration of protein is 2.0g/L or greater with (2) the entire volume of refold buffer. The refold mixture has a high protein concentration, where 'high protein concentration' is at or above about 1g/L protein."

The parties agree that the refold mixture results from contacting the protein-containing volume with the refold buffer volume. Defendants' construction, however, clarifies that the refold mixture only exists once the *entire* protein-containing volume is contacted with the *entire* volume of refold buffer. As Dr. Zhou explains, a POSA would understand that the "refold mixture" does not exist at the instant the first drop of refold buffer solution contacts the protein-containing volume (or vice versa). Any dropwise addition must be completed before the "refold mixture" can be considered fully formed. Zhou Decl., ¶ 54.[13]

Importantly, Defendants' construction is also consistent with the *Apotex* court's holding

[13] Defendants' use of "2.0 g/L or greater" to refer to the protein-containing arises from the plain language of the claim and the parties' agreed-upon construction of "a protein … present in a volume at a concentration of 2.0 g/L or greater." *See* Dkt. No. 101, at 3.

that the term "refold mixture," read in light of the specification and common knowledge in the art, requires ***"a high protein concentration, where 'high protein concentration' is at or above about 1g/L protein."*** Ex. 7, p. 9. Because the *Apotex* court ultimately found (and the Federal Circuit affirmed) that the protein concentration in Apotex's refold mixture was below 1 g/L, this construction, too, was necessary to the final judgment of non-infringement. Ex. 5; Ex. 6. Amgen abandons that construction here (because Kashiv's refold mixture also has a protein concentration under 1 g/L). However, the *Apotex* court got it right and the doctrine of collateral estoppel once again precludes Amgen's about-face.

In the *Apotex* litigation, Amgen's expert, Richard C. Willson, opined at length in support of this construction. *See* Ex. 12,¶¶ 31-50. Here, Dr. Zhou agrees with Dr. Willson's characterization of the understanding of a POSA as of 2009 on this point. Zhou Decl., ¶¶ 55-58. In particular, the '138 patent specification distinguishes the purported invention from prior art approaches involving protein concentrations in refold mixtures of "typically 0.01-0.5 g/L." 1:52-54. In contrast, the specification teaches that, upon dilution with the refold buffer, refolding takes place at a protein concentration of 1 g/L or greater. *See* 10:12-16 (invention "allows for refolding at concentrations of 1-40 g/L"); 12:44-49 ("The dilution results in a protein concentration in the range of 1 to 15 g/L"); *see also* Zhou Decl., ¶ 57. Thus, the inventors explicitly disclosed 1 gram per liter as the minimum protein concentration in the refold mixture.

Moreover, a POSA would further understand from the disclosure in the '138 patent that the claimed invention "relates to refolding proteins at high concentrations." *See, e.g.*, 1:11-12 (invention "generally relates to refolding proteins at high concentrations") (emphasis added); *see also* 2:22, 24, 28-29; 4:9, 19, 23, 58 (using phrase repeatedly); *see also* Zhou Decl., ¶ 58. Again, as Dr. Willson said, a POSA as of 2009 would have understood that "the boundary at or above

which the protein concentration in a refold mixture would be considered "high" was about 1 g/L. Ex. 12,¶¶ 42-49. Prior art publications regarding protein refolding, of which a POSA would have been aware, refer to 1 g/L as the boundary between "high" and "low" protein concentrations. *Id.* (citing Maeda *et al., Protein Engineering* 9(1): 95-1000 (1996) at 99; Maeda *et al., Protein Engineering* 8(2): 201-205 (1995); Cleland and Wang, *Biochemistry* 29: 11072-11078, at 11072 (1990)); Sakane *et al., J. Mol. Biol.* 367: 1171-1185 (2007); *see also* Zhou Decl., ¶ 58. Thus, the specification, in conjunction with this art-recognized boundary, would have led a POSA in 2009 to understand claim 1 of the '138 patent to require a protein concentration upon formation of the refold mixture of at least 1 g/L. Amgen is precluded from arguing otherwise.

V. THE '287 PATENT

The '287 patent, which claims priority to the '138 patent, has an identical specification as the '138 patent. Like the '138 patent, the '287 patent is generally directed to high-concentration refolding of proteins expressed in bacterial cells through the use of a controlled redox state. The claims of the '287 patent also share many limitations with those of the '138 patent, including a "thiol-pair ratio," "thiol-pair buffer strength," and "refold mixture."

