UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

v.

AMGEN INC. and AMGEN MANUFACTURING, LIMITED,
Patent Owner

Case PGR2019-00001
Patent 9,856,287

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

LIST OF EXHIBITS

Exhibit	Description
EX2001	*Amgen Inc. et al. v. Adello Biologics, LLC*, Case No. 2:18-cv-03347 (D.N.J.), DE1 (Amgen's Complaint)
EX2002	*Amgen Inc. et al. v. Adello Biologics, LLC*, Case No. 2:18-cv-03347 (D.N.J.), DE50 (Amgen's Amended Complaint)
EX2003	*Amgen Inc. et al. v. Adello Biologics, LLC*, Case No. 2:18-cv-03347 (D.N.J.), DE54 (Defendant Adello Biologics, LLC's Answer, Defenses and Counterclaims to Plaintiffs' First Amended Complaint)
EX2004	*Amgen Inc. et al. v. Adello Biologics, LLC*, Case No. 2:18-cv-03347 (D.N.J.), DE57 (Amneal Pharmaceuticals, Inc. Proof of Service)
EX2005	*Amgen Inc. et al. v. Adello Biologics, LLC*, Case No. 2:18-cv-03347 (D.N.J.), DE58 (Amneal Pharmaceuticals, LLC Proof of Service)
EX2006	*Amgen Inc. et al. v. Adello Biologics, LLC*, Case No. 2:18-cv-03347 (D.N.J.), DE59 (Miller Appearance for Amneal Pharmaceuticals, LLC and Amneal Pharmaceuticals, Inc.)
EX2007	*Amgen Inc. et al. v. Adello Biologics, LLC*, Case No. 2:18-cv-03347 (D.N.J.), DE60 (Gabay Appearance for Amneal Pharmaceuticals, LLC and Amneal Pharmaceuticals, Inc.)
EX2008	File History of U.S. Patent 9,856,287
EX2009	Luis Felipe Vallejo & Ursula Rinas, *Optimized Procedure for Renaturation of Recombinant Human Bone Morphogenetic Protein-2 at High Protein Concentration*, Biotechnology and Bioengineering, Vol. 85 No. 6, 601-09 (March 2004)
EX2010	*Amgen Inc. et al v. Apotex Inc. et al*, Case No. 0:15-cv-61631 (S.D. Fla.), DE250 (Day 4 Transcript of Bench Trial held on July 14, 2016)
EX2011	Declaration of Saurabh Gupta
EX2012	Declaration of Catherine Nyarady
EX2013	Amneal Pharmaceuticals, Inc., Form S-1 (May 7, 2018)
EX2014	Amneal Pharmaceuticals LLC, M&A Call Transcript (October 17, 2017)
EX2015	"Lenders' Presentation" by Amneal Pharmaceuticals LLC and Impax Laboratories (March 7, 2018)

Exhibit	Description
EX2016	*Amgen Inc. et al. v. Adello Biologics LLC*, Case No. 2:18-cv-03347 (D.N.J.), DE47 (October 1, 2018 letter to U.S. Magistrate Judge Mark Falk)
EX2017	*Mylan Pharmaceuticals Inc. v. Yeda Research and Development Co. Ltd.*, IPR2015-00643, EX1076 (Stipulated Protective Order in *In re Copaxone 40 mg Consolidated Cases*, No. 1:14-cv-01171 (GMS))
EX2018	*Amgen Inc. et al. v. Adello Biologics, LLC*, Case No. 2:18-cv-03347 (D.N.J.), DE70-1 (Brief in Support of Motion to Dismiss)
EX2019	*Amgen Inc. v. Apotex Inc.*, Appeal No. 17-1010 (Fed. Cir.), DE 42-3 (Joint Appendix Volume III of III)
EX2020	*Amgen Inc. et al v. Apotex Inc. et al*, Case No. 0:15-cv-61631 (S.D. Fla.), DE247 (Day 1 Transcript of Bench Trial held on July 11, 2016)
EX2021	*Amgen Inc. et al v. Apotex Inc. et al*, Case No. 0:15-cv-61631 (S.D. Fla.), DE245 (Partial Findings Regarding Apotex's Assertion of Invalidity of the '138 Patent)
EX2022	Impax Laboratories, Inc., Schedule 14A (Feb. 12, 2018)
EX2023	Emails between counsel for Petitioners and counsel for Patent Owners, dated January 2, January 8, January 10, and January 11, 2019
EX2024	Email from counsel for Amgen to counsel for Petitioner Adello Biologics, LLC, dated September 19, 2018, and attachments
EX2025	Email from counsel for Petitioners to the Board, dated January 15, 2019

TABLE OF CONTENTS

Page

TABLE OF CONTENTS (CONTINUED)

Page

TABLE OF CONTENTS (CONTINUED)

Page

TABLE OF AUTHORITIES

Page(s)

CASES

TABLE OF AUTHORITIES (CONTINUED)

Page(s)

TABLE OF AUTHORITIES (CONTINUED)

Page(s)

TABLE OF AUTHORITIES (CONTINUED)

Page(s)

TABLE OF AUTHORITIES (CONTINUED)

Page(s)

TABLE OF AUTHORITIES (CONTINUED)

Page(s)

TABLE OF AUTHORITIES (CONTINUED)

Page(s)

STATUTES

REGULATIONS

OTHER AUTHORITIES

Pursuant to 37 C.F.R. §42.207,[1] Patent Owners[2] Amgen Inc. and Amgen Manufacturing, Limited (collectively, "Amgen") submit this Preliminary Response to the above-captioned Petition for Post-Grant Review of U.S. Patent No. 9,856,287 ("Petition" or "Pet." Pap. 3), which should be denied in its entirety for Petitioners' failure to name all real parties-in-interest under §322(a)(2); pursuant to the Board's discretion under §325(d); Petitioners' failure to address whether terms critical to their patentability analysis are limiting; Petitioners' failure to address the construction of terms that they were required to address; and Petitioners' failure to show a reasonable likelihood of prevailing on any asserted ground. Further, because of the procedural and substantive failings of the Petition, institution would not be in the interest of justice, or an efficient use of the Board's limited time and resources. Thus, in light of *SAS Institute v. Iancu*, 138 S. Ct. 1348 (2018), even if

---

[1] All emphasis/annotations added, and all statutory and regulatory citations are to 35 U.S.C. or 37 C.F.R., as the context indicates, unless otherwise stated.

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

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.

I. Introduction

Petitioners' submission failed to provide the Board the basic evidence required to institute any post-grant review. If the Board nonetheless institutes trial on the Challenged Claims,[3] Patent Owners will address in detail in their §42.220 Response the numerous substantive errors and shortcomings in Petitioners' arguments and their purported evidence. Here, however, where testimonial evidence raising an issue of material fact "will be viewed in the light most favorable to the petitioner" (§42.208), Amgen addresses only Petitioners' fatal procedural error in failing to name all real parties-in-interest, together with the reasons the Board should exercise its discretion to deny institution under §325(d), Petitioners' failure to address whether certain terms are limiting, Petitioners' failure to construe several of the Challenged Claims' pertinent terms, and Petitioners' failure to demonstrate, as to any of the Challenged Claims, a reasonable likelihood of success on *any* asserted ground of invalidity. Because of

[3] Claims 1-30 of U.S. Patent No. 9,856,287 ("'287").

these threshold failures, the Petition should be denied and no post-grant review should be instituted under §324.

First, Petitioners failed to name all of the real parties-in-interest and thus the Petition is incomplete under §322(a)(2) and untimely under §42.206(b), and any attempt to correct this now would be too late: Petitioners waited to file their Petition until just before the statutory 9-month window for PGRs closed under §321(c).

Second, the same or substantially the same evidence or arguments were *already considered by the Examiner and not found to render the claims unpatentable*. For this reason, the Petition should not be instituted under §325(d).

Third, Petitioners failed to address the construction of terms that it was required to address, and failed to analyze whether certain claim terms critical to its patentability analysis are limitations that should be given any weight. Petitioners simply assumed without analysis that the claim phrases "so that at least about 25% of the proteins are properly refolded" and "so that about 30-80% of the proteins are properly refolded" are limiting, failing to address both case law and statements in the file history indicating that such analysis was required. Petitioners also failed to provide a construction for "so that about 25% of the proteins are properly refolded," while quietly assuming the term is limiting and actually means 25% to 100%, and failed to address the construction of the term "calculated."

Fourth, the '287 claims priority to 2009 and is therefore not eligible for PGR. Petitioner's written description and enablement arguments, on which Petitioners' entire PGR standing argument is premised in an attempt to break the priority chain, are flawed.

Fifth, to justify institution of post-grant review, Petitioners' papers must make a *prima facie* showing that, as a factual and legal matter for each asserted ground, Petitioners have demonstrated a reasonable likelihood of proving at least one Challenged Claim unpatentable. *See, e.g.*, §324; §42.208(c). But Petitioners' own arguments and evidence confirm they cannot meet that burden for *any* asserted ground. For instance:

- Petitioners improperly assume that independent claims 1 and 16 have the same scope, and that independent claims 10 and 26 have the same scope, failing to map any liquids disclosed in Petitioners' references to the claimed "preparation" (independent claims 1 and 10, and their dependent claims) and "solution" (independent claims 16 and 26, and their dependent claims).
- Petitioners made fundamental errors of arithmetic in purporting to calculate the thiol-pair ratio in their Vallejo reference.
- Petitioners simply ignored disclosures in their own prior art that undermine their arguments, such as by failing to address the statement in Vallejo that pH, and *not* the ratio of redox reagents, is important to refolding.

- Petitioners failed to explain how their Schlegl reference teaches a non-mammalian expression system when it discloses a *bovine* α-lactalbumin protein presumably derived from its natural mammalian source.
- Petitioners failed to account for the presence of a chemical in Schlegl in calculating thiol-pair ratio and thiol-pair buffer strength, despite accounting for the same chemical in their calculations for a different reference, Hevehan.
- Petitioners failed to address that the process in their Ruddon reference does not result in a properly refolded protein, but rather biologically inactive subunits requiring subsequent assembly.
- Petitioners failed to address how any of their references disclose maintaining the solubility of the preparation or the solution when that term is properly understood.
- Petitioners failed to present any argument regarding the dependent claims requiring thiol-pair ratio and thiol-pair buffer strength to be "calculated" (claims 8, 9, 14, 15, 23, 24, 25, and 30) when that term is properly construed.
- Petitioners failed to address known secondary indicia of nonobviousness.

In view of post-*SAS* all-or-nothing institution, even if the Board were to find some of Amgen's arguments unavailing at this preliminary stage, given the

numerous significant shortcomings in the Petition, the Board should exercise its discretion here and deny institution, which would not be an efficient use of the Board's limited time and resources. *See, e.g.*, *Chevron Oronite Co. LLC v. Infieum USA LP*, IPR2018-00923, Pap. 9, 9-11 (Nov. 7, 2018).

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

The '287 is directed to a novel and efficient protein refolding method based on control of redox conditions with reductant and oxidant ("redox") reagents. EX1001, 2:61-3:5. The goal of protein refolding is to increase and maximize yield of properly folded proteins. EX1001, 1:32-38. Desired proteins are recombinantly expressed in non-mammalian culture systems (*e.g.*, bacteria). But, these expressed proteins misfold and precipitate in intracellular limited-solubility compartments known as inclusion bodies. *Id.*, 1:25-30. These bodies are formed because the bacterial host cell is unable to fold recombinant proteins properly. *Id.*, 1:29-31. These host cells are collected and lysed, and then the released inclusion bodies are solubilized in a denaturing buffer to linearize the proteins into individual protein chains. *Id.*, 1:43-50.

Prior to the '287, those skilled in the art needed to manipulate a large number of variables—through trial and error—to achieve high yields of properly refolded proteins. *Id.*, 8:47-65. The inventors of the '287 addressed the difficulty of identifying acceptable refolding conditions by controlling the concentrations of

the reductant and oxidant present in the refolding buffer in a particular manner (*e.g.*, using the interrelationship of thiol-pair ratio (*i.e.*, $\frac{[reductant]^2}{[oxidant]}$) and thiol-pair buffer strength ($2[oxidant] + [reductant]$)) for the purpose of properly refolding a recombinantly expressed protein. *Id.*, 4:52-5:10, 6:50-55, 6:63-67.

III. The Petition Should Be Rejected Because Petitioners Failed To Name Real Party-In-Interest ("RPI") Amneal Pharmaceuticals LLC, And It Is Now Too Late To Do So

A petition for post-grant review "may be considered only if…the petition identifies all real parties in interest." §322(a)(2) (petition may be considered "only if" it "identifies all real parties in interest"); §42.106(b) ("Where a party files an incomplete petition, no filing date will be accorded…"); *see Worlds Inc. v. Bungie, Inc.*, 903 F.3d 1237, 1240 (Fed. Cir. 2018) ("Correctly identifying all real parties in interest with respect to each IPR petition is important, as the determination may impact whether a petition may be instituted."). While the "petitioner's initial identification of the real parties in interest should be accepted unless and until disputed by a patent owner," the patent owner need only "produce *some* evidence that tends to show that a particular third party should be named a real party in interest" ("RPI") to sufficiently raise the issue. *Worlds Inc.*, 903 F.3d at 1242-44 (emphasis original). Once this has occurred, mere reliance on attorney representations is insufficient, and, contrary to some earlier Board decisions, the

Federal Circuit has held that there is no "rebuttable presumption" that the proper RPIs have been named. *Id.* at 1242-43, 1245-46. Moreover, the ultimate burden of persuasion remains with *Petitioners* to establish that they have complied with the statutory requirement to identify *all* RPIs. *Id.* at 1242-43.

