UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ADELLO BIOLOGICS, LLC,
APOTEX INC. and APOTEX CORP.,
Petitioners

v.

AMGEN INC. and AMGEN MANUFACTURING, LIMITED,
Patent Owners.

Case PGR2019-00001
Patent 9,856,287 B2

PATENT OWNERS' RESPONSE
UNDER 37 C.F.R. § 42.220

LIST OF EXHIBITS

Exhibit	Description
EX2026	Expert Declaration of Richard C. Page, Ph.D.
EX2027	Deposition of Anne S. Robinson (Jul 10, 2019)
EX2028	Joint Claim Construction and Prehearing Statement, *Amgen Inc., et al. v. Kashiv Biosciences LLC, et al.*, No. 2:18-cv-03347 (CCC-MF), DE 101 (March 22, 2019)
EX2029	Gohda, S., et al., "The Superreactive Disulfide Bonds in α-Lactalbumin and Lysozyme," *Journal of Protein Chem.*, 14(8): 731-737 (1995)
EX2030	Excerpt of Declaration of Anne S. Robinson, Ph.D. in Support of Defendants' Opening Claim Construction Brief, *Amgen Inc., et al. v. Apotex Inc., et al.*, No. 15-cv-61631-CV-COHN, DE 76-4 (Dec. 11, 2015).
EX2031	Excerpt of Declaration of Anne S. Robinson, Ph.D. in Support of Petition for *Inter Partes* Review of U.S. Patent No. 8,940,878, *Kashiv Biosciences, LLC v. Amgen Inc.*, IPR2019-00791 (EX1002) (March 7, 2019)
EX2032	Declaration of Sayem Osman
EX2033	Pereira, D.A., Williams, J.A., "Origin and Evolution of High Throughput Screening," *Br. Journal of Pharmacology*, 152(1): 53-61 (Sep. 2007)
EX2034	Oganesyan, N., et al., "On-Column Protein Refolding for Crystallization," J. Structural & Functional Genomics, 6:177-182 (2005)
EX2035	Intentionally Omitted
EX2036	Palandra, J., et al., "Flexible Automated Approach for Quantitative Liquid Handling of Complex Biological Samples," *Anal. Chem.*, 79, 9010-9015 (2007)
EX2037	Cohen, S. et al., "Fully Automated Screening Systems," *Methods Mol. Biol.*, 190:213-228 (2002)
EX2038	Tsumoto, K., et al., "Highly Efficient Recovery of Functional Single-Chain Fv Fragments from Inclusion Bodies Overexpressed in *Escherichia Coli* by Controlled Induction of Oxidizing Reagent—Application to a Human Single Chain Fv Fragment," *Journal of Immunological Methods*, 219:119-129 (1998)

Exhibit	Description
EX2039	Lutz, M.W., et al., "Experimental Design for High-Throughput Screening," *Drug Discovery Today*, 1(7): 277-286 (July 1996)
EX2040	Tye, H., "Application of Statistical 'Design of Experiments' Methods in Drug Discovery," *Drug Discovery Today*, 9(11): 485-491 (June 2004)
EX2041	Gerami et al., "Co-Solute Assistance in Refolding of Recombinant Proteins," *African Journal of Biotechnology*, 10(53): 10811-10816 (Sep. 2011)
EX2042	Sethuraman, A. et al., "Protein Structural Perturbation and Aggregation on Homogeneous Surfaces," *Biophysical Journal*, Vol. 88: 1322-1333 (Feb. 2005)
EX2043	"Explain the four levels of protein structure, indicating the significance of each level," *available at* http://www.old-ib.bioninja.com.au/higher-level/topic-7-nucleic-acids-and/75-proteins.html
EX2044	U.S. Patent No. 5,428,130

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STATUTES

REGULATIONS

I. Introduction

U.S. Patent No. 9,856,287's ("'287") invention addressed the difficulty of identifying acceptable protein refolding conditions by controlling the concentrations of the reductant and oxidant present in the refolding buffer in a particular manner, and presented a novel and efficient protein refolding method based on control of redox conditions with reductant and oxidant ("redox") reagents. Patent Owners[1] now address the Petition's numerous errors and omissions, supported by Dr. Page's expert testimony (EX2026), and free of §42.108(c)'s institution-only constraints.[2]

First, as demonstrated below, the '287 is not eligible for PGR since it issued from a transition application that properly claims priority to applications filed well before the March 16, 2003 statutory cut-off for PGRs. Petitioners attempt to break

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[1] Petitioners listed both Amgen Inc. and Amgen Manufacturing, Limited in the caption as "Patent Owner." Amgen Manufacturing, Limited is an exclusive licensee. Nevertheless, consistent with the caption, this Response refers collectively to both parties, collectively, as "Patent Owners" or "Amgen."

[2] All emphasis/annotations added unless noted; statutory/regulatory citations are to 35 U.S.C. or 37 C.F.R., as context indicates.

the priority chain to establish PGR eligibility, but their written description and enablement arguments are incomplete and without merit. The 25% yield number in the claims for which Petitioners challenge written description is supported by the specification and figures in the priority application, as found during prosecution. And, with respect to enablement, POSITA could achieve close to 100% refolding in 2009, and this invention made it *easier* for POSITA to identify *optimal* refolding conditions. Thus, POSITA would certainly have been able to achieve close to 100% refolding without undue experimentation using the teachings of the patent in 2009.

Second, even if Petitioners were to succeed in breaking the priority chain, Grounds 1 (written description) and 2 (enablement) fail because their analyses are based in the wrong decade. For these Grounds, Petitioners assert that the '287 application, which was filed in *2017*, does not provide sufficient written description or enablement support. However, Petitioners' analyses are based solely on the state of the art and POSITA's knowledge as of *2009*—the date of the first priority application. Petitioners merely incorporate their same PGR eligibility arguments without bothering to update their analysis to account for the state of the art in *2017*. And their expert analyzed the state of the art only as of *2009*. Accordingly, these Grounds fail for a lack of proof, and, even if the Board were to

consider Petitioners' 2009-based arguments, the '287 specification provides sufficient support for the claims.[3]

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[3] Petitioners have made no arguments for any of their grounds (including, *inter alia*, enablement, written description, novelty, obviousness, or indefiniteness) based on the state of the art in 2017. Thus, Amgen has no arguments from Petitioner as of the alleged 2017 priority date that Amgen can respond to and rebut with evidence and argument of its own. This failure of proof violated the basic rules for the contents of a petition, *see, e g.,* Rule 104(b)(3), and Petitioners should not be able to remedy this deficiency on Reply (which, *inter alia*, would deprive Amgen of a meaningful opportunity to respond). *See Wasica Fin. GmbH* v. *Cont'l Auto. Sys., Inc*., 853 F.3d 1272, 1286 (Fed. Cir. 2017) (rejecting reply brief attempting to cure deficiencies in petition and noting the "obligation for petitioners to make their case in their petition"); *In re NuVasive, Inc.*, 841 F.3d 966, 972-73 (Fed. Cir. 2016) (vacating final written decision when Board relied on factual assertion by petitioner not asserted until after patent owner's Response because patent owner was not given fair notice and opportunity to respond); *Intelligent Bio-Sys., Inc.* v. *Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367–68 (Fed. Cir. 2016); Trial Practice Guide,77 Fed.Reg. at 48,767 (Aug. 14, 2012) ("[A] reply that raises

Third, with respect to Grounds 3-7, which present Petitioners various anticipation and obviousness analyses, Petitioners have not met their burden for at least the following reasons:

- Petitioners failed to present any analysis for any Ground under the proper constructions of the "maintains the solubility" terms.
- With respect to Vallejo, Petitioners' thiol-pair buffer pair ratio calculation is incorrect, Petitioners improperly mix and match embodiments, and Petitioners provide no proof that the yield described in Vallejo is calculated in the same way as the yield in the claims.
- With respect to Schlegl, *inter alia*, Petitioners offered no proof that the *bovine* α-lactalbumin protein Petitioners rely on in Schlegl was produced in a *non-mammalian* expression system; Petitioners mixed and matched Schlegl's "renaturation buffer" and "refold buffer" (which are different) in mapping both the "preparation" and "solution" in the claims; Petitioners performed the wrong math in calculating the thiol-pair ratio; and Petitioners

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a new issue or belatedly presents evidence will not be considered and may be returned.").

provided no proof that the yield described in Schlegl is calculated in the same way as the yield described in the claims.

- Ruddon does not teach refolding recombinantly produced protein into properly refolded biologically active protein as required by the claims.
- Petitioners failed to present any argument regarding the dependent claims requiring thiol-pair ratio and thiol-pair buffer strength to be "calculated" (claims 8, 9, 14, 15, 23, 24, 25, and 30) when that term is properly construed.
- Petitioners' obviousness arguments are legally insufficient. With respect to Ruddon and Vallejo, for example, Petitioners failed to show how the references could be combined to arrive at the claimed invention, why POSITA would have been motivated to combine the teachings of the references, and why POSITA have a reasonable expectation of success in doing so.

Fourth, with respect to Ground 8, which alleges that the term "maintains the solubility of the preparation" is indefinite, this Ground fails because the plain meaning of that term is clear from the claims, as further confirmed by the admissions of Petitioners' expert, Dr. Anne S. Robinson, in a related case. Indeed, Petitioners admit the plain meaning of "maintains the solubility of the preparation" indicates that the solubility of the *preparation* does not refer to the solubility of the

proteins, which undercuts and eliminates one supposed source of ambiguity asserted by the Petitioners. And Dr. Robison admitted in previous testimony that the "preparation" does not itself include protein.

Fifth, because Dr. Robinson's testimony is contradictory, inconsistent, and self-serving, her statements are not credible and should not be given any weight.

Petitioners' evidence fails to establish unpatentability for any instituted Ground, and every claim should be confirmed.

II. The Challenged Claims Of The '287 And The Level Of Skill In The Art

The '287 is directed to a novel and efficient protein refolding method based on control of reduction-oxidation ("redox") conditions with reductant and oxidant reagents. EX1001, 2:62-3:5; EX2026, ¶47. The goal of protein refolding is to increase and maximize the yield of properly refolded proteins. EX1001, 1:32-38; EX2026, ¶47. Desired proteins are recombinantly expressed in non-mammalian culture systems (*e.g.*, bacteria). EX1001, 3:37-38; EX2026, ¶¶47, 49. But, these expressed proteins misfold and precipitate in intracellular limited-solubility precipitates known as inclusion bodies. EX1001, 1:25-30; EX2026, ¶¶47, 49. These inclusion bodies are formed because the bacterial host cell is unable to fold recombinant proteins properly. EX1001, 1:29-31; EX2026, ¶¶47, 49. These host cells are collected and lysed, and then the released inclusion bodies are solubilized

in a denaturing solution to linearize the proteins into individual protein chains. EX1001, 1:43-50; EX2026, ¶¶47, 49.

Prior to the ’287, POSITA were able to achieve high yields (including over 80%, and even close to 100%) of properly refolded protein. EX2026, ¶45; EX2027, 22:8-20 (Robinson); EX2038 (Tsumoto) (reporting refolding human single-chain Fv fragment from inclusion bodies with a total yield of 95%).[4] To achieve these high yields, those skilled in the art manipulated relevant variables to achieve high yields of properly refolded proteins. EX1001, 4:27-30, 8:47-65; EX2026, ¶45. Further, robots were available in 2009 to help with choosing among and determining those variables. EX2026, ¶46; EX2033 (Pereira & Williams reference on the high-throughput screening and the use of robotics for automation); EX2034 (Oganesyan reference discussing methods enabling high-throughput or automated screening); EX2039 (describing how to design full factorial or fractional factorial screens); EX2027, 7:8-12:5 (Robinson); EX2036 (Paladra);

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[4] And although Schlegl’s percentage “yields” are inapplicable for reasons discussed *infra*, §VI.B.E, Schlegl itself reports “the yield of refolded protein is 90%” in 2007—although Petitioners pointedly ignore this higher percentage while pointing to other, low refolding results. EX1007, [0082].

EX2037 (Cohen); EX1002, ¶¶54-55.[5] For instance, robots were available to assist with otherwise tedious, repetitive functions, providing greater speed, accuracy, and reproducibility. EX2026, ¶46; EX2036; EX2037; EX2033; EX2027, 7:8-12:5 (Robinson); EX2010, 197:3-198:25 (Robinson). In addition to standard liquid handling duties, EX2027, 11:6-12:5, the use of robotics to assay and assess failure or success of an experiment was well-known and regularly performed. *See. e.g.*, EX2026, ¶46; EX2033; EX2024; EX2039; EX2027, 7:8-12:5 (Robinson). With the aid of robotics, even if a large number of assays and tests were required, it would not have represented undue experimentation, and many tests could be run at once and in succession and in little time. EX2026, ¶46; EX2036.

The inventors of the ’287 made it easier to identify optimized refolding conditions by controlling the concentrations of the reductant and oxidant present in the refolding buffer in a particular manner (*e.g.*, using the interrelationship of thiol-

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[5] EX2029 (published in 1995), EX2033 (published in 2007), EX2034 (published in 2005), EX2036 (published in 2007), EX2037 (published in 2002), EX2038 (published in 1998), EX2039 (published in 1996), and EX2040 (published in 2004), and EX2042 (Sethuraman) were all published in regularly published journals and thus also publicly available as of those dates. EX2026, ¶15.

pair ratio ($i.e.$, $\frac{[reductant]^2}{[oxidant]}$) and thiol-pair buffer strength ($2[oxidant] + [reductant]$)) for the purpose of properly refolding a recombinantly expressed protein. EX1001, 4:18-5:10, 6:50-55, 6:63-67; EX2026, ¶¶48-55. The method disclosed in the '287 therefore also made it easier to efficiently refold large quantities of protein on a commercial scale. EX1001, 13:44-46.

A POSITA would have had a Ph.D. in biochemistry, biochemical engineering, molecular biology, or a related biological/chemical/ engineering discipline, or a master's degree in such disciplines and several years of industrial experience producing proteins in non-mammalian expression systems, as of the '287 Patent priority date of June 22, 2009. EX2026, ¶30. Indeed, those in the art of refolding therapeutic biologics (the audience for the '287 invention), would have had a Ph.D. or at least a masters in such disciplines and several years of industrial experience producing proteins in non-mammalian expression systems. However, the analysis below would not change if Petitioners' POSITA definition were applied. *See* EX2026, ¶32.

As discussed below, Petitioners have only provided analysis of their Grounds as of 2009. However, for any claims the Board has found to give rise to PGR standing, the Petition's Grounds, for purposes of this proceeding only, must be analyzed as of *the May 25, 2017 filing date of the '287 application itself*.

Petitioners have provided no such evidence, and to the extent Petitioners are allowed to supplement the record (they should not be (*see* n.3)), Amgen reserves its right to submit evidence and argument as of 2017.