A. Overlapping Terms Have The Same Meaning As In The '138 Patent.

"Where multiple patents 'derive from the same parent application and share many common terms, [the Court] must interpret the claims consistently across all asserted patents.'" *SightSound Techs., LLC v. Apple Inc.*, 809 F.3d 1307, 1316 (Fed. Cir. 2015) (quoting *NTP, Inc. v. Research In Motion, Ltd.*, 418 F.3d 1282, 1293 (Fed. Cir. 2005)); *see also* Zhou Decl., ¶¶ 60, 62. The parties appear to agree on this common-sense principle by each advocating for substantially the same constructions of the same terms in both the '138 and '287 patents.

Accordingly, Defendants request that the Court adopt the following constructions and/or determinations of indefiniteness, for the same reasons explained above, with respect to:

refold mixture: "A mixture formed from contacting (1) the entire protein-containing volume with (2) the entire volume of the preparation.[14] The refold mixture has a high protein concentration, where 'high protein concentration' is at or above about 1g/L protein." *See supra* pp. 12-14; Zhou Decl., ¶¶ 59-60; 1:15-19; 1:60; 2:30-38; 4:23-24; 4:34-39; 5:9-10; 10:41-45; 13:12-18.

thiol-pair ratio: Indefinite; alternatively, "Defined by the following equation: [*reductant*]2/[*oxidant*], where the concentrations are the concentrations in the redox component." *See supra* pp. 9-10; Zhou Decl., ¶¶ 61-62; 6:50-55; 12:31-34; Figs. 1a-1f.

thiol-pair buffer strength[15]: "Defined by the following equation: 2[oxidant] + [reductant], where the concentrations are the concentrations in the redox component, and where the thiol-pair buffer strength is effectively bounded at a maximum of 100 mM." *See supra* pp. 10-11; 6:56-67.

B. Other Disputed Claim Terms.

1. "wherein the amounts of the oxidant and the reductant are related through a thiol-pair ratio and a thiol-pair buffer strength"

Amgen's Proposed Construction	Defendants' Proposed Construction
"wherein the amounts of the oxidant and the reductant are defined by the following equations: $\frac{\left(\sqrt{bufferTPR^2 + 8 * bufferTPR * BS}\right) - bufferTPR}{4}$ and $\frac{(\text{Concentration of Reduced Redox Component})^2}{TPR}$ "	"wherein the amounts of the oxidant and the reductant are selected by performing the following equations: $\frac{\left(\sqrt{bufferTPR^2 + 8 * bufferTPR * BS}\right) - bufferTPR}{4}$ and $\frac{(\text{Concentration of Reduced Redox Component})^2}{TPR}$ "

[14] The parties have elsewhere agreed that "preparation" in the '287 patent means substantially the same thing as "refold buffer" in the '138 patent.

[15] It is undisputed that the specifications and claims of the '138 patent and the '287 patent use the term "thiol-pair buffer strength" interchangeably with "redox buffer strength." *See, e.g.,* '287 patent at 6:55-58.

Every independent claim of the '287 patent contains this term. The core dispute is whether (as Defendants submit) the term affirmatively requires that the amounts of oxidant and reductant used for refolding be selected by performing the equations provided in the specification; or whether (as Amgen suggests) the equations may be applied in hindsight to *any* redox system containing any amounts of oxidant and reductant. Defendants' construction is consistent with the plain language of the claims in the context of the disclosure as a whole; Amgen's is not.

The '287 patent specification provides the equations as a description of "[t]he relationship between the thiol-pair ratio and thiol-pair buffer strength." 7:1-2. These equations, along with the equations for the thiol-pair ratio and buffer strength values embedded therein, collectively are at the core of the purported invention:

> As described herein, the relationship between thiol buffer strength and redox thiol-pair ratio has been investigated and optimized in order to provide a reproducible method of refolding proteins at concentrations of 2.0 g/L and higher on a variety of scales. A mathematical formula was deduced to allow the precise calculation of the ratios and strengths of individual redox 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.

'287 patent, 4:52-63. Said differently, there is nothing inventive about using amounts of oxidant and reductant to refold proteins; if there is anything inventive at all (and ultimately Defendants will prove there is not), it must be in the claimed "relationship" used to select the amounts of oxidant and reductant. *See* Zhou Decl., ¶ 65; *see also Phillips v. AWH Corp.*, 415 F.3d 1303, 1327 (Fed. Cir. 2005) (internal citations omitted) (courts should construe claims in favor of preserving validity). Further, the plain language of the claims confirms that the relationship must be actively measured by the practitioner of the claimed method as part of the process of refolding proteins, rather than in hindsight. The claims do not merely recite the thiol-pair ratio and buffer strength of

any given redox system (which could conceivably be measured in hindsight); they require that the amounts used are related through those measurements. *See* Zhou Decl., ¶¶ 64-66. Defendants' proposed construction accurately reflects this required active step, and the Court should adopt it.