As the Federal Circuit has confirmed in rejecting the "unduly restrictive" analysis applied in prior Board decisions, identifying "a 'real party in interest' demands a flexible approach that takes into account both equitable and practical considerations, with an eye toward determining whether the non-party is a clear beneficiary that has a preexisting, established relationship with the petitioner." *Applications in Internet Time, LLC v. RPX Corp.*, 897 F.3d 1336, 1339, 1351 (Fed. Cir. 2018). Congress intended "that 'real party in interest' have its expansive common-law meaning," *id*. at 1351, and "when it comes to evaluating the relationship between a party bringing a suit and a non-party, the common law seeks to ascertain ***who, from a 'practical and equitable' standpoint, will benefit*** from the redress that the chosen tribunal might provide." *Id.* at 1349, 1351. No express or implied agreement with the named Petitioners to file a petition is needed, *id*. at 1354, and an RPI need not have control or an opportunity to control. *See, e.g.*, *Cisco Systems, Inc. v. Hewlett-Packard Enter. Co*., IPR2017-01933, Pap. 9, 13 (Mar. 16, 2018) (denying institution for failure to name all RPIs). Further, this key consideration of "whether [the third party] actually 'desire[d] review…'"

(*RPX*, 897 F.3d at 1354) requires evaluating "the entirety of the record." *Id*. at 1351.

Here, Petitioners unquestionably and admittedly failed to meet their burden, and their Petition is fatally incomplete under §322(a)(2). In particular, Petitioners failed to identify Amneal Pharmaceuticals LLC as an RPI in their October 1 Petition, and—in response to Patent Owners' explicit inquiry and questioning—they have since acknowledged this was required. EX2023; EX2012 ¶6.

Petitioners' late acknowledgment is unsurprising: Amneal Pharmaceuticals LLC, as the entity actually responsible for selling (as well as marketing and pricing) the proposed filgrastim product biosimilar to Amgen's Neupogen® product accused of infringing the '287 challenged here, clearly stands to incur financial benefits or losses depending on the outcome of this PGR challenge and the related district court proceeding identified by Petitioners, and desires the result the Petition seeks. *See* Pet. 3. As named RPI Amneal Pharmaceuticals, Inc. (Pet. 2) stated in a May 7, 2018 S-1 filing with the SEC,

> On October 1, 2017, Amneal [Pharmaceuticals LLC ("Amneal")] and Adello [Biologics, LLC ("Adello")] entered into a license and commercialization agreement. Adello granted Amneal an exclusive license, under its NDA [New Drug Application], to distribute and sell two bio-similar products [filgrastim and pegfilgrastim] in the United States. Adello is responsible for development, regulatory filings,

> obtaining FDA approval, and manufacturing, and Amneal is responsible for marketing, selling, and pricing activities. The term of the agreement is 10-years from the applicable product's launch date."

EX2013, 97, 146; *see* EX2003 (Defendant Adello Biologics, LLC's Answer, Defenses and Counterclaims to Plaintiffs' First Amended Complaint), ¶19. Amneal Pharmaceuticals LLC has also publicly confirmed during an M&A call on October 17, 2017 that it has "the commercial rights" for the biosimilar filgrastim product, which was developed by its "research partner," named Petitioner Adello Biologics, LLC. EX2014, 5; *see also, e.g.*, EX2015, 20 (March 7, 2018 "Lenders' Presentation" by Amneal Pharmaceuticals LLC and Impax Laboratories, Inc., listing Amneal's "2017 Achievements" as including "Filgrastim (Neupogen™) biosimilar filing accepted by the FDA").

In addition, although a showing of control is not required, *see, e.g.*, *Cisco*, IPR2017-01933, Pap. 9 at 13, Amneal Pharmaceuticals, Inc., which Petitioners named as an RPI, and Amneal Pharmaceuticals LLC additionally "have a very close parent and wholly-owned subsidiary relationship with aligned interests," *see, e.g.*, *Zoll Lifecor Corp. v. Philips Electronics North America Corp.*, IPR2013-00606, Pap. 13, 10 (Mar. 20, 2014) (denying institution for failure to name all RPIs), and Petitioners were required to include *all* RPI entities, including those that share a corporate affiliation. *See, e.g.*, *Amazon.com, Inc. v. Appistry, Inc.*,

IPR2015-00480, Pap. 18, 3-6 (July 13, 2015) (denying institution for failure to name all RPIs, including intervening entities in corporate chain between two named companies). Amneal Pharmaceuticals, Inc. was formed as a holding company, combining the business of Amneal Pharmaceuticals LLC and Impax Laboratories, Inc. (now, Impax Laboratories, LLC). EX2013, 8-9. Amneal Pharmaceuticals LLC is a subsidiary of Amneal Pharmaceuticals, Inc., and Amneal Pharmaceuticals, Inc. is Amneal Pharmaceuticals LLC's sole managing member. *Id.* at 8-9, 16. At least some, if not all, board members of Amneal Pharmaceuticals LLC are also board members of Amneal Pharmaceuticals, Inc. *Id.* at 175-179. And named Petitioner Adello Biologics, LLC and other Amneal companies doing business with Amneal Pharmaceuticals LLC *share legal and other services* through another related company. *See, e.g.*, EX2022, 261 ("AE Companies LLC ("AE LLC") is an independent company which provides *certain shared services and finance, legal and other administrative functions* to a number of entities with which Amneal [Pharmaceuticals LLC] conducts business, including [named Petitioner] Adello [Biologics, LLC], AmDerma, Asana, Kashiv and Prolong."). Further, Amneal Pharmaceuticals LLC and Amneal Pharmaceuticals, Inc. (named as an RPI) have the same address and the same representative on whom the New Jersey complaint was served, EX2004-EX2007 (*Amgen Inc. v. Adello Biologics LLC*, Case No. 2:18-cv-03347 (D.N.J.), DE57, DE58, DE59, DE60), and both

made their appearance in the District of New Jersey through the same counsel, on October 24, 2018.

Moreover, although Petitioners made no mention of Amneal Pharmaceuticals LLC in this proceeding and took no steps to correct their failure to name it as an RPI until Patent Owners raised the issue, *see, e.g.,* EX2023; EX2012 ¶¶3, 5-6, Petitioners were well aware of the role and significance of Amneal Pharmaceuticals LLC in connection with the '287, with the accused biosimilar filgrastim product and infringement litigation that led to this PGR, and with the other named Petitioners and RPIs. Indeed, the significance of Amneal Pharmaceuticals LLC to this dispute was being *actively discussed* with the named Petitioner Adello Biologics, LLC (which shared legal functions with various Amneal-affiliated companies, EX2022, 261) *at precisely the time that this PGR Petition was being finalized and filed*.

As Petitioners acknowledge in their Petition, on March 8, 2018, Amgen filed suit against Adello Biologics, LLC in the District of New Jersey, asserting infringement of the '287. *See* Pet., 2; *Amgen Inc. v. Adello Biologics, LLC*, 2:18-cv-03347 (D.N.J.). The New Jersey suit concerns Petitioner Adello Biologics, LLC's submission of an abbreviated Biologics License Application to the United States Food and Drug Administration seeking licensure to market a biosimilar version of Amgen's Neupogen® (filgrastim) product. *See* EX2001 (Amgen's

complaint). But, as Petitioners conspicuously omit, on October 3, 2018, Amgen formally amended its complaint to add Amneal Pharmaceuticals LLC and Amneal Pharmaceuticals, Inc. *See* EX2002 (Amgen's amended complaint). This was the result of an extended discussion with, *inter alia*, named Petitioner Adello Biologics, LLC (the "partner" of Amneal Pharmaceuticals LLC in connection with the accused biosimilar product, *e.g.*, EX2014, 5), including in the weeks and days leading up to October 1—the ***same day*** that the PGR Petition was filed (naming Amneal Pharmaceuticals, Inc. but not Amneal Pharmaceuticals LLC as an RPI), ***and*** that the proposed amended complaint naming both Amneal Pharmaceuticals LLC and Amneal Pharmaceuticals, Inc. as additional defendants was sent to both the District Court and counsel for Adello Biologics, LLC and the other existing defendants, following a meet-and-confer process in which named Petitioner "Adello Biologics, LLC [indicated it] does not oppose Amgen's application for leave to amend, but reserve[d] all rights with respect to its response to the proposed Amended Complaint." *See* EX2016 (October 1, 2018 letter to U.S. Magistrate Judge Mark Falk, *Amgen Inc. v. Adello Biologics LLC*, Case No. 2:18-cv-03347 (D.N.J.), DE47); EX2024; EX2012 ¶4. In fact, Amgen sent Petitioner Adello Biologics, LLC its proposed amended complaint identifying both Amneal Pharmaceuticals, Inc. and Amneal Pharmaceuticals LLC as defendants, on September 19, 2018, a week and a half before Petitioners filed this Petition.

EX2024. There is thus no question that the issue of Amneal Pharmaceuticals LLC's role and significance was front-and-center for Petitioners and their named RPIs in the period immediately before and including Petitioners' October 1 filing.[4] Indeed, it appears the very officer signing the Power of Attorney for Petitioner Adello Biologics, LLC in this proceeding, Kenneth Cappel (*see* Pap. 2 at 3), was also previously Vice President of Global Intellectual Property for Amneal Pharmaceuticals LLC. *See, e.g.*, EX2017, 14. *See also* EX2022, 261 (Adello shared legal and other services with various Amneal-affiliated companies). But Amneal Pharmaceuticals LLC was nonetheless omitted from the Petition, rendering it incomplete under §322(a)(2).[5]

---

[4] The significance of naming the proper RPIs was also a matter of significant public discussion at the time the petition was filed on October 1, 2018, including as a result of the Federal Circuit's well-publicized decisions vacating decisions of the Board concerning RPIs in the *RPX* (July 8, 2018) and *Worlds* (September 7, 2018) cases discussed above.

[5] Moreover, although the role of Amneal Pharmaceuticals LLC continued to be the subject of active litigation involving named Petitioner Adello Biologics, LLC and named RPI Amneal Pharmaceuticals, Inc., Petitioners continued to say *nothing*

about their omission of Amneal Pharmaceuticals LLC from the October 1 Petition until Amgen confronted them in January. *See, e.g.*, Cisco, IPR2017-01933, Pap. 9, 17 (noting among the pertinent circumstances in denying institution "Petitioner's failure to apprise the Board before *or after* the filing of the Petition"). In particular, on December 5, 2018, the litigation defendants moved to dismiss Amneal Pharmaceuticals LLC and Amneal Pharmaceuticals, Inc. as defendants—not because they were not involved with the accused biosimilar product, but because, according to defendants, there had not yet been a statutory act of infringement involving those parties. *See, e.g.*, EX2018 (Brief in Support of Motion to Dismiss, DE70-1), 10 ("Plaintiffs' Amended Complaint does not allege that Amneal has done anything relating to the filgrastim biosimilar besides 'enter[ing] into a license and commercialization agreement with Adello,' which assigns Amneal responsibility for 'marketing, selling and pricing the Adello Filgrastim Product' *sometime in the future if and when FDA approval has been obtained. Id.* ¶ 19. Plaintiffs do not allege that Amneal is *doing anything currently*…"), 20-21 ("the fact that Adello and Amneal may intend to commercially launch a product *if* the FDA gives approval at some point in the future does not create a controversy of sufficient immediacy" (italics original)), 23

Because Petitioners failed to meet their obligation of identifying each real party-in-interest, the Petition is incomplete and should not be accorded a filing date. *See, e.g.*, §42.206(b); *Zoll*, IPR2013-00606, Pap. 13, at 11-12. Moreover, because the deadline for filing a PGR has passed (it is more than 9 months since the January 2, 2018 issue of the '287, *see* §42.202(a); §321(c)), and Petitioners cannot timely file a complete petition for PGR now, the Petition should be denied as untimely. *See, e.g.*, *Zoll*, IPR2013-00606, Pap. 13, 12; *Cisco*, IPR2017-01933, Pap. 9, 8-9, 17; *Amazon.com*, IPR2015-00480, Pap. 18, 6-7.[6]

("Plaintiffs do not allege facts showing they are *currently* being harmed by the possibility that Amneal could work with Adello to market Adello's biosimilar product if and when Adello receives FDA approval").

[6] Following Patent Owners' January 2, 2019 questioning of Petitioners' failure to name Amneal Pharmaceuticals LLC as an RPI, Petitioners on January 15 requested the Board's permission to add that entity as an RPI and suspend the rules that would otherwise render their Petition untimely under §321(c). *See, e.g.*, §42.106(b); EX2025. Following a conference call on January 18, 2019, the Board ordered briefing on this issue, and Patent Owners will respond on the schedule provided by the Board. Patent Owners additionally reserve their right to pursue

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

The Board also has discretion to deny institution here under §325(d), which provides that "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.*, *Hospira, Inc. v. Genentech, Inc.*, IPR2017-00739, Pap. 16, 17-19 (July 27, 2017) ("[T]he examiner considered fully the written description and enablement issues underlying Applicant's claim to priority in allowing the claims to issue, and Petitioner has not presented new evidence or arguments that would convince us that the Examiner's determination was unreasonable.").

Here, the written description and enablement arguments *on which Petitioners stake their entire argument for PGR standing* were previously considered by the original Examiner who allowed the claims of the '287—along

---

this issue further should further pertinent information become available through discovery or otherwise. *See, e.g., Atlanta Gas Light Co. v. Bennett Regulator Guards, Inc.*, IPR2013-00453, Pap. 88 (Jan. 6, 2015) (vacating institution decision and terminating review based on evidence showing Petition failed to name all RPIs).

with many of the prior art and arguments Petitioners have repeated here in the context of §§102 and 103. Indeed, as is evident from the face of the '287, the Examiner had the full benefit of materials from earlier proceedings between Petitioners Apotex Inc. and Apotex Corp. and Amgen—an IPR regarding a related patent, U.S. Patent 8,952,138 ("'138") (EX1004), *Apotex Inc., v. Amgen Inc.,* IPR2016-01542 ("the '138 IPR"), and a litigation between Amgen and Petitioners Apotex Inc. and Apotex Corp. regarding the '138, *Amgen Inc. v. Apotex Inc.*, Case No. 0:15-cv-61631 (S.D. Fla.). It would be a waste of the Board's limited resources and harassing to Amgen to re-litigate these issues already considered and decided by the USPTO. *See, e.g.*, *Intel Corp. v. Godo Kaisha IP Bridge 1*, IPR2018-00753, Pap. 11, 14-22 (Oct. 9, 2018) (denying institution where Petition repackaged art and arguments considered during prosecution).

