Filed on behalf of: AbbVie Biotechnology Ltd.

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMGEN INC.
Petitioner

v.

ABBVIE BIOTECHNOLOGY LTD.
Patent Owner

Case IPR2015-01517
U.S. Patent No. 8,916,158

PATENT OWNER'S PRELIMINARY RESPONSE

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2001	Simon King, *The Best Selling Drugs of All Time; Humira Joins The Elite*, FORBES (Jan. 28, 2013, 9:58 AM), http://www.forbes.com/sites/simonking/2013/01/28/the-best-selling-drugs-of-all-time-humira-joins-the-elite/print/
2002	*Abbott Laboratories 2003 Annual Report*, Abbott Laboratories (2004)
2003	Luke Timmerman, *Abbott's Humira, the 3rd-in-Class Drug That Toppled Lipitor as No. 1*, XCONOMY (Apr. 16, 2012), http://www.xconomy.com/national/2012/04/16/abbotts-humira-the-3rd-in-class-drug-that-toppled-lipitor-as-no-1/
2004	Marco van de Weert & Theodore W. Randolph, *Chapter 6: Physical Instability of Peptides and Proteins*, *in* PHARMACEUTICAL FORMULATION DEVELOPMENT OF PEPTIDES AND PROTEINS 107 (2012)
2005	Theodore W. Randolph & John F. Carpenter, *Engineering Challenges of Protein Formulations*, 53 AM. INST. CHEM. ENG. J. 1902 (2007)
2006	Branden A. Salinas, et al., *Understanding and Modulating Opalescence and Viscosity in a Monoclonal Antibody Formulation*, 99 J. PHARM. SCIS. 82 (2010)
2007	U.S. Serial No. 13/521,999 (U.S. Pat. No. 8,883,151) (Amgen), Dec. 3, 2013 Office Action Response
2008	Sampathkumar Krishnan, et al., (Amgen) *Chapter 16: Development of Formulations for Therapeutic Monoclonal Antibodies and Fc Fusion Proteins*," *in* FORMULATION AND PROCESS DEVELOPMENT STRATEGIES FOR MANUFACTURING BIOPHARMACEUTICALS 383 (2010)
2009	U.S. Serial No. 14/091,938 (U.S. Pat. No. 8,795,670), Jan. 29, 2014 Office Action
2010	U.S. Serial No. 14/091,661 (U.S. Pat. No. 8,802,100), Jan. 27, 2014 Office Action
2011	U.S. Serial No. 14/091,888 (U.S. Pat. No. 8,802,101), Apr. 16, 2014 Office Action Response
2012	U.S. Serial No. 14/147,287 (U.S. Pat. No. 8,802,102), Apr. 16, 2014 Office Action Response
2013	U.S. Serial No. 14/322,565 (U.S. Pat. No. 8,940,305), Sept. 26, 2014 Office Action Response

EXHIBIT	DESCRIPTION
2014	U.S. Serial No. 13/401,496 (U.S. Pat. No. 8,828,947) (Immunex/Amgen), Apr. 21, 2014 Office Action Response
2015	U.S. Serial No. 11/784,538 (U.S. Pat. No. 7,648,702) (Amgen), July 24, 2009 Office Action Response
2016	U.S. Serial No. 11/437,602 (U.S. Pat. No. 8,858,935) (Amgen), June 25, 2009 Office Action Response
2017	John F. Carpenter, et al., *Chapter 7: Freezing- and Drying-Induced Perturbations of Protein Structure and Mechanisms of Protein Protection by Stabilizing Additives*, *in* FREEZE-DRYING/LYOPHILIZATION OF PHARMACEUTICAL AND BIOLOGICAL PRODUCTS 167 (2d ed. 2004)
2018	Eva Y. Chi, et al., *Physical Stability of Proteins in Aqueous Solution: Mechanism and Driving Forces in Nonnative Protein Aggregation*, 20 PHARM. RES. 1325 (2003)
2019	U.S. Serial No. 11/437,602 (U.S. Pat. No. 8,858,935) (Amgen), June 25, 2009 Declaration by Dr. Grace C. Chu
2020	Emily Ha, et al., *Peroxide Formation in Polysorbate 80 and Protein Stability*, 91 J. PHARM. SCIS. 2252 (2002)
2021	Masako Ohnishi & Hiromichi Sagitani, *The Effect of Nonionic Surfactant Structure on Hemolysis*, 70 J. AM. OIL CHEMISTS' SOC'Y 679 (1993)
2022	"ORTHOCLONE OKT®3 Sterile Solution", PHYSICIANS' DESK REFERENCE, 2498-2502 (56th ed. 2002)
2023	"RITUXAN®", PHYSICIANS' DESK REFERENCE, 1428-1430, 1750-1752 (56th ed. 2002)
2024	"CAMPATH®", PHYSICIANS' DESK REFERENCE, 992-995 (56th ed. 2002)
2025	"REOPRO®", PHYSICIANS' DESK REFERENCE, 1958-1962 (56th ed. 2002)
2026	"WINRHO SDF™", PHYSICIANS' DESK REFERENCE, 2297-2299 (56th ed. 2002)
2027	Douglas D. Banks, et al., (Amgen) *Native-State Solubility and Transfer Free Energy as Predictive Tools for Selecting Excipients to Include in Protein Formulation Development Studies*, 101 J. PHARM. SCIS. 2720 (2012)

EXHIBIT	DESCRIPTION
2028	Andrew Humphreys, *Top 200 Medicines - Special Report*, PHARMALIVE (Aug. 12, 2015), http://www.pharmalive.com/special-report-top-200-medicines/
2029	John F. Carpenter, et al., *Inhibition of Stress-Induced Aggregation of Protein Therapeutics*, 309 METHODS IN ENZYMOLOGY 236 (1999)
2030	Christine C. Lee, et al., *Toward aggregation-resistant antibodies by design*, 31 TRENDS IN BIOTECH. 612 (2013)
2031	Robert G. Hamilton, THE HUMAN IgG SUBCLASSES (2001)
2032	Rajesh Krishnamurthy & Mark C. Manning, *The Stability Factor: Importance in Formulation Development*, 3 CURRENT PHARM. BIOTECH. 361 (2002)
2033	Romain Rouet, et al., *Stability engineering of the human antibody repertoire*, 588 FEBS LETTERS 269 (2014)
2034	Michio Nishida, et al., *Characterization of novel murine anti-CD20 monoclonal antibodies and their comparison to 2B8 and c2B8 (rituximab)*, 31 INT'L. J. ONCOLOGY 29 (2007)
2035	U.S. Serial No. 14/091,938 (U.S. Pat. No. 8,795,670), Apr. 16, 2014 Office Action Response
2036	U.S. Serial No. 14/091,661 (U.S. Pat. No. 8,802,100), Apr. 16, 2014 Office Action Response
2037	U.S. Serial No. 14/091,888 (U.S. Pat. No. 8,802,101), Jan. 28, 2014 Office Action
2038	U.S. Serial No. 14/147,287 (U.S. Pat. No. 8,802,102), Feb. 7, 2014 Office Action
2039	U.S. Serial No. 14/322,565 (U.S. Pat. No. 8,940,305), Sept. 17, 2014 Office Action
2040	Tim J. Kamerzell, et al., *Increasing IgG Concentration Modulates the Conformational Heterogeneity and Bonding Network that Influence Solution Properties*, 113 J. PHYS. CHEM. B 6109 (2009)
2041	"NUTROPIN AQ®", PHYSICIANS' DESK REFERENCE, 1420-1423 (56th ed. 2002)

I. INTRODUCTION

In two petitions (IPR2015-01514 & IPR2015-01517), Amgen (the "Petitioner") seeks *inter partes* review of two AbbVie patents[1] directed to stable liquid aqueous antibody formulations (U.S. Pat. Nos. 8,916,157 ("the '157 patent") and 8,916,158 ("the '158 patent")), alleging that all challenged claims of each are rendered obvious by the same two combinations of prior art. Because the petitions are both substantively and legally defective, they should be denied.

A. Petitioner's Analysis Is Tainted by Hindsight, Overreliance on "Routine" Experimentation, and Conclusory Assertions

First, Petitioner's obviousness arguments depend on impermissible hindsight, as evidenced by the prior art, as well as numerous prior inconsistent statements made by both Petitioner and its Declarant, Dr. Theodore Randolph. Specifically, the Petition depends upon two false premises: (i) that the antibody formulation art in 2002 was routine and predictable, and (ii) that once a stable formulation was discovered for one antibody, a skilled artisan would expect the

[1] The '157 and '158 patents are members of the same patent family and share identical disclosures. Petitioner filed a separate petition on the '157 patent based on identical prior art combinations and a near-identical Declaration. AbbVie's Response to the '158 Petition differs from that of the '157 Petition chiefly in its treatment of the '158 patent's dependent claims 27-30, which recite buffers.

same formulation to stabilize other, completely different antibodies. But these premises are contrary to both the scientific literature and numerous representations that Petitioner made before this Office. As described in Section IV.A.3, prior to filing its petition, Petitioner emphasized that antibody formulation is *not routine* and that one of skill in the art *would not expect* different antibodies to be similarly stable in the same formulation. Likewise, Dr. Randolph repeatedly explained in the scientific literature the complexities of preparing such formulations, and stated that developing stable formulations was simply "not possible" for some proteins. In fact, due to the unpredictability and difficulties associated with inventing stable liquid formulations, Dr. Randolph's publications at the time of AbbVie's invention *taught away* from the preparation of stable liquid antibody formulations, and instead toward lyophilized (freeze-dried) formulations.

The contemporaneous scientific literature—as well as Petitioner's prior representations to this Office and Dr. Randolph's to the scientific community—demonstrate that the Petition's false premises do not reflect the views of a person of ordinary skill in the art ("POSA") at the time of the invention in 2002.[2] At best, the Petition is grounded in hindsight, using the successful teaching of the '158

[2] Petitioner failed to serve evidence of its numerous prior inconsistent positions as required by PTAB rules. *See* 37 C.F.R. § 42.51(b)(1)(iii).

patent as a roadmap through the prior art.

Second, Petitioner does not conduct a proper obviousness analysis for a formulation patent because it: (i) fails to identify a lead or reference composition; and (ii) fails to establish any motivation to combine the cited prior art references with a reasonable expectation of success. Petitioner argues extensively that the claimed elements are found in the prior art (which is true for nearly all inventions), yet fails to establish why a POSA at the time of the invention would have selected the proposed combinations or expected them to result in stable liquid formulations as claimed in the '158 patent.