2. "wherein the thiol-pair buffer strength maintains the solubility of the preparation"

Amgen's Proposed Construction	Defendants' Proposed Construction
"wherein the thiol-pair buffer strength maintains the solubility of the solutes in the refold buffer"	Indefinite.

As Dr. Zhou explains, this term (found in independent claims 1 and 10) fails to inform a POSA about the scope of the claimed invention. Indeed, in the context of the claims and the specification, "maintaining the solubility of the preparation" makes no sense at all to a POSA.

Solubilization is well-understood by practitioners of protein refolding. The '287 patent specification defines "solubilization" consistently with the common understanding of the art: "'solubilization' means a process in which salts, ions, denaturants, detergents, reductants and/or other organic molecules are added to a solution comprising a protein of interest, thereby ***removing some or all of a protein's secondary and/or tertiary structure and dissolving the protein into the solvent."*** 7:28-33 (emphasis added). Thus, "solubility," in this context, is a concept applicable to a solution containing *proteins*. *See* 7:39-45 (defining "solubilized protein" and "solubilization pool" with respect to proteins); *see also* Zhou Decl., ¶ 69.

The disputed term of claims 1 and 10, however, refers to "maintaining the solubility of the *preparation*" – a liquid volume which the claim language itself makes clear does not contain proteins. The claims recite "contacting the proteins with a preparation." Thus, the preparation must be separate and distinct from the proteins, otherwise it could not be "contact[ed] with" the proteins. Also, the preparation is expressly defined by the claims to comprise "at least one

ingredient selected from the group consisting of a denaturant, an aggregation suppressor and a protein stabilizer; an amount of oxidant; and an amount of reductant[.]" None of those listed ingredients is a protein; there is nothing in the preparation to "solubilize". A POSA would have no way of knowing what is meant by the thiol-pair buffer strength "maintaining the solubility of the preparation" – much less understand how to do so – because that phrase makes no scientific sense. *See* Zhou Decl., ¶¶ 68-71.[16] All claims containing the term "wherein the thiol-pair buffer strength maintains the solubility of the preparation" are indefinite. *See Nautilus*, 572 U.S. at 901.

VI. THE '878 PATENT

The '878 patent claims priority to provisional application No. 61/220,477, filed June 25, 2009. The '997 patent is a divisional of the '878 patent application, and, like the '878 patent, also claims priority to June 25, 2009. The '878 and '997 patents share a nearly identical specification in all material respects and many of the same claim terms. Indeed, independent claim 7 of the '878 patent and independent claim 9 of the '997 patent are both directed to routine protein purification methods comprising the same core steps. For purposes of claim construction, all disputed terms are identical between the patents except one: the '878 patent claims require "***directly*** applying the refold solution to a separation matrix," while the '997 patent claims require merely "***applying*** the refold solution to a separation matrix."

A. The Disputed Terms.

1. "the protein"

Amgen's Proposed Construction	Defendants' Proposed Construction

[16] Amgen's proposed definition does not provide any further clarity. Amgen suggests that the term means "maintain[ing] the solubility of the solutes in the refold buffer." By "refold buffer," Amgen apparently intends to refer to the same volume as the preparation. But regardless of what it is called, the refold buffer/preparation still does not contain proteins and cannot be solubilized. To the extent that "solutes" is intended to refer to something other than proteins, Amgen's definition provides no guidance as to what those solutes could be. *See* Zhou Decl., ¶ 71.

"a protein expressed in a non-native limited solubility form in a non-mammalian expression system"	"the protein to be purified"

The parties dispute whether "the protein" that is recited in the claims refers to any protein generally (Amgen's construction) or the expressed protein of interest to be purified, as referenced in the earlier steps of the claim (Defendants' construction). This exact dispute regarding the '878 patent was resolved by the court in *Amgen Inc. v. Sandoz Inc.*, No. 14-cv-04741-RS, (N.D. Cal. Aug. 4, 2016). Ex. 13, pp. 26-27. The *Sandoz* court correctly adopted Defendants' proposed construction, "the protein to be purified." *Id.*

The claim language supports Defendants' construction. Specifically, claim 7 recites a "method of purifying ***a*** protein expressed in a non-native solubility form in a non-mammalian expression system" comprising a series of ordered steps, each of which involves doing something to the expressed protein, e.g., "solubilizing ***the*** expressed protein," "directly applying the refold solution to a separation matrix under conditions suitable for ***the*** protein to associate with the matrix," and "eluting ***the*** protein." *See* Claim 7 (emphases added). Thus, "***the*** protein" as recited in the claims refers to the protein that is being purified by the claimed method. *Wi-LAN, Inc. v. Apple Inc.*, 811 F.3d 455, 462 (Fed. Cir. 2016) ("Subsequent use of the definite articles 'the' or 'said' in a claim refers back to the same term recited earlier in the claim.").

