UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

v.

AMGEN INC.,
Patent Owner.

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Case IPR2019-01183
Patent 9,643,997

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

# 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) |

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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, 13-21, and 23-30 ("Challenged Claims") of U.S. Patent 9,643,997 ("'997 patent"), filed by Petitioners Fresenius Kabi USA, LLC and Fresenius Kabi SwissBioSim GmbH (together, "Petitioners").[1]

## I. Introduction

The Petition failed to provide the Board the basic evidence and analysis required to institute an IPR. If the Board nonetheless institutes trial on the Challenged Claims, Amgen will address in detail in its §42.120 Response the numerous substantive errors and shortcomings in Petitioners' 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 325, and Petitioners' failure to demonstrate, as to any of the Challenged Claims, a reasonable likelihood

[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.

of success on *any* asserted Ground of invalidity. Because of these threshold failures, the Petition should be denied and no IPR should be instituted.

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 Petitioners had made their threshold showing for some claims or Grounds—they have not—the Board, in its discretion, should deny institution on all Challenged Claims and Grounds in the Petition.

***First***, Petitioners made no effort to distinguish their references and arguments from those previously considered by the Office and being considered now by the Board. For example, in Grounds 4 and 5, Petitioners recycled the same or substantially the same art and arguments previously raised in an earlier IPR petition filed by another petitioner, *Kashiv Biosciences, LLC v. Amgen Inc.*, IPR2019-00797, Pap.2 (Mar. 7, 2019) ("Kashiv Pet."). There are no significant differences, and the Board should exercise its discretion under §325(d) to deny the Petition to avoid wasteful parallel proceedings.

***Second***, as discussed below, the *General Plastic* factors weigh heavily in favor of denying institution under §314 to avoid burdensome and oppressive serial IPR proceedings. And given that Petitioners have apparently coordinated with Kashiv (formerly known as Adello)—the petitioner in the first '997 IPR and also a

petitioner in PGR2019-00001 challenging U.S. Patent 9,856,287 (also challenged by the Fresenius Petitioners in IPR2019-00971)—the Board should deny the Petition to avoid this abuse of the Board's procedures and forum.

***Third***, Petitioners' own arguments and evidence confirm they cannot meet their 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 with and address issues known to them from various pending litigations, Petitioners ignored self-evident claim construction issues on claim terms that affect all of their anticipation and obviousness Grounds and render their analyses of the references incomplete, flawed, and ultimately without merit:

- Despite being aware of key claim construction issues concerning "applying the refold solution," Petitioners failed to set forth a construction that clearly addressed what "intermediate" steps are and are not allowed by the claims.
- Petitioners failed to present any argument under the correct construction of "refold buffer" for any Ground, or even to address the requirement that it act as an actual buffer.
- Petitioners failed to engage in sufficient analysis of the "applying the refold solution…" element for any Ground, despite being aware of fundamental issues from litigation involving the '997 patent.

- Petitioners failed to perform any analysis construing various dependent claims, relying instead on an unsupported assertion that the limitations in those claims are not actually limiting and that, therefore, the art need not teach any element in those dependent claims to render them anticipated.

***Fourth***, Petitioners offered, in support of their obviousness Grounds (Grounds 2 and 5), only cursory and conclusory analyses concerning the alleged motivations to combine references and a POSITA's reasonable expectation of success in doing so.

***Fifth***, Petitioners failed to establish that any of their primary, secondary, or background non-patent references is a printed publication that qualifies as prior art or reflects information known to a POSITA at or around the relevant priority date.

In view of the post-*SAS* all-or-nothing institution rule and the many gaps of proof in Petitioners' arguments, even if the Board were to unearth a Ground with merit buried within Petitioners' pile of arguments and combinations *reflecting five separate challenges to each claim*, 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 Petitioners' imprecise scattershot approach here. *See, e.g.*, *SAS Inst.*, 138 S. Ct. at 1355-56; *Chevron Oronite Co. v. Infineum 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 subset of claims); *see also Deeper, UAB v. Vexilar, Inc*., IPR2018-01310, Pap.7, 41-43 (Jan. 24, 2019) (informative) (denying institution because "instituting a 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 U.S.C. § 316(b)), the entire petition should be denied under 35 USC § 314(a)"). This is particularly so given Petitioners' failure to clearly map each claim element to the art, instead lumping together multiple aspects of the claims into a single heading, then generally asserting (often without any specific mapping) that the art teaches or renders obvious that collection of claim elements.

For these reasons, the Petition should be denied.

## II. The Challenged Claims Of The '997 Patent Are Directed To A Novel Invention

The '997 patent "relates generally to processes for purifying proteins expressed in non-mammalian systems." EX1001, 1:13-14.[2] Protein purification is a critical step in the manufacture of biological products using recombinant DNA technology. Before the invention of the '997 patent, it was believed in the art that certain of the specialized chemical compounds used to refold 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; EX1038. 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 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 separation to work and the protein to be purified. EX1001, 1:46-55, 15:50-67; EX1038. In the prior art, processing steps, such as substantial dilution, were performed ***between*** protein refolding and application to a first chromatographic separation matrix. *See, e.g.*, *ibid.* The inventors recognized

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

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 can be achieved by applying a refold solution to a separation matrix, ***without*** certain intervening processing steps. *Id.*, 12:14-20, 15:50-67.

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

The Board has discretion to deny institution here under §325(d), which provides "the Director may take into account whether, and reject the petition or request because, the same or substantially the same prior art *or* arguments previously were presented to the Office." §325(d); *see, e.g.*, *Neology, Inc. v. Star Sys. Int'l Ltd.*, IPR2019-00367, Pap.9, 12 (June 6, 2019) (denying institution under §325(d) where patent owner argued same or substantially the same art and arguments considered during prosecution); *Juniper Networks Inc. v. Finjan, Inc.*, IPR2019-00060, Pap.7, 14-17 (Apr. 29, 2019) (denying institution under §314 and §325(d); "On balance, we find that the instant Petition presents one ground without merit and two grounds based primarily on [a reference] we are considering in the ongoing 391 case. Notwithstanding some differences in the prior art combined with [the reference], we are persuaded that instituting trial here would be an

inefficient use of Board resources and would result in substantial overlap and duplication of issues, arguments, and evidence.").

The Board has also repeatedly denied institution when—as here—a petition fails to explain why this discretion to deny should *not* be exercised. *See, e.g.*, *Unified Patents, Inc. v. Berman*, IPR2016-01571, Pap.10, 11-12 (Dec. 14, 2016) (informative). Petitioners here relied on much of the same art considered by the Examiner during the initial prosecution and/or relied on by the petitioner challenging the '997 patent in *Kashiv Biosciences, LLC v. Amgen, Inc.*, IPR2019-00797 ("Kashiv IPR"). Yet, although Petitioners made the conclusory assertion that "there are no persuasive grounds for denying institution under §314(a) or §325(d)" (Pet.2), they made no effort to distinguish their supposedly invalidating references from those considered in initial prosecution and asserted in the Kashiv IPR. Nor do they explain or identify what, if anything, their prior art purportedly adds over the art in the Kashiv IPR that would justify the burden of a parallel proceeding.

Petitioners have simply failed to make the appropriate showing and, for that reason alone, the Board should deny the Petition under §325(d). *See Neil Ziegmann, N.P.Z., Inc. v. Stephens*, IPR2015-01860, Pap.13, 8 (Sept. 6, 2017) (expanded panel decision) ("A party making assertions relevant to Section 325(d)

should identify such differences (or lack thereof), whether substantive or procedural, and explain the relevance of those differences (or lack thereof).").

