UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

KASHIV BIOSCIENCES, LLC,
Petitioner

v.

AMGEN INC.,
Patent Owner

Case IPR2019-00791

Patent 8,940,878

PATENT OWNER'S PRELIMINARY RESPONSE UNDER 37 C.F.R. §42.207

LIST OF EXHIBITS

Exhibit	Description
EX2001	Defendant Adello Biologics, LLC's Preliminary Invalidity Contentions Pursuant to L. Pat. R. 3.3, C.A. No. 1:18-cv-03347-CCC-MF (D.N.J. Oct. 5, 2018)
EX2002	Amgen's Responses to Adello's Invalidity Contentions, C.A. No. 1:18-cv-03347-CCC-MF (D.N.J. Nov. 6, 2018)
EX2003	Declaration of Sayem Osman
EX2004	Declaration of Naz Wehrli
EX2005	Omitted
EX2006	Omitted
EX2007	Summons Returned Executed, C.A. No. 1:18-cv-03347-CCC-MF (D.N.J. Served Mar. 12, 2018)
EX2008	Amgen Inc. and Amgen Manufacturing, Limited's Preliminary Proposed Claim Constructions, C.A. No. 1:18-cv-03347-CCC-MF (D.N.J. Feb. 27, 2019)
EX2009	*Amgen v. Hospira* Claim Construction Transcript, C.A. No. 18-1064-CFC (D. Del. May 15, 2019)
EX2010	Amgen's Responses to Defendants' Invalidity Contentions, C.A. No. 1:18-cv-03347-CCC-MF (D.N.J. Apr. 19, 2019)
EX2011	Defendant Adello Biologics, LLC's Answer Defenses, and Counterclaims to Plaintiffs' Second Amended Complaint, C.A. No. 1:18-cv-03347-CCC-MF (D.N.J. Feb. 21, 2019)
EX2012	Omitted
EX2013	Merriam-Webster's Medical Desk Dictionary (2006)
EX2014	Oxford Dictionary of Biochemistry and Molecular Biology (2005)
EX2015	Merriam-Webster's Collegiate Dictionary (2009)
EX2101	U.S. Patent No. 9,643,997

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Patent Owner Amgen Inc. ("Amgen") submits this §42.107 Preliminary Response to the Petition for *Inter Partes* Review ("Petition" or "Pet.") of claims 9-10, 13-15, 17-21, 23, and 26-30 ("Challenged Claims") of U.S. Patent No. 9,643,997 ("the '997 patent"), filed by Petitioner Kashiv BioSciences, LLC ("Petitioner").[1] The Petition should be denied in its entirety pursuant to the Board's discretion under §314 and for Petitioner's failure to show a reasonable likelihood of prevailing on any asserted ground. Because of the failings of the Petition, institution would not be in the interests of justice, or an efficient use of the Board's limited time and resources. And, in light of *SAS Institute Inc. v. Iancu*, 138 S. Ct. 1348 (2018), even if Petitioner had made its threshold showing for some claims or grounds—it has not—the Board, in its discretion, should deny institution on all challenged claims and grounds in the Petition.

I. Introduction

Petitioner's submission failed to provide the Board the basic evidence and analysis required to institute any *IPR*. If the Board nonetheless institutes trial on

[1]Unless noted, all section references are to 35 U.S.C. or 37 C.F.R., as the context indicates, and all emphasis is added.

the Challenged Claims,[2] Amgen will address in detail in its §42.120 Response the numerous substantive errors and shortcomings in Petitioner's arguments and purported evidence.

In this Preliminary Response, however, where testimonial evidence raising an issue of material fact "will be viewed in the light most favorable to the petitioner" (§42.108(c)), Amgen addresses only the reasons the Board should exercise its discretion to deny institution under §314, and Petitioner's failure to demonstrate, as to any of the Challenged Claims, a reasonable likelihood of success on *any* asserted ground of invalidity. Because of these threshold failures, the Petition should be denied and no *inter partes* review should be instituted under §314.

First, Petitioner has engaged in improper gamesmanship, using Amgen's validity contentions in litigation as a roadmap for its Petition, studying the contentions for four months, and delaying the filing of its Petition until the very end of the one-year bar period, engaging in IPR practice to *multiply* litigation of the same issues, rather than as an alternative contemplated by Congress and the Board. For this reason, the Board should exercise its discretion and deny

[2]Claims 7-8, 11-13, 15-19, and 21 of U.S. Patent No. 8,940,878 ("the '878 patent").

institution under §314. However, even if the Board were to determine to allow such use of litigation proceedings to "roadmap" a petition (respectfully, it should not), this Petition should be denied because Petitioner failed to come to the Board with a petition that fully engages with and addresses known issues. Instead, Petitioner cherry-picks among known arguments and information, selecting some to present but ignoring the shortcomings and contradictions revealed by the remainder, and leaving it to Amgen and the Board to fill in the gaps and read between the lines. This places an improper burden on Amgen and the Board, particularly in light of the unfair advantage Petitioner has already taken. If Petitioner is to be permitted to rehearse its arguments in litigation, refine them based on Amgen's litigation responses, force a further response from Amgen at the PTAB, then return to litigation and repeat, Petitioner should at least address in its Petition the clear gaps in its arguments that were made well known to Petitioner in this process. Because Petitioner failed to do so, its Petition should be denied.

Second, Petitioner's own arguments and evidence confirm Petitioner cannot meet its burden at the institution stage of demonstrating a reasonable likelihood of proving at least one Challenged Claim unpatentable. *See, e.g.*, §314; §42.108(c). Beyond failing to engage in issues known to it from litigation, Petitioner's arguments across grounds are inconsistent and contradictory, and Petitioner failed

to address disclosures in its own prior art that contradict its arguments. For instance:

- Petitioner failed to present any argument under the correct construction of "refold buffer" for any ground—or even to address the issue—even though it knew about that proposed construction from litigation.
- Petitioner failed to engage in sufficient analysis of the "directly applying the refold solution…" element for any ground, despite being aware of such issues from litigation. *E.g.*:
  - Petitioner did not address whether the 20mM Tris-HCl it identifies as a protein stabilizer and aggregation suppressor in Ferré functions as a protein stabilizer or aggregation suppressor in that reference.
  - In arguing Komath teaches "applying the refold solution," Petitioner cited Komath's disclosure about contaminants being removed by an ion exchange column, but failed to address Komath's various conflicting disclosures, showing that the solution applied to the column is *already* purified.
- Petitioner failed to sufficiently explain and support its obviousness grounds with respect to motivation to combine and reasonable expectation of success. *E.g.*:

- Petitioner argued a POSITA would have had a reasonable expectation of successfully associating the protein with the separation matrix but ignored the results reported in Komath itself, with a percentage recovery of "no elution" to "<1%."
- Petitioner did not even attempt to reconcile its argument that a POSITA would be motivated to avoid dilution with its argument that a POSITA would be motivated to optimize protein purification conditions.
- Petitioner argues a POSITA "would have been motivated to use the components of Rosendahl in the methods of Ferré and Komath to allow for proper formation of the disulfide bond(s) of each method's protein of interest," but never identified any issues in proper formation of the disulfide bonds in those primary references to begin with.
- Petitioner does not explain why its asserted reasonable expectation of success for Grounds 4 and 6 ("successful formation of the protein's native disulfide bonds") is *different* from the reasonable expectation of success it alleges would have been achieved in connection with Komath's obviousness grounds in this Petition.

- Petitioner failed to present any argument or evidence establishing Ferré or the GE Handbook are prior art printed publications, or addressing when various of the disclosures in its background references were purportedly known.

Further, in view of post-*SAS* all-or-nothing institution and the many gaps of proof in Petitioner's arguments, even if, *arguendo*, the Board were to unearth a Ground with merit buried within Petitioner's pile of arguments and combinations, the Board should exercise its discretion here and deny institution because a trial would not be an efficient use of the Board's limited time and resources given Petitioner's imprecise scattershot approach here. *See, e.g.*, *SAS Inst. Inc. v. Iancu*, 138 S. Ct. 1348, 1355-56 (2018); *Chevron Oronite Co. v. Infieum USA LP*, IPR2018-00923, Pap. 9, 9-11 (Nov. 7, 2018) (informative) (denying institution on all claims under §314(a) when petitioner's arguments and proofs were deficient with respect to a subset of claims); *see also Deeper, UAB v. Vexilar, Inc*., IPR2018-01310, Pap. 7, 41-43 (Jan. 24, 2019) (informative) (denying institution because "instituting trial with respect to all twenty-three claims and on all four grounds based on evidence and arguments directed to only two claims and one ground would not be an efficient use of the Board's time and resources."); *SAS* Q&As, D3, at p. 8 (USPTO June 5, 2018), available at https://www.uspto.gov/sites/default/files/documents/

sas_qas_20180605.pdf (noting that, although "[t]he Board does not contemplate a fixed threshold for a sufficient number of challenges for which it will institute," it will "evaluate the challenges and determine whether, in the interests of efficient administration of the Office and integrity of the patent system (*see* 35 USC § 316(b)), the entire petition should be denied under 35 USC § 314(a).").