The specification likewise teaches that it is the protein to be purified, *i.e.*, "the protein of interest" that "associate[s]" with the separation matrix and is eluted from the matrix:

> After ***the protein of interest*** has been associated with the separation matrix by contacting the cell lysate containing ***the protein*** with the separation matrix, thereby allowing ***the protein*** to associate with the adsorbent component of the separation matrix, the separation matrix is washed to remove unbound lysate and impurities.
> …
> After the separation matrix with which ***the protein*** has associated has been washed, ***the protein of interest*** is eluted from the matrix using an appropriate solution. ***The protein of interest*** can be eluted using a solution that interferes with the binding of the adsorbent component of the separation matrix to ***the protein***, for example by

disrupting the interactions between the separation matrix and ***the protein of interest***. '878 patent, 10:25-30, 44-50 (emphasis added). The specification also distinguishes between the protein to be purified from other proteins, which are considered "impurities" and are separated out using a separation matrix. *See id.*, 10:3-7 ("The separation matrix can be any media by which ***the protein of interest*** can be separated from the components of the resuspension and/or lysis buffer, including ***impurities such as host cell proteins***, ...") (emphasis added). Accordingly, "the protein" as recited in the claims should be construed as "the protein to be purified."

2. "the solubilization solution"

Amgen's Proposed Construction	Defendants' Proposed Construction
the solution comprising the solubilized protein and one or more of a denaturant, a reductant, and a surfactant. "The solubilization solution" of 7(d) may differ from "a solubilization solution" of 7(c), at least because the 7(d) solubilization solution contains the solubilized protein that is the product of 7(c).	the "solubilization solution" in Step (d) of Claim 7 must refer to the same solubilization solution used to solubilize the protein in Step (c).

Step (c) of claim 7 of the '878 patent recites "solubilizing the expressed protein ***in a solubilization solution***...." Step (d) of claim 7 then recites "forming a refold solution ***comprising the solubilization solution*** and a refold buffer...." The parties' dispute whether the solubilization solution that is part of the refold solution in step (d) is the same solubilization solution that is used in step (c) to solubilize the expressed protein. Amgen's construction, that it is not the same solution, was expressly rejected by the court in *Amgen Inc. v. Mylan, Inc.*, No. 2:17-cv-01235, (W.D. Pa. Nov. 20, 2018). Ex. 14, pp. 16-17. While the *Mylan* court addressed the same term from a different patent (the related '997 patent), "[w]here multiple patents 'derive from the same parent application and share many common terms, [the Court] must interpret the claims consistently across all asserted patents.'" *SightSound Techs., LLC*, 809 F.3d at 1316. *See also Markman*, 517 U.S. at 390; *LG Display Co.*, 709 F. Supp. 2d at 320.

The claim language again is dispositive. The use of "the" in the claims (like "***the*** protein" discussed above) shows that "***the*** solubilization solution" refers back to the same solution[17] recited earlier. *Wi-LAN, Inc.*, 811 F.3d at 462. As the *Mylan* court explained:

> [O]nce a particular solubilization solution is utilized in Step [c] to solubilize the protein, any further introduction of "the solubilization solution" must necessarily refer to that *particular* solution that was utilized in Step [c] to solubilize the protein. If components were removed from a particular solubilization solution that was utilized in Step [c], it would no longer be the same solution being referred to in Step [d]. The patentee chose to refer to "*the* solubilization solution" in subsequent recitations of the term, meaning that it must refer back to some particular solubilization solution.

Ex. 14, pp. 15-16 (emphasis in original). Amgen itself appears to concede this point. In distinguishing the '878 patent claims over prior art, Amgen argued that the prior art solution used to form the refold solution is not the solubilization solution of the claims because "the solubilization solution is 'partially purified by DEAE chromatography' ***before*** forming the refold solution," which "is expected to 'remov[e] contaminating host proteins and materials." *See* Ex. 23, p. 20 (emphasis added). Thus, as the *Mylan* court observed, nothing in the claims or the specification suggests "that the solubilization solution or its components may otherwise be altered *prior to* forming the refold solution." Ex. 14, p. 16 (emphasis in original).