Even setting aside Petitioners' failure to properly address §325(d), Ground 4 of the present Petition (anticipation by Dietrich, Pet.41-48) relies on the same prior art reference, Dietrich, as the Kashiv IPR's Ground 5 (anticipation by Dietrich, Kashiv Pet.62-67). Further, despite Petitioners' assertion that they "drafted this petition independently of Kashiv," Pet.3, this Ground reads as virtually a *verbatim* copy. *Compare* Pet.41-48, *with* Kashiv Pet.62-67; *see also* Kashiv Pet.67-71 (Ground 6 alleging obviousness of Dietrich in view of Rosendahl); *Expedia, Inc. v. Int'l Bus. Mach. Corp.*, IPR2019-00404, Pap.8, 11, 12, 14 (June 5, 2019) (where reasons to combine and two paragraphs in expert declarations were identical in two IPRs, there was "no justification for why we should nevertheless expend Board resources to revisit those arguments" in later filed IPR).

In addition, Petitioners' Ground 5, which argues the Challenged Claims are obvious over Komath '994 in combination with Komath '056 (Pet.50-58), relies on substantially the same art and arguments as the Kashiv IPR's Grounds 2 and 3, which argue that claims are anticipated by or obvious over Komath '056 (Kashiv Pet.41-56). Indeed, despite attempting to hide Komath *'056* behind Komath '994 in their Ground 5, Petitioners asserted that Komath *'056* explicitly discloses every claim limitation of independent claim 9, as well as dependent claims 10, 13-20,

and 23-28. *See* Pet.50-58 (asserting for the two Komath references that "each teach[es]," "each disclose[es]," or "each describes" the limitations); Pet.51-52, 56 (asserting that Komath '056 "discloses" or "teaches" limitations). Petitioners' addition of Komath '994 as a fig leaf does not make this ground substantively different from the Kashiv IPR's Grounds 2 and 3. *See Ivantis, Inc. v. Glaukos Corp.*, IPR2019-00483, Pap.8, 24 (July 8, 2019) ("Petitioner does not make any argument that the information found in Grieshaber A1 [similar to Komath '944 here] is not found in other Grieshaber documents [similar to Komath '056 here] considered by the office. Thus, there is nothing new or additional within this reference that would warrant further consideration."); *Neil Ziegmann*, IPR2015-01860, Pap.13, 11, 14-15 (the Board "considers the relevance of any differences between the prior art and arguments presented in the petition and that were 'previously…presented to the Office'").

Despite the obvious fact that many of Petitioners' arguments and asserted art, including two allegedly invalidating references, are substantially the same as those raised in the initial prosecution and/or the Kashiv IPR, Petitioners never substantively addressed §325(d). That there may be some non-identical references or arguments from those considered during the initial prosecution or in the Kashiv IPR is of no moment, and Petitioners did not explain how any differences would be relevant to the Board decision. *See Conopco, Inc. v. Procter & Gamble Co.*,

IPR2014-00506, Pap.17, 6-8 (July 7, 2014) (informative) (denying institution because petitioner presented substantially same arguments compared to petition already considered by Board, notwithstanding that seven out of thirteen cited prior art references were new); *NetApp Inc. v. Crossroads Sys. Inc*., IPR2015-00777, Pap.12, 7-8 (Sept. 3, 2015) (declining to institute when obviousness arguments were based on prior art combinations that overlapped with prior art combinations relied on in prior petition, even though combinations in prior petition were not composed of exactly the same prior art references as in current petition).

The Board should exercise its discretion to deny institution under §325(d) and avoid a do-over and unnecessary parallel proceedings. *See Neil Ziegmann*, IPR2015-01860, Pap.13, 8 ("A party making assertions relevant to Section 325(d) should identify such differences (or lack thereof), whether substantive or procedural, and explain the relevance of those differences (or lack thereof)."); *see also Shenzhen Zhiyi Tech. Co. v. iRobot Corp*., IPR2017-02050, Pap.8, 11-12 (Mar. 12, 2018) (declining to institute when petitioner failed to address §325(d) and thus failed to explain why challenges that raise the same or substantially the same prior art and arguments previously presented to Office should be reconsidered by Board); *Baker Hughes Oilfield Operations, Inc. v. Smith Int'l, Inc.*, IPR2016-01451, Pap.9, 10 (Dec. 22, 2016) (noting "the failure of Petitioner to address the impact of…325(d)" as reason not to institute).

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

Institution of *inter partes* review is discretionary. *See* §314(a); §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 IPR proceeding"). Here, Petitioners acknowledged they should have conducted some form of analysis under the Board's *General Plastic* factors, but failed to provide a complete or meaningful analysis. Pet.2-3.

### A. The *General Plastic* Factors Support Denial Of Institution

#### 1. Factor 1: Whether Petitioners Are The Same

While not formally a party to the earlier Kashiv IPR, Petitioners—well aware of the IPR and acting in a conscious tag-team—now put before the Board still more permutations of previously-considered art and arguments, as well as some of the same grounds already pending in the IPR. For example, Kashiv (then Adello) was one of the petitioners on an October 2018 PGR petition challenging Amgen's U.S. Patent No. 9,856,287, PGR2019-00001 ("'287 PGR").[3] Months

[3] ***Adello Biologics, LLC is Kashiv Biologics, LLC***. On January 1, 2019, Kashiv Pharma, LLC acquired Adello Biologics, LLC, and the resulting entity was

later, in April 2019, Petitioners here submitted a strikingly similar IPR petition challenging the '287 patent (IPR2019-00971 ("'287 IPR")), and then actually ***attended*** the July 10 deposition in the '287 PGR.

The same choreography has played out here. Here again, Kashiv filed the first petition. And now, Petitioners here have filed the second, using some of the same Grounds already pending in the Kashiv IPR, even copying one Ground essentially *verbatim*, and then adding more Grounds in a thinly veiled attempt to look "different." These serial attacks on the '997 patent and the relationship and apparent coordination between the Petitioners here and those in the Kashiv proceedings weigh against institution. As the Board has observed, the "application of the *General Plastic* factors is not limited solely to instances in which multiple petitions are filed by the same petitioner," but rather, "when different petitioners challenge the same patent, we consider *any relationship* between those petitioners

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renamed Kashiv Biosciences, LLC. EX2050, 1. On June 10, 2019, a few days after Petitioners filed their Petition, the caption of *Amgen Inc. v. Adello Biologics LLC*, Case No. 2:18-cv-03347-CCC-MF (D.N.J.), which Petitioners included in their mandatory notice, Pet.4, was changed to reflect this reality. EX2050, 2; *see also* Amgen's Mandatory Notice, Pap.5, 2.

while weighing the *General Plastic* factors." *Valve Corp. v. Elec. Scripting Prods., Inc.*, IPR2019-00064, Pap.10, 10 (May 1, 2019) (precedential).

Petitioners did not address the relevant case law, instead resting on generic assertions that Petitioners here and Kashiv are "unrelated" corporate entities and (erroneously) that §§314(a) and 325(d) do not apply to a first-time petitioner. Pet.2-3.

This factor weighs in favor of denying institution.

**2. Factor 2: Knowledge Of Prior Art**

Petitioners failed to address their knowledge of the prior art in the Petition. However, much of the background art and Petitioners' primary base reference, Dietrich, were considered by the Examiner during the '997 patent's initial prosecution, which Petitioners attached (EX1033).[4] Many of the background references were previously submitted in proceedings challenging this patent and the '287 patent, which includes overlapping claim limitations. For example:

[4] The '997 patent identifies or discusses Dietrich (EX1005), Whitford (EX1009), Georgiou & Valax (EX1014), De Bernardez Clark 2001 (EX1016), Neubauer (EX1019), Jungbauer (EX1020), De Bernardez Clark 1998 (EX1021), U.S. Appl. Pub. No. 2007/0238860 (EX1022), GE Healthcare (EX1037), and Wang 1997 (EX1038). EX1001, 1-5.

