IPR2019-00971 U.S. Patent 9,856,287

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FRESENIUS KABI USA, LLC AND FRESENIUS KABI SWISSSBIOSIM GmbH., Petitioners

v.

AMGEN INC. and AMGEN MANUFACTURING, LIMITED, Patent Owners

Case IPR2019-00971 Patent 9,856,287

PATENT OWNERS' PRELIMINARY RESPONSE UNDER 37 C.F.R. § 42.107

LIST OF EXHIBITS

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EX2003	Excerpt of Joint Claim Construction Chart (Amgen Inc., et al. v.
	Kashiv Biosciences, LLC, No 2:18-cv-03347-CCC-MF, DE 101, at
	Appx. D (D.N.J. March 22, 2019))

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Pursuant to 37 C.F.R. §42.107,¹ Patent Owners² Amgen Inc. and Amgen Manufacturing, Limited (collectively, "Amgen") submit this Preliminary Response to the above-captioned Petition for *Inter Partes* Review of U.S. Patent No. 9,856,287 ("Petition" or "Pet." Pap. 3), which should be denied in its entirety: for being filed before the termination of instituted PGR2019-00001 under §311(c)(2) and §41.102(c)(3); pursuant to the Board's discretion under §§314 and 325(d); for Petitioners' failure to take affirmative positions with respect to the correctness of, and failure to provide any analysis or record citations supporting, the constructions they identify; Petitioners' failure to address whether Claims 1, 4-6, 8-10, 12, and 14-15 are indefinite (as asserted in PGR2019-00001); and Petitioners' failure to show a reasonable likelihood of prevailing on any asserted ground. Further,

¹ All emphasis/annotations added, and all statutory and regulatory citations are to 35 U.S.C. or 37 C.F.R., as the context indicates, unless otherwise stated.
² Petitioners, apparently copying Petitioners in PGR2019-00001, 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 Preliminary Response refers collectively to both parties as "Patent Owners."

because of the procedural and substantive failings of the Petition, institution would not be in the interest of justice, or an efficient use of the Board's limited time and resources. And, in light of *SAS Institute, Inc. v. Iancu*, 138 S. Ct. 1348 (2018), even if Petitioners had made their threshold showing for some claims or grounds they have not—the Board, in its discretion, should deny institution under §314(a) for these additional reasons on all challenged claims and grounds in the Petition.

I. Introduction

Petitioners' submission failed to provide the Board the basic evidence required to institute any *inter partes* review. If the Board nonetheless institutes trial on the Challenged Claims,³ Amgen will address in detail in its §42.120 Response the numerous substantive errors and shortcomings in Petitioners' arguments and their purported evidence. Here, however, where testimonial evidence purporting to raise an issue of material fact "will be viewed in the light most favorable to the petitioner" (§42.108(c)), Amgen addresses only a subset of the Petition's procedural and substantive shortcomings. Because of these threshold failures, the Petition should be denied and no IPR instituted under §314.

³ Claims 1, 4-6, 8-10, 12, 14-16, 19-21, 23-26, 29-30 of U.S. Patent No. 9,856,287 ("287").

First, §311(c)(2) and §42.102(c) forbid the filing of an IPR before PGR2019-00001 (hereinafter "the PGR" or "the '287 PGR") is terminated. *See* §III.

Second, the same or substantially the same art, evidence and/or arguments are already being considered by the Board in the PGR, and were already considered by the Examiner and not found to render the claims unpatentable. *See* §IV. Petitioners' Ground 1 (alleging anticipation by Vallejo) overlaps with PGR Ground 3 (alleging anticipation by Vallejo). Petitioners' Ground 2 (alleging anticipation by Ruddon) overlaps with PGR Ground 6 (alleging obviousness based on Ruddon). Petitioners' Ground 3 (alleging obviousness based on Ruddon and other references) and Ground 4 (alleging obviousness based on a combination of Vallejo, Ruddon and other references) overlap with PGR Ground 6 (alleging obviousness based on Ruddon in view of Vallejo) and PGR Ground 3 (alleging anticipation by Vallejo). For this additional reason, the Petition should be denied under §325(d).

Third, the Petition is a follow-on petition that should not be instituted under §314(a). *See* §V. For example, Petitioners knew of the art from the PGR, and had Amgen's POPR from the PGR in hand before filing the instant Petition. Moreover, Petitioners failed to even address §314(a) and the *General Plastic* factors.

Fourth, Petitioners failed to provide an analysis of the proper construction of terms it was required to address, or to take an affirmative position as to the constructions they identify, instead summarily asserting that Petitioners "will assume" constructions from the PGR while asserting they would do so "[f]or purposes of this IPR only." Pet. 20-21; *see* §VI. In so doing, Petitioners also provided no citations to the record supporting the constructions they decided to "assume," apparently (and improperly) attempting to await some future litigation to reveal their real positions regarding the proper constructions of the claims.

Fifth, although indefiniteness was raised (and instituted) in the PGR, Petitioner fails to take any position as to the definiteness of claims 1, 4-6, 8-10, 12, and 14-16, let alone provide any analysis setting forth how or why the terms it seeks to invalidate should be understood by the Board. *See* §VI.

Sixth, Petitioners' own arguments and evidence confirm they cannot make a *prima facie* showing that, as a factual and legal matter for each asserted ground, there is a reasonable likelihood of proving at least one Challenged Claim unpatentable. *See, e.g.*, §314; §42.108(c); §VII. For instance:

• For Grounds 1 and 2, Petitioners failed to present any argument regarding dependent claims requiring thiol-pair ratio and thiol-pair buffer strength to be "calculated" (claims 8, 9, 14, 15, 23, 24, 25, and 30) under their identified construction, inexplicably relying on *additional references* in asserting the

limitations added by these dependent claims would have been *anticipated* by Vallejo or Ruddon;

- For Grounds 1 and 2, Petitioners failed to address how any of their references disclose maintaining the solubility of the solution even under Petitioners' identified construction;
- For Ground 1, Petitioners failed to address how Vallejo discloses maintaining the solubility of the preparation when that term is properly understood;
- For Ground 2, Petitioners failed to address that the process in Ruddon does not result in a properly refolded protein, but results, instead, in a subunit (hCG-β) that is competent to assemble with a second native (already folded) subunit (hCG-α) to form a biologically active protein (hCG);
- For Grounds 3 and 4, Petitioners' obviousness arguments are unclear, confusing and legally insufficient. Petitioners, *inter alia*, (a) fail to delineate clearly what grounds they assert, using an ambiguous "and/or" approach that could reflect as many as four *different* grounds for each of Grounds 4 and 5, (b) fail to clearly specify the references and sections of the references Petitioners rely on for each combination, let alone each given limitation, (c) fail to clearly identify the base reference and how or why it is allegedly

modified in the proposed combination, (d) fail to provide any meaningful explanation for reasonable expectation of success, (e) fail to provide any argument that any value was actually calculated for the claims Petitioners concede require calculation, and (f) fail to cite expert support for assertions about what a POSITA would have known, understood, and expected.

In view of post-*SAS* all-or-nothing institution, even if, *arguendo*, the Board were to unearth a Ground with merit buried within Petitioners' pile of arguments and combinations reflecting as many as five to ten different challenges per claim,⁴ the Board should exercise its discretion here and deny institution, which would not be an efficient use of the Board's limited time and resources given Petitioners' imprecise scattershot approach. *See, e.g., SAS Inst. Inc. v. Iancu*, 138 S. Ct. 1348, 1355-56 (2018); *Chevron Oronite Co. v. Infieum USA LP*, IPR2018-00923, Pap. 9, 9-11 (Nov. 7, 2018) (informative) (denying institution on all claims when Petitioners' arguments and proofs were deficient with respect to a subset of

⁴ As explained above, and in more detail below (*infra*, §VII.C.1), because of Petitioners' inappropriate use of an "and/or" approach in identifying secondary references for Grounds 3 and 4, each reflects as many as four different grounds per "Ground."

claims); *see also Deeper, UAB v. Vexilar, Inc.*, IPR2018-01310, Pap. 7, 41-43 (Jan. 24, 2019) (informative) (denying institution because instituting trial with respect to all twenty-three claims and on all four grounds based on evidence and arguments directed to only two claims and one ground would not be an efficient use of the Board's time and resources."); *SAS* Q&As, D3, at p. 8 (USPTO June 5, 2018), available at https://www.uspto.gov/sites/default/files/documents/ sas_qas_20180605.pdf (noting that, although "[t]he Board does not contemplate a fixed threshold for a sufficient number of challenges for which it will institute," it will "evaluate the challenges and determine whether, in the interests of efficient administration of the Office and integrity of the patent system...the entire petition should be denied under 35 U.S.C. § 314(a).").

For these reasons, the Petition should be denied.

II. The Challenged Claims Of The '287 Are Directed To A Novel Invention

The '287 is directed to a novel and efficient protein refolding method based on control of redox conditions with reductant and oxidant ("redox") reagents. EX1001, 2:62-3:5. The goal of protein refolding is to increase and maximize yield of properly folded proteins. EX1001, 1:32-38. Desired proteins are recombinantly expressed in non-mammalian culture systems (*e.g.*, bacteria). But, these expressed proteins misfold and precipitate in intracellular limited-solubility intracellular precipitates known as inclusion bodies. *Id.*, 1:25-30. These inclusion bodies are

formed because the bacterial host cell is unable to fold recombinant proteins properly. *Id.*, 1:29-31. 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. *Id.*, 1:43-50.

Prior to the '287, those skilled in the art needed to manipulate a large number of variables—through trial and error—to achieve high yields of properly refolded proteins. *Id.*, 8:47-65. The inventors of the '287 addressed the difficulty of identifying acceptable 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-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. *Id.*, 4:52-5:10, 6:50-55, 6:63-67.

III. The Petition Should Be Rejected Under 37 C.F.R. §42.102(a)(3) And §311(c)(2) Because A PGR Was Instituted On This Patent

§311(c)(2), entitled "Inter partes review" states:

"(c) Filing Deadline – A petition for inter partes review shall be filed after the later of either—

(1) the date that is 9 months after the grant of the patent; or
(2) *if a post-grant review is instituted* under chapter 32, the *date of the termination of such post-grant review*."