3. "refold buffer"

Amgen's Proposed Construction	Defendants' Proposed Construction
"a pH-buffered solution that provides conditions for the protein to refold into its biologically active form, comprising one or more of a denaturant, an aggregation suppressor,	"a solution comprising one or more of the following: (i) a denaturant; (ii) an aggregation suppressor; (iii) a protein stabilizer; and (iv) a redox component.

[17] This does not mean, however, that the "refold solution ***comprising the solubilization solution*** and a refold buffer" somehow does not contain the expressed protein. Rather, as the Federal Circuit has made clear, the open-ended term "comprising" means that the refold solution can contain components other than those expressly recited in the claim, including, *e.g.*, the expressed protein. *See* Ex. 14, p. 17 (citing *Smith & Nephew, Inc. v. Ethicon, Inc.*, 276 F.3d 1304 (Fed. Cir. 2001)).

a protein stabilizer and a redox component"	The refold buffer need not necessarily contain a buffering component or have the ability to buffer pH."

Here, Amgen improperly attempts to depart from the plain and ordinary meaning of "refold buffer" to limit said buffer to a "pH-buffered solution that provides conditions for the protein to refold into its biologically active form." Amgen's proposed construction again already has been rejected by the *Mylan* court, which found that "there is no basis to limit a 'refold buffer' to 'pH buffered' solutions." *Id*., p. 20. *See* Zhou Decl., ¶ 73.

As Amgen's own expert, Dr. Willson, explained, "the word 'buffer' refers to a solution that resists changes in pH, ***but the same term is also commonly used in the art to refer to liquid preparations in biochemistry generally, regardless of whether such a preparation resists pH changes***." Ex. 24, ¶ 44 (emphasis added). As explained by Dr. Zhou, this is consistent with the understanding of a POSA as of 2009. Zhou Decl., ¶ 74. Moreover, the claim language itself expressly defines a "refold buffer" as simply "comprising one or more of the following: (i) a denaturant; (ii) an aggregation suppressor; (iii) a protein stabilizer; and (iv) a redox component." The claim does not mention pH-buffering or any other requirement.

Similarly, the specification does not require that a "refold buffer" be a pH-buffered solution. Instead, the specification states that there are many "components of a refold buffer," the specific concentrations of which "can be determined by routine optimization." '878 patent, 14:36-37. These "components of a refold buffer" include "denaturant, aggregation suppressor, protein stabilizer and redox component." *Id.* at 14:36-45; *see also id.* at 14:7-9. The specification provides that an additional component of the refold buffer ***can*** be a "buffer component" whose function "is to maintain the pH of the refold solution and can comprise any buffer that buffers in the appropriate pH range." *Id.* at 14:50-51. The specification, however, does not ***require*** that the "refold buffer" include this component. Likewise, the claims do not list

a "buffer component" as a required part of the "refold buffer." The Court should reject Amgen's invitation to import any such limitations into the term. *See* Zhou Decl., ¶¶ 75-77.

4. "directly applying the refold solution to a separation matrix under conditions suitable for the protein to associate with the matrix"

Amgen's Proposed Construction	Defendants' Proposed Construction
"applying the refold solution to the separation matrix without removing components of or diluting[18] the refold solution under conditions suitable for protein to have specific, reversible interactions with a separation matrix in order to effect the separation of protein from its environment"	"applying the refold solution to a separation matrix without removing any components of or diluting the refold solution, under conditions suitable for the protein to be purified to bind to the matrix"

As a preliminary matter, Defendants agree that "directly applying" means "applying the refold solution to the separation matrix without removing components of or diluting the refold solution." The parties disagree whether "without removing components" means without removing ***any*** components of the solution (Defendants' construction, as adopted by the *Sandoz* court), or if some components may be removed while others may not (Amgen's construction).

The specification states that the prior art taught that "after a protein has been refolded ***it was necessary to dilute or remove the components of the refold mixture*** in a wash step." 1:44-46 (emphasis added). The specification explains that this was because "it was expected that the highly ionic and/or chaotropic compounds ***and various other components of the refold solution*** would inhibit the association of the protein with the separation matrix." *Id.*, 15:30-33 (emphasis added). *See also id.*, 15:1-5; 15:43-46. The specification thus describes the claimed invention as "the direct capture" of a target protein (*id.*, 3:45-46) and further states:

[18] The parties appear to agree that the excluded "diluting" from both parties' constructions refers to prior-art, "***significant*** dilutions." Ex. 15, p. 16 (emphasis added); '878 patent, 12:33-50. According to Amgen, a POSA "would understand that the patent specification ***is not referring to diluting a refold solution by adding a minor amount of liquid.***" Ex. 15, p. 20. (emphasis added). Defendants agree with this interpretation of "diluting." *See also* Zhou Decl., ¶ 84.