This is particularly true post-*SAS*, given that the PTO has determined it will institute on every ground asserted by a Petitioner: even if, *arguendo*, the Board were to determine that any of the Petition's grounds merited institution (they do not), it can no longer institute on those grounds without dragging into institution—and subjecting both the Board and Patent Owners to a full trial on—the overwhelming number of meritless arguments the Office has previously rejected but that Petitioners now seek to relitigate. *See Chevron Oronite Co. LLC v. Infieum USA LP*, IPR2018-00923, Pap. 9, 9-11 (Nov. 7, 2018) (denying institution

on all claims under §314(a) when the petitioner's arguments and proofs were deficient with respect to a subset of claims).

A. Petitioners' Written Description And Enablement Arguments, Which Are Critical To PGR Standing, Were Already Considered by the Examiner During Prosecution

With respect to Petitioners' §112 arguments (Grounds 1-2), Petitioners made substantially the same written description arguments here as those raised and overcome during prosecution. Indeed, Petitioners do not even suggest they are making any new arguments. Instead, Petitioners merely say they *disagree* with the Office's resolution of this question, arguing that the Examiner "misapprehended the lack of support provided in the specification," and that Petitioners attach a new declaration that the Examiner could not have considered. Pet., 32. But the very aspects of the specification that Petitioners now argue are insufficient—*i.e.*, Figures IA-IF, col. 9 ll. 9-15, and col. 15 ll. 51-53 (Example 3)—are the same ones Amgen pointed to for support during prosecution and that the Examiner considered and found sufficient to support the claims. *Compare, e.g.*, Pet., 28-30, 34-35; *with* EX2008, 88-89, EX2008, 911 (Notice of Allowance from '287 File History); *see* EX2008, 19, 29, 37-42 (original '287 application in File History); *see also Telebrands Corp. v. Tinnus Enters., LLC*, PGR2017-00024, Pap. 15, 12-14 (Nov. 30, 2017) (denying institution where petitioner merely disagreed with the examiner

referring to the same application figures examiner expressly determined supported the claim language at issue).[7]

Further, Petitioners' conclusory expert declaration is not a reason to revisit these arguments that the Examiner squarely rejected. *See, e.g., Telebrands Corp.*, PGR2017-00024, Pap. 15, at 9-14 (rejecting petitioner's argument that its expert declaration distinguished the record before the Board from the record before the examiner, and denying institution pursuant to §325(d)); *Hospira, Inc.*, IPR2017-00739, Pap. 16, at 17-19 (denying institution under §325(d) despite submission in

[7] Petitioners assert that the percentages in the figures do not add up to 100%, and suggest this "cast[s] doubt" on the "particulars of the experiment." Pet., 29 n.6; EX1002 ¶73. But Petitioners tellingly ignore the explanation: Figures 1a-1f only report the percentages of certain protein species whose representative peaks lie within a certain time window on a High Performance Liquid Chromatography chromatogram. *See* EX1001, Figures 2-3, 9:6-15. As such, the peaks, whose areas were integrated to calculate the values presented in Figures 1a-1f, do not represent all the peaks of the chromatogram. The unintegrated peaks account for the remainder of the proteins, which, if analyzed, would have brought the mass balance to 100%.

IPR of new expert declaration because examiner considered fully the written description and enablement issues underlying applicant's claim to priority in allowing the claims). Indeed, many statements made by Petitioners' expert here were before the '287 Examiner from her testimony in the '138 IPR and the litigation between Amgen and Petitioners Apotex Inc. and Apotex Corp. regarding the '138, *Amgen Inc. v. Apotex Inc.*, Case No. 0:15-cv-61631 (S.D. Fla.). Rather than providing any independent evidentiary support, Petitioners' expert largely parrots the attorney arguments made in the Petition, making conclusory assertions that are entitled to no weight, and anything she adds is merely cumulative. EX1002, ¶¶72-78; *see Nintendo Co.*, *Ltd. v. Genuine Enabling Tech. LLC*, IPR2018-00543, Pap. 7, 24 (Aug. 6, 2018) (denying institution because the petitioner's "only support [was] a conclusory statement [from their expert] without any evidentiary support, which has no weight"); *AM General LLC v UUSI, LLC*, IPR2016-01048, Pap. 13, 13, 16 (Nov. 17, 2016) (denying institution and refusing to consider expert's conclusory statements). For example, Petitioners' expert's opinion that the "higher the percentage of properly folded protein sought, the more difficult that percentage is to achieve" and her citations supporting that opinion (EX1002, ¶77; Pet., 30) are entirely cumulative: this obvious proposition is discussed in the '287 specification, itself, and thus would have been known by the Examiner. *See, e.g.*, EX1001 8:47-9:60; *Hospira*, IPR2017-00739, Pap. 16, 17-19.

Petitioners' enablement arguments were also considered by the Examiner because they overlap substantially with the written description arguments and rely on the same disclosures of the specification (*e.g.*, Example 3 (pp. 23-24 of the '287 original application) and Figs 1A-F of the '287) specifically considered by the Examiner, EX2008, 884, 885, 911. *Compare* Pet., 28 ("fail to provide support for the full scope of 25-100%"), 29 ("scope of claims cover the yields resulting from the refolding of any protein"), 30 ("do not provide the particular protein tested," "no disclosure for any percentages of properly refolded protein over 80%," "higher yields of refolded protein are more difficult to achieve and thus the complete absence of support in the specification is especially compelling"), *with* Pet., 34 ("vast number of proteins and redox conditions covered by the claims"), 35 ("fail to name the protein used," "no guidance for the higher ends of [properly refolded] range"), 36 ("no showing in the priority applications that the patentees were able to overcome the extreme difficulty in achieving the higher levels of properly refolded protein").

Further, with respect to enablement, the Examiner considered §112 issues, including the very portions of the application Petitioners rely on to argue no enablement, and declined to issue an enablement rejection when he issued his written description rejection and later found the claims allowable. *See* MPEP §2103 (Patent Examination Process) (explaining that "[o]nce examiners have

concluded the above analyses of the claimed invention under *all* the statutory provisions, including 35 U.S.C. 101, *35 U.S.C. 112*, 35 U.S.C. 102, and 35 U.S.C. 103, they should review *all* the proposed rejections and their bases to confirm that they are able to set forth a *prima facie* case of unpatentability. *Only then should any rejection be imposed* in an Office action"). For example, Petitioners allege that Example 3 (pp. 23-24 of the '287 original application) and Figs 1A-F of the '287 are non-enabling. Pet., 33-36. However, the prosecution Examiner specifically considered these same disclosures in allowing the '287. EX2008, 884, 885, 911. Although there was no express discussion of enablement during prosecution, the Examiner had in mind both §112 requirements because both were quoted. EX2008, 844. But the Examiner proceeded to reject the pending claims only on the basis of new matter. *Id.* And, in light of the same disclosures of the '287, the Examiner allowed the claims, specifically asserting that "[t]he support for the new matter rejection is found in p.13, 23 and Fig 1A-F of the specification." EX2008, 911. Without providing any new facts or arguments, Petitioners ask the Board to revisit the decision of the Examiner who considered the very same evidence and allowed the claims. *See Telebrands Corp.*, PGR2017-00024, Pap. 15, at 9-14 (rejecting petitioner's §§112(a), 112(b), and 103 grounds even though the examiner did not issue any office action during prosecution rejecting the claims on those grounds, noting that the notice of allowance indicated that the examiner

already considered the same evidence). As with written description, Petitioner's expert similarly provides no evidence other than what was already considered by the Examiner. EX1002, ¶¶79-85. In any case, her testimony should be given no weight because she merely parroted Petitioner's attorney arguments and provided only conclusory assertions with no underlying facts or data on which her opinions are based. §42.65(a); *Nintendo Co.*, *Ltd.*, IPR2018-00543, Pap. 7, at 24 (denying institution because the petitioner's "only support [was] a conclusory statement [from their expert] without any evidentiary support, which has no weight"); *Irwin Seating Co. v. Camatic Proprietary Ltd.*, IPR2017-00385, Pap. 10, 13, 15 (June 12, 2017) (denying institution because the expert's testimony was not sufficiently supported by objective evidence and did not disclose underlying facts or data and was thus given "no weight").

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

With respect to Petitioners' anticipation and obviousness arguments (Grounds 3-7), at least three of Petitioners' four cited references are either the same as (Schlegl and Hevehan), or substantially the same as (Vallejo), the prior art already considered by the Examiner. And to the extent it is argued to be different from Schlegl, Hevehan and Vallejo (*cf.*, *e.g.*, Pet. 61, 65, 67, 69, 71, 75 (Petitioner arguing purported *similarities* between Vallejo and Ruddon to motivate their

combination)), the shortcomings of the fourth reference (Ruddon) are detailed *infra* (§VII.D).

The identical Schlegl and Hevehan references cited by Petitioners were explicitly and substantively discussed during the '287's prosecution.[8] Both were expressly included in the grounds in an earlier proceeding—the '138 IPR—that was cited and considered extensively during prosecution of the '287. Indeed, the '287 was pulled back from allowance so the Examiner could reconsider the decision to allow the application in light of the Petitioners' Reply (Pap. 25) and Dr. Robinson's reply declaration (Ex.1056) in the '138 IPR. *See* EX2008 (Corrected Notice of Allowability), 931; *see also* '138 IPR, Pap. 25, 14-18 (discussing Hevehan and Schlegl). The Examiner allowed the claims because the discussed references, Schlegl and Hevehan, failed to teach the thiol-pair ratio and thiol-pair strength, as claimed. *See* EX2008 (Notice of Allowance), 911.

---

[8] Additionally, Petitioners Apotex Inc. and Apotex Corp. asserted that Schlegl anticipated the '138 during the Florida litigation, EX2020, 40-42, and then withdrew this argument during trial, EX2010, 185, 214-215, following which the Florida court issued a judgment that the '138 is not invalid for anticipation under § 102, EX2021, 3, 5.

Vallejo, as argued by the Petitioners, is "substantially the same as" the Schlegl and Hevehan references that were before the Examiner during prosecution because it has the same failings the Examiner identified in Schlegl and Hevehan: it fails to teach the claimed thiol-pair ratio and thiol-pair strength. EX2008, 124, 164, 911.

Additionally, Vallejo (EX1038), which is the basis for Grounds 3, 5, and 7 in the present Petition, is also similar to another publication (EX1014) by the same author, also cited by Petitioners here, which ***was*** considered and expressly acknowledged by the Examiner during prosecution of the '287 as part of an Information Disclosure Statement (IDS) by Amgen. EX2008, 55, 123, 124. For example, the Vallejo reference in the IDS (EX1014) is similar to the Vallejo reference (EX1038) in discussing methods of refolding proteins produced by bacterial cells using batch or pulse addition. *Compare* EX1014, 4 (discussing "direct dilution" refolding methods where protein is diluted into a refolding buffer directly and refolding methods where the protein is added into the refolding buffer "in pulses or continuously"; citing to reference [40]), *with* EX1038, [001], [0010]-[0012] (discussing "renaturation of the solubilized cystine-knot protein in batch or by pulse addition of said solubilized cystine-knot protein to a refolding buffer…"). Indeed, citation no. [40], in Vallejo EX1014 is a scientific publication derived from Vallejo EX1038 and discloses the same work by the same authors. *Compare*

EX2009, *with* EX1038. The Examiner considered the IDS that cited Vallejo EX1014, and selected several other references from the IDS including Schlegl and Hevehan (but not Vallejo (EX1014)) to consider as obviousness references. EX2008, 125, 164. *See, e.g.*, *Unified Patents, Inc. v. Velocity Patent LLC*, IPR2017-01723, Pap. 10, 21, 24 (Jan. 19, 2018) (denying institution under §325(d) where one of the references was cited in a reexamination IDS, notwithstanding examiner's caveat that only a "cursory" evaluation of the disclosed references had been performed).

Petitioners did not explain why their §§102 and 103 arguments are new, nor why the Board should readjudicate them. *See, e.g.*, *Hengdian Grp. Dmegc Magnetics Co., Ltd. v. Hitachi Metals, Ltd.*, IPR2017-01313, Pap. 7, 15-16 (Nov. 6, 2017) (denying institution pursuant to §325(d) because Petitioner failed to provide "any arguments distinguishing the Examiner's prior consideration of [the prior art], or any compelling reason why [the Board] should re-evaluate substantially the same prior art as that presented during prosecution and considered by the Examiner."); *Sandoz, Inc. v. Genentech, Inc.*, IPR2017-02036, Pap. 13, 6 (Mar. 4, 2018) (denying institution pursuant to §325(d); "To the extent that any such differences exist, Petitioner has not explained or even alleged that the prior art and the arguments presented in the Petition are not *substantially the same* as those considered and abandoned by the Examiner during prosecution, and as those

presented and considered previously by the Board" (emphasis in original)); *West Pharm. Serv., Inc. v. Sanofi-Aventis Deutschland GmbH*, IPR2018-01162, Pap. 7, 13 (Dec. 6, 2018) (denying institution even when Petitioner set forth different arguments and additional evidence not raised by, or available to, the Examiner because the Examiner had rejected one of the claims based on the same combination of references pursuant to the same statutory authority).

Moreover, the Robinson declaration is not new evidence that would impact the §325(d) analysis. Petitioners' expert declaration did not provide any facts or analysis substantially beyond what was already considered by the Examiner.[9]

---

[9] Petitioners' citation to *Guardian Indus. Corp. v. Pilkington Deutschland AG*, IPR2016-01635, Pap. 9, 9-10 (Feb. 15, 2017); *Hospira, Inc. v. Genentech, Inc.*, IPR2017-00804, Pap. 13, 11-13 (July 27, 2017); and *Apotex Inc. v. Novartis AG*, IPR2017-00854, Pap. 11, 13-14 (July 18, 2017) are thus inapposite. Unlike the petitioner in *Hospira*, as discussed above, Petitioners here did not present any new evidence in support of their arguments that is meaningfully different from what was already considered by the Examiner. *Cf. Hospira, Inc.*, IPR2017-00804, at 11(declining to exercise its §325(d) discretion because petitioner presented, *inter alia*, new calculations not before the examiner during prosecution). Similarly,

"Merely repeating an argument from the prosecution history and the Petition in the declaration of a proposed expert, does not give that argument enhanced probative value." *Robert Bosch Tool Corp. v. SD3, LLC*, IPR2016-01754, Pap. 15, 19 (Mar. 22, 2017) (denying institution under § 325(d); Petitioner's expert's declaration, although not previously before the examiner, "does not provide any new arguments, or persuasive facts, data, or analysis to support the opinions stated.").