Petitioners contend they can avoid §311(c)(2) because they filed their Petition after the PGR was filed, but just five days before the PGR was instituted. PGR2019-00001, Pap. 13 (Apr. 19, 2019) ("PGR DI"). However, the Board rejected this position in *Intex Recreation Corp. v. Team Worldwide Corp.*, IPR2019-00245, Pap. 7, 10 (May 15, 2019). There, a Petitioner *simultaneously* filed a PGR and an IPR. *Id.* The PGR was instituted. *Id.* The Board denied institution of the IPR (although it was filed *earlier* relative to its related PGR than the IPR filed by Petitioners here), stating that "because *we are conducting* a post-grant review proceeding of the '979 patent, a Petition seeking *inter partes* review of the '979 patent may not be filed until that post-grant review proceeding is completed." *Id.* (citing §311(c)(2)). For the same reasons, this IPR should be denied.

In addition, the rule corresponding to §311(c), 37 C.F.R. §42.102, states:

(a) A Petition *inter partes* review of a patent must be filed after *the later of the following* dates, where applicable:

(1) If the patent is a patent described in section 3(n)(1) of the Leahy-Smith America Invents Act, the date that is nine months after the date of the grant of the patent;
(2) If the patent is a patent that is not described in section 3(n)(1) of the Leahy-Smith American Invents Act, the date of the grant of the patent; or

(3) If a post-grant review is instituted as set forth in subpart C of this part, the date of the termination of such post-grant review

Here, §42.102(a)(3) (amongst other provisions) is "applicable" because Petitioner filed its IPR Petition before the termination of the PGR. Therefore, this IPR may not be properly instituted.

Tellingly, while Petitioner was clearly aware of and cited §42.102 in asserting the ability to file an IPR any time for a pre-AIA patent (*i.e.*, under 41.102(a)(2)), Petitioner conspicuously decided not to address §42.102(a)(3).

IV. The Board Should Exercise Its Discretion And Deny Institution Under 35 U.S.C. §325(d)

The Board has discretion to deny institution here under §325(d), which provides "the Director may take into account whether, and reject the petition or request because, the same or substantially the same prior art *or* arguments previously were presented to the Office." §325(d); *see, e.g., Neology, Inc. v. Star Sys., Int'l Ltd.*, IPR2019-00367, Pap. 9, 12 (June 6, 2019) (denying institution under §325(d) where patent owner argued same or substantially the same art and arguments considered during prosecution); *Juniper Networks Inc. v. Finjan, Inc.*, IPR2019-00060, Pap. 7, 14-17 (Apr. 29, 2019) (denying institution under §314 and §325(d); "On balance, we find that the instant Petition presents one ground without merit and two grounds based primarily on [a reference] we are considering in the ongoing 391 case. Notwithstanding some differences in the prior art combined with [the reference], we are persuaded that instituting trial here would be an inefficient use of Board resources and would result in substantial overlap and duplication of issues, arguments, and evidence.") The Board has also repeatedly denied institution when—as here—the petition fails to explain why this discretion to deny should *not* be exercised. *See, e.g., Unified Patents, Inc. v. Berman,* IPR2016-01571, Pap. 10, 11-12 (Dec. 14, 2016) (informative).

Here, all of the alleged base references in the IPR were asserted or are substantially the same as the art asserted in the PGR. Further, Grounds 1 and 4 (anticipation by Vallejo and obviousness over Vallejo in view of secondary references) overlap with PGR Grounds 3, 5, and 6 (anticipation by Vallejo, as well as obviousness over Schlegl and Vallejo, and obviousness over Ruddon in view of Vallejo), and Grounds 2 and 3 (anticipation by Ruddon and obviousness over Ruddon⁵ in view of various secondary references) overlap with PGR Ground 6 (obviousness over Ruddon in view of Vallejo).

⁵ As discussed in Section VII.C.3, *infra*, Petitioners' analysis switches between relying on Ruddon and Clark 1998 as the base reference for Ground 3, but

In addition, many of the references and arguments Petitioners repeat here in the context of §§102 and 103 were considered by the original Examiner. Indeed, as is evident from the face of the '287, the Examiner had the full benefit of materials from earlier proceedings between PGR Petitioners Apotex Inc. and Apotex Corp. and Amgen—including an IPR regarding related U.S. Patent 8,952,138 ("138"), Apotex Inc. v. Amgen Inc., IPR2016-01542 ("the '138 IPR"), and a litigation between Amgen and Apotex Inc. and Apotex Corp. regarding the '138, Amgen Inc. v. Apotex Inc., Case No. 0:15-cv-61631 (S.D. Fla.). Those materials included Schlegl ('138 IPR EX1003), and Petitioners' alleged secondary reference, Clark 1998 ('138 IPR EX1041). It would be a waste of the Board's limited resources and harassing to Amgen to re-litigate these issues already considered and decided by the USPTO. See, e.g., Intel Corp. v. Godo Kaisha IP Bridge 1, IPR2018-00753, Pap. 11, 14-22 (Oct. 9, 2018) (denying institution where PGR Petition repackaged art and arguments considered during prosecution).

Despite the fact that numerous of Petitioners' references, including *all* alleged primary references, were previously considered, Petitioners never

Petitioners' identification of the Ground in its Ground 3 argument header identifies *Ruddon* as the base reference. Pet. 47.

substantively address §325(d). See Shenzhen Silver Star Intelligent Tech. Co. v. iRobot Corp., IPR2017-02050, Pap. 8, 11-12 (March 12, 2018) (declining to institute when Petitioner failed to address §325(d) and thus failed to explain why challenges that raise the same or substantially the same prior art and arguments previously presented to the Office should be reconsidered by the Board); Baker Hughes Oilfield Ops., Inc. v. Smith Int'l, Inc., IPR2016-01451, Pap. 8, 10 (Dec. 22, 2016) (noting "the failure of Petitioner to address the impact of...§ 325(d)" as a reason not to institute); Activision Blizzard, Inc. v. Acceleration Bay, LLC, IPR2016-00931, Pap. 13, 8-11 (June 23, 2016) (noting Petitioner failed to address §325(d) and declining to institute). Indeed, Petitioner admits the Petition raises some arguments previously presented to the Office (Pet. 3), but fails to provide any additional analysis identifying, e.g., what its purportedly "new" arguments are and explaining why they are not duplicative. Instituting trial on these same arguments, in the face of Petitioners' silence with respect to §325(d), would both waste the Board's limited resources and invite substantial abuse—encouraging petitioners to scour prior proceedings to mix and match previously-utilized material and use the PTO's prior decisions as a roadmap. See Cultec, Inc. v. Stormtech LLC, IPR2017-00777, Pap. 7, 7-13 (Aug. 22, 2017) (informative) (previously considered by examiner); Hospira, Inc. v. Genentech, Inc., IPR2017-00739, Pap. 16, 17-19 (July 27, 2017) (informative); NetApp Inc. v. Crossroads Sys. Inc., IPR2015-00777, Pap.

12, 7-8 (Sept. 3, 2015) (denying institution on grounds with combinations of prior art that overlap with those previously considered by Board); *Conopco, Inc. v. Procter & Gamble Co.*, IPR2014-00506, Pap. 17, 6-8 (July 7, 2014) (denying institution because the petitioner presented substantially the same arguments compared to the petition already considered by the Board notwithstanding that seven out of thirteen cited prior art references were new).

A. Petitioners' Ground 1 (Vallejo) Art Is the Same as That Already Considered by the Board

Petitioners' Ground 1 overlaps with PGR Ground 3—as both allege anticipation by Vallejo. *Compare* Pet. 23-38 *with* PGR Pet. 50-59. The PGR Ground (covering all claims challenged in Ground 1 here and more) has already been instituted. PGR DI, 26-28, 33. Further, the Petition articulates no reason for the Board to reconsider these issues. Institution should accordingly be denied. *See Taiwan Semiconductor Mfg. Co., v. Godo Kaisha IP Bridge 1*, IPR2017-00931, Pap. 9, 6 (Aug. 16, 2017) (denying institution where same art and "same two grounds" were presented in prior petition); *Shenzhen*, IPR2017-02050, Pap. 8, 11-12; *Baker Hughes*, IPR2016-01451, Pap. 8, 10; *Activision Blizzard*, IPR2016-00931, Pap. 13, 8-11 (June 23, 2016) (noting Petitioner failed to address §325(d) and declining to institute).

B. Petitioners' Ground 2 (Ruddon) Relies on Substantially the Same Art and Substantially the Same Arguments as Considered in the PGR

Petitioners' Ground 2 (alleging anticipation by Ruddon for claims 16, 19-21, 23-26, and 29-30) overlaps with PGR Ground 6 (alleging obviousness based on Ruddon in view of Vallejo, including for claims 16, 19, 23-26, and 29-30). *Compare* Pet. 38-47 *with* PGR Pet. 61-71.

While alleging obviousness, PGR Petitioners argued, *inter alia*, that Ruddon taught every element of both independent claims 16 and 26 asserted in Ground 2. PGR Pet. 62-71. But Petitioners here give no indication how their arguments rely on substantially different prior art teachings than the PGR. This is because there is nothing new in Petitioners' assertions, and institution here should be denied. See NetApp Inc., IPR2015-00777, Pap. 12, 7-8 (declining to institute when obviousness arguments were based on prior art combinations that overlapped with prior art combinations relied upon in a prior petition, even though the combinations in the prior petition were not composed of exactly the same prior art references as in the current petition); Conopco, IPR2014-00506, Pap. 17, 6-8; Edge Endo, LLC v. Scianamblo, IPR2018-01322, Pap. 15, 11-13 (Jan. 14, 2019) (declining to institute where Petitioner relied on same reference considered for anticipation and obviousness during prosecution); Fustibal LLC v. Bayer Healthcare LLC, IPR2016-01490, Pap. 9, 16 (Feb. 8, 2017) (declining to institute where Petitioner

relied on alleged anticipatory reference Examiner considered and found to be closest prior art during prosecution, but allowed the claims nonetheless); *see also Finjan*, IPR2019-00060, Pap. 7, 17 ("we find that the instant Petition presents one ground without merit and two grounds based primarily on [a reference] we are considering in the ongoing 391 case. Notwithstanding some differences in the prior art combined with [the reference], we are persuaded that instituting trial here would be an inefficient use of Board resources..."). Institution should be denied for these reasons.