III. Claim Construction

For purposes of post-grant review for a petition filed before November 13, 2018, "[a] claim in an unexpired patent . . . shall be given its broadest reasonable construction in light of the specification of the patent in which it appears." §42.200(b); Final Rule, 83 Fed.Reg. at 51340 (Oct. 11, 2018) ("This rule [change from broadest reasonable construction] is effective on November 13, 2018 and applies to all IPR, PGR and CBM petitions filed on or after the effective date."). However, even under the broadest reasonable interpretation, the Board's construction must "be consistent with the specification, and that claim language should be read in light of the specification as it would be interpreted by one of ordinary skill in the art." *In re Abbott Diabetes Care Inc.*, 696 F.3d 1142, 1149 (Fed. Cir. 2012).

A. "At Least About 25%" Should Not Be Construed To Require Exactly 25% To 100% Refolding (Claims 1-9 and 16-25)

While Petitioners never offer any claim construction analysis, the Petitioners implicitly construe "at least about 25%" to ***require*** that "at least about 25%" mean

exactly "***25% to 100%***." Pet., 28 ("The specification does not provide support for 'at least about 25% of the proteins are properly refolded,' i.e., 25%-100%.").

In view of the claims' "*at least about*" language, the range need not start at *exactly* 25%. *See, e.g.*, *Hybritech Inc. v. Abbott Labs.*, 849 F.2d 1446, 1455 (Fed. Cir. 1988) (reasonable likelihood of success of proving literal infringement of claim reciting affinity of "at least about 10^8 liters/mole" by accused products with affinities of 4.8 x 10^7 and 7.1 to 7.5 x 10^7 liters/mole). And, as discussed below in §IV.A, Figures 1a-1f disclose that, at a given thiol buffer strength, the percentages of the misfolded (dashed lines) and properly folded (solid lines) have a negative correlation as the thiol-pair ratio increases, and they intersect where, as the patent indicates, they have an equal or "comparable" species distribution starting around 25%. From that point of intersection disclosed in the specification, if one were to lower the thiol-pair ratio, then one would ensure that more "properly folded protein species" were generated than misfolded species. EX1001, Figs 1a-1f, 9:6-31, 17:20-41. From reviewing Figures 1a-1f, POSITA would have recognized that the intersection point in the figures starts at "about 25%." EX2026, ¶66-70, *esp.* ¶6.

Moreover, POSITA would not have understood the range to include exactly "***100%***" for any and all proteins. While POSITA would have understood in 2009 that close to 100% of certain proteins may be refolded, EX2026, ¶73; EX2027, 22:8-20; EX1007, [0082]; EX2038, POSITA would have understood that exactly

100% refolding would likely not be achieved (EX2026, ¶45). *See, e.g.*, *Perkinelmer Health Scis., Inc. v. Agilent Techs., Inc.*, 962 F. Supp. 2d 304, 309 (D. Mass. 2013) (in construing "greater than," "the intrinsic evidence presented here implies the existence of some upper limit"); *see also, e.g.*, *Andersen Corp. v. Fiber Composites, LLC*, 474 F.3d 1361, 1376-77 (Fed. Cir. 2007) (support for open-ended ranges may be found based on, *inter alia*, "an inherent, albeit not precisely known, upper limit [when] the specification enables one of skill in the art to *approach that limit*"); *Scripps Clinic & Research Found. v. Genentech, Inc.*, 927 F.2d 1565, 1572 (Fed. Cir. 1991) ("Open-ended claims are not inherently improper; as for all claims their appropriateness depends on the particular facts of the invention, the disclosure, and the prior art. They may be supported if there is an inherent, albeit not precisely known, upper limit and the specification enables one of skill in the art to approach that limit), *overruled on other grounds by Abbott Labs v. Sandoz, Inc.*, 566 F.3d 1282 (Fed. Cir. 2009); *Ex Parte Adams*, Appeal 2018-005365, 7 (PTAB Dec. 21, 2018) ("an ordinary artisan would be able to determine the practical inherent limits for the claimed range of ratios to be able to practice the claimed invention").

B. The Claimed Yields (Refolding Percentages) Relate To The Yield Of Target Protein Not All Protein

Petitioners assert that "the scope of the claims cover [sic] the yields resulting from the *refolding of* ***any protein*** *that happens to be present*, whether that protein is a protein of interest or a protein considered to be an impurity." Pet., 29; EX1002, ¶74. This is not how the yields ("at least about 25%" and "about 30-80%") in the claims would be understood by POSITA. The yields in the patent are the refolding "[y]ields of desired product" (in other words, the refolding yields of the protein of interest) not the refolding yield of all protein. EX1001, 15:51-53, 16:40-42; EX2027, 23:14-25:3. Thus, the percent yields in the claims would be understood as the amount of properly refolded protein of interest divided by total protein, expressed as a percentage. *See, e.g.*, EX1001, 8:47-49, 9:39-41, 15:51-53 ("yields of the desired product"); EX2026, ¶71; EX2027 23:3–25:3. This approach is consistent with the problem the inventors were trying to solve, which did not include any concern about properly refolding impurities. *CVI/Beta Ventures, Inc. v. Tura LP*, 112 F.3d 1146, 1160 (Fed. Cir. 1997) ("In construing claims, the problem the inventor was attempting to solve, as discerned from the specification and the prosecution history, is a relevant consideration.").

C. "Wherein The Thiol-Pair Buffer Strength Maintains The Solubility Of The Preparation" And "Wherein The Thiol-Pair Buffer Strength Maintains The Solubility Of The Solution"

Claim construction begins with the words of the claims themselves. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1314-15 (Fed. Cir. 2005) (*en banc*). "Wherein the thiol-pair buffer strength maintains the ***solubility of the preparation***" should be construed as "wherein the concentrations of oxidant and reductant result in a thiol-pair buffer strength at which the solubility of solutes in the preparation recited in the claims effectuating protein refolding is maintained." This claim term means exactly what it says: that the thiol-pair buffer strength maintains the solubility of the solutes in the preparation that participate in the function of getting the unfolded protein to properly refold. These solutes include (1) at least one of a denaturant, an aggregation suppressor, and a protein stabilizer; (2) an oxidant; and (3) a reductant, but do not include any protein. And, the plain language of the claims shows that protein is not part of the preparation. Rather, protein is "*contacted*" with "a preparation." Petitioners' admit that their construction, requiring the thiol-pair buffer strength maintain the solubility of the proteins (and only the proteins), is inconsistent with the plain language of the claims. Pet., 22; EX1002, ¶66-67. It should therefore be rejected.

Dr. Robinson also acknowledged that the solubility of (at least) the oxidants and reductants in the preparation must be maintained. For example, Dr. Robinson

testified that "typically you would want those [reductant and oxidant chemicals] to be in solution." EX2027, 55:18-56:7. Dr. Robinson also testified at her April 2016 deposition in the Florida litigation (in which the related U.S. Patent No. 8,952,138 ("'138") was asserted against Petitioners Apotex Inc. and Apotex Corp.) about the desirability of the ***redox chemicals (oxidants and reductants)*** remaining soluble in a refold buffer (*i.e.*, the preparation):

> Q. Would you agree that you certainly want these chemicals to remain in solution? You don't want them dropping out of solution?
>
> A. I would agree that typically you would want the -- a thiol-pair or redox component to be present in the soluble part of a refold buffer.

EX2019, 312-314.

Moreover, Petitioners' identified construction is unsupported by the '287 specification. *See Sumitomo Dainippon Pharma Co. v. Emcure Pharm. Ltd.*, 887 F.3d 1153, 1159 (Fed. Cir. 2018) (construing a chemical compound claim as not limited to a racemic mixture of the compound when plain language of the claim does not include such a limitation and specification is "inconclusive"); *RF Del., Inc. v. Pac. Keystone Techs., Inc.*, 326 F.3d 1255, 1265 (Fed. Cir. 2003) (rejecting constructions that "improperly imported limitations from the specification into the broad claim[s]"). Indeed, it is clear from the specification that the "refold buffer"

is the "preparation." For instance, just like the "preparation" in the claims, the specification describes the refold buffer as including (1) at least one of a denaturant, an aggregation suppressor, and a protein stabilizer; (2) an oxidant; and (3) a reductant, but not any protein. EX1001, 2:62–3:4. This was confirmed by Petitioners' expert's testimony in another matter, where Dr. Robinson stated that "refold buffer" "would have been readily understood by [POSITA] to mean 'a preparation that supports the renaturation of protein to a biologically active form" and described *contacting the refold buffer with a protein* (reflecting an understanding that the refold buffer/preparation does not itself include protein). EX2030, ¶¶65-66; EX2027, 57:7-25 ("And, in this case the refold buffer that -- it is clear that what Hevehan is envisioning -- let me go back, in terms of refolding is, is an idea where that preparation, sorry, where ***the refold buffer is the same as this preparation***.").

Moreover, in analyzing this claim term, Petitioners' expert admitted that under her approach, the "preparation" is the "refold buffer" in the beginning of the claims but "solution" (*i.e.*, refold mixture) at the end of the claims:

> So, in performing my analysis, I assumed that the, in general, looking at contacting the proteins with the preparation that supports renaturation, in that part [the preparation] is ***refold buffer***.
> And then in the later part of Claim 1 where it says, "Thiol-pair buffer

> strength maintains the solubility of the preparation," my assumption was that that was looking at the ***refold mixture***.

EX2027, 62:19–63:6 (Robinson); EX1001, 2:62–3:4 (explaining the protein is contacted with a refold buffer to form a refold mixture). Interpreting the same word in a claim to mean two different things is inconsistent with proper claim construction analysis. *Rexnord Corp. v. Laitram Corp.*, 274 F.3d 1336, 1342 (Fed. Cir. 2001) ("[A] claim term should be construed consistently with its appearance in other places in the same claim or in other claims of the same patent.").

"Wherein the thiol-pair buffer strength maintains the ***solubility of the solution***" should be construed as "wherein the concentrations of oxidant and reductant result in a thiol-pair buffer strength at which the solubility of solutes in the solution recited in the claims effectuating protein refolding is maintained and the refolded protein is soluble." Petitioners' construction would require the solubility of only the proteins be maintained, and not also the solubility of the other solutes recited in the claims that actually effectuate the refolding of the protein. Nothing in the claims or specification supports Petitioners' construction. Petitioners' construction, which excludes the refolding solutes, is contrary to the actual invention of the patent, which teaches controlling the non-protein, chemical solutes to effectuate protein refolding. EX1001, 8:56-65. To be clear, the terms at issue in this case need only be construed "to the extent necessary to resolve the

controversy." *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999); *VIZIO, Inc. v. Nichia Corp*., IPR2017-00558, Pap. 9, 8 (July 7, 2017) (declining to address unnecessary constructions). Thus, at this stage, the solubility of protein in the solution is not addressed and is not an issue that needs to be determined in this case.

Further, Amgen's construction is consistent with the specification. Nothing in the specification limits the invention to a thiol-pair buffer strength at which only the solubility of the proteins and not the solubility of other solutes recited in the claims is maintained. Rather, the specification refers to an embodiment in which the other solutes, including a denaturant, an aggregation suppressor, a protein stabilizer and a redox pair (*i.e*., the reductant and the oxidant) are in solution, *i.e.*, soluble. *See, e.g*., EX1001, 13:12-22 ("The solubilized inclusion bodies are then diluted to achieve reduction of the denaturants and reductants in the solution to a level that allows the protein to refold. The dilution results in protein concentration in the range of 1 to 15 g/L in a refold buffer containing urea, glycerol or sucrose, arginine and the redox pair (e.g., cysteine and cystamine) . . . . ***The solution*** is then mixed during incubation over a time that can span from 1 hour to 4 days").

And the specification teaches, for instance, that the redox-state is important for effective refolding and is affected by "the number of cysteine residues contained in the protein, the ratio and concentration of the redox couple chemicals

in the refold solutions (*e.g.*, cysteine, cystine, cystamine, cysteamine, glutathione-reduced and glutathione-oxidized), the concentration of reductant carried over from the solubilization buffer . . . and the concentration of oxygen in the solution." *Id.*, 8:56-65. In other words, these chemicals in the refold mixture or "solution" remain in solution. The very definition of thiol-pair buffer strength in Equations 2 and 3 make clear that the amounts of oxidant and reductant in solution affect that value; thus, if the solubility of oxidant and reductant in the solution is not maintained, the thiol-pair buffer strength would change. *Id.*, 6:46-67; EX2026, ¶115. Petitioners' construction is nonsensical because it appears to permit oxidant and reductant amounts in the solution to change (by not being maintained in solution) even though those amounts are what are used to define the thiol-pair buffer strength. EX1001, 6:46-46; EX2026, ¶115.

D. "Is Calculated" (Dependent Claims 8, 9, 14, 15, 23, 24, And 25)

The term "is calculated" in dependent claims 8, 9, 14, 15, 23, 24, and 25 should be construed as "is determined using an equation as part of practicing the method, rather than using the equation in hindsight." In the co-pending litigation between Amgen and Petitioner Adello, the parties agreed on this construction. EX2028, 3. Indeed, the construction must include an *active step of using the equations to find optimal refolding conditions*. Each of the dependent claims requires by its plain language that the "thiol-pair ratio," the "thiol-pair buffer

strength," or both "is calculated." *See* EX1001, claims 8, 9, 14, 15, 23, 24, and 25; EX1001, 4:52-63. This language further limits the independent claims, and cannot be ignored.

The prosecution history confirms that "calculated" requires a thiol-pair ratio or thiol-pair buffer strength to actually ***be calculated***. EX2008, 163, 167-68. During prosecution, Amgen stated, for example, that then-dependent claims 34 and 35 recite that the thiol-pair ratio and thiol-pair buffer strength are "***calculated***, ***and thus derived***," according to the equations $\frac{[the\ reductant]^2}{[the\ oxidant]}$, and $2[the\ oxidant] + [the\ reductant]$, respectively. *Id.* Amgen then argued that these dependent claims (not the independent claims from which they depended, which did not recite "calculated"), were distinguishable from references cited by the Examiner (Oliner, Hevehan (EX1024), and Schlegl (EX1007)) because, *inter alia*, those references did not disclose the use of these equations to calculate the thiol-pair ratio or thiol-pair buffer strength. EX2008, 163; *accord id.*, 167-168 (distinguishing over Schlegl and Hevehan).

IV. Petitioners Failed To Establish That The '287 Is A Post-AIA Patent

The '287 is a transitional application that has a priority date that antedates the enactment of the AIA. But Petitioners' written description and enablement

arguments, on which Petitioners' entire PGR standing argument is premised in an attempt to break the priority chain, are flawed.

As the Petitioners admit, the '287 is a "transitional application" because it was filed after March 16, 2013 (when the AIA was enacted) but claims priority to applications filed prior to that date, including U.S. Application No. 12/820,087 (EX1036), which shares a substantively identical specification with the '287, and issued as the '138 patent (EX1004). Petitioners thus have the burden to prove by a preponderance of the evidence that the '287 cannot claim priority prior to March 16, 2013 and is, therefore, eligible for PGR. *Mobile Tech, Inc. v. InVue Sec. Prods. Inc.*, PGR2018-00004, Pap. 15, 5-7 (May 3, 2018); *US Endodontics, LLC v. Gold Standard Instruments, LLC*, PGR2015-00019, Pap. 17, 11-12 (Jan. 29, 2016); 35 U.S.C. §326(e) ("In a post-grant review instituted under this chapter, the petitioner shall have the burden of proving a proposition of unpatentability by a preponderance of the evidence."). But if the Board determines that the challenged claim terms are in fact supported and enabled by a pre-AIA application, then this PGR is statutorily barred. AIA, §§3(n)(1) and 6(f)(2)(A).