- Ten of Petitioners' references were previously submitted *by Petitioners* in the '287 IPR. *Compare* EX1009, EX1010, EX1012, EX1014, EX1015, EX1016, EX1018, EX1019, EX1021, EX1022, *with* '287IPREX1034, '287IPREX1017, '287IPREX1024, '287IPREX1012, '287IPREX1007, '287IPREX1008, '287IPREX1014, '287IPREX1020, '287IPREX1042,'287IPREX1028.
- Seven of Petitioners' references were previously submitted for consideration in the '287 PGR. *Compare* EX1009, EX1012, EX1014, EX1019, EX1020, EX1021, EX1022, *with* '287PGREX1006, '287PGREX1018, '287PGREX1019, '287PGREX1015, '287PGREX1022, '287PGREX1051,'287PGREX1007.
- Ten of Petitioners' references were submitted in the Kashiv IPR. *Compare* EX1005, EX1007 (Komath '056), EX1009, EX1014, EX1016, EX1019, EX1020, EX1021, EX1036, EX1037, *with* KashivEX1008, KashivEX1005, KashivEX1017, KashivEX1020, KashivEX1022, KashivEX1010, KashivEX1024, KashivEX1023, KashivEX1007, KashivEX1073.

In sum, ***15 of Petitioners' 24 background references*** were also used by petitioners in the '287 PGR, the '287 IPR, and/or the Kashiv IPR.

Petitioners knew at least of its primary reference Dietrich, "secondary"[5] reference Komath '056, and many of the background references because they were cited on the face of the patent or cited in the Kashiv IPR petition (which Petitioners have reviewed (*see* Pet.2-3)) or in the previous challenges to the '287 patent. *See Valve*, IPR2019-00064, Pap.10, 11.

And, with respect to the other relied-upon, allegedly invalidating references—Wang (EX1003), Cutler (EX1028), Reardon (EX1004), and Komath '944 (EX1006)—Petitioners offered no explanation or discussion of the timing of the Petition and when and whether Petitioners should have known about these references through the exercise of reasonable diligence. *See id.*, 11-12 (finding this factor weighed against institution because references could be found through reasonable exercise of diligence where petition was filed five months after another petitioner's petition).

Accordingly, this factor favors denying institution. *See id*.

**3. Factor 3: Availability Of Information From Prior Proceedings**

Petitioners had access to Amgen's POPR, POR, and expert declarations from IPR2016-01542 ("'138 IPR," which challenged U.S. Patent 8,952,138 ("the

[5] *See* §VI.D.2.

'138 patent")), and Amgen's POPR in the '287 PGR. *See Samsung Elecs. Co. v. Elm 3DS Innovations, LLC*, IPR2017-01305, Pap.11, 20-21 (Oct. 17, 2017) (relying on availability of expert testimony and patent owner response from other related proceedings in denying institution).[6] Further, although Amgen submitted its preliminary response to the Kashiv IPR petition shortly after the present Petition was filed, Petitioners were able to review, and in some cases copy, the Kashiv IPR petition. Despite Petitioners' suggestion that they have not gained any unfair advantage because they "fil[ed] their petition before [Amgen] file[d] its response to Kashiv's petition," Pet.3, Petitioners have clearly taken advantage of the prior Kashiv IPR petition itself, and would have the advantage of future papers in the Kashiv IPR previewing positions before Petitioners' later responses here. This factor favors denial of institution.

[6] The '138 patent claims priority to the same provisional application as the '287 patent. The '997, '138, and '287 patents are all assigned to Amgen and directed to refolding protein. The '138 and '997 both claim a refold buffer, including a denaturant, an aggregation suppressor, a protein stabilizer, and a redox component. And the '287 and '997 patents both claim refolding proteins expressed in a non-mammalian expression system using a reductant, a denaturant, an aggregation suppressor, and/or a protein stabilizer.

### 4. Factors 4 And 5: Timing Of Instant Petition And Petitioners' Explanation For Their Delay

As discussed above (*see* §IV.A.2), Petitioners knew or should have known of the references they rely on before or around the time the Kashiv IPR petition was filed, March 7, 2019, whether from their citation on the face of the patent or in the Kashiv IPR petition, or located quickly with reasonable diligence. Notably, Petitioners have not suggested they had any difficulty locating the remaining references. *See NetApp Inc. v. Realtime Data LLC*, IPR2017-01195, Pap.9, 11-12 (Oct. 12, 2017) ("The record also contains no evidence that NetApp could not have located Kitagawa (a U.S. Patent) at an earlier date"). Yet, the present Petition was not filed until June 8, 2019, three months after the Kashiv IPR petition, and Petitioners provided ***no explanation*** for this timing. This is particularly notable in view of Petitioners' copying of Ground 4 almost *verbatim*, and relying on the Komath '056 theory and disclosures from the Kashiv IPR in their Ground 5. *See id.* (finding factor 5 weighed against institution where petitioner offered no explanation for its delay); *cf. Valve Corp. v. Elec. Scripting Prods., Inc.*, IPR2019-00062, Pap.11, 13-14 (Apr. 2, 2019) (finding factors 4 and 5 weighed against institution despite petitioners' explanation for delay); *Juniper Networks, Inc. v Parity Networks, LLC*, IPR2018-01642, Pap.11, 10 (Apr. 10, 2019) (finding

factor 5 weighed against institution where petitioner offered merely "generic justification" for delay).

### 5. Factors 6 And 7: Board Considerations Of Finite Resources/One-Year Time Line

These related factors consider the "finite resources of the Board" and the timing requirement for the Board's final determination. Here, *five challenges per claim* are included in the present Petition, and *six* challenges per claim were packed into the Kashiv IPR petition. Petitioners had ample opportunity to file their Petition sooner, but did not. And, if they wanted a chance (as appears from the substance of the Petition) to repeat the arguments made in the Kashiv IPR petition, they could have filed a petition earlier (or filed a formal copycat petition and then sought joinder). Instead, Petitioners waited and filed their own rehash of these arguments. Although Petitioners mentioned that they would be "amenable to a coordinated schedule with Kashiv's IPR to minimize any additional burden on the Board and [Amgen]," this offer rings hollow since Petitioners waited ***three months*** to file and used a different expert. Such "coordination" would not save briefing or discovery, and would mean extending the Kashiv IPR schedule out past the one-year deadline to alleviate, *inter alia*, time-pressure on the Board and accommodate depositions of Petitioners' new expert. Thus, both factors weigh in favor of denying institution.

### 6. Additional Factors Warrant Denial

Several additional factors warrant denial under §314(a). While Petitioners recycled previous prior art, they provided "no explanation why [the Board] should substantively entertain yet another set of grounds that also rely on one of those references as teaching or suggesting" the claims. *Alcatel-Lucent USA Inc. v. Oyster Optics, LLC*, IPR2018-00257, Pap.14, 25 (June 4, 2018). As in *Alcatel-Lucent*, Petitioners failed to explain why these grounds are not cumulative. *Id.* "This lack of explanation also favors denying the Petition." *Id*.

Two other factors are sometimes also considered when a different petitioner files a subsequent petition: whether there is potential prejudice to the subsequent petitioner if institution is denied and the pending proceedings involving the first petitioner are terminated, and whether multiple petitions filed against the same patent are a direct result of patent owner's litigation activity. *Am. Honda Motor Co. v. Intellectual Ventures II LLC*, IPR2018-00348, Pap.10, 20-21 (June 27, 2018). Here, Petitioners are not prejudiced because they have not been sued, and thus could have sought to later file a Petition in the event the Kashiv IPR is terminated. Moreover, if Petitioners' desire is to see that the Kashiv IPR is not terminated before a final written decision, they can move for joinder. And, the filing of the present Petition is not the direct result of Amgen's litigation activity, as the '997 patent is not currently being litigated against Petitioners—indeed,

Amgen is not currently asserting any of its protein refolding patents against Petitioners. Thus, these factors favor the Board exercising its discretion to deny institution.

* * *

For all these reasons, the *General Plastic* factors weigh in favor of denying institution under §314(a). The Board should exercise its discretion to do so.