C. Petitioners' Ground 3 (Ruddon in View of Clark 1998 in Light of Schafer "or" Gilbert) and Ground 4 (Vallejo in Combination With Ruddon and Clark 1998, in Light of Schafer "or" Gilbert) Rely on Substantially the Same Art and Arguments as the PGR

Petitioners' Ground 3 (alleging obviousness over Ruddon in view of Clark 1998 in light of Schafer and/or Gilbert for claims 1, 4-6, 8-10, 12, 14-16, 19-21, 23-26, and 29-30) and Ground 4 (alleging obviousness over Vallejo in combination with Ruddon and Clark 1998 in view of Schafer and/or Gilbert) overlap with PGR Ground 6 (alleging obviousness of Ruddon in view of Vallejo, including for claims 1, 4, 8-10, 12, 14-16, 19, 23-26, and 29-30) and, for IPR Ground 4, PGR Ground 3 (alleging anticipation by Vallejo). *Compare* Pet. 47-63 *with* PGR Pet. 50-59, 61-76. Although the base reference for Ground 3 cannot be discerned from Petitioners' analysis (*see infra*, §VII.C.3), Petitioners' Ground 3 header identifies Ruddon as the base reference (Pet. 47), which is the same as the base reference for PGR Ground 6. And, the alleged base reference for Ground 4 (Vallejo) is the same as the base reference for PGR Ground 3. The Petition should therefore be denied under §325(d). *See Finjan*, IPR2019-00060, Pap. 7, 17 ("the instant Petition presents one ground without merit and two grounds based primarily on [a reference] we are considering in the ongoing 391 case. Notwithstanding some differences in the prior art combined with [the reference], we are persuaded that instituting trial here would be an inefficient use of Board resources ..."); *Dr. Reddy's Labs. S.A. v. Indivior UK Ltd.*, IPR2019-00328, Pap. 19, 16, 21 (June 3, 2019) (declining to institute under §325(d) when the same base reference was considered by Examiner during prosecution, notwithstanding additional secondary reference).

Further, as explained above, both these Petitioners and the PGR Petitioners argue Ruddon and Vallejo each taught each of the claim elements. *Supra*, §§IV.A-B. In addition, just as PGR Petitioners argued *Vallejo* taught in the PGR, Petitioners argue here that *Clark 1998* taught a method of refolding proteins produced as insoluble inclusion bodies in *E. coli* using a "preparation" or "solution" to support refolding that contains amounts of oxidant and reductant related through thiol-pair buffer strengths and thiol-pair ratios and incubating to produce refolding efficiencies at or above the claimed ranges. *Compare* Pet. 56-59 *with* PGR Pet. 62-71. And just as PGR Petitioners argued for *Vallejo*, Petitioners here also argue *Clark 1998* taught the same equation as Equation 2 of the '287 to calculate thiol-pair buffer strength. *Compare* Pet. 53, 62 *with* PGR Pet. 49-50. Similarly, Petitioners here argue *Schafer* and *Gilbert* taught Equation 1 and Equation 2 of the '287 Patent for calculating thiol-pair ratio and buffer strength, respectively, which PGR Petitioners argue *Vallejo* disclosed. *Compare* Pet. 53, 62 *with* PGR Pet. 49-50. Indeed, Clark 1998, Schafer, and Gilbert are not asserted to disclose *anything* not already argued to be disclosed in Vallejo, as Vallejo was alleged to be anticipatory in the PGR (and even in the present IPR).⁶ PGR Pet. 38-50. Institution should also be denied for these reasons.

⁶ And, with respect to Claims 5, 6, 20 and 21, Clark 1998 is argued to disclose the same limitations as the Hevehan reference in the PGR. *Compare* Pet. 61 *with* PGR Pet. 76-79; *Neology*, IPR2019-00367, Pap. 9, 12 (finding petition's reference cumulative of another reference considered by Examiner during prosecution where Examiner relied on the other reference for substantially the same teachings). This is not surprising given the titles of Clark 1998 ("Oxidative Renaturation of Hen Egg-White Lysozyme. Folding vs Aggregation") and Hevehan ("Oxidative Renaturation of Lysozyme at High Concentrations"), and the fact that Hevehan and

D. Petitioners' §§102 And 103 Prior Art And Arguments Are Either Identical To Or Substantially The Same Art And Arguments As Already Considered And Rejected By The Examiner

One of Petitioners' two alleged primary references (Vallejo) and Petitioners' purported main secondary reference (Clark 1998) are substantially the same as the art already considered by the Examiner.⁷ And to the extent the other primary reference (Ruddon) is argued to be different from Vallejo or Clark 1998 (*cf., e.g.*, Pet. 54-55, 62-63 (Petitioners arguing purported *similarities* between Ruddon, Vallejo, Clark 1998 to motivate their combination)), its shortcomings are detailed *infra* (§VII.B).

Vallejo (EX1031), which is the basis for Grounds 1 and 4 in the present Petition, is similar to another publication by the same author (cited by Petitioners here as EX1030), which *was* considered and expressly acknowledged by the Examiner during the '287's prosecution as part of an Information Disclosure

Clark worked in the *same laboratory* and are *co-authors* of both references. *Compare* EX1007, 6 *with* PGR EX1024, 1.

⁷ As discussed in Section VII.C.3, *supra*, Petitioners do not clearly identify their base reference in arguing Ground 3, but list Ruddon as the base reference in the argument header for Ground 3. Pet. 47.

Statement (IDS) by Amgen. EX2001, 55. For example, the Vallejo reference in the IDS (EX1030) is similar to the Vallejo reference (EX1031) in discussing methods of refolding proteins produced by bacterial cells using batch or pulse addition. Compare EX1030, 4 (discussing "direct dilution" refolding methods where protein is diluted into a refolding buffer directly and refolding methods where the protein is added into the refolding buffer "in pulses or continuously"; citing to reference [40]) with EX1031, [001], [0010]-[0012] (discussing "renaturation of the solubilized cystine-knot protein in batch or by pulse addition of said solubilized cystine-knot protein to a refolding buffer..."). Indeed, citation no. [40], in Vallejo EX1030 is a scientific publication derived from Vallejo EX1031 and discloses the same work by the same authors. The Examiner considered the IDS that cited Vallejo EX1030, and selected several other references from the IDS including Schlegl and Hevehan to explicitly analyze as obviousness references. EX2001, 125 (discussing Schlegl (U.S. Pub. 2007/02348860) and Hevehan).

Clark 1998, as argued by Petitioners, is also "substantially the same as" the Hevehan references that were explicitly and substantively discussed during the '287's prosecution. Clark 1998–argued to disclose the same limitations as the Hevehan reference in prosecution–is thus cumulative. *Compare* EX1007, 8 (reporting the renaturation of denatured lysozyme by a "rapid 8-fold or 16-fold

dilution . . . into renaturation buffer consisting of TE buffer with various amounts of GSSG" at a 1 mg/mL protein concentration) *with* PGR EX1024, 2-3 (reporting renaturation of denatured lysozyme "by a rapid 8-fold or 16-fold dilution . . . into renaturation buffer to yield a final concentration of 1-5 mg/mL"). This is not surprising given the references' titles (*see* n.6, *supra*) which indicate both references disclose methods for the oxidative refolding of the model protein eggwhite lysozyme (which was not made in a non-mammalian expression system as required by the claims). Moreover, Hevehan and Clark worked in the *same laboratory* and are *co-authors* on both publications. *Compare* EX1007, 6 *with* PGR EX1024, 1.

Petitioners did not explain why their arguments are new, nor why the Board should re-adjudicate them. *See, e.g., Hengdian Grp. DMEGC Magnetics Co., v. Hitachi Metals, Ltd.*, IPR2017-01313, Pap. 7, 15-16 (Nov. 6, 2017) (denying institution under §325(d) and noting Petitioner failed to provide "any arguments distinguishing the Examiner's prior consideration of [the prior art], or any compelling reason why [the Board] should re-evaluate substantially the same prior art"); *Sandoz, Inc. v. Genentech, Inc.*, IPR2017-02036, Pap. 13, 6 (Mar. 4, 2018) (denying institution under §325(d); "to the extent that any...differences exist, Petitioner has not explained or even alleged that the prior art and the arguments presented in the Petition are not *substantially the same* as those considered and

abandoned by the Examiner during prosecution, and as those presented and considered previously by the Board." (emphasis original)); *West Pharm. Servs., Inc. v. Sanofi-Aventis Deutschland GmbH*, IPR2018-01162, Pap. 7, 11-13 (Dec. 6, 2018) (denying institution even when Petitioner set forth different arguments and additional evidence not raised by, or available to, original Examiner where Examiner "rejected at least one claim based on the same art in the same combination under the same statutory basis" (emphasis in original)).

Because, as discussed above, substantially all of the references and arguments urged in the Petition are the same or substantially the same as references and/or arguments previously considered by, and overcome before, the Office during the '287's prosecution, the Board should exercise its discretion to deny institution under §325(d). Even if, *arguendo*, the Board were to determine that there is some subset of Petitioners' arguments that is new and merits review (and Amgen respectfully submits there is not), the significant, wasteful burden that would be imposed on both the Board and Amgen in relitigating *every one of these previously-considered arguments* as a result of the binary all-or-nothing institution approach that applies post-*SAS* further counsels strongly in favor of denying institution under §325(d). Further, these issues are currently being litigated before two United States District Courts in pending cases where the '287 is at issue—

Amgen Inc. v. Apotex Inc., No. 0:18-cv-61828 (S.D. Fla.) and Amgen Inc. v. Adello Biologics, LLC, No. 2:18-cv-03347 (D.N.J.).

V. The Board Should Exercise Its Discretion And Deny Institution Under 35 U.S.C. §314(a)

Institution of *inter partes* review is discretionary. *See* 35 U.S.C. § 314(a); 37 C.F.R. § 42.108(a) ("the Board *may* authorize the review to proceed"); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2140 (2016) (the "decision to deny a petition is a matter committed to the [PTO's] discretion."); *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1367 (Fed. Cir. 2016) ("the PTO is permitted, but never compelled, to institute an [*inter partes* review] proceeding").

Petitioner has failed to address §314(a) and the non-exhaustive list of factors articulated by the Board to be considered in evaluating whether to exercise its §314(a) discretion to deny a petition challenging a patent previously considered by the Board. *Gen. Plastic Indus. Co. v. Canon Kabushiki Kaisha*, IPR2016-01357, Pap. 19 (Sept. 6, 2017). Petitioners were aware of §314(a), but asserted only (and incorrectly) that because they are a first-time petitioner, institution should not be denied.