For these reasons, the Petition should be denied.

II. The Challenged Claims Of The '878 Patent Are Directed To A Novel Invention

The'997 patent "relates generally to processes for purifying proteins expressed in non-mammalian systems." *See* EX1001 1:12-13. Protein purification is a critical step in the manufacture of biological products using recombinant DNA technology. Before the invention of the '878 patent, it was believed in the art that certain of the specialized chemical compounds used to refold proteins needed to be diluted, reduced, or removed before applying the refold solution to a separation matrix for purification. *See, e.g.*, EX1001 1:46-55. The conventional thinking was that if these specialized chemical compounds in the refold solution were not diluted, reduced, or removed before the refold solution was applied to the separation matrix, they could prevent or disrupt the interactions between the protein and the separation matrix, which were necessary interactions for the column to work and the protein to be purified. *Id.* 15:25-43. In the prior art,

processing steps, such as dilution, were performed ***between*** protein refolding and application to a first chromatographic separation matrix. *See, e.g.*, *Id.* 15:25-43. The inventors recognized that such additional processing can be costly and time-consuming, particularly at a large manufacturing scale. *Id.* 11:58-63, 12:21-26, 15:25-43.

The '878 patent reflects the inventors' insight that protein purification can be achieved by applying a refold solution to a separation matrix, ***without*** certain intervening processing steps. *Id.* 11:58-63, 15:25-43.

III. The Board Should Exercise Its Discretion And Deny Institution Under 35 U.S.C. §314

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

Here, the Board should exercise its discretion and deny institution because Petitioner has unfairly used Amgen's litigation validity contentions as a roadmap to experiment with changes to its original invalidity arguments, taking four months to digest and react to the contentions just before filing its Petition at the very end of

the 1-year statutory bar period. *See TruePosition, Inc. v. Polaris Wireless, Inc.*, No. 12-cv-646, 2013 WL 5701529, at *6 (D. Del. Oct. 21, 2013) (IPR filings "made well after the initiation of litigation…may suggest an unfair tactical advantage or dilatory motive.").

Petitioner served its invalidity contentions on October 5, 2018 asserting anticipation based on Ferré and Komath (corresponding to Grounds 1 and 2 here), amongst others, and obviousness based on a variety of grounds including the combinations of Ferré or Komath in view of Rosendahl (corresponding to Grounds 4 and 6[3]) and Ferré or Komath in view of the GE Handbook[4] in October 2018. EX2001. In November 2018, Amgen served responsive validity contentions. EX2002.[5] Petitioner nevertheless waited until March 7, 2019 (just days before the

[3]Amgen refers herein to Petitioner's multiplicity of grounds listed as single "Ground 3"—covering Ferré in view of Rosendahl and Komath in view of Rosendahl—as Grounds 3 and 5, respectively.

[4]Patent Owner refers herein to Petitioner's multiplicity of grounds listed as single "Ground 4"—covering Ferré in view of the GE Handbook and Komath in view of the GE Handbook—as Grounds 4 and 6, respectively.

[5]The parties exchanged proposed claim constructions in the litigation by February 27, 2019 (EX2008). Adello served supplemental invalidity contentions on March

one-year bar date (EX2007)) to file the present petition, despite reusing the art from litigation.[6]

Further, Petitioner took into account and attempted to experiment here with responses to only a selected subset of arguments from Amgen's contentions, using Amgen's litigation contentions as a roadmap for Petitioner's revised theories in its Petition, and, in turn, to get feedback here that it can next use to re-calibrate its litigation positions (all while completely ignoring other identified shortcomings in its arguments, as discussed below). For instance, Amgen asserted in its litigation validity contentions that Komath does not anticipate because, *inter alia*, it does not disclose every element as arranged in the claim, and the techniques disclosed in Komath are discussed individually in different sections. EX2002, 70. In response, and openly quoting Amgen's validity contentions, Petitioner has added, in its IPR petition, a ground relying on a single reference obviousness theory to remedy this deficiency. Pet. 52. Similarly, in connection with the obviousness combinations

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29, 2019, and Amgen served supplemental validity contentions on April 19, 2019. EX2010.

[6]Adello Biologics, LLC was served with a complaint alleging infringement of, *inter alia*, the '878 patent on March 12, 2018. EX2007. Petitioner acquired Adello in January 2019. EX2011, 2 n.1.

of Ferré or Komath in view of Rosendahl, Adello argued "Rosendahl teaches methods for refolding proteins…. Rosendahl discloses a solubilization step that includes the use of a solubilization buffer, which contains a reductant, 'a disulfide reducing agent' such as cysteine and reduced glutathione." EX2001, 65, 80. Amgen in litigation explained that "Rosendahl however discloses only methods where a refolded solution is subjected to centrifugation before it [is] loaded onto a chromatography column." EX2002, 55, 61, 79, 86, 90, 121, 133, 153. But then in its Petition, Petitioner asserted that "[w]hile Rosendahl discloses that a refold solution is clarified using centrifugation before it is loaded onto a chromatography column…Rosendahl does not teach that this step is necessary when using the particular reductants/redox components…." Pet. 66.

Section 314 has been applied to deny institution of a follow-on IPR in circumstances when a patent owner's filings provide petitioner an unfair advantage, or when institution would be unjust, such as when a petitioner has taken advantage of previous patent owner statements and used them as a roadmap to modify its positions accordingly. *Gen. Plastic Indus. Co. v. Canon Kabushiki Kaisha*, IPR2016-01357, Pap. 19, 15-16 (Sept. 6, 2017) (precedential) (applying factors to evaluate the equities of permitting a follow-on petition is a proper exercise of PTO's discretion under 35 U.S.C. § 314); *Nvidia Corp. v. Samsung Elecs. Co.*, IPR2016-00134, Pap. 9, 11-12 (May 4, 2016) (considering petitioner's

delay in filing second IPR, noting it was "unjust" to patent owner to institute second proceeding in view of delay); *Toyota Motor Corp. v. Cellport Sys., Inc*., IPR2015-01423, Pap. 7, 8 (Oct. 28, 2015) ("[T]he opportunity to read Patent Owner's Preliminary Response in [the prior challenge], prior to filing the Petition here, is unjust."). The Board has also recognized the inequity of a petitioner being able to adjust litigation positions based on PTAB proceedings. *Nvidia*, IPR2016-00134, Pap. 9, 8 (denying institution and noting potential inequity of being able to adjust litigation positions, including based on patent owner's contentions in the PTAB, stating such inequity "is real and cannot be ignored").

This Petition forces Amgen to respond further to Petitioner's incrementally-updated invalidity theories in the Petition. These responses will provide Petitioner additional information it may use to adjust and hone its positions still further in litigation as it moves towards, *e.g.*, expert invalidity reports. This ranging exercise by Petitioner—firing off multiple versions of selected arguments in the hopes that one might eventually "hit"—creates a multiplicity of clustered simultaneous proceedings considering arguments about the same prior art, and directly contradicts the purpose of post-grant proceedings, which are intended "to provide an effective and efficient alternative to district court litigation." *Gen. Plastic*, IPR2016-01357, Pap. 19, 16-17; *see* 157 Cong. Rec. S1361 (daily ed. Mar. 8, 2011) (statement of Sen. Leahy) ("This bill will establish a more efficient and

streamlined patent system that will improve patent quality and limit unnecessary and counterproductive litigation costs…."); *Abiomed, Inc. v. Maquet Cardiovascular, LLC*, IPR2017-02134, Pap. 7, 7-8 (Apr. 16, 2018) (goal of AIA includes "make the patent system more efficient" and to provide "an effective and efficient alternative to [litigation]") (quoting *Gen. Plastic*, IPR2016-01357, Pap. 19, 16-17). The Board should not devote its limited resources to Petitioner's requested do-over of its poorly conceived invalidity contentions, multiplying and extending unnecessary litigation activity and costs that Petitioner seeks to shift to Amgen and the Board.