A. Petitioners Have Not Established That Claims 1-9 And 16-25 Were Not Fully Disclosed In The '287's Priority Applications Before March 16, 2013

For written description support under §112, ¶1, "the test for sufficiency is whether the disclosure of the application relied upon reasonably conveys to those

skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (*en banc*). "There is no requirement that the disclosure contain either examples or an actual reduction to practice; rather, the critical inquiry is whether the patentee has provided a description that in a definite way identifies the claimed invention in sufficient detail that a person of ordinary skill would understand that the inventor was in possession of it at the time of filing." *Alcon Research Ltd. v. Barr Labs., Inc.*, 745 F.3d 1180, 1190-91 (Fed. Cir. 2014) (internal quotations and citations omitted); *accord Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1365-66 (Fed. Cir. 2006). "The 'written description' requirement states that the patentee must describe the invention; it does not state that every invention must be described in the same way," *Capon v. Eshhar*, 418 F.3d 1349, 1357-58 (Fed. Cir. 2005), "or that the specification recite the claimed invention *in haec verba*." *See Ariad*, 598 F.3d at 1352.

Further, the specification is written ***for POSITA***. Thus, "the failure of the specification to specifically mention a limitation that later appears in the claims is not a fatal one when one skilled in the art would recognize upon reading the specification that the new language reflects what the specification shows has been invented." *All Dental Prodx LLC v. Advantage Dental Prods., Inc.*, 309 F.3d 774, 779 (Fed. Cir. 2002). The written description requirement is satisfied "when 'the

essence of the original disclosure' conveys the necessary information—'regardless of ***how*** it' conveys such information," *Inphi Corp. v. Netlist, Inc.*, 805 F.3d 1350, 1354 (Fed. Cir. 2015) (emphasis original), and since the specification is viewed from the perspective of a POSITA, "a patentee can rely on information that is 'well-known in the art.'" *Streck, Inc. v. Research & Diagnostic Sys., Inc.*, 665 F.3d 1269, 1285 (Fed. Cir. 2012).

The proper inquiry in this case is, thus, whether the disclosure of the '287 reasonably would have conveyed to POSITA at the time of filing that the inventor had possession of the claimed range of "at least about 25% of the proteins are properly refolded."[6] And, as discussed below, the answer to the query is "yes."

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[6] The Petition alleges a failure of written description support only concerning the limitation of "at least about 25% of the proteins are properly refolded," as recited in independent claims 1 and 16, and does not allege that any other limitation of any other claim lacks written description support.

1. Petitioners Failed to Demonstrate That The Priority Applications Lack Written Description Support for "At Least About 25% Of The Proteins Are Properly Folded"

(a) Lower Bound of "At Least About 25%" Is Supported By Written Description In The Priority Applications

Petitioners assert that the '287's pre-AIA priority applications do not provide written description support as of 2009 for the claim term "at least about 25% of the proteins are properly folded." Pet., 27-31.[7] In Petitioners' view,

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[7] Petitioners made substantially the same written description arguments here as those raised by Examiner and overcome during prosecution. But the very aspects of the specification Petitioners now argue are insufficient—*e.g.*, EX1001, Figs. 1a-1f, 9:9-15, 15:51-53—are ones Amgen pointed to for support during prosecution and that the Examiner considered and found sufficient to support the claims. *Compare, e.g.*, Pet., 28-30, 34-35; *with* EX2008, 88-89, EX2008, 911 (Notice of Allowance from '287 File History); *see* EX2008, 19, 29, 37-42 (original '287 application in File History). Petitioners allege that this limitation was not examined for written description support in the priority 14/793,590 application. Pet., 27 n.5. However, this limitation was examined during prosecution of the '287 application, which Petitioners admit has the same specification as the'138 and the specification submitted with the '138 application. Pet., 18, 23; EX1005; EX1036.

because the words "about 25%" do not appear anywhere in the specification or the priority specifications, there is no written description support in the priority applications. But written description analysis is not so simple. *See Crown Operations Int'l, Ltd. v. Solutia Inc.*, 289 F.3d 1367, 1376 (Fed. Cir. 2002) (to satisfy the written description requirement, claim terms "need not be used *in haec verba*" and terms may be supported by the figures of the patent). And, as explained below, Figures 1a-1f, found in the priority applications, support this lower bound of about 25%.[8] EX1004, Figs. 1a-1f; EX1036, Figs. 1a-1f; EX2026, ¶¶66-76.

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[8] Petitioners concede that the non-provisional applications share a common specification, and cited the '138 as representative of the "priority applications." Pet., 23 n.3. Amgen's citation to the '138 are therefore representative of these priority applications. Petitioners have not asserted any written description, enablement, or priority arguments based on the provisional application. Petitioners' expert likewise did not list the provisional application in materials relied upon (EX1002, 6-7, 95-98) or perform any analysis of the provisional application (EX2027, 17:8-20:7). And Petitioners did not make the provisional application part of the record when they filed the Petition. Whether the provisional

The ’138/’287 teaches that the optimal refold chemistry for a given protein represents a careful balance that maximizes the folded/oxidized state while minimizing undesirable product species. EX1004, 8:19-26; EX1036, 12; EX1001, 8:47-54; EX2026, ¶67. The ’138/’287 inventors investigated the relationship between *thiol buffer strength* and *thiol-pair ratio*, both of which are based on concentrations of oxidants and reductants, although different mathematical equations are used to express each term. EX1004, 4:35-58, 6:20-39; EX1036, 6-7; EX1001, 4:52–5:10, 6:56-67; EX2026, ¶67. The inventors discovered the relationship could be used to optimize protein refolding. EX1004, 7:65–9:33; EX1036, 12-14; EX1001, 8:27–9:60; EX2026, ¶67.

As seen in Figures 1a-1f, the inventors disclosed that thiol-pair buffer strengths and thiol-pair ratios can be adjusted to affect the distribution among: (1) “protein species with oxidized amino acid residues, single chain species, and

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application provides written description and enablement for the ’287 claims does not need to be determined for the purpose of this proceeding. However, Petitioners’ analyze the state of the art as of 2009, and therefore have not supported their arguments that the 2010 priority application fails to provide written description and enablement support. *See, e.g.*, *infra* §V (collecting cases).

stable mixed disulfide intermediates" (depicted with dotted lines); (2) "mis-paired or incorrectly formed disulfide protein species and protein species with partially unformed disulfide linkages" (dashed lines); and (3) "properly folded protein species" (solid lines). EX1004, Figs. 1a-1f, 2:34-41, 8:44–9:19, 16:40-67; EX1036, 2, 13-14, 25, Figs. 1a-1f; EX1001 Figs. 1a-1f, 2:43-51, 9:6-47, 17:15-41; EX2026, ¶67.

As disclosed in Figures 1a-1f and Example 5, when the thiol-pair ratio is set at a higher value (more reduction), the product-species distribution indicates that more of the reduced product species (dashed lines) is produced. EX1004, Figs. 1a-1f, 2:34-41, 8:44-9:19, 16:40-67; EX1036, 2, 13-14, 25, Figs. 1a-1f; EX1001 Figs. 1a-1f, 2:43-51, 9:6-47, 17:15-41; EX2026, ¶¶68-70. When the thiol-pair ratio is set at a lower value (more oxidizing), the product-species distribution indicates that more of the oxidized residues, single chain forms, and stable mixed disulfide intermediate species (dotted lines) are produced. *Ibid.* This ability to vary the product-species distribution based on the thiol buffer strength and the thiol-pair ratio leads to identification of redox conditions at which the yield of desired refolded protein species (solid line) is maximized, and at which the resultant undesired product species may be more easily removed in purification steps. *Ibid.*

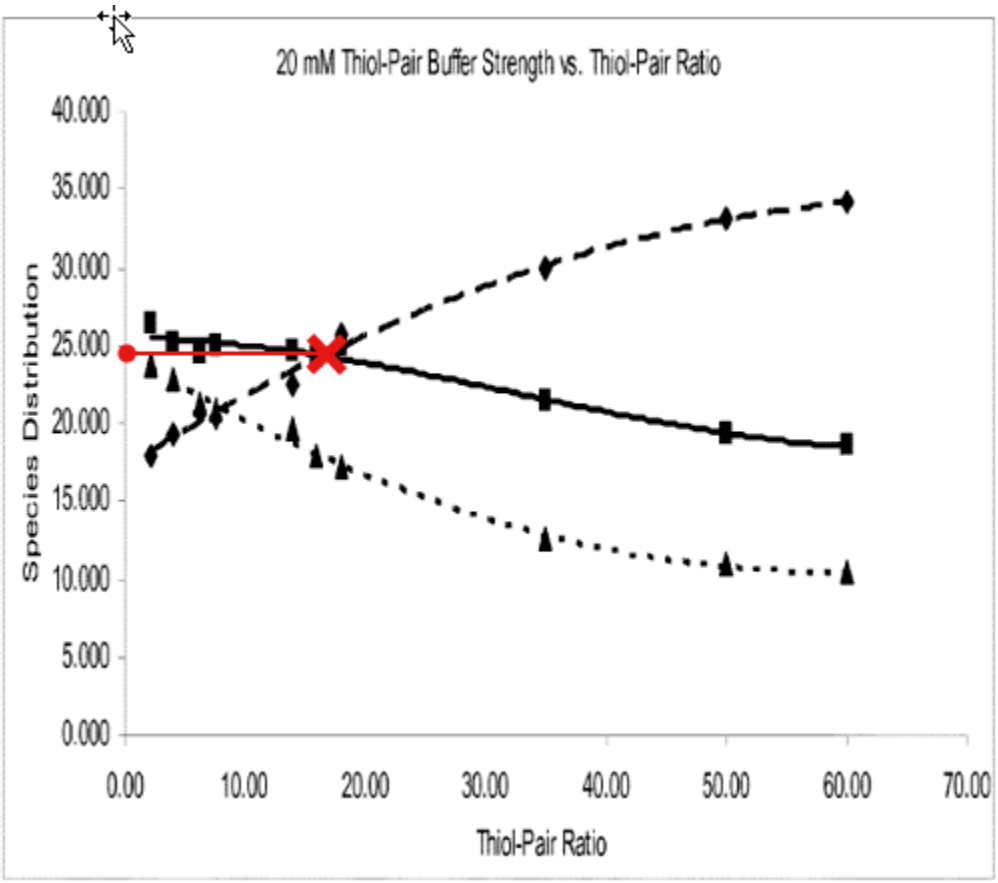

Figure 1f of the '138 and '287 Patents (with red annotations added)

Figures 1a-1f also disclose that, at a given thiol buffer strength, the percentages of the misfolded protein (dashed lines) and properly refolded protein (solid lines) have a negative correlation as the thiol-pair ratio increases and they intersect where, as the patent indicates, they have an equal or "*comparable*" species distribution—*at around 25% in Figure 1a through Figure 1f.* As an example, Figure 1f has been reproduced above with red annotations showing the "comparable" species distribution point. *See* EX1004, Figs. 1a-1f, 2:34-41, 8:44–9:19, 16:40-67; EX1036, 2, 13-14, 25, Figs. 1a-1f; EX1001 Figs. 1a-1f, 2:43-

51, 9:6-47, 17:15-41; EX2026, ¶69. From that point of intersection, if one were to lower the thiol-pair ratio, then one would ensure that more "properly folded protein species" were generated than misfolded species.[9] *Ibid.* Additionally, POSITA would have also appreciated that a decrease in misfolded protein species along with an increase in product-species, as discussed above, would have been easier to remove during purification. EX1004, Figs. 1a-1f (*see. e.g.*, annotated Figure 1f above showing the "comparable" species distribution point), 2:34-41, 8:44–9:19, 16:40-67; EX1036, 2, 13-14, 25, Figs. 1a-1f; EX1001 Figs. 1a-1f, 2:43-51, 9:6-47, 17:15-41; EX2026, ¶70. Notably, each of Figures 1a-1f, as well as the paragraphs

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[9] Petitioners and Dr. Robinson erroneously assert that, since "the percentages of the properly refolded and not properly refolded species do not add up to 100%," it "cast[s] doubt on the particulars of the experiment[s]." Pet., 29 n.6. But this is typical for such a graph. EX2026, ¶71. The graphs showed only certain "product-related species," that came off the column during a certain time period (*e.g.*, 5-15 min, as shown in Fig. 2). *Id.*; EX1004, 8:44-47; EX1036, 13; EX1001, 9:6-8. Thus, the figures do not account for other proteins, including those that came off the columns at other times, such as at least some aggregates, which would frequently elute last from the column. EX2026, ¶71.

describing them, were disclosed in the priority applications. EX1004, Figs. 1a-1f, 2:34-41, 8:44–9:19, 16:40-67. The specification thus indicates the importance of the relationships disclosed in Figures 1a-1f, and also describes, in text, a range of refolding percentages with the lower end of the range being at 27% (*i.e.*, about 25%). EX1004, 15:64-67; EX1001,16:40-43; EX2026, ¶70. Indeed, POSITA would have recognized in 2009 that these minimum percentages around 25% were important because that is where, as the inventors disclosed in their specification and priority applications, the percentage of properly folded proteins converged with the percentage of improperly folded proteins. There is no lower disclosed yield percentage where the percentage of properly folded proteins exceeds the percentage of improperly folded species. EX2026, ¶70.

(b) Upper Bound of "At Least About 25%" Is Supported By Written Description In The Priority Applications

Petitioners also assert that the upper bound of "at least about 25%" is not supported by written description in the priority applications. Pet., 28, 34-36. Petitioners point to Figures 1a-1f, which Petitioners assert show refolding that "never rises above about 35%" as well as Example 3 which discloses refolding of 30-80%. EX1004, Figs. 1a-1f; EX1036, Figs. 1a-1f; EX1001, Figs. 1a-1f. However, as Dr. Robinson admits, POSITA would have understood in 2009 that it was known to refold various proteins to "close to 100%." EX2027, 22:8-20; *see*

also EX2026, ¶73; EX2038 (Tsumoto) (reporting refolding human single-chain Fv fragment from inclusion bodies with a total yield of 95% biologically active refolded protein); *supra* n.4.[10] What the inventors discovered and disclosed is that the refolding efficiencies could be more systematically controlled and optimized by focusing on the relationship between thiol-pair ratio and thiol-pair buffer strength, taking protein concentration into account as well. *See, e.g.*, EX1001, 3:66–4:6, 4:18-22, 4:26-35; EX1004, 3:53-59, 4:4-8, 4:12-19; EX1036, 5-6; *see* EX2026, ¶34. With this approach, POSITA would have maximized refolding efficiency and/or increased the percentage of more-easily-removed product species, which would have made purification easier. *See* EX1001 9:39-47, EX1004, 9:11-19; EX1036, 13-14; EX2026, ¶¶72-73. Further, the disclosed yields of 80% were for particularly complex proteins. EX1004, 14:50–15:27 (Example 3 discloses refolding for "a recombinant protein comprising a plurality of polypeptides joined to an Fc moiety."); EX1036, 22-23; EX1001, 15:24–16:3; EX2026, ¶73. For a less complex protein, POSITA would have expected to obtain yet higher yields. EX2026, ¶¶73-74. Indeed, given the state of the art in 2009,

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[10] According to Petitioners, this yield is calculated in the same way as the yield in the claims. *But see infra*, III.B.