Third, while purporting to rely on only two pairs of references, Petitioner attempts to fill gaps in its prior art combinations by citing broadly to dozens of additional references. But conclusory statements about "routine experimentation" and non-specific allusions to numerous prior art references cannot overcome deficiencies in the primary combination. In short, Petitioner fails to establish the core aspects of the obviousness inquiry.

B. The Petition Is Particularly Deficient with Respect to at Least Dependent Claims 3, 15, 24, and 26

The Petition is particularly deficient with regard to at least two sets of dependent claims. First, claims 3 and 26 recite a stable liquid formulation of a

D2E7[3] antibody with a concentration of 50 mg/ml, but Petitioner fails to carry its burden to establish any teaching or suggestion in the art that would cause the skilled artisan to reasonably expect to successfully arrive at a concentration as high as 50 mg/ml merely by applying an existing formulation for a different antibody to D2E7. The Lam reference and other art cited by Petitioner actually *teach away* from such a high concentration. While Lam included an example of a single antibody (not D2E7) formulated at 40 mg/ml, it also expressly advised that a lower concentration might be needed to reduce protein aggregation. And Dr. Randolph's own table of then-existing commercial antibody formulations illustrates why a skilled artisan would not have expected success in applying that Lam formulation to other antibodies, much less at a still higher concentration: All of the commercial liquid antibody formulations available at the time had a concentration between 1 and 10 mg/ml, *i.e.*, between 1/5 and 1/50 of the claimed concentrations. Simply put, there was no teaching or suggestion in the art to quintuple (or more) these commercial antibody concentrations to 50 mg/ml in a liquid formulation for a D2E7 antibody, nor was there any reasonable expectation of successfully doing so.

Second, dependent claims 15 and 24 recite a pH between 4.8 and 5.5.

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[3] As used in this paper, D2E7 refers to a human IgG1 anti-TNFα antibody with the V_L and V_H regions of D2E7.

Although Petitioner tries to establish that prior art antibody formulations had a pH within the range of the independent claims (*i.e.*, 4.0 to 8.0), that same evidence reveals that those formulations were well above the 4.8 to 5.5 pH range recited by claims 15 and 24. Here again, while the Lam reference exemplified formulations of certain antibodies at pH 5.0, Petitioner's own evidence *teaches away* from any expectation that such a pH would work for a different antibody. All the commercially available antibodies instead pointed toward the need for higher pH. Thus, Petitioner fails to present meaningful evidence that addresses the specific limitations found in dependent claims 3, 15, 24, and 26.

C. Petitioner's Arguments Were Overcome by the Patentee During Prosecution, and the Petition Adds Nothing More

All four of the references relied upon in Grounds 1 and 2 were already considered during prosecution of the '158 and its parent patents. All four are listed on the face of the '158 patent, and the Examiner considered virtually the *same arguments* involving the *same references* during prosecution of parent and grand-parent patents. In fact, the only new material this Petition adds is the Declaration of Dr. Randolph—which deserves no weight because it contradicts numerous prior statements by Petitioner and Dr. Randolph and advances arguments and references not properly set forth in the Petition.

D. The Petition's Violation of PTAB Rules Supports Denial of Institution

Amgen's petition should be denied for violating any of four separate provisions: 37 C.F.R. §§ 42.104(b)(2), 42.22(a)(2), 42.6(a)(3) and 42.24(a)(1)(i). In particular, the Petition violates the Board's requirement to (i) identify specific references relied upon for each ground (37 C.F.R. § 42.104(b)(2)); and (ii) include a full statement of the reasons for the relief requested, including a detailed explanation of the significance of the evidence (37 C.F.R. § 42.22(a)(2)). Attempting to fill gaps left by the four references enumerated in Grounds 1 and 2, the Petition makes numerous conclusory statements, citing large portions of Dr. Randolph's 150-page Declaration—which refers through convoluted internal cross-referencing and nested arguments to dozens of additional references. This extensive reliance on Dr. Randolph's Declaration and its many cited references also amounts to an improper incorporation by reference (37 C.F.R. § 42.6(a)(3)) and a violation of the Board's strict 60-page limit (37 C.F.R. § 42.24(a)(1)(i)). Petitioner's violations of these rules alone mandate denial of institution.

II. LEVEL OF ORDINARY SKILL IN THE ART AND CLAIM CONSTRUCTION

A. Level of Ordinary Skill in the Art

For the limited purpose of this Preliminary Response, Patent Owner deems it unnecessary to contest at this time the level of ordinary skill in the art. Pet. at 7-8.

B. Claim Construction

Petitioner's claim construction positions are unreasonably broad even under the "broadest reasonable interpretation" standard applicable to these proceedings, (*see In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1279 (Fed. Cir. 2015)), leading to an improper and unrealistic assessment of obviousness. To the extent Dr. Randolph's opinions and Petitioner's arguments are grounded in these constructions, they are further flawed.

1. *"stable"*

The term "stable" is explicitly defined in the specification of the '158 patent:

> A "stable" formulation is one in which the antibody therein essentially retains its physical stability and/or chemical stability and/or biological activity upon storage.

Ex. 1001 ('158 patent) at 7:23-25. Given the practical realities of therapeutic antibodies, a POSA would have understood that a formulation would need to be stable for storage and use, and, as Dr. Randolph concedes, that "formulations intended as commercial products needed to be robust enough to withstand shipping stress and long term storage." Ex. 1002 at ¶ 47. For example, the '158 patent describes the "invention" as "a liquid aqueous pharmaceutical formulation … having a shelf life of at least 18 months" (Ex. 1001 at 3:18-22) or "with an extended shelf life." *Id*. at 3:10-11; *see also id*. at Abstract. "Stable" is properly read in the context of the "pharmaceutical formulation" to which it applies. As

explained in the '158 patent, "the term 'pharmaceutical formulation' refers to preparations which are in such form as to permit the biological activity of the active ingredients to be unequivocally effective, and which contain no additional components which are significantly toxic to [] subjects . . . ." *Id*. at 7:14-18.

Nonetheless, Petitioner proposes an illogical construction of a "stable" formulation as one "that retains its physical stability *and/or* chemical stability *and/or* biological stability upon storage" and "*for any period of time, no matter how short*." Pet. at 11 (emphasis added).[4] In other words, Petitioner attempts to define "stable" to encompass formulations stable either chemically *or* physically *or* biologically, and then only for a fraction of a second—which is to say, not stable at all. This not only contradicts arguments Petitioner made in the Petition, (*see* Pet. at 21 (arguing that a POSA would have been motivated to make a "stable formulation" for long term storage)), but is, even under a "broadest reasonable interpretation" standard, virtually the complete opposite of what a POSA would understand the term to mean in the context of the invention, particularly in view of the "pharmaceutical formulation" claim language and the extensive guidance provided in the specification. *See* Ex. 1001 at 7:23-64.

[4] In this paper, all emphases are added unless otherwise indicated.

2. *"a human IgG1 anti-human Tumor Necrosis Factor alpha (TNFα) antibody, or an antigen-binding portion thereof, . . . wherein the antibody comprises the light chain variable region and the heavy chain variable region of D2E7"*

Petitioner tries to pull itself up by its bootstraps, pressing an unreasonably broad construction that encompasses many antibodies, while arguing that such a construction undermines the contention that different antibodies require different formulations. *See* Pet. at 9-13. In fact, the individual words of this phrase are interrelated and should be construed together to convey their proper meaning—not in isolation as Petitioner has done. *See, e.g.*, *Cadence Pharm., Inc. v. Paddock Labs. Inc.*, 886 F. Supp. 2d 445, 455 (D. Del. 2012). The correct construction is: A human anti-human TNFα antibody of the IgG1 subclass, or an antibody fragment thereof, that retains binding activity against human TNFα and includes the complete light chain variable (V_L) region and the heavy chain variable (V_H) region of the antibody D2E7. While the claim language encompasses antibody fragments that retain binding to TNFα, the claim also specifically recites that the complete V_L and V_H regions of D2E7 are present.

Petitioner's constructions ignore the patent specification and settled antibody science. First, Petitioner's construction of "IgG1…antibody" to mean "immunoglobulin molecules comprised of four polypeptide chains, two heavy (H) chains and two light (L) chains interconnected by disulfide bonds," (Pet. at 9)

completely reads out the recitation of "IgG1." IgG1 is a particular antibody subclass distinct in sequence, physical, and chemical properties from other IgG subclasses and other immunoglobulin classes, and cannot simply be omitted. *See* Ex. 2031 at 7-9.

Next, Petitioner's construction of "antigen-binding portion" to mean "one or more fragments of an antibody that retain the ability to specifically bind to an antigen (e.g., hTNFα)" similarly reads out the requirement that the V_L and V_H regions of D2E7 are present. As a result, Petitioner incorrectly construes this claim to read on "an antibody fragment that can be as small as one CDR (5 to 17 amino acids)." Pet. at 12.

Finally, Petitioner's construction of "wherein the antibody comprises the light chain variable region and the heavy chain variable region of D2E7" as "any antibody that includes one heavy and one light chain variable region that retain the CDR3 sequences of a D2E7 antibody disclosed in the Salfeld patent (Ex. 1005)" (Pet. at 10) again reads out the complete V_L and V_H region sequences of D2E7 recited in the claims. Petitioner appears to rely on a flatly incorrect statement by Dr. Randolph (Ex. 1002 at ¶ 44) that the Salfeld patent only discloses the CDR3 sequence of D2E7. However, Salfeld discloses the *entire* V_L and V_H region sequences, *e.g.*, in SEQ ID Nos. 1 and 2, and in Figs. 1, 2, 7, and 8. Thus, Petitioner's constructions are improper and should be rejected.

III. THE PETITION'S VIOLATION OF PTAB RULES SUPPORTS DENIAL OF INSTITUTION

Amgen's petition should be denied for violating any of four separate provisions: 37 C.F.R. §§ 42.104(b)(2), 42.22(a)(2), 42.6(a)(3) and 42.24(a)(1)(i).