In *Dorco Co. v. Gillette Co.*, IPR2017-00500, Pap. 7, 13 (June 21, 2017), for example, the Board declined institution under §325(d) because the grounds "merely raise[d] the same issues that the Office has already considered and rejected," even though the petitioner's asserted grounds comprised references not expressly considered during original prosecution. The Board further dismissed

---

while in *Guardian* the Board noted the petitioner argued the original examiner had made a statement about a particular disclosure in the prior art that was "clear error" (*Guardian Indus. Corp.*, IPR2016-01635, at 9-10), no such evidence of "clear error" was provided by Petitioners here. And while, in *Apotex*, petitioner's expert provided new evidence that applicants' attorneys had made incorrect assertions during prosecution to overcome the rejection (*Apotex Inc.*, IPR2017-00854, at 13-14), there is no such evidence or argument in the present Petition.

petitioner's newly submitted expert declaration as "not add[ing] facts or analysis substantially beyond what was considered by the Office during prosecution." *Id.*; *see Unified Patents, Inc.*, IPR2017-01723, Pap. 10, at 24-25 (recognizing that petition relied on new expert declaration but denying institution because, *inter alia*, the declaration did "not meaningfully or directly address whether [the prior art reference] is more than cumulative of the secondary references relied upon in the prior proceedings"). The same holds true here. And although Petitioners cite Schlegl paragraph [0082] as something that "do[es] not appear to have been considered by the Examiner" and "discusses the yield of properly refolded protein . . . exceeding the required at least about 25% of the claims" (Pet., 52), this does not change the conclusion that the Petition raises, at most, substantially the same prior art and arguments under §325(d). As discussed above, Schlegl was previously considered by the Office together with Hevehan (EX1024), which *also* discloses yields of proteins exceeding at least about 25% (*see, e.g.*, EX1024, at 5, 6, Fig. 4), and thus, as presented by Petitioners, this teaching in paragraph [0082] of Schlegl is cumulative to what was previously before the Office and disposed of by the Examiner during original prosecution, and Petitioners are making substantially the same argument here with Schlegl paragraph [0082] alone.

Because, as discussed above, substantially all of the references and arguments urged in the Petition are the same or substantially the same as references

and arguments the Office previously considered and overcome during prosecution of the '287, the Board should exercise its discretion to deny institution under §325(d). Even if, *arguendo,* the Board were to determine that there is some subset of Petitioners' arguments that is new and merits review (and Patent Owners respectfully submit there is not), the significant, wasteful burden that would be imposed on both the Board and Patent Owners in relitigating *every one of these previously-considered arguments* as a result of the binary all-or-nothing institution approach that applies post-*SAS* further counsels strongly in favor of denying institution under §325(d). Further, these issues will be litigated before two United States District Courts in pending cases where the '287 is at issue—*Amgen Inc. v. Apotex Inc.*, No. 0:18-cv-61828 (S.D. Fla.) and *Amgen Inc. v. Adello Biologics, LLC*, No. 2:18-cv-03347 (D.N.J.).

V. Claim Construction

For purposes of *post-grant* review, "[a] claim in an unexpired patent . . . shall be given its broadest reasonable construction in light of the specification of the patent in which it appears." §42.200(b). However, "[e]ven under the broadest reasonable interpretation, the Board's construction cannot be divorced from the specification and the record evidence, and must be consistent with the one that those skilled in the art would reach." *Microsoft Corp. v.*

Proxyconn, Inc., 789 F.3d 1292, 1298 (Fed. Cir. 2015) (internal quotations and citations omitted).

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." §42.204(b)(3)-(4). Petitioners were *required* to construe at least the following terms in their Petition because they are necessary to arguments Petitioners advanced, *id.*, but Petitioners failed to do so. The Petition's grounds should all be rejected on this basis. *See, e.g.*, *Synopsys, Inc. v. Mentor Graphics Corp.*, IPR2012-00041, Pap. 16, 5-7 (Feb. 22, 2013) (rejecting Petitioner's implicitly proffered construction and denying institution); *Macronix Int'l Co. v. Spansion LLC*, IPR2014-00106, Pap. 13, 8-13 (Apr. 24, 2014) (denying institution where petitioner failed to provide explicit construction of "elliptical shape" and Board rejected petitioner's implicitly-applied construction); *Sharkninja Operating LLC v. Flexible Techs., Inc.*, IPR2018-00903, Pap. 8, 6-9, 23 (Oct. 17, 2018) ("Petitioner has not met its burden to provide a construction of the claims at issue, as required by 37 C.F.R. 42.104(b)(3) and (4)").

A. Petitioners Failed To Explain Whether And Why The Board Should Construe The Claim Phrases "So That At Least About 25% Of The Proteins Are Properly Refolded" And "So That About 30-80% Of The Proteins Are Properly Refolded" As Limiting (All Claims)

Without a word of explanation, Petitioners implicitly assumed the claim phrases "so that at least about 25% of the proteins are properly refolded" and "so that about 30-80% of the proteins are properly refolded" are limiting, and made this construction a required foundation on which various of their arguments for unpatentability—including *their only arguments for standing*—depend. Pet., 23-37 (arguing that the '287 does not get the benefit of June 22, 2009 priority because its priority application does not fully disclose or enable these limitations). But Petitioners never even acknowledged making this assumption, let alone explained why these phrases are limiting—even though during the '287's prosecution the Examiner himself suggested that related phrases were *non*-limiting (*see* EX2008, 843 ("the patented claims will inherently yield at least about 25% properly folded proteins")) and the Federal Circuit has found similar language *non*-limiting, as discussed below. This failure violates the basic rules for the contents of a Petition, *see, e g.,* Rule 104(b)(3), and would be reason enough by itself to deny institution, particularly where, as here, the limitations are the basis of Petitioner's PGR standing arguments. *See, e.g.*, *Synopsys*, IPR2012-00041, Pap. 16, at 5-7; *Macronix*, IPR2014-00106, Pap. 13, at 8-13.

This issue, flagged by the Examiner during prosecution, is both simple and fundamental: when a claim term only expresses a purpose or intended result of the claimed method, it is non-limiting. For example, in *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, the court held certain terms non-limiting because they "merely express[ed] a purpose" and "only state[d] an intended result of that claimed method." 246 F.3d 1368, 1374-75 (Fed. Cir. 2001). The court found that express dosage amounts were material claim limitations, but a statement of intended results from their administration, such as "an antineoplastically effective amount," "does not change those amounts or otherwise limit the claim." *Id.* at 1375; *see In re Copaxone Consol. Cases*, 906 F.3d 1013, 1023 (Fed. Cir. 2018) ("Claim language without any bearing on the claimed methods should be deemed non-limiting when it does not result in 'a manipulative difference in the steps of the claim.'"); *see also Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1378 (Fed. Cir. 2005) (agreeing with district court that the term "in a stabilizing amount" simply described the intended result of using the claimed weight-to-volume ratios); *In re Omeprazole Patent Litig.*, 536 F.3d 1361, 1370 (Fed. Cir. 2008) (affirming district court's conclusion that the claim term "such that the stability of the preparation is enhanced" was non-limiting because enhanced stability was intended result of other recited steps); *Ex Parte Jonas Ove Philip Eliasson, Niels Agersnap Larsen, Jens Bastue, & Jens Wagenblast Ostergaard*, Appeal 2013-002222, 2015

WL 1938823, at *3 (PTAB Apr. 22, 2015) (holding "***such that***" functional clause at issue was akin to a "whereby" clause that merely stated intended result of disposing a tool in a particular claimed configuration and environment) (citing *Texas Instruments, Inc. v. U.S. Int'l Trade Comm'n*, 988 F.2d 1165, 1172 (Fed. Cir. 1993)).

Here, Petitioners failed even to discuss *whether*—let alone provide an explanation *why*—the phrases in the independent claims 1, 10, 16, and 26 beginning with "so that" are limiting in light of Federal Circuit precedent.

Petitioners should have been aware of this issue because the '287 Examiner himself suggested during prosecution that similar phrases are *not limiting*. EX2008, 843. For example, throughout the '287's prosecution, the Examiner rejected all claims as unpatentable on the basis of non-statutory obviousness-type double patenting over claims 1-24 of the '138 (EX1004), which *do not have a similar limitation*. *See* EX2008, 127, 843, 884. Importantly, the Examiner found no patentable distinction between the claims even though the '138 claims *did not include* the then-proposed phrases "such that incubating the refold mixture achieves consistent yields of at least about 25% properly refolded proteins" and "to consistently yield at least about 25% properly refolded protein." *Id.* at 161-162 Instead, the Examiner argued that yielding 25% properly folded proteins is ***inherent*** when practicing the steps of the '138 and of the '287 application: "As

both claims comprise identical method steps, the patented claims will inherently yield at least about 25% properly folded proteins." *Id.* at 843; *see, e.g.*, *In re Schreiber*, 128 F.3d 1473, 1478 (Fed. Cir. 1997) (finding examiner was justified in declining to give claimed functional limitations patentable weight because they were inherent when structural limitations were met). The Examiner maintained the non-statutory obviousness-type double patenting rejection (EX2008, 843), and Amgen submitted a terminal disclaimer over the '138. EX2002, 884, 900-903.

Further, the Examiner never distinguished prior art based on a failure to meet any yield requirement such as expressed in these claim phrases. Although Amgen, in distinguishing a prior art reference, noted it was "silent regarding the yield of properly refolded protein that would result from the steps described in Example 5," EX2008, 161, the Examiner did not adopt this view. Instead, the Examiner withdrew the rejection "in light of [Amgen's] amendment to the claims," *id.* at 842, and later clarified the claims were allowable "because the most pertinent prior art neither teaches nor suggests the final thiol-pair ratio or strength as set forth in claims 34, 35, 56-57, 65-67 and 72." EX2008, 911 (Notice of Allowance from '287 File History). Accordingly, in light of the '287's prosecution history,

Petitioners certainly should have explained whether[10] and why they construe "so that at least about 25% of the proteins are properly refolded" and "so that about 30-80% of the proteins are properly refolded" as limiting.

B. If (As Their Petition Indicates) Petitioners' Arguments Require These Phrases To Be Limiting, Petitioners Were Required To Construe "At Least About 25%" Still Further, But Failed To Do So (Claims 1-9 and 16-25)

While Petitioners never offer any claim construction analysis or support, the Petition later reveals that Petitioners' arguments—including their only arguments for PGR standing—*require* that "at least about 25%" must mean "25% *to 100%.*" *See, e.g.*, Pet., 28 ("The specification does not provide support for 'at least about 25% of the proteins are properly refolded,' i.e., 25%-100%."). But Petitioners never addressed the claims' "*at least about*" language, and do not explain why this range would start at *exactly* 25%. *See, e.g.*, *Hybritech, Inc. v. Abbott Labs.*, 849 F.2d 1446, 1455 (Fed. Cir. 1988) (reasonable likelihood of success of proving literal infringement of claim reciting affinity of "at least about 10^8 liters/mole" by

---

[10] As noted, Petitioners implicitly argue these phrases *are* limiting in asserting that the specification lacks written description and enablement support for these limitations (Pet., 26-37), but they never acknowledge, let alone explain and support, this implicit construction.

accused products with affinities of 4.8 x 10^7 and 7.1 to 7.5 x 10^7 liters/mole). Nor did Petitioners explain whether or why persons of ordinary skill in the art ("POSITA") would purportedly have understood the claimed range for refolding achieved in the claim to include "*100%*." This is particularly striking given Petitioners' acknowledgment that "the higher the percentage of properly folded protein sought, the more difficult that percentage is to achieve" (Pet., 35), and Petitioners are conspicuously and fatally silent about whether POSITA—for whom the claims are written—would have understood this term to have had an upper limit, even if not precisely known. *See, e.g.*, *Perkinelmer Health Scis., Inc. v. Agilent Techs., Inc.*, 962 F. Supp. 2d 304, 309 (D. Mass. 2013) (in construing "greater than," "the intrinsic evidence presented here implies the existence of some upper limit"); *see also, e.g.*, *Andersen Corp. v. Fiber Composites, LLC*, 474 F.3d 1361, 1376-77 (Fed. Cir. 2007) (support for open-ended ranges may be found based on, *inter alia*, "an inherent, albeit not precisely known, upper limit [when] the specification enables one of skill in the art to approach that limit").[11] Petitioner's failure to address the construction of this claim (and thus attempt to

[11] POSITA, from reading the '287 specification, would see that yields as high as 80% had been achieved by the inventors.

support the "100%" they later apply as an implicit construction) requires rejection of its written description and enablement arguments (Pet., 27-37) relying on this unstated construction, which negates Petitioners' standing to challenge the '287 in a PGR proceeding and Petitioners' Grounds 1-2, and requires denial of the Petition. *See, e.g.*, *Synopsys*, IPR2012-00041, Pap. 16, at 5-7; *Macronix*, IPR2014-00106, Pap. 13, at 8-13.