## V. Claim Construction[7]

Petitioners here failed to fulfill their obligation under the Rules to explain "[h]ow the challenged claim is to be construed" and, when construed properly, "[h]ow the construed claim is unpatentable." §42.104(b)(3)-(4). Petitioners were *required* to construe at least "aggregation suppressor," "protein stabilizer," and "refold buffer" as necessary to the arguments they have advanced, but they failed

[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 the 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.

to do so. The Petition's Grounds should all be rejected on this basis. *See, e.g.*, *Hologic, Inc. v. Enzo Life Scis. Inc.*, IPR2018-00019, Pap.21, 6 (Nov. 28, 2018) ("Petitioner does not satisfy Rule 42.104(b)(3) when, in a proceeding applying the *Phillips* claim-construction standard, it 'expressly disagree[s] with its proffered construction.'"); *SharkNinja Operating LLC v. Flexible Techs., Inc.*, IPR2018-00903, Pap.8, 6-10, 23 (Oct. 17, 2018) ("The Petition indicates Petitioners' own understanding that the meaning of the claim was unclear from the specification, and it was therefore incumbent on Petitioner to engage in further analysis or to propose a construction in order to satisfy the rules…. Petitioner has not met its burden to provide a construction of the claims at issue, as required by 37 C.F.R. §42.104(b)(3) and (4)."). Nevertheless, Amgen provides constructions for these and other relevant terms below.

### A. "Refold Buffer" (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. |

**Refold Buffer Must Be pH Buffered.** Petitioners failed to provide a construction for this term, despite knowing it is at issue in the Kashiv IPR, a matter Petitioners cited as related in their mandatory notices, Pet.4, and, as discussed

above, a petition that Petitioners *copied* at least in part. For that reason alone, the Petition should be rejected. *See, e.g.*, *Orthopediatrics Corp. v. K2M, Inc.*, IPR2018-01547, Pap.9, 10 (Feb. 22, 2019) (denying institution where "the Petition fails to identify how the challenged claims are to be construed and applied to the prior art, and Petitioner also takes conflicting positions between this proceeding and the related district court litigation"); *SharkNinja*, IPR2018-00903, Pap.8, 6-9, 23 (denying institution where "Petitioner has not met its burden to provide a construction of the claims at issue, as required by 37 C.F.R. 42.104(b)(3) and (4)").

If the Board nevertheless were to overlook this failure in compliance and consider this Petition on the merits, the refold buffer should be construed so as 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 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 canon of claim construction that different words ("solution" and "buffer" here) 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***" instead of "refold ***solution***" in the claims the applicant made clear that a "refold buffer" is not just a solution, but a *pH* ***buffered*** solution.

Amgen's construction is further supported by the specification and claims, which differentiate among different components of the refold buffer. The independent claims and specification make clear that the "refold buffer" need not necessarily utilize each of a denaturant, aggregation suppressor, protein stabilizer, and 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, 15:5-11. Thus, there would be no reason for a buffering capacity to be separately recited in the claims since that requirement 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 buffering capacity. The claims' use of "comprising" also reflects that the "refold buffer" is not limited to a denaturant, aggregation suppressor, protein stabilizer, and redox component. *See Regeneron Pharm., Inc. v. Merus N.V.*, 864 F.3d 1343, 1352 (Fed. Cir. 2017); *accord* MPEP §2111.03. Moreover, there is no reason the inclusion of and requirement for a denaturant, aggregation suppressor, protein stabilizer, and/or redox component would render the recited word "buffer" in the claims meaningless.[8]

The court in *Amgen Inc. v. Hospira Inc*., Case 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, 86:21-87:3. The 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.*, 86:19-87:3.

[8] For at least these reasons, the *Mylan* court erred in construing "refold buffer." EX2053, 17-20.

Extrinsic evidence further supports Amgen's construction. For example, 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 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).

**Refold Buffer Must Refold Protein Into Its Biologically Active Form.** The refold buffer must actually provide conditions suitable so that the protein refolds into its biologically active form. Petitioners were aware of Amgen's position on this issue from the claim construction briefing in the *Mylan* case, but Petitioners simply ignored it in their Petition by failing to propose a construction of "refold buffer." EX1034, 14; EX1035, 17. The '997 patent "relates generally to processes for purifying proteins expressed in non-mammalian systems" and 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."*** EX1001, 1:13-14, 11:62-63, 12:19-20, 12:29-32. The "refold buffer" (which, according to the independent claims, 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.

The '997 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." *Id.*, 12:29-32. Thus, after solubilizing the protein, the protein is refolded into its native three-dimensional structure. This is accomplished, for example, in claim 9 by "forming a refold solution comprising the solubilization solution and a refold buffer." *Id.*, 2:29-33. 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." *Id.*, 14:27-40. 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 in the refold solution. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1316 (Fed. Cir. 2005) (en banc). The construction of "refold buffer" must account for this.

### 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,***[9] ***centrifugation, dialysis, or precipitation*** under conditions suitable for protein to have specific, reversible interactions with a separation matrix in order to effect the separation of protein from its environment" | "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." |

Despite asserting that its art does not contain any prohibited intervening steps, Petitioners expressly "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," but then assert 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. Petitioners failed to fulfill their obligation under the Rules to explain "[h]ow the challenged claim is to be construed" and, when construed properly, "[h]ow the construed

[9] "Dilution" here refers to substantial dilution. The exact bounds of "substantial dilution" need not be determined for the purpose of institution. *See supra*, n.7.

claim is unpatentable." §42.204(b)(3)-(4). The Petition's Grounds should all be rejected on this basis.

Amgen's construction (which Petitioners were admittedly aware of from litigation), defines "applying the refold solution…" as "applying the refold solution to a column that contains the separation matrix without intervening steps of ***dilution***, centrifugation, dialysis, or precipitation under conditions suitable for protein to have specific, reversible interactions with a separation matrix in order to effect the separation of protein from its environment." As Petitioners admitted, this construction was adopted by the court in *Amgen Inc. v. Mylan Inc*., Case No. 2:17-cv-01235-MRH (W.D. Pa.). Pet.14-15.[10]

As explained above, before the invention of the '997 patent, it was believed that it was *necessary* to substantially dilute, reduce, or remove certain of the specialized chemical compounds used to refold proteins before applying the refold solution to a separation matrix for purification in order for refolding to be achieved. *See, e.g.*, *id.*, 1:46-55; EX1038 (reflecting at least 30x dilution). The

[10] Petitioners failed to provide the Board with a copy of the *Mylan* court's claim construction ruling that they criticize, so Amgen has included it here as EX2053. The *Mylan* court sets forth its construction for this term, including supporting intrinsic evidence, on pages 23-29.

specification explicitly describes the invention as "eliminat[ing]…the need to ***dilute*** the protein out of a refold solution prior to capturing it on a separation matrix." EX1001, 3:53-57. The specification also teaches that, in the prior art, components that facilitate protein refolding could "inhibit purification," and that prior art reflected a need "to isolate or ***dilute*** the protein from these components for further processing, particularly before applying the protein to a separation matrix." *Id.*, 4:52-57. The inventors of the '997 patent, in contrast, recognized that substantial dilution can be time-consuming and resource-intensive, *see id.*, 12:45-46, and that it "***significantly increases*** the volumes that need to be handled, as well as the associated tankage requirements, which can become limiting when working on large scales." *Id.*, 12:46-49. Their invention thus eliminated the need to substantially dilute the components of the solution used for refolding the protein; their invention achieved refolding in a manner other than by substantially diluting. *Id.*, 15:50-54. For these reasons, "applying the refold solution…." cannot involve substantial "dilution." *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); EX2053, 23 n.11 ("Here, as in *Sandoz*, both parties agree that 'the patent teaches a method of purification that does not require dilution of

the refold solution.'") (citing *Amgen Inc. v. Sandoz Inc.*, Case No. 14-cv-04741-RS, 2016 U.S. Dist. LEXIS 102755, at *41 (N.D. Cal. Aug. 4, 2016)).