A. The Petition Fails to Identify the Specific Printed Publications and Patents upon Which It Relies

First, the Petition violates 37 C.F.R. § 42.104(b)(2), which requires that "the petition must set forth … a statement of … [t]he specific statutory grounds under 35 U.S.C. 102 or 103 on which the challenge to the claim is based *and the patents or printed publications relied upon for each ground.*" In its stated grounds, the Petition identifies only four references—two for each combination. But in reality, Petitioner sweeps in dozens of other references—styled as the "state of the art"—to fill gaps left by its asserted combinations. For example, for the seemingly simple assertion that there was a motivation to try excipients, Petitioner cites nine paragraphs of Dr. Randolph's Declaration (Pet. at 14-15, citing Ex. 1002 at ¶¶ 53-58, 74-76), which cite 15 more paragraphs (¶¶ 49, 50, 59-71), which in total cite *29 additional references* (Exs. 1011-1039), not including the further nested citations and cross-referencing. *See also* Pet. at 15 (citing Ex. 1002 at ¶¶ 46-49, 59-71 (citing *at least 11 additional references* (Exs. 1011-1017, 1020, 1025-1027), not including the further nested citations and cross-referencing); Pet. at 15-16 (citing

Ex. 1002 at ¶¶ 74-75 (citing *five additional references,* Exs. 1018, 1023, 1037-1039, not including further nested citations and cross-referencing)).

The Board should reject the Petition on this ground alone. *See Boehringer Ingelheim Int'l GmbH v. Biogen Inc.*, No. IPR2015-00418 (P.T.A.B. July 13, 2015), Paper 14 at 17 (denying institution for failure to comply with § 42.104(b)(2) where Petitioner "represents this challenge as based on McNeil alone, yet relies on at least eight additional references to explain why [the asserted claim] would have been obvious over McNeil") (citations omitted); *see also id.* at 31.

B. The Petition Fails to Provide a Detailed Explanation of the Significance of the References upon Which It Relies

Second, these practices also violate 37 C.F.R. § 42.22(a)(2), which requires that the "petition … must include … [a] full statement of the reasons for the relief requested, *including a detailed explanation of the significance of the evidence* including material facts…." The Petition includes numerous conclusory statements, and, under the guise of demonstrating what was "known in the art," relies heavily on large portions of the 150-page Declaration (which itself contains convoluted cross-referencing and nested arguments that obfuscate the supporting evidence, or lack thereof). *See* 77 Fed. Reg. 48,756, 48,763 (Aug. 14, 2012) (Trial Practice Guide) (recommending that parties "focus on concise, well-organized, easy-to-follow arguments supported by readily identifiable evidence of record").

In particular, like the petitioner in *Boehringer*, Petitioner fails to address with specificity where and how the additional references it relies on would suggest attaining the claimed invention with a reasonable expectation of success. For example, Petitioner argues that a POSA "would have reasonably expected" pH values recited in the dependent claims to be effective, and cites to ¶¶ 138-139 of Dr. Randolph's Declaration. Pet. at 40 (citing Ex. 1002 at ¶¶ 138-139). Upon closer review, ¶¶ 138-139 refer through nested citations back to ¶¶ 55-57 (spanning four pages), 59, and 74-76 (spanning 10 pages), which, in turn, cite dozens of exhibits (as well as additional Declaration paragraphs) with no meaningful attempt to show why or how the references would lead to a reasonable expectation of success for formulations of D2E7 at the claimed pH. *See also* Pet. at 14-17 (citing Ex. 1002 at ¶¶ 45-49, 53-79 and at least 24 additional references (Exs. 1011-1018, 1020, 1023, 1025-1035, 1037-1039) not included in main combinations, purportedly to establish an expectation of success); Pet. at 22 (citing Ex. 1002 at ¶¶ 91-92, referring in turn to ¶¶ 66-71, a six-page span that cites six exhibits (Exs. 1011, 1015, 1016, 1020, 1026, 1027) to purportedly show "the many prior examples of success using a surfactant").

C. The Petition Improperly Incorporates by Reference Large Portions of the Randolph Declaration

Petitioner's practice of citing Dr. Randolph's Declaration and thereby the

dozens of references cited therein to support Petitioner's otherwise unsupported conclusory statements (*see, e.g.*, Pet. at 14-17 (citing tables and summaries from Ex. 1002 at ¶¶ 74-76 that incorporate information from 19 additional references)) violates 37 C.F.R. § 42.6(a)(3). *See Cisco Sys., Inc. v. C-Cation Techs., LLC*, No. IPR2014-00454 (P.T.A.B. Aug. 29, 2014), Paper 12 at 8, 9 (informative) (finding that "cit[ing] large portions of another document, without sufficient explanation of those portions, amounts to incorporation by reference" and the "practice of citing the Declaration to support conclusory statements that are not otherwise supported in the Petition also amounts to incorporation by reference"); *see also Apple Inc. v. ContentGuard Holdings, Inc.*, No. IPR2015-00454 (P.T.A.B. July 13, 2015), Paper 9 at 4-9.

D. The Petition Circumvents the 60-Page Limit

Finally, and in the same vein, Petitioner also violates 37 C.F.R. § 42.24(a)(1)(i) because its practice of citing the Declaration—and thereby the dozens of references cited therein—to support otherwise unsupported conclusory statements amounts to an improper incorporation by reference, which serves to effectively circumvent the Board's strict 60-page limit. *See Cisco*, Paper 12 at 9-10 (denying consideration of arguments not made in Petition because "incorporation by reference of numerous arguments from [the] 250-page Declaration into the Petition serves to circumvent the page limits imposed on petitions…while

imposing on our time by asking us to sift through over 250 pages of [the] Declaration to locate the specific arguments corresponding to the numerous paragraphs cited to support Petitioner's assertions"); *see also S.S. Steiner, Inc. v. John I. Haas, Inc.*, No. IPR2014-01490 (P.T.A.B. Mar. 16, 2015), Paper 7 at 16-17 (declining to consider arguments not made in the Petition, *e.g.*, because "in support of a one-sentence contention that there is a reasonable expectation of success…Petitioner cites over 34 pages [and 16 paragraphs of the] Declaration" and the "Declaration itself contains numerous internal cross-references," which amounted to an improper incorporation by reference, circumventing the 60-page limitation).

Petitioner's blatant violations of each of these rules mandates denial of institution. The outcome is especially warranted because, as set forth below, these violations go to the heart of the Petitioner's failure to prove even a reasonable likelihood of obviousness. Petitioner's reliance on numerous extraneous references, and its inability to point out concise statements from the references Dr. Randolph cites to support its arguments, reveal the deep flaws in its obviousness analysis.

IV. THE PETITION FAILS TO DEMONSTRATE A REASONABLE LIKELIHOOD THAT ANY CHALLENGED CLAIM IS UNPATENTABLE

Under 35 U.S.C. § 314(a), an *inter partes* review may not be instituted

"unless the Director determines . . . that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." The Board should deny the Petition and refuse to institute trial because Petitioner failed to provide sufficient evidence to establish a reasonable likelihood that it will prevail as to at least one challenged claim.

A. Background and State of the Art

The '158 patent covers HUMIRA® (hereinafter "HUMIRA"), one of the top selling drugs in the world and one used by hundreds of thousands of patients. Ex. 2028 at 1. When it launched in 2003, HUMIRA was considered a breakthrough in the field of antibody therapeutics, achieving something that no predecessor commercial antibody formulation could, despite the long-felt need. Specifically, HUMIRA was the first stable liquid high concentration antibody formulation for subcutaneous (s.c.) administration to be commercialized.

1. *Despite a long-felt need, no commercial stable high concentration liquid antibody formulations had been successfully developed before HUMIRA*

In 2002, only two types of antibody formulations were commercially available: (i) low concentration liquid formulations, and (ii) lyophilized formulations. The table below is adapted from Dr. Randolph's list of available commercial antibody products (Ex. 1002 at ¶ 74) and identifies liquid and

lyophilized[5] formulations, as well as the concentrations of the liquid formulations.

Table 1. Commercially Available Antibody Formulations (08/16/2002)

Name	Reference	Concentration	Delivery
Liquid Antibody Formulations			
ORTHOCLONE OKT3 (muromonab-CD3) *(anti-CD23)*	Ex. 2022	**1 mg/ml**	i.v.
RITUXAN (rituximab) *(anti-CD20)*	Ex. 2023	**10 mg/ml**	i.v.
REOPRO (abciximab) *(anti-GPIIb/IIIa receptor)*	Ex. 2025	**2 mg/ml**	i.v.
CAMPATH (alemtuzumab) *(anti-CD52)*	Ex. 2024	**10 mg/ml**	i.v.
ZENAPAX (dacilizumab) *(anti-IL2)*	Ex. 1036	**5 mg/ml**	i.v.
Lyophilized Formulations			
REMICADE (infliximab) *(anti-TNFα)*	Ex. 1035	100 mg/vial (powder) **10 mg/ml reconstituted**	i.v.
HERCEPTIN (trastuzumab) *(anti-HER2)*	Ex. 1034	440 mg/vial (powder) **21 mg/ml reconstituted**	i.v.
WINRHO SDF *(gamma globulin)*	Ex. 2026	0.120–1 mg/vial (powder) **0.048–0.240 mg/ml reconstituted**	i.v. or intra-muscular

As shown above, commercially available liquid antibody formulations at the time were provided at a concentration of 10 mg/ml or less. *See* Exs. 1036; 2022-

[5] Antibody concentration in the lyophilized formulations is not relevant because those formulations are not intended to be stable *following reconstitution*.

2025.[6] These low concentration antibody formulations, as well as the lyophilized formulations (once reconstituted), were all administered by intravenous (i.v.) administration—which had numerous drawbacks, as acknowledged by Dr. Randolph. *See* Ex. 1002 at ¶ 51. For example, unlike subcutaneous (s.c.) administration, i.v. administration required patients to go to a clinic, have an i.v. line set up, and then wait (sometimes for hours) for the drug to slowly enter the bloodstream. *Id.*

Although Dr. Randolph argues (using hindsight) that a POSA would pursue high concentration liquid antibody formulations for s.c. administration (Ex. 1002 at ¶¶ 51-52), he ignores the fact that all commercially available liquid antibody formulations in 2002 were exclusively *low concentration* formulations. No one had succeeded in commercializing a formulation like those claimed by AbbVie. The reality at the time was that it was extremely difficult, and sometimes impossible, to make *any* stable liquid aqueous antibody formulations, particularly at the high concentrations needed for the small injection volumes that would support s.c. administration. *See, e.g.*, Ex. 2033 at 271 ("[A] considerable proportion of human

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[6] Even the non-antibody proteins Dr. Randolph cites illustrate this point. Of the eight protein formulations listed, three were lyophilized, and four of the remaining five had a concentration of 10 mg/ml or less. Ex. 1029-1032, 2041.

monoclonal antibody candidates *fail formulation studies*"); Ex. 2005 at 1905 ("Development of these [high concentration antibody] formulations *poses a number of serious obstacles to commercialization*."); Ex. 2029 at 237; Ex. 2030 at 612; Ex. 2006 at 82.