IV. Claim Construction[7]

A. "Aggregation Suppressor" And "Protein Stabilizer"

[7]The terms at issue in this case need only be construed "to the extent necessary to resolve the controversy." *Vivid Techs., Inc. v. Am. Sci & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999); *VIZIO, Inc. v. Nichia Corp.*, IPR2017-00558, Pap. 9, 8 (July 7, 2017) (declining to address constructions unnecessary to institution decision). Thus, at this stage, Amgen's proposed constructions reflect only disputes relevant to the arguments it presents regarding the Board's upcoming institution decision.

The claims require "a refold solution comprising … a refold buffer, the refold buffer comprising one or more of the following: (i) a denaturant; (ii) an aggregation suppressor…" An *aggregation suppressor* must actually disrupt or decrease or eliminate interactions between two or more proteins at the concentration used. *See* EX1001 5:33-35. If it does not "disrupt and decrease or eliminate interactions between two or more proteins" when in the presence of proteins, then it is not an "aggregation suppressor." *Id.* 5:34-35. And, a *protein stabilizer* must actually stabilize protein in the refold solution at the concentration used. *Id.* 5:41-44. If it does not "change a protein's reaction equilibrium state, such that the native state of the protein *is* improved or favored," it is not a protein stabilizer. *Id.* 5:42-44.

Petitioner admits that the proper construction of "aggregation suppressor" requires the compound to have the ability to disrupt or decrease or eliminate interactions between two or more proteins. Pet. 27; EX1001 5:33-35. Petitioner also admits that "protein stabilizer" requires the ability to change a protein's reaction equilibrium state, such that the native state of the protein is improved or favored. Pet. 27-28; EX1001 5:41-44. However, Petitioner's use of "ability" in its construction is misleading. Petitioner relies on "ability" to include in the definition of "aggregation suppressor" and "protein stabilizer" compounds that *do not* function as an aggregation suppressor or protein stabilizer at, *e.g.*, the

concentration used when those compounds only function as an aggregation suppressor or protein stabilizer at a *different* concentration.

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

Amgen's Proposed Construction	Petitioner's Proposed Construction
"applying the refold solution to the separation matrix without removing components of or diluting the refold solution under conditions suitable for protein to have specific, reversible interactions with a separation matrix in order to effect the separation of protein from its environment."	"applying the refold solution to a separation matrix without removing any components of or diluting the refold solution." Pet. 28.

The parties' dispute, *inter alia*, whether "directly applying" should be construed to mean applying "without removing or diluting components of the refold solution" (as Amgen proposes) or applying "without removing or diluting ***any*** components of the refold solution" (as Petitioner proposes). Petitioner has not identified why the addition of "any" is necessary or appropriate, or what effect it would have on this case. Nevertheless, for the purpose of institution, this dispute issue need not be addressed.

C. "Refold Buffer" (All Challenged Claims)

Amgen's Proposed Construction	Petitioner's 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	"a solution comprising one or more of the following: (i) a denaturant; (ii) an aggregation suppressor; (iii) a protein stabilizer; and

stabilizer and a redox component." EX2003, 20.	(iv) a redox component. The refold buffer need not necessarily contain a buffering component or have the ability to buffer pH." Pet. 35.

Refold Buffer Must Be pH Buffered. The parties dispute whether the refold buffer must 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 uses the word "buffer." The claims, when claiming a solution without pH buffering capacity, said so. For instance, the claims require a "solubilization *solution*," a "refold *solution*," and a "refold *buffer*." It is a basic cannon of claim construction that different words ("solution" and "buffer" here) have different meanings. *Bd. of Regents of Univ. of Tex. Sys. v. Benq Amer. 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 the use of "data feed" elsewhere in the patent supports conclusion that the 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*," instead of "refold *solution*," the applicant made clear that a "refold buffer" is not just a solution, but a *pH buffered* solution. This distinction between

"solution" and "buffer" was simply not accounted for in the decision Petitioner attached at EX1048.

Amgen's construction is further supported by the specification and claims, which differentiate among different components of the refold buffer. The claims and specification make clear that the "refold buffer" need not necessarily utilize a denaturant, aggregation suppressor, protein stabilizer, and a redox component, but rather may utilize a subset of *those four components*. In contrast, the specification makes clear that the inclusion of a *buffer* component is *not* optional. The specification teaches that the "refold buffer" contains a "buffering component" such as "phosphate buffers, citrate buffers, tris buffer, glycine buffer, CHAPS, CHES, and arginine-based buffers" and explains that "[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 14:49-55. Thus, there would be no reason for "buffer component" to be separately recited in the claims since the requirement for a pH buffering component is already subsumed by "refold buffer." Put another way, while the "refold buffer" must include one or more of the components listed in the claims, the claim language itself already requires that the solution be a buffer (*i.e.*, have buffering capacity)

without additionally reciting a "buffer component."[8] The Court in the *Amgen Inc. v. Hospira, Inc.* case in Delaware agreed that the same language in column 15 of the '997 patent (EX2101 15:5-8) supports Amgen's construction of "refold buffer," and concluded that "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." EX2009 86:19-25.

Petitioner's extrinsic evidence "may not be used to vary or contradict the claim language," *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1583-84 (Fed. Cir. 1996), and even if it could, it does not establish a POSITA would have understood "refold buffer" to include a solution that does not resist changes in pH. Indeed, Petitioner's EX1049 ¶44 states "the word 'buffer' refers to *a solution that resists changes in pH*" (and *only then* goes on to describe other possible variants of

[8]The claims' use of "comprising" also reflects that the "refold buffer" is not limited to a denaturant, aggregation suppressor, protein stabilizer, and redox component. *Regeneron Pharm., Inc. v. Merus N.V.*, 864 F.3d 1343, 1352 (Fed. Cir. 2017); *accord* MPEP §2111.03. Moreover, the inclusion of and requirement for a denaturant, aggregation suppressor, protein stabilizer, and/or redox component does not render "buffer" meaningless.

the term). And Petitioner's own EX1072, which it ignores in the context of claim construction, states "[b]uffers used to formulate proteins…should exhibit little or no change in pH with temperature…and have maximum buffer capacity at a pH where the protein exhibits optimal stability." *Id.* at 1. Further, dictionaries from the time confirm that 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 WL 3978883, at *3 (D. Del. June 26, 2015) (construing buffer and concluding "the fundamental characteristic of a buffer is that it buffers, or resists changes to, pH"); EX1007, 39 (describing importance of pH to ion exchange chromatography). Nor did Petitioner address how "commonly" the phrase "buffer" was allegedly used to refer to a preparation that does not resist changes in pH. Pet. 35.

Refold Buffer Must Refold Protein Into Its Biologically Active Form.

Petitioner's construction also ignores the fact that the refold buffer must actually provide conditions suitable so that the protein refolds into its biologically active form. Petitioner was aware of this shortcoming in its construction (EX2008, 7; IPR2019-00797, EX1041, 14), but simply ignored it in its Petition. The '878 patent "relates generally to processes for purifying proteins expressed in non-mammalian systems" and that the asserted claims are directed to "proteins expressed in a non-native limited solubility form" that must be solubilized *and*

"refolded into a biologically active form." See EX1001 1:11-12, 11:62-63, 12:5-8. Nevertheless, Petitioner has simply failed to address whether the "refold buffer" (which needs to contain one or more of a denaturant, an aggregation suppressor, a protein stabilizer, and a redox component) must provide conditions suitable for refolding—and it must.

The '878 patent explains that "to produce a functional protein, these inclusion bodies often need to be carefully denatured so that the protein of interest can be extracted and refolded into a biologically active form." *See* EX1001 12:5-8. Thus, after solubilizing the protein, the protein is refolded into its native three-dimensional structure. This is accomplished, for example, in claim 7 by "forming a refold solution comprising the solubilization solution and a refold buffer." *See* EX1001 2:24-28. As the specification explains, the function of the (i) denaturant; (ii) aggregation suppressor; (iii) protein stabilizer; and/or (iv) redox component in the refold buffer is to modify "the thermodynamics of the solution, thereby shifting the equilibrium towards an optimal balance of native form…[,] preventing non-specific association…[and] promoting stable native protein structure." EX1001 14:5-17. Thus, "what the inventors actually invented and intended to envelop with the claim" includes a refold buffer that provides conditions so that the protein refolds into its biologically active native form. *See Phillips v. AWH Corp.*, 415

F.3d 1303, 1316 (Fed. Cir. 2005) (en banc). The construction of "refold buffer" must account for this.