The '997 prosecution history shows that the intervening steps of ***dialysis, precipitation, and centrifugation*** must also be carved out, consistent with Amgen's construction. Petitioners here agreed that in prosecution, Amgen surrendered specific intervening steps that had been disclosed in a prior-art reference, including dialysis, precipitation, and centrifugation. Pet.16-17. Claim 9 was initially rejected by the Examiner as anticipated by and obvious over U.S. Patent No. 7,138,370 ("Oliner"). EX2012. 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].

EX1037, 11; *see* EX2012, 76:51-61. 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. "[W]here the patentee has unequivocally

disavowed a 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 accordingly narrows the scope of the claim term "congruent with the scope of the surrender," by expressly identifying and excluding the following steps recited in Oliner: dialysis, precipitation, and centrifugation. EX1037, 11; *see* EX2012, 76:51-61. And, Amgen's construction is consistent with the specification, which, as explained above, excludes the step of dilution (*i.e.*, substantial dilution).

### C. "Aggregation Suppressor" And "Protein Stabilizer" (All Challenged Claims)

| Amgen's Proposed Constructions | Petitioners' Proposed Constructions |
|---|---|
| Aggregation suppressor: "disrupt and decrease or eliminate interactions between two or more proteins"<br><br>Protein stabilizer: "change a protein's reaction equilibrium state, such that the native state of the protein *is* improved or favored" | None proposed. |

Independent claim 9 requires "a refold solution comprising…a refold buffer, the refold buffer comprising one or more of the following: (i) a denaturant; (ii) an *aggregation suppressor*, (iii) a *protein stabilizer*…." EX1001, 22:44-50. An aggregation suppressor must actually disrupt or decrease or eliminate interactions

between two or more proteins at the concentration used. EX1001, 5:45-47. 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.*, 5:46-47. This is what it means to have the "ability to disrupt and decrease or eliminate interactions between two or more proteins." EX1001 5:45-53, 14:34-37.

And a protein stabilizer must actually stabilize protein in the refold solution at the concentration used. *Id.*, 5:54-57. 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.*, 5:55-57, 14:37-40. This is what it means to have the "ability to change a protein's reaction equilibrium state…."

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

Claim 9 recites two groups, "a solubilization solution comprising one or more of the following: (i) a denaturant; (ii) a reductant; and (iii) a surfactant" and 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. Claim 14 requires "wherein the denaturant of the solubilization solution of the refold buffer comprises one or more of urea, guanidinium salts, dimethyl urea, methylurea and ethylurea." *Id.*, 22:66-23:2.

Claims 15-19 and 23-27 similarly select one of the elements of the groups from the independent claim, and further narrow that element to particular kinds of reductant, surfactant, aggregation suppressor, protein stabilizer, or redox component. However, without citing any legal authority, Petitioners made the blanket assertion:

> [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 avoid having to prove that the prior art teaches (or even renders obvious) the limitations of various dependent claims. Petitioners implicitly assume (without authority) that the dependent claims should be construed such that, once an independent claim is anticipated by or rendered obvious over the prior art, that in itself is sufficient to invalidate the dependent claims, without any more proof. *See, e.g.*, Pet.27-29, 31-32 (Wang allegedly 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 (alleged anticipation of dependent claims 16 and 24 by Reardon, without addressing substance of dependent claims); Pet.46 (alleged anticipation of dependent claims 16 and 24 by Dietrich, without addressing substance of dependent claims); Pet.55, 57 (alleged obviousness of dependent claims 15, 23, 16, 24, 19 and 27 over the Komath references, without addressing substance of dependent claims).

However, under *Phillips*, 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.*, Case No. 1:10-cv-00045-LPS, 2012 U.S. Dist. LEXIS 30528, *30 (D. Del. Feb. 13, 2012) (construing similarly-phrased independent and dependent claims containing *Markush* groups in same way Amgen proposes here, "the aqueous gel medium of the dependent claim *must* have at least one carbomer/carbomer 940, but *may* further include one or more (or none) of the remaining members of the *Markush* group among its ingredients"). The Examiner also interpreted claims 14-19 during prosecution as 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 another reference that disclosed sodium dodecylsulfate to reject claim 16).

Indeed, the plain reading of dependent claim 16, "wherein the surfactant comprises one or more of sarcosyl and sodium dodecylsulfate," requires, *e.g.*, that the solubilizing solution comprises at least a surfactant and that the surfactant comprises one or more of sarcosyl and sodium dodecylsulfate. In contrast, under Petitioners' understanding of the claims, since claim 9 recites a solubilization solution comprising "one or more of" a denaturant, a reductant, and a surfactant, claim 16's requirement is a mere narrowing of one of these three group members and, consequently, is discarded and can be ignored—but claim 16 is still somehow satisfied—where one of the *other* two members (a denaturant or a reductant, but *not* a surfactant) is disclosed by a prior art reference, but sarcosyl and sodium dodecylsulfate are not.

Petitioners' construction is contrary to the plain reading of the claims, 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 23, 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).

And the flaws of Petitioners' position are further highlighted by the maxim that "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). For example, 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).

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

Because the Petition failed to establish that any of the prior art references disclose—explicitly or inherently—each and every limitation of the Challenged Claims, alone or in combination, Petitioners failed to meet their burden for institution not only on all of their anticipation arguments in Grounds 1, 3, and 4, but also on all of their obviousness arguments in Grounds 2 and 5.

### A. Grounds 1 And 2: Petitioners Have Not Shown A Reasonable Likelihood Of Prevailing In Establishing That The Challenged Claims Are Anticipated By Wang Or Rendered Obvious Over Wang In View Of Cutler

### 1. 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 concluded, 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. But Petitioners said nothing about where the pages they attached as exhibits were found or generated. For instance, 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 presented no evidence establishing the Cutler "textbook" was publicly available in 2004. Even if Petitioners had relied on the dates from the text of the exhibits (which Petitioners do not assert), they provided no explanation as to why such dates are not hearsay. Petitioners 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.*, *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); *Hulu, LLC v. Sound View*

*Innovations, LLC*, IPR2018-01039, Pap.12, 9-12 (Dec. 3, 2018) (denying institution where petitioner did not demonstrate public accessibility of asserted prior art reference, and rejecting argument that copyright notice by itself could be relied upon for that purpose), *request for reh'g submitted for POP review*, Pap.15 (Apr. 3, 2019); *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.").

**2. Petitioners Failed To Clearly Map Wang To The Claim Elements**

In contradiction of §42.22(a)(2), which requires the Petition to contain "a detailed explanation of the significance of the evidence," Petitioners assert Wang teaches "the refold step," but fail to provide any guidance to the Board or Amgen as to where any such disclosure may be found and what significance might attach to it. And throughout their analysis, Petitioners make assertions about what Wang or the '997 patent teach, but fail to provide a citation to the underlying document. *See, e.g.*, Pet.23 ("Wang describes a process…" citing Petitioners' expert report, but not Wang itself). Even when Petitioners do provide citations to Wang, it is not clear the exact disclosures they are relying on within the cited pages. Finally, Petitioners appear to mix and match embodiments between "Procedures for the Refolding with Simultaneous Purification" and "Refolding of rhSCF by Dilution"

and/or rely on some unstated form or obviousness argument, stating, for instance, "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. "The experiment" is apparently one made up by Petitioners, without explanation. As the Board has stated previously, it is not the role of the Board to weave together quotations from references and synthesize Petitioners' case. *See VIZIO, Inc. v. Nichia Corp.*, IPR2017-00551, Pap.9, 9-12 (July 7, 2017). Petitioners have not satisfied their burden, but have instead improperly attempted to shift it to the Board and Amgen. *Id.*

**3. "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"**

**(a) "Protein Stabilizer" And "Aggregation Suppressor"**

Petitioners did not provide any analysis of Wang under the proper construction of "protein stabilizer" or "aggregation suppressor." Petitioners simply asserted that "Wang describes a process of refolding by diluting the solution from the solubilization step using a refold buffer that contains, *inter alia*, Tris, GSH, and GSSG" and that "Tris is an aggregation suppressor and a protein stabilizer, as defined in the '997 patent." Pet.23.