2. *The art at the time taught away from liquid formulations and toward lyophilized formulations*

Recognizing this impracticality, the prior art actually taught away from making liquid formulations and instead toward lyophilization, as reflected in a publication cited by Petitioner and Dr. Randolph:

> Aqueous, ready-to-use solutions are preferable dosage forms for many reasons . . . but *most proteins are not sufficiently stable in solution* to allow practical expiration dating. Therefore, *most protein dosage forms are solid forms* in the commercial package with the solid form being produced by freeze-drying [lyophilization].

Ex. 1016 at 50; *see also* Ex. 1011 at 10, 99-100, 110; Ex. 1014 at 545. In fact, in 2002, Dr. Randolph was also directing formulation scientists toward the development of *lyophilized* formulations:

> [W]ith many proteins*, it is not possible ... to develop sufficiently stable aqueous formulations*. … In contrast, a properly lyophilized formulation can maintain adequate physical and chemical stability of the protein during shipping and long-term storage, even at ambient temperatures. … [D]eveloping stable lyophilized protein formulations should be a rational, straightforward process, which for most proteins

> should be rapid. *With liquid formulation development, it may only be possible to obtain adequate protein stability after lengthy studies.* Furthermore, sometimes there are conflicting conditions (e.g., pH) needed to slow sufficiently multiple degradation pathways in aqueous solution. *Considering these issues plus the fact that formulation scientists now have to deal with numerous proteins and/or variants of a given protein, lyophilization should be considered as a primary mode for product development.*

Ex. 1011 at 109-10 (citations omitted); *see also id.* at 188 ("It can be assumed that *most proteins will not exhibit sufficient stability in aqueous solution to allow a liquid formulation to be developed*. Our understanding of the basic requirements for obtaining a stable *lyophilized* protein formulation is relatively well developed"); Ex. 2017 at 167.

These teachings toward lyophilization by Dr. Randolph (and others) run directly contrary to his current Declaration, which asserts that in 2002 "stable [liquid] formulations of antibodies were common and achievable through routine experimentation." Ex. 1002 at ¶ 52(e). In reality, development of stable liquid antibody formulations, especially those at a concentration high enough to be suitable for s.c. administration, was far from routine. *See, e.g.*, Ex. 2005 at 1906. The available commercial formulations of the day demonstrate the strong preference for lyophilized or, at best, low concentration liquid formulations.

3. *Formulating proteins, particularly antibodies, was (and remains) complicated and unpredictable*

In 2002, the antibody formulation process typically required a large amount of scientific judgment with little guidance or predictability about what might work in a particular circumstance, or whether formulation would work *at all* given that "many proteins" were "not possible" to formulate as a liquid formulation. Ex. 1011 at 109-10. Before setting forth the litigation-inspired positions on display in the Petition and Declaration, both Petitioner and Dr. Randolph consistently acknowledged the complex and unpredictable nature of protein formulation that thwarted efforts to commercialize protein and antibody therapeutics. *See, e.g.*, *Endo Pharm. Inc. v. Depomed, Inc.*, No. IPR2014-00654 (P.T.A.B. Sept. 21, 2015), Paper 69 at 25 (discrediting expert testimony in view of contradictory statements by Petitioner's expert that formulating a reliable dosage form was "very difficult"). As of 2002, this unpredictability stemmed from at least the two factors discussed below.

a. First, many possible components and combinations existed with no direction as to which would be successful

One of the many complexities of protein formulation involved the large number of possible permutations of the various components, concentrations, and physical parameters (*e.g.*, viscosity, opalescence, aggregation, antibody amino acid sequence, pH, buffer, preservatives, and so on). *See, e.g.*, Ex. 1017 at 178 ("In the

development of a protein formulation, the most challenging task is the stabilization of a protein to achieve an acceptable shelf life. . . . [T]here is no single pathway to follow in selection of a suitable stabilizer(s), partly due to the lack of a clear and definitive understanding of protein-cosolute interactions and proteins' multiple inactivation mechanisms."); *id.* at 164-167; Ex. 1013 at 307. Petitioner repeatedly admitted this fact in pursuit of its own patents at the PTO. For example, during prosecution of U.S. Pat. No. 8,883,151[7], an antibody formulation patent, Petitioner argued that as of 2010—eight years after the '158 patent's earliest claimed priority date—an "endless number" of possible formulation options existed:

> At the time the invention was made, *one of skill in the art would be faced with, for all practical purposes, an endless number of possible formulations given all the permutations of the various components, concentrations of components, and physical parameters* (monoclonal antibody sequence, pH, viscosity, etc.). The *number of possible options are not finite or known*, as required by law, and therefore it is not "obvious to try" and invariably and predictably arrive at the claimed invention.

Ex. 2007 at 7 (citation omitted); Ex. 2027 at 2720-21 (Petitioner stating that in 2012 "exploring" various solvent conditions for protein formulations is a "tedious and time-consuming process," requiring "large and cumbersome studies");

[7] U.S. Pat. No. 8,883,151, claiming priority to January 15, 2010.

Ex. 1017 at 178 ("there is no single pathway to follow in selection of suitable stabilizers…[, and] research activities directed toward a general solution to protein instability will continue for at least a few decades").

Likewise, in 2007—five years after the date of the challenged invention—Dr. Randolph noted that the plethora of formulation components available yielded "far too many possible sets of formulations to allow a purely empirical screening approach to be successful." Ex. 2005 at 1902; Ex. 1009 at 1554 (explaining that a wide variety of excipients in FDA approved formulations "provid[ed] the formulation developer with a huge number of possible excipient combinations").

Choosing among numerous potential formulation components was made more difficult because there were many reasons why a protein might be unstable, and different components would address different types of instability. As Dr. Randolph described the problem: "[I]t was well known that protein molecules were prone to physical and chemical degradation in solution (*e.g.*, denaturation, aggregation, fragmentation, isomerization, deamidation, oxidation, disulfide scrambling, oligomerization and cross-linking)." (Ex. 1002 at ¶ 46); *see also* Ex. 1017 at 177-178; 1011 at 13. And different antibodies have different degradation profiles. *See, e.g.*, Ex. 2008 at 386; Ex. 2033 at 270; *see also* Ex. 1011 at 185-186; Ex. 2015 at 8; Ex. 2007 at 8-9. The large number of potential problems and even larger number of potential avenues to address them further diminished the already

low expectation of success for making stable liquid formulations. *See, e.g.*, Ex. 1013 at 307; Ex. 1017 at 164-167, 178. Accordingly, mere routine experimentation was not a viable avenue for obtaining new stable liquid antibody formulations of the type claimed in the '158 patent.

b. Second, a stable formulation of one antibody could not be expected to work for a different antibody

Numerous scientific publications at the time—as well as Petitioner's (and Dr. Randolph's) own prior admissions—acknowledged that a major problem in the field was determining which of the many potential excipients would yield a stable liquid protein formulation. No such problem would have existed if new proteins, such as novel antibodies, could simply be added to existing formulations with a reasonable probability of success.

In fact, a 1999 review article by Wang described achieving acceptable stability as "the most formidable challenge in formulating a liquid protein pharmaceutical." Ex. 1017 ("Wang") at 178; *id.* at 130 ("Very often, proteins have to be evaluated individually and stabilized on a trial-and-error basis."); Ex. 2032 at 365 ("[A] comprehensive strategy to achieve stable liquid formulations has not yet emerged."). Both Petitioner and Dr. Randolph also wrote about the unpredictability and difficulty of making stable aqueous protein formulations. For example, during

prosecution of U.S. Pat. No. 7,648,702,[8] Petitioner argued the unpredictability of the protein formulation art in 2002, relying on Wang:

> *The [a]rt is [u]npredictable. . . . [O]ptimization of stable liquid pharmaceutical compositions of polypeptides is not routine. . . . Different proteins have different characteristics that affect their stability, folding, solvent interaction, hydrophobicity, and degradation pathways*. … Wang [at 130] explains that "the structural differences among different proteins are so significant that generalization of universal stabilization strategies has not been successful." . . . Wang concludes by stating that "…*Unfortunately, there is no single pathway to follow in formulating such a product.*" Wang [at 178].

Ex. 2015 at 8. In the same Office Action Response, Petitioner further argued that because different antibodies behave unpredictably in solution, teachings relating to one antibody cannot be transferred to another with a reasonable expectation of success:

> The declaratory evidence submitted herewith further supports the *lack of reasonable expectation of success in reaching a stable aqueous formulation*. In particular, [inventor] *Dr. Remmele opines that simply because an excipient stabilizes one protein, does not predict that it will stabilize another*. Dr. Remmele points to additional support in the literature, where even antibodies, which as a class can share distinct

[8] U.S. Pat. No. 7,648,702, claiming priority to February 27, 2002.

> structural similarities will respond differently in solution…. *Accordingly, even proteins from the same class, antibodies, respond differently and unpredictably to formulation in solution.*

Id.; Ex. 2014 at 6 (during prosecution of related family member, U.S. Pat. No. 8,828,947, Petitioner argued that, in 2002, "the teaching relating to one protein cannot simply be transferred to another protein") (citing Wang at 178);[9] Ex. 1017 at 130 ("[v]ery often, proteins have to be evaluated individually and stabilized on a trial-and-error basis").

Likewise, during prosecution of another of its antibody patents, U.S. Pat. No. 8,858,935,[10] Petitioner argued:

> [A]rt disclosing results with other antibodies is not particularly

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[9] Notwithstanding its repeated prior reliance on Wang to demonstrate the complexity and unpredictability of protein formulation, Petitioner now asserts the opposite: that this very same Wang reference "actually provides guidance" about excipients and optimization. Pet. at 28. Petitioner's new characterization of protein formulation development as "routine" (Pet. at 30) or "not a complex process" (Pet. at 28) is, however, contradicted by the teachings of Wang, as Petitioner understood the Wang reference when it prosecuted its own patents.

[10] U.S. Pat. No. 8,858,935, claiming priority to May 19, 2005.