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

Because the Petition failed to establish that any of the prior art references disclose—explicitly or inherently—each and every limitation of the Challenged Claims, alone or in combination, Petitioner failed to meet its burden for institution not only on all of its anticipation grounds (Grounds 1 and 2), but also on all of its obviousness grounds (Ground 3 (which is a single reference obviousness theory based on the art from Ground 2 in which Petitioner simply argues that the steps disclosed in the Ground 2 reference would be combined), and Grounds 4-7 (which cover claims that ultimately depend from those in Grounds 1 and 2)).

Amgen additionally notes that Petitioner has failed to submit any evidence or argument attempting to address numerous flaws in its asserted Grounds that were identified by Amgen in litigation, and that the Board has warned that the failure to address known evidence supporting validity at the pre-trial stage is a reason to exercise its discretion and deny institution. *See Unified Patents Inc. v. Berman*, IPR2016-01571, Pap. 10, 11-12 (Dec. 14, 2016) (informative) (denying institution under §325(d) where petition failed to address relevant facts petitioner was aware of and to present argument as to why the Board should not exercise its

discretion to deny institution); *cf. Robert Bosch Tool Corp. v. SD3, LLC*, IPR2016-01751, Pap. 15, 23 (Mar. 22, 2017) (denying institution and stating "known evidence of secondary considerations should be addressed in the petition."); *Merial Ltd. v. Virbac*, IPR2014-01279, Pap. 13, 26-27 (Jan. 22, 2015) (denying institution for, *inter alia*, failure to address known evidence of unexpected results). This is particularly true where, as here, Petitioner was aware of but chose not to address in its Petition known support for patentability. If a petition is to be allowed to proceed when the petitioner has taken advantage of the patent owner's validity contentions in litigation to gain an unfair advantage and present multiple re-framings of the same argument (as discussed *supra* §III, it should not be), the petitioner's failure to address issues with and shortcomings in its unpatentability positions known to the petitioner from litigation is particularly egregious, and should be fatal for the same reasons.

Throughout its Petition, Petitioner has cut corners, avoided addressing questions that were self-evident, and simply ignored portions of evidence that, on their face, contradict Petitioner's argument. Indeed, Petitioner and its expert, Dr. Robinson, perform no meaningful analysis of what would have been known to a POSITA at the time, which is necessary with respect to anticipation to assess both a POSITA's understanding of a reference and enablement issues and, of course, is

one of the *Graham* factors necessary for a complete obviousness analysis.[9] Dr. Robinson, for her part, at least acknowledges that a reasoned analysis is required, but she fails to provide one. EX1002 ¶¶19-21. Rather, she simply provides a conclusory assertion of a definition of a POSITA, and fails to account for what such a person (even if correctly defined) would have known and understood in reading the cited references. Although a POSITA is a hypothetical construct, it should be tethered to reality, and what a POSITA brings to a reference is a key part of the patentability analysis. Petitioner's failure to provide this fundamental analysis is a failure to satisfy its burden.[10] *See* 37 C.F.R. §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.").

[9]It is not surprising that Petitioner fails to cite *Graham* (or *KSR*) in its obviousness analyses, because Petitioner fails to address all the *Graham* factors. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007); *Graham v. John Deere Co*., 383 U.S. 1, 17-18 (1966).

[10]Amgen reserves further discussion about the qualifications of a POSITA as may be appropriate for its Patent Owner Response under §42.120, if a trial is instituted.

A. Ground 1: Petitioner Has Not Shown A Reasonable Likelihood Of Prevailing In Establishing That Claims 7-8, 11-12, 15-16, 18-19, And 21 Are Anticipated By Ferré

1. Petitioner Presented No Argument About Ferré Being A Printed Publication

Petitioner did not make any attempt to establish Ferré is a prior art printed publication. Petitioner merely concluded without support that Ferré "is a …printed publication" and "was published" in 2005. Pet. 18. But Petitioner said nothing about where the pages it attached as an exhibit was found or generated. For instance, Petitioner presented no evidence establishing the Ferré exhibit was from a regularly published journal, and gave no explanation for the asserted 2005 date. Even if Petitioner took the date from the text of the exhibit (which Petitioner did not assert), it provided no explanation as to why such date is not hearsay. Petitioner thus failed to meet its burden on a basic element of anticipation: establishing its references are prior art printed publications and are authentic. *See, e.g.*, *Dr. Reddy's Labs., Inc. v. Celgene Corp*., IPR2018-01507, Pap. 7, 8-11 (Feb. 11, 2019) (denying institution for lack of proof regarding printed publication status of references and collecting cases); *TRW Auto. U.S. LLC v. Magna Elecs. Inc.*, IPR2014-01347, Pap. 25, 8-9 (Jan. 6, 2016) ("[C]opyright notice is…not probative that the article was ever published by IEEE or anyone else.").

2. "Forming A Refold Solution Comprising The Solubilization Solution And A Refold Buffer, The 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"

Petitioner did not provide any analysis of Ferré under the proper construction of "protein stabilizer" or "aggregation suppressor." Petitioner asserted that the "refold buffer in Ferré contains 20mM Tris-HCl[], which the '878 patent acknowledges is both a protein stabilizer and aggregation suppressor." Pet. 38. But nowhere does the patent disclose that Tris-HCl *at the concentration of 20mM* is either a protein stabilizer or an aggregation suppressor, and Petitioner offers no other evidence for this assertion. As Petitioner is aware, in litigation against Adello (who is now Petitioner Kashiv), Amgen asserted that 20mM Tris-HCl in Ferré does not function as, *e.g.*, a protein stabilizer or aggregation suppressor. EX2002, 48. Nevertheless, Petitioner did not acknowledge or attempt to address this issue in the Petition. Instead, Petitioner (and its expert) present carefully worded arguments to allege that Tris *can act* as a protein stabilizer and aggregation suppressor (*i.e.*, it has the ability *at some concentration* to be a protein stabilizer or aggregation suppressor), but tellingly without *ever* asserting that Tris acts as a protein stabilizer and aggregation suppressor *at 20mM*, *as it is disclosed in Ferré*. Indeed, this shortcoming is reflected in Petitioner's EX1072 and EX1073, which Petitioner alleges support its argument that Ferré's disclosure of Tris-HCl discloses a protein stabilizer and aggregation suppressor. However,

neither of those exhibits confirms that Ferré's *20mM* Tris is a protein stabilizer or aggregation suppressor. EX1072 teaches Tris at *50mM* (and even so Petitioner fails to explain how this exhibit discloses Tris as a protein stabilizer or aggregation suppressor in the context of refolding). EX1072, 2. EX1073 teaches Tris at 50mM and 100mM, both of which are *different* than what Petitioner asserts Ferré discloses. EX1073, 7. And even the Petitioner's own reference teaches that *severe protein aggregation* was detected in a solution containing 20mM Tris. EX1071, 5. By failing to show 20mM Tris-HCl *as it is disclosed in Ferré* is either a protein stabilizer or an aggregation suppressor, Petitioner has simply failed to establish this required element of its case for Ground 1, and its Petition should be denied.

Petitioner further failed to address the requirement that the "refold buffer" under the correct construction must have a pH buffering capacity and that it provides conditions for the protein to refold into its biologically active form—again, issues it was aware of from litigation. EX2008, 7; *see also* IPR2019-00797, 14 EX1041. In the context of Ground 1, Petitioner *did not address buffering or refolding at all*. Petitioner's silence as to refolding is particularly telling given its arguments in Ground 4 (and 6), in which it asserted that a POSITA would *modify* Ferré to use components of Rosendahl in the refold buffer *because the components of Rosendahl "allow* ***for proper formation of the disulfide bond(s)****" in Ferré's protein of interest*. 997 Pet. 69-70. The Petition's statement on this point is a

concession that the process described in Ferré, standing alone, **does *not* result in proper refolding**, which is required by the proper construction of "refold buffer" (*see* §IV.C).