A. General Plastic Factors Support Denial of Institution

1. Factor 1: Whether Petitioners Are the Same

While not formally a party to the earlier '287 PGR Petition, Petitioner—well aware of the PGR and acting in a conscious tag-team with the PGR Petitioners
(including by attending the July 10 PGR deposition) now puts before the Board still more permutations of previously-considered art and arguments, as well as some of the very same grounds already pending in the PGR. See infra §IV. As in Samsung Elecs. Co. v. ELM 3DS Innovations, LLC, IPR2017-01305, Pap. 11, 19 (Oct. 17, 2017), the Petition here has a "high degree of similarity" with the previously-filed PGR Petition, which included Vallejo (EX1031, PGR EX1014) and Ruddon (EX1025, PGR EX1040) in its grounds asserting anticipation and/or obviousness, as well as Clark 1998 (EX1042, PGR EX1051) as a background reference. Indeed, as discussed above, substantially the same art and/or arguments as set forth in this IPR Petition were previously presented to the Board. Clearly, Fresenius recycled the PGR in preparing its arguments in its Petition and expert report here, even copying some of the arguments verbatim (compare, e.g., Pet. 25) with PGR Pet. 40; Pet. 27-29 with PGR Pet. 43-45; Pet. 31-32 with PGR Pet. 45-46; Pet. 32-33 with PGR Pet. 47-48; EX1002 ¶¶89, 103, 104 with PGR EX1002 ¶118, 137, 138) and using the same organization and formatting (*compare, e.g.*, Pet. 34-40 with PGR 38-45 (using same tables under subheaders); compare, e.g., EX1002 18, 20, 23, 25, 26 with PGR EX1002 15, 17, 18, 21, 22, respectively (presenting same subheaders and content)).

Although Petitioners have not previously filed an IPR against this patent, this is but one of many factors considered in whether the Board exercises its

discretion to deny institution, and Petitioners were clearly tracking the PGR, timing the filing of their petition just before institution. See, e.g., Valve Corp. v. Elec. Scripting Prods., Inc., IPR2019-00062, Pap. 11 (Apr. 2, 2019) (precedential) (denying institution and applying *General Plastic* factors to first-time Petitioner); Abiomed Inc. v. Maguet Cardiovascular, LLC, IPR2017-02134, Pap. 7, 9-10 (April 16, 2018) (finding this factor did not favor institution when Petition challenged claims of scope similar in an earlier IPR). And, as noted, Petitioners' counsel of record here attended the July 10, 2019 deposition of PGR Petitioners' expert, appearing alongside PGR Petitioners' counsel who defended and redirected that witness. Valve Corp., IPR2019-00062, Pap. 11, 2 ("when different petitioners challenge the same patent, we consider any relationship between those petitioners when weighing the General Plastic factors"). Petitioners do not address the relevant case law, instead resting on the false blanket assertion that §314(a) does not apply to a first-time petitioner. Pet. 3.

2. Factor 2: Knowledge of Prior Art

Petitioners fail to address their knowledge of the prior art in the Petition. However, Petitioners clearly (1) knew of its two base references (Vallejo and Ruddon) because they were relied on in the PGR (which Petitioners acknowledge they were aware of (Pet. 3 n.2, 4)) and (2) knew of Clark 1998 because it was cited as background art in the PGR. *Supra* §IV. In addition, the IPR for the *parent* of the '287 patent, IPR2016-01542 (challenging U.S. Patent No. 8,952,138 and discussed by Petitioner at Pet. 18-19), was filed on August 25, 2016, and a final written decision issued February 15, 2018. Vallejo was filed as Exhibit 1014 with that Petition and Clark 1998 was filed as Exhibit 1041. Petitioners also do not deny knowing of the remaining references, Schafer and Gilbert.

As in *Valve Corp. (supra)* and *Juniper Networks, Inc. v. Parity Networks, LLC*, IPR2018-01642, this factor weighs in favor of denying institution because Petitioners knew, or should have known, of the references cited in the PGR and '138 IPR filed by other petitioners for months before filing their Petition here. IPR2019-00062, Pap. 11, 11; IPR2018-01642, Pap. 11, 8 (April 10, 2019). *See also Abiomed*, IPR2017-02134, Pap. 7, 10.

3. Factor 3: Availability of Information from Prior Proceedings

As in *Samsung* and *NetApp*, this factor weighs strongly in favor of denying institution. IPR2017-01305, Pap. 11, 20-21; IPR2017-01660, Pap. 17, 10-11; *see also Valve Corp.*, IPR2019-00062, Pap. 11, 12-13; *Nichia Corp. v. Document Sec. Sys.*, *Inc.*, IPR2019-00398, Pap. 10, 16-17 (April 15, 2019).

Petitioners had the benefit of the prior PGR Petition as well as Amgen's POPR, unfairly providing Petitioners with Amgen's analysis concerning references Petitioners rely on here. *See* PGR POPR 24-27, 54-74 (showing Amgen's analysis of Vallejo, Ruddon, and Hevehan, which as discussed *supra* in Section IV.D is substantially the same as Clark 1998). The fact that Petitioners here rely on substantially the same art and/or arguments (*see supra*, §§IV.A-C) "evinces benefit Petitioner [] derived from those prior proceedings." *Samsung*, IPR2017-01305, Pap. 11, 20. As the Board explained in *Samsung*, "[t]he *availability* of the Patent Owner's Response and Patent Owner's expert testimony from other proceedings also weighs strongly in favor of exercising our discretion, as does Petitioners' *use* of such information in its Petition." *Id.* at 21.

Finally, Vallejo and Clark 1998 were also discussed as purported background art in related proceedings about the '138 patent. *Supra* §IV. And Petitioners had the unfair advantage of the Board's, Amgen's, and various expert's lengthy statements in the related '138 proceedings about Hevehan, which is substantially the same as Petitioners' Clark 1998 reference (*see* §IV.D, *supra*). *See, e.g., Apotex Inc. v. Amgen Inc.*, IPR2016-01542, Pap. 60, 13-14, 24, 27-45 (Feb. 15, 2018) (discussing Hevehan and the arguments and opinions of Petitioner, Patent Owner, and experts regarding Hevehan); '138 POR, 22-49, 60-61 (Patent Owner discussing Hevehan); '138 IPR EX1056, 10-12, 16-37 (Petitioners' expert discussing Hevehan); '138 IPR EX2020, 8-61 (Patent Owner's expert discussing Hevehan); *see Samsung*, IPR2017-01305, Pap. 11, 20-21 (noting new Petitioner gained benefit from patent owner's response and expert testimony in related proceedings and, "if we were to institute a review here, Petitioner would be able to use the final written decisions" from those proceedings, as well, to "improve its position"); *Am. Honda Motor Co. v. Intellectual Ventures II LLC*, IPR2018-00347, Pap. 10, 15 (June 27, 2018) (finding factor weighed against institution when Petitioner had the benefit of seeing patent owner's initial position and the Board's institution decision in prior IPR); *Instrumentation Lab. Co. v. Hemosonics, LLC*, IPR2018-00264, Pap. 8, 10-12 (May 10, 2018) (finding factor weighed against institution when Petitioners' second petition address deficiencies from the first petition). Petitioners clearly knew about the '138 proceeding and recognize the similarity of the claims at issue here and in the '138 proceedings (Pet. 18-19), but nevertheless failed to provide any §314(a) analysis about the '138 proceeding.

Petitioners have clearly taken advantage of these prior Petitions and at least one institution decision to "improve their position" before filing this instant Petition. This factor favors denial of institution.

4. Factor 4: Timing of Instant Petition

The PGR Petition was filed October 1, 2018, and the POPR in the PGR was filed January 23, 2019. PGR2019-00001, Paps. 3 ("PGR Pet."), 8 ("PGR POPR"). The present Petition, however, was not filed until almost three months later, on April 14, 2019. Further, as discussed above, the IPR Petition for the '138 patent was filed in 2016, and the final written decision issued in 2018. *Supra* §IV.

Petitioners provide no explanation for their delay in filing the present Petition. Indeed, based on Petitioners' §311(c) argument (Pet. 1-3), it appears Petitioners were actively tracking the PGR and waiting until just before the PGR institution decision to file.

This factor favors denial as it did in *Valve Corp.*, IPR2019-00062, Pap. 11, 14, and *Parity Networks*, IPR2018-01642, Pap. 11, 9.

5. Factor 5: Petitioners' Explanation

Despite filing the present Petition after *Valve Corp.* was designated precedential, Petitioners failed to provide a substantive analysis of §314(a). *See* Pet. 3. Indeed, they provided no explanation for their failure to file their Petition sooner. Thus, even more than in *Samsung*, where Petitioner explained its delay but institution was still denied, this factor weighs heavily in favor of denying institution. IPR2017-01305, Pap. 11, 22-23; *see Valve Corp.*, IPR2019-00062, Pap. 11, 13-14 (finding this factor weighed against institution despite Petitioners' explanation for delay); *Parity Networks*, IPR2018-01642, Pap. 11, 10 (finding this factor weighed against institution where petitioner offered merely "generic justification" for delay).

6. Factors 6 and 7: Board Considerations of Finite Resources/One-Year Time Line

These related factors consider the "finite resources of the Board" and the timing requirement for the Board's final determination. As detailed *supra*, §§IV, both the Examiner and the Board have already expended significant effort to consider (and reject) similar art and arguments. Asking the Board to do so again does not conserve the Board's finite resources, and Petitioners offer no justification for requesting this. This is particularly egregious given the multiplicity of five to ten challenges per claim packed into the present Petition.

As in *NetApp*, Petitioners had ample opportunity to file their Petition sooner, but did not. If they wanted a chance (as appears from the substance of the PGR Petition) to repeat the arguments made by PGR Petitioners, they could have filed a petition earlier and sought to coordinate the proceedings—instead, Petitioners chose to wait. Thus, while factor seven (concerning the one-year timeline) may not weigh significantly for or against institution, factor six weighs in favor of denying institution.

7. Additional Factors Warrant Denial

Several additional factors warrant denial under §314(a). While Petitioners recycle previous prior art, they provide "no explanation why [the Board] should substantively entertain yet another set of grounds that also rely on one of those

references as teaching or suggesting" the claims. *Alcatel-Lucent USA Inc. v. Oyster Optics, LLC*, IPR2018-00257, Pap. 14, 25 (June 4, 2018). As in *Alcatel-Lucent*, Petitioners fail to explain why these grounds are not cumulative. *Id.* "This lack of explanation also favors denying the Petition." *Id.*

Two other factors are sometimes also considered when a different petitioner files a subsequent petition: whether there is potential prejudice to the subsequent petitioner if institution is denied and the pending instituted proceedings involving the first petitioner are terminated, and whether multiple petitions filed against the same patent are a direct result of patent owner's litigation activity. *Am. Honda Motor Co. v. Intellectual Ventures II LLC*, IPR2018-00348, Pap. 10 (June 27, 2018). Here, Petitioners are not prejudiced because they have not been sued, and thus could seek to later file a Petition in the event the PGR is terminated. And, the filing of the present petition is not the direct result of patent owner's litigation activity, as the '287 patent is not currently being litigated against Petitioners. Thus, these factors favor the Board exercising its discretion to deny institution.

* * *

For all these reasons, Petitioners' improper gamesmanship in trying to use the PGR and '138 IPR to improve its position here should not be rewarded, and their Petition should be denied under §314(a).

VI. Petitioners Failed To Provide Sufficient Claim Construction Analysis Of Key Claim Terms⁸

Petitioners here failed to fulfill their obligation under the Rules to explain "[h]ow the challenged claim is to be construed" and, when construed properly, "[h]ow the construed claim is unpatentable." §42.104(b)(3)-(4). Petitioners were *required* to construe at least "preparation," "is calculated," and "maintains solubility" as necessary to the arguments they have advanced. But Petitioners did not take an affirmative position as to the proper constructions, explain why the constructions they present are correct, or even cite *any evidence whatsoever*. Instead, without any analysis, Petitioners simply recite constructions they do not even concede are correct. Petitioners apparently hope to preserve their ability to argue entirely different constructions in other proceedings, but the claim construction standard in this IPR is the *same* as the standard applicable in district

⁸ With respect to claim language directed to the percentage of properly refolded proteins, Petitioners erroneously claimed Amgen "asserted that this claim language was non-limiting" in its PGR POPR. Pet. 18. That is not the case. Rather, Amgen argued that PGR Petitioners *failed to address* whether this claim language is limiting. PGR2019-00001, Pap. 8, 33-37. Petitioners here "*assume* that the term is limiting." Pet. 31.

court, 37 C.F.R. § 42.100(b); Expedia, Inc. v. Int'l Bus. Mach. Corp., IPR2019-00404, Pap. 8, 7 n.3 (June 5, 2019); see also Phillips v. AWH Corp., 415 F.3d 1303 (Fed. Cir. 2005) (en banc), and Petitioners have failed to satisfy their explicit obligation to tell the Board what Petitioners assert the claims mean. The Petition's grounds should all be rejected on this basis. See, e.g., Hologic, Inc. v. Enzo Life Scis. Inc., IPR2018-00019, Pap. 21, 6 (Nov. 28, 2018) ("Petitioner does not satisfy Rule 42.104(b)(3) when, in a proceeding applying the *Phillips* claim-construction standard, it 'expressly disagree[s] with its proffered construction.""); SharkNinja Operating LLC v. Flexible Techs., Inc., IPR2018-00903, Pap. 8, 6-10, 23 (Oct. 17, 2018) ("Petitioner has not met its burden to provide a construction of the claims at issue, as required by 37 C.F.R. § 42.104(b)(3) and (4) and how to apply the prior art to the claim. . . . The Petition indicates Petitioners' own understanding that the meaning of the claim was unclear from the specification, and it was therefore incumbent on Petitioner to engage in further analysis or to propose a construction in order to satisfy the rules").

"Wherein The Thiol-Pair Buffer Strength Maintains The Solubility Of The Preparation" (Claims 1, 4-6, 8-10, 12, and 14-15) and "Wherein The Thiol-Pair Buffer Strength Maintains The Solubility Of The Solution" (Claims 16,

19-21, 23-26, and 29-30).⁹ Petitioners state that "the specification and file history *do not provide clear guidance as to the meanings of the terms*." This concession "indicates Petitioner[s'] own understanding that the meaning of the claim was unclear from the specification, and it was therefore incumbent on Petitioner to engage in further analysis" for both of these phrases. *Sharkninja*, IPR2018-00903, Pap. 8, 9, 23 (denying institution, noting "Petitioner has failed to satisfy its burden under 37 C.F.R. § 42.104(b).").

PGR Petitioners contended that "wherein the thiol-pair buffer strength maintains the solubility of the preparation" was *indefinite*. PGR Pet. 79-81; *see also* PGR DI, 26. And, in litigation, Adello has publicly asserted that "wherein the thiol-pair buffer strength maintains the solubility of the preparation" is indefinite. EX2003. Petitioners' failure here to explain what these claims mean and why, so that review may proceed on this basis, is fatal to their Petition.

⁹ Particularly in view of Petitioners' failure to present claim construction analysis, Amgen's POPR-stage analysis reflects disputes relevant to the arguments it presents about Petitioners' failure of proof and the Board's upcoming institution decision. If instituted, Amgen may present in more detail additional claim construction analysis.

Petitioners' statement they "will assume the terms mean 'maintains the solubility of the protein that properly refolds during incubation" (Pet. 21) does not save the Petition. Petitioners' statement is not accompanied—as required—by any affirmative statement that such construction is correct, any analysis of how to construe the term, or any citations to intrinsic or extrinsic evidence. Petitioners certainly do not grapple with the question of indefiniteness. Hologic, Inc. v. Enzo Life Scis. Inc., IPR2018-00019, Pap. 21, 6 (Nov. 21, 2018) (denying institution when Petitioner applied construction with which it disagrees); CareFusion Corp. v. Baxter Int'l, Inc., IPR2016-01456, Pap. 9, 6-7 (Feb. 6, 2017) (denying institution when petitioner "failed to indicate that it agrees with, proposes, or adopts the constructions" that it applies); Robert Bosch LLC v. Orbital Australia PTY Ltd., IPR2015-01249, Pap. 9, 6 (Dec. 21, 2015) (denying institution when petition "include[d] no explanation for the proposed construction" and "no analysis of the claim language, the written description, or the prosecution history"). Apparently hoping to preserve their ability to argue indefiniteness later, Petitioners omit the required analysis. Pet. 21. This behavior should not be encouraged by institution, and, for each of these reasons above, institution should be denied.

To the extent Petitioners' §§102 and 103 arguments are considered—and they should not be—"wherein the thiol-pair buffer strength maintains the solubility of the preparation" should be construed with reference to the solutes in

the preparation, not with respect to solubility of proteins. According to the claims, those 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. Indeed, the claims' plain language (claims 1 and 10, reciting "the preparation") requires that the solutes in the *preparation*, i.e., those solutes that effectuate protein refolding, remain soluble.¹⁰ *See Phillips*, 415 F.3d at 1312-13. The preparation contains no proteins. Therefore, construing "the preparation" in relation to solubility of proteins makes no sense and would be contrary to the plain language of the claims. In fact, the preparation claims make clear that maintenance of solubility recited in theoseclaims refers to the effectuators of protein refolding rather than protein itself.

Petitioners' identified construction is also unsupported by the '287 specification. First, it is clear from the specification that the "refold buffer" is the "preparation." For instance, just like the "preparation" in the claims, the

¹⁰ In the PGR, both PGR Petitioners and their expert (whose deposition was attended by counsel for Petitioners here) concede that the very construction Petitioners propose here is inconsistent with the plain meaning of the limitation. PGR Pet. 21; PGR EX1002, ¶66-67.

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. Petitioners' expert took a consistent position, for example, in describing *contacting the refold buffer with a protein*, which reflects an understanding that the refold buffer/preparation does not itself include protein. EX1002, ¶96.

Independent claims 16 and 26 recite the same solutes that effectuate protein refolding as the preparation in independent claims 1 and 10, namely (1) at least one of a denaturant, an aggregation suppressor, and a protein stabilizer; (2) an oxidant; and (3) a reductant. As such, the construction of "wherein the thiol-pair buffer strength maintains the solubility of the solution" likewise should address the solubility of those solutes recited in the claims that effectuate protein refolding. At any given buffer strength within the scope of the claims, some protein-but not necessarily all-is acted upon by the chemical components that effectuate refolding for the given protein and that refolded protein is soluble. Petitioners' proposed construction (requiring the solubility of the proteins and only the proteins to be maintained) ignores these refolding solutes/components. In addition to being inconsistent with the plain language of the claims, Petitioners' identified construction is also inconsistent with the specification, which refers to refolding components as being in solution. See, e.g., EX1001, 13:12-15, 8:56-65.

VII. The Petition Failed To Establish Anticipation Or Obviousness Of Any Challenged Claim

Because the Petition failed to establish that any of the prior art references disclose—explicitly or inherently—each and every limitation of the Challenged Claims, alone or in combination, Petitioners have failed to meet their burden for institution. *See, e.g., Endo Pharm. Inc. v. Depomed, Inc.*, IPR2014-00653, Pap. 12, 9-11, 13-14 (Sept. 29, 2014) (prior art reference lacking one or more elements cannot anticipate that claim or any dependent claim). Indeed, in view of all-ornothing institution post-*SAS* and the many gaps in Petitioners' proof, even if the Board were to find, buried within Petitioners' pile of arguments and combinations, an asserted Ground with merit (there isn't), the burden of a full trial on all the others would weigh heavily in favor of non-institution, and the Board should exercise its discretion here to deny institution. *Chevron Oronite Co.*, IPR2018-00923, Pap. 9, 9-11; *Deeper, UAB*, IPR2018-01310, Pap. 7, 41-43 (informative).

- A. Petitioners Failed To Show That Claims 1, 4, 8-10, 12, 14-16, 19, 23-26, and 20-30 Are Anticipated By Vallejo (Ground 1)
 - 1. Petitioners Failed To Show Vallejo Teaches The Limitation "Thiol-Pair Buffer Strength To Maintain The Solubility Of The Preparation/Solution"
 - (a) Petitioners Failed To Show Vallejo Teaches The Limitation "Thiol-Pair Buffer Strength To Maintain The Solubility Of The Solution (Claims 16, 19-21, 23-26, and 29-30)

Petitioners did not meet their burden to establish Vallejo teaches the limitation "maintains the solubility of the solution" as required in independent claims 16 and 26. Pet. 30. Petitioners presented no analysis of the correct construction of this phrase, and presented no analysis of Vallejo under any correct construction. Thus, Petitioners did not meet their burden.

Even assuming, *arguendo*, that Petitioners' construction of "wherein the thiol-pair buffer strength maintains the solubility of the preparation" is correct, and the focus of the claim is the solubility of the protein and only the protein, Petitioners simply argued that the "result" of protein refolding in Vallejo "*would not have occurred <u>unless</u>* the redox components maintained the solubility of the protein that properly refolded." *Id.* This apparent *inherency* argument (though never identified as inherency in the Petition) is not sufficiently supported, as Petitioners provided no explanation as to why protein refolding necessarily (and thus inherently) requires that the solubility of the protein be "maintained." *Crown*

Operations Int'l, Ltd. v. Solutia Inc., 289 F.3d 1367, 1377 (Fed. Cir. 2002) (citing *Cont'l Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268–69 (Fed. Cir. 1991)); *Fluidmaster, Inc. v. Danco, Inc.*, IPR2017-00770, Pap. 13, 20-21 (July 28, 2017) (denying institution because Petitioners' contention that the prior art "would necessitate" the claimed limitation, without providing additional argument or identifying persuasive evidence, was not enough). Petitioners also failed to square their assertion that the refolding *would not be "possible" without* the redox components with the fact that Schlegl, asserted in the PGR cited by Petitioners,

teaches that an alpha-LA protein *is* capable of refolding *without* redox

chemicals. *See* PGR Pet., 51 ("Schlegl discloses that redox chemicals are optional for refolding of α-LA."); *see also* PGR POPR 51. Petitioners' expert failed to present evidence sufficient to support this assertion. *See* EX1002, ¶135; *Lifewave, Inc. v. Edward Blendermann*, IPR2016-00571, Pap. 7, 8-9 (Sep. 7, 2016) (denying institution where petitioner's expert provides conclusory assertion of inherency that mirrors language in petition and is not supported by objective evidence); *TCL Corp. v. Telefonaktiebolaget LM Ericsson*, IPR2015-01584, Pap. 74, 47 (Jan. 24, 2017) (finding conclusory assertion insufficient to demonstrate express or inherent disclosure); *Roland Corp. v. inMusic Brands, Inc.* IPR2018-00335, Pap. 14, 26 (July 2, 2018) (denying institution because "Petitioner proffers no evidence or

argument to support its assertion that [the claimed] feature is inherent aside from the conclusory assertion that it is").

(b) Petitioners Failed To Show Vallejo Teaches The Limitation "Thiol-Pair Buffer Strength To Maintain The Solubility Of The Preparation" (Claims 1, 4-6, 8-10, 12, and 14-15)

Petitioners presented no argument in the Petition as to whether Vallejo teaches "thiol-pair buffer strength to maintain the solubility of the preparation" under the correct construction of this phrase. *See supra*, §VI. Petitioners were aware that the construction they identified was inconsistent with the plain claim language. PGR Pet. 21; PGR POPR 77-79.¹¹

¹¹ Petitioners' only acknowledgement of a construction requiring something other than the solubility of the proteins be maintained appears in a conclusory footnote in Petitioners' expert declaration. But, this assertion 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). And in any case, Petitioners' expert's assertion is itself unexplained and conclusory, and therefore cannot meet Petitioners' burden. *See, e.g., TCL Corp.*, IPR2015-01584, Pap. 74, 47 (conclusory assertion insufficient to demonstrate express or inherent disclosure); *Roland Corp.*, IPR2018-00335, Pap. 14, 26 (denying institution To the extent the Board adopts Petitioners' incorrect and merely assumed (but not explained or supported) construction (Pet. 21), Petitioners' proof is insufficient for the same reasons discussed above (§VII.A.1(a)).

2. Petitioners Improperly Mix And Match Different Embodiments

Petitioners do not address how Vallejo discloses every element of the asserted claims *arranged as in the claim*, as required for anticipation. *SynQor, Inc. v. Artesyn Techs., Inc.*, 709 F.3d 1365, 1375 (Fed. Cir. 2013).¹² Vallejo describes different, separate "Examples." And Petitioner, in analyzing Vallejo, relies on bits and pieces pulled from different examples without acknowledging or explaining why it picks and chooses across multiple examples of Vallejo for each claim. *See, e.g.*, Pet. 24 ("Examples 2 and 6 of Vallejo disclose refolding rhBMP-2 "), 25-26 (relying on and quoting Example 8, [0054] before jumping back to Examples 2 and 6), 28-29 (relying on Example 8 [0055] before jumping back to Examples 2

because "Petitioner proffers no evidence or argument to support its assertion that [the claimed] feature is inherent aside from the conclusory assertion that it is"). ¹²See also Microsoft Corp. v. Biscotti, Inc., 878 F.3d 1052, 1069 (Fed. Cir. 2017) ("anticipation is not proven by 'multiple, distinct teachings that the artisan might somehow combine to achieve the claimed invention."").

and 6); EX1002, ¶119 ("Vallejo discloses several Examples of protein refolding, including Examples 2 (refolding at different pH and redox conditions) and Example 6 ("pulse refolding" in which the protein concentration is increased over time)."), ¶¶122, 130-134, 136 (relying on Example 8 [0055] before jumping back to Examples 2 and 6), ¶¶125-129 (relying on Example 8 [0055] before jumping back to Example 6), ¶137 (relying on Description [0012] before jumping to Examples 3 [0046] and 4 [0047]). Petitioners have therefore failed to establish anticipation by Vallejo.

The Claimed Refold Mixture. Petitioners' mixing and matching across embodiments is particularly problematic in connection with Petitioners' analysis of "the claimed refold mixture" limitations (Pet. 24-25). There, Petitioners rely on Vallejo's "standard renaturation buffer" in Example 8 in arguing that "Examples 2 and 6 of Vallejo ... us[e] the same 'standard renaturation buffer." Pet. 26. But Petitioners ignore the fact that Example 4 identifies a *different* "standard renaturation buffer." *Compare* EX1031, ¶55 *with id.*, ¶47. Petitioners do not explain why it is that the renaturation buffer of Example 8 would be used in Examples 2 and 6, and not a different renaturation buffer, for example, the one in Example 4. Indeed, the Example 4 buffer undermines Petitioners' assumption that there is one single "standard renaturation buffer" used across all of Vallejo's different examples.

3. Petitioners Failed To Present Any Argument Applying Their Assumed Construction Of "Is Calculated" And Cited To Art Other Than Vallejo In Arguing "Anticipation"

With respect to claims 8, 9, 14, 15, 23-25, and 30, Petitioners failed to present *any* argument that Vallejo teaches the "is calculated" limitation under of its proffered construction of the term. Pet. 33-34. Petitioners assert, without analysis, that Vallejo "inherently discloses examples of refolding using thiol-pair ratios and thiol-pair buffer strengths that fall within the ranges.... Adding Equations 1 and 2...does not render them patentable." Pet. 33. But in construing these claims, Petitioners stated they would construe "is calculated" in these claims to require an "active step of determining" and that the ratio and buffer strength "actually be calculated." Pet. 20. Petitioners further stated they would construe "is calculated" to mean "is determined using an equation as part of practicing the method, rather than using the equation in hindsight." Pet. 20-21. Petitioners provide no analysis, however, to show how these claims are purportedly anticipated under this construction of "is calculated."

Further, despite asserting *anticipation* by Vallejo, Petitioners actually argue something very different: "[t]he equations would have been part of the . . . knowledge of a POSA in 2009 and *their use by a POSA* to calculate thiol-pair ratios and buffer strengths *would have been trivial*." Pet. 33. Petitioners cite no expert support for this assertion, again fail to apply the construction of "is

calculated" they identified in the Petition, and do not explain how this assertion (apparently suggesting, at most, obviousness) would fit into a theory of anticipation. Indeed, Petitioners actually cite four additional prior art references to argue "use by a POSA to calculate thiol-pair ratios and buffer strengths would have been trivial and elementary." Pet. 33; InVue Sec. Prods. Inc. v. Mobile Tech, Inc., PGR2019-00019, Pap. 7, 8-10 (May 29, 2019) (denying institution; "Marszalek is one of the references discussed in Section IV.B of the Petition (Pet. 17), but it is not identified as forming the basis for unpatentability in Petitioner's identification of 'Ground 1'"); Investors Exch., LLC. v. NASDAQ Tech. AB, IPR2018-01796, Pap. 11, 6-7 (May 6, 2019) ("we determine that the Petition fails to identify 'in writing and with particularity' the printed publications that are the basis for the challenges ... Contrary to the chart presented in its Reply [to patent owner's POPR], Petitioner's analysis in the Petition cites to the additional documents, not just Exhibits 1005-1007 ... The above statements indicate that the Petition relies additionally upon Exhibits 1004 and 1008 to teach elements of 'the comm-diff combination' and not just as background references."). For this additional reason, Petitioners failed to show that those claims are "anticipated" by Vallejo.

B. Petitioners Fail To Establish That Claims 16, 19-21, 23-26, and 29-30 Are Anticipated By Ruddon (Ground 2)

1. Petitioners Failed To Show Ruddon Discloses A Process That Properly Refolds Proteins Into Biologically Active Forms

Petitioners failed to explain how Ruddon's refolding process for the hCG- β subunit results in properly folded, biologically active protein. Instead, Petitioners argued Ruddon's refolding process results in "properly-refolded hCG-β protein that is *competent for assembly into* the full hCG hormone with biological activity." Pet. 40. But Petitioners and their expert acknowledged that *only the fully* assembled hCG hormone is capable of binding to hormone receptors and that hormone-receptor binding is biological activity. Id.; EX1002, ¶¶150-151. Neither Petitioners nor their expert explain how a protein subunit that is merely "competent for assembly" into a biologically active hormone with other components is itself biologically active. Petitioners also fail to address the contradictory disclosure in Ruddon itself, which 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." EX1025, 1. Indeed, biological activity was shown in Ruddon only after the refolded β subunit was combined with a *native* α subunit (e.g., the α

subunit was not made in a non-mammalian expression system and subsequently refolded). EX1025, 53:7-28.

2. Petitioners Failed To Show Ruddon Teaches The Limitation "Thiol-Pair Buffer Strength To Maintain The Solubility Of The Solution"

Petitioners also did not meet their burden to establish Ruddon teaches the limitation "maintains the solubility of the solution" as required in independent claims 16 and 26. Pet. 41-42. Petitioners presented no analysis of the correct construction of this phrase, and presented no analysis of Vallejo under any correct construction. Thus, Petitioners did not meet their burden.

Even assuming, *arguendo*, that Petitioners' construction of "wherein the thiol-pair buffer strength maintains the solubility of the preparation" is correct, Petitioners explicitly rely on their flawed analysis for the same limitation in Vallejo (Pet. 41-42), and it fails for the same reasons discussed above. *See supra* §VII.A.1.