But Wang also notes that, in the anion exchange column used for refolding, "[t]he column was equilibrated with solution A consisting of 1 mmol·l$^{-1}$ EDTA, ***20 mmol·l$^{-1}$ Tris*** (pH 8.0), 10 mmol·l$^{-1}$ GSH, and 0.1 mmol·l$^{-1}$ GSSG." EX1003, 184. Nowhere does the patent disclose that Tris *at the concentration of 20mM* is either a protein stabilizer or an aggregation suppressor, and Petitioners offered no other evidence for this assertion. Petitioners did not address this issue in the Petition. Instead, Petitioners (and their expert) presented carefully worded arguments to allege that "Tris is an aggregation suppressor and a protein stabilizer, as defined in the '997 patent," which simply discloses that Tris has the ability ***at some concentration*** to be a protein stabilizer or aggregation suppressor, but tellingly Petitioners never asserted that Tris acts as a protein stabilizer and aggregation suppressor ***at 20mM, as it is disclosed in Wang***. *See* Pet.23; EX1002, ¶144; EX1001, 2:48-60, 14:44-58. By failing to show 20mM Tris ***as it is disclosed in Wang*** is either a protein stabilizer or an aggregation suppressor, Petitioners failed to establish this required element of their case for Ground 1. Furthermore, with respect to Ground 2, Petitioners did not suggest that Cutler makes up for this shortcoming. Pet.31-32. Accordingly, Petitioners failed to satisfy their burden on Grounds 1 and 2.

**(b) "Refold Buffer"**

With respect to Wang as used in Grounds 1 and 2, Petitioners further failed to address the requirement that the "refold buffer" under the correct construction must have a pH buffering capacity and provide conditions for the protein to refold into its biologically active form—issues they were aware of from the *Mylan* litigation. EX1034, 14; EX1035, 17. And, with respect to Ground 2, Petitioners did not suggest that Cutler makes up for this shortcoming. Thus, Petitioners did not establish a reasonable likelihood of prevailing on Grounds 1 or 2.

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

As properly construed (*see* §V.D), claims 16-18 and 24-26 require that the solubilization solution and/or refold solution include the recited chemicals (*e.g.*, a surfactant comprising sarcosyl or sodium dodecylsulfate in the case of Claim 16). Petitioners' analysis erroneously assumes the limitations in the dependent claims can be read out entirely. *See* §V.D. 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, it renders obvious claims 16-18 and 24-26 (Grounds 1 and 2).

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

Despite arguing obviousness, Petitioners failed to provide any meaningful analysis of ***how a POSITA would have modified*** Wang. *See* Pet.31-32; *see, e.g.*, *Health Care Logistics, Inc. v. Kit Check, Inc.*, IPR2019-00385, Pap.7, 14 (June 3, 2019) (denying institution because petitioner failed to explain how to modify reference to meet limitation and why POSITA would be motivated to do so); *ADT LLC v. Applied Capital, Inc.*, IPR2017-01825, Pap.7, 15 (Jan. 24, 2018) (denying institution because petitioner failed to explain whether and why it would have been obvious to modify prior art disclosure); *John Crane, Inc. v. Finalrod IP, LLC*, IPR2016-01827, Pap.6, 14 (Jan. 31, 2017) (Petitioner must "articulat[e] how and why specific teachings of the references would have been combined. It is Petitioner's responsibility 'to explain specific evidence that support[s] its arguments, not the Board's responsibility to search the record and piece together what may support Petitioner's arguments.'") (quoting *Dominion Dealer Sols., LLC v. Autoalert, Inc.*, IPR2013-00225, Pap.15, 4 (Oct. 10, 2013)); *adidas AG v. Nike, Inc.*, IPR2016-00920, Pap.6, 6-7 (Oct. 20, 2016) (denying institution where Board "left to guess as to what limitations [Petitioner] seeks to supply from the teachings of each of the references that it cites as a part of the proposed ground"); *Axon*

*Enter., Inc. v. Digital Ally, LLC*, IPR2017-00515, Pap.10, 18-19 (July 6, 2016) (denying institution, stating neither Petitioner nor its expert "explains in sufficient detail the nature of Petitioner's proposed modification" and "Petitioner does not explain in sufficient detail *how* the proposed modification is supposed to work").

In addition to failing to point out specific modifications to the base reference, Petitioners failed to explain ***why POSITA would be motivated to make any proposed modification***. *See, e.g., Apple, Inc. v. ContentGuard Holdings, Inc.*, IPR2015-00358, Pap.9, 9 (July 2, 2015) (denying institution when petition "lack[ed] an articulated or apparent reason supported by 'some rationale or underpinning' to modify/combine the purportedly known elements" of the prior art); *Linear Tech. Corp. v. In-Depth Test LLC*, IPR2015-00421, Pap.15, 17 (July 21, 2015) (denying institution when petition failed to adequately explain motivation to modify prior art). Quite the contrary, Petitioners' argument regarding motivation to combine is insufficient, generic, and conclusory. Pet.31-32.

In addition, 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. *See Broadcom Corp. v. Emulex Corp.*, 732 F.3d 1325, 1335 (Fed. Cir. 2013) ("An invention is not obvious just 'because all of the elements that comprise the

invention were known in the art;' rather a finding of obviousness at the time of invention requires a 'plausible rational [sic] as to why the prior art references would have worked together.'") (quoting *Power-One, Inc. v. Artesyn Techs., Inc*., 599 F.3d 1343, 1351 (Fed. Cir. 2010)); *Microsoft Corp. v. Improved Search LLC*, IPR2017-01614, Pap.8, 13-14 (Dec. 22, 2017) (denying institution where petition failed to address reasonable expectation of success).

Petitioners' expert, even if Petitioners' attempts at improper incorporation are overlooked, does not remedy these failings, offering little more than conclusory statements that a POSITA "would have been motivated to combine Wang and Cutler, and would have had a reasonable expectation of success." EX1002, ¶168; *cf. Cisco Sys., Inc. v. C-Cation Techs., LLC*, IPR2014-00454, Pap.12, 9 (Aug. 29, 2014) (informative) (The "practice of citing the [Expert] Declaration to support conclusory statements that are not otherwise supported in the Petition also amounts to incorporation by reference."); §42.6(a)(3) ("Arguments must not be incorporated by reference from one document into another document."); §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.").

### B. Ground 3: Petitioners Have Not Shown A Reasonable Likelihood Of Prevailing In Establishing That The Challenged Claims Are Anticipated By Reardon

#### 1. "Forming A Refold Solution Comprising…A Refold Buffer"

With respect to Reardon in Ground 3, Petitioners failed to address the requirement that the "refold buffer" under the correct construction must have a pH buffering capacity and provide conditions for the protein to refold into its biologically active form—issues they were aware of from the *Mylan* litigation. EX1034, 14; EX1035, 17. Thus, Petitioners did not establish a reasonable likelihood of prevailing on Ground 3.

#### 2. "Applying The Refold Solution…"

Petitioners did not address whether the adjusting of the pH to 5.5 would result in, *e.g.*, precipitation (*i.e.*, the removal of components of the solution), which is also prohibited by the claims as properly construed. *See* §V.B.

#### 3. Dependent Claims: Petitioners' Arguments Regarding Claims 13, 16-18, 24-26 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. With respect to Claim 13, Petitioners asserted Reardon teaches recovering recombinant protein from a bacteria cell, but points only to Reardon's disclosure of "recovering recombinant FGF18 or trFGF18 protein from a *prokaryotic cell*." Pet.38.

Petitioners then asserted "Prokaryotic cells are bacteria cells." But Petitioners' logic is backwards. While bacteria are prokaryotic cells, not all prokaryotic cells are bacteria. EX2054, 5 For this reason, Petitioners have not made even a *prima facie* showing that Reardon discloses production of recombinant protein in bacteria.