B. Ground 2 And 3: Petitioner Has Not Shown A Reasonable Likelihood Of Prevailing In Establishing That Claims 7-8, 11-12, 15 And 16 Are Anticipated Or Rendered Obvious By Komath

1. Petitioner Did Not Address Komath's Enablement Issues (Ground 2)

"To anticipate, the reference must also enable one of skill in the art to make and use the claimed invention." *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1374 (Fed. Cir. 2001). In litigation, Amgen explained that Komath lacks evidence that the reference accomplishes expression, solubilization, refolding, or purification of RGH-CSF. EX2002, 70-71. As Amgen pointed out (EX2002, 71), Komath's Table 1 is *the only* disclosure in the reference of any reported yield or recovery following solubilization, and the recovery reported ranges from "No elution" to "<1%" recovery (EX1005, 13), which are only the results for varying concentrations of NaCl used for elution; no yield or recovery is reported for the solubilization or refolding techniques or any other chromatography conditions disclosed in the reference. Yet, despite being aware of this failing of Komath, Petitioner failed to address this issue in its Petition. *See In re Magnum Tools Int'l, Ltd.*, 829 F.3d 1364, 1374-77 (Fed. Cir. 2016) (finding burden of proof

on invalidity remains with petitioner throughout the IPR and never shifts to patent owner); *cf. Unified Patents Inc. v. Berman*, IPR2016-01571, Pap. 10, 12 (Dec. 14, 2016) (informative) (exercising discretion and denying institution, stating "Petitioner fails to present any argument distinguishing the Examiner's prior consideration of Russell or to provide a compelling reason why we should readjudicate substantially the same prior art and arguments…"). And, in any case, even if one were to assume for the purpose of institution that Komath could enable someone to do what it teaches, what it teaches (*e.g.*, recovering none of or less than 1% of the protein of interest) is insufficient. The Petition therefore failed to establish reasonable likelihood of success in establishing that Komath accomplishes the claimed result because Petitioner provided no evidence that the reference accomplishes expression, solubilization, refolding, or purification of the disclosed protein. *Cf. Robert Bosch Tool Corp. v. SD3, LLC*, IPR2016-01751, Pap. 15, 23 (Mar. 22, 2017) ("[K]nown evidence of secondary considerations should be addressed in the petition.").

2. "Forming A Refold Solution Comprising The Solubilization Solution And A Refold Buffer…"

Petitioner does not specifically identify the components of what it argues are the refold buffer and the refold solution. Petitioner simply asserts Komath discloses forming a refold 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. Pet. 47. Petitioner does not identify what, if anything, is added to the solution to achieve a pH of 8.0-8.5, what is added to the solution to achieve a pH of 4.0-5.0, what the components of the refold buffer are (other than to assert it "compris[es] an aggregation suppressor"), and which solution is the refold solution.

To the extent Petitioner is pointing to 0.1% polysorbate as the aggregation suppressor in the refold buffer, Petitioner did not provide any analysis of Komath's disclosure of 0.1% polysorbate 20 under the proper construction of "aggregation suppressor."[11] Petitioner asserted that "[t]he '878 patent discloses that polysorbate

[11]Petitioner states that the refold solution comprises "a refold buffer comprising an aggregationsuppressor." Pet. 47. But subsequently Petitioner asserts that "polysorbate 20 *may* also act as a protein stabilizer." *Id.* Petitioner did not provide any analysis of Komath's disclosure of 0.1% polysorbate 20 under the proper construction of "protein stabilizer." Nor did Petitioner address whether the 0.1% polysorbate acts as a protein stabilizer in Komath, and Petitioner's theory in any case is that the refold buffer comprises an aggregation suppressor (without mention of a protein stabilizer). *Id*.

20 is an aggregation suppressor." Pet. 47. But nowhere does the patent disclose that polysorbate 20 *at a concentration of 0.1%* is an aggregation suppressor.

Petitioner further asserted that Komath "broadly discloses that a refold solution may also include a surfactant." Pet. 47. But Petitioner does not identify a surfactant as part of any refold buffer. Further, Petitioner asserts that surfactants "may be used as both aggregation suppressors and protein stabilizers." *Id.* But Petitioner also does not address whether a surfactant would act as an aggregation suppressor or protein stabilizer in Komath.

Petitioner also presented no argument that Komath teaches or renders obvious a "refold buffer" under the correct construction (a construction it knew about (EX2008, 7; IPR2019-00797, EX1041, 14), which requires (a) a pH buffering capacity and (b) that the buffer provide conditions for the protein to refold into its biologically active form. S*ee supra* §IV.B; Pet. 47-48, 52-54. Petitioner's obviousness arguments similarly make no attempt to fill this hole in the Petition's proof.

Petitioner's silence as to refolding is again telling given Petitioner's arguments in Ground 6, where Petitioner asserted that a POSITA would *modify* Komath to use components of Rosendahl in the refold buffer *because the components of Rosendahl "allow* ***for proper formation of the disulfide bond(s)****" in Komath's protein* of interest. Pet. 65. Again, Petitioner's assertion to the Board

is an admission that the process described in Komath **does *not* result in proper refolding**.

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

Petitioner argues Komath teaches "directly applying the refold solution" by asserting Komath teaches that "all of the contaminants like endotoxins and host DNA are removed by an ion exchange column." Pet. 49. But Petitioner failed to address Komath's conflicting disclosure that "[t]he final washed IB pellet so obtained [prior to ion exchange chromatography] is [already] *essentially free of endotoxins, host cells proteins and host DNA*." EX1005, 9. Nor did Petitioner address Komath's disclosure about a process (prior to ion exchange chromatography) that "strips the IB pellet of *any* residual cell debris particles, especially lipopolysaccharides units that contribute to the unacceptable levels of endotoxins in protein preparations from E.coli." *Id.*, 11. In ignoring these teachings, Petitioner apparently hoped to conceal a hole in its argument: Komath does not (as the Petition argued) disclose using the ion exchange column to purify the protein, which (as discussed above) Komath teaches has *already been purified*. EX1005, 9 ("The *purified* IB pellet of G-CSF, which is essentially pure G-CSF, is then ready to be solubilized, refolded to native form and *concentrated* by ion exchange chromatography").

Petitioner ignores the teaching of the prior art as a whole and cherry picks disclosures, relying on impermissible hindsight and discarding, rather than explaining, the remainder other teachings of the prior art. *See Polaris Indus., Inc. v. Arctic Cat, Inc*., 882 F.3d 1056, 1069 (Fed. Cir. 2018) ("[A] reference must be considered for all it taught, disclosures that diverged and taught away from the invention at hand as well as disclosures that pointed towards and taught the invention at hand.…But even if a reference is not found to teach away, its statements regarding preferences are relevant to a finding regarding whether a skilled artisan would be motivated to combine that reference with another reference.").

Further, particularly if (as Petitioner asserts), the pellet is not purified before it is applied to the ion exchange column in solubilized form, Petitioner failed to address teachings in its own art (including the GE Handbook, which it combines with Komath in Ground 7) when asserting that "Komath does not remove any components of the refold solution." Pet. 48. That art states, *e.g.*, "[i]t is highly recommended to *centrifuge* and filter any sample *immediately before* chromatographic purification." EX1031, 131; EX1007 (GE Handbook), 41 ("samples *must* be clear and free from particulate matter"), 153-161 (discussing the importance of, *e.g.*, precipitation, centrifugation and desalting before chromatography); EX1019, 87 (stating it is important that dirty samples are

cleaned by filtration or centrifugation before being applied to the ion exchange column); EX1063 18:1-6. Petitioner did not address why a POSITA would have understood or assumed that such steps would *not* have been performed as a matter of course in Komath.

In asserting Komath teaches "directly applying a refold solution," Petitioner also did not address the fact (as Amgen pointed out in litigation, EX2002, 78-79), that Petitioner's asserted refold solution includes urea (*see* Pet. 46-47), but the sample loaded onto the column in Komath is identified as using a sodium acetate buffer, with no mention of urea. *See* EX1005 10:11-12 ("pH of the refolded protein solution is shifted to 4.5 with sodium acetate buffer for loading on an ion exchange column"). Petitioner does not address these disclosures, nor the disclosure that the *sample* (not the refolded protein solution) is loaded *in 25mM sodium acetate buffer*. *Id.* 12:27-28. In fact, Petitioner never even mentioned urea in its anticipation analysis of "directly applying." And in the context of obviousness, Petitioner merely assumed, without addressing the disclosures above, that urea remains in the solution applied to the column. Pet. 59-60. Certainly, Petitioner did not address how urea might be removed from the solution, and whether such removal by unspecified additional step(s) would mean that Komath does not teach "applying the refold solution."