C. Petitioners Failed To Construe "Calculated" (Dependent Claims 8, 9, 14, 15, 23, 24, And 25)

The term "calculated" in dependent claims 8, 9, 14, 15, 23, 24, and 25 should be construed to include an *active step of determining*. Each of the dependent claims requires the "thiol-pair ratio," the "thiol-pair buffer strength," or both to be "calculated according to the following equation," which is then recited in the claim. *See* EX1001, claims 8, 9, 14, 15, 23, 24, and 25. And the prosecution history confirms that "calculated" requires a thiol-pair ratio or thiol-pair buffer strength to actually ***be calculated***. EX2008, 163, 167-68. During prosecution, Amgen stated, for example, that then-dependent claims 34 and 35 recite that the thiol-pair ratio and thiol-pair buffer strength are "***calculated***, ***and thus derived***," according to the equations $\frac{[the\ reductant]^2}{[the\ oxidant]}$, and $2[the\ oxidant] + [the\ reductant]$, respectively. *Id.* Amgen then argued that these dependent claims (not the independent claims from which they depended, which did not recite

"calculated"), were distinguishable from references cited by the Examiner (Oliner, Hevehan (EX1024), and Schlegl (EX1007)) because, *inter alia*, those references did not disclose the use of these equations to calculate the thiol-pair ratio or thiol-pair buffer strength:

> Oliner does not even suggest that either ***equation is used to calculate*** the thiol-pair ratio value or the thiol-pair buffer strength. It appears that the Office Action simply used hindsight gleaned from the claimed present invention to select data from a single example in Oliner, and insert that data into the claimed equations in an attempt to show the claimed thiol-pair ratio range. Clearly, Oliner did not use the equations to derive the claimed thiol-pair ratio range, or the thiol-pair buffer strength.

Id. at 163; *accord id.* at 167-168 (distinguishing over Schlegl and Hevehan). Additionally, Amgen contrasted Hevehan's and Schlegl's reliance on "*trial-and-error* to determine redox conditions" with the methods of the claims. *Id.* at 168.

As this evidence confirms, the recitation in dependent claims 8, 9, 14, 15, 23, 24, and 25 of "calculated" is a further limitation from the independent claims that cannot be ignored, as Petitioners have done. This term requires that the "thiol-pair ratio" and "thiol-pair buffer strength" be "calculated."

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

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

For written description support under §112, ¶1, "the test for sufficiency is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010). "There is no requirement that the disclosure contain either examples or an actual reduction to practice; rather, the critical inquiry is whether the patentee has provided a description that in a definite way identifies the claimed invention in sufficient detail that a person of ordinary skill would understand that the inventor was in possession of it at the time of filing." *Alcon Research Ltd. v. Barr Labs., Inc.*, 745 F.3d 1180, 1190-91 (Fed. Cir. 2014) (internal quotations and citations omitted). "The 'written description' requirement states that the patentee must describe the invention; it does not state that every invention must be described in the same way," *Capon v. Eshhar*, 418 F.3d 1349, 1358 (Fed. Cir. 2005); *accord id.* at 1357, "or that the specification recite the claimed invention *in haec verba*." *See Ariad*, 598 F.3d at 1352; *Apple Inc. v. Papst Licensing GmbH & Co. KG,* IPR2016-01844, Pap. 10, 20 (Mar. 10, 2017); *In re Herschler*, 591 F.2d 693, 700-701 (C.C.P.A. 1979); *see also All Dental Prodx, LLC v. Advantage*

Dental Prods., Inc., 309 F.3d 774, 779 (Fed. Cir. 2002) (quoting *Eiselstein v. Frank*, 52 F.3d 1035, 1038–39 (Fed. Cir. 1995)).

Further, the specification is written *for POSITA*. Thus, "the failure of the specification to specifically mention a limitation that later appears in the claims is not a fatal one when one skilled in the art would recognize upon reading the specification that the new language reflects what the specification shows has been invented." *Id.* at 779. The written description requirement is satisfied "when 'the essence of the original disclosure' conveys the necessary information—'regardless of *how* it' conveys such information," *Inphi Corp. v. Netlist, Inc.*, 805 F.3d 1350, 1354 (Fed. Cir. 2015) (emphasis in original), and "a patent *need not teach, and preferably omits, what is well known* in the art." *Hybritech Inc. v. Moncolonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986).

The proper inquiry in the present case is, thus, whether the disclosure of the '287 reasonably would have conveyed to POSITA at the time of filing that the inventor had possession of the claimed range of "at least about 25% of the proteins

are properly refolded."[12] And, as discussed below, the answer to the query is "yes."

1. Petitioners Fail To Address Whether "At Least About 25% Of The Proteins Are Properly Folded" Is Limiting And, If Limiting, How It Is Correctly Construed

As discussed above, *see supra* §V.A, Petitioners failed to analyze whether "at least about 25% of the proteins are properly folded" should be construed as limiting to begin with, and provided no analysis or evidence that it is. Nor did Petitioners' establish that "at least about 25%" would have been understood by POSITA to mean a range that, *inter alia*, reaches all the way up "to 100%," as it argues without any analysis or support. *See supra* §V.B; Pet., 28; *Union Oil Co. of California v. Atl. Richfield Co.*, 208 F.3d 989, 995 (Fed. Cir. 2000) (stating that "[t]he first step in *any* invalidity ... analysis is claim construction" and construing the claims before deciding whether the specification contained a written description of the invention); *U.S. Ethernet Innovations, LLC v. Acer, Inc.*, No. C

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

10-03481 JW, 2012 WL 370619, at *5 (N.D. Cal. Jan. 31, 2012) ("the Court must construe the meaning of the words and phrases used in the additional limitation before examining the written description for corresponding structure."). This is improper, and this alone is sufficient reason to deny institution. *Zero Gravity Inside Inc. v. Footbalance System Oy.*, IPR2015-01770, Pap. 17, 9 (Jan. 13, 2016) (denying institution because petitioner failed to provide a construction of a critical term); *ClearCorrect Operating LLC v. Align Tech., Inc.*, IPR2017-01829, Pap. 10, 7 (Feb. 5, 2018) (denying institution for failure to demonstrate adequately how the challenged claims are to be construed); *Synopsys, Inc.*, IPR2012-00041, Pap. 16, at 5-7. And given this failure, Petitioners have not shown that these phrases require written description support.

2. To The Extent "At Least About 25%" Is Limiting, The Law Does Not Require Disclosure Of Examples Across The Entire Range Of Results Recited in the Claim

Assuming, *arguendo*, that the results phrase ("so that") in independent claims 1, 10, 16, 26 is limiting, Petitioners assert that written description law requires Amgen to have given explicit examples in the specification across the entire range of the results recited in its method claims (*i.e.*, "so that at least about 25% of the proteins are properly refolded"). Pet., 27-33. Not so. The Federal Circuit rejected a similar argument in *Andersen Corp. v. Fiber Composites, LLC*, where the patents at issue claimed structural members with a particular level of

tensile strength—"a Youngs modulus of greater than 500,000." 474 F.3d 1361, 1371 (Fed. Cir. 2007). At trial, one of the inventors testified that the inventors had not obtained results with a modulus value of greater than 1.2 million, and the defendant argued that, "without that upper limit, the patents necessarily cover more than they enable and more than the inventors actually invented." *Id.* at 1376. The jury found no failure to comply with the written description and enablement requirements, and the district court denied defendant's related post-trial motions. *Id.* The Federal Circuit affirmed, confirming that "[o]pen-ended claims are not inherently improper" and "their appropriateness depends on the particular facts of the invention, the disclosure, and the prior art." *Id.* (quoting *Scripps Clinic & Research Found. v. Genentech, Inc.*, 927 F.2d 1565, 1572 (Fed. Cir. 1991); *see Scripps Clinic & Research Found.*, 927 F.2d at 1572 (finding that a claim reciting a "highly purified" constituent did not require disclosure of 100% purity).

Petitioners' case law is inapposite because it addresses *inputs* required for achieving a result, not the result itself. For example, Petitioners cite *In re Wertheim*, 541 F.2d 257, 262 (C.C.P.A. 1976), in which the court held the claimed limitation of "at least 35%" lacked written description support when the original specification included a range of "25 to 60%" and specific examples of 36% and 50%. Pet., 31. But the claim term at issue there dealt with *inputs* into a process—coffee extracts concentrated to "at least 35%" for use in later steps—not the recited

result of performing that process with the concentrated coffee extracts. *Id.* at 258-259.

Petitioners argue the '287 specification does not provide written description support for the claimed range because it fails to demonstrate any significance of the claimed range. Pet., 30-31 (citing *Grünenthal GmbH v. Antecip Bioventures II LLC*, PGR2017-00008, Pap. No. 7 (July 7, 2017)). But *Grünenthal*, too, is inapposite. In *Grünenthal*, the limitation at issue was about an input, not a result—administering "about 80 to about 500mg of zoledronic acid within a period of six months"—and there was no disclosure of the 80mg lower limit over the period of six months. *Grünenthal*, PGR2017-00008, Pap. No. 7 at 18-20. Here, in contrast, the phrase argued by Petitioners has only one numeric endpoint, which is a *result* (not an input), and which is disclosed (*see, e.g.,* Example 3 (pp. 23-24) and Figs 1A-F of the '287's original application). Further, Petitioners ignored that the important feature of the claimed invention is to vary the redox reagents that are related through a thiol-pair ratio and a thiol-pair buffer strength which, unlike *Grünenthal*, are clearly described in the '287 specification.

B. Ground 2: Petitioners Did Not Meet Their Burden To Prove That Claims 1-9 and 16-25[13] Were Not Fully Enabled By The '287's Priority Applications Before March 16, 2013

As discussed above, *see supra* §V.A, Petitioners failed to analyze whether the phrases "so that at least about 25% of the proteins are properly refolded" and "so that at least about 30-80% of the proteins are properly refolded" are limiting, and provide no analysis or evidence that they are.

Further, even if the Board were nonetheless to construe "at least about 25%" and "about 30-80% of the proteins are properly refolded" (in claims 1 and 10, respectively) as limiting, contrary to Petitioner's assertion (Pet., 34-36), claims need not have working examples across their entire range[14] in order to be enabled. *See, e.g.*, *Andersen Corp.*, 474 F.3d at 1376; *Rimfrost AS v. Aker BioMarine Antarctic AS*, PGR2018-00033, Pap. 9, 10-14 (Aug. 29, 2018). In *Rimfrost*, for example, the Board denied institution, finding petitioners had not adequately

---

[13] Although Petitioners referenced claims 1-30 in their heading for Ground 2 (VIII.D), Pet., 36, the body of that section of the Petition (and Petitioners' chart on page 37) challenges only claims 1-9 and 16-25.

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

established that the limitation "3% to 15% ether phospholipids w/w of said krill oil" was not enabled, even though the specification included only two working examples showing how to make a krill oil composition having 7.4% ether phospholipids. *Rimfrost AS*, PGR2018-00033, at 10-14. The Board reasoned that blending various lipid components to create a krill oil composition was within the ability of one skilled in the art and that the specification, including the examples, provided guidance to one skilled in the art as to how to make a composition containing the recited amounts of ether phospholipids. *Id.* The same is true here, where the specification provides POSITA with the necessary information to practice the claims. *See infra.*

Additionally, Petitioners assert that some experimentation would be required to produce the properly refolded results, but do not explain why any experimentation needed would be *undue*. The Federal Circuit has made clear that the fact that some experimentation may be needed does not necessarily mean "undue experimentation" would be required. *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1565 (Fed. Cir. 1996) ("Where the specification provides 'guidance in selecting the operating parameters that would yield the claimed result,' it is fair to conclude that the experimentation required to make a particular embodiment is not 'undue.'"). Indeed, as discussed below, Petitioners did not do any meaningful analysis of the *Wands* factors, such as the quantity of

experimentation necessary, the amount of direction or guidance presented, or the presence or absence of working examples. *Merck Sharp & Dohme Corp. v. Wyeth LLC*, IPR2017-01211, Pap. 9, 12-13 (Oct. 20, 2017) (denying institution; "[n]or does the Petition provide adequate reasons why [ ] statements [regarding unpredictability of arriving at the claimed invention] substitute for an analysis tethered to the *Wands* factors," which would include the "guidance or working examples set forth in" the parent applications).

Petitioners have also not alleged, let alone established, that POSITA could not achieve properly refolded protein within the recited ranges using the conditions described in the priority application. Petitioners say only that at "higher" percentages it would be "more difficult" to achieve (Pet., 35; EX1002, ¶83), but (in addition to failing to show this is a limitation, and failing to show that the range of claim 1 would be understood to extend to 100%[15]), Petitioners did not assert that it

---

[15] Tellingly, the paragraph of Dr. Robinson's declaration relied on here by Petitioners (EX1002, ¶83) mentions, as supposed examples of "higher levels of properly refolded protein" for which she complains there was no specific example in the priority document, only 85%, 90%, 95% and 100% refolding—all above claim 10's 80% upper limit, and none of which was shown by Petitioners to be

could not be done nor explain what would actually need to be done to achieve it. Petitioners and their expert nevertheless summarily assert that the specification provides "no guidance" for achieving properly refolded at the higher ends of the range. Pet., 35. But Petitioners failed to show that the guidance provided in the '287 specification with respect to how to vary the thiol-pair ratio and thiol-pair buffer strength in order to obtain "at least about 25%" of proteins properly refolded for any protein (including to achieve, *e.g.*, "30 to 80%" refolding in Example 3, EX1001, 15:50-53) is insufficient for POSITA. For example, the '287 specification explains in the following passage how to optimize refolding yield for any protein:

> ***The ability to select an optimal Thiol-Pair Ratio and Thiol-pair Buffer Strength allows for the optimization of the yield of a desired folded protein form***. This optimized yield can be achieved by maximizing the mass or yield of desired folded protein species in the refolding pool or by purposefully shifting the resultant undesired product-related species to a form that is most readily removed in the subsequent purification steps and thusly leads to an overall benefit to process yield or purity.

---

within POSITA's understanding of the scope of claim 1 ("at least about 25%"). *See supra* §V.B; Pet., 35; EX1002, ¶83.

> ***Optimization of the redox component Thiol-pair Ratios and Thiol-pair Buffer Strengths can be performed for each protein.*** A matrix or series of multifactorial matrices can be evaluated to optimize the refolding reaction for conditions that optimize yield and distributions of desired species. An optimization screen can be set up to systematically evaluate redox chemistries, Thiol-pair ratios, Thiol-pair Buffer Strengths, incubation times, protein concentration and pH in a full or partial factorial matrix, with each component varied over a range of at least three concentration or pH levels with all other parameters kept constant. The completed reactions can be evaluated by RP-HPLC and SE-HPLC analysis for yield and product quality using standard multivariate statistical tools.