> Since ***the method omits the need for removing <u>any</u> components of the refold mixture before the refold mixture is applied to a separation matrix***, the method can have the effect of saving steps, time and resources that are typically expended on removing the protein from refolding and dilution buffers in purification processes.

Id., 4:49-4:60 (emphases added). This construction is also consistent with the claim language of "***directly*** applying ***the*** refold solution." Claim 7 recites first "forming **a** refold solution" and then applying "***the*** refold solution" to a separation matrix. *See Wi-LAN, Inc.*, 811 F.3d at 462. Thus, "directly applying the refold solution" does not include any intermediate step that removes ***any*** components of the solution or dilutes the solution before applying to the separation matrix.

The prosecution history also supports a construction of "directly applying" that does not involve any intermediate steps. The Examiner originally rejected the claims over Oliner *et al*. by finding that "[t]here is nothing in the claim which precludes additional purification steps" and cited, as support, the fact that "in all of the examples in the specification of the claimed method, the refolded protein ***was filtered through 'a series of depth and/or membrane filter to remove particulates'*** before applying the 'conditioned and filtered protein mixture' to the column." Ex. 16, p. 7 (emphasis added). *See, e.g.*, '878 patent, 19:9-15, 20:30-33. Amgen amended the claim to add the word "directly" to overcome this rejection. Ex. 17, p. 8. Amgen thus agreed that "directly applying" does not include any intermediate steps such as, but not limited to, dilution, filtration, centrifugation, dialysis, or precipitation. *See also* Zhou Decl., ¶¶ 82-83.

Amgen has also previously asserted that "directly applying" means without removing ***any*** components of the refold solution in *Amgen Inc. v. Sandoz Inc.*, No. 14-cv-04741-RS (N.D. Cal.). *See* Ex. 18, p. 20 ("Nothing in the specification identifies components that can be removed within the scope of 'direct application.' **This is not an accident**."); pp. 19-20 (citing '878 patent, 15:25-29, 1:44-57, 3:45-49, 4:49-60, 12:14-25). As Amgen argued,

> [T]he claim makes clear that ***there are other components in the refold solution***

> beyond a denaturant, a reductant, a surfactant, an aggregation suppressor, and a protein stabilizer. …Furthermore the specification makes clear that the inventors had discovered that ***it was not necessary to remove <u>any</u> component of the refold solution*** prior to directly applying it to a separation matrix, ***and that "any component" would include host protein and DNA.***

Ex. 19, p. 12 (bold and italics emphasis added, underline in original); *see also id.* (the specification "provides that the ***refold solution encompasses other components*** such as 'impurities such as host cell proteins, DNA and chemical impurities introduced by components of the solubilization and/or lysis buffer'"); Ex. 20, pp. 4-6; *id.*, pp. 6-7 ("[T]he refold solution…also does not undergo steps such as Oliner *et al*.'s ***precipitation and filtration that could remove, e.g., host cell DNA from the refold solution***.") (emphasis added); Ex. 21, 162:3-7 ("The components are not limited to a certain subset. The material that we're talking about being directly applied can include lots of different things. ***It does not just include the materials that were added for purposes of refolding.***") (emphasis added). *See also* Zhou Decl., ¶¶ 79-81.

The *Sandoz* court adopted the construction Amgen then advocated for "directly applying." Ex. 13, p. 21. The court noted that Amgen "contends the word 'directly' means ***there are no intermediary steps of any kind*** between refolding and purification." *Id.* (emphasis added). Citing the prosecution history and the specification, the court agreed:

> The six components listed in the claim ***are not necessarily the only components of the refold solution.*** Moreover, the patentee's attempt to distinguish the claimed method from the prior art, and the '370 Patent [Oliner], in particular, clarify that ***the patentee believed there should not be any intermediary steps between the refolding process and application of such solution to the separation matrix***.

Id., p. 23 (emphasis added). Thus, "directly applying the refold solution to a separation matrix," means application "without removing ***any*** components of or diluting the refold solution."