Komath teaches that the "pH of the refolded protein solution is shifted to 4.5 [from 8.0] with sodium acetate buffer for loading on an ion exchange column." EX1005, 10. Petitioner asserts that a POSITA would understand this pH adjustment does not require any "significant dilution" of the refold solution. Pet. 48-49. However, in construing the claim, Petitioner asserted that the term should be construed to mean "without…diluting." Pet. 28. Petitioner does not explain how no "significant dilution" is the same as "without…diluting." Further, to the extent "directly applying…" allows for some but not "significant" dilution, Petitioner does not analyze or explain *how much* dilution is disclosed in Komath. Pet. 48 n.6. Petitioner also did not address whether the significant shifting from a pH of 8.0 to a pH of 4.5 would result in *e.g.*, precipitation (*i.e.*, the removal of components of the solution). *See supra* §IV.B.

Petitioner also ignores the inconsistency between its Komath arguments (*e.g.*, that Komath does not "remove any components of the refold solution" (Pet. 48)) and its assertion in Ground 6 that one would *modify* Komath using Rosendahl to "reduce[] the…steps required in the overall process for refolding…." Pet. 64 (quoting EX1006, ¶[0038]). Petitioner does not address what the "reduce[d]" steps would be, and whether those steps would otherwise remove components of the alleged refold solution.

4. Petitioner Improperly Mixes And Matches Across Different Embodiments (Ground 2)

As Petitioner is aware, Amgen pointed out in litigation that Komath fails to disclose every element of the asserted claims *arranged as in the claim*, and thus cannot anticipate. EX2002, 70; *SynQor, Inc. v. Artesyn Techs., Inc.*, 709 F.3d 1365, 1375 (Fed. Cir. 2013). [12] More specifically, as Amgen noted in litigation, the techniques disclosed in Komath are separately discussed in different discrete sections addressing distinct processes (*e.g.*, "Source of RHG-CSF Gene," "Fermentation," "Purification," and "Ion Exchange Chromatography") and different examples. EX2002, 68. Nevertheless, instead of addressing or even acknowledging this deficiency in its anticipation ground (Ground 2, to which this failure is fatal), Petitioner separately added to its invalidity theories a single-reference obviousness ground (Ground 3, which Petitioner did not assert in litigation, and which suffers from its own additional deficiencies, as detailed *infra*, §V.B.5).

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

Petitioner's failure is particularly egregious where, as here, the reference itself raises questions as to how a POSITA would understand its disclosures. For instance, as mentioned above, in some sections of the reference—including one expressly titled "Purification"—the document discloses that the endotoxins and host DNA are removed *by washing the inclusion bodies*. EX1005, 9; *see also id.* 1 (Abstract), 9 ("Purification", the reference states that "[r]epeated washings of the…pellets is done by fine dispersion homogenization and centrifugation in a combination of buffers" with the result that "[t]he final washed IB pellet so obtained is essentially free of endotoxins, host cells proteins and host DNA" and is "essentially pure G-CSF"); 11 ("EXAMPLE 2": "This strips the IB pellet of any residual cell debris particles, especially lipopolysaccharides units that contribute to the unacceptable levels of endotoxins in protein preparations from *E. coli*"); *supra* §V.B.3. In another section, however, Komath includes a brief statement, on which Petitioner relies, that "[a]ll the contaminants like endotoxins and host DNA are removed *by an ion exchange column*." EX1005, 6-7. Petitioner offers no attempt to reconcile these, or to address whether or how a POSITA would understand them to provide a unified disclosure across Komath's various sections. For instance, for limitation (c), Petitioner points to Example 3 and the separate "purification" section (Pet. 46 (citing EX1005, 10, 12), and for limitation (d), Petitioner points to Example 3, the separate "purification" section, and the "summary of the invention"

sections (Pet.47 (citing EX1005, 6, 10, 12)). More specifically, Example 3 describes a pH shift "to between 4.0 and 5.0" using sodium acetate or *sodium phosphate* (EX1005, 12), but the "purification" section discloses shifting the solution to pH 4.5 with *sodium acetate only* (EX1005, 10). Similarly, Petitioner relies on Komath's introductory statements that "G-CSF is eluted" and "[t]he recovery of G-CSF …was found to be ***maximal***" (Pet. 50 (citing, *e.g.*, EX1005, 10)), but at the same time Petitioner relies on the results in Example 4, which state that the percentage recovery of the protein was ***"No elution" to "<1%,"*** depending on certain conditions (Pet. 50 (citing EX1005, Table 1)); *see* EX1005, 12-13. These unexplained and unreconciled disclosures in the hodgepodge of material cited by Petitioner raise questions about whether and how the different steps and approaches disclosed by Komath might fit together, and how, together, they might be understood by a POSITA—again, questions the Petition never answers, even though they have long been known to Petitioner.

5. Petitioner Failed To Establish A Reasonable Expectation Of Success Regarding Motivation To Combine And Reasonable Expectation Of Success (Ground 3)

The only difference between Petitioner's anticipation and obviousness grounds for Komath is that, with respect to obviousness, Petitioner asserted that a POSITA would have been motivated to "combine the steps of Komath." Pet. 54. But Komath provides *different choices* for various steps, and the Petition does not

explain *which* options a POSITA would have chosen and *why* or *how* such selection of certain options would impact reasonable expectation of success. *See also* §V.B.4*, supra*. For instance, for the teaching of elution, the Petition relies both on page 10 of Komath, which says "G-CSF is ***eluted*** from this column ***using 0.1M Tris HCl buffer at pH 8.0***," and also on page 12, which says "***[e]lution*** of the protein from the column was done ***using various concentrations of sodium chloride in the equilibration buffer***." Pet. 50, 54 (relying on same disclosures for obviousness as relied on for anticipation). But the Petition never addresses ***which*** solution would have been selected for elution under its obviousness theory, or ***how*** selection of one solution rather than the other would have impacted any reasonable expectation of success. This does not meet the requirements for showing obviousness. *See In re Stepan Co.*, 868 F.3d 1342, 1346-48 (Fed. Cir. 2017) (vacating PTAB unpatentability judgment and discussing requirement for a reasonable expectation of success); *Amgen Inc. v. F. Hoffman-La Roche Ltd*., 580 F.3d 1340, 1362 (Fed. Cir. 2009) ("An obviousness determination requires that a skilled artisan would have perceived a reasonable expectation of success in making the invention in light of the prior art."); *Apple Inc. v. Memory Integrity, LLC*, IPR2015-00159, Pap. 12, 27 (May 11, 2015) (finding obviousness ground deficient where petition did not address reasonable expectation of success); *cf. AOL Inc. v. Coho Licensing LLC*, IPR2014-00966, Pap. 6, 13 (Nov. 20, 2014) ("A petitioner

who does not state the differences between a challenged claim and the prior art, and relies instead on the Patent Owner and the Board to determine those differences risks having the corresponding ground of obviousness not included for trial for failing to adequately state a claim for relief.").

The Petition also states a POSITA "would have been highly motivated to avoid extra downstream processing" (Pet. 55), but never specifies *which* steps would be eliminated from Komath in Petitioner's unexplained obviousness theory, or *how* this would have resulted in modification of Komath, let alone *whether* a specific modification would reasonably have been expected by a POSITA to succeed. Further, if, as Petitioner asserted, a POSITA would have been motivated to ***eliminate extra steps***, the Petition never explains why Komath would use "6M Guanidine hydrochloride…as a denaturant" when "***additional steps to reduce the conductivity of GdnHCl need to be included*** before refolding of the denatured protein." Pet. 59, n.7; EX1005, 10. Again, Petitioner's internally contradictory and unexplained assertions cannot make out a *prima facie* case for obviousness. *See, e.g.*, §312(a)(3); §42.104(b)(4); *Jaguar Land Rover N. Am., LLC v. Blitzsafe Tex., LLC*, IPR2018-00544, Pap. 8, 21 (Aug. 10, 2018) (denying institution and finding motivation to combine for certain claims contradicted motivations to combine for others); *LG Elecs., Inc. v. 3G Licensing SA*, IPR2018-00559, Pap. 15, 15-17 (Aug. 9, 2018) (petitioner failed to meet its burden in light of inconsistent

positions taken with respect to application of claim limitations); *Magnum Oil Tools*, 829 F.3d at 1380; *John Crane, Inc. v. Finalrod IP, LLC*, IPR2016-01827, Pap. 6, 14 (Jan. 31, 2017) (explaining it is petitioner's responsibility "to explain specific evidence that support[s] its arguments, not the Board's responsibility to search the record and piece together what may support [p]etitioner's arguments") (citing *Dominion Dealer Sols., LLC v. Autoalert, Inc.*, IPR2013-00225, Pap. 15, 4 (Oct. 10, 2013)); *Axon Enter., Inc. v. Digital Ally, LLC*, IPR2017-00515, Pap. 10, 18-19 (July 6, 2016) (denying institution because petitioner and its expert did not explain what specific modification to the prior art would have been necessary or how a person of ordinary skill would have been motivated to make the necessary modification based on the structure and operation of the prior art); *Dep't of Justice v. Envisionit, LLC*, IPR2017-00186, Pap. 8, 26 (May 3, 2017) (denying institution, noting that the Board is "not inclined to play archaeologist with the record in an attempt to fill the gaps in [p]etitioner's argument").