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* §V.D), the plain reading of dependent claims 16 and 24 requires 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. Thus, on its face, Ground 3 fails for this additional reason. *See* §VI.A.5.

With respect to claims 17, 18, 25 and 26, Petitioners asserted that Reardon's disclosure of Tris and arginine hydrochloride amounts to a disclosure of an aggregation suppressor and protein stabilizer. But Petitioners did not provide any analysis of Reardon under the proper construction of "protein stabilizer" or

"aggregation suppressor." Indeed, the Petition provided no analysis of whether the Tris or arginine in Reardon actually functions as an aggregation suppressor or protein stabilizer, let alone both.

### C. Ground 4: Petitioners Have Not Shown A Reasonable Likelihood Of Prevailing In Establishing That The Challenged Claims Are Anticipated By Dietrich

#### 1. "Forming A Refold Solution Comprising…A Refold Buffer"

With respect to Dietrich and Ground 4, Petitioners failed to address the requirement that the "refold buffer" under the correct construction must have a pH buffering capacity and provide conditions for the protein to refold into its biologically active form, which are issues they were aware of from the *Mylan* litigation. EX1034, 14; EX1035, 17. Thus, Petitioners did not establish a reasonable likelihood of prevailing on Ground 4.

#### 2. "Applying The Refold Solution…"

Petitioners provided no analysis of "applying the refold solution" under the correct construction. *See* Pet.43-44. For instance, Petitioners admitted Dietrich discloses that, "[s]ubsequently to refolding, the refolding step ***is filtrated*** before the first chromatographic step is conducted." Pet.43. Dietrich also discloses that the ***pH of the solution is adjusted to pH 3.2*** (before such filtering). EX1005, [0070]. But Petitioners did not address ***why*** the filtering is performed (*e.g.*, because a

POSITA would understand that the pH adjustment would result in precipitation, which would mean Dietrich does not disclose "applying the refold solution").

Further, Petitioners did not address the conclusion in their own art 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. Petitioners did not address why a POSITA would not have understood or assumed that such steps would have been performed as a matter of course to avoid fouling or clogging the column. *See id.*, 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….It is highly recommended to centrifuge and filter any sample immediately before chromatographic purification.").

In addition, while Petitioners asserted that Dietrich discloses the "applying" step, Petitioners ***never*** addressed how the conductivity of Guanidine-HCl (part of Dietrich's alleged solubilization solution, Pet.42-43) would have been reduced without dilution, centrifugation, dialysis or precipitation so that proper refolding could occur, contradicting Amgen's proposed construction of the refold buffer. *See* EX1007, 9:13-15 ("6M Guanidine hydrochloride can also be used as a denaturant, although additional steps to reduce the conductivity of the GdnHCl need to be included before refolding the denatured protein").

#### 3. Dependent Claims: Petitioners' Arguments Regarding Claims 16-17 and 24-26 Are Legally Flawed And Unsupported By Evidence

As properly construed (*see* §V.D), Claims 16 and 24 require "the surfactant comprises one or more of sarcosyl and sodium dodecylsulfate." Petitioners did not assert that Dietrich teaches a solubilization solution comprising a surfactant. Instead, Petitioners asserted that Claims 16 and 24 do not require any surfactant at all. Pet.45. Petitioners' interpretation of these claims is incorrect, and their showing as to these claims is thus deficient for the additional reasons explained above in §VI.A.5.

With respect to claims 17, 18, 25 and 26, Petitioners asserted that Dietrich's disclosure of Tris amounts to a disclosure of an aggregation suppressor and protein stabilizer. But Petitioners did not provide any analysis of Dietrich under the proper construction of "protein stabilizer" or "aggregation suppressor." Indeed, the Petition provided no analysis of whether the Tris in Dietrich actually functions like an aggregation suppressor or protein stabilizer, let alone both.

### D. Ground 5: Petitioners Have Not Shown A Reasonable Likelihood Of Prevailing In Establishing That The Challenged Claims Are Rendered Obvious By Komath '994 In View Of Komath '056

#### 1. Petitioners Did Not Clearly Identify Which Komath Reference They Rely On For Which Limitation

It is ***not clear which reference Petitioners rely on for which alleged teaching*** in their obviousness combination. *See* 35 U.S.C. §312(a) (petition may

be considered only if it "identifies, in writing and with particularity, each claim challenged, the grounds on which the challenge to each claim is based, and the evidence that supports the grounds for the challenge to each claim"); *Clim-A-Tech Indus., Inc. v. Ebert*, IPR2017-01863, Pap.13, 27-28 (Feb. 12, 2018); *Costco Wholesale Corp. v. Robert Bosch LLC*, IPR2016-00042, Pap.28, 3-4 (July 7, 2016) (denying rehearing and confirming "[i]t is not [the Board's] role to sift through the information provided and determine on our own if there is a reasonable likelihood that the asserted references show unpatentability").

For example, for certain claim limitations (*e.g.*, the "the preamble," "the solubilization step," "the capture or 'applying' step," "the wash step," and "the elution step") (Pet.50-54), Petitioners cited to disclosures from both Komath '994 and Komath '056 without explaining which one they rely on for each limitation. As the Board has previously stated, it is not the role of the Board to weave together quotations from references and synthesize Petitioners' case. *See VIZIO*, IPR2017-00551, Pap.9, 9-12; *Dish Network Corp. v. Customedia Techs., LLC*, IPR2017-00936, Pap.13, 10-11 (Aug. 24, 2017) (denying institution because petitioner failed to articulate with sufficient particularity which of two disclosures in prior art mapped to two distinct claim elements); *John Crane*, IPR2016-01827, Pap.6, 12 (denying institution where "it is unclear which prior art reference Petitioner relies upon to teach these limitations, or whether Petitioner relies upon an unarticulated

combination of the prior art references"); *Dep't of Justice v. EnvisionIT, LLC*, IPR2017-00186, Pap.8, 26 (May 3, 2017) (denying institution, noting Board is "not inclined to play archaeologist with the record in an attempt to fill the gaps in Petitioner's argument"); *adidas*, IPR2016-00920, Pap.6, 6-7 (denying institution where 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 Petition").

### 2. Petitioners Failed To Establish A Motivation To Combine With Komath '054

Petitioners also failed to explain ***why and how a POSITA would have modified Komath '944***. *See Apple*, IPR2015-00358, Pap.9, 9 (denying institution when petition "lack[ed] an articulated or apparent reason supported by 'some rationale or underpinning' to modify/combine the purportedly known elements" of the prior art); *Linear Tech. Corp.*, IPR2015-00421, Pap.15, 17 (denying institution when petition failed to adequately explain motivation to modify prior art). Instead, Petitioners offered only arguments regarding motivation to combine that are generic, conclusory, and insufficient. Pet.49-52. Indeed, because Petitioners cite both Komath references for most limitations, it is impossible to tell for which

limitations Petitioners propose modifying their base reference.[11] And, as explained above, despite listing Komath '994 as the primary reference in Ground 5, Petitioners asserted that Komath *'056* explicitly discloses every claim limitation of independent claim 9, as well as dependent claims 10, 13-20, and 23-28. *See* Pet.50-58 (asserting for the two Komath references that "each teach[es]," "each disclose[es]," or "each describes" the limitations); Pet.51-52, 56 (asserting that Komath '056 "discloses" or "teaches" limitations). But Petitioner admits Komath '994 is missing at least one disclosure in claim 9, for example. Pet.51-52.

Petitioners' first set of motivation-to-combine arguments, *id.* 49-50, is actually just a set of arguments 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

[11] This is not surprising given that Petitioners' reliance on Komath '944 here is merely a poorly veiled attempt to make this ground look different from the Komath '054 ground in the Kashiv IPR.

'the same design incentives with each other and with the [patent at issue] itself' does not establish that it would have been obvious to combine their features.") (internal citations omitted).