> relevant since, as the inventor states in the attached declaration [by inventor Grace C. Chu, Ph.D.], *one of skill in the art [in 2005] would not necessarily expect different antibodies to be similarly stable in a particular formulation*.

Ex. 2016 at 15 (citation omitted); *see also* Ex. 2019 at 1 (Chu Declaration in support of Petitioner's '935 patent). Petitioner states the same in its publications. Ex. 2008 at 386 ("Exposed surface residues of each antibody are unique and require specific formulation excipients to provide maximal stability . . .").

Further, as recently as 2012, Dr. Randolph acknowledged that protein folding and physical instability remain "complex phenomena," such that "*[e]ven minor differences in amino acid sequence or posttranslational modification may result in significantly different physical instability*." Ex. 2004 at 125; *see also* Ex. 2018 at 1326; Ex. 2029 at 244; Ex. 2030 at 613; Ex. 2033 at 270.

Thus, the state of the protein formulation art in 2002 was complex and unpredictable.[11] Although this fact is shown by the scientific literature of the time

[11] Petitioner argues that data presented in 2009 during the prosecution of a European counterpart to the '158 patent (Ex. 1054) demonstrates the general applicability of the claimed formulations to different antibodies. Pet. at 51. Petitioner's argument is fundamentally flawed because a POSA in 2002 would have no way of knowing or predicting later results.

and was repeatedly acknowledged by Petitioner and Dr. Randolph in prior PTO proceedings and scientific publications, they now assert the opposite. These newly adopted positions reflect a litigation-inspired hindsight analysis, and thus should be accorded no weight.

4. *AbbVie invented a stable, high concentration liquid antibody formulation*

Notwithstanding the complexities and unpredictability of the formulation art, AbbVie was the first to invent and commercialize a stable liquid high concentration antibody formulation for s.c. administration. This formulation comprises a D2E7 antibody and is sold as HUMIRA, one of the best selling drugs of all time and a highly successful treatment for rheumatoid arthritis and other inflammatory conditions. *See* Ex. 1041 at 187; *see also* Exs. 2001 at 3, 2002 at 15, 2028 at 1-2. That success was driven in large part by (i) the ability of patients to self-administer a liquid antibody formulation via s.c. administration (*see* Ex. 2003 at 4) without lyophilization and the accompanying need for reconstitution, and (ii) the fact that it is stable enough to be commercially viable (*e.g.*, to withstand shipping and storage for periods of time typical for biologic therapies). In short, HUMIRA was the first of its kind and filled a long-standing patient need for easy self-administration.

B. Petitioner Relies on Impermissible Hindsight to Arrive at the Claimed Invention

Against the backdrop of the state of the art at the time of the '158 patent's invention, it is evident that, for both asserted grounds, Petitioner and Dr. Randolph employ impermissible hindsight and use the challenged claims as a starting point to combine individual elements from the prior art. As but one example, *compare* Pet. at 34 ("Even if the Salfeld patent did not teach the claimed antibody concentration and pH range, the Heavner patent taught that anti-TNFα antibody formulations should have these values") *with* Ex. 1006 ("Heavner") at 31:19-33:47 (bulk disclosure reciting numerous potential pH values, formulation components, and excipients, while providing no specific guidance or actual formulations).

In addition, to bolster its otherwise unsupported assertion that a POSA "would have sought," *e.g.*, a buffer with a particular pH range, tonicity agent, and surfactant (*see, e.g.*, Pet. at 15), Petitioner cites (and attempts to incorporate) multiple paragraphs from Dr. Randolph's Declaration, which repeatedly state that a POSA "would not have been surprised" to find that a certain claimed element would work in a formulation. *See, e.g.*, Ex. 1002 at ¶ 51 ("[A] POSA "would not have been surprised if a new protein (e.g., antibody) formulation *had been formulated for subcutaneous administration*"); *see also id.* at ¶¶ 65 (tonicity agent), 69 (polysorbate), 70(e) (polysorbate 80 at 1 mg/ml), and 159 (0.1 mg/ml

polysorbate 80). But, the phrase "would not have been surprised" is the viewpoint of a person looking backward after an event has happened. This is classic hindsight, rather than a proper forward looking analysis that views the prior art as a whole in 2002 without the benefit of the '158 patent's teachings. In fact, Petitioner's hindsight approach—locating a single claimed formulation element in the prior art, and then asserting that inclusion of the element is "not surprising"—is a lens through which virtually any valid invention would appear obvious.

Dr. Randolph's conclusory proclamations concerning what a POSA allegedly would have understood about individual elements, or "would be encouraged" to do by the cited references are entitled to little or no weight. *See In re Am. Acad. of Sci. Tech Ctr.*, 367 F.3d 1359, 1368 (Fed. Cir. 2004) ("[T]he Board is entitled to weigh the declarations and conclude that the lack of factual corroboration warrants discounting the opinions expressed in the declarations"); *see also, e.g.*, *Apotex Inc. v. Wyeth LLC*, No. IPR2015-00873 (P.T.A.B. Sept. 16, 2015), Paper 8 at 13 (finding an expert's statements unpersuasive because they are not supported by objective evidence or analysis). This is especially so here—where Petitioner's and Dr. Randolph's numerous prior inconsistent statements constitute powerful proof that their newly formed and litigation-inspired positions are hindsight-driven and do not reflect the views of a POSA at the time of the invention. *See* Section IV.A.3.

C. The Challenged Claims Would Not Have Been Obvious over Lam and Barrera (Ground 1)

Petitioner argues that the challenged claims would have been obvious because "[t]he Barrera article reported positive clinical results with a D2E7 formulation, and the Lam patent … taught all the formulation components recited in claim 1." Pet. at 17-18. Petitioner purports to combine Lam and Barrera in two ways: first, arguing that a POSA would have been motivated to add Barrera's D2E7 antibody to "the Lam formulation," (Pet. at 19), and second, arguing that a POSA would have been motivated to select the surfactant and pH from Lam and add them to the Barrera D2E7 formulation. Pet. at 21.

Both arguments fail. A POSA would not have made either combination, much less with a reasonable expectation of success.

Lam's disclosure provides examples of liquid formulations for only two antibodies: an anti-CD18 Fab antibody fragment and an anti-CD20 antibody. *See* Ex. 1003 ("Lam") at 24:29-46:20. Although Lam indicates that the antibodies to be formulated can be directed against any one of a list of *over 100 distinct antigens* (*see id.* at 10:5-63), it does not disclose actual identities or amino acid sequences of such antibodies, much less any formulations specific for them. Most significantly, nowhere does Lam identify D2E7 or formulations thereof.

Barrera discloses an early clinical trial and with a formulation of D2E7 that

is not encompassed by the claims of the '158 patent, as it lacks any surfactant and is silent as to pH. Importantly, nothing in Barrera suggests whether the formulation was stable or unstable or that there was any reason or way to "improve" it, much less by combination with the formulations in Lam.

1. *Petitioner fails to establish a reasonable expectation of success in applying a formulation of Lam to the D2E7 antibody of Barrera (or vice versa)*

A patent claim "is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). The obviousness inquiry requires that a POSA "would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and…would have had a reasonable expectation of success in doing so." *Insite Vision Inc. v. Sandoz, Inc.*, 783 F.3d 853, 859 (Fed. Cir. 2015) (citations omitted). Petitioner offers no specific evidence to show *why* a POSA would expect that adding the D2E7 antibody of Barrera to the formulations in Lam would result in successful stable formulations through so-called "routine" optimization.

Instead, Petitioner merely asserts in a conclusory fashion that a reasonable expectation of success existed "because the Lam patent taught formulations for anti-TNFα antibodies and D2E7 was an anti-TNFα antibody, and because the art *provided guidance on formulating antibodies*." Pet. at 20 (citing Ex. 1002 at ¶¶ 85-

86). But Lam does not disclose *any* actual formulation for an anti-TNFα antibody. To overcome this deficiency, Petitioner asserts that a POSA would be "*motivated to try* excipients used in formulations of *other antibodies and proteins*." Pet. at 14-15. But a mere *motivation to try* without a corresponding reasonable expectation of success is not sufficient to show obviousness. *See, e.g.*, *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009).

Contrary to the hindsight-driven assertions by Petitioner (Pet. at 29-30) and Dr. Randolph (Ex. 1002 at ¶ 85(b)), the contemporaneous scientific literature in 2002 (and Petitioner's prior assertions to this Office) prove that a POSA would *not* have reasonably expected formulations designed for these different antibodies to successfully apply to D2E7. For example, as discussed in Section IV.A, each antibody can have different reasons for instability. One antibody may be sensitive to chemical instability, like oxidation or deamidation, while another may be more prone to aggregation, insolubility, or other mechanisms of protein degradation. *See, e.g.*, Ex. 2008 at 386; Ex. 2033 at 270; Ex. 1011 at 13, 185-186; Ex. 2015 at 8. Moreover, a formulation that prevents chemical breakdown by deamidation of one antibody may not prevent deamidation of a different antibody, which may be more sensitive or unstable for different reasons. *See id.* Thus, a POSA would have no way of knowing whether and to what extent Lam's data on, for instance, oxidation or deamidation of anti-CD18 Fab fragments and anti-CD20 antibodies would apply

to, *e.g.*, D2E7. *See* Ex. 2014 at 6 ("the teaching relating to one protein cannot simply be transferred to another protein"); Ex. 2015 at 8 ("even proteins from the same class, antibodies, respond differently and unpredictably to formulation in solution"); Ex. 1013 at 307; Ex. 1017 at 130, 178; *see also* Section IV.A.3.

The same unpredictability undermines Petitioner's suggestion to combine these references in the other direction—that is, to supplement the formulation in Barrera with selected components from Lam. Although Barrera discloses a D2E7 formulation (one without surfactant and silent as to pH), the Petition fails to establish sufficient motivation as to *why* a POSA would seek to modify that formulation.

Petitioner argues that a POSA would have been motivated to import elements from Lam to improve the stability of the Barrera D2E7 formulation because the Barrera formulation allegedly "did not need to be stored (since it was used for short-term phase I clinical studies)." Pet. at 21 (citing Ex. 1002 at ¶ 88). But Barrera discloses no shortcomings of its formulation, and in any event is silent on stability and storage. Moreover, the fact that a *study* is "short-term" says nothing about whether the *formulation used in the study* is stable during storage. Nonetheless, Petitioner summarily concludes that Barrera discloses a "short-term formulation." Pet. at 20 (citing equally conclusory Ex. 1002 at ¶ 84). Petitioner's contrived reasoning is hindsight-based and cannot supply the requisite motivation.