Additional unexplained contradictions abound in the Petition's arguments for obviousness. For example, while Petitioner argues a POSITA would have been motivated to ***avoid*** dilution, because "dilution was known to be time consuming and resource intensive" (Pet. 56), the Petition never reconciles or even acknowledges the conflict between its obviousness argument with the affirmative ***inclusion*** of dilution in Komath (to which Petitioner purports to *apply* this ***no***-

dilution motivation): "[a] 1:2 dilution of the lysate before centrifugation helps reduce viscosity and to get a better yield of inclusion bodies." EX1005, 11; *see also id.*, 10 ("[t]he protein solution is diluted further").

Nor does Petitioner ever attempt to reconcile its argued ***no***-dilution motivation with its argued "optimization of protein purification conditions" motivation. Strikingly, the Petition never addresses whether such "optimization" would ***require or involve dilution***, let alone steps that would remove components (*see* §IV.B, *supra*), or whether or how its arguments about "[o]ptimiz[ing] purification conditions" (Pet. 56) would be consistent with its arguments about "avoid[ing] extra downstream processing steps," which Petitioner also asserts would have motivated its POSITA (Pet. 55). For example, Petitioner never explains how a POSITA would *optimize* conditions *without adding steps*, and leaves this conflict in its basic motivation arguments unresolved (and entirely unaddressed).

In addition, while Petitioner asserted a POSITA would have known how to adjust "pH and ionic strength" to be sure that the proteins of interest bind to the column (Pet. 13, 58), Petitioner never discusses, let alone explains, what that pH and ionic strength would have needed to be or how they would have been achieved.

Further, Petitioner's only assertion about reasonable expectation of success is an assertion that a POSITA would have had "a reasonable expectation of success that using the particular solutions disclosed by Komath creates conditions suitable for the protein to associate with the separation matrix." Pet. 61. Petitioner does not explain why this is the right reasonable expectation of success to analyze for this claim. Nor does Petitioner explain why what is argued as the reasonable expectation of success in IPR2019-00797 is different in this IPR, despite the similarities in the claim language. IPR2019-00797, Pap. 2, 53 (Mar. 7, 2019). Moreover, Petitioner never reconciles its assertion that a POSITA would have had a reasonable expectation of successfully associating the protein with the separation matrix (Pet. 61) in light of the results reported in Komath itself for percentage recovery of ***"no elution" to "<1%,"*** as discussed above. EX1005, 13. If Petitioner's obviousness theory was somehow supposed to change these reported results, Petitioner has certainly left the Board and Amgen to guess about how and why. Because Petitioner's vague and unexplained assertions improperly leave the Board and Amgen to speculate about what Petitioner might be suggesting, the Petition fails to make out a *prima facie* case for obviousness. *John Crane*, IPR2016-01827, Pap. 6, 14 (explaining it is petitioner's responsibility "to explain specific evidence that support[s] its arguments, not the Board's responsibility to

search the record and piece together what may support [p]etitioner's arguments"); *Dep't of Justice*, IPR2017-00186, Pap. 8, 26 .

C. Ground 4 (And Un-Numbered Ground 6): Petitioner Has Not Shown A Reasonable Likelihood Of Prevailing In Establishing That Claims 13 And 17 Are Obvious Over Ferré Or Komath In View Of Rosendahl

Petitioner did not meet its burden of establishing obviousness for Grounds 4 or 6 (obviousness over Ferré in view of Rosendahl and obviousness over Komath in view of Rosendahl, respectively) for at least the reasons already described above for the Ferré and Komath grounds (Grounds 1-2), which cover the claims from which the Grounds 4 and 6 claims depend.[13] The Petition also fails this threshold for Grounds 4 and 6 for the additional reasons cataloged below.

1. Petitioner Did Not Establish Motivation To Combine, And Its Motivation To Combine Theories Are Inconsistent With Its Obviousness Arguments

With respect to motivation to combine, Petitioner asserted a POSITA "would have been motivated to use the buffer or [] components of Rosendahl in the methods of Ferré or Komath to allow for proper formation of the disulfide bond(s)

[13]Petitioner's single-reference obviousness theory in Ground 3 for Komath does not appear to be incorporated in Ground 6. Therefore, Petitioner's obviousness theory for Ground 6 must fail if Ground 2 fails, regardless of Ground 3.

of each method's protein of interest." Pet. 65. But Petitioner never directly addressed whether there were issues in proper formation of the disulfide bonds in those primary references to begin with. Indeed, as noted above, Petitioner has effectively admitted in these Grounds (4 and 6) that there *were* issues with proper refolding (although it does not address them), and thus has conceded a fatal flaw in Grounds 1-2 under the proper construction of "refold buffer," which requires proper protein refolding (*see* §IV.C, *supra*).

In Ground 1, the Petition asserts Ferré teaches a refold buffer with a protein stabilizer and an aggregation suppressor. Pet. 38. In Ground 2, the Petition also asserts Komath teaches a refold buffer. Pet. 47. But in arguing Grounds 4 and 6, Petitioner asserts a POSITA would *modify* these alleged refold buffers and argues that "[a] POSA seeking to solubilize and refold proteins … would have looked to Rosendahl for its disclosure of particular reductants/redox components …" asserting, without explanation, that their use somehow "reduces the number of … steps required." Pet. 64. But the Petition never even states that the cysteine or reduced glutathione would be a reductant or redox component as used in Ferré or Komath. The Petition also asserts that Rosendahl "discloses that these reductants/redox components are 'useful' and 'preferred'…." Pet. 64. But the Petition fails to explain whether its proposed combination would ***substitute*** Rosendahl's reductants/redox components for the components in the alleged refold

buffers of Ferré and Komath, or ***add*** Rosendahl's reductants/redox components ***to*** what is argued to be the existing refold buffer in each of the primary references (which, among other things, would appear to ***increase the number of steps***, in contradiction of Petitioner's motivation arguments about reducing the number of steps (*see* Pet. 64)). Nor did Petitioner explain whether or how any such substitution or addition of components (whatever unexplained permutation Petitioner might have in mind) would otherwise impact the process of Ferré and Komath, or how using the solutions described in Rosendahl would reduce the number of steps. Further, Petitioner failed to explain what steps are eliminated from the prior art and explain how elimination of any such steps would be consistent with its anticipation analysis (*e.g.*, its argument that "Komath does not remove any components of the refold solution" to begin with (Pet. 48)). Petitioner's obviousness argument here is hopelessly incomplete, and in contradiction of other aspects of its obviousness assertions. *See, e.g.*, §312(a)(3); §42.104(b)(4); *LG Elecs., Inc*., IPR2018-00559, Pap. 15, 15-17 (petitioner failed to meet its burden in light of inconsistent positions taken with respect to application of claim limitations); *John Crane*, IPR2016-01827, Paper 6 at 14 (explaining it is petitioner's responsibility "to explain specific evidence that support[s] its arguments, not the Board's responsibility to search the record and piece together what may support [p]etitioner's arguments"); *Axon Enter., Inc.*, IPR2017-00515,

Pap. 10, 18-19 (denying institution because petitioner and its expert did not explain what specific modification to the prior art would have been necessary or how a person of ordinary skill would have been motivated to make the necessary modification based on the structure and operation of the prior art); *Adidas AG v. Nike, Inc*., IPR2016-00920, Pap. 6, 6-7 (Oct. 20, 2016) (denying institution where the Board "[was] generally [] left to guess as to what limitations [petitioner] seeks to supply from the teachings of each of the references that it cites as a part of the proposed ground" and "[t]hose uncertainties and vagaries also deprive[d] [patent owner] of an appropriate basis for it to formulate a response to the [p]etition.").