EX1001 9:39-60. Petitioners offer no reasoned basis that this approach would not suffice, or that it would require experimentation that would be "undue" under a proper assessment of the *Wands* factors.

In sum, Petitioners' conclusory assertions that these claims are not enabled rests on implicit claim constructions it has not even articulated, let alone supported, and a failure to analyze the specification's actual teachings—not any demonstration that following the actual direction they provide would require "undue experimentation." Petitioners have thus failed to show a reasonable likelihood of prevailing on their enablement arguments, as with their written

description arguments, and thus cannot even establish PGR standing, much less a basis for instituting trial on these grounds.

Petitioners' failure to show that claims 1-9 and 16-25 lack written description support and that claims 1-30 are not enabled (Grounds 1-2) is fatal to this PGR because it means Petitioners have failed to meet their burden to disqualify the priority from the Provisional Application No. 61/219,257 filed June 22, 2009, and thus failed to demonstrate that '287 is a post-AIA patent eligible for PGR.

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

Because the Petition failed to establish that any of the prior art references disclose—explicitly or inherently—each and every limitation of the Challenged Claims, alone or in combination, Petitioners have failed to meet their burden for institution not only on all of their anticipation arguments (Grounds 3-4), but also on all of their arguments for obviousness (Ground 5-7). *See, e.g.*, *Endo Pharm. Inc. v. Depomed, Inc.*, IPR2014-00653, Pap. 12, 9-11, 13-14 (Sept. 29, 2014) (prior art reference lacking one or more elements of a claim cannot anticipate that claim or any of its dependent claims). Indeed, in view of all-or-nothing institution post-*SAS* and the many gaps of proof in Petitioners' arguments, even if the Board were to find that, buried within Petitioners' pile of arguments and combinations, there

were an asserted Ground with merit (there isn't), the burden of the wasteful exercise of a full trial on all the others would weigh heavily in favor of non-institution under §324(a), and the Board should exercise its discretion here to deny institution. *Chevron Oronite Co. LLC v. Infieum USA LP*, IPR2018-00923, Pap. 9, 9-11 (Nov. 7, 2018) (denying institution on all claims under §314(a) [for IPRs] when the petitioner's arguments and proofs were deficient with respect to a subset of claims).

A. Petitioners' Analysis Improperly Assumed That Claims 1 And 16, As Well As Claims 10 And 26, Have The Same Scope, And Thus Failed Even To Attempt To Show That Any Cited Prior Art Discloses The Actual Limitations Of At Least One Set Of Independent Claims (And Their Dependent Claims)

Although ignored by Petitioners, Claims 1 and 10 have a different scope than claims 16 and 26, respectively. Claims 1 and 10 recite a "preparation" comprising at least one of a denaturant, aggregation suppressor, and a protein stabilizer; an amount of oxidant; and an amount of reductant. Claims 1 and 10 further recite that the thiol-pair ratio and the thiol-pair buffer strength are determined in the ***preparation***, which does not contain the proteins. Claims 16 and 26, on the other hand, recite a "solution" comprising the proteins; at least one of denaturant, aggregation suppressor, and a protein stabilizer; an amount of oxidant; and an amount of reductant. Unlike claims 1 and 10, claims 16 and 26 recite that the thiol-pair ratio and the thiol-pair buffer strength are determined in the ***solution***,

which does contain the proteins. However, Petitioners' analysis with respect to the thiol-pair ratio and thiol-pair buffer strength for claims 1, 10, 16, and 26 is the same for each claim—*i.e.*, Petitioners purport to determine thiol-pair ratios and thiol-pair buffer strengths in a single liquid for each reference without specifying whether that liquid purportedly maps to the claimed "preparation" or "solution."

For example, for Vallejo, Petitioners assert that "Vallejo discloses multiple examples of refolding a protein using a thiol-pair ratio within the range of 0.001-100" (Pet., 44) and that "when Vallejo teaches a final concentration of glutathione of 3mmol L^{-1} (i.e. 3 mM), it is also disclosing a thiol-pair buffer strength greater than 2 mM" (Pet., 44-45). But, even putting aside Petitioners' fundamentally flawed arithmetic, as discussed below, *infra* §VII.B.1, Petitioners and their expert do not say whether their purported thiol-pair ratios and thiol-pair buffer strength are determined in a "preparation" or in a "solution." Indeed, Petitioners and their expert never map any liquids disclosed in Vallejo to the claimed "preparation" or to the claimed "solution." Further, neither Petitioners nor their expert attempt to provide any clarity as to whether the concentrations reported in Vallejo are measured in a liquid with the protein or without the protein:

> This solution containing 2 to 25 mg mL^{-1} of unfolded and reduced rhBMP-2 was stored in aliquots at -70°C and thawed directly prior to the refolding experiment. Standard renaturation conditions were as

> follows: Dilution of unfolded and reduced rhBMP-2…in standard renaturation buffer with a final concentration of…3 mmol L^{-1} total glutathione in a 2:1 ratio of glutathione reduced to glutathione oxidized (GSH:GSSG).

EX1038, [0055]. It is not clear whether the reported concentrations of the components of Vallejo's "renaturation buffer" are those prior to or after the addition of the "solution containing 2 to 25 mg mL^{-1} of unfolded and reduced rhBMP-2." *Id.*

As more examples: For Schlegl, Petitioners purportedly determine the thiol-pair ratio and thiol-pair buffer strength of Schlegl's "redox component," without any explanation as to which of the claimed liquids (the "preparation" or the "solution") Schlegl's "redox component" maps to. Pet., 56-57; *see infra* § VII.C.1. For Ruddon, Petitioners purportedly determine the thiol-pair ratio and thiol-pair buffer strength of Ruddon's "redox buffer," without any explanation as to which of the claimed liquids (the "preparation" or the "solution") Ruddon's "redox buffer" maps to. Pet., 67, 73. For Hevehan, Petitioners purportedly determine the thiol-pair buffer strength of Hevehan's "renaturation buffer," without any explanation as

to which of the claimed liquids (the "preparation" or the "solution") Hevehan's "renaturation buffer" maps to. Pet., 77-78.[16]

Therefore, because Petitioners did not even address the difference in scope between the claims, Petitioners failed to properly map any of their §§102 or 103 grounds. For this reason alone, the Board should deny the institution on all anticipation/obviousness Grounds (3-7).

B. Petitioners Failed To Show That Claims 1-4, 7-19, And 22-30 Are Anticipated By Vallejo (Ground 3), Or That Claims 5, 6, 20, And 21 Are Obvious Over Vallejo In View Of Hevehan (Ground 7)

1. Petitioners Have Not Shown A Reasonable Likelihood Of Success In Establishing That Claims 1-4, 7-19, And 22-30 Are Anticipated By Vallejo

Thiol-Pair Ratio. Petitioners and their expert purport to determine thiol-pair ratios disclosed by Vallejo, but their determinations are fundamentally flawed, eliminating any possibility that the Petitioners could have met their burden to show that Vallejo discloses this limitation. Pet., 43-44 n.10; EX1002, ¶100. Even if it

---

[16] In Hevehan, DTT, which is the only chemical Petitioners identify as providing a reductant, Pet., 78; EX1002 ¶190, is present only in Hevehan's "denatured solution," which contains the protein. EX1024, 3. Thus, the concentration of reductant in any "preparation" would be zero.

were assumed, *arguendo*, that Petitioners are correct that Vallejo includes examples where rhBMP-2 is refolded using varied concentrations of reductant and oxidant; that Vallejo varies the *ratio* of GSH to GSSG from 40:1 to 1:20; that the concentration of GSH is the concentration of the claimed reductant; that the concentration of GSSG is the concentration of the claimed oxidant; and that these concentrations are measured in the appropriate liquid (*see supra* §VII.A), Pet., 43-44, Petitioners failed to explain how, as a matter of arithmetic, one could possibly compute, from this information alone, the thiol-pair ratio according to the equation $\frac{[reductant]^2}{[oxidant]}$. Petitioners claim that Vallejo discloses the ***ratio*** of the concentration of reductant to the concentration of oxidant, *not* that Vallejo discloses the ***actual concentrations*** of reductant and oxidant used. But a reader of Vallejo cannot determine, as a matter of arithmetic, the ***actual concentrations*** of reductant and oxidant used from knowing only that ***ratio***.[17] Ignoring this, Petitioners and their

[17] For example, knowing merely that the ratio of the concentration of reductant to the concentration of oxidant is 2, one cannot deduce the concentrations of the oxidant and reductant or the thiol-pair ratio: the concentration of the reductant could be 4mM and the concentration of the oxidant could be 2mM; or the concentration of the reductant could be 0.00004mM and the concentration of the

expert simply took and squared the *numerators of the* ***ratios*** allegedly disclosed in Vallejo, and mistakenly concluded that this is the thiol-pair ratio (*i.e.*, $\frac{[reductant]^2}{[oxidant]}$). Pet., 43-44 n.10; EX1002, ¶100. For example, Petitioners never established that for the alleged thiol-pair ratio of 0.05 ($[1]^2/[20]$), the actual concentration of reductant was 1mM and the actual concentration of oxidant was 20mM. For this reason alone, Petitioners failed to show that the thiol-pair ratio limitation is disclosed by Vallejo.

Petitioners mixed-and-matched Vallejo's examples. With respect to dependent claims 2, 3, 11, 13, 17, 18, 27 and 28, Petitioners mixed and matched examples, *e.g.*, by pulling different values across different example experiments, without any explanation of whether or why this could properly be done. With respect to independent claims 1, 10, 16, and 26, for example, Petitioners purported to determine Vallejo's thiol-pair ratio by relying on an example discussed in

---

oxidant could be 0.00002mM. Although both results in a ratio of concentration of reductant to concentration of oxidant of 2, the former results in a thiol-pair ratio of 8 ($\frac{4^2}{2}$), which is within the range recited in the claims; and the latter results in a thiol-pair ratio of 0.00008 ($\frac{0.00004^2}{0.00002}$), which is below the range recited in the claims.

Vallejo's Fig. 2. Pet., 43-44; EX1038, [0042] ("**Figure 2.** Effect of pH and redox conditions on renaturation of rhBMP-2. Renaturation was carried out at 20°C and *a total concentration of 0.1 mg mL^{-1}* rhBMP-2 in standard renaturation buffer (A) with 3 mmol L^{-1} total glutathione in a 2:1 ratio (GSH:GSSG) and the pH adjusted to the indicated values or (B) at pH 8.5 and 3 mmol L^{-1} total glutathione at the indicated redox ratios. The renaturation yield is expressed as percentage of dimerized rhBMP-2."), Fig. 2.

However, for dependent claims 2, 3, 11, 13, 17, 18, 27 and 28, which *depend, respectively, from those same claims*, Petitioners relied on a *different* example from Vallejo, described in [0012], to purportedly show that the refold mixture has a protein concentration "in a range of 1-40 g/L," or "refold mixture with a protein concentration of 2.0 g/L or greater." Pet., 47; EX1038, [0012] ("A further increase in the concentration of rhBMP-2 was achieved by a pulsed refolding procedure (pulse refolding being a particularly preferred embodiment to be used in the method of the invention) that *resulted in a final concentration of 2.1 mg mL^{-1} rhBMP-2* with an overall renaturation yield of 33 to 38%, corresponding to 0.7 to 0.8 mg/ml renatured dimeric rhBMP-2."). Moreover, Petitioners do not address that Vallejo discloses a "***final***" concentration that its procedure "***resulted in***," not the concentration in which the protein is actually refolded, which would have been less than the concentrations recited in the dependent claims of the '287.

EX1038, [0012]. This is because Vallejo uses a "pulsed refolding procedure," where the protein is added in pulses separated by periods of time or continuously over a period of time, into the refolding buffer. *Id.* at [0011]; EX1014, 4.

Further, the example Petitioners relied on for their analysis of claim 1 (EX1038 at [0042], Fig. 2) cannot meet the additional limitation of claim 2, which requires the "refold mixture [to have] a protein concentration in a range of 1-40 g/L," because the concentration of protein in that example (EX1038 at [0042], Fig. 2) is only 0.1 mg/ml. Petitioners, without explanation, point to EX1038, [0012] for claim 2 which is different from the disclosure they relied on for independent claim 1. Pet., 47. Petitioners failed to address this discrepancy, and do not explain why or how POSITA would understand the concentration disclosed in EX1038, [0012] relates to the concentration disclosed in EX1038, [0042], Fig. 2. Petitioners also did not explain why the thiol-pair ratios allegedly disclosed in Fig. 2 would also be applicable to the example disclosed in EX1038, [0012]. *Fujian Sanan Grp. Co., Ltd. v. Epistar Corp.*, IPR2018-00971, Pap. 9, 15-16 (Nov. 20, 2018) (denying institution because petitioner's citation to a different embodiment with inconsistent disclosure confused petitioner's contentions); *SecureNet Techs., LLC v. Icontrol Networks, Inc.* IPR2016-01919, Pap. 9, 25-26 (Mar. 30, 2017) (denying institution because "mixing-and-matching of references' elements without adequate explanation is confusing rather than clarifying"). This pointing

to one set of values for the independent base claims, and then a different set of values for the claims depending from those same base claims, is a critical error, requiring denial.