See Mintz v. Dietz & Watson, Inc., 679 F.3d 1372, 1377 (Fed. Cir. 2012); *see also Mylan Pharm., Inc. v. Gilead Scis., Inc.*, No. IPR2014-00886 (P.T.A.B. Dec. 17, 2014), Paper 15 at 18 (noting that the Board must be "careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention") (citation omitted).

Given the lack of instability data or any perceived problem to be solved, Petitioner offers no credible explanation why a POSA would turn to Lam—much less focus on Lam's pH and surfactant disclosures—to modify Barrera instead of simply looking to one of the dozens of commercial (and other) protein formulations available at the time. *See, e.g.*, Pet. at 14-15 (citing Ex. 1002 at ¶¶ 53-58 and 74-76 (citing Exs. 1028-1035, 1016 at 54-56)). Elsewhere in his Declaration, Dr. Randolph suggests that a POSA would have looked for guidance to the formulation of REMICADE, the only other anti-TNFα antibody on the market at the time, which was lyophilized (and included instructions to begin using it within 3 hours after reconstitution into liquid form). Ex. 1002 at ¶ 74, *see also* Ex. 1035 at 10. While REMICADE was administered intravenously, that is not a distinction from Barrera, which also involved intravenous administration. Ex. 1004 ("Barrera") at 661. Thus the art taught away from the claimed invention or any motivation to combine Lam with Barrera.

Finally, even if a POSA did for some reason look to Lam to make the Barrera formulation more stable, Lam does not disclose that a surfactant (or polysorbate) would increase stability. Lam instead suggests avoiding potential aggregation problems by *reducing protein concentration*. *See* Lam at 22:13-17, 42:64-65.

Notwithstanding, Petitioner asserts that the addition of polysorbate was *not unexpected* because "the most common way to stabilize and prevent aggregation of protein formulations was to add a nonionic surfactant to the formulation, and the most common surfactant used commercially for this purpose was polysorbate 80." Pet. at 46 (citing Ex. 1002 at ¶¶ 68-69). The mere fact that polysorbate 80 was known in the art, however, says nothing about the desirability or motivation to include it in D2E7 formulations. A POSA would have also appreciated that surfactants, such as polysorbates, had numerous, well-known drawbacks. *See, e.g.*, Ex. 1011 at 169 (showing that non-ionic surfactants may have the "opposite effect" and cause aggregation); *id.* at 14-15 (noting that even high grade surfactant may cause stability problems); Ex. 2020 at 2253 (noting oxidative damage effect of peroxides in surfactants); Ex. 2021 at 679 (noting hemolysis effect of surfactants). In fact, one of Petitioner's own references teaches away from using polysorbates (also called "Tweens") in formulations. *See* Ex. 1011 at 15 ("The use of excipients… e.g., Tweens… should be avoided if possible due to the risk

associated with transmissible diseases").

And finally, even if a POSA did wish to apply Lam's polysorbate teachings to D2E7, Petitioner's cited art specifically teaches that surfactant concentrations cannot simply be transferred from one formulation to another because the optimal concentrations of surfactant "depend on the mechanism(s) by which a particular protein is protected from damage by surfactant addition." Ex. 1011 at 170; *see also* Ex. 1013 at 353; Ex. 1016 at 74.

2. *Petitioner fails to identify a lead or reference composition to be modified in Lam*

Highly telling is that Petitioner fails to identify a starting point for its obviousness analysis. In the context of a composition or formulation patent, an obviousness analysis should be based on a "reference composition," similar to an analysis involving a chemical lead compound. *See Unigene Labs., Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1361-62 (Fed. Cir. 2011). After identifying a reference composition, a patent challenger must demonstrate a motivation to modify the reference composition to arrive at the patented invention with a reasonable expectation of success. *See id.* at 1363; *see also In re Omeprazole Patent Litig.*, 536 F.3d 1361, 1380 (Fed. Cir. 2008) (requiring clear and convincing evidence that a POSA would have appreciated the need to combine the teachings of prior art references); *Oxford Nanopore Techs. Ltd. v. Univ. of Wash.*, No. IPR2014-00512

(P.T.A.B. Sept. 15, 2014), Paper 12 at 15-17 (requiring that the Petition set forth detailed reasons why a POSA would be motivated to combine the references).

Here, Petitioner fails to even identify, much less analyze, a reference composition—or to articulate any rational underpinning to support a POSA's motivation to modify it with any expectation of success. Even had one chosen the anti-CD18 Fab antibody fragments or anti-CD20 antibodies of Lam as a putative reference composition, any obviousness argument would be unavailing because those antibodies are humanized or chimeric antibodies[12] that bind to different antigens and have different amino acid sequences, *e.g.*, in their V_L and V_H regions compared with the fully human D2E7 antibody. Lam offers no information about how its formulations designed for anti-CD18 Fab antibody fragments or anti-CD20 antibodies could be adapted to stably formulate any other particular antibody, and certainly not D2E7.

Instead of identifying a lead formulation, Petitioner offers the conclusory statement that Lam discloses every feature "except the particular anti-TNFα antibody, D2E7," (Pet. at 19 (citing equally conclusory Ex. 1002 at ¶ 83)), offering

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[12] While defined as "humanized," the anti-CD20 antibody in Lam is identified as C2B8, (Lam at 44:24, 27, 67), a laboratory name for the chimeric antibody rituximab. *See, e.g.*, Ex. 2034 at 30.

no specifics about why a POSA would select the TNFα antigen from Lam's list of *over 100 possibilities*. *See* Lam at 9:64-10:63. According to the Petition, a POSA would at this point be led to D2E7 because Barrera "reports positive results with a clinical formulation." Pet. at 19 (citing Ex. 1002 at ¶ 84). But REMICADE was already approved. Ex. 1035. And even if a POSA did wish to formulate D2E7, Petitioner does not explain which Lam formulation would be the starting point or why that particular formulation would be expected to stably formulate D2E7.

3. *Petitioner's recourse to "routine experimentation" cannot support its obviousness argument*

Having failed to explain how a specific formulation from Lam would be expected to stably formulate D2E7 from Barrera (or *vice versa*), Petitioner cannot excuse the infirmities in its position by conclusory references to so-called "routine" optimization. *See, e.g.*, Pet. at 21-22, 28-31 (citing Ex. 1002 at ¶¶ 74, 89, 109, 110, 111). As discussed in Section IV.A, Petitioner's own prior statements and the scientific literature, including publications by Dr. Randolph, demonstrate that a POSA in 2002 could not have developed a new stable formulation for a particular antibody by mere routine experimentation based on existing formulations and ingredients. Too many choices and potential pitfalls existed for such an approach to be viable. Petitioner tries to fill in this gap by (improperly) incorporating by reference vast numbers of additional pages of the Randolph Declaration, which, in

turn, cite dozens of additional references. Pet. at 14-16; *see also* Section III. But even these references cannot bridge that gap because, like Lam, they offer no scientific basis from which a POSA could have reasonably expected to succeed in making a formulation of D2E7 within the scope of the patent claims.

4. *The dependent claims are nonobvious over Lam and Barrera*

Beyond the deficiencies in the Petition as a whole, Petitioner further fails in its attack on the challenged dependent claims. Petitioner barely addresses the additional elements in the dependent claims and is especially deficient in regard to dependent claims 3, 15, 24, and 26, as set forth below.

a. The Petition Is Particularly Deficient with Respect to Dependent Claims 3 and 26

Claims 3 and 26 of the '158 patent limit antibody concentration to 50 mg/ml. Petitioner attempts to show that formulations of this concentration were obvious by pointing to a general disclosure in Lam of several broad concentration ranges. Pet. at 23 (citing Lam at 22:10-17). As an initial matter, however, this passage teaches that lower concentrations are preferred ("[f]rom about 0.1 mg/mL to about 50 mg/mL, *preferably from about 0.5 mg/mL to about 25 mg/mL and most preferably from about 2 mg/mL to about 10 mg/mL*"). Further, Petitioner makes no effort to explain why such a broad disclosure would teach a concentration of D2E7 at 50 mg/ml other than to offer the unsupported statement that a POSA "understood that antibodies often had to be formulated at higher concentrations due to … volume

limitations of subcutaneous administration." Pet. at 25 (citing Ex. 1002 at ¶¶ 95-96). While Lam includes an example of an anti-CD20 antibody at a concentration at 40 mg/ml, as discussed in the context of the independent claims, Petitioner does not provide a basis for a POSA to reasonably expect such a formulation to stabilize the D2E7 antibody in Barrera. The art at the time recognized that the higher the antibody concentration, the more difficult it was to make a stable liquid formulation. *See, e.g.*, Ex. 1017 at 152; Ex. 2008 at 405; Ex. 2040 at 6109; Ex. 2007 at 8. Indeed, Petitioner ignores Lam's explicit preference for lower concentrations given that higher concentrations can cause aggregation problems. *See* Lam at 22:13-17, 42:64-65 ("[f]urther reduction in aggregation rate may require a decrease in the protein concentration"). Thus, there was no expectation from Lam and Barrera that a 50 mg/ml stable formulation of D2E7 could be achieved.

Moreover, Petitioner ignores the teaching of the art as a whole, for instance: (i) even if a POSA sought to prepare a 50 mg/ml antibody formulation, the art in 2002 pointed to lyophilization rather than liquid formulation (*see, e.g.*, Ex. 1011 at 109-110); and (ii) preparation of high concentration liquid antibody formulations was particularly complex, as confirmed by numerous pre-litigation statements by Petitioner and Dr. Randolph (*see, e.g.*, Ex. 2005 at 1905; Ex. 2029 at 237), as well as other art in the field (*see, e.g.*, Ex. 2030 at 612; Section IV.A).

Petitioner also omits the fact that Patent Owner AbbVie was the first to successfully develop and commercialize a stable liquid high concentration human antibody formulation at 50 mg/ml (*see* Section IV.A.4), notwithstanding the fact that all commercially available antibody formulations in 2002 were formulated as either low concentration (less than 10 mg/ml) liquid formulations or lyophilized preparations (and therefore not comparable). *See* Ex. 1002 at ¶ 74 (Table 2); *see also* Section IV.A.1.