POSITA would certainly have understood the inventors had possession of refolding of close to 100% since refolding close to 100% was already known to POSITA, and the invention described in the priority applications only made that easier to achieve. *Id.*; EX2027, 22:8-20; *see* EX1007, [0082] (Schlegl); EX2038 (Tsumoto).[11]

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[11] Petitioners cite *In re Wertheim*, 541 F.2d 257 (C.C.P.A. 1976), to argue that a range of "at least about 25%" with an (assumed) upper limit of 100% is unsupported where the specification's specific disclosures are not coterminous with the claimed range. Pet., 31. But the claim term at issue there dealt with inputs into a process—coffee extracts concentrated to "at least 35%" for use in later steps—not the recited result of performing that process with the concentrated coffee extracts. 541 F.2d at 258-259. Moreover, in *Wertheim* the inventors were unable to point to any evidence indicating that the claimed ranges had any support beyond the narrower ranges disclosed in the specification's examples. As demonstrated above, that is not the case here.

B. Petitioners Failed To Demonstrate That Claims 1-9 And 16-25[12] Were Not Fully Enabled By The '287's Priority Applications

The specification need not have working examples across their entire ranges[13] in order to be enabled, contrary to Petitioners' assertion. Pet., 34-36; *see, e.g.*, *Andersen Corp.*, 474 F.3d at 1376; *Rimfrost AS v. Aker BioMarine Antarctic AS*, PGR2018-00033, Pap. 9, 10-14 (Aug. 29, 2018). In *Rimfrost*, for example, the Board found that the petitioners failed to adequately establish that the limitation "3% to 15% ether phospholipids w/w of said krill oil" was not enabled, even though the specification included only two working examples showing how to make a krill oil composition having 7.4% ether phospholipids. *Rimfrost*, PGR2018-00033, Pap. 9, 7, 10-14. The Board reasoned that blending various lipid components to create a krill oil composition was within the ability of one skilled in

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[12] Although Petitioners referenced claims 1-30 in their Ground 2 heading (VIII.D), Pet., 36, that section mentions only "at least about 25% of the proteins are properly refolded," which is found only in claims 1-9 and 16-25. And Petitioners' chart on page 37 also lists only claims 1-9 and 16-25 as being challenged in Ground 2.

[13] As discussed *supra* §V.A, Petitioners also failed to address whether POSITA would have understood the term "at least about 25%" to have had an upper limit below 100%.

the art, and that the specification, including the examples, provided guidance to one skilled in the art as to how to make a composition containing the recited amounts of ether phospholipids. *Id.* The same is true here, where the specification provides POSITA with the necessary information to practice the claims in view of the knowledge of POSITA as of 2009.

"The purpose of the enablement requirement is to ensure that the public knowledge is enriched by the patent specification to a degree at least commensurate with the scope of the claims." *Crown*, 289 F.3d at 1378-79 (alternations and internal quotations omitted). Petitioners assert "undue experimentation" would be required, but they fail to provide sufficient explanation as to how much experimentation would be required or why any such experimentation would be "undue." Pet., 33-36; EX1002, ¶¶36, 80-84; *see Fox Factory, Inc. v. SRAM, LLC*, PGR2016-00043, Pap. 9, 14-15 (Apr. 3, 2017) ("Petitioner's enablement contentions rest on the conclusory testimony of [its expert] that making or using the invention. . .would require 'undue' experimentation. [Petitioner's expert] provides no analysis, however, of the *Wands* factors, and no account of *what kinds of experimentation would be necessary or how much*. . . . Thus, we determine that this evidence, even if unrebutted, would be insufficient to meet Petitioner's burden"); *see also* §42.65(a) ("Expert testimony that does not disclose the underlying facts or data on which the opinion is based is

entitled to little or no weight."); *Rohm & Haas Co. v. Brotech Corp.*, 127 F.3d 1089, 1092 (Fed. Cir. 1997) ("Nothing in the rules or in our jurisprudence requires the fact finder to credit the unsupported assertions of an expert witness.").

Patents are written to enable POSITA to practice the invention, and need not disclose what is well known. *In re Wands*, 858 F.2d 731, 735 (Fed. Cir. 1988). In fact, applicants are encouraged *not* to include in the specification that which was known in the art. *See Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986). The scope of enablement is that which is disclosed in the specification plus the scope of what would be known to one of ordinary skill in the art such that the claimed invention could be practiced without undue experimentation. *Nat'l Recovery Techs., Inc. v. Magnetic Separation Sys., Inc.*, 166 F.3d 1190, 1196-97 (Fed. Cir. 1999). Importantly, enablement does not *preclude* experimentation: "The key word is 'undue,' not 'experimentation.'" *Wands*, 858 F.2d at 737. "The determination of what constitutes *undue* experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art." *Id.* at 737. To determine whether "undue experimentation" is required, the factors considered may include: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6)

the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. *Id.* Here, the specification provides guidance and formulas for optimizing various factors including thiol-pair ratio and thiol-pair buffer strength, to achieve the desired results within the claimed ranges. EX1004, Figs 1-a-1f, 2:34-41, 8:44–9:19, 16:40-67; EX1036, Figs. 1a-1f, 3, 13-14, 25; EX1001, Figs. 1a-1f, 2:43-51, 9:6-47, 17:15-41; EX2026, ¶¶77-85, *esp.* ¶78.

Indeed, as discussed above, the specification itself describes yields of 80% even for proteins more complex than the baseline described for "complex proteins" in the patent (EX1004, 14:50-15:27; EX1036, 22-23; EX1001, 15:24-16:3, and POSITA would have expected yet higher yields for less complex proteins. EX2026, ¶¶73 n.7, 79. Further, the art had already obtained refold percentages well above 80%, and even close to 100%, even without the advances and techniques disclosed in the patent. *Id.* ¶79; EX2027, 22:2-22 (Robinson); EX2038 (Tsumoto) (reporting refolding human single-chain Fv fragment from inclusion bodies with a total yield of 95%); *see also* n.4. And POSITA in 2009 would have had a background that made her familiar with the, sophisticated laboratory techniques and technology. *See* EX2026, ¶79; *supra* §II. In addition, even before the invention described in the '138 specification (and claimed in the '287), POSITA would have readily executed full factorial or partial factorial screens to determine the requisite refolding conditions. EX2026, ¶80; EX2039; EX2040.

POSITA would have been familiar with strategies presented by simple screening or fractional factorial screening efforts that had been applied for many years prior to the ’287 priority date. EX2026, ¶80; EX2033; EX2039; EX2040. And the redox conditions described in the ’138 priority specification would have made this process yet easier. EX2026, ¶80; EX1001, 4:18–5:10, 6:50-55, 6:63-67; EX1004, 4:4-58, 6:24-29, 6:35-39; EX1036, 5-7, 9. Further, robotics were available in 2009 to make screening of conditions faster and easier. *See* §II, EX2026, ¶81; EX2033; EX2037. With the aid of robotics, widely available before 2009, or even completed by hand using multi-channel pipettes and multi-well assay plates, even if a number of assays and tests were performed to optimize conditions, such well-known and regularly performed testing would not amount to undue experimentation, since many tests could be run at once and in succession and in little time and given the guidance provided by the specification. EX2026, ¶¶80-81; EX2027, 6:22-10:6 (Robinson) (admitting that the use of robots for screening had been around for a while by 2009); *Wands*, 858 F.2d at 736-37 (“Enablement is not precluded by the necessity for some experimentation such as routine screening [of antibodies].”); *Ex Parte Xiong Cai*, Appeal 2011-005302, 6, 12-13 (BPAI Dec. 9, 2011) (reversing enablement rejection based on the use of robotics and existence of “high-throughput methods of crystal growth and analysis” that are capable of rapidly testing “thousands” of compounds); *Ex Parte Liu*, Appeal 2009-015302, 8

(BPAI Sept. 17, 2010) (reversing enablement rejection and noting, "[e]ven accepting that the experimentation required to produce prodrugs and metabolites based on the compound of Formula I would be tedious and time-consuming, the Examiner has not established that it would have been anything other than routine and empirical for one of skill in the art.").

Petitioners focus their criticism on the inventors' supposed failure to identify the specific protein and its concentration used in Figures 1a-1f. Pet., 34-35. However, the specification does disclose the concentration: "6 g/L." EX1004, 8:53-56; EX1001, 9:15-18; EX2026, ¶82. And, that the identity of the proteins in the Examples are not disclosed by exact name is of no moment. Further, for example, Example 3 describes the protein concentration of 12 g/L, various refolding conditions, and that the protein was "a recombinant protein comprising a plurality of polypeptides joined to an Fc moiety." EX1001 15:27-53; EX2026, ¶82. There is no requirement that the specific name of the protein be disclosed, especially where, as here, the purpose of the patent is to describe a method applicable to a wide range of proteins. Further, here, the disclosures show that the refolding was achieved with quite complex proteins (EX1004, 14:53-55, 15:34-37, 8:44-47; EX1001, 15:27-32, 16:10-16, 9:6-9), indicating to a POSITA that less complex proteins would have refolded at yet higher percentages. EX2026, ¶¶73

n.7, 79. The inventors' disclosed optimization technique, as discussed above, was applicable to a wide range of proteins.

Petitioners make the conclusory assertion that, without providing the specific identity of the proteins used in the Examples, POSITA would need to perform undue experimentation to practice the claims, but they make no attempt to explain what additional information POSITAs need or why the information given is insufficient. For example, in Example 4, the inventors disclosed that the protein was a "recombinant protein comprising a biologically active peptide linked to the C-terminus of the Fc moiety of an IgG 1 molecule via a linker and having a molecular weight of about 57 kDa and comprising 8 disulfide bonds." EX1004, 15:34-37; EX1036, 23; EX1001, 16:10-14. Petitioners fail to explain what else POSITA would need and why they would need it. POSITA reading Example 4 of the '287 did not need to be informed what exact protein was being refolded because they understood it was a member of a class of hybrid molecules that was well understood in the art. *See, e.g.*, EX2026, ¶82; EX2044, 10:9-29. And Petitioners' demand for an identification of the exact proteins refolded takes them far afield from the law on enablement, which does not even demand working examples, allows for prophetic examples, and does not even demand actual reduction to practice. *Alcon*, 745 F.3d at 1189-1191.

In light of the specification's disclosures, Petitioners' and Dr. Robinson's unsubstantiated conclusory statements are insufficient. They adduce no evidence that a POSITA would be unable to practice the method to achieve the claimed results or that it would not work for any specific protein. *Alcon*, 745 F.3d at 1189. Without that evidence, and in light of the specification's disclosures, there is no foundation for their non-enablement arguments. *Id.* (finding no foundation for non-enablement rulings where challenger failed to provide evidence that changing variables would render the claimed invention inoperable); §42.65(a) ("Expert testimony that does not disclose the underlying facts or data on which the opinion is based is entitled to little or no weight."); *see Rohm & Haas*, 127 F.3d at 1092 ("Nothing in the rules or in our jurisprudence requires the fact finder to credit the unsupported assertions of an expert witness.").

Furthermore, the claims are not directed to refolding a specific protein, but to refolding proteins generally. That larger scope is what needs to be enabled, which is why a disclosure concerning a class of proteins better informs a POSITA. And, although Petitioners have not provided any evidence, beyond Dr. Robinson's conclusory assertions and surmise, that one or more specific proteins might exist whose refolding could not be optimized over the full range claimed using the patent's teachings, even if it were true, it would not matter. *In re Angstadt*, 537 F.2d 498, 502-03 (C.C.P.A. 1976) (reversing decision that a method claim was not

enabled where guidance was provided in the specification to perform the method, a POSITA could determine whether it was successful for a given species, and despite the fact that there were species, even disclosed in the specification, for which the method did not produce the claimed results); *Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 750 F.2d 1569, 1576-77 (Fed. Cir. 1984) (affirming decision that a method claim did not lack enablement where sufficient guidance to perform the method was provided in the specification and despite the fact that certain species within the scope of the claim would not work, *i.e.*, would be "inoperative"). And Petitioners have adduced no evidence that the number of proteins for which the full range of refolding percentages is not attainable is significant (or that there are any at all) such that one might question the teachings of the patent and the enablement of the claimed method. *See Atlas*, 750 F.2d at 1576-77.

It is not clear from the Petition that Petitioners challenged enablement of "about 30-80% of the proteins are properly refolded." Indeed, in the listing of specific grounds, Petitioners list Ground 2 as covering claims 1-9 and 16-25, which are the claims directed to "at least about 25%." In subheading IX.B, Petitioners list claims 1-30, but only list lack of enablement based on "at least about 25% of the proteins are properly refolded." Pet., 37. Petitioners' expert's conclusion is likewise confusing. *See* EX1002, ¶84.

In any case, to the extent Petitioners make any argument about the limitation of 30-80% not being enabled, Petitioners' argument seems to be that Example 3, which Petitioners acknowledge discloses "[y]ields of desired product of approximately 30-80% were obtained," Pet., 34-35; EX1002, ¶82, does not *name* the protein used, and POSITA would have to resort to undue experimentation to obtain these yields. However, as explained above, the patent does explain that the protein in Example 3 is a "recombinant protein comprising a plurality of polypeptides joined to an Fc moiety." EX1004, 14:53-59; EX1001, 15:27-32. And, as also explained above, screening for optimum refolding conditions did not require undue experimentation in 2009. EX2026, ¶83; *Xiong Cai*, Appeal 2011-005302, 6, 12-13; *see Liu*, Appeal 2009-015302, 8; *Wands*, 858 F.2d at 736-37; EX2039; EX2040; *see also* EX2027, 7:8-12:5 (Robinson); EX2010, 197:3-198:25 (Robinson).

V. Petitioners Failed To Establish Lack Of Written Description Or Enablement For Ground 1 And 2

For the reasons discussed above, the '287 patent is entitled to claim priority to its pre-2013 priority applications. Therefore, this PGR cannot proceed and the institution decision should be vacated and the proceedings terminated. *See Google Inc. v. Unwired Planet, LLC*, CBM2014-00006, Pap. 51, 2 (Aug. 13, 2018) (concluding Petitioner failed to prove CBM standing after instituting, and vacating

and terminating review); *cf. I.M.L. SLU v. WAG Acquisition, LLC*, IPR2016-01658, Pap. 46, 16 (Feb. 27, 2018) (vacating institution decision and terminating proceedings where petitioners failed to satisfy the statutory requirement to name all real parties-in-interest in petition).