Thiol-pair buffer strength to maintain the solubility of the preparation/solution. Petitioners also did not meet their burden in establishing that the thiol-pair buffer strength "maintains the solubility of the preparation" as required in independent claims 1 and 10, or "maintains the solubility of the solution" as required in independent claims 16 and 26. Pet., 45. Petitioners' arguments regarding Vallejo for the independent claims were *anticipation* arguments, but Petitioners pointed to no explicit teaching in Vallejo regarding solubility of any solutes in any preparation or solution. Moreover, even assuming, *arguendo*, that Petitioners' construction of "wherein the thiol-pair buffer strength maintains the solubility of the preparation" is correct (it is not, *see infra* §IX), and that the focus of the claim is the solubility of the protein only, Petitioners simply argued that the "result" of protein folding in Vallejo "***would not be possible unless*** the redox components maintained the solubility of the protein while the protein refolded." *Id.* This apparent ***inherency*** argument (though never identified as inherency in the Petition) is not sufficiently supported, as Petitioners provided no explanation as to why protein refolding ***necessarily*** (and thus inherently) requires that the solubility be "maintained." *Crown Operations Int'l, Ltd. v. Solutia Inc.*,

289 F.3d 1367, 1377 (Fed. Cir. 2002) (citing *Cont'l Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268–69 (Fed. Cir. 1991)); *Fluidmaster, Inc. v. Danco, Inc.*, IPR2017-00770, Pap. 13, 20-21 (July 28, 2017) (denying institution because petitioner's contention that the prior art "would necessitate" the claimed limitation without providing additional argument or identifying persuasive evidence was not enough). Petitioners also failed to square their assertion that the refolding ***would not be "possible" without*** the redox components with the fact that their own prior art ***Schlegl teaches that an alpha-LA protein is capable of refolding without redox chemicals***. *See* Pet., 51 ("Schlegl discloses that redox chemicals are optional for refolding of α-LA."). And Petitioners' expert, rather than providing any evidence that could support this argument, merely repeated verbatim the same one-sentence assertion from the Petition. *See* EX1002, ¶102. *See, e.g.*, *TCL Corp. v. Telefonaktiebolaget LM Ericsson*, IPR2015-01584, Pap. 74, 47 (Jan. 24, 2017) (conclusory assertion insufficient to demonstrate express or inherent disclosure); *Roland Corp. v. inMusic Brands, Inc.* IPR2018-00335, Pap. 14, 26 (July 2, 2018) (denying institution because "Petitioner proffers no evidence or argument to support its assertion that [the claimed] feature is inherent aside from the conclusory assertion that it is").

Calculated. With respect to claims 8, 9, 14, 15, 23, 24, 25, and 30, Petitioners failed to present ***any*** argument under the correct construction of

"calculated." Pet., 49-50; *supra* §V.C. And thus Petitioners failed for this additional reason to show that those claims are disclosed by Vallejo.

Incubating. Petitioners failed to present any argument with respect to purported disclosure of the "incubating" limitation required in claims 1, 10, 16, and 26. While the word "incubating" appeared in the heading to Petitioners' argument on page 45 of the Petition, it was never actually discussed in that section, and because it is required in every independent claim (and thus every dependent claim) Petitioners' failure to address it and demonstrate how it is argued to be disclosed in Vallejo is fatal to their anticipation and obviousness arguments relying on Vallejo (Grounds 1, 7) for *every claim*.

2. Petitioners Have Not Shown A Reasonable Likelihood Of Success In Establishing That Claims 5, 6, 20, And 21 Are Obvious Over Vallejo In View Of Hevehan

Petitioners failed to address and account for important affirmative teachings in Vallejo when attempting to argue there is a motivation to combine Vallejo and Hevehan. Pet., 76 (citing to EX1038, ¶45). For example, Petitioners simply ignored Vallejo's teaching that "in case of rh-BMP-2, *the pH and not the ratio of GSH:GSSG [redox reagents] is the critical variable* for optimum renaturation." EX1038, [0045]. But this teaching of Vallejo is at odds with the teachings of Hevehan that Petitioners argue should be combined with Vallejo's: Hevehan teaches that, rather than optimizing pH (as Vallejo teaches) or even redox reagents,

it is instead the *concentration of denaturants* whose optimizing is the "most effective" at improving yields. EX1024, 8. Petitioners further ignore that Vallejo teaches that "*[n]o renaturation was observed up to a pH of 8,*"EX1038, [0045], whereas Hevehan's experiments were performed *at a pH of 8*. EX1024, 2, 3. But Petitioners never offered any explanation why POSITA would combine these two teachings to begin with (in light of the clear tensions of their teachings regarding, *e.g.*, pH), and would then ignore *both* Hevehan's teaching of optimizing the concentration of denaturants *and* Vallejo's teaching of optimizing pH and eliminating salt, and, instead, optimize thiol-pair buffer strength as claimed in the '287 but disclosed in *neither* Vallejo nor Hevehan. Petitioners thus failed to reconcile the teachings of Vallejo and Hevehan and explain why POSITA would ignore these explicit teachings of Vallejo and be motivated to combine Vallejo with Hevehan such that "thiol-pair buffer strength is increased proportionally to an increase in a total protein concentration," as claimed. Petitioners further failed to explain why POSITA would have a reasonable expectation of success in this combination—another failure fatal to this obviousness argument. *See, e.g.*, *Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367-68 (Fed. Cir. 2016) (affirming Board's finding of non-obviousness, and noting "two different legal concepts" required for obviousness: (1) reasonable expectation of success and (2) motivation to combine); *Amgen, Inc. v. Chugai Pharm. Co.*, 927

F.2d 1200, 1208-09 (Fed. Cir. 1991) (affirming finding of non-obviousness, and stating reasonable expectation of success needed even if invention was otherwise obvious to try); *Johnson Matthey Inc. v. BASF Corp.*, IPR2015-01267, Pap. 35, 30 (Nov. 30, 2016) (finding no reasonable expectation of success, noting prior art "simply provid[ed] incentive 'to explore a new technology or general approach that seemed to be a promising field of experimentation'").

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

1. Petitioners Have Not Shown A Reasonable Likelihood Of Success In Establishing That Claims 1-4, 8-19, And 23-30 Are Anticipated By Schlegl

Non-Mammalian Expression System. All of the claims require that the protein be expressed in a *non-mammalian* system, but Petitioners failed to address the system in which Schlegl's model protein is expressed. In the example Petitioners rely on for their anticipation argument, Schlegl discusses decreasing protein aggregation using a model protein, ***bovine*** α-lactalbumin, EX1007, [0073], but the Petition failed to address whether this protein's expression system is non-mammalian, *see* Pet., 53. Assuming Schlegl's bovine α-lactalbumin had been obtained from its natural source, it would not be made in a non-mammalian expression system, since a cow is a mammal. Thus, Schlegl did not refold a protein that initially started out as misfolded, aggregated protein in an inclusion

body, and does not disclose refolding proteins expressed in a non-mammalian expression system.

Thiol-Pair Ratio and Thiol-Pair Buffer Strength. The Petition also failed to address how the presence of DTT in Schlegl would impact any calculations of thiol-pair ratio and thiol-pair buffer strength. Pet., 56; EX1002, ¶122. Schlegl uses DTT when alpha-LA is denatured and reduced. EX1007, [0074]. This denatured and reduced protein is then added to the renaturation buffer containing cysteine and cystine. EX1007, [0075]. Even though Petitioners and their expert purport to account for the presence of DTT in their thiol-pair ratio and thiol-pair buffer strength calculations when analyzing a different reference, Hevehan, *see* Pet., 78; EX1002, ¶190, Petitioners and their expert (without explanation) did not take DTT into account in purporting to determine Schlegl's thiol-pair ratio and thiol-pair buffer strength. Petitioners articulated no basis for ignoring the DTT in Schlegl while accounting for it in Hevehan, and—as their own Hevehan arguments evidence—their calculations of thiol-pair ratio and thiol-pair buffer strength are incomplete for at least this reason, and cannot be relied on to carry their burden.

Proteins. Petitioners failed to address where Schlegl discloses "contacting ***proteins*** with a preparation" (independent claims 1 and 10, and their dependent claims) or "preparing a solution comprising: the ***proteins***" (independent claims 16 and 26, and their dependent claims). Petitioners assert that the "[e]xample in

Schlegl discloses contacting the bovine α-lactalbumin [(a single "model protein")] with a buffer containing Tris-HCl, cysteine, and cystine." Pet., 53. But the claims of the '287 require "proteins" (plural).[18] The "model protein" bovine α-lactalbumin used in Schlegl's example was not reported to be expressed, for example, as an inclusion body, which would contain not only the desired protein but also other, contaminating proteins, *see* EX1002 ¶46. Instead, Schlegl reports starting with only a single model protein that is presumably not in the presence of any other proteins. EX1007, [0073]. With no discussion of, much less demonstration that, Schlegl's process disclosing the "protein**s**" requirement of all the claims, Petitioners failed to establish that they will prevail with Schlegl as either a §102 or §103 reference.

Petitioners mixed-and-matched Schlegl's liquids. Further, Petitioners glossed over Schlegl's teaching of two different types of buffers—a "refolding buffer" and a "renaturation buffer"—and used them interchangeably in attempting

---

[18] The '287 claims' use of the plural "proteins" is one of the ways the '287 claims differ from the claims of the related '138. *Compare, e.g.*, EX1001, claim 1 ("contacting the proteins"), *with* EX1004 ("contacting the protein"). Petitioners do not address this difference.

to map them on the claimed preparation and solution. *Compare* EX1007, ¶74 *with* EX1007, ¶75; Pet., 5553-56. In Schlegl's only example, the refolding buffer is used to denature the protein (¶74), and the renaturation buffer is used to renature or refold the protein (¶75). In order to show the claimed preparation (claims 1, 10) and solution (claims 16, 26), Petitioners alleged that POSITA would understand that cysteine and cystine are added to Schlegl's refolding buffer to "serve as the redox system or redox component." Pet., 55-56. But, Schlegl teaches that cysteine and cystine are in the renaturation buffer, and not in the refolding buffer. EX1007, ¶75. Petitioners failed to explain why POSITA would add cysteine and cystine to the refolding buffer when Schlegl uses its refolding buffer to denature the proteins and not to refold them. Moreover, Petitioners purport that Schlegl's "redox component has a thiol-pair ratio of 2," Pet., 56, and then summarily assert that "Schlegl discloses a thiol-pair ratio within the range of 0.001-100," *id.* But Petitioners provide no explanation as to the relevance of the thiol-pair ratio of Schlegl's "redox component," nor what the claimed "solution" or "preparation" are in Schlegl, nor why the thiol-pair ratio of a "solution" or "preparation" in Schlegl is within the claimed range. Additionally, the protein concentration in Schlegl's renaturation buffer is 0.516 mg/ml (EX1007, ¶75), which is outside the range recited in the dependent claims, and Petitioners' arguments thus fail for this reason, as well.

Thiol-pair buffer strength to maintain the solubility of the preparation/solution. As with their arguments concerning Vallejo, Petitioners failed to show that the thiol-pair buffer strength "maintains the solubility of the preparation" (claims 1 and 10) or the "solution" (claims 16 and 26). Pet., 56. Petitioners pointed to no explicit teaching in Schlegl regarding the solubility of any solutes in any preparation or solution. Moreover, even assuming, *arguendo*, that Petitioners' construction of "wherein the thiol-pair buffer strength maintains the solubility of the preparation" is correct (it is not, *see infra* §IX), and that the focus of the claim is the solubility of the protein only, Petitioners said only that the "result" of protein folding in Schlegl "***would not be possible unless*** the redox components maintained the solubility of the protein while the protein refolded." Pet., 56. Again, this apparent argument about ***inherency*** (though not identified as inherency in the Petition) is not sufficiently supported, as Petitioners again provided no explanation as to why protein refolding ***necessarily*** (and thus inherently) requires that the solubility be "maintained," and Petitioners' expert merely repeated verbatim the same one-sentence assertion from the Petition. *See* EX1002, ¶123; *see supra* §VII.B.1. Here, Petitioners also failed to square their assertion that the refolding ***would not be "possible" without*** the redox components with the fact that ***Schlegl itself teaches that an alpha-LA protein is capable of refolding without redox chemicals***. *See* Pet., 51.

Calculated. As with their arguments regarding Vallejo, Petitioners failed to present ***any*** argument under the correct construction of "calculated" for claims 8, 9, 14, 15, 23, 24, 25, 30. Pet., 49-50; *see supra* §VII.B.1. And thus Petitioners failed to show that those claims are disclosed by Schlegl.

2. Petitioners Have Not Shown A Reasonable Likelihood Of Success In Establishing That Claims 7 And 22 Are Unpatentable Over Schlegl In View Of Vallejo

Claims 7 and 22 depend from independent claims 1 and 16, respectively. In addition to the shortcomings described above, including those for claims 1 and 16, Petitioners' cursory obviousness analysis is also insufficient. *Facebook, Inc. v. Uniloc USA, Inc.*, IPR2017-01523, Pap. 7, 15-19 (Dec. 4, 2017) (denying institution because Board "will not, and cannot, piece together Petitioner's inconsistent and contradictory arguments into a cogent and coherent explanation"). Petitioners failed to explain what they argue is lacking in Schlegl's disclosures and why POSITA would look to the teachings of Vallejo to fill any such gap in Schlegl. For example, Petitioners alleged that POSITA would have combined the teachings of Schlegl and Vallejo because they both teach using batch methods to refold proteins, Pet., 60, but Petitioners omitted Schlegl's teaching that "[b]atch dilution has many *disadvantages*." EX1007, [0017], [0018]. As an initial matter, Petitioners do not specify whether they are relying on Schlegl's or Vallejo's method for refolding Vallejo's complex protein. If relying on Schlegl's method,

Petitioners failed to explain why, in light of Schlegl's teachings, POSITA would use Schlegl's batch method with Vallejo's complex protein and have a reasonable expectation of success. EX1038, [0001]. If, instead, Petitioners are arguing that POSITA would use Vallejo's method to refold Vallejo's complex protein, then Petitioners did not explain what in Schlegl POSITA would rely on for disclosure of the combination of Schlegl and Vallejo. *Cf.* Pet., 60 (Vallejo "indicates that *its* method can be used to refold a number of other complex molecules"). Petitioner's vaguely and inconsistently defined combination of elements is not sufficient to allow for a reasoned analysis of the proposed combination or to allow proper consideration of whether POSITA would have had a reasonable expectation of success in combining the teachings of the prior art references to arrive at the claimed invention. *See, e.g.*, *10X Genomic, Inc. v. Bio-Rad Labs., Inc.*, IPR2018-00301, Pap. 18, 14-16 (June 15, 2018).