Accordingly, claims of the '158 patent reciting an antibody concentration of 50 mg/ml are not obvious over the combination of Lam and Barrera because a POSA would not have reasonably expected to successfully formulate antibodies at such a high concentration, and the state of the art—including statements by Dr. Randolph and in Lam itself—actually *taught away* from such formulations.

b. The Petition Is Also Particularly Deficient with Respect to Dependent Claims 15 and 24

Claims 15 and 24 limit the formulation pH range—which Dr. Randolph calls "the most important variable in a protein formulation" (Ex. 1002 at ¶ 59)—to between 4.8 and 5.5. In asserting that this pH range is obvious, Petitioner cites Lam's so-called "express disclosure" of certain pH values, alleges that "the *state of the art generally guided* the skilled person to *avoid extremes in pH*," and finally falls back on the unsupported assertion that "pH optimization was routine." Pet. at

27 (citing Ex. 1002 at ¶¶ 59-62).

A POSA would have no reasonable expectation that any pH range recited in Lam would stabilize D2E7. While Lam discloses a formulation with pH 5, as discussed above, a POSA would have had no reason to look to Lam's anti-CD18 fragment and anti-CD20 chimeric antibody formulations when formulating D2E7. And Petitioner concedes not only that "the pH of a particular formulation depends on the particular antibody," (Pet. at 27), but also that on balance the art taught that "nearly all commercially available protein formulations, including antibody formulations, had a pH [between about 6.0 and about 8.0]." Pet. at 34.[13] Petitioner here flatly concedes that the art taught away from the claimed pH range, which is well *below* 6.0. And indeed, all eight commercial antibody formulations identified by Dr. Randolph were formulated at a pH of 6.0 or above. *See* Ex. 1002 at ¶¶ 48-49. Petitioner should not be free to invoke the corpus of commercially available formulations when convenient, and ignore it when not.

[13] Elsewhere, citing the same evidence, Petitioner claims that "nearly all" commercially available formulations at the time were "within" a different pH range, 4.5 to 6.0. Pet. at 21. This contradictory assertion is not supportable.

c. The Petition Is Also Deficient with Respect to Dependent Claims 27-30

Claims 27-30 of the '158 patent recite specific components of buffer systems. Petitioner asserts that the claimed buffers (histidine, succinate, acetate, phosphate, and gluconate) were known in the art (Pet. at 25-26 (citing Ex. 1002 at ¶¶ 62, 97-98), but does not explain—save for hindsight—*why* any particular buffer would actually be selected from the numerous available options when formulating D2E7. *See* Ex. 1002 at ¶¶ 62(b) ("it *would not have been surprising* for the skilled person to design a formulation that had a citrate, phosphate, acetate, and/or histidine buffer . . . ."). Specifically, Petitioner does not point to any particular buffer used in any particular formulation as supplying either the necessary motivation to combine or a reasonable expectation of success for any buffer claimed. In sum, Petitioner offers no rational underpinning as to why a POSA would (i) select histidine (claim 27), succinate (claim 28), acetate (claim 29), or phosphate or gluconate (claim 30) from broad disclosures in the art, or (ii) have any reasonable expectation of successfully arriving at the claimed formulations of D2E7.

d. The Petition Is Also Deficient with Respect to the Remaining Dependent Claims

In addition to the deficiencies with respect to claims 3, 15, 24, and 26-30, the Petition is also defective with respect to the other dependent claims of the '158

patent. For example, Claims 4, 9-13, 18 and 20-22 require specific excipients in the formulation, such as polyols (claims 4 and 18) or surfactants (claims 9-13 and 20-22). However, Petitioner merely argues in a conclusory fashion that a skilled person understood that sugar alcohols are a type of polyol commonly used in pharmaceutical formulations (Pet. at 26 (citing Ex. 1002 at ¶¶ 63, 64, 74-76, 99-100)) and that a skilled person understood polysorbate 80 was the most common surfactant (Pet. at 26 (citing Ex. 1002 at ¶¶ 101-102)). Petitioner fails to explain why these specific excipients would be selected from the lists recited in Lam with any expectation of success.

In particular, Petitioner (by way of the incorporated arguments of Dr. Randolph) concedes that "[d]ifferent polyols (*e.g.*, sugars) may stabilize a protein to a similar or different degree, depending on the protein." Pet. at 26 (citing Ex. 1002 at ¶ 63 (citing Ex. 1017 at 165)); *see also* Ex. 1017 at 166 ("Not all proteins can be stabilized by sugars or polyols").

Again, Petitioner's cited art also specifically teaches that surfactant concentrations cannot simply be transferred between formulations since the optimal surfactant level "depend[s] on the mechanism(s) by which a particular protein is protected from damage by surfactant addition." Ex. 1011 at 170; *see also* Ex. 1013 at 353; Ex. 1016 at 74.

D. The Challenged Claims Would Not Have Been Obvious over Salfeld and Heavner (Ground 2)

Petitioner's combination of U.S. Patent No. 6,090,382 ("Salfeld") (Ex. 1005) and U.S. Patent No. 7,250,165 ("Heavner") (Ex. 1006) also fails to render the challenged claims obvious.

Salfeld discloses human IgG1 antibodies with D2E7 light and heavy chains. It includes a sizeable recitation of potential formulation ingredients, but lacks specific guidance concerning certain elements (such as antibody concentration and pH) and offers no data on stability of any formulation whatsoever.

Heavner relates to an anti-TNFα antibody that is separate and distinct from human D2E7. *See, e.g.*, Heavner at claim 1. Heavner also includes column after column of bulk recitations of potential formulation ingredients, and covers virtually every imaginable route of administration (*e.g.*, lyophilized, tablet, nebulizer, pills, *etc.*), concentration, excipient, and the like. *See* Heavner at 42:59-48:4. But Heavner offers no guidance at all on how to actually select from this massive number of possible combinations to prepare *any* antibody—much less a D2E7 antibody—as a stable liquid antibody formulation.

1. *The combination of Salfeld and Heavner fails to disclose all the claimed elements*

Even if a POSA were to combine Salfeld with Heavner, this could not render the '158 patent claims obvious because certain claimed elements are missing.

a. Neither Salfeld nor Heavner disclose actual formulations

First, Heavner does not disclose any specific pharmaceutical formulations for its antibody, leaving one of skill to guess what components and amounts should be selected. Given Heavner's extensive lists of possible components available in the art—which amount to millions of combinatorial possibilities—together with an utter lack of guidance as to which of the many combinations would work, a POSA equipped with Heavner is effectively no better off than a POSA *without* Heavner.

Salfeld's scant teachings relating to formulations are also provided merely as a general approach. Like Heavner, Salfeld teaches various other dosage forms, including "liquid, semi-solid and solid dosage forms,…dispersions or suspensions, tablets, pills, powders, liposomes and suppositories." *See* Salfeld at 21:12-16. Further, Salfeld does not teach a formulation optimized for stability (*cf*. Pet. at 32) or disclose any examples or data concerning stable formulations. Absent a specific formulation to optimize, a POSA would not even have a starting point.

Thus, Heavner or Salfeld, alone or in combination, do not disclose any specific antibody formulation at all, but only broad sweeping lists of possible components leading to an endless number of possible combinations. There is no teaching or direction as to which, if any, of these combinations is likely to be successful. Moreover, neither reference identifies the problem that the '158 patent

solves: creating a stable high concentration liquid formulation of IgG1 antibodies having D2E7 light and heavy chain variable regions. *See, e.g.*, *Novartis Pharm. Corp. v. Watson Labs., Inc.*, 611 F. App'x 988, 996 (Fed. Cir. 2015) (in discussing impermissible hindsight, "[w]ithout the knowledge of a problem, one of skill in the art would not have been motivated to modify [the prior art]").

b. Salfeld does not teach antibody concentration

Further, as Petitioner concedes, Salfeld does not teach antibody concentration. *See* Pet. at 33. Although Salfeld teaches that "[t]he composition can be formulated as a solution…suitable to high drug concentration," (Salfeld at 21:29-30), the term "high drug concentration" is not defined. But, for example, Dr. Randolph's cited commercially available antibody formulations—all of which, if not lyophilized, are 10 mg/ml or lower—offer evidence that "high concentration" in August 2002 could well have meant 10 mg/ml. *See* Ex. 1002 at ¶¶ 48-49, 74; Ex. 1036; Exs. 2022-2025.

Using hindsight, Dr. Randolph relies on a dosage disclosure (Salfeld at 23:12-15) to derive the claimed antibody concentration. This attempt to read antibody concentration into Salfeld is misguided and factually flawed. Dr. Randolph figures that a dosage of 1-10 mg/kg translates to 50-90 mg/ml, which falls within the claimed 20-150 mg/ml range (*see* Pet. at 33, 38 (citing Ex. 1002 at ¶¶ 52, 119)), but Dr. Randolph fails to account for the very real possibility of a

multi-dose therapy, in which case the formulation for each dose would only require a fraction of the antibody concentration. Moreover, given the disclosure Petitioner cites (Salfeld at 23:12-15), the injection volumes Petitioner proposes would yield a *thousand-fold range of concentrations*—from 4.6 to 4,666 mg/ml. There is no guidance that would direct a POSA to successfully arrive at the specific ranges recited in the present claims.

c. Salfeld does not disclose formulation pH

Petitioner also concedes that Salfeld does not teach formulation pH, but attempts to read pH into Salfeld by making conclusory statements alleging that phosphate buffered saline and "physiologically compatible" carriers necessarily require a pH of between 4 and 8. *See* Pet. at 33-34 (citing Ex. 1002 at ¶ 118). However, Petitioner provides no support in the references or elsewhere for its hindsight-driven attempt to map the claimed pH range where none is disclosed.

2. *Petitioner fails to identify a lead or reference formulation to be modified, or any motivation to combine Salfeld with Heavner*

Petitioner fails to disclose a reference composition in either Heavner or Salfeld as a starting point to arrive at the challenged claims. Instead, Petitioner makes an unsupported, conclusory statement that "[t]he skilled person would have been motivated to combine the disclosures of the Salfeld and Heavner patents because both focus on anti-TNFα antibodies, both focus on IgG antibodies, and

both teach how to formulate these antibodies." Pet. at 34 (citing Ex. 1002 at ¶¶ 115, 121). Indeed, Petitioner merely points to Heavner's extensive recitation of potential formulation components without identifying a single passage or disclosure in either Salfeld or Heavner that could guide a POSA as to what parts of the disclosure to select and combine to arrive at the claimed invention with a reasonable expectation of success.