However, if the Board proceeds to a final written decision, it will presumably be because the Board has accepted Petitioners' PGR standing arguments with respect to written description and/or enablement. In such case, for any claims the Board has found to give rise to PGR standing, the Petition's Grounds, for purposes of *this* proceeding only, must be analyzed as of *the May 25, 2017 filing date of the '287 application itself*. But there is no evidence on which the Board could rely to do this: Petitioners failed to provide any evidence or analysis of the state of the art after 2009, and Petitioners' written description and enablement grounds are entirely argued as of 2009, not 2017. *See* Pet., 37 (Grounds 1 and 2 incorporating by reference the written-description and enablement analyses for the 2009-2010 priority applications); EX2027, 6:22–7:4, 67:5-13 (Dr. Robinson admitting that the background section of her declaration concerns 2009); EX1002, ¶37; *Ex Parte Baxter Int'l, Inc*., Appeal 2009-006493, 27 (BPAI Mar. 18, 2010) (informative) (finding no error in refusing to credit expert testimony where "experts testified on the knowledge of a [POSITA] at a time period significantly before the relevant filing date").

Claim Construction. Petitioners' Ground 1 and 2 analyses (as well as their expert's) simply refer back to the analyses for PGR standing, without taking into account any changes in the art between 2009 and 2017, and without taking into consideration whether the different priority date would impact claim construction. *See Phillips*, 415 F.3d at 1313-14 ("We have made clear, moreover, that the ordinary and customary meaning of a claim term is the meaning that the term would have to a person of ordinary skill in the art in question ***at the time of the invention, i.e., as of the effective filing date of the patent application***.").

Written Description. The written description requirement, for example, requires analysis of how POSITA would understand the application at its effective date. *See Ariad*, 598 F.3d at 1351 ("[T]he test for sufficiency [of the written description support] is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter ***as of the filing date*** . . . . [T]he written description requirement will necessarily vary depending on the context. Specifically, the level of detail required . . . varies depending on the nature and scope of the claims and on ***the complexity and predictability of the relevant technology***."); *Streck*, 665 F.3d at 1285 ("This test requires an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art. Given

this perspective, in some instances, a patentee can rely on information that is 'well-known in the art' to satisfy written description.") (internal quotations omitted).

Enablement. The state of the art is also a necessary consideration when determining whether a claim is enabled and whether any experimentation to practice the scope of the claims is undue. Petitioners' 2009 enablement analysis cannot suffice for a priority date in 2017. Pet. 37, 33-36; s*ee Wands*, 858 F.2d at 737 (stating "[t]he determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and *the state of the art*" and identifying the "state of the prior art" as one of the eight *Wands* factors); *Baxter Int'l*, Appeal 2009-006493, 27.

Because Petitioners failed to present any argument as to the state of the art *in 2017*, and its implications for whether POSITA could practice the challenged claims, they have failed to establish a *prima facie* case that the claims are not enabled by the specification. And none of Dr. Robinson's opinions, which would be based in the wrong decade, should be credited. *Baxter Int'l*, Appeal 2009-006493, 27 (finding no error in refusal to credit expert testimony where "experts testified on the knowledge of a [POSITA] at a time period significantly before the relevant filing date"). Moreover, because Petitioners failed to present any such argument and evidence in their Petition, they are barred from doing so now, in part

because they have prevented Amgen from responding to any such arguments herein. Petitioners needed to set forth a case in order for Amgen to rebut it, and they presented nothing. *See supra* § VI.A.1(a); *supra* n.3 (collecting authority). In any case, the passage of eight years would only serve to strengthen the state of the art, which would only further buttress the written description and enablement analysis.

VI. The Challenged Claims Are Not Anticipated By Or Obvious Over Any Prior Art

A. Claims 1-4, 7-19, And 22-30 Are Not Anticipated By Vallejo (Ground 3), Nor Are Claims 5, 6, 20, And 21 Obvious Over Vallejo In View Of Hevehan (Ground 7)

1. Claims 1-4, 7-19, And 22-30 Are Not Anticipated By Vallejo (Ground 3)

(a) Petitioners' Calculations Of Thiol-Pair Ratio and Thiol-Pair Buffer Strength In Vallejo Are Incorrect

Petitioners and their expert purport to determine thiol-pair ratios disclosed by Vallejo, but as the Board correctly recognized at institution (DI, 27-28), their arithmetic in calculating the thiol-pair ratios in Vallejo is fundamentally flawed, eliminating any possibility that the Petitioners properly established anticipation by Vallejo. Pet., 43-44 n.10; EX1002, ¶100.

It is clear from the '287 that the calculation of the thiol-pair ratio is calculated using actual concentrations. EX1001, 6:46-55. Petitioners claim that Vallejo discloses the ***ratio*** of the concentration of reductant to the concentration of

oxidant, *not* that Vallejo discloses the ***actual concentrations*** of reductant and oxidant used.[14] But Petitioners and their expert squared the *numerators of the* ***ratios*** allegedly disclosed in Vallejo, and erroneously concluded that this is the thiol-pair ratio (*i.e.*, $\frac{[reductant]^2}{[oxidant]}$). Pet., 43-44 n.10; EX1002, ¶100. For example, Petitioners never established that, for the alleged thiol-pair ratio of 0.05 ($[1]^2/[20]$), the actual concentration of reductant was 1mM and the actual concentration of oxidant was 20mM. Nor did Petitioners establish that, for the alleged thiol-pair ratio of 1600 ($[40]^2/[1]$), the actual concentration of reductant was 40mM and the actual concentration of oxidant was 1mM.[15] For this reason alone, Petitioners have failed to show the thiol-pair ratio limitation is disclosed by Vallejo (*i.e.*, that the ratio falls within a range of 0.001-100), and this Ground should be rejected—and any improper future attempt to somehow recalculate this ratio should also be rejected. *See supra* §VI.A.1(a); *supra* n.3 (collecting authority).

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[14] Petitioners themselves recognize that mM is used to calculate the thiol-pair buffer strength. *See* Pet., 44-45.

[15] In contrast, Petitioners' expert seems to calculate the thiol-pair ratio for Schlegl using the actual concentration of reductant squared (2mM*31/32) over the actual concentration of oxidant (2mM*31/32). EX1002 ¶122 n.7.

Even setting aside Petitioners' fundamentally flawed arithmetic, Petitioners' thiol-pair ratio analysis is also flawed because Petitioners purported to calculate only one thiol-pair "ratio" and thiol-pair buffer strength for one of Vallejo's volumes, but claims 1-15 require the thiol-pair ratio and thiol-pair buffer strength be calculated in "the preparation" (*i.e.*, the "refold buffer," which does not include protein), and claims 16-30 require that the calculations be done in "the solution" (*i.e.*, the "refold solution," which does include protein). Neither Petitioners nor their expert attempt to provide any clarity as to whether the concentrations reported in Vallejo are measured in a volume with or without the protein. EX1038, [0055]. And it is not clear from Vallejo whether the oxidant to reductant value in Vallejo's "renaturation buffer" that Petitioners use to calculate the thiol-pair ratio are amounts prior to or after the addition of the "solution containing 2 to 25 mg mL^{-1} of unfolded and reduced rhBMP-2." *Id.*

(b) Petitioners' Vallejo Anticipation Theory Mixes and Matches Across Examples With Disparate Refolding Conditions

Petitioners do not address how Vallejo discloses every element of the claims *arranged as in each claim*, as required for anticipation. *SynQor, Inc. v. Artesyn*

Techs., Inc., 709 F.3d 1365, 1375 (Fed. Cir. 2013).[16] Petitioners' analysis of Vallejo begins by reliance on a generic framework for "producing a biologically active recombinant cystine-knot protein" in Vallejo. Pet., 39-41; EX1038, [0001]; EX2026, ¶¶86-87. Petitioners then pick and choose among Vallejo's different "Examples" to find disclosures they say meet the limitations of the '287 claims. *See* EX2026, ¶¶87-88. But Petitioners cannot mix and match examples under a theory of anticipation, picking disclosures from one example to substitute into part of the framework for one limitation, other examples to substitute into the framework for other limitations, and then ignore the framework entirely in arguing Vallejo teaches yet other limitations. *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1371 (Fed. Cir. 2008) (For anticipation, "it is not enough that the prior art reference discloses . . . multiple, distinct teachings that the artisan might somehow combine to achieve the claimed invention."); *Symantec Corp. v. RPost Commc'ns Ltd.*, IPR2014-00357, Pap. 14, 20 (July 15, 2014) (same). Petitioners rely on this mixing and without any acknowledgment or explanation.

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[16]*See also Microsoft Corp. v. Biscotti, Inc.*, 878 F.3d 1052, 1069 (Fed. Cir. 2017) ("[A]nticipation is not proven by 'multiple, distinct teachings that the artisan might somehow combine to achieve the claimed invention.'").

For example, Petitioners rely on the "standard renaturation buffer" of Example 8 in asserting Vallejo discloses "[c]reating a mixture of components for protein refolding." Pet., 39-40 (citing EX1038, [0054] [17]); EX2026, ¶88. But then Petitioners rely on the "standard renaturation buffer" of Example 4 in asserting Vallejo teaches the "[c]omponents of the mixture," Pet., 40-41 (citing EX1038, [0047]), as well as other disclosures in the patent not associated with a numbered example (Pet., 41 (citing EX1038, [0021]). EX2026, ¶88. However, Vallejo does not disclose the consistent use of renaturation conditions across each of its examples. EX2026, ¶88. For example, the only chemicals that are necessarily common to both the "standard renaturation buffer[s]" of Vallejo Example 4, EX1038, [0047], and Vallejo Example 8, *id.*, [0052]-[0055], are "0.5 mol L^{-1} Gdn-HCl, 0.75 mol L^{-1} CHES and 1 mol $^{-1}$ NaCl." EX2026, ¶88. But Example 8 also lists 0.1 mol L^{-1} Tris-HCL, 5 mmol L^{-1} EDTA, and 3 mmol L^{-1} total glutathione, while Example 4 does not. *Compare* EX1038, [0047], *with* [0052]-[0055]; EX2026, ¶88. And, there is no disclosure of a reductant or oxidant in Example 4. EX2026, ¶88. Moreover, Vallejo Examples 2, 3, 4, and 5 each ***vary*** conditions for

[17] Petitioners mistakenly cite to EX1038, [0054] but quote [0055].

refolding by design without saying exactly how the conditions are varied. EX1038, [0045]-[0048]; EX2026, ¶88.

Petitioners go on to assert that Vallejo "varies the ratio of GSH to GSSG from 40:1 to 1:20" (Pet., 43), but ignore the fact that the framework they started with (*see* Pet., 39-41) discloses a "ratio of reduced to oxidized glutathione . . . equal or above 1:10" (Pet., 40-41 (citing EX1038, [0001]); EX2026, ¶89. Further, Petitioners rely on Vallejo Example 2 to disclose the reductant and oxidant. Pet., 43-45; EX1038, [0042], [0045]; EX2026, ¶89. But again, it is not clear from Vallejo that the conditions used in Example 2 are the same conditions reported as the standard renaturation conditions in Example 8. EX2026, ¶89. Indeed, Example 2 purports to carry out renaturation experiments "at different pH" and "a very broad range of redox conditions." EX1038, [0045]; EX2026, ¶89. Petitioners then conclude that the "final yield[s]" disclosed in paragraph 12 of Vallejo, which correspond to an unnumbered example, are somehow the claimed "yield" under a theory of anticipation after Petitioner mixed and matched across examples. Pet., 45-46; EX2026, ¶89. But because of Petitioners' improper mixing and matching among different examples with no explanation, Petitioners failed to prove that Vallejo discloses each of the components required by the claims as arranged in the claims by relying on a combination of the disclosures across Vallejo's various examples. *See* EX2026, ¶89.

The inconsistencies created by Petitioners' mapping are magnified by its further mapping of dependent claims 2, 3, 11, 13, 17, 18, 27 and 28. For those claims, Petitioner relied on the unnumbered example in EX1038, [0012], identifying a "final concentration of 2.1 mg mL^{-1}," to attempt to show that the refold mixture has a protein concentration "in a range of 1-40 g/L," or "refold mixture with a protein concentration of 2.0 g/L or greater." Pet., 47; EX1038, [0012]. However, examples Petitioners relied on for their analysis of claim 1, such as Example 2 (*e.g.*, EX1038, [0042], Fig. 2), cannot meet the additional limitation of claim 2, which requires the "refold mixture [to have] a protein concentration in a range of 1-40 g/L." EX1001, 18:42-44. For example, the concentration of protein in Example 2, is only 0.1 mg/mL.[18] EX2026, ¶90; EX1038, [0042], Fig. 2. Nor can this disclosure meet the requirements of claims 3, 11, 13, 17, 18, 27, or 28. *Ibid.* Petitioners failed to address this discrepancy. Petitioners also did not explain

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[18] Nor can the other paragraphs and examples petitioner relied on meet the additional limitations. Example 4 reported refolding at "a total concentration of 0.3 mg mL^{-1} rhBMP-2." *Id.*, [0042], Figs. 4-6. Example 8's "[s]tandard renaturation conditions" reports "a final concentration of 0.1 mg mL^{-1} rhBMP-2." *Id.*, [0055]; EX2026, ¶90 n.10.

why the thiol-pair ratios allegedly disclosed in Fig. 2 would also be applicable to the example disclosed in EX1038, [0012]. *Fujian Sanan Grp. Co. v. Epistar Corp.*, IPR2018-00971, Pap. 9, 15-16 (Nov. 20, 2018) (denying institution because petitioner's citation to a different embodiment with inconsistent disclosure confused petitioner's contentions); *SecureNet Techs., LLC v. Icontrol Networks, Inc.* IPR2016-01919, Pap. 9, 25-26 (Mar. 30, 2017) (denying institution because "mixing-and-matching of references' elements without adequate explanation is confusing rather than clarifying"). Petitioners' cannot prove anticipation by relying on one set of values for the independent base claims, and then a different set of values for the claims depending from those same base claims. *Microsoft Corp. v. Biscotti Inc.*, IPR2014-01459, Pap. 49, 22 (March 17, 2016), *aff'd* 878 F.3d 1052 (Fed. Cir. 2017) (finding no anticipation when Petitioner combined separate embodiments in a reference to account for the limitations of the claim).

Petitioners also ignore the fact that Vallejo discloses a "***final***" concentration that its procedure "***resulted in," not the concentration at which the protein is actually refolded, which would have been less than the concentrations recited in the dependent claims of the '287***. EX1038, [0012]; EX2026, ¶91.