The parties also dispute whether the term "associate" means to "bind" (Defendants' construction) or "to have specific, reversible interactions with a separation matrix in order to effect the separation of protein from its environment" (Amgen's construction). The *Sandoz* court

resolved this exact dispute previously, rejecting Amgen's construction as "confusing and no clearer than the text of the claim itself." *Id.*, pp. 27-29. The *Sandoz* court correctly determined that the specification does not provide any definition of "associate,"[19] but does use the words "associate" and "bind" interchangeably. *See, e.g.*, '878 patent, 15:43-46 ("After the protein of interest has ***associated*** with the separation matrix, the separation matrix is washed to remove ***unbound*** protein, lysate, impurities and unwanted components of the refold solution.") (emphasis added); 15:65-67 ("The protein of interest can be eluted using a solution that interferes with the ***binding*** of the absorbent component of the separation matrix to the protein.") (emphasis added).

VII. THE '997 PATENT

A. Overlapping Terms Have The Same Meaning As In The '997 Patent.

As discussed above, the '997 patent and the '878 patent share a nearly identical specification in all material aspects as well as many common limitations and claim terms. The Court therefore should construe the following terms consistent with those proposed by Defendants for the '878 patent. *See SightSound Techs., LLC*, 809 F.3d at 1316.

***the protein*:** "the protein to be purified." *See* Ex. 4, 4:18, 26, 37-38, 42, 59, 62; 5:25, 26, 29, 7:17, 40, 52, 61; Ex. 13, p. 26-27; Ex. 14, p. 30-32.

***the solubilization solution*:** "the 'solubilization solution' in Step (b) of Claim 9 must refer to the same solubilization solution used to solubilize the protein in Step (a)." *See* Ex. 4; Ex. 14, pp. 14-17; Ex. 23.

***refold buffer*:** "A solution comprising one or more of the following: (i) a denaturant; (ii) an aggregation suppressor; (iii) a protein stabilizer; and (iv) a redox component. The refold buffer

[19] The *Sandoz* court correctly found that Amgen's reliance on the specification's definition of "separation matrix," which includes "any adsorbent material that utilizes ***specific, reversible interactions*** between synthetic and/or biomolecules…***in order to effect the separation of the protein from its environment***" (14:65-15:5) is not a definition of the term "associate." Ex. 13, p. 27.

need not necessarily contain a buffering component or have the ability to buffer pH." *See* '997 patent, 2:26-37; 4:35-51; 14:7-9, 27-31; Ex. 14, p. 14-17; Ex. 24, ¶ 44; Zhou Decl., ¶¶ 85-86.

B. Other Disputed Claim Terms.

1. "applying the refold solution to a separation matrix under conditions suitable for the protein to associate with the matrix"

Amgen's Proposed Construction	Defendants' Proposed Construction
"applying the refold solution to a column that contains the separation matrix without intervening steps of dilution, centrifugation, dialysis, or precipitation under conditions suitable for protein to have specific, reversible interactions with a separation matrix in order to effect the separation of protein from its environment"	"applying the refold solution to a separation matrix, regardless of whether there are intermediate processing steps, under conditions suitable for the protein to be purified to bind to the matrix"

The parties dispute three issues related to this term: (1) whether a POSA would understand that "applying" the refold solution (as opposed to "directly applying," as recited in the related '878 patent) means any general application, regardless of whether there are intermediate processing steps (Defendants' construction) or application without certain specific, defined steps that are only mentioned briefly in the prosecution history (Amgen's construction); (2) whether a "separation matrix" refers to any separation matrix (Defendants' construction) or is limited to column chromatography (Amgen's construction); and (3) whether "associate" means "bind" (Defendants' construction) or something more convoluted (Amgen's construction). For each term, Amgen's construction is not supported by the intrinsic evidence or the law.

(i) "applying the refold solution"

The '997 patent specification describes various embodiments of purification methods that involve "applying the refold solution to a separation matrix," including embodiments where the refold solution is ***directly*** applied to a separation matrix, as well as embodiments where the refold solution is subjected to some intervening or intermediate process before it is applied. *See*

'997 patent, 1:13-17. In one embodiment, "the present invention relates to a method of isolating a protein of interest…[where] it is necessary to isolate or dilute the protein from these components for further processing, particularly before applying the protein to a separation matrix." *Id.*, 4:41-45, 4:54-57. Indeed, the examples of the '997 patent include an intermediate step before applying the refold solution to a separation matrix. *See id.*, 20:56-62 (Example 3) (refold solution "was diluted 3-fold with water, titrated with 50% hydrochloric acid to ~pH 4.5 and was filtered through a series of depth and/or membrane filter…" before applying to a separation matrix); 19:34-40 (Example 2) (refold solution is "conditioned and filtered" before applying); 21:45-50 (Example 4) (same). In a different embodiment, the disclosed method "omits the need for removing any components of the refold mixture before the refold mixture is applied to a separation matrix." *Id.*, 4:58-5:4 (emphasis added); *see id.*, 3:53-57, 15:23-30, 16:1-4. Thus, as Dr. Zhou explains, a POSA would understand that the plain and ordinary meaning of "***applying*** the refold solution," in contrast to "***directly*** applying the refold solution," encompasses any application regardless of whether there are any intermediate steps. Zhou Decl., ¶¶ 88-92.