Petitioners' second set of motivation-to-combine arguments simply asserts that Komath '944 describes "using any appropriate buffer suitable for maintaining pH in the acidic range" and "a POSA would turn to the references cited in the '944 patent…to determine suitable buffers." Pet.51. But Petitioners never explained why a POSITA would have chosen the particular buffer in Komath '056.

### 3. Petitioners' Reasonable Expectation Of Success Argument Is Deficient

The Petition's cursory obviousness analysis includes only a single conclusory sentence directed to reasonable expectation of success. Pet.50. And Petitioners' expert's analysis, which parrots the Petition, does not remedy this failure. EX1002, ¶231. Even when Petitioners identified an incomplete overlap between the Komath references— *e.g.*, for the "isolated after elution" steps of dependent claims 21, 29, and 30—Petitioners and their expert focused on whether the limitations are disclosed, not whether there would have been a motivation to combine them or a reasonable expectation of success in doing so. Such cursory analysis is insufficient to satisfy Petitioners' burden here. *See Nintendo Co. v. Genuine Enabling Tech., LLC*, IPR2018-00543, Pap.7, 24 (Aug. 6, 2018) (denying

institution because petitioners' "only support [was] a conclusory statement [from their expert] without any evidentiary support, which has no weight"); *Johnson Matthey Inc. v. BASF Corp*., IPR2015-01267, Pap.35, 30 (Nov. 30, 2016) (finding no reasonable expectation of success, noting prior art "simply provid[ed] incentive 'to explore a new technology or general approach that seemed to be a promising field of experimentation'"); *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.").

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

Although their mapping is lacking in clarity, Petitioners apparently relied on Komath '054 as teaching the claimed refold buffer. Pet.51-52. Petitioners asserted Komath '054 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. *Id.* 51. But Petitioners did 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, or what the components of the refold buffer are (other than to assert it "compris[es] an aggregation suppressor"). Further,

Petitioners did not provide any analysis of Komath '054's disclosure of 0.1% polysorbate 20 under the proper construction of "aggregation suppressor." Petitioners asserted that "Polysorbate 20 is an aggregation suppressor as defined by the '997 patent." *Id.* 52. And nowhere does the patent disclose that polysorbate 20 *at a concentration of 0.1%* is an aggregation suppressor. *See* §V.A.

With respect to Komath '056 as used in this Ground, Petitioners further failed to address the requirement that the "refold buffer" under the correct construction must have a pH buffering capacity and provide conditions for the protein to refold into its biologically active form—issues they were aware of from the *Mylan* litigation. EX1034, 14; EX1035, 17. Thus, Petitioners did not establish a reasonable likelihood of prevailing on Ground 5.

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

Petitioners argued Komath '944 teaches that "the refolded protein solution…is loaded on an ion exchange column" and the G-CSF protein is refolded at a high pH "so as to be suitable for direct loading on a cation exchange column." Pet.52. But Petitioners ignored Komath '056's 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.*" EX1007, 8:13-14. Indeed, Komath '056 does ***not*** disclose using the ion exchange column to

purify the protein, which (as discussed above) it teaches has *already been purified*. EX1007, 8:14-16 ("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."). Nor did Petitioners address Komath '056'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.*, 10:29-31. In ignoring these teachings, Petitioners failed to explain why POSITA would have been motivated to combine the Komath references in the way proposed by Petitioners and, specifically, why a POSITA would have chosen one method over the other or, more precisely, why a POSITA would have chosen Komath '944 to be the base reference in the combination to be modified by the other, rather than Komath '056.

Petitioners' assertions about the refold solution being applied to the column with no intervening steps are inconsistent not only with the text of the Komath references, but also with the disclosures of Petitioners' own background art: "It is highly recommended to centrifuge and filter any sample immediately before chromatographic purification." EX1036, 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….It is highly recommended to

centrifuge and filter any sample immediately before chromatographic purification."). Indeed, Petitioners ignored the teachings of the prior art as a whole and cherry-pick disclosures, relying on impermissible hindsight and discarding, rather than explaining, other teachings of the prior art. *Cf. 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.").

In asserting Komath '944 teaches "applying a refold solution" (Pet.52), Petitioners also did not address the fact that the alleged refold buffer includes urea, EX1006, 7, but urea is not described as being part of the sample loaded onto the column in Komath '944, which instead indicates using a "suitable buffer that can maintain the pH at an acidic range," preferably "[b]uffers of phosphate and acetate…although citrate salts can also be used," *id.*, 10. Notably, how urea would be removed from the buffer is not mentioned, indicating it may violate the proper

construction of refold solution by requiring a prohibited intermediate step, but Petitioners never addressed this.[12]

Komath '944 teaches that "the refolded protein solution in the pH range of 3.5 to 5.5 is loaded on an ion exchange column." EX1006, 10. But, before that, Komath '944 discloses that "[t]he IB pellet is solubilized using a combination of a suitable denaturant (urea or guanidinium chloride) at alkaline pH in the range of 8.0 to 11.0." *Id.* However, Petitioners did not analyze or explain *how* this pH shift is done and 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).

### 6. Dependent Claims: Petitioners' Arguments Regarding Claims 15-18 And 23-27 Are Legally Flawed And Unsupported By Evidence

As properly construed (*see* §V.D), claims 15 and 23 require "the *reductant* comprises...," claims 16 and 24 require "the *surfactant* comprises…," and claims 17 and 27 require "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,

[12] Komath '056 is the same in this regard. EX1007, 9:11-12 ("pH of the refolded protein solution is shifted to 4.5 with sodium acetate buffer for loading on an ion exchange column.").

Petitioners asserted that these claims do not require any reducatant, surfactant, or redox component. Pet.55-56. But Petitioners' interpretation of these claims is incorrect, and their arguments regarding these claims are deficient for the additional reasons explained above in §VI.A.5.

With respect to claims 17, 18, 25, and 26, Petitioners asserted that Komath '056's disclosure of polysorbate 20 amounts to a disclosure of an aggregation suppressor and protein stabilizer. But Petitioners did not provide any analysis of Komath '056 under the proper construction of "protein stabilizer" or "aggregation suppressor." In other words, the Petition provided no analysis of whether the polysorbate 20 in Komath '056 actually functions like an aggregation suppressor or protein stabilizer, let alone both.

## VII. 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.1), 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 prior art printed publications. They provide no evidence 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 version, of a document as published—although there is *no evidence of any of this* to begin with. EX1027, 1. Similarly, EX1036 notes that it is "Edition AA" without explanation. EX1036, 1.

As a further example, with respect to EX1031, although Petitioners suggested 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 these materials supposedly reflecting background knowledge in the prior art became printed publications. Petitioners thus failed to establish the level of background knowledge at the time of the challenged '997 patent inventions. *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.").

## VIII. Conclusion

Even with this preliminary record, due to failures in both proof and specificity, Petitioners failed to show that the Challenged Claims are anticipated by Wang, Reardon, or Dietrich, or rendered obvious by Wang in view of Cutler, or over Komath '994 in view of Komath '056. Petitioners also failed to explain why the Board should not exercise its discretion and deny institution under §§314 and/or 325(d) and, as detailed above, the Board should do so here.

Because the Petition failed to show that there is a reasonable likelihood that Petitioners will prevail in proving any Challenged Claim is unpatentable, the Petition should be denied in its entirety, and, pursuant to §314, no *inter partes* review should be instituted. To the extent the Board determines that Petitioners have met their burden on any subset of these Grounds (they have not), the Board should use its discretion under §§325(d) and/or 314(a) to deny institution on all Grounds because, in light of the evidence and arguments presented in this Petition, requiring the Board and Amgen to bear the wasteful burden of a trial on all Grounds to reach such a subset of Grounds would not be an efficient or appropriate use of the Board's limited time and resources.

Respectfully submitted by: Dated: September 11, 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 13,370 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 Petitioners listed below:

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