(c) Petitioners Failed To Show Vallejo Teaches The Limitations "Thiol-Pair Buffer Strength Maintains The Solubility Of The Preparation" Or "Thiol-Pair Buffer Strength Maintains The Solubility Of The Solution"

Petitioners failed to establish that the thiol-pair buffer strength "maintains the solubility of . . . the solution" in Vallejo as required in independent claims 16 and 26. Pet., 45. Petitioners identified no explicit teaching in Vallejo regarding solubility of any solutes in any preparation or solution, as required under the correct construction. *Supra* §III.C.

Petitioners also presented no argument or evidence in the Petition showing that Vallejo teaches "thiol-pair buffer strength maintains the solubility of the preparation" under the correct construction of this phrase. *See supra* §III.C.[19] Petitioners' only analysis of this limitation was under the incorrect construction, which requires the solubility of *proteins* (and only the proteins) be maintained.

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[19] Petitioners were aware the construction they identified was inconsistent with the plain claim language and were aware of Amgen's construction. Pet., 21. Petitioners chose not address this issue in the Petition and should not be allowed to address it in Reply. *See supra* §VI.A.1(a); *see, e.g.*, *supra* n.3 (collecting authority).

But even under Petitioners' erroneous construction(s) that reference the solubility of the protein (not present in the preparation), Vallejo does not disclose this claim element for the reasons discussed above (*supra* §VI.A.1.(b)).

(d) Vallejo Does Not Teach The Claimed Yield of Properly Refolded Protein

Petitioners and their expert argue that Vallejo's refolding method "allowed for a refolding yield of 44%," and that POSITA "would understand that the 'renaturation yield'" reported in Vallejo "would mean the yield of properly refolded protein." Pet., 45-46; EX1002, ¶¶103-104. However, Petitioners and their expert provide no explanation of how the "renaturation yield" in Vallejo is determined, and no analysis of whether that calculation is the same as the yield in the '287 claims. The Board need not credit these conclusory statements. *Hyundai Motor Co. v. Blitzsafe Texas, LLC*, IPR2016-01477, Pap. 13, 21 (Jan. 27, 2017) (noting that the Board was "not persuaded by and do not credit these conclusory and unexplained representations [from petitioner's expert] as to what the cited disclosures of [the asserted reference] would have conveyed to a person of ordinary skill."); *see* §42.65(a) ("Expert testimony that does not disclose the underlying facts or data on which the opinion is based is entitled to little or no weight."); *Rohm & Haas*, 127 F.3d at 1092 ("Nothing in the rules or in our

jurisprudence requires the fact finder to credit the unsupported assertions of an expert witness.”).

And while Petitioners’ incorrectly assert that the ’287 claims covers “the yields resulting from the refolding of *any* protein that happens to be present,” (Pet., 29; EX1002, ¶74), Petitioners identify the so-called yield in Vallejo as relating to the target protein of interest only, rhBMP-2 (*see* Pet., 46; EX1002, ¶105).

Vallejo uses the terms “renaturation yield” and “refolding” yield inconsistently, although Petitioners assert that “renaturation yield” is the same thing as “refolding yield.” Pet., 45-46; EX1002, ¶104; EX2027, 33:7–34:19 (Robinson); EX2026, ¶¶92-93. For example, the captions for Figure 2-7 each refer to “renaturation yield.” EX1038, [0042]. However, Figures 2 and 4 refer to “Refolding yield (dimer/initial prot. (%)).” Figure 3(B) refers to “Refolding yield (dimer/total prot. (%)), while Figure 3(C) refers to “Refolding yield (dimer/soluble prot. (%)).” Figures 6 and 7 refer to “Refolding yield (%)” without further explanation. POSITA would not have been able to determine how Vallejo’s 44% “renaturation yield” is calculated, and therefore POSITA could not have determined whether Vallejo’s results fall within the refold ranges in the claims (“at least about 25% of the proteins are properly refolded” or “about 30-80% of the proteins are properly refolded”). EX2026, ¶93.

(e) Vallejo Does Not Teach "Is Calculated" Under The Correct Construction (Claims 8, 9, 14, 15, 23, 24, 25, 30)

Petitioners failed to present ***any*** argument under the correct construction of "is calculated." Pet., 49-50; EX1002, ¶113; *supra* §III.D. Thus, Petitioners failed for this additional reason to show that those claims are disclosed by Vallejo. It is too late for Petitioners to try to do so in Reply, and any future attempt to add a new argument should be rejected. *See supra* §VI.A.1(a); *see, e.g.*, *supra* n.3 (collecting authority).

In any case, Vallejo does not teach "is calculated" under the correct construction, as Vallejo does not teach that any alleged thiol-pair ratio or the thiol-pair buffer strength is determined using an equation *as part of practicing the method* (*see supra*, §III.D), rather than using the equation in hindsight.

(f) Petitioners Present No Argument About Vallejo Teaching "Incubating" The Refold Mixture Or Solution

Petitioners failed to present any argument with respect to purported disclosure of the "incubating" limitation required in claims 1, 10, 16, and 26. While the word "incubating" appeared in the heading to Petitioners' argument on page 45 of the Petition, the Petitioners never mapped "incubating" to a disclosure in Vallejo. Because it is required in every independent claim (and thus every dependent claim) Petitioners' failure to address it and demonstrate how it is argued

to be disclosed in Vallejo is fatal to their Vallejo arguments (Grounds 1, 7) for *every claim*. As with Petitioners other waived arguments, they should not be allowed to raise new arguments on Reply to address this shortcoming in the Petition. *See supra* §VI.A.1(a); *see, e.g.*, *supra* n.3.

2. Petitioners Have Not Established That Claims 5, 6, 20, And 21 Are Obvious Over Vallejo In View Of Hevehan (Ground 7)

Because Ground 3 fails, and the Ground 7 claims depend from claims 1 and 16 in Ground 3, Ground 7 also fails. In addition, Petitioners fail to account for important affirmative teachings in Vallejo when arguing motivation to combine Vallejo and Hevehan. Pet., 76-77 (citing to EX1038, [0045]); EX1002, ¶¶186-191. For example, Petitioners ignored Vallejo's teaching that "in case of rh-BMP-2, *the pH and not the ratio of GSH:GSSG [redox reagents] is the critical variable* for optimum renaturation." EX1038, [0045]. But this teaching of Vallejo is at odds with the teachings of Hevehan that Petitioners argue should be combined with Vallejo: Hevehan teaches that, rather than optimizing pH (as Vallejo teaches) or even redox reagents, it is instead the *concentration of denaturants* whose optimizing is the "most effective" at improving yields. EX1024, 8. Petitioners further fail to address that Vallejo teaches that "*[n]o renaturation was observed up to pH 8,*" EX1038, [0045], whereas Hevehan's experiments were performed *at a pH of 8*. EX1024, 2, 3.

Moreover, Petitioners offer no explanation for why POSITA would ignore *both* Hevehan's teaching of optimizing the concentration of denaturants *and* Vallejo's teaching of optimizing pH and eliminating salt, and, instead, optimize redox chemicals as claimed in the '287 but disclosed in *neither* Vallejo nor Hevehan. Petitioners thus failed to prove why POSITA would have combined Vallejo with Hevehan such that "thiol-pair buffer strength is increased proportionally to an increase in a total protein concentration," as claimed.

Petitioners further failed to explain why POSITA would have a reasonable expectation of success in this combination—another failure fatal to this obviousness argument. *See, e.g.*, *Intelligent Bio-Sys.*, 821 F.3d at 1367-68 (affirming Board's finding of non-obviousness, and noting "two different legal concepts" required for obviousness: (1) reasonable expectation of success and (2) motivation to combine); *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1208-09 (Fed. Cir. 1991) (affirming finding of non-obviousness, and stating reasonable expectation of success needed even if invention was otherwise obvious to try); *Johnson Matthey Inc. v. BASF Corp.*, IPR2015-01267, Pap. 35, 30 (Nov. 30, 2016) (finding no reasonable expectation of success, noting prior art "simply provid[ed] incentive 'to explore a new technology or general approach that seemed to be a promising field of experimentation'"). Petitioners did not explain why POSITA would have expected to be able to apply the refolding conditions in

Hevehan to Vallejo because each reference discloses refolding conditions optimized for a particular purified and denatured protein, the dimeric cystine-knot rhBMP-2 protein in Vallejo and the non-recombinant lysozyme in Hevehan (*i.e.*, a protein not made in a non-mammalian expression system, but rather derived from hen eggs). EX1038, [0054]; EX1024, 1; EX2026, ¶¶94-95. Vallejo describes at length the cystine-knot proteins that it is specifically concerned with refolding, which are an unusual complex dimeric protein. EX1038, [0001]-[0004], [0008]; EX2026, ¶95. Petitioners have not explained why POSITA would have thought Hevehan's work with a simple, model, monomeric globular protein with a hydrophobic core would work to refold cysteine knot proteins lacking a hydrophobic core (especially at a high concentration)—indeed, it would not. EX2026, ¶95. Thus, Petitioners have not established that POSITA would have expected that combining the references would achieve that Hevehan and Vallejo could be successfully combined.

B. Petitioners Failed To Establish That Claims 1-4, 8-19, And 23-30 Are Anticipated By Schlegl (Ground 4), And That Claims 7 And 22 Are Obvious Over Schlegl In View Of Vallejo (Ground 5)

1. Petitioners Have Not Established That Claims 1-4, 8-19, And 23-30 Are Anticipated By Schlegl (Ground 4)

(a) Petitioners Mixed And Matched Schlegl's "Renaturation Buffer" And "Refold Buffer"

(i) Petitioners Inappropriately Mixed And Matched Schlegl's Liquids In Arguing Schlegl Teaches The Claimed Preparation And Solution

Claims 1 and 10 require a preparation comprising at least a denaturant, aggregation suppressor, or protein stabilizer, an oxidant, and a reductant. Claims 14 and 24 require a solution containing at least a denaturant, aggregation suppressor, or protein stabilizer, an oxidant, and a reductant as well as protein. Schlegl teaches that "α-LA is denatured and reduced in a refolding buffer containing 0.1M Tris-HCl, pH 8.0, 6 M GdmHCl, 1mM EDTA and 20mM DTT." EX1007, [0074]. The α-LA is then "Refold[ed] by Dilution," in which "[d]enatured and reduced aliquots at 16.5 mg/ml are rapidly diluted (batch-dilution) 32 fold into renaturation buffer consisting of 100mM Tris-HCl, 5mM $CaCl_2$, 2mM cysteine and 2 mM cysteine, pH 8.5." *Id.*, [0075]. However, as the Board recognized at Institution, Petitioners glossed over Schlegl's teaching of *two different buffers*—a "refolding buffer" and a "renaturation buffer"—and *used them*

interchangeably in attempting to map them on the claimed preparation and solution. *Compare id.*, [0074] *with id.*, [0075]; Pet., 55-56; DI, 29-30.

In Schlegl's only example, the refolding buffer is used to denature the protein (EX1007, [0074]), and the renaturation buffer is used to renature or refold the protein (*id.,* [0075]). EX2026, ¶96. The Board acknowledged that this observation appears consistent with the teachings of Schlegl. DI, 30. In an attempt to establish that Schlegl teaches the claimed preparation (claims 1, 10) and solution (claims 16, 26), Petitioners asserted that POSITA would understand that cysteine and cystine are added to Schlegl's refolding buffer to "serve as the redox system or redox component." Pet., 55-56; EX1002, ¶122. But, Schlegl teaches that cysteine and cystine are in Schlegl's "***renaturation*** buffer," and ***not in its "refolding buffer."*** EX1007, [0075]. Petitioners failed to explain why POSITA would add cysteine and cystine to the refolding buffer when Schlegl uses its refolding buffer to denature the proteins and ***not*** to refold them. In any case, such modification of Schlegl would not be consistent with an anticipation theory. Further, as the Board observed, the chemicals that Petitioners map as the aggregation suppressor, protein stabilizer, and denaturant (Pet., 53-55), are chemicals identified in Schlegl as being in the refold buffer, not the renaturation buffer. EX1007, [0036], [0054], [0075]; DI, 30. The claims, however, require that the oxidant, reductant, and the other

refolding chemicals (at least one of a denaturant, aggregation suppressor, and protein stabilizer) *all* be in the preparation and *all* be in the solution.

(ii) Petitioners Mixed And Matched Schlegl's Liquids In Arguing Schlegl Teaches The Claimed Protein Concentrations In Claims 2-3, 11-12, 17-18, and 27-28

Petitioners rely on the protein concentration of Schlegl's "refold buffer" in arguing that Schlegl teaches the claimed protein concentrations. Pet., 57; EX1002, ¶128. However, the protein concentration in Schlegl's exemplified renaturation buffer is 0.516 mg/ml (EX1007, [0075]), which is outside the range recited in the dependent claims. Petitioners failed to meet their burden of establishing these dependent claims are anticipated by Schlegl because they relied on the protein concentration in Schlegl's "refold buffer" without explaining why that protein concentration, rather than the concentration in the exemplified "renaturation buffer" should be mapped to these dependent claims. Moreover, the "refold buffer" is not the solution in which the protein is actually refolded, but rather the solution where the protein is solubilized before refolding. Indeed, Petitioners ignore the hallmark of Schlegl's refolding method, *i.e.*, working at extremely dilute, "ideal mixing" protein concentrations. *See* EX1007, [0039] ("In the process of the invention, the *actual* protein concentration immediately after mixing *is much lower* as compared to conventional refolding methods.").

(b) Petitioners' Calculation Of Thiol-Pair Ratio In Schlegl Is Incomplete And Incorrect

Petitioners assert that Schlegl's "redox component has a thiol-pair ratio of 2," Pet., 56; EX1002, ¶122, and then summarily argue that "Schlegl discloses a thiol-pair ratio within the range of 0.001-100," Pet., 56; EX1002, ¶122.[20] But again, Petitioners' improper mixing and matching of solutions in Schlegl (*supra* §VI.B.1.(a)(i)) leads to error. Petitioners provide no explanation about why the thiol-pair ratio of Schlegl's "redox component" is purportedly relevant, nor what the claimed "solution" or "preparation" are in Schlegl, nor why the thiol-pair ratio of a "solution" or "preparation" in Schlegl is within the claimed range.

In addition, the Petition failed to address how the presence of DTT in Schlegl would impact any calculations of thiol-pair ratio and thiol-pair buffer strength. Pet., 56; EX1002, ¶122. Schlegl uses DTT when α-LA is denatured and reduced. EX1007, [0074]. This denatured and reduced protein is then added to the renaturation buffer containing cysteine and cystine. *Id.*, [0075]. Even though

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[20] Petitioners reference a "redox component" repeatedly in their Petition. The '287 patent does not claim a "redox component." The claims require "an amount of oxidant" and "an amount of reductant" in the preparation (claims 1-15) and in the solution (claims 16-30).

Petitioners and their expert purport to account for the presence of DTT in their thiol-pair ratio and thiol-pair buffer strength calculations when analyzing Hevehan, *see* Pet., 78; EX1002, ¶190, it is clear that in fact Petitioners and their expert did not take DTT into account in purporting to determine thiol-pair ratio and thiol-pair buffer strength in Schlegl. Petitioners articulated no basis for ignoring DTT in Schlegl while accounting for it in Hevehan, and—as their own Hevehan arguments evidence—their calculations of thiol-pair ratio and thiol-pair buffer strength are incomplete for at least this reason, and cannot be relied on to carry their burden.