D. Petitioners Fail To Establish That Claims 1-4, 7-19, And 22-30 Are Obvious Over Ruddon In View Of Vallejo (Ground 6)

As an initial matter, Petitioners never explain why Ruddon's refolding process results in "properly refolded" protein. Ruddon discusses a method of refolding ***subunits*** of a specific type of protein, namely glycoprotein hormones. EX1040, 1. Ruddon's refolding of subunits of protein, however, does not result in the production of a biologically active protein. As stated in Ruddon, the subunits,

instead, must be subsequently assembled into the biologically active dimeric protein. EX1040, 1 ("Unfolded glycoprotein hormone subunits are expressed in procaryotic cells, then re-folded in vitro in a thiol redox buffer *to form* ***assembly-competent subunits***. The subunits *are assembled to produce* ***active hormones***."). Petitioners stated that "[o]ne way a POSA would know whether a protein was properly refolded to its native form would be to determine if it retained the biological activity of the native form of the protein." Pet., 46, 70-71. But the result of Ruddon's refolding process does not result in biologically active protein, and neither Petitioners nor their expert provided any other explanation as to why Ruddon's refolding process results in "properly refolded" protein.

Further, Petitioners failed to explain why POSITA would be motivated to combine Ruddon, which focuses on refolding protein subunits (and specifically glycoprotein hormones) with Vallejo. For each claim limitation, Petitioners cited to disclosures from both Vallejo and Ruddon without explaining what they assert is lacking in Ruddon and why would POSITA look to the teachings of Vallejo to fill that gap. *See, e.g.*, *Feit Electric Co., Inc. v. Philips Lighting North America Corp.*, IPR2018-00790, Pap. 9, 16 (Oct. 10, 2018) (denying institution because petitioner failed to articulate a persuasive explanation for prior art mapping contrary to the requirements of §312(a)(3)); *Dish Network Corp. v. Customedia Tech., LLC*, IPR2017-00936, Pap. 13, 10 (Aug. 24, 2017) (same). In addition to failing to point

out specific modifications to Ruddon, Petitioners failed to explain why POSITA would be motivated to make each such modification. The Petition is also devoid of any discussion of reasonable expectation of success other than a conclusory statement, repeated verbatim by their expert, that the combination would work "because Vallejo explicitly teaches so"—a position that, despite Petitioners' unsupported assertion, does not apply to combinations with teachings from Ruddon that Vallejo never discusses (and that Petitioners have not even specified). Pet., 72; EX1002 ¶174. In other words, an assertion that Vallejo is enabled does not mean that the combination of Ruddon with unspecified teachings of Vallejo is enabled. Petitioners and their expert apparently expect the Board to accept their arguments based on this one conclusory statement, but this does not constitute evidence that could carry Petitioners' burden. *See, e.g.*, *Nintendo Co.*, *Ltd.*, IPR2018-00543, Pap. 7, at 24 (denying institution because the petitioners' "only support [was] a conclusory statement [from their expert] without any evidentiary support, which has no weight"). Petitioners also argued that POSITA would have a motivation to add Vallejo's teachings to Ruddon's in order to produce clinically sufficient quantities, but Ruddon—albeit using an approach different than the claimed method—*already solves that problem*, disclosing (different) methods to produce glycoprotein hormones in quantities sufficient for clinical use. EX1040, 1:11-15. Thus, this argued motivation fails as well. *Arris Int'l PLC v. Sony Corp.*,

IPR2016-00828, Pap. 10, 13-18 (Oct. 7, 2016) (no motivation where prior art already addressed alleged problem/need).

For the same reasons as described in connection with Vallejo and Schlegl, *see supra* §§VII.B.1 and VII.C.1, unarticulated and unsupported inherency arguments that redox components must maintain the solubility of the protein are not sufficient to meet Petitioners burden with respect to Ruddon in light of Vallejo. Pet., 69; EX1002, ¶164. And for same reasons as described above, *see supra* §§V.C, VII.B.1, and VII.C.1, Petitioners' proof regarding "calculated" is lacking for its Ruddon-based combination, as well.

VIII. Petitioners Fail To Address Known Secondary Indicia Of Nonobviousness

Although it is a mandatory part of any obviousness analysis, Petitioners also failed to address known secondary indicia of nonobviousness that are expressly set forth in the '287 specification. Secondary indicia, such as unexpected results and unmet long-felt need, must be considered in any obviousness analysis. *See, e.g.*, *Graham v. John Deere Co. of Kansas City*, 383 S. Ct. 684 (1966) at 17-18 ("[S]econdary considerations . . . give light to the circumstances surrounding the origin of the subject matter sought to be patented."); *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013) ("Objective indicia of nonobviousness play a critical role in the obviousness analysis."); *Transocean Offshore Deepwater*

Drilling, Inc. v. Maersk Drilling USA, Inc., 699 F.3d 1340, 1349 (Fed. Cir. 2012) (quoting *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983)) ("[E]vidence rising out of the so-called 'secondary considerations' must always when present be considered en route to a determination of obviousness."). Moreover, the Board has determined that the failure to address evidence of such indicia at the pre-trial stage is a reason to deny institution. *See Lupin Ltd. v. Vertex Pharm. Inc.*, IPR2015-00405, Pap. 13, 21-22, 26-27 (July 9, 2015). This is particularly true where, as here, Petitioners were aware of but chose not to address known evidence of nonobviousness. *See Merial Ltd. v. Virbac*, IPR2014-01279, Pap. 13, 26-27 (Jan. 22, 2015) (denying institution for, *inter alia*, failure to address known evidence of unexpected results). As the Board has warned, it is "unfair to impose on [Patent Owner] in the first instance the burden of establishing unexpected results in a trial" when a petitioner knew of those unexpected results. *Id.*

Here, as in *Lupin* and *Merial*, significant objective evidence squarely before the Petitioners in the intrinsic record (indeed, in the very words of the '287 itself) affirmatively supports nonobviousness of the Challenged Claims.

Long-Felt but Unmet Need. Prior to the invention of the '287, there was no rationale for selecting redox conditions. *See* EX1001, 3:65-4:6. Indeed, as Petitioners' Hevehan and Schlegl references illustrate, POSITA regularly were

forced to resort to trial-and error. *See* EX2008, 167-168; EX1007, [0036]; EX1024, 5, 6. Thus, there was a need for the rational design of refolding proteins using redox chemicals, specifically, an efficient method that could predictably refold proteins, including at high protein concentrations and for more complex proteins (*e.g.*, multimeric proteins such as antibodies and Fc-protein conjugates) beyond more than just trial and error. *See* EX1001, 3:65-4:30; 6:22-32. With such a method, greater amounts of biologically active proteins could be produced at industrial scale at a given time, saving both time and money.

Unexpected Results. The inventors defined and applied a unique equation for thiol-pair ratio (*i.e.*, $\frac{[reductant]^2}{[oxidant]}$) that accurately reflects the complex redox chemistry of disulfide bond formation in proteins. *See id*. at 4:52-63, 6:46-55. By identifying and applying a relationship not known in the prior art between that unique equation and the redox buffer strength equation (2[oxidant] + [reductant]), the ’287 provides greater predictability in identifying optimal conditions for refolding proteins. *Id*. The novel method disclosed in the ’287 surprisingly and unexpectedly led to a more rational design of refolding recombinant proteins expressed in non-mammalian expression systems, *e.g.*, bacteria. *Id*. at 9:66–10:7. In addition, the ’287 applies to complex proteins (*e.g.*, antibodies, multimeric proteins, and Fc- protein conjugates), which have a large molecular weight or large

number of amino acid residues and have two or more disulfide bonds. *Id.* at 2:25-39, 4:36-51, 6:22-32. Prior to the disclosure of the '287, these proteins could not be refolded at high concentrations "with any meaningful degree of efficiency" on neither a small scale nor an industrial scale. *Id.* at 2:25-39, 4:36-51.

Like the petitioner in *Merial*, Petitioners here were acutely aware of but ignored this evidence of long-felt but unmet need and unexpected results when filing their petition. *Cf. Transocean*, 699 F.3d at 1349 (such evidence "*must* [] be considered"). This failure to perform a required step of any obviousness analysis is yet another basis on which the Board should deny institution on the obviousness ground set forth in the Petition.

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

Petitioners argue that "[s]hould the Board find that the term 'wherein the thiol-pair buffer strength maintains the solubility of the preparation' be interpreted to mean anything other than that the thiol-pair buffer strength maintains the solubility of the proteins, then claims 1-15 are indefinite." Pet., 79-80. Not so. Without any explanation, Petitioners fail to consider that the term "wherein the thiol-pair buffer strength maintains the solubility of the preparation" may mean exactly what it says: that the thiol-pair buffer strength maintains the solubility of

the solutes in the preparation, which include (1) at least one of a denaturant, an aggregation suppressor, and a protein stabilizer; (2) an oxidant; and (3) a reductant.

Petitioners completely ignored the ’287 specification’s teaching that denaturants and reductants should be dissolved in solution. *See* EX1001, 13:12-15 (“The solubilized inclusion bodies are then diluted to achieve reduction of the denaturants and reductants in the solution to a level that allows the protein to refold”). What is more, although they omit any mention of it from their Petition materials, Petitioners and their expert, Dr. Robinson, knew that the thiol-pair buffer strength maintains the solubility of (at least) the oxidants and reductants in the preparation or solution. For example, Dr. Robinson testified at her April 2016 deposition in the Florida litigation (in which the related ’138 was asserted against Petitioners Apotex Inc. and Apotex Corp.) about the desirability of the ***redox chemicals (oxidants and reductants)*** to remain soluble in a refold buffer:

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

EX2019, 312-314. Dr. Robinson was also asked why the specification of the ’138 (which is the same as that of the ’287) says that the thiol-pair buffer strength is

"effectively bounded at a maximum of 100 millimolar." EX2019, 312-313; EX1004, 3:2-4. Dr. Robinson answered that there is an upper boundary "probably because of the *concentrations of the **chemicals** that you're going to be able to be able to **solubilize*** in a certain amount of volume with a redox component." EX2019, 313. Further, an inventor of the '138 and '287 patents, Dr. Roger Hart, also recognized that the effective boundary mentioned in the '138 specification addresses concerns of the solubility of the redox chemicals. At the trial for the Florida litigation, which Dr. Robinson attended and in which she testified, Dr. Hart testified that if the thiol-pair buffer strength were greater than 100 mM, "nothing adverse would happen," so long as "all components [of the redox component] stayed in solution." EX2020, 142:20-143:4. Indeed, it is well known in the art that certain oxidants, particularly cystine, as Dr. Robinson testified at that same trial, are not very soluble in water. EX2010, 167:8-169:4.

X. Conclusion

Even with this preliminary record, the Petitioners have failed to show that claims 1-9 and 16-25 lack written description support or that claims 1-30 are not enabled (Grounds 1-2), and thus have failed to show that the '287 qualifies for PGR to begin with. Petitioners also failed to identify all RPIs, and thus the Petition is incomplete under §322(a)(2) and should be denied on this basis as well. Additionally, due to failures in both proof and specificity of argument, the

Petitioners failed to show that claims 1-30 are anticipated or rendered obvious in view of Vallejo, Schlegl, Ruddon and Hevehan (Grounds 2-7). The Petitioners also failed to show that claims 1-15 are indefinite (Ground 8). Because the Petition failed to show that there is a reasonable likelihood that the Petitioners will prevail in proving any Challenged Claim is unpatentable, the Petition should be denied in its entirety, and, pursuant to §324, no post-grant review should be instituted. To the extent the Board determines that the Petitioners have met their burden on any subset of these grounds (they have not), post-*SAS*, the Board should use its discretion under §§325(d) and/or 324(a) to deny institution on all grounds because, in light of the evidence and arguments presented in this Petition, requiring the Board and the Patent Owners to bear the wasteful burden and of a trial on all grounds to reach such a subset of grounds would not, *inter alia*, be an efficient use of the Board's limited time and resources.

Respectfully submitted by:

Dated: January 23, 2019

/J. Steven Baughman/
J. Steven Baughman (Reg. No. 47,414)
Paul, Weiss, Rifkind, Wharton & Garrison LLP
2001 K Street, NW
Washington, DC 20006-1047
P: 202-223-7340/F: 202-403-3740
sbaughman@paulweiss.com

Megan Raymond (Reg. No. 72,997)

Catherine Nyarady (Reg. No. 42,042)
Paul, Weiss, Rifkind, Wharton & Garrison LLP
1285 Avenue of the Americas
New York, NY 11019
Telephone: 212-373-3532
Facsimile: 212-492-0532
cnyarady@paulweiss.com

Jennifer Wu (Reg. No. 75,232)

Paul, Weiss, Rifkind, Wharton &
Garrison LLP
2001 K St. NW
Washington, DC 20006
Tel: (202) 223-7300
Fax: (202) 403-3777
mraymond@paulweiss.com

Paul, Weiss, Rifkind, Wharton &
Garrison LLP
1285 Avenue of the Americas
New York, NY 11019
Telephone: 212-373-3640
Facsimile: 212-492-0640
jwu@paulweiss.com

Attorneys For Patent Owners

CERTIFICATE OF WORD COUNT

The undersigned certifies that the foregoing PATENT OWNER'S PRELIMINARY RESPONSE UNDER 37 C.F.R. §42.207 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 17,766 words, excluding the parts of the brief exempted by 37 C.F.R. §42.24(a)(1).

Dated: January 23, 2019

Respectfully Submitted,

By: /Megan Raymond /
Megan Raymond (Reg. No. 72,997)
Paul, Weiss, Rifkind, Wharton & Garrison LLP
2001 K St. NW
Washington, DC 20006
Tel: (202) 223-7300
Fax: (202) 403-3777
mraymond@paulweiss.com

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of PATENT OWNER'S PRELIMINARY RESPONSE UNDER 37 C.F.R. § 42.207 has been served in its entirety by causing the aforementioned document to be electronically mailed to the following attorneys of record for the Petitioner listed below:

Petitioner's Counsel of Record:

Teresa Stanek Rea (Reg. No. 30,427)
Deborah H. Yellin (Reg. No. 45,904)
Shannon Lentz (Reg. No. 65,382)
CROWELL & MORING LLP
Intellectual Property Group
1001 Pennsylvania Avenue, N.W.
Washington, DC 20004-2595
TRea@Crowell.com
DYellin@Crowell.com
SLentz@Crowell.com

Dated: January 23, 2019

Respectfully Submitted,

By: /Sayem Osman/
Sayem Osman