Heavner and Salfeld do not even come close to providing motivation to reach the claimed formulation. Heavner discloses virtually every conceivable antibody concentration. *See* Heavner at 44:42-51. Likewise, Heavner discloses long lists of other components spanning several columns (*id.* at 30:13-34:55), allowing for a virtually endless number of combinatorial possibilities. Such extensive inventories of components and ranges effectively *teach away* from any specific formulation. *See Unigene*, 655 F.3d at 1361 ("When a field is 'unreduced by direction of the prior art,' and when prior art gives 'no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful,' an invention is not obvious to try"); *Novartis*, 611 F. App'x at 996; *BioDelivery Scis. Int'l, Inc. v. MonoSol Rx, LLC*, No. IPR2015-00167 (P.T.A.B. May 20, 2015), Paper 6 at 19-20 (denying institution of ground where prior art merely suggests varying all parameters or trying each of numerous possible choices until possibly arriving at successful result); *see also* Section

IV.A.3 (discussing Petitioner's previous admissions that a POSA would face an "endless number" of possible combinations of excipients "not finite" in number).

Against the backdrop of Heavner and Salfeld's boilerplate disclosures, Petitioner attempts to fill gaps by asserting that a POSA would have looked beyond Salfeld and Heavner to contemporary commercial antibody formulations: "The skilled person was further guided by the commercial formulations of antibodies and proteins available as of August 16, 2002, which also illustrated the use of a limited list of each type of excipient." Pet. at 42 (citing Ex. 1002 at ¶¶ 144-147). But as detailed in Section IV.A.1, existing non-lyophilized commercial preparations were all formulated at 10 mg/ml or less. *See* Ex. 1002 at ¶¶ 48-49, 74; Ex. 1036; Exs. 2022-2025. Absent the use of hindsight, such lyophilized and low concentration liquid commercial formulations actually *teach away* from the claimed high concentration liquid formulations of the '158 patent.

3. *No reasonable expectation of success exists in combining Salfeld with Heavner*

Even if Heavner did disclose a specific formulation (which it does not) a POSA would not expect it to successfully apply that formulation to D2E7, which is a different antibody than that disclosed in Heavner.

Petitioner's argument in support—that "antibodies of the same class (*e.g.*, IgG1) share similar three dimensional structure and behave similarly"— is without

merit. *See* Pet. at 34-35 (citing Ex. 1002 at ¶¶ 56, 121 (citing ¶¶ 54-58 and 74-76)). This is particularly true in view of Petitioner's own contrary admissions. *See* Ex. 2015 at 8; Ex. 2016 at 15 ("one of skill in the art [in 2005] would not necessarily expect different antibodies to be similarly stable in a particular formulation."); *see also* Ex. 2014 at 6; Section IV.A.3. At best, Heavner offers only general guidance and invites undue experimentation, which fails to provide a POSA with any reasonable expectation of success. *See, e.g.*, *BioDelivery*, Paper 6 at 28.

As with Lam and Barrera, Petitioner's attempts to import "routine" optimization to fill gaps in its obviousness combinations are unavailing. *See, e.g.*, Pet. at 31-35, 41-44 (citing Ex. 1002 ¶¶ 52, 59-62, 118, 121, 145, 152, 153). For instance, Petitioner argues that "the skilled person would have rationally selected from a *standard, limited set* of buffers, tonicity agents, and surfactants—excipients that were known to be safe and effective in pharmaceutical formulations—and *optimized to find the best combinations and amounts through routine experimentation*." Pet. at 42 (citing Ex. 1002 at ¶¶ 144-147). But Heavner's extensive disclosure of formulation parameters hardly presents a "limited set." And Petitioner's recourse to routine optimization effectively reduces Heavner's contribution to zero—in addition to being flatly contradicted by Petitioner's and Dr. Randolph's prior statements. *See, e.g.*, Ex. 2015 at 8 ("The [a]rt is [*u*]*npredictable* [and] optimization of stable liquid pharmaceutical compositions of

polypeptides is *not routine*"); *see also* Section IV.A.3.

4. *The dependent claims are nonobvious over Salfeld and Heavner*

For dependent claims, Petitioner's conclusory, cherry-picking statements are inadequate and fail to raise even a reasonable likelihood that any challenged claim is obvious. For instance, in addressing dependent claims 3 and 26—which limit antibody concentration to 50 mg/ml—Petitioner simply states in a conclusory manner that "the Heavner patent expressly discloses a formulation having an anti-TNFα antibody concentration of 50 mg/ml, and the skilled person *would have been motivated to use that concentration for the composition of Salfeld*." Pet. at 38 (citing Ex. 1002 at ¶ 127). But as stated in Section IV.C.4.a, Petitioner offers no reason *why* 50 mg/ml should be plucked from Heavner's broad disclosure of *ninety-seven* individual possibilities spanning concentrations from 0.1 to 100 mg/ml (or mg/gm). *See* Heavner at 44:42-51.

The Petition does not meaningfully address claims 15 and 24, which claim specific pH ranges below 6.0. As discussed in the context of Lam and Barrera, the art actually *taught away* from claims to pH ranges below 6.0, and Heavner's recitation of broad ranges, including 4.0 to 9.0, 5.0 to 10.0, and a "most preferred range of 6.0 to 8.0," would not have countered that teaching. *See* Section IV.C.4.b. Petitioner completely fails to explain why a POSA would choose the narrow

ranges of the dependent claims in view of Heavner.

With regard to dependent claims 4 and 18, Petitioner makes a similarly unsupported statement asserting that "skilled persons would have been motivated to use the sugar alcohol (mannitol) of the Heavner patent as the polyol in the Salfeld patent *because both patents relate to the formulation of anti-TNFα antibodies*." Pet. at 39 (citing Ex. 1002 at ¶ 133). The Petition advances this same flawed argument for claims 9-10 and 20-21, (relating to polysorbate). *See* Pet. at 39 (citing Ex. 1002 at ¶¶ 134-135). But again, these excipients each must be selected from an exhaustive disclosure (Heavner at 30:27-53, 30:63-31:5), and no reason or rationale is given for doing so. For claims 11-13 and 22 (relating to polysorbate concentration), Petitioner again improperly resorts to assertions of routine experimentation in an attempt to fill the gaps in the references. Pet. at 40 (citing Ex. 1002 at ¶¶ 66, 67, 136). *See* Section IV.C.4.d. The same holds true for claims 27-30, relating to buffers (Pet. at 38 (citing Ex. 1002 at ¶¶ 62, 128-130). *See* Section IV.C.4.c.

E. Secondary Considerations Support the Nonobviousness of the Challenged Claims

Objective indicia "help inoculate the obviousness analysis against hindsight," and help "turn back the clock and place the claims in the context that led to their invention." *Mintz*, 679 F.3d at 1378-79; *see also Graham v. John Deere*

Co., 383 U.S. 1, 36 (1966). Here, as set forth in Section IV.A, the invention is supported by evidence of commercial success, unexpected results, and long-felt need. Petitioner alleges that objective indicia here "would not be commensurate in scope with the claimed invention." Pet. at 45 (citing *In re Huai-Hung Kao*, 639 F.3d 1057, 1069 (Fed. Cir. 2011)). But in *Kao*, "the record [was] nearly silent on whether the commercial success was caused by the merits of the invention as distinct from the prior art." 639 F.3d at 1069. Not so here. Moreover, an applicant "need not sell every conceivable embodiment of the claims in order to rely upon evidence of commercial success." *Rambus Inc. v. Rea*, 731 F.3d 1248, 1257 (Fed. Cir. 2013) (citations omitted); *see also In re Glatt Air Techniques, Inc.*, 630 F.3d 1026, 1030 (Fed. Cir. 2011).

As set forth in Section IV.A, the '158 patent covers HUMIRA—the first stable liquid antibody formulation for subcutaneous administration ever commercialized, and a marked advance over the low concentration and lyophilized formulations of its day—which has become one of the world's best-selling drugs. The claimed stable high concentration formulations are necessary to provide the easy subcutaneous self-administration that was long sought in the industry and that AbbVie unexpectedly achieved, yielding this commercial success. In the unlikely event it is required, Patent Owner can and will present additional compelling evidence of these objective indicia.

F. Petitioner's Art and Arguments Were Previously Considered During Prosecution

In addition to the reasons above, the Board should exercise its authority to reject the Petition under 35 U.S.C. § 325(d) because the Examiner previously advanced substantially the same prior art combinations during prosecution of the '158 patent and its parent patents and nonetheless found the claims of the '158 patent patentable. Petitioner's four enumerated references—Lam, Barrera, Salfeld, and Heavner—were cited and considered by the PTO in an Information Disclosure Statement submitted during prosecution of the '158 patent (*see* Ex. 1008 at 57, 58, 63), and are listed on the face of the '158 patent. More importantly, during prosecution of claims in parent patents, the PTO expressly raised the *same arguments* Petitioner now advances.

The PTO also explicitly advanced the Heavner and Salfeld combination (Petitioner's "Ground 2") during prosecution of the grandparent (U.S. Pat. No. 8,795,670) and great-grandparent (U.S. Pat. No. 8,802,100) of the '158 patent. There, the Examiner initially rejected the pending claims using the same flawed rationale set forth in the Petition (*see* Pet. at 34-35, 55) by alleging that "[t]he person of ordinary skill in the art reasonably would have expected success because similar preparations were already being generated at the time the invention was made and the *substitution of one known TNF antibody for another would have*

yielded predictable results." Ex. 2009 at 6-8; *see also* Ex. 2010 at 17-18. Patent Owner successfully rebutted this argument, relying, *inter alia*, on the well-established unpredictability of trying to transfer the same formulation from one antibody to another. Ex. 2035 at 16-18; *see also* Ex. 2036 at 16-18.

Similarly, during prosecution of three parent patents (U.S. Pat. Nos. 8,802,101; 8,802,102; and 8,940,305), the PTO expressly advanced a Lam and Salfeld obviousness combination essentially identical to Petitioner's Lam and Barrera ("Ground 1") obviousness combination—the only real difference being that Petitioner uses Barrera, not Salfeld, to supply D2E7. *See* Ex. 2037 at 6-8; Ex. 2038 at 3-4; Ex. 2039 at 3-4. Patent Owner also rebutted this argument, since a POSA would not