Finally, even ignoring the errors above, Petitioners' calculation of the ratio itself is insufficient. Petitioners assert "[t]hat [the] redox component has a thiol-pair ratio of 2." Pet., 56. But the Petition does not explain how this number was calculated. And while Petitioners' expert does explain her calculation (EX1002, ¶122 n.7), this calculation is improper incorporation by reference and cannot be considered. *Costco Wholesale Corp. v. Robert Bosch LLC*, IPR2016-00035, Pap. 23, 10-11 (Aug. 12, 2016).

(c) Schlegl Does Not Teach That Its Bovine α-Lactalbumin Is Expressed In A Non-Mammalian Expression System

All of the claims require that the protein be expressed in a *non-mammalian* system. Petitioners, however, rely on Schlegl's disclosures of ***bovine*** α-lactalbumin in arguing anticipation. EX1007, [0073]. Schegl does not identify the

system in which its ***bovine*** α-lactalbumin is expressed, and Petitioners' expert could not say what type of expression system was used to express the protein in Schlegl. EX2027, 54:12-15 (Robinson); EX2026, ¶¶97-98. Indeed, bovine α-lactalbumin could be easily obtained commercially in purified form from cow's milk (*i.e.*, a *mammalian* system). *See* EX2029, 2; EX2026, ¶97; *see also* EX2027, 54:5-8. Thus, POSITA reading Schlegl would not have understood it as disclosing the bovine α-lactalbumin to have been produced in a non-mammalian system. EX2026, ¶¶97-98; *see also* EX2027, 54:12-15.

The single reference in Schlegl to bacterial and yeast expression systems for producing recombinant proteins cannot rectify Petitioners' failure to map the teachings of Schlegl to this claim element. EX1007, [0004]. Schlegl says only that such nonmammalian expression systems exist and can be used to produce recombinant protein, but Schlegl also says recombinant protein can be produced in animal cells (EX1007, [0004]), which POSITA would have understood to include mammalian cells. *Id.*; EX2026, ¶98. Schlegl does not say it used nonmammalian expression systems to produce its α-lactalbumin, or that α-lactalbumin could be produced using these systems. EX2026, ¶98.

(d) Petitioners Failed To Show Schegl Teaches The Limitations "Thiol-Pair Buffer Strength Maintains The Solubility Of The Preparation" Or "Thiol-Pair Buffer Strength *Maintains The Solubility* Of The Solution"

As with their arguments concerning Vallejo (*supra*, §VI.A.1(c)), Petitioners failed to show that the thiol-pair buffer strength "maintains the solubility of the preparation" (claims 1 and 10) or the "solution" (claims 16 and 26). Pet., 56; EX1002, ¶123. Petitioners pointed to no teaching in Schlegl regarding the solubility of any solutes in any preparation or solution under the correct construction of these terms.

(e) Schlegl Does Not Teach The Claimed Yield of Properly Refolded Protein

Petitioners failed to show Schlegl achieves either refolding limitation. Petitioners and their expert point to the statement in Schlegl that "[t]he final yield of refolded protein at equilibrium is 63% for the batch system and 81% for the fed-batch system." Pet., 56; EX1002, ¶124. At her July deposition, Dr. Robinson testified that these percentages represent yield of refolded protein relative to initial or unfolded total protein:

> Q. And how do you understand yield as used in Paragraph 82?
>
> A. So, my understanding of the total yield in this, the total yield of the protein that they are looking at, alpha-lactalbumin, is, is based on combining Paragraphs 82 and Paragraph 80 where

> they quantify the, what is equivalent to the '287 solubilized protein to measure the total protein present in the solution before refolding and then total albumin present. And then they quantify the refolded protein.
> So, they are looking at the yield of refolded protein relative to initial or unfolded total protein. Total alpha-lactalbumin.

EX2027, 47:20-22. Dr. Robinson is mistaken. Paragraph 80 of Schlegl, which Dr. Robinson identifies as "where [Schlegl] quantif[ies] the . . . the total protein present in the solution before refolding," EX2027, 47:11-19, states that "[p]rior to analysis, all samples are centrifuged . . . to remove insoluble material." EX1007, [0080]. Thus, POSITA would understand that before analysis, insoluble material, including protein that aggregated during refolding and precipitated out of solution, is removed. EX2026, ¶99; EX2027, 47:25–48:1 (Dr. Robinson admits that "alpha-lactalbumin is capable of aggregating."). Schlegl therefore cannot be reporting percent refolded protein over initial protein ("total protein present in the solution before refolding") as Dr. Robinson asserts. EX2027, 47:17-18.

Moreover, the circular dichroism spectra reported in Schlegl and cited by Petitioners and their expert do not reflect the ***amount*** of protein properly refolded—only that some protein with correct secondary structure is present. EX2026, ¶100; EX1007, Fig. 6. But Petitioners admit that the primary, secondary, *and tertiary structure* are required for the protein's native structure "and confer the

protein's biological function." Pet., 4. Thus, Petitioners failed to show that the "refolded" protein in Schlegl is properly refolded (into the native, biologically active form). EX2026, ¶100.

(f) Schlegl Does Not Teach "Is Calculated" Under The Correct Construction (Claims 8, 9, 14, 15, 23, 24, 25, 30)

As with their arguments regarding Vallejo, Petitioners failed to present ***any*** argument under the correct construction of "is calculated" for claims 8, 9, 14, 15, 23, 24, 25, 30. Pet., 49-50; EX1002, ¶¶131-132; EX2026, ¶101; *see supra* §VII.B.1. Thus Petitioners failed to show that those claims are disclosed by Schlegl. It is too late for Petitioners to try to do so in Reply, and any future attempt to add a new argument should be rejected. *See supra* §VI.A.1(a); *see*, *e.g.*, *supra* n.3 (collecting authority). In any case, Schlegl does not teach "is calculated" under the correct construction, as Schlegl does not teach that any alleged thiol-pair ratio or the thiol-pair buffer strength is determined using an equation *as part of practicing the method*, rather than using the equation in hindsight.

2. Petitioners Have Not Established That Claims 7 And 22 Are Unpatentable Over Schlegl In View Of Vallejo (Ground 5)

Claims 7 and 22 depend from independent claims 1 and 16, respectively. In addition to the shortcomings described above(*see supra* §VI.B.1), Petitioners' cursory obviousness analysis is also insufficient. *Kingston Tech. Co. v. Spex*

Techs., Inc., IPR2017-01021, Pap. 39, 29-30 (Oct. 1, 2018) (stating "Petitioner . . . has not made out a persuasive case of obviousness [where] . . . 'despite asserting obviousness, Petitioner [did] not identify which, if any, of the limitations of the [prior art] reference may be missing and how those limitations might be obvious.'"). Petitioners failed to explain what they argue is lacking in Schlegl's disclosures and why POSITA would look to the teachings of Vallejo to fill any such gap in Schlegl. Petitioners also failed to specify which aspects of Schlegl's or Vallejo's methods they rely on to achieve refolding of a complex protein.

In addition, Vallejo describes the particular cystine-knot proteins that it is specifically concerned with refolding. EX1038, [0001]-[0004], [0008]. These proteins are dimers that lack "a hydrophobic core common to globular proteins" that stabilizes protein structure. *Id.*, [0003]. Schlegl, on the other hand, uses a simple, monomeric, model protein α-lactalbumin, which is a globular protein with a hydrophobic core, for its refolding studies. EX1038, [0001]. Dr. Robinson did not explain why POSITA would have reasonably expected to obtain Schlegl's results in refolding Vallejo's protein. EX2026, ¶101.

C. Petitioners Have Not Established That Claims 1-4, 7-19, And 22-30 Are Obvious Over Ruddon In View Of Vallejo (Ground 6)

1. Ruddon Does Not Teach Refolding Protein Expressed In A Non-Mammalian System Into Properly Refolded Biologically Active Protein

As an initial matter, Petitioners fail to explain how Ruddon's refolding process for the hCG-β ***subunit*** results in properly folded, biologically active protein. Petitioners and their expert assert that "Ruddon teaches that its refolded rehCG-β is biologically active" but offer no support beyond quoting a statement in Ruddon that "rehCG-β *folded and assembled with hCG-α* in a conformation very similar to that of glycosylated hCG-β that is made in human cells." Pet., 71; EX1002, ¶171. But the hCG hormone is assembled from two pieces: a piece that is produced recombinantly and refolded (rehCG-β) and *native* urinary hCG-α. Ruddon does not teach that the refolded rehCG-β is biologically active, only that it is "assembly-competent" to form active hCG when combined with native hCG-α. EX2026, ¶102; EX1040, 1, 51:7-28. Thus, as the Board observed, Ruddon teaches that rehCG-β and hCG-α are protein subunits that must be assembled in order to function as the biologically active dimeric protein. DI, 31; EX1040, Abstract; EX2026, ¶102. Neither Petitioners nor their expert explain how a protein that is merely competent for assembly into a biologically active hormone with other components *is itself biologically active*. Indeed, it is not. EX2026, ¶102. Ruddon

itself drew a distinction between biological activity and competence for assembly: "Unfolded glycoprotein hormone subunits are expressed in procaryotic cells, then re-folded in vitro in a thiol redox buffer *to form* ***assembly-competent subunits***. The subunits *are assembled to produce* ***active hormones***." EX1040, 1; EX2026, ¶102. Petitioners' reliance on Ruddon as their base reference, asserting Ruddon teaches a method for refolding biologically active proteins, is misplaced (*see* Pet., 61-62), and Petitioners therefore cannot prove that Ruddon in view of Vallejo renders obvious the Ground 6 claims.

Further, hCG-α indicates the subunit is not recombinant, as compared to *re*hCG-β, wherein the "re" indicates it is recombinant. EX2026, ¶103. There is no showing in Ruddon that the α-subunit was ever made recombinantly or that a recombinant α-subunit could be reassembled with *re*hCG-β to make a biologically active dimer. *Id.* In fact, the only showing of biological activity is with a dimer made from a recombinant β-subunit (*re*hCG-β) combined with *native* α-subunit. *Id.*; EX1040, 3:19-31, 14:33–15:6, 47:19-23, 51:32–52:4. Further, native α-subunit will be glycosylated whereas the recombinant β-subunit will not be. EX2026, ¶103. There is also no showing in Ruddon that a non-glycosylated dimer is biologically active. *Id.*

Moreover, the hcG-α subunit used by Ruddon to assemble the biologically active hormone is obtained from human (mammalian) urine, and not a non-mammalian expression system. EX1040, 4:35–5:18, 46:11-14; EX2026, ¶104. Thus, the active hormone is not expressed in a non-mammalian expression system as required by the claims.

2. Petitioners Failed To Show How Or Why Ruddon And Vallejo Would Be Combined To Arrive At The Claimed Invention

Petitioners failed to explain why POSITA would be motivated to combine Ruddon, which focuses on refolding protein subunits (and specifically glycoprotein hormones) with Vallejo. Petitioners also failed to explain clearly how POSITA would modify Ruddon based on Vallejo to arrive at each claim limitation for Ground 6. Rather than identifying which claim limitations are missing from each reference and explaining how the combination of references would meet the missing limitations, Petitioners provide a laundry list of the teachings of each reference. Indeed, for each claim limitation, Petitioners cited to disclosures from both Vallejo and Ruddon without explaining what they assert is lacking in Ruddon and why would POSITA look to the teachings of Vallejo to fill that gap. This is not sufficient to prove obviousness, and Amgen cannot determine from the Petition the exact combination sufficiently to provide a complete rebuttal. *See, e.g.*, *Intelligent Bio-Sys.*, 821 F.3d at 1369 ("It is of the utmost importance that

petitioners in the IPR proceedings adhere to the requirement that the initial petition identify 'with particularity' the 'evidence that supports the grounds for the challenge to each claim.'"); *St. Jude Med., LLC v. Snyders Heart Valve LLC*, IPR2018-00105, Pap. 59, 37 (May 2, 2019) ("[N]either the Petitioner nor [petitioner's expert] indicates with sufficient particularity as required by 35 U.S.C § 312(a)(3), what elements of Andersen are interchanged with elements of Leonhardt and, thus, in what manner Leonhardt and Andersen are combined.").

Petitioners also argued that POSITA would have a motivation to use Vallejo's teachings in Ruddon in order to produce clinically sufficient quantities. But Ruddon—albeit using an approach different than the claimed method—*already solves that problem* (EX2026, ¶105), disclosing (different) methods to produce glycoprotein hormones in quantities sufficient for clinical use. EX1040, 1:11-15. Thus, this argued motivation fails as well. *Arris Int'l PLC v. Sony Corp.*, IPR2016-00828, Pap. 10, 13-18 (Oct. 7, 2016) (no motivation where prior art already addressed alleged problem/need).

3. POSITA Would Not Reasonably Expect That The Teachings Of Ruddon And Vallejo Could be Successfully Combined

The Petition is also devoid of any discussion of reasonable expectation of success other than a conclusory statement, repeated verbatim by their expert, that the combination would work "because Vallejo explicitly teaches so"—a position

that, despite Petitioners' unsupported assertion, does not apply to combinations with teachings from Ruddon that Vallejo never discusses (and that Petitioners have not even specified). Pet., 72; EX1002, ¶174. Petitioners and their expert apparently expect the Board to accept their arguments based on this one conclusory statement, but this does not constitute evidence that could carry Petitioners' burden. *See, e.g.*, *Nintendo Co. v. Genuine Enabling Tech., LLC*, IPR2018-00543, Pap. 7, 24 (Aug. 6, 2018) (denying institution because the petitioners' "only support [was] a conclusory statement [from their expert] without any evidentiary support, which has no weight").

POSITA would not have reasonably expected that the teachings of Ruddon and Vallejo could be combined successfully. POSITA would not have thought that the teachings of Ruddon for a specific glycoprotein subunit with a cystine-knot motif would be applicable to the very different cystine-knot protein in Vallejo. EX2026, ¶106. The subject protein of Ruddon is a glycoprotein subunit hCG-β that contains a cystine-knot motif. EX1040, 26:10-17. The hCG-β subunit can assemble with the hCG-α subunit for form active hCG protein. EX1040, 2:3-9. Ruddon explicitly teaches that its methods are specifically directed to these types of glycoprotein subunits that have "strong" sequence homology, "particularly in regions involved in protein folding." *Id.*, 2:3-24. This would suggest to POSITA that Ruddon's method would not be broadly applicable to proteins generally or all

other cystine-knot proteins specifically. *Id.*, 24:1-13 ("The folding constraints described hereinabove for hCG-β are expected to be equally applicable to both α and β subunits of other glycoprotein hormones, due to the high conservation of disulfide bonds among the various hormones."). Ruddon also explains the special considerations, such as specific folding pathways for hCG-β, for folding these types of glycoprotein subunit proteins with cystine-knots, considerations that POSITA would understand are not universally applicable. *Id.*, 24:16-25:9; EX2026, ¶107. Vallejo however does not disclose methods for refolding glycoprotein subunits. *See supra* §VI.A.2; EX2026, ¶107. Thus, POSITA would have understood that Vallejo cannot make up for Ruddon's lack of a glycosylated recombinantly produced α-subunit. EX2026, ¶107; EX1040, 2:32-33, 4:4-15. Consequently, POSITA would not have thought that Vallejo's disclosed teachings to apply to Ruddon and would not have reasonably expected to be able to successfully combine them. EX2026, ¶107.