Neither the claim language nor the specification supports Amgen's construction. The claims do not indicate to a POSA that specific steps of dilution, centrifugation, precipitation, and dialysis are excluded from "applying the refold solution," as compared with any other intermediate process. Similarly, the specification does not discuss centrifugation, dialysis, or precipitation as excluded steps performed prior to "applying." Dialysis and precipitation are not mentioned at all, and centrifugation is only mentioned in an unrelated context. *See* Zhou Decl., ¶89 (*citing* '997 patent, 9:35-49, 11:45-49,13:21-25, 13:48-56, 17:7-10,18:23-25, 19:8-10, 19:14-21, 20:37-46). And, at least one of the steps that Amgen's construction excludes (dilution) is expressly included in a representative example in the '997 patent. *See* 20:56-62 (Example 3).

The basis for Amgen's construction appears to come from the prosecution history of the '997 patent. The prosecution histories of both the '997 and '878 patents, however, support Defendants' plain meaning construction of this term. Original claim 9 of the '997 patent and the '878 patent were identical, both including the term, "applying the refold solution." *Compare* Ex. 25 *with* Ex. 26. During prosecution of the '878 patent application, the Examiner rejected the claims, finding that "[t]***here is nothing in the claim which precludes additional purification steps***" and that "in *all* of the examples in the specification of the claimed method, the refolded protein ***was filtered through 'a series of depth and/or membrane filter to remove particulates'*** before applying the 'conditioned and filtered protein mixture' to the column." Ex. 16, p. 7 (emphasis in bold added). In response, Amgen expressly amended the claim language from "applying" to "***directly*** applying" to capture unequivocally, in the '878 patent, the embodiment that omitted intermediate steps. Ex. 17, pp. 3, 7-8.

In contrast, Amgen did ***not*** amend the language of claim 9 to overcome Oliner during prosecution of the '997 patent. Instead, Amgen made several different statements about Oliner, including that Oliner (1) "recites that the refolded protein is subject to dialysis, precipitation, and centrifugation;" (2) that "[t]he supernatant of [Oliner] is then pH adjusted and loaded onto a column;" and (3) that Oliner "does not recite ***forming a refold solution*** and applying the refold solution to a separation matrix." Ex. 27, p. 11 (emphasis added). The Examiner summarily withdrew the rejection. Ex. 28, p. 4; Ex. 29. As Dr. Zhou explains, a POSA would not have understood from Amgen's prosecution arguments whether it was the *combination* of processing steps that distinguished Oliner from the '997 patent, or the use of each process *individually*, or some other issue with Oliner in terms of "forming a refold solution." Zhou Dec., ¶ 91.

Thus, because the specification describes multiple embodiments including direct and

indirect application, and because Amgen did not make a clear and unmistakable disavowal of particular intermediate processes from the scope of the claims, the Court should not limit "applying the refold solution" to exclude specifically dilution, centrifugation, precipitation, or dialysis. *Continental Circuits LLC v. Intel Corp.*, 915 F.3d 788, 798 (Fed. Cir. 2019) ("[t]o operate as a disclaimer, the statement in the prosecution history must be clear and unambiguous, and constitute a clear disavowal of scope.") (citation omitted).

(ii) "a separation matrix"

Amgen previously attempted to limit "a separation matrix" to column chromatography, but conceded that the limiting language was not appropriate. Ex. 22, p. 20; Ex. 14, p. 23 n.10. Likewise, as the *Sandoz* court noted, "the word 'column' does not appear in the claim, and thus there is no reasonable argument for the proposition [that] 'column' is a synonym for any word appearing therein." Ex. 13, p. 23. Moreover, the specification expressly provides for a broad range of separation matrices that "***can*** be disposed in a column" but are not required to be. '997 patent, 17:1-13; *see also id.* at 11:28-29 ("In ***some cases*** it will be desirable to provide the separation matrix in a column format.") (emphasis added); 17:52-55 (describing the disclosed cleaning step with "no need to extract the separation matrix from a column ***or other matrix retaining device***") (emphasis added). Thus, Amgen's construction limiting the claims to column chromatography should be rejected.

(iii) "associate"

For the same reasons as discussed for the '878 patent above, Amgen's construction should be rejected. *See supra* 25-26.

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Respectfully submitted,

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