Further, Petitioner asserted a POSITA seeking to solubilize and refold proteins would have been motivated to combine Ferré with Rosendahl, "look[ing] to Rosendahl for its disclosure of particular reductants/redox components that are successfully able to solubilize and refold aggregated proteins." Pet. 64. But the Petition never explains why a POSITA would have modified Ferré, given Petitioner's assertion (in the context of arguing Ferré anticipates) that "Ferré's approach 'uncouples the events of protein refolding and capture, thereby allowing each event to be optimized individually." Pet. 38. Indeed, if Ferré's refolding were *already optimized*, as Petitioner asserts (Pet. 38), a POSITA would not modify it using Rosendahl *to optimize,* as Petitioner argues.

2. Petitioner Did Not Establish Reasonable Expectation of Success

The Petition's cursory obviousness analysis of these grounds included only a single conclusory sentence directed to reasonable expectation of success, flatly asserting a reasonable expectation of "successful formation of the protein's native disulfide bonds" while ignoring differences in the underlying primary references. Pet. 65. Not only did Petitioner fail to *explain* this assertion, but Petitioner's asserted reasonable expectation of success for Grounds 4 and 6 (Pet. 65 ("POSA would have reasonably expected…successful formation of the protein's native disulfide bonds")) is also *different* (but without explanation) from the reasonable expectation of success it alleges would have been achieved in connection with Komath's obviousness grounds. *See* Pet. 61 ("POSA would have expected with a reasonable expectation of success that using the particular solutions … creates conditions suitable for the protein to associate with the separation matrix"); *see also LG Elecs., Inc.*, IPR2018-00559, Pap. 15, 15-17 (petitioner failed to meet its burden in light of its inconsistent positions). Further, Petitioner provided no analysis of how substituting Rosendahl's components would affect downstream aspects of the process, whether any alleged refold buffer would need intermediate processing (such as centrifugation) before applying it to the column, or whether one would reasonably expect to successfully elute folded protein at the end. As

Amgen pointed out in litigation (EX2002, 19, 66), Rosendahl discloses methods where the solution with allegedly refolded protein is *subjected to centrifugation before loading it onto the chromatography column*, but the Petition nonetheless failed to meaningfully address why centrifugation would not be used here in its asserted combination. EX1006, ¶60. Indeed, Petitioner's conclusory assertion that "Rosendahl does not disclose this step is necessary when using the particular reductants/redox components" (Pet. 66) neither identifies what those particular reductants/redox components are (*see supra*, 44), nor addresses whether a POSITA would have understood that centrifugation would be performed (or whether Petitioner is seeking to modify Komath to remove centrifugation, which it does not explain).

D. Ground 5 (And Un-Numbered Ground 7): Petitioner Has Not Shown A Reasonable Likelihood Of Prevailing In Establishing That That Claims 18, 19 And 21 Are Obvious Over Ferré Or Komath In View Of The GE Handbook

Petitioner did not meet its burden of establishing obviousness for Grounds 5 or 7 (obviousness over Ferré in view of the GE Handbook, and Komath in view of the GE Handbook, respectively) for at least the reasons already described above for the Ferré and Komath grounds (Grounds 1-3), which cover the claims from which the Grounds 5 and 7 depend. The Petition also fails this threshold for Grounds 5 and 7 for the additional reasons cataloged below.

1. Petitioner Presented No Argument About the GE Handbook Being A Printed Publication

As with Ferré, Petitioner did not *even attempt* to establish the GE Handbook is a prior art printed publication. Petitioner merely asserted this is so, offering only the unsupported conclusion that the GE Handbook "is a …printed publication" and "was published" in 2004. Pet. 18, 21. But Petitioner said nothing about where the pages it attaches as an exhibit was found or generated. Nor did Petitioner explain the words "Edition AA," which might reflect a draft, rather than a final version, of a published document—although there is *no evidence of any of this* to begin with. EX1007, 1.

And, even setting aside the questions regarding an "Edition AA," even if Petitioner purported to take the date from the copyright page of the exhibit (which it did not assert), Petitioner provided no explanation as to why such date is not hearsay. Petitioner thus failed to meet its burden on a basic element of anticipation: establishing its references are prior art printed publications and are authentic. *See, e.g.*, *Dr. Reddy's Labs., Inc.*, IPR2018-01507, Pap. 7, 8-11 (denying institution for lack of proof regarding printed publication status of references and collecting cases); *TRW Auto.*, IPR2014-01347, Pap. 25, 8-9 ("[C]opyright notice is … not probative that the article was ever published by IEEE or anyone else.").

2. Petitioner Did Not Establish Motivation to Combine Or Reasonable Expectation Of Success, and its Obviousness Theories Are Inconsistent With its Obviousness Arguments

Petitioner asserts that a POSITA would have been motivated to regenerate the matrices of Ferré and Komath by performing a wash with NaOH, and would have expected the wash to work. Pet. 68. However, Petitioner fails to address that the GE Handbook itself stressed the importance of, *e.g.*, centrifuging, filtering, and desalting a solution before applying it to the matrix to avoid clogging or fouling the column. EX1007, 153-154 ("Simple steps to clarify a sample before beginning purification will avoid clogging the column … and can extend the life of the chromatographic medium…[i]t is highly recommended to centrifuge and filter any sample immediately before chromatography "), 155-158; EX1031, 19, 130; EX1034, 76:55-61.But Petitioner asserts in Ground 1 and 2 that such processes are not used in Ferré or Komath. Pet. 39-41, 48-50. Petitioner does not address whether a POSITA would have a motivation to regenerate a fouled or clogged column and whether a POSITA would have reasonable expectation of success in regenerating a clogged or fouled column with NaOH.

VI. Petitioner Failed To Establish That Its Non-Patent Literature Background References Are Prior Art Or Reflect Information Known To A POSITA By 2009

Just as with Ferré and the GE Handbook, Petitioner did not make any attempt to establish that various of its background references (EXS1009-1012;

1016-1033; 1050-1062; 1064; 1065; 1068 and 1071-1073) are prior art printed publications. The Petition merely asserts this is so, without providing any information about where the pages it attaches as an exhibit were found or generated.[14] For instance, like EX1007 discussed above, EX1019 contains the unexplained words "Edition AA," which might appear to reflect a draft, rather than a final version, of a document as published—although there is *no evidence of any of this* to begin with. Certainly, Petitioner presents no explanation or evidence as to when or whether these materials became printed publications. Petitioner has thus failed to establish the level of background knowledge at the time of the challenged '878 patent. *See, e.g.*, *Dr. Reddy's Labs.*, IPR2018-01507, Pap. 7, 8-11 (denying institution for lack of proof regarding printed publication status of references and collecting cases); *TRW Auto.*, IPR2014-01347, Pap. 25, 8-9 ("[C]opyright notice is … not probative that the article was ever published by IEEE or anyone else.").

VII. Conclusion

[14]For EX1012 and EX1055, the exhibit list indicates a website where the references are allegedly "available," but Petitioner makes no representation or argument that these websites are where it obtained the pages submitted as those exhibits.

Even with this preliminary record, due to failures in both proof and specificity of argument, Petitioner failed to show that the challenged claims are anticipated or rendered obvious based on Ferré, Komath, Hahm, or Dietrich. Petitioner also failed to explain why the Board should not exercise its discretion and deny institution under §314.

Because the Petition failed to show that there is a reasonable likelihood that Petitioner will prevail in proving any Challenged Claim is unpatentable, the Petition should be denied in its entirety, and, pursuant to §314, no *inter partes* review should be instituted. To the extent the Board determines that Petitioner has met its burden on any subset of these grounds (it has not), post-*SAS*, the Board should use its discretion under §314(a) to deny institution on all grounds because, in light of the evidence and arguments presented in this Petition, requiring the Board and the Amgen to bear the wasteful burden and of a trial on all grounds to reach such a subset of grounds would not, *inter alia*, be an efficient use of the Board's limited time and resources.

Respectfully submitted by:

Dated: June 14, 2019

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CERTIFICATE OF WORD COUNT

The undersigned certifies that the foregoing PATENT OWNER'S PRELIMINARY RESPONSE UNDER 37 C.F.R. §42.107 complies with the type-volume limitation in 37 C.F.R. §42.24(c)(1). According to the word-processing system's word count, the brief contains 11, 552 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 PRELIMINARY RESPONSE UNDER 37 C.F.R. §42.107 has been served in its entirety by causing the aforementioned document to be electronically mailed to the following attorneys of record for the Petitioner listed below:

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