4. Neither Ruddon Nor Vallejo Teach The Limitations "Thiol-Pair Buffer Strength Maintains The Solubility Of The Preparation" Or "Thiol-Pair Buffer Strength Maintains The Solubility Of The Solution"

Petitioners failed to establish that the thiol-pair buffer strength "maintains the solubility of the solution" in Vallejo as required in independent claims 16 and 26. *See supra*, §IV.A.1.c. Petitioners also failed to establish that Vallejo teaches

"thiol-pair buffer strength maintains the solubility of the preparation" under the correct construction of this phrase. *See id.* Petitioners also presented no evidence or argument that Ruddon teaches that the thiol-pair buffer strength "maintains the solubility of the preparation" (claims 1 and 10) or the "solution" (claims 16 and 26), under any proper construction of the terms. Petitioners make no argument to fill this hole in their Ground 6 obviousness arguments. Therefore, Petitioner did not meet its burden in establishing obviousness over Ruddon in view of Vallejo.

5. Neither Ruddon Nor Vallejo Teach "Is Calculated" Under The Correct Construction (Claims 8, 9, 14, 15, 23, 24, 25, 30)

For same reasons as described above, *see supra* §§III.D, VI.A.1(e), VI.B.1(f), Petitioners' proof regarding "is calculated" is lacking for its Ruddon-based combination, as well. Pet., 75-76; EX1002, ¶¶183-184. As discussed above (§VI.A.1(e)), Vallejo does not teach "is calculated" under the correct construction. Similarly, Ruddon does not teach that any alleged thiol-pair ratio or the thiol-pair buffer strength is determined using an equation *as part of practicing the method*, rather than using the equation in hindsight.

VII. Petitioners Failed To Establish That Claims 1-15 Are Indefinite (Ground 8)

As a threshold matter, Petitioners failed to provide any evidence or analysis of the state of the art after 2009, and Petitioners' indefiniteness ground is entirely

argued as of 2009, not 2017. *See* Pet., §V (discussing art from 2009 and before); EX2027, 6:22-7:4, 67:5-13 (Dr. Robinson admitting that the background section of her declaration concerns 2009). *See Nautilus, Inc. v. Biosig. Instruments, Inc.*, 572 U.S. 898, 908 (2014) ("[D]efiniteness is measured from the viewpoint of a person skilled in [the] art *at the time the patent was filed*." (quotation omitted)).

Even setting aside Petitioner's failure to present any evidence of indefiniteness as of 2017, Petitioners argue that "[s]hould the Board find that the term 'wherein the thiol-pair buffer strength maintains the solubility of the preparation' be interpreted to mean anything other than that the thiol-pair buffer strength maintains the solubility of the proteins, then claims 1-15 are indefinite." Pet., 79-80. Not so. As is clear from Amgen's construction, the plain meaning of the claim informs "with *reasonable certainty*, those skilled in the art about the scope of the invention." *Nautilus*, 572 U.S. at 901. The fact that the parties disagree about *which components* of the preparation are maintained in solution (*i.e.*, which ones are solubilized) does not mean the term cannot be understood and is indefinite.

The claims themselves identify components of the preparation: (1) at least one of a denaturant, an aggregation suppressor, and a protein stabilizer; (2) an oxidant; and (3) a reductant. POSITA would understand that all of the ingredients of the preparation must be solubilized to serve as oxidants, reductants, denaturants,

aggregation suppressors, or protein stabilizers. EX2026, ¶¶108-110. In addition, the specification defines the thiol-pair buffer strength by a relationship between an oxidant and a reductant as based on concentrations of an oxidant and reductant. EX1001, 6:56–6:67; EX2026, ¶¶111. Thus, it would have been clear to POSITA that the amounts of oxidant and reductant (which define the thiol-pair buffer strength) must remain soluble in order for the oxidant and reductant to work, and in order to calculate the claimed thiol-pair ratio and thiol-pair buffer strength. EX2026, ¶111. Indeed, it is well known in the art that certain oxidants, particularly cystine, as Dr. Robinson testified, are not very soluble in water. EX2010, 167:8–169:4; EX2019, 312:24–313:9. POSITA would have understood that its limited solubility needs to be accounted for in the preparation because at thiol-pair buffer strengths that are too high, its solubility would not be maintained. EX2026, ¶111.

Petitioners also completely ignore that denaturants and reductants are dissolved in solution. If the denaturants and reductants are in solution in the claimed solution, as would be necessary for them to have their effect, then a POSA would have also understood that their solubility would be maintained in the preparation, to which the protein is added to form the claimed solution of independent claims 16 and 26. EX2026, ¶112. Indeed, Petitioners' expert, Dr. Robinson, understood that that the thiol-pair buffer strength maintains the

solubility of (at least) the oxidants and reductants in the preparation. And she agrees that it "makes sense" for the solutes in the preparation that effectuate protein refolding to be soluble:

> Q. So, the components that you put into the refold buffer, you also want to be soluble, in order to refold the protein.
> You need the protein to be soluble and you want the components of the refold buffer to be soluble?
>
> A. In a general sense, I think having the components be soluble makes sense.
> I can envision theoretically, that there could be components that would facilitate refolding that are not soluble.

EX2027, 14:24–15:9. Dr. Robinson has also acknowledged that POSITA would understand the solubility of (at least) the oxidants and reductants in the preparation should be maintained. For example, Dr. Robinson testified that "typically, you would want those [reductant and oxidant chemicals] to be in solution." EX2027, 56:3-7. Dr. Robinson also testified at her April 2016 deposition in the Florida litigation (in which the related '138 was asserted against Petitioners Apotex Inc. and Apotex Corp.) about the desirability of the ***redox chemicals (oxidants and reductants)*** to remain soluble in a refold buffer:

> Q. Would you agree that you certainly want these chemicals to remain in solution? You don't want them dropping out of solution?

A. I would agree that typically you would want the -- a thiol-pair or redox component to be present in the soluble part of a refold buffer.

EX2019, 314:11-15. Further, for chemicals to effectuate refolding of a protein, these chemicals must be able to interact with or react with the protein without facilitating aggregation or precipitation. EX2026, ¶113; EX2042.

And, as explained above (*supra* §III.C), it is clear from the specification that the "refold buffer" is the "preparation." EX2026, ¶114. For instance, just like the "preparation" in independent claims 1 and 10, the specification describes the refold buffer as including (1) at least one of a denaturant, an aggregation suppressor, and a protein stabilizer; (2) an oxidant; and (3) a reductant, but not any protein. EX1001, 2:62–3:4. This is consistent with Petitioners' expert, who stated that "refold buffer" "would have been readily understood by [POSITA] to mean 'a preparation that supports the renaturation of protein to a biologically active form" and described *contacting the refold buffer with a protein* (reflecting an understanding that the refold buffer/preparation does not itself include protein). EX2030, ¶¶65-66. It is clear that the refold buffer contains in solution (*i.e.*, solubilized) the refold components/chemicals. EX1001, 2:62–3:4; EX2026, ¶114; EX1002, ¶54; EX2027, 14:24–15:9 (Robinson). And Dr. Robinson herself repeatedly uses the term "refold buffer" in concluding that the prior art teaches the

claimed preparation. EX1002, ¶¶98, 107, 116, 117, 119-122, 130, 135, 137, 147, 157, 173, 175. Petitioners' assertion that "it is not clear . . . which ingredients of the preparation is the solvent and which is the solute," Pet., 80, is belied by the claims and the specification, including the specification's description of "refold buffer." EX2026, ¶114.[21]

VIII. Petitioners' Expert Is Not Credible Or Reliable

Petitioners' expert's testimony is not credible. For instance, her testimony at deposition in this proceeding is not consistent with her declaration in the related IPR2019-00791 (EX1002):

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[21] Petitioners' assertion that it is not clear from the specification "how the thiol-pair buffer strength maintains such solubility" is not an argument about indefiniteness. Further, Petitioners' assert that this phrase is *not* indefinite if it is read to pertain to the solubility of the proteins, but Petitioners do not explain how the specification teaches how the thiol-pair buffer strength maintains the solubility of the proteins and not the claimed refolding components/chemicals of the preparation.

Robinson '878 Declaration (IPR2019-00791) (EX2031).	Question at Deposition	Answer at Deposition
"For proteins containing disulfide bonds, which are common in eukaryotic proteins, a refold buffer must promote disulfide bond formation." EX2031, ¶53	Do you agree with the following statement: "[f]or proteins containing disulfide bonds, which are common in eukaryotic proteins, a refold buffer must promote disulfide bond formation"? EX2027, 65:18-22	"I'm not sure I would agree with that, exactly how that is worded." EX2027, 65:24–66:7.
"As such, it was known to include redox components (reducing and oxidizing) in a refold buffer to promote disulfide formation." EX2031, ¶53.	In 2009, would you … agree or disagree with the following statement "It was known in 2009 to include redox components in a refold buffer to promote disulfide bond formation"? EX2027, 66:9-14.	"I would say that pre-2009 it was known that if you included redox agents, you could, you could alter the redox state of the buffer." EX2027, 66:16-22.
"By 2009, these variables were well understood and could be easily screened using a variety of well-developed parameters and techniques." EX2031, ¶54.	"In 2009, were these refolding variables things that could easily be screened using a variety of well-developed parameters or techniques?" EX2027, 68:5-8.	"I mean in the sense that there were a number of commercial products . . . in that sense there were methods developed to refold these proteins. Easily be screened? I, that is, that is sort of a – there is a lot to parse in that. That is not, that is not a simple phrase. ***I'm not sure anyone in the***

		refolding business would say it is easy to screen or identify refolding conditions for any protein." EX2027, 68:10–69:2.

Similarly, in this case where indefiniteness is asserted, Dr. Robinson claims that she does not understand what "preparation" means in the claims. EX2027, 61:17-25; EX1002, ¶¶192-193. However, in litigation, she herself used the word "preparation," stating that the refold buffer in claim 1 of the '138 patent "would have been readily understood by [POSITA] to mean '***a preparation*** that supports the renaturation of protein to a biologically active form.'" EX2030, ¶65. Further, in answering questions from her own attorney in this case, when asked a question about the state of the art ("in 2009, were there a number of well-known techniques for refolding certain proteins"), she herself responded by using the phrase "preparation": "in 2009 there were a number of approaches to refolding proteins, that – I would say contacting proteins. So, the phrase contacting the protein with the preparation, that approach to how you contact the protein with the preparation. There were lots of methods . . . ." EX2027, 72:19–73:12.

It is also clear that the Robinson declaration in this PGR was not carefully prepared or overstated her positions. For instance, Robinson's declaration suggests that Schlegl discloses that bovine α-lactalbumin is expressed in bacteria or yeast.

EX1002, ¶114. But at deposition, she admitted that Schlegl does not identify the system in which the bovine α-lactalbumin was expressed. EX2027, 54:12-15. And, there are plain mistakes in her thiol-pair ratio calculations, and she takes disparate (and inconsistent) approaches in how she performs those calculations across the Grounds. *Compare* EX1002, ¶100 (squaring numerator of reductant/oxidant ratio) *with id.*, ¶122 n.7; *see also supra,* §VI.B.1(b).

Further, Dr. Robinson admitted that her analysis for claims 1-15 depends on the same term ("the preparation") meaning different things within a single claim. Under her approach, the "preparation" is the "refold buffer" at the beginning of the claims but is then the "solution" (*i.e.*, refold mixture) at the end of the claims:

> So, in performing my analysis, I assumed that the, in general, looking at contacting the proteins with the preparation that supports renaturation, in that part [the preparation] is ***refold buffer***. And then in the later part of Claim 1 where it says, 'Thiol-pair buffer strength maintains the solubility of the preparation,' my assumption was that that was looking at the ***refold mixture***.

EX2027, 62:22–63:6; EX1001, col. 2:62–3:4 (explaining the protein is contacted with a ***refold buffer*** to form a ***refold mixture***).

While Dr. Robinson in her declaration states that the yield in the '287 claims covers "the yields resulting from the refolding of *any* protein that happens to be present," (EX1002, ¶74), her analysis of Vallejo relates to the yield of only

rhBMP-2 (*id.*, ¶¶105, 171; *see also* EX2027, 36:1-12, 37:2-17; EX1038, [0012], [0049]). Dr. Robinson's analysis is also imprecise. Setting aside more typical mistakes of, for instance, citing the incorrect exhibits (*compare* EX1002, ¶55 *with* EX2027, 8:16-24), Dr. Robinson also asserted that the '287 Patent does not disclose the concentration for the refolded proteins. EX1002, ¶82 ("A POSA could not replicate the full range of percentages of properly refolded species in Figure 1a-f [of the '287 Patent] without undue experimentation, as neither the specific protein, its disulfide bonding, oligomeric state, or its concentration is provided."). But, in fact, it does: 6 g/L. EX1001, 9:15-18; EX2026, ¶82.

IX. Conclusion

Petitioners have failed to show that claims 1-9 and 16-25 lack written description support or that claims 1-30 are not enabled as of the claimed priority of the '287, thus have failed to show that the '287 qualifies for PGR, and this proceeding should be terminated. If this proceeding is nevertheless allowed to proceed to a Final Written Decision, Petitioners have failed to show that claims 1-9 and 16-25 lack written description support or that claims 1-30 are not enabled *as of the filing of the '287*, and have therefore failed to establish its Grounds 1-2. Additionally, due to failures in both proof and specificity of argument, the Petitioners failed to show that claims 1-30 are anticipated or rendered obvious (Grounds 2-7). The Petitioners also failed to show that claims 1-15 are indefinite

(Ground 8). Because the Petition failed to establish unpatentability by a preponderance of the evidence, the patentability of the claims of the ’287 should be confirmed.

Respectfully submitted by:

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CERTIFICATE OF WORD COUNT

The undersigned certifies that the foregoing PATENT OWNER'S PRELIMINARY RESPONSE UNDER 37 C.F.R. §42.220 complies with the type-volume limitation in 37 C.F.R. §42.24(1)(1)(ii) and (b)(1). According to the word-processing system's word count, the brief contains 18,640 words, excluding the parts of the brief exempted by 37 C.F.R. §42.24(a)(1).

Dated: July 26, 2019

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The undersigned hereby certifies that a copy of PATENT OWNER'S RESPONSE UNDER 37 C.F.R. § 42.220 has been served in its entirety by causing the aforementioned document to be electronically mailed to the following attorneys of record for the Petitioners listed below:

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