3. Petitioners Failed To Present Any Argument Applying Their Assumed Construction Of "Is Calculated" And Cited To Art Other Than Ruddon In Arguing "Anticipation" (Claims 23-25, And 30)

With respect to claims 23-25 and 30, as with Vallejo (*see supra*, §VII.A.3), Petitioners failed to present *any* argument that Ruddon teaches this limitation under the correct construction of "is calculated." Pet. 33-34. While Petitioners stated they would assume "is calculated" requires an "active step of determining" and that the ratio and buffer strength "actually be calculated" (Pet. 20), and stated they would construe "is calculated" to mean "is determined using an equation as part of practicing the method, rather than using the equation in hindsight" (Pet. 20-21), Petitioners provide no analysis under this construction.

For claim 23, Petitioners assert only that the thiol-pair ratio is "expressly calculate[d]" but without asserting, let along explaining, how Ruddon teaches the "active step of determining" or trying to show how the ratio is determined in Ruddon "as part of practicing the method, rather than using the equation in hindsight." *See* Pet. 43. Further, while Petitioners argue about what "[a] POSA would have understood" or "expected," they never cite any expert or other evidence for that proposition. *See* Pet. 43-44 n.7.

For claims 24, 25, and 30, Petitioners' analysis is the same as for Vallejo and cites back to their Vallejo arguments regarding the "is calculated" claims. Pet. 44. Thus, Petitioners failed to show Ruddon anticipates these claims for the same reasons described above for Vallejo. *Supra*, §VII.A.3.

C. Petitioners' Obviousness Grounds Are Unclear, Confusing, and Legally Insufficient (Grounds 3 and 4)

As an initial matter, Petitioners did not make any attempt to establish Clark 1998, Gilbert, or Schafer are prior art printed publications. Petitioners merely

assert without support that Clark 1998 "was published in a printed publication as of 1998." Pet. 48. Similarly, Petitioners merely concluded without support that Gilbert, and Schafer "were each published in a printed publication before June 2008." Pet. 48. But Petitioners said nothing about where the pages they attached as an exhibit were found or generated. For instance, Petitioners presented no evidence establishing the Clark 1998, Gilbert, or Schafer exhibits were from regularly published journals, and gave no explanation for the asserted 1998 or 2008 dates. Even if Petitioners took the date from the text of the exhibits (which Petitioners did not assert), they provided no explanation as to why such date would not be hearsay. Petitioners thus failed to meet their burden on a basic element of anticipation: establishing their references are prior art printed publications and authentic. See, e.g., Dr. Reddy's Labs., Inc. v. Celgene Corp., IPR2018-01507, Pap. 7, 8-11 (Feb. 11, 2019) (denying institution for lack of proof regarding printed publication status of references, collecting cases); TRW Auto. U.S. LLC v. Magna Elecs. Inc., IPR2014-01347, Pap. 25, 8-9 (Jan. 6, 2016) ("[C]opyright notice is...not probative that the article was ever published by IEEE or anyone else.").

Moreover, in violation of the Board's rules and the Federal Circuit's minimum requirements for any showing of obviousness (*see, e.g.*, 35 U.S.C. § 312(a)(3); 37 C.F.R. § 42.104(b)(4)-(5); *In re Magnum Oil Tools, Int'l. Ltd.*, 829 F.3d 1364, 1380 (Fed. Cir. 2016)), the Petition fails to articulate and explain any of

its obviousness arguments, and also fails to specify where each element of the claim is found in the prior art and to identify the specific portions of evidence supporting its challenge, improperly leaving it to the Board and Patent Owner to guess what Petitioners might be suggesting. *Clim-A-Tech Indus., Inc. v. Ebert,* IPR2017-01863, Pap. 13, 27-28 (Feb. 12, 2018) (denying institution when Petition "fail[ed] to identify 'with particularity' the grounds and evidence that form the underlying basis for the patentability challenge"); *Teoxane S.A. v. Allergan, PLC,* IPR2017-01906, Pap. 15, 24-25 (March 9, 2018) ("Petitioner should not expect the Board to search the record to piece together what may support a challenge."); *John Crane, Inc. v. Finalrod IP, LLC,* IPR2016-01827, Pap. 6, 11 (Jan. 31, 2017)

(describing Petitioner's responsibility "to explain specific evidence that support[s] its arguments, not the Board's responsibility to search the record and piece together what may support Petitioner's arguments"); *InfoBionic, Inc. v. Braemer Mfg., LLC*, IPR2016-01236, Pap. 8, 13 (Dec. 23, 2016) (denying institution where petitioner "does not persuasively articulate an adequate reason why and how the teachings of the three relied-upon references would have rendered obvious the claimed subject matter"); *Free-Flow Packaging Int'l, Inc. v. Automated Packaging Sys., Inc.,* IPR2016-00351, Pap. 7, 14 (June 27, 2016) (denying institution where petitioner failed to show "a person of ordinary skill in the art would have had a reason to combine" prior art references); *Apple, Inc. v. ContentGuard Holdings, Inc.*,

IPR2015-00358, Pap. 9, 7-8 (July 2, 2015) (denying institution where Petitioner failed to "identify sufficiently the differences between the claimed invention and the prior art, or how the prior art teachings are to be modified or combined" making it "difficult to understand the distinctions (if any) between the asserted grounds, because they are lumped together"); *AOL Inc. v. Coho Licensing LLC*, IPR2014-00966, Pap. 6, 13 (Nov. 20, 2014) ("A petitioner who does not state the differences between a challenged claim and the prior art, and relies instead on the Patent Owner and the Board to determine those differences risks having the corresponding ground of obviousness not included for trial for failing to adequately state a claim for relief.").

1. Grounds 3 And 4 Are A Combination Of Multiple Poorly-Delineated Grounds

Ground 3, asserted to be an obvious ground based on "Ruddon in view of Clark 1998 in light of Schafer *or* Gilbert" (Pet. 47) is also referred to as "Ruddon and Clark 1998 and [if necessary] Schafer *and* Gilbert" (Pet. 55) ("a POSA would have combined the teaching of Ruddon and Clark 1998, and if necessary Schafer and Gilbert..."). Ground 4, to the extent it can be understood at all, apparently adds Vallejo as a base reference to Ground 3. Pet. 62-63. But Petitioners also contend neither Schafer nor Gilbert are necessary to these grounds. Pet. 55 ("if necessary Schafer and Gilbert"). Thus, "Ground 3" is apparently at least four

different grounds: Ruddon in view of Clark 1998; Ruddon in view of Clark 1998 and in light of Schafer and Gilbert; Ruddon in view of Clark 1998 and in light of Schafer; and Ruddon in view of Clark 1998 and in light of Gilbert. Similarly, "Ground 4" is also at least four different grounds: Vallejo in view of Ruddon and Clark 1998; Vallejo in view of Ruddon and Clark 1998 and in light of Schafer and Gilbert; Vallejo in view of Ruddon and Clark 1998 and in light of Schafer; and Vallejo in view of Ruddon and Clark 1998 and in light of Schafer; and

Petitioners' suggestion of the use of these additional, alternative references in an apparent hope the Board might find something—*anything*—that is compelling is improper and a waste of the Board's and Amgen's resources. It makes it nearly impossible for Amgen to adequately respond to the unwieldy Petition and for the Board to oversee and manage such a trial. It also inappropriately shifts Petitioners' burden under \$312(a)(3) to the Board and Amgen. See InVue Sec. Prods., PGR2019-00019, Pap. 7, 8-9 (denying institution and stating, with respect to "and/or" combinations, "the Obviousness Challenges are not set forth with particularity because it is unclear what each challenge encompasses and what evidence Petitioner relies upon to establish unpatentability under each challenge"); Zetec, Inc. v. Westinghouse Elec. Co., IPR2014-00384, Pap. 10, 14 (Jul. 23, 2014) ("Moreover, numerous grounds are presented and argued together in the Petition, thereby obfuscating the arguments ... [this]

place[s] a significant and unfair burden on the Patent Owner to respond adequately."). Again, Petitioners failed to meet their obligations under §312(a)(3), and the Board should not institute trial.

2. Petitioners Do Not Clearly Identify Which "Gilbert" Reference Is Intended To Be Part Of Grounds 3 And 4

Petitioners include two references by Gilbert in their exhibit list, EX1013 and EX1014. But it is not clear from the Petition which Gilbert reference Petitioners are relying on. In the beginning of their Ground 3 analysis, Petitioners assert "Gilbert" was published in 1995, apparently referencing the document corresponding to Exhibit 1014 (though without actually identifying the exhibit). Pet. 48. However, just five pages later, Petitioners reference what "Gilbert 1990show[s]" and cite Exhibit 1013. Pet. 53. Subsequently, Petitioners refer to "Gilbert," making assertions about what Gilbert teaches and why would have allegedly combined it with other references. However, Petitioners do not identify which Gilbert exhibit is relied upon for these assertions, let alone a page. Ground 4 simply incorporates this analysis. Pet. 62. Amgen and the Board are thus left to guess at which Gilbert reference is meant to be part of the combinations, and it would be prejudicial and almost impossible for Amgen to know what to rebut in any Patent Owner Response. Teoxane, IPR2017-01906, Pap. 15, 24-25 ("We will not search the record (including [Petitioner's expert's] declaration) to ascertain

whether any evidence supports that bare argument."); *ContentGuard Holdings, Inc.*, IPR2015-00358, Pap. 9, 7-8 ("Petitioner leaves it to the Board to ascertain what gaps to fill Patent Owner need not present a showing to 'render' its claims patentable. The burden is on Petitioner to show unpatentability.").

3. Petitioners Do Not Clearly Identify The Base Reference For Ground 3 And Fail To Explain The Modifications To The Base Reference For Grounds 3 And 4 Or Analyze The Motivation To Combine

Petitioners do not clearly identify their base reference for Ground 3. While the section header for Ground 3 might suggest that Ruddon is the primary reference, Petitioners' actual analysis muddies this assertion. *Petitioners switch between Ruddon and Clark 1998 as the primary references*, first asserting, for instance what "Clark 1998 in combination with Ruddon teach[es]" (Pet. 56) and then, for the next limitation, asserting what "Ruddon in combination with Clark 1998" (Pet. 57) allegedly teaches. Ground 4 only builds and relies upon these deficiencies. Pet. 62-63.

Because of these failings, and because of Petitioners' failure to provide appropriate citations, it is also *not clear which reference Petitioners are relying on for what* alleged teaching. *Clim-A-Tech Indus.*, IPR2017-01863, Pap. 13, 27-28; *Costco Wholesale Corp. v. Robert Bosch LLC*, IPR2016-00042, Pap. 28, 3-4 (July 7, 2016) (denying rehearing and confirming "[i]t is not [the Board's] role to

sift through the information provided and determine on our own if there is a reasonable likelihood that the asserted references show unpatentability."). For example, for certain claim limitations (e.g., the "redox components" limitations (Pet. 57-58)), Petitioners cited to disclosures from both Ruddon and Clark 1998 without explaining what they assert is lacking in the primary reference or explaining how the secondary reference would fill whatever gap they have in mind. See, e.g., Feit Elec. Co. v. Philips Lighting N. AM. Corp., IPR2018-00790, Pap. 9, 16 (Oct. 10, 2018) (denying institution because petitioner failed to identify with particularity how the prior teaches or suggests the structures of the claim elements as required by §312(a)); Dish Network Corp. v. Customedia Techs., LLC, IPR2017-00936, Pap. 13, 10-11 (Aug. 24, 2017) (denying institution because petitioner failed to articulate with sufficient particularity which of two disclosures in the prior art mapped to two distinct claim elements); John Crane, Inc., IPR2016-01827, Pap. 6, 12 (denying institution when it was unclear which prior art reference petitioner relied upon to teach each claim element or unclear whether petitioner relied upon an unarticulated combination of the prior art references); *Dep't of Justice v. EnvisionIt, LLC*, IPR2017-00186, Pap. 8, 26 (May 3, 2017) (denying institution, noting the Board is "not inclined to play archaeologist with the record in an attempt to fill the gaps in [p]etitioner's argument"); Adidas AG v. Nike, Inc., IPR2016-00920, Pap. 6, 6-7 (Oct. 20, 2016) (denying institution where

the Board "[was] generally [] left to guess as to what limitations [petitioner] seeks to supply from the teachings of each of the references that it cites as a part of the proposed ground" and "[t]hose uncertainties and vagaries also deprive[d] [patent owner] of an appropriate basis for it to formulate a response to the [p]etition."). As a second example, with respect to the claimed preparation and solution (Pet. 56-57), it is not apparent whether, in Petitioners' combination, only elements of Ruddon or elements of Clark 1998 are being relied upon, or whether Ruddon is being modified based on Clark 1998's teachings or vice versa. The same is true with respect to the "redox components" limitations. Pet. 57-58.

In part due to these deficiencies, Petitioners also fail to provide any meaningful analysis of *how a POSITA would modify* the base reference(s). *See, e.g., Healthcare Logistics, Inc. v. Kit Check, Inc.*, IPR2019-00385, Pap. 7, 14 (June 3, 2019) (denying institution because petitioner failed to explain how to modify a reference to meet a limitation and why a POSITA would be motivated to do so); *Adt LLC v. Applied Capital, Inc.*, IPR2017-01825, Pap. 7, 15 (Jan. 24, 2018) (denying institution because petitioner failed to explain whether and why it would have been obvious to modify a prior art disclosure); *John Crane, Inc.*, IPR2016-01827, Pap. 6, 14 (petitioner must "articulat[e] how and why specific teachings of the references would have been combined. It is Petitioner's responsibility to explain specific evidence that support[s] its arguments, not the Board's

responsibility to search the record and piece together what may support Petitioners' arguments.") (citing *Dominion Dealer Sols., LLC v. Autoalert, Inc.*, IPR2013-00225, Pap. 15, 4 (Oct. 10, 2013)); *Adidas AG*, IPR2016-00920, Pap. 6, 6-7 (denying institution where Board "left to guess as to what limitations [Petitioner] seeks to supply from the teachings of each of the references that it cites as a part of the proposed ground"); *Axon Enter., Inc. v. Digital Ally, LLC*, IPR2017-00515, Pap. 10, 18-19 (July 6, 2016) (denying institution, stating neither Petitioner nor its expert "explains in sufficient detail the nature of Petitioner's proposed modification ... Petitioner does not explain in sufficient detail *how* the proposed modification is supposed to work").

In addition to failing to point out specific modifications to the base reference, Petitioners failed to explain *why POSITA would be motivated to make each such modification*. *ContentGuard Holdings, Inc.*, IPR2015-00358, Pap. 9, 9 (denying institution when petition "lack[ed] an articulated or apparent reason supported by 'some rationale or underpinning' to modify/combine the purportedly known elements" of the prior art); *Linear Tech. Corp. v. In-Depth Test LLC*, IPR2015-00421, Pap. 15, 17 (July 21, 2015) (denying institution when petition failed to adequately explain motivation to modify the prior art). Indeed, Petitioners' arguments regarding motivation to combine are insufficient, generic, and conclusory. Pet. 54-55. Petitioners fail to address motivation to combine

particular elements of the prior art, and, at best, Petitioners' motivation to combine arguments are really just arguments about analogous art. Front Row Techs., LLC v. MLB Adv. Media, L.P., IPR2015-01932, Pap. 7, 20-21 (March 25, 2016) ("The fact that the cited references are 'analogous art' [] and 'are all in the same field of endeavor as the claimed invention' [] does not, by itself, however, establish that it would have been obvious to combine their features." (internal citations omitted)); Shopkick Inc. v. Novitaz, Inc., IPR2015-00279, Pap. 7, 29-30 (May 29, 2005) ("The fact that the cited references are 'analogous to the claimed invention' and share 'the same design incentives with each other and with the [patent at issue] itself' [] does not establish that it would have been obvious to combine their features." (internal citations omitted)). Petitioners never explain (nor could they, given the deficiencies identified above) the benefit of any proposed combination, or how the proposed combination would improve the primary reference.

Further, nowhere in Petitioners' section on these issues do Petitioners cite any expert support, despite making numerous assertions about what a POSITA would have understood or done. Pet. 53-55. Nor do Petitioners cite any expert declaration where asserting what its combination teaches or what a POSITA would have allegedly understood. *See, e.g.*, Pet. 56 ("Clark 1998 in combination with Ruddon teach a method of refolding..." without expert citation), 57 ("Ruddon in combination with Clark 1998 disclose formation of the claimed mixtures..."

without expert citation); 57 ("a POSA would have known…" without expert citation); 58 ("a POSA would have understood… A POSA also would have understood…" without expert citation). These unsupported attorney arguments are insufficient and should be rejected. *Olympus Corp. v. Maxell, Ltd.*, IPR2018-00905, Pap. 9, 16-17 (Nov. 19, 2018) (attorney argument for how POSITA would understand prior art was unpersuasive and insufficient for institution).

4. Petitioners Failed To Articulate A Reasonable Expectation Of Success For Grounds 3 And 4

The Petition is also devoid of any discussion of reasonable expectation of success other than a conclusory statement that the combination would work "given the success reported in Ruddon and Clark 1998" (Ground 3) and "[b]ecause of the success reported in these references" (Ground 4). Pet. 56, 63. But those teachings *do not even apply to combinations of teachings from Ruddon and Clark 1998*, let alone, *e.g.*, Schafer and Gilbert. Pet. 55; *see, e.g.*, *Nintendo Co. v. Genuine Enabling Tech LLC*, IPR2018-00543, Pap. 7, 24 (Aug. 6, 2018) (denying institution because the PGR Petitioners' "only support [was] a conclusory statement [from their expert] without any evidentiary support, which has no weight"). Petitioners also cite no expert in support of their assertion regarding reasonable expectation of success. In any case, it is impossible to analyze Petitioners' reasonable expectation of success arguments given the other problems
with their analysis noted above, including the fact that one cannot discern from the Petition what Petitioners' proposed modifications are. Petitioners' vaguely- and inconsistently-defined combination of elements is not sufficient to allow for a reasoned analysis of the proposed combination or to allow proper consideration of whether POSITA would have had a reasonable expectation of success in combining the teachings of the prior art references to arrive at the claimed invention. See, e.g., 10X Genomics, Inc. v. Bio-Rad Labs., Inc., IPR2018-00301, Pap. 18, 14-16 (June 15, 2018) ("Petitioner's vaguely and inconsistently defined combination of elements is not sufficient to allow for a reasoned analysis of the proposed combination or to allow proper consideration of whether one of ordinary skill in the art would have had a reasonable expectation of success in combining the teachings of the prior art references to arrive at the claimed invention."); see also In re Stepan Co., 868 F.3d 1342, 1346-48 (Fed. Cir. 2017) (vacating PTAB unpatentability judgment and discussing requirement for a reasonable expectation of success); Amgen Inc. v. F. Hoffman-La Roche Ltd., 580 F.3d 1340, 1362 (Fed. Cir. 2009) ("An obviousness determination requires that a skilled artisan would have perceived a reasonable expectation of success in making the invention in light of the prior art."); Apple Inc. v. Memory Integrity, LLC, IPR2015-00159, Pap. 12, 27 (May 11, 2015) (finding obviousness ground deficient where petition did not address reasonable expectation of success).

5. Petitioners Failed To Present Any Argument Applying Its Assumed Construction Of "Is Calculated"

As with their arguments regarding Vallejo (*supra*, §VII.A.2), with respect to claims 8, 9, 14, 15, 23-25, and 30, Petitioners failed to present *any* argument that the proposed combination or combinations teach this limitation under the correct construction of "is calculated," (Pet. 61-63), which Petitioners concede requires the "thiol-pair ratio or thiol-pair buffer strength to actually *be calculated*" (Pet. 20). Petitioners assert only that these ratios were known, not that *actually calculating them* would have been obvious. Thus, Petitioners failed for this additional reason to show that claims 8, 9, 14, 15, 23-25, and 30 are obvious based on Grounds 3 or 4.

VIII. Conclusion

§311(c) prohibits the filing of this Petition before PGR2019-00001 has concluded. Further, due to failures in both proof and specificity of argument, the Petitioners failed to show that the Challenged Claims are anticipated or rendered obvious. Because the Petition failed to show that there is a reasonable likelihood that the Petitioners will prevail in proving any Challenged Claim is unpatentable, the Petition should be denied in its entirety, and, pursuant to §314, no *inter partes* review should be instituted. To the extent the Board determines that the Petitioners have met their burden on any subset of these grounds (they have not), post-*SAS*,

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the Board should use its discretion under §§325(d) and/or 314(a) to deny

institution on all grounds because, in light of the evidence and arguments presented

in this PGR Petition, requiring the Board and Amgen to bear the wasteful burden

and of a trial on all grounds to reach such a subset of grounds would not, inter alia,

be an efficient use of the Board's limited time and resources.

Respectfully submitted by:

Dated: July 17, 2019

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CERTIFICATE OF WORD COUNT

The undersigned certifies that the foregoing PATENT OWNER'S

PRELIMINARY RESPONSE UNDER 37 C.F.R. §42.107 complies with the type-

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of PATENT OWNER'S

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