UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FRESENIUS KABI USA, LLC and
FRESENIUS KABI SWISSBIOSIM GMBH,
Petitioners,

v.

AMGEN INC.,
Patent Owner.

Case IPR2019-01183
Patent 9,643,997

PATENT OWNER'S RESPONSE

LIST OF EXHIBITS

Exhibit	Description
EX2001	Omitted
EX2002	Omitted
EX2003	Declaration of Sayem Osman
EX2004	Declaration of Naz Wehrli
EX2005	Omitted
EX2006	Omitted
EX2007	Omitted
EX2008	Omitted
EX2009	Transcript of Claim Construction Hearing, *Amgen Inc. v. Hospira Inc*., Case No. 1:18-cv-01064-CFC (D. Del. May 15, 2019)
EX2010	Omitted
EX2011	Omitted
EX2012	U.S. Patent No. 7,138,370 ("Oliner")
EX2013	Merriam-Webster's Medical Desk Dictionary (2006)
EX2014	Oxford Dictionary of Biochemistry and Molecular Biology (2005)
EX2015	Merriam-Webster's Collegiate Dictionary (2009)
EX2016-EX2049	Omitted
EX2050	Stipulation Regarding Substitution of Parties, *Amgen Inc. v. Kashiv Biosciences, LLC*, Case No. 2:18-cv-03347-CCC-MF (D.N.J. June 10, 2019) (D.I. 127)
EX2051	Docket, *Amgen Inc. v. Kashiv Biosciences, LLC*, Case No. 2:18-cv-03347-CCC-MF (D.N.J.)
EX2052	Docket, *Amgen Inc. v. Hospira Inc*., Case No. 1:18-cv-01064-CFC (D. Del.)
EX2053	Claim Construction Opinion, *Amgen Inc. v. Mylan Inc*., Case No. 2:17-cv-01235-MRH (W.D. Pa. Nov. 20, 2018) (D.I. 171)
EX2054	Enger & Ross, Concepts in Biology (10th ed. 2003)
EX2055	Excerpt of *Kashiv Biosciences, LLC v. Amgen, Inc.*, IPR2019-00797, Declaration of Anne S. Robinson (Exhibit 1002) (March 7, 2019)
EX2056	Declaration of Chanming (Mike) Zhang, PhD
EX2057	Declaration of Saurabh Gupta
EX2058	Deposition of Peter M. Tessier

Exhibit	Description
EX2059	Chi, E.Y., *et al.*, Physical Stability of Proteins in Aqueous Solution: Mechanism and Driving Forces in Nonnative Protein Aggregation, Pharm. Res. 20 (9):1325–1336 (September 2003)
EX2060	Joint Claim Construction Chart in *Amgen Inc. v. Hospira, Inc.*, Case No. 1:18-cv-1064 (D. Del. February 8, 2019) (D.I. 40 & 40-1).

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I. Introduction

The ’997 patent “relates generally to processes for purifying proteins expressed in non-mammalian systems.” EX1001, 1:13-14.[1] Protein purification is a critical step in the manufacture of biological products (proteins) from non-mammalian expression systems using recombinant DNA technology. In non-mammalian expression systems, proteins are frequently “deposited in the expressing cells in limited solubility forms, such as inclusion bodies, that require refolding.” *Id.*, 1:28-30. The ’997 patent explains that “Protein A chromatography is typically not performed in a purification process until after the protein has been refolded to a degree that it can associate with the Protein A molecule….” *Id.*, 1:42-45.

Before the invention of the ’997 patent, it was believed in the art that certain of the specialized chemical compounds used to refold the proteins needed to be substantially diluted, reduced, or removed before applying the refold solution to a separation matrix for purification. *See, e.g., id.*, 1:46-55. The conventional thinking was that if these specialized chemical compounds in the refold solution were not substantially diluted, reduced, or removed before the refold solution was

[1] For citations with columns, the citation is provided in column:line form. For other references with line numbers, citations are in original page:line form.

applied to the separation matrix, they could prevent or disrupt the interactions between the protein and the separation matrix (*e.g.*, Protein A column), which were necessary for the separation to work and the protein to be purified. *Id.*, 1:46-55, 15:50-67. Therefore, prior to the invention of the '997 patent, additional processing steps were performed after protein refolding to remove (or substantially reduce the concentrations of) components of the refold mixture from the solution and before applying the protein to a chromatographic separation matrix. *See, e.g.*, *ibid.* The inventors recognized that such additional processing can be costly and time-consuming, particularly at a large manufacturing scale. EX1001, 12:14-20, 12:45-50, 15:50-67. The '997 patent reflects the inventors' insight that protein purification could be achieved by applying a refold solution to a separation matrix ***without*** certain intervening processing steps. *Id.*, 12:14-20, 15:50-67.

Petitioners' Grounds largely ignore this important aspect of the '997 patent, and Petitioners failed to meet their burden of establishing unpatentability of any claim. Patent Owner now addresses the Petition's numerous errors and omissions, supported by Dr. Zhang's expert testimony (EX2056), and free of §42.108(c)'s institution-only constraints.[2]

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

First, Petitioners' own arguments and evidence confirm they cannot meet their burden to prove any of the Challenged Claims (claims 9-10, 13-21, and 23-30) unpatentable. *See, e.g.*, §314; §42.108(c). Petitioners ignored key claim limitations that affect all of their anticipation and obviousness Grounds and render their analyses of the references incomplete, flawed, and ultimately without merit:

- Under a correct construction of "applying the refold solution," certain steps such as precipitation and centrifugation are not allowed by the claims. Petitioners failed to engage in sufficient analysis of this element, despite being aware of fundamental issues from litigation. And, Petitioners' own cited references contradict their assertions that there were no intermediate steps in the references on which they rely. Petitioners further ignored the case law confirming that mere silence in prior art cannot prove the absence of disallowed steps. Petitioners failed to meet their burden of proof for this element in Grounds 1-5.
- With respect to at least Grounds 1-3, Petitioners improperly mixed and matched disclosures from different embodiments within references for which they asserted anticipation. The references, however, failed to disclose the elements *as arranged in the claim*, and Petitioners' Ground 2 obviousness arguments did address this improper mixing and matching.

- Petitioners failed to perform any analysis construing various dependent claims, instead making the unsupported assertion that their explicit limitations are *not actually limiting*. On that basis, Petitioners argued the asserted references need not teach any element in those dependent claims to anticipate. But these dependent claims *do* require the components that they recite, and Petitioners failed to meet their burden to show them unpatentable.

Second, in support of their obviousness Grounds (Grounds 2 and 5), Petitioners offered only vague and conclusory assertions concerning the alleged motivations to combine references and a person of ordinary skill in the art ("POSITA")'s reasonable expectation of success in doing so. Such arguments are insufficient for Petitioners to meet their burden. For instance, with respect to Ground 5, Petitioners argued that a statement in their base reference about adding a buffer to an already-refolded protein motivated the use of a "refold buffer" in a secondary reference for the protein refolding itself. However, Petitioners did not explain how a statement about a buffer added to an *already refolded* protein could motivate the addition of a buffer *prior to refolding*. Further, the solution Petitioners identified in the secondary reference *has no pH buffering capacity*, as required by the claims, and is therefore not the claimed buffer. In addition, Petitioners' failure to meaningfully address reasonable expectation of success is

particularly problematic for Ground 5 because the very solution Petitioners sought to import from the secondary reference into the first actually *failed to result in protein that was successfully bound and eluted from the column*, as the claims require.

Third, Petitioners failed to establish that any of their primary, secondary, or background non-patent references are printed publications that qualify as prior art or that the background references reflect information known to a POSITA at or around the relevant priority date.

Fourth, Petitioners' expert's testimony should be given little to no weight. It is conclusory, inconsistent, and misleading, and copies various sections verbatim from another expert's declaration in an earlier '997 PGR by a different petitioner (although Petitioners' expert here claims never to have read it).

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

II. Level Of Skill In The Art

A POSITA, for purposes of the '997 patent, would have had a Ph.D. in biochemical engineering, biomedical engineering, biochemistry, or a related discipline, with at least two years of work experience in the field of protein chromatography as of the '997 patent's priority date of June 25, 2009. Additional training or study could substitute for additional work experience, and additional

work experience or training could substitute for formal education. However, to the extent Petitioners' definition is adopted, it would not change the analysis below. *See generally* EX2056, ¶19.

III. Claim Construction[3]

For purposes of *inter partes* review for a petition filed on or after November 13, 2018 (like Petitioners' here), claim terms are construed under the standard provided by the Federal Circuit in *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (*en banc*). §42.100(b). Claim construction begins with the claim language itself. *See Microsoft Corp. v. Proxyconn, Inc.*, 789 F.3d 1292, 1299 (Fed. Cir.

[3] 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); *Smart Modular Techs. Inc. v. Netlist, Inc.*, IPR2014-01372, Pap.45, 13 (Mar. 9, 2016) ("Only terms which are in controversy need to be construed, and only to the extent necessary to resolve the controversy."). Thus, unless otherwise stated, Amgen's proposed constructions reflect only disputes relevant to the arguments it presents in this POR. For instance, Amgen has not presented a construction for "aggregation suppressor" or "protein stabilizer" in the POR as it has not raised a dispute regarding application of these terms as it relates to the substantive analysis.

2015) ("Beginning with the language of the claims….The specification *confirms* that the phrase…is limited."), *overruled on other grounds by Aqua Prods., Inc. v. Matal*, 872 F.3d 1290 (Fed. Cir. 2017). Claim terms are presumed to have their ordinary and customary meaning in light of the patent's specification as understood by POSITA at the time of invention, unless (1) the patentee sets out a definition and acts as his own lexicographer, or (2) the patentee disavows the full scope of a claim term either in the specification or during prosecution. *Thorner v. Sony Computer Entm't Am. LLC*, 669 F.3d 1362, 1365 (Fed. Cir. 2012).

A. "Refold Buffer Comprising One Or More Of…" (All Challenged Claims)

Amgen's Proposed Construction	Petitioners' Proposed Construction
"a pH-buffered solution that provides conditions for the protein to refold into its biologically active form, comprising one or more of a denaturant, an aggregation suppressor, a protein stabilizer and a redox component."	None proposed.

As the Board correctly determined at institution (D.I.16), the "refold buffer" should be construed to require that it be pH-***buffered***. Amgen's proposed construction requiring that the "refold buffer" be "a pH-buffered solution" is supported by the express language of the term itself, which includes the word "buffer." The affirmative choice of the word "buffer" distinguishes this term from solutions without pH buffering capacity. For instance, the claims require a

"solubilization ***solution***," a "refold ***solution***," and a "refold ***buffer***." It is a fundamental canon of claim construction that these different words—"solution" and "buffer"—have different meanings. *See Bd. of Regents of Univ. of Tex. Sys. v. BENQ Am. Corp.*, 533 F.3d 1362, 1371 (Fed. Cir. 2008) (noting presumption that use of different terms connotes different meanings); *SimpleAir, Inc. v. Sony Ericsson Mobile Commc'ns AB*, 820 F.3d 419, 431 (Fed. Cir. 2016) (finding decision to use "data channel" rather than "data feed," despite use of "data feed" elsewhere in patent, supports conclusion that phrases mean different things); *Emerson Elec. Co. v. IP Co. LLC*, IPR2017-00252, Pap.37, 33 (May 30, 2018) (noting inference that different words have different meanings). By using the term "refold ***buffer***," the applicant made clear that a "refold buffer" is not just any solution, but a ***pH-buffered*** solution.[4]

The specification also makes clear that the "refold buffer" must be pH-bufferedas the Board correctly recognized at institution. D.I.16. The specification explains "***[t]he function of the buffer component of the refold solution is to maintain the pH of the refold solution*** and can comprise ***any buffer that buffers in the appropriate pH range***." EX1001, 15:5-11. The court in *Amgen Inc. v.*

[4] Generic uses of term "buffer" outside the context of the asserted claims do not dictate a contrary result. *Cf.* EX2053, 17-20.

Hospira Inc., No. 1:18-cv-01064-CFC (D. Del.), agreed that column 15 of the '997 patent supports Amgen's construction of "refold buffer" because of "the lexicography that was performed in column 15 of the patent," and because "it's also consistent…with the written description." EX2009, 86:19-87:3. That court concluded "refold buffer" means "[a] solution that comprises one or more of the components listed in the language of the claim and that contains a buffering component to maintain the appropriate pH range of the refold solution." *Id.*.

Extrinsic evidence further supports Amgen's construction. For example, dictionaries from the time confirm a buffer was understood to maintain approximately constant pH despite small additions of acid or base. EX2013-EX2015; *see also Reckitt Benckiser Pharm. Inc. v. Watson Labs., Inc*., No. 13-1674, 2015 U.S. Dist. LEXIS 83131, at *7 (D. Del. June 26, 2015) (construing buffer and concluding "the fundamental characteristic of a buffer is that it buffers, or resists changes to, pH"); EX1036, 41 (describing importance of pH to ion exchange chromatography). Thus, the plain claim language, specification, and extrinsic evidence all indicate that the "refold buffer" must have pH buffering capacity.[5]

[5] With respect to Grounds 1 through 5, Petitioners failed to address the requirement that the "refold buffer" must have a pH buffering capacity, despite being aware of

the support for such a construction. EX1034, 14; EX1035, 17. Petitioners should not be permitted to remedy this failure on Reply where they failed to make any assertion about this claim requirement in the Petition in the first place. *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 where 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 a new issue or belatedly presents evidence will not be considered and may be returned.").

B. "Applying The Refold Solution To A Separation Matrix" (All Challenged Claims)

Amgen's Proposed Construction	Petitioners' Proposed Construction
"applying the refold solution to a column that contains the separation matrix without intervening steps of ***dilution,***[6] ***dialysis, centrifugation or precipitation*** under conditions suitable for protein to have specific, reversible interactions with a separation matrix in order to effect the separation of protein from its environment"	"Petitioners take no position on whether the challenged claims allow other intervening processes… a POSA would not construe the term to exclude an intervening step of ***dilution***, at least on the scale of a 3-fold water dilution described in Example 3 of the '997 patent." Pet.17-18.

Despite asserting their references do not contain any prohibited intervening steps, Petitioners expressly stated that they "take ***no position*** on whether the challenged claims allow other intervening processes between forming the refold solution and applying the solution to the separation matrix," arguing only that a POSITA "would ***not*** construe the term 'applying the refold solution to the separation matrix' ***to exclude*** an intervening step of ***dilution***, at least on the scale of a 3-fold water dilution described in Example 3 of the '997 patent." Pet.17-18.

[6] "Dilution" in the context of this claim construction refers to substantial dilution. The exact bounds of "dilution" or "substantial dilution" need not be determined for the purpose of this proceeding, as Patent Owner's arguments distinguishing the art here do not rely on dilution. *See supra*, n.3.

The parties thus do agree that some amount of dilution (*e.g.*, 3-fold dilution) is allowed.

Patent Owner's construction of the claims is consistent with the specification, which confirms the importance of applying the refold solution "directly to the separation matrix, ***without*** the need for diluting or ***removing the components*** of the solution required for refolding the protein." EX1001, 15:50-54; *see 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…is a relevant consideration."); *SNF Holding Co. v. BASF Corp*., IPR2015-00600, Pap.49, 7 (Aug. 2, 2016) (same); *Apotex Inc. v. Abraxis Bioscience, LLC*, IPR2018-00152, Pap.11 at 6-7 (May 8, 2018) (discussing significance of "the" in claim language); *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1356 (Fed. Cir. 2003) ("It is a rule of law well established that the definite article 'the' particularizes the subject which it precedes. It is a word of limitation as opposed to the indefinite or generalizing force of 'a' or 'an.'" (internal citation omitted)).

The '997 patent's prosecution history shows that the intervening steps of ***dialysis, centrifugation, and precipitation*** must be excluded, consistent with Amgen's construction. Petitioners here *agreed* that in prosecution Amgen "disclaim[ed]" from the scope of the claim specific intervening steps that had been

disclosed in a prior-art reference, including dialysis, precipitation, and centrifugation." Pet.16-17. In particular, claim 9 was initially rejected by the Examiner as anticipated by and obvious over U.S. Patent No. 7,138,370 ("Oliner") (EX2012). But Amgen distinguished Oliner, stating:

> …Claim 9 recites, *inter alia*, (b) forming a refold solution; and (c) applying the refold solution to a separation matrix under conditions suitable for the protein to associate with the matrix. In contrast, ***[Oliner] recites that the refolded protein is subject to dialysis, precipitation, and centrifugation***. *See*, [Oliner], col 76, lns 51-59. The supernatant of [Oliner] is then pH adjusted and loaded onto a column. Because **[*Oliner*] *does not recite forming a refold solution and applying the refold solution to a separation matrix***, [Oliner] fails to teach each and every element of claim [9].

EX1033, 102; *see* EX2012, 76:51-61.[7] Amgen unequivocally and repeatedly distinguished Oliner because of the dialysis, precipitation, and centrifugation that occurred between Oliner's forming its refold solution and applying the refold solution to a separation matrix, confirming that these steps are excluded from the claim. EX1033, 102. "[W]here the patentee has unequivocally disavowed a

[7] While the Board may have taken a permissive view of this claim limitation for institution purposes (*see* D.I.38), the file history confirms and Petitioners (Pet.17) agree that some intermediate steps are disallowed.

certain meaning to obtain [its] patent, the doctrine of prosecution disclaimer attaches and narrows the ordinary meaning of the claim congruent with the scope of the surrender." *Omega Eng'g, Inc. v. Raytek Corp.*, 334 F.3d 1314, 1324 (Fed. Cir. 2003). Amgen's proposed construction is "congruent with the scope of the surrender," because it expressly identifies and excludes the following steps recited in Oliner and disavowed in prosecution: dialysis, precipitation, and centrifugation. EX1033, 102; *see* EX2012, 76:51-61. Amgen's construction is also very similar to the construction adopted by the court in *Amgen Inc. v. Mylan Inc.*, Case No. 2:17-cv-01235-MRH (W.D. Pa.) and consistent with the parties' agreed-to construction in *Amgen Inc. v. Hospira, Inc.*, Case No. 1:18-cv-1064 (D. Del.). Pet.14-15; EX2053, 23-29; EX2060.

C. Dependent Claims: The Recited Elements In Claims 14-19 And 23-27 Are Required Limitations

Independent claim 9 recites two groups, (1) "a solubilization solution comprising one or more of the following: (i) a denaturant; (ii) a reductant; and (iii) a surfactant," and (2) a "refold buffer comprising one or more of the following: (i) a denaturant; (ii) an aggregation suppressor; (iii) a protein stabilizer; and (iv) a redox component." EX1001, 22:39-50. Dependent claim 14 requires "wherein the denaturant of the solubilization solution or the refold buffer comprises one or more of urea, guanidinium salts, dimethyl urea, methylurea and ethylurea." *Id.*, 22:66-

23:2. And dependent claims 15-19 and 23-27 similarly call out one of the elements of the groups from the independent claim, and further narrow that element to particular kinds of reductants, surfactants, aggregation suppressors, protein stabilizers, or redox components.

Without citing any legal authority, Petitioners made the blanket assertion that:

> [B]ecause claim 9 recites the components of the solubilization solution and refold buffer in the alternative, and the additional claim limitations recited in dependent claims 14-19 and 23-27 merely limit the scope of one of these components to certain reagents, under a plain reading, these dependent claims ***do not require use of one of the recited chemicals***, ***so long as one of the alternative components recited in claim 9 is present*** in the solubilization solution or refold buffer.

Pet.13. Petitioners repeatedly relied on this reasoning in an attempt to excuse their failure to prove that the prior art teaches the limitations of various dependent claims. Petitioners implicitly assumed that if an independent claim is invalidated by the prior art, the corresponding dependent claims are automatically invalidated without more proof. *See, e.g.*, Pet.27-29, 31-32 (arguing Wang anticipates and, with Cutler, renders obvious, dependent claims 15, 23, 16, 24, 17, 25, 18, and 26, without addressing substance of dependent claims); Pet.39 (arguing anticipation of dependent claims 16 and 24 by Reardon, without addressing substance of

dependent claims); Pet.46 (arguing anticipation of dependent claims 16 and 24 by Dietrich, without addressing substance of dependent claims); Pet.55, 57 (arguing obviousness of dependent claims 15, 23, 16, 24, 19 and 27 over the Komath references, without addressing substance of dependent claims). Contrary to the intrinsic evidence and basic canons of claim construction, Petitioners read all of the limitations added by the dependent claims as meaningless nullities.

Under *Phillips*, and consistent with the plain meaning of the claims and basic principles of claim construction, these dependent claims should be construed to mean that *the group member recited* by the dependent claim *must* be present (and further limited as the dependent claim specifies), while one or more (or none) of the other remaining members of the independent claim's group may also be present. *See Galderma Labs., LP v. Tolmar Inc.*, No. 1:10-cv-00045-LPS, 2012 U.S. Dist. LEXIS 30528, *30 (D. Del. Feb. 13, 2012) (construing claims depending from independent claims with *Markush* groups to require a particular member of the *Markush* where the dependent claim specified the particular member).

First, the use of the word "the" in these dependent claims (*e.g.*, "*the* surfactant," "*the* aggregation suppressor") derives its antecedent basis from the original *Markush* group member and positively recites a requirement that this particular member be selected. For example, in *Ex Parte Hadar*, Appeal 2015-

001412, 2016 WL 4151075 (PTAB July 28, 2016), the independent claim recited "a transient database or a permanent database." *Id.* at *2. The Board found that the transient database was optional with respect to the independent claim. *Id.* However, the dependent claim specified that the processor was configured to store knowledge "in *the* transient database." *Id.* at *4. The Board determined that the transient database was no longer optional in the dependent claim because the claim "*positively recites* the requirement" that the knowledge be stored in "the transient database," which derived antecedent basis from "a transient database" in the independent claim. *Id*. Because the Board disagreed that the cited references disclosed the transient database, the Board reversed the Examiner's rejection of the dependent claim. *Id.* The same result attaches here.

Second, absent lexicography that Petitioners have not argued here (and should not be permitted to argue on Reply (see n.5)), the *Phillips* standard requires a construction according to a claim's "ordinary meaning." *Phillips*, 415 F.3d at 1314. The ordinary meaning of the term "wherein the [component] comprises" or "wherein the [component] *is* selected from" (in, *e.g.*, dependent claim 17)—as opposed to, *e.g.*, "***if*** selected"—following the recitation of the required component of the first *Markush* group (*e.g.*, "the surfactant," "the aggregation suppressor") is that the component *is in fact selected, and thus exists*. EX2056, ¶¶38-41. For example, the plain reading of dependent claim 16, "wherein the surfactant

comprises one or more of sarcosyl and sodium dodecylsulfate," requires that the solubilizing solution *does comprise* at least a surfactant and that the surfactant is sarcosyl and/or sodium dodecylsulfate. In contrast, under Petitioners' understanding of the claims, claim 16 can be satisfied where one of the *other* two members (a denaturant or a reductant) is disclosed by a prior art reference, but the recited surfactant (sarcosyl and sodium dodecylsulfate) is not. That is, according to Petitioners, the language in claim 16 specifying requirements for "the surfactant" is satisfied *when there is no surfactant at all*.

Third, "[u]nder the doctrine of claim differentiation, dependent claims are presumed to be of narrower scope than the independent claims from which they depend." *AK Steel Corp. v. Sollac*, 344 F.3d 1234, 1242 (Fed. Cir. 2003). And the case law requires a "presumption that each claim in a patent has a different scope." *Dow Chem. Co. v. United States*, 226 F.3d 1334, 1341 (Fed. Cir. 2000). But under Petitioners' theory, claims 14-19 and 23-27 are not necessarily any narrower than independent claim 9, from which they depend. And, though Petitioners read the dependent claims as requiring nothing beyond that required in the independent claim to invalidate them, "the limitations stated in dependent claim[s] should ordinarily not be read into independent claim[s]." *Id.* To the contrary, "each claim must be considered as defining a separate invention." *Jones v. Hardy*, 727 F.2d 1524, 1528 (Fed. Cir. 1984); *see also Pall Corp. v. Micron Separations, Inc.*, 66

F.3d 1211, 1220 (Fed. Cir. 1995) ("[E]ach claim is a separate statement of the patented invention"). Petitioners' approach does not align with longstanding precedent.

Fourth, Petitioners' approach does not attribute appropriate patentable weight to the dependent claim terms, and would improperly render the claim terms meaningless. *Cf. Ex Parte Gopalan*, Appeal 2017-007009, 2018 WL 2386111, at *4-5 (PTAB May 21, 2018) (reversing Examiner's construction of conditional limitations because it did not attribute patentable weight to conditional limitations and conditions were not mutually exclusive); *see also Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1362 (Fed. Cir. 2008) (holding claim constructions that render claim terms meaningless should be avoided). In *Gopalan*, the Board rejected the Examiner's reasoning that, simply because they are conditional in nature, the Examiner need not find, in the prior art, steps of a method that occur only "if" or "when" certain conditions are met in order to render the claimed method obvious. 2018 WL 2386111, at *1-2. The Board instead agreed with Appellants that the Examiner's construction would result in the claimed method not requiring any step at all. *Id.* Such a construction would be "overly broad and unreasonable" because a POSITA considering the claim in combination with the specification would interpret the claim to be "limited to the method described in which the recited conditions occur." *Id.* at *2. The dependent

claims here are similarly limited to the instances in which the particular *Markush* group members are actually selected and exist. Indeed, "it is axiomatic that that which would literally infringe if later anticipates if earlier." *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1378 (Fed. Cir. 2001). But under Petitioners' construction, one could infringe claim 16 if the infringing product's solubilizing solution did not have a surfactant at all (but instead merely satisfied the other requirements, or options, of independent claim 9). This is nonsensical, and Amgen is unaware of any case finding infringement of such a dependent claims under these circumstances.

Amgen's proposed construction—unlike Petitioners' assumed interpretation—is also consistent with the file history. The Examiner interpreted claims 14-19 during prosecution as affirmatively requiring the prior art to disclose the claimed group member and kind, even under the more accommodating broadest reasonable interpretation standard. EX1033, 76-78 (rejecting claims 14-15 and 17-19 in view of reference and bringing in an additional reference that disclosed sodium dodecylsulfate in order to reject claim 16); EX2056, ¶41; *see also Personalized Media Commc'ns, LLC v. Apple Inc.*, 952 F.3d 1336, 1345 (Fed. Cir. 2020) (explaining "prosecution history provides persuasive evidence that informs the meaning of the disputed claim phrase").

Further, although resort to extrinsic evidence is unnecessary because the meaning of the dependent claims here is apparent based on the intrinsic evidence, a POSITA would have read the dependent claims to impose limitations on the independent claim. EX2056, ¶40. Thus, for instance, a POSITA would have read claim 15 to require that a reductant be included in the solubilization solution (and that the reductant be one of those listed in claim 15). *Id.* Indeed, to read these claims otherwise would be to ignore the very limitations recited in the dependent claims, which a POSITA would not have done. *See id.*

IV. Petitioners Failed To Establish Anticipation Or Obviousness Of Any Challenged Claim

A. Grounds 1 And 2: Petitioners Did Not Show That The Challenged Claims Are Anticipated By Wang Or Rendered Obvious Over Wang In View Of Cutler

1. "Applying The Refold Solution"[8]

Petitioners asserted that a POSITA would have understood the refold solution was purified without intervening steps in Wang's "refolding by dilution" method because, they said, "the protocol for this arm of the experiment would have been kept as close as possible to the protocol for 'Refolding with Simultaneous purification.'" Pet.24. And Petitioners assert that "refolding with simultaneous

[8] Petitioners did not assert obviousness of this claim limitation using Cutler in Ground 2. Therefore, the only theory for this limitation is one of anticipation.

purification" does not involve intervening steps because the solution is "directly injected into the column." *Id.* But far from establishing anticipation, Petitioners' loose and unsupported "would have" argument—falling well short of inherency—was actually a concession that Wang does *not* explicitly address whether there are intervening steps for "refolding by dilution." Instead, Petitioners' assertion improperly attempted to shoehorn an obviousness argument (without the required proof) into anticipation. *Intelligent Bio-Sys*, 821 F.3d at 1367-68 (affirming Board finding of non-obviousness, and noting obviousness showing requires both a showing of reasonable expectation of success and motivation to combine.); *Duro-Last, Inc. v. Custom Seal, Inc.*, 321 F.3d 1098, 1107-08 (Fed. Cir. 2003) ("Succinctly put, the various unenforceability and invalidity defenses that may be raised by a defendant—inequitable conduct, the several forms of anticipation and loss of right under § 102, and obviousness under § 103—require different elements of proof."); *see also Eli Lilly & Co. v. Los Angeles Biomedical Research Inst.*, IPR2014-00693, Pap.45, 8 (Oct. 22, 2015) ("to anticipate, a prior art reference 'must not only disclose all elements of the claim within the four corners of the document, but must also disclose those elements *arranged as in the claim*.'" (quoting *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008)) (internal quotation marks omitted); *Net MoneyIN*, 545 F.3d at 1371 (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); *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.'").

Petitioners' argument is similar to the one rejected in *Eli Lilly*, where the Board analyzed a claim that required administering a PDE5 inhibitor once a day for 45 days. IPR2014-00693, Pap.45, 7. The petitioner there pieced together the phrase "daily dosing" from the prior art reference's title with disclosure that treatment should continue as long as the patient suffers from the affliction (which would be months) to argue that the claim was anticipated by the reference. *Id.* at 8-9. The Board concluded that this was "at best" an obviousness argument and did not demonstrate anticipation. *Id.* at 9.

Petitioners are also incorrect that a POSITA would have kept the "refolding by dilution" protocol in Wang "as close as possible" to Wang's "refolding by simultaneous purification" protocol in the way Petitioners propose, such that no intermediate steps would have been performed. Pet.24-25. Petitioners' arguments ignored important differences between the two protocols. Notably, in "refolding by dilution," the refolding is completed *before* applying the protein to the column,

while in "refolding by simultaneous purification," refolding is performed *after* applying the protein to the column. EX1003, 184[9]; EX2058, 41:16-42:8; EX2056, ¶¶45-46; *see also id.* ¶¶42-44. Refolding the protein *before* applying it to the column (as in "refolding by dilution") as opposed to *after* applying it to the column would be more likely to involve steps after refolding the protein and prior to applying it to the column that could cause precipitation. EX2056, ¶46. Given the disclosures (and lack thereof) in Wang, a POSITA would have assumed any such precipitates were removed before applying the protein solution to the column to avoid clogging and fouling it.[10] *Id.* Wang does not explicitly discuss removing such precipitates in "refold[ing] by dilution" before applying the solution to the column, but a POSITA would have expected and understood such steps to be performed. *Id.* Notably, Wang's more detailed subsequent discussion of a known refolding by dilution method does explicitly disclose "acid precipitation." EX1003, 188; EX2056, ¶46.

Petitioners' expert's testimony fails to support their argument. With respect to refold by dilution and refold by simultaneous purification, Petitioners' expert

[9] Citations to Wang are to the original (not stamped) page number to follow the convention used by Petitioners.

[10] This is different from refolding protein *after* applying it to the column.

asserted in his written testimony that the "all variables should be held constant *with the exception of the independent variable being studied*." EX1002, ¶146. But when asked to identify that *independent variable* at deposition, he struggled to answer and eventually said "the type of purification process was the thing that was being held constant," and he "meant to convey … the process after the refolding step is the thing that's being held constant." EX2058, 40:18-23, 41:13-15. He then admitted that, with respect to refolding by simultaneous purification, the protein loaded onto the column "has not yet been refolded," making his assertion about keeping the refold by dilution process the same as refold by simultaneous purification process "after the refolding step" and before applying the protein to the column nonsensical. *Id.*, 41:16-42:8. Nor did he know whether variables such as the volume or concentration of protein in the solution applied to the column were held constant in Wang's two protocols, or whether the sample solution used in the two protocols was the same. *Id.*, 28:24-30:11; *see also id.*, 48:6-49:12. For these reasons, his opinions regarding Wang's refolding by dilution process as they relate to "applying the refold solution," and his opinion that the process would

have been kept as similar as possible to refold by simultaneous purification are unsupported and incoherent, and should be given no weight.[11]

Further, Wang's "refolding by dilution" method involves diluting the sample of protein 100-fold, whereas the "simultaneous purification" technique does not. EX2056, ¶47; EX1003, 184; *cf.* EX2058, 47:6-48:8. Because the "refolding by dilution" approach would result in the protein being in a very large volume of solution at a low concentration (unlike in refolding by simultaneous purification), a POSITA may very well have taken steps to concentrate the protein in the "refold by dilution" protocol before applying it to the column. EX2056, ¶47. Such a concentration step likely would have resulted in, *inter alia*, precipitation, which is a prohibited intermediate step (and which precipitates would have needed to be removed before applying the protein to the column, possibly by centrifugation). *Id.* Petitioners' own background reference states that when "[r]efolding by dilution," "[c]oncentration steps have to be included in the production scheme."

[11] While a POSITA would have expected certain variables to have been kept constant, such as the identity of the protein, there is no reason a POSITA would have expected others—such as the procedures between solubilization and applying the protein to the column—to be kept constant particularly where those differences in protocols were what was being studied. EX2056, ¶47n.4.

EX1020, 6[12]; EX2056, ¶47; EX2058, 12:2-10. And yet another of Petitioners' own references states "[t]he main disadvantages of dilution refolding for commercial applications are the need for larger refolding vessels and additional concentration steps after renaturation." EX1016, 8; EX2058, 12:2-16:3. Nevertheless, Petitioners did not address the protein concentration in Wang's refold by dilution protocol, or whether it would result in the use of prohibited intermediate steps.

Here, Petitioners simply failed to establish that a POSITA would have understood Wang's "refolding by dilution" protocol to exclude precipitation and centrifugation, both of which are prohibited intermediate steps. Petitioners

[12] Petitioners' expert, Dr. Tessier did not know the concentration of the protein or volume of the solution applied to the column in Wang's "refolding by dilution" method. EX2058, 28:24-30:11. However, if a POSITA were to try to keep the two protocols "as close as possible" (and, as noted, there is no reason to believe this would be the case), a POSITA would have had to concentrate the protein in "refolding by dilution" to make the protein concentration and solution volume the same as that applied to the column in "refolding by simultaneous purification." EX2056, ¶49. But based on Dr. Tessier's admission (EX2058, 28:24-30:11), Dr. Tessier did not know if concentration occurred and if the solution volume and protein concentration was the same across the two protocols.

asserted that a POSITA would have understood the refold solution was purified by ion exchange chromatography without intervening steps "because no intervening steps are disclosed." Pet.24. However, mere silence in a reference does not satisfy Petitioners' burden to establish that there ***actually*** were no intervening steps: a petitioner cannot prove a negative simply by omission. *Google, Inc. v. Core Wireless Licensing S.A.R.L.*, IPR2015-01715, Pap.30, 12-18 (Sept. 27, 2019) (remand decision concluding after detailed analysis that silence in the prior art is not sufficient *per se* to disclose a negative limitation); *see also Int'l Bus. Machines Corp. v. Iancu*, 759 F. App'x 1002, 1011 (Fed. Cir. 2019). It is "incumbent on petitioner to show that the limitation is adequately described," such as, in Wang, the lack of precipitation or centrifugation. *Google*, Pap. 30, 18. Petitioners here made no attempt to do so. And, Petitioners' conclusion regarding Wang is inconsistent with disclosures in their own background art stating that it was "highly recommended" at the time to *centrifuge* a solution before loading it onto a column: "[i]t is highly recommended to centrifuge and filter any sample immediately before chromatographic purification." EX1036, 154; *see also* EX2058, 19:10-20:4 (Petitioners' expert admitting "I would agree that removal of particular matter is important and it is common before chromatographic purification … And so I agree that centrifugation and filtration are common before chromatography"); EX2056, ¶50, ¶64 (explaining that filtering and centrifuging are not redundant steps).

Petitioners failed to address why a POSITA would have understood or assumed that such steps would not have been performed in Wang as a matter of course to avoid fouling or clogging the column. *See* EX1036, 153-54 ("Simple steps to clarify a sample before beginning purification will avoid clogging the column…and can extend the life of the chromatographic medium….It is highly recommended to centrifuge *and* filter any sample immediately before chromatographic purification."); *see generally* EX2056, ¶64. Indeed, POSITA would have understood the benefits of centrifugation, and may very well have expected that centrifugation was performed after refolding by dilution in Wang. EX2056, ¶50. But centrifugation is prohibited by the claims. Further, the solution in which the protein was refolded in Wang is referred to as "the solution," but Wang says only that "the rhSCF was purified by IEC" (*not* that "the solution was purified by IEC"). EX1003, 184; EX2056, ¶51.

Petitioners' expert's explanation for his opinion that Wang teaches no intervening steps is also illogical and contradictory, and should be given no weight, especially in view of his admission that he "do[es]n't know [about] anything that's not written [in Wang]." EX2058, 34:14-35:7. When asked if there could be something that's not written in Wang but that was done to the solution before applying it to the column, Dr. Tessier admitted "***I don't know***." *Id.*, 35:1-7. After discussing the substance of his testimony with Petitioners' counsel (*id.*, 93:22-

94:3), he tried to walk back this admission (*id.*, 87:18-89:24). But even on re-direct under questioning from Petitioners' own attorney, he admitted "***of course there can be intervening steps that we don't see here***." *Id.*, 89:8-9. And, of course, this includes prohibited intermediate steps that are outside the claim. Petitioners' expert attempted to get around his admission by asserting that the "simplest thing the POSA would do is look at the previous paragraph [regarding refold by simultaneous purification]" where, he contends, the solution is "directly injected." *Id.*, 87:18-89:24. He asserted the "simplest explanation" is that the solution containing the refolded protein was directly injected in "refold by dilution." *Id*. But then, when asked on re-cross what he meant by his phrase "simplest explanation," he admitted he was not offering anything other than a circular argument: he simply ***assumed*** this was the case based on the reference's silence. *Id.*, 94:4-22; *see also* EX2056, ¶48.

2. "Under Conditions Suitable For The Protein To Associate With The Matrix"[13]

In attempting to show anticipation, Petitioners improperly mixed and matched separate disclosures from different distinct embodiments in Wang, and therefore failed to prove Wang teaches "under conditions suitable for the protein to

[13] *See supra*, n.8.

associate with the matrix." Pet.24; *see, e.g.*, *Net MoneyIN*, 545 F.3d at 1371 ("The district court was also wrong to combine parts of the separate protocols"; 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*, IPR2014-00357, Pap.14, 20 (same); *Eli Lilly*, IPR2014-00693, Pap.45, 8 ("[T]o anticipate, a prior art reference 'must not only disclose all elements of the claim within the four corners of the document, but must also disclose those elements *arranged as in* the *claim*.'" (quoting *Net MoneyIN*, 545 F.3d at 1369)) (internal quotation marks omitted)); *see also In re Arkley*, 455 F.2d 586, 587 (C.C.P.A. 1972) ("[T]he [prior art] reference must clearly and unequivocally disclose the claimed [invention] or direct those skilled in the art to the [invention] without *any* need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference."). For instance, Petitioners referred to Wang's discussion of "solution II" as purportedly disclosing the solubilization solution. Pet.23. And, Petitioners relied on "refolding by dilution" for the "forming a refold solution" step and for the "applying the refold solution to a separation matrix" step. Pet.23-24. But, in their attempt to prove that Wang discloses "under conditions suitable for the protein to associate with the matrix," Petitioners relied on data from Table 1. Pet.24. Table 1, however, does not show any results from solubilization performed

with "solution II" because the *pH conditions reported in Table 1 are different than solution II's*. EX1003, 183, 187; EX2056, ¶52; EX2058, 27:3-17 (Petitioners' expert Dr. Tessier agreeing pH does not match between solution II and results reported in connection with Table 1 footnote b). Solution II is described as ".05 $mol \cdot l^{-1}$ Tris, ***pH 12.5*** containing 0.05 $mol \cdot l^{-1}$ Na_2HPO_4 and 2.0 $mol \cdot l^{-1}$ urea," but Table 1 presents results for "rhSCF solubilized by 8.0$\cdot l^{-1}$ urea" in the first row of data (as indicated in Table 1 footnote "a") and "rhSCF solubilized by ".05 $mol \cdot l^{-1}$ Tris (***pH 13.0***) containing 0.05 $mol \cdot l^{-1}$ Na_2HPO_4 and 2.0 $mol \cdot l^{-1}$ urea" in the second row of data (as indicated in Table 1 footnote "b"). EX1003, 183, 187; EX2058, 27:3-17.[14] Petitioners thus improperly plucked disclosures from two different embodiments in pointing to various solutions, such as "solution II," for the disclosure of "solubilization solution" one the one hand, and Table 1's results for *different* solutions, on the other hand. Petitioners did not identify refolding results for a process that used "solution II," and thus did not establish that Wang

[14] Similarly, Table 1 does not appear to provide results for solubilization performed with "solution III." EX1003, 183, 187; EX2056, ¶¶52-53; EX2058, 28:5-23. While the Petition does not mention "solution III" (Pet.23), Petitioners' expert relies on "solution III" in passing. EX1002, ¶142. But even if credited, this theory similarly (and improperly) mixes and matches disclosures.

discloses the limitation that requires "conditions suitable for the protein to associate with the matrix."

3. Dependent Claims: Petitioners' Arguments Regarding Claims 16-18 And 24-26 Are Legally Flawed And Unsupported By Evidence

As properly construed (*see* §III.C), claims 16-18 and 24-26 require that the solubilization solution and/or refold solution include the ingredients recited in the given dependent claim (*e.g.*, a surfactant comprising sarcosyl or sodium dodecylsulfate in the case of claim 16). But instead of submitting any evidence showing how Petitioners argue these limitations are met, the Petition's analysis erroneously assumed the limitations in the dependent claims can be read out entirely. *See* §III.C. Petitioners' decision to punt on the additional requirements of these dependent claims, and their failure even to attempt to make any showing that their asserted references disclose them, is an additional reason Petitioners have failed to show that Wang anticipates or that, with Cutler, Wang renders obvious claims 16-18 and 24-26 (Grounds 1 and 2). Indeed, Petitioners did not seek to combine Wang with Cutler for the purpose of any obviousness argument with respect to the dependent claims' limitations.

4. Ground 2 Only: Petitioners' Conclusory Motivation To Combine And Reasonable Expectation Of Success Arguments Are Insufficient To Establish Obviousness

Petitioners' brief and conclusory obviousness arguments were limited to certain aspects of the separation matrix steps and related to the basics of purifying protein using ion exchange chromatography—washing and eluting a protein after application to the column. Pet.31-32.[15] Petitioners made no obviousness arguments at all in connection with various holes in their anticipation arguments including, *e.g.*, with respect to the "applying the refold solution" to the separation matrix and "under conditions suitable" limitations. EX1001, 12:57-58. And for the few obviousness assertions that Petitioners did make, Petitioners never even undertook to ***identify the differences between Wang and the claims***—another requirement for establishing obviousness. *See, e.g., Instrumentation Lab. Co. v. Hemosonics LLC*, IPR2017-00855, Pap.55, 48 (Feb. 13, 2019) ("Petitioner, however, fails to address any similarities or differences between the two devices . . . ."); *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1360 (Fed. Cir. 2012) ("Obviousness is a question of law based on underlying factual findings: (1) the scope and content of the prior art; (2) the differences between the claims

[15] With respect to Grounds 2 and 5, Patent Owner herein addresses the obviousness arguments to the extent they were understood by the Board at institution.

and the prior art; (3) the level of ordinary skill in the art; and (4) objective indicia of nonobviousness." (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966))); *Apple Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1048 (Fed. Cir. 2016) ("A determination of whether a patent claim is invalid as obvious under § 103 requires consideration of all four Graham factors, and it is error to reach a conclusion of obviousness until all those factors are considered.").

Petitioners additionally failed to provide any meaningful analysis of ***how a POSITA would have modified Wang***. *See* Pet.31-32; *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 Petition 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."); *Canfield Sci., Inc. v. Melanoscan, LLC*, IPR2017-02125, Pap.62, 24 (Mar. 26, 2019) (final written decision holding claims not obvious where petitioner failed to explain how POSITA would have modified the references, the references did not explicitly disclose the modification, and the petition relied on the expert declaration to explain the modification); *Elec. Arts Inc.*

v. Terminal Reality, Inc., IPR2016-00928, Pap.48, 27, 38, 40, 42 (Oct. 23, 2017) (final written decision holding claims not obvious where petitioner did not provide "how or why" a POSITA would modify the teachings of the references in the manner suggested); *Ariosa Diagnostics v. Verinata Health, Inc.*, IPR2013-00276, Pap.64, 9 (Aug. 15, 2016) (remand decision affirming final written decision holding claims not obvious where petitioner pointed to disparate elements of references, mapped them to the claims, but made "virtually no effort" to explain how a POSITA would combine the elements or what modifications it would need to make). This similarly requires rejection of the few obviousness arguments Petitioners attempted to advance.

In addition to failing to point out specific modifications to Wang, the base reference, Petitioners failed to explain ***why POSITA would be motivated to make any proposed modification***—another fatal failing. *See, e.g., Cisco Sys., Inc. v. Oyster Optics, LLC*, IPR2017-01881, Pap.29, 33-38 (Feb. 26, 2019) (final written decision holding claims not obvious where petitioner did not explain in the Petition why a POSITA would modify the teachings of the references in the manner suggested, even though petitioner further expanded on the modification at oral argument); *Samsung Elecs. Co. v. Elm 3DS Innovations, LLC*, IPR2016-00691, Pap.42, at 33, 35-39 (Aug. 22, 2017) (final written decision holding claims not obvious where "Petitioner's testimony [wa]s conclusory without explaining what

types of improvements in 3D integrated circuits would have motivated one of ordinary skill in the art to make Petitioner's proposed substitution" of one element into another). As in *Samsung*, Petitioners' argument regarding motivation to combine is insufficient, generic, and conclusory. Pet.31-32.

Moreover, the Petition's cursory obviousness analysis for Ground 2 included only a single conclusory assertion directed to reasonable expectation of success. *See* Pet.32. Petitioners provided no explanation for this assertion, which also ignores any reasonable expectation of success *when Wang is somehow modified using Cutler*. *See Intelligent Bio-Sys.*, 821 F.3d at 1367-68; *Canfield*, IPR2017-02125, Pap.62, 15-16, 24 (final written decision holding claims not obvious where petitioner failed to establish a reasonable expectation of success).

Petitioners' expert testimony does not remedy these failings, offering little more than similarly conclusory (and insufficient) statements that a POSITA "would have been motivated to combine Wang and Cutler, and would have had a reasonable expectation of success." EX1002, ¶168; *Samsung Elecs. Co., v. Elm 3DS Innovations, LLC*, IPR2016-00386, Pap.68, 53-54 (June 23, 2017) (final written decision holding claims not obvious where petitioner's expert testimony was conclusory and the petition merely cited the testimony without further discussing or explaining relevance); §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 also* §42.6(a)(3) ("Arguments must not be incorporated by reference from one document into another document.").

Finally, even if Petitioners now recognize the palpable weaknesses in their obviousness arguments, Petitioners may not add new arguments in Reply to address them. Petitioners are only permitted to rely on—and Amgen can only be expected to respond to—the arguments Petitioners actually made in their Petition. *See Wasica*, 853 F.3d at 1286 (rejecting reply brief attempting to cure deficiencies in petition and noting the "obligation for petitioners to make their case in their petition"); *NuVasive*, 841 F.3d at 972-73 (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.*, 821 F.3d at 1367-68; Trial Practice Guide,77 Fed.Reg. at 48,767 (Aug. 14, 2012) ("[A] reply that raises a new issue or belatedly presents evidence will not be considered and may be returned.").

5. Petitioners Adduced No Evidence And Presented No Argument About Wang Or Cutler Being A Printed Publication

Petitioners did not make any attempt to establish Wang or Cutler are prior art printed publications. Petitioners merely asserted, without support, that Wang "is a prior-art printed publication" and "was published" in February 2008. Pet.20. Similarly, Petitioners merely asserted—again without support—that Cutler "is a

textbook…published in 2004" and concluded "Cutler is a prior-art printed publication." Pet.31. Petitioners said nothing about where the pages they attached as exhibits were found or generated. Indeed, Petitioners presented no evidence or argument establishing Wang was from a regularly published journal, and gave no explanation for the asserted 2008 date. Similarly, Petitioners identified no admissible evidence establishing the Cutler "textbook" was publicly available in 2004. Petitioners have thus failed to meet their burden on a basic element of anticipation by Wang (Ground 1) and obviousness over Wang and Cutler (Ground 2): establishing the references are authentic prior art printed publications. *See, e.g.*, *Schlumberger Tech. Corp. v. Integrated Drive Sys. LLC*, IPR2018-00604, Pap.40, 13-24 (Sept. 3, 2019) (final written decision holding petitioner did not meet its burden of proving that product brochure was publicly accessible where brochure bore copyright date of 2013); *Celltrion, Inc. v. Biogen, Inc.*, IPR2016-01614, Pap.65, 13-20 (Feb. 21, 2018) (final written decision holding petitioners did not meet their burden of proving that drug label was publicly accessible where label bore a copyright date of 1997); *Carefusion Corp. v. Baxter Int'l, Inc.*, IPR2016-01463, Pap.38, 32-36 (Jan. 2, 2018) (final written decision holding petitioner did not meet its burden of proving that user manual was publicly accessible where label bore a copyright date of 1990); *see also Nobel Biocare Servs. AG v. Instradent USA, Inc.*, 903 F.3d 1365, 1376 (Fed. Cir. 2018)

(explaining date on a catalog is not dispositive of the date of public accessibility, but rather is "relevant evidence"); *TRW Auto. U.S. LLC v. Magna Elecs. Inc.*, IPR2014-01347, Pap.25, 8-9 (Jan. 6, 2016) (informative) ("[C]opyright notice is…not probative that the article was ever published by IEEE or anyone else.").[16] And the Board has explained previously that where the petitioner does not provide sufficient evidence to prove public accessibility, "it is not incumbent upon the Board to seek it out." *ABS Global, Inc. v. Inguran, Inc.*, IPR2016-00927, Pap.33, 22-23 (Oct. 2, 2017).

B. Ground 3: Petitioners Did Not Establish That The Challenged Claims Are Anticipated By Reardon

1. Petitioners Improperly Mixed And Matched Embodiments In Mapping Independent Claim 9

Petitioners improperly mixed and matched separate disclosures from different distinct embodiments in Reardon, and therefore failed to prove Reardon

[16] *Hulu, LLC v. Sound View Innovations, LLC*, IPR2018-01039, Pap.29, 19-21 (Dec. 20, 2019) (precedential) relates to the requirements for establishing prior art status *only for the purpose of institution*. Further, there are fewer indicia in this case pointing to a conclusion of public accessibility than in *Hulu.* For instance, in *Hulu*, there was evidence that the textbook, which included a printing date and ISBN date, was part of a "well-known book series." *Id.* at 19.

anticipates the challenged claims, including independent claim 9. *See, e.g.*, *Net MoneyIN*, 545 F.3d at 1371 (holding that the district court was wrong to combine "parts of the separate protocols shown in the . . . reference" when it concluded that the claim was anticipated, even if there were "only slight differences between the protocols disclosed in the . . . reference" and the allegedly anticipated claim); *Symantec*, IPR2014-00357, Pap.14, 20 (same); *see also In re Arkley*, 455 F.2d at 587; *see Eli Lilly*, IPR2014-00693, Pap.45, 8 (stating a prior art reference "must not only disclose all elements of the claim within the four corners of the document, but must also disclose those elements '*arranged as in* the *claim.*'" (quoting *Net MoneyIN*, 545 F.3d at 1369)).

Petitioners mapped the "applying the refold solution" step to Reardon's claim 23 and Example 12(C).[17] However, Petitioners did not rely on the disclosures in Example 12(C) for other claimed steps such as the solubilization step found in independent claim 9. Moreover, Reardon's Example 12(C) involves a different embodiment than Reardon's claim 23: claim 23 requires loading solution on a column equilibrated to ***pH 8.0***, whereas Example 12(C) involves,

[17] Petitioners also include a "*see also*" citation to claims 20 and 47 of Reardon, but have not attempted to map those Reardon claims to, *e.g.*, the "applying" step of claim 9. *See* Pet.35-37.

inter alia, loading solution onto a column equilibrated to ***pH 5.5***. *Compare* EX1004, [0172] *with* EX1004, cl. 23; EX2058, 58:18-60:8. Because of, *inter alia*, the differences in the pH of the equilibrated columns between Reardon's claim 23 and Example 12(C), a POSITA would also have expected the pH of the solutions loaded onto each column to be different in the two embodiments because the solution loaded onto the column normally has a pH the same as or similar to that of the equilibrated column. EX2056, ¶¶54-55; EX2059, 2; *cf.* EX2058, 60:9-24 (admitting it is "common practice" to equilibrate column to pH similar to that of solution being loaded). In addition, Reardon's Example 12(C) describes an expanded-bed column, whereas Reardon's claim 23 appears to use a different kind of column. EX2056, ¶55. Reardon's claim 23 is the only embodiment Petitioners consistently mapped to '997 claim 9, and therefore only Reardon's claim 23 embodiment should be considered in analyzing whether Reardon anticipates claim 9 of the '997 patent.

2. Neither Reardon's Claim 23 Nor Example 12(C) Discloses "Applying The Refold Solution…"

Petitioners cite Reardon's Example 12(C) and claim 23 as allegedly disclosing "applying the refold solution," but Petitioners have not established that either actually does, and the citation to Example 12(C) should not be considered in any case. *See* IV.B.1; EX2056¶¶56-60.

With respect to the disclosure in Example 12(C), Petitioners did not address whether adjusting the pH to 5.5 would result in, *e.g.*, precipitation, which is prohibited by the claims as properly construed. *See* §III.B. And in fact, a POSITA would not have been able to determine whether such pH adjustment would result in precipitation, which is not allowed under the proper construction of "applying the solution." EX2056, ¶57. Even Petitioners' expert, when asked if the pH adjustment to 5.5 resulted in any precipitation, responded "*I don't know*." EX2058, 63:18-22.[18] And, as discussed above, Petitioners cannot establish a lack of precipitation merely by pointing to a lack of explicit disclosure in Reardon. *See Google*, IPR2015-01715, Pap.30, 12-18.

Reardon's claim 23 does not say that the solution in which the protein is refolded is applied to the column without intervening steps. In fact, the plain language of the claim suggests the opposite. The claim recites "filtering *the* solution" and then simply "loading solution on resin column." EX1004, cl. 23; This language ("loading solution" not "loading the solution") affirmatively suggests that the loaded solution is not necessarily the same as the filtered

[18] In contrast, Dr. Tessier's declaration seems to imply that there was no precipitation. *See* EX1002, ¶87 (recognizing precipitation is not allowed), ¶¶179-184.

solubilized solution. EX2056, ¶58. Further, the preamble of Reardon's claim 23 recites "comprising," and is not explicitly limiting as to intermediate steps unless the claims steps themselves create such a restriction, which they do not here. *MagSil Corp. v. Hitachi Glob. Storage Techs., Inc.*, 687 F.3d 1377, 1383 (Fed. Cir. 2012). And, as discussed above, one cannot prove a negative by mere lack of discussion in the prior art. *See Google*, IPR2015-01715, Pap.30, 12-18; *see also* EX1036, 154; EX2056, ¶59. In addition, the only disclosures in Reardon of loading protein onto a column of pH 8.0 also describe, *e.g.*, concentration using tangential flow filtration. *See, e.g.*, EX1004, [00082]. But this concentrated solution was then "diluted 3-10 fold with buffer or water to allow unfolded and aggregated proteins *to precipitate*." *Id.* Thus, a POSITA would not have understood that Reardon teaches "applying the refold solution" under the correct construction due to precipitation. EX2056, ¶60.

3. Dependent Claims: Petitioners' Arguments Regarding Claims 14-21 and 23-30 Are Legally Flawed And Unsupported By Evidence

In addition to the shortcomings discussed above with respect to claim 9, Petitioners' proof is also deficient with respect to various dependent claims.

As discussed above, in attempting to prove anticipation by Reardon of claim 9, Petitioners mixed and matched different Reardon embodiments. The only embodiment Petitioners mapped across all limitations was Reardon's claim 23.

See supra IV.B.1. However, in attempting to prove anticipation of each of dependent claims 14-15, 17-21, 23, and 25-30, Petitioners did not cite Reardon's claim 23 at all. Instead, they cited Reardon's paragraphs 79 and 80 for claims 14, 17-19, and 25-27; paragraph 75 for claims 15 and 23; and Examples 12C and 15 for claims 20-21, and 28-30. *See supra* IV.B.1 & IV.B.2. For these reasons, even if the Board were to conclude that claim 9 is anticipated by claim 23 of Reardon, Petitioners cannot establish anticipation of dependent claims 15-19 and 23-27 because they did not map the claim 23 embodiment of Reardon to these dependent claims. *See* IV.B.1.

In addition, claims 16 and 24 require that "the surfactant comprises one or more of sarcosyl and sodium dodecylsulfate." But in arguing anticipation of this claim, Petitioners asserted only that Reardon teaches a solubilization solution comprising denaturants and reductants—not surfactants. Pet.39-40. However, as discussed above (*see* §III.C), dependent claims 16 and 24 require that the solubilizing solution includes a surfactant, and that the surfactant comprises one or more of sarcosyl and sodium dodecylsulfate. *See Ex Parte Gopalan*, 2018 WL 2386111, at *2-3. Accordingly, by ignoring the additional requirements of claims 16 and 24, Petitioners failed to show that Reardon satisfies the limitations added by these dependent claims. *See* III.C.

C. Ground 4: Petitioners Have Not Established That The Challenged Claims Are Anticipated By Dietrich

1. "Applying The Refold Solution…"

Petitioners provided no analysis of any purported disclosure by Dietrich of "applying the refold solution" under the correct construction. *See* Pet.43-44. Dietrich discloses that the ***pH of the solution Petitioners rely on is adjusted to pH 3.2*** (before applying it to the column). EX1005, [0070]. And a POSITA ***would have expected precipitation to occur as a result*** of the substantial pH adjustment using highly concentrated 2M citric acid. EX1005, [0070]; EX2056, ¶¶61-62.[19] Such precipitation is a disallowed intermediate step. *See* III.B.

Further, Petitioners never addressed the conclusion in their own art that it was "highly recommended" at the time to *centrifuge* a solution before loading it

[19] Regarding precipitation in Dietrich after the pH 3.2 adjustment step, Dr. Tessier admitted, "***I don't know if it happened or not, if precipitation happened or not***." EX2058, 78:6-8. And while he attempted to recant this testimony during redirect (*id.*, 92:20-93:16) *after* speaking with Petitioners' counsel about the substance of his testimony (*id.*, 93:22-94:3), he admitted again on re-cross that he did not know whether particles or precipitates formed (*id.*, 94:23-95:11). Nor could he say

onto a column. EX1036, 154. Petitioners did not address why a POSITA would not have understood or assumed that such steps were performed in Dietrich as a matter of course to avoid fouling or clogging the column. *See id.* A POSITA would have understood that centrifugation of the solution prior to applying the solution to the column would beneficially remove particles, including precipitates, to allow the chromatography process to run smoothly. EX2056, ¶63. But such centrifugation (and precipitation) is a disallowed intermediate step under the proper construction of the claims, and Petitioners failed to prove that this "highly-recommended," customary step was not performed in the art they argue anticipates. *See* III.B.

2. Dependent Claims: Petitioners' Arguments Regarding Claims 16 and 24 Are Legally Flawed And Unsupported By Evidence

As properly construed (*see* §III.C), Claims 16 and 24 require that "the surfactant comprises one or more of sarcosyl and sodium dodecylsulfate." But Petitioners did not assert that Dietrich discloses a solubilization solution comprising a surfactant. Instead, Petitioners attempted to ignore this limitation in its entirety, asserting that Claims 16 and 24 do not require any surfactant at all.

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whether the filtration (which is depth filtration) in Dietrich removes precipitates other than aggregated protein. EX2058, 76:13-77:6.

Pet.45. Petitioners' interpretation of these claims is incorrect, and their showing as to these claims is thus fatally deficient. *See* §III.C.

D. Ground 5: Petitioners Have Not Established That The Challenged Claims Are Rendered Obvious By Komath '994 In View Of Komath '056

1. Petitioners Failed To Establish A Motivation To Combine Komath '944 With Komath '056 For "Forming A Refold Solution Comprising The Solubilization Solution And A Refold Buffer…"

Although Petitioners' mapping lacks clarity, the Board at institution understood Petitioners to rely on Komath '056 as a secondary reference purportedly disclosing the claimed refold buffer in an attempt to fill a hole in Komath '944. D.I.35; Pet.51-52.[20] Petitioners argued that Komath '944 motivates the identification of a refold buffer in Komath '056 by describing "a refolding step, wherein '[t]he pH of the refolded protein solution is maintained in the range of 3.5 to 5.5 ***using any appropriate buffer suitable for maintaining pH in the acidic range***.'" Pet.51. Petitioners then asserted Komath '056 discloses forming a refold

[20] Petitioners' statement that Komath '944 teaches refolding "at a *high* pH" appears to be a typo meant to refer to refolding at a *low* pH, and Patent Owner's response here rests on that understanding. *Compare* Pet.52 *with* EX1006, 6 ("The protein is refolded at low pH").

solution by diluting the solubilization solution with 0.1% polysorbate 20 in water at pH 8.0-8.5 for 6 hours and then at pH 4.0-5.0 for 6 to 8 hours. *Id.* Petitioners' arguments have a variety of flaws, and Petitioners' expert adds nothing more to Petitioners' conclusory assertions. *See* EX1002, ¶¶239-240.

In asserting Komath '944 would encourage a POSITA to identify a suitable buffer for refolding, Petitioners pointed to Komath '944's disclosure of "*maintain[ing]*" the "pH of the refolded protein solution." Pet.51-52. But this statement refers to maintaining the solutions' pH ***after the protein is refolded***, not to buffering/maintaining the pH of the solution ***in which protein is refolded*** as the claims require. EX1006, 8.[21] And in fact, the "buffer" disclosures of Komath '944 are in the context of solubilizing, equilibrating, washing, and eluting the column, ***not*** the actual refolding of protein. *See* generally EX1006. Thus, contrary to Petitioners' theory, the identified statement in Komath '944 would not motivate a POSITA to look for a buffer in which to refold protein. EX2056, ¶¶65-67.

Petitioners asserted that Komath '944 describes "using any appropriate buffer suitable for maintaining pH in the acidic range" and that "a POSA would turn to the references cited in the '944 patent, including Komath '056 to determine

[21] Citations to EX1006 (Komath '944) and EX1007 (Komath '056) are to original (not stamped) page numbers, consistent with Petitioners' chosen citation format.

suitable buffers." Pet.51. But even if a POSITA would have been motivated to identify a buffer for use in refolding based on the identified teaching of Komath '944 (they would not have been), ***the solution Petitioners identified as the "refold buffer" in Komath '056—***0.1% polysorbate 20—***is not a buffer*** because it has no buffering capacity. EX2056, ¶¶65-68; *see also* III.A. Petitioners' expert further admitted he ***did not know*** whether there is a conventional buffer present in Komath '056's 0.1% polysorbate in water with a pH of 8.0-8.5. *Id.*, 83:14-18. And Petitioners' expert recognized that 0.1% polysorbate 20 is not a traditional buffer and admitted he did not know whether it had buffering capacity. EX2058, 83:14-24. Thus, even if a POSITA were to look to Komath '056 to identify a "refold buffer," Komath '056 does not teach using anything with a buffering capacity to refold its protein. EX2056, ¶68.

Petitioners' motivation to combine theory is also flawed because Petitioners look to the mention of a "buffer" in Komath '944 to motivate the inclusion of an alleged aggregation suppressor and protein stabilizer in Komath '056. Pet.51. Petitioners (and their expert) apparently assume (without explaining) that Komath '944's reference to a buffer would be understood to include, *inter alia*, an aggregation suppressor or protein stabilizer. Pet.52; EX1002, ¶239. But a POSITA would not have assumed that the buffer referred to in Komath '944 additionally includes, *e.g.*, an aggregation suppressor or protein stabilizer since

buffers do not traditionally include such ingredients. EX2056, ¶69. Indeed, this is why claim 9 separately enumerates the inclusion of one or more of a denaturant, an aggregation suppressor, a protein stabilizer, and a redox component. Thus, although Petitioners relied on Komath '944's teaching of polysorbate as an aggregation suppressor, Petitioners did not establish why a POSITA would have been motivated to look to Komath '944 to identify an aggregation suppressor to begin with, since (1) Komath '944 only suggests refolding be done at an acidic pH (and says nothing about using a buffer to accomplish refolding), and (2) even Komath '944's reference to a post-refold buffer references only a buffer, and neither says nor implies anything about an aggregation suppressor. EX2056, ¶69. In contrast, Komath '056 does not teach refolding entirely at an acidic pH. *Id.*, ¶70.

And finally, in addition to being incorrect, even if they are given the most generous reading, Petitioners' arguments regarding motivation to combine are also generic, conclusory, and insufficient for lack of explanation. Pet.49-52. *See St. Jude*, IPR2018-00105, Pap.59, 37 ("[N]either the Petition nor [petitioner's expert] indicates with sufficient particularity . . . what elements of Andersen are interchanged with elements of Leonhardt and, thus, in what manner Leonhardt and Andersen are combined."); *Elec. Arts*, IPR2016-00928, Pap.48, 42 (final written decision holding claims not obvious where petitioner did not provide "how or

why" a POSITA would modify the teachings of the references in the manner suggested). Indeed, Petitioners' first set of arguments purporting to address motivation to combine (Pet.49-50), is actually just a set of assertions about analogous art. *See Front Row Techs., LLC v. MLB Adv. Media, L.P.*, IPR2015-01932, Pap.7, 20-21 (Mar. 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)).

2. Petitioners Did Not Establish A Reasonable Expectation Of Success

To establish obviousness, Petitioners were required to demonstrate, *inter alia*, a reasonable expectation of success of achieving the claimed invention. *Intelligent Bio-Sys.*, 821 F.3d at 1365. Here, the claimed invention requires that the refolded protein, *inter alia*, associate with (bind to) the separation matrix.

EX1001, cl.9. However, in Komath '056, the results indicate that the protein did ***not*** successfully bind to the column. EX1007, 12 (Table 1).

The Petition included only a single conclusory sentence directed to reasonable expectation of success: "given the results disclosed in Komath '944, [a POSITA] would have had a reasonable expectation of success at achieving a method for purifying a protein expressed in limited soluble form in a non-mammalian expression system." Pet.50. Petitioners' expert's analysis simply parroted the Petition and did not remedy or elaborate on this inadequate, conclusory assertion. EX1002, ¶231; *Samsung*, IPR2016-00386, Pap.68, 53-54; §42.6(a)(3); §42.65(a). This failure is particularly glaring here, because (as noted above), the results in Komath '056 indicate the contrary, *i.e.*, that ***no refolded protein successfully bound to the column***. EX1007, 12 (Table 1); EX2056, ¶71. Thus, even setting aside the failings cataloged in IV.D.1 above, any assertion that a POSITA would have had a reasonable expectation of success in binding properly refolded protein to the column when using Komath '056's "buffer for refolding" is ***belied by Komath '056 itself*** and Petitioners' own assertions about the similarities between the two Komath references. *See* Pet.49-50. And certainly Petitioners' cursory analysis, which addresses only refolding of the protein and not a reasonable expectation of success of achieving the *claimed invention*, was insufficient to satisfy Petitioners' burden. *See In re Nuvasive*, 842 F.3d 1376,

1381-83 (Fed. Cir. 2016) (holding conclusory statements insufficient if not supported by a reasoned explanation) *Samsung*, IPR2016-00386, Pap.68, 53-54 (holding claims not obvious where petitioner's expert testimony was conclusory and the Petition merely cited the testimony without further discussing or explaining relevance); *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.").

3. "Applying The Refold Solution To A Separation Matrix Under Conditions Suitable For The Protein To Associate With The Matrix"

As explained above (§IV.D.1), Petitioners have not identified a refold buffer in their obviousness analysis. Because the "refold solution compris[es] the solubilization solution ***and a refold buffer***" (EX1001, 22:44-45), Petitioners' argued Komath combination lacks the claimed "refold solution." Therefore, the Komath combination also does not and cannot render obvious "applying the refold solution to a separation matrix," since no claimed "refold solution" is applied to the separation matrix.

4. Dependent Claims 10, 13-21, and 23-30: Petitioners' Arguments Regarding The Dependent Claims Are Legally Flawed And Unsupported By Evidence

Because Petitioners did not establish that claim 9 is obvious, they also failed to establish obviousness of any of the dependent claims.[22] In addition, as properly construed (*see* §III.C), claims 15 and 23 impose requirements on what "the *reductant* comprises," claims 16 and 24 impose requirements on what "the *surfactant* comprises," and claims 19 and 27 impose requirements on what "the *redox component* comprises." In analyzing these dependent claims, however, Petitioners did not assert that ***either*** Komath reference teaches or renders obvious a reductant, surfactant, or redox component. Instead, Petitioners rested solely on their erroneous assertion that, despite their explicit language, these claims do not require the recited component(s). Pet.55-56. Having failed to provide any evidence or explanation under the proper claim construction, Petitioners did not and cannot meet their burden on these claims.

Further, in addition to the issues with the motivation to combine in Petitioners' efforts to find disclosure of a "refold buffer," Petitioners' citations to Komath '056 in arguing obviousness of other elements of the dependent claims are also misplaced and unavailing. *See* Pet.54-58 (*e.g.*, claims 10, 14, 20, 28).

[22] Further, with respect to Komath '944 itself, Petitioners' expert stated only that polysorbate is an aggregation suppressor and not, as required in claims 18 and 26, a protein stabilizer. EX1002, ¶¶239-240, 256.

Petitioners offer no explanation for any motivation to combine or modify the references to cobble together a disclosure of these dependent claim elements, and no explanation for any reasonable expectation of success in doing so. Petitioners' obviousness arguments for claims 21, 29, and 30 are similarly indecipherable and confusing as they argue a reasonable expectation of success regarding isolation of a protein after elution, but do not explain any role of Komath '056 in the dependent claim combination. *See ZTE (USA), Inc. v. Elecs. & Telecomms. Research Inst.*, IPR2015-00029, Pap.12, 6 (Mar. 20, 2015) ("[a] brief must make all arguments accessible to the judges, rather than ask them to play archeologist with the record."); *see also A.C. Dispensing Equip. Inc. v. Prince Castle LLC*, IPR2014-00511, Pap.16, 5-6 (Sept. 10, 2014). Again, Petitioners have failed to carry their burden.

V. Petitioners Failed To Establish That Their Non-Patent Literature Background References Are Prior Art Or Reflect Information Known To A POSITA By 2009

Just as with Wang and Cutler (*see* §VI.A.6), Petitioners did not make any attempt to establish that various of their non-patent background references cited in the Petition or relied upon by Petitioners' expert (or both) are actually prior art printed publications. They provide no evidence, declaration, or argument about where the pages they attach as exhibits were found or generated. EX1008-EX1012, EX1014-EX1021, EX1027-EX1028, EX1031, EX1036-EX1038.

For example, EX1027 contains the unexplained words "Edition AC," which might reflect a draft, rather than a final, published version of a document—although there is *no evidence of any of this* to begin with. EX1027, 1. Similarly, EX1036 notes that it is "Edition AA," again without any explanation. EX1036, 1.

As a further example, with respect to EX1031, although Petitioners suggested (albeit only in their List of Exhibits) that it is a copy of a handbook published in 2000 (Pet.vi), they provide no evidence of this. And it is clear from the exhibit itself that it is a version that was published as late as ***2009***, which, depending on when in that year it was published and made available, ***may post-date the date of the '997 patent's 2009 provisional application***. EX1031, 306 ("© 2000–2009 General Electric Company").

Petitioners presented no explanation or evidence as to whether or when any of these materials supposedly reflecting background knowledge in the prior art became properly available as prior art printed publications. Petitioners thus failed to establish the level of background knowledge at the time of the challenged '997 patent inventions. *See*, *e.g.*, *Schlumberger*, IPR2018-00604, Pap.40, 13-24 (holding copyright date of 2013 alone was not sufficient to show publicly accessibility); *Nobel*, 903 F.3d at 1376 (explaining date printed on catalog is not dispositive of date of public accessibility, but rather is just "relevant evidence").

VI. Petitioners' Expert's Opinions Should Be Given Little To No Weight

Petitioners' expert's opinions are conclusory and contradicted by his own admissions, as described above. *See supra* pp. 28-30, 37, 46, 48-49, 52; *see also supra* pp. 24-27, 42-43. For that reason, Dr. Tessier's opinions should be given little to no weight. *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*, 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."); *Pungkuk Wire Mfg. Co. v. Seong*, IPR2016-00762, Pap. 63, 10-11 (Aug. 16, 2017) (conclusory expert testimony entitled to little weight). And while Petitioners' expert now claims that statements in his declaration following "I understand that…" are actually his own expert opinions, rather than an understanding gained from lawyers (in other words, Petitioners' expert claims his usage is *different from* how "I understand" is typically used in expert declarations), this implausible position simply undercuts any credibility Petitioners may have argued he possesses. Indeed, under the "Legal Principles" section of his declaration, he states "counsel for Petitioners have informed me about the legal standards for patentability" (EX1002, ¶18), and then he goes on to state "I understand that…" in describing the legal principles (*e.g.*, EX1002, ¶¶19-39). Presumably such understanding came from counsel, showing he used "I understand" in a way that

contradicts his deposition testimony. Further, he was not even sure what materials he reviewed in forming such "I understand" opinions. EX2058, 46:17-20 (despite asserting he formed an opinion on claim construction, he was not sure whether he considered the file history).

In addition, although Dr. Tessier claims never to have seen the expert declaration from an earlier '997 PGR (EX2055; EX2058, 6:22-25), many of his opinions are ***cut and pasted verbatim*** from it, including most of the opinions he recites concerning Dietrich.[23] *Compare* EX1002, 2 (Table of Contents §VI) with EX2055, 2 (Table of Contents §V); *compare* EX1002, ¶¶43, 45 *with* EX2055, ¶36, 38; *compare* EX1002, ¶¶204-209 *with* EX2055, ¶¶220-224. Whether this calls into question the honesty of his answer at deposition or the actual origin of the conclusory assertions he signed off on makes little difference because either way, Petitioners' expert's opinions should be given little to no weight. *See Pfizer, Inc. v. Genentech, Inc.*, IPR2017-01488, Pap.87, 61 (Nov. 29, 2018) ("Although we do take into account the evidence that Buss substantially copied the declaration of another expert from a related case, and the amount of time he spent on his

[23] A copy of the earlier expert declaration is attached as EX2055, with highlights showing the portions of that declaration that appear to have been ***copied into the expert declaration in this case***.

declaration, this also goes the weight we accord his opinions."). Petitioners' expert plainly did not closely study the prior art. Despite relying on the disclosure in Reardon's claim 23 in forming his opinions, for example, Dr. Tessier first remarked on an asserted "oddity" with claim 23 at his deposition—an issue he never addressed in his declaration, and which he realized only then "doesn't make sense." EX2058, 57:18-58:13, 59:16-19. This "oddity" caused him to hesitate to answer even the simplest question about the pH of Reardon's claim 23 column before loading. EX2058, 57:18-58:13. Petitioners' expert also could not describe the details of what is happening to the "buffer" solution during the process described in Reardon. EX2058, 65:13-21.

And finally, Dr. Tessier's testimony has been inconsistent, and, to put it most charitably, flexible. For instance, after discussing the substance of his testimony with Petitioners' counsel, Dr. Tessier attempted to flip his testimony on redirect at deposition, calling into question both his credibility and the nature of the analysis he performed in rendering the written opinions Petitioners relied on in their Petition—particularly as Dr. Tessier would not agree with simple statements in the very references he relied on in forming his opinions. *Compare, e.g.*, EX1002(B), 2 (listing EX1036) *with* EX2058, 16:16-20:14 (*esp*. 20:10-14); *see supra*, pp. 29-30, 49 n.19; *cf.* EX2058, 60:9-63:13.

Dr. Tessier's testimony is also misleading and evasive. For instance, when asked whether refolding by direct injection was a known technique as of 2008, his roundabout answer implied that it was. EX2058, 30:12-31:25. But when challenged further, he had to admit that he simply did not know. *Id.*, 32:1-33:20 (*esp.* 33:13-20). He also could not plainly answer simple questions such as the identity of what he had called an "independent variable" in his own declaration. *Id.*, 39:14-41:15; *see also id.* 12:1-16:3, 17:24-20:14, 57:18-58:3. And, finally, Dr. Tessier's testimony was illogical. For instance, he testified that a POSITA would not have assumed particles formed "because it's hard to predict." EX2058, 92:20-93:10. But being "difficult" to predict does not support his conclusion that particles would not have formed.

VII. Conclusion

Petitioners failed to show that claims 9-10, 13-21, and 23-30 are anticipated or rendered obvious. Because the Petition failed to establish unpatentability by a preponderance of the evidence, the patentability of the Challenged Claims of the '997 patent should be confirmed. *See* EX2056, ¶72.

Respectfully submitted by: Dated: May 15, 2020

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CERTIFICATE OF WORD COUNT

The undersigned certifies that the foregoing PATENT OWNER'S RESPONSE UNDER 37 C.F.R. §42.120 complies with the type-volume limitation in 37 C.F.R. §42.24(b)(2). According to the word-processing system's word count, the brief contains 13,423 words, excluding the parts of the brief exempted by 37 C.F.R. §42.24(a)(1).

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of PATENT OWNER'S RESPONSE UNDER 37 C.F.R. §42.120 has been served in its entirety by causing the aforementioned document to be electronically mailed to the following attorneys of record for Petitioners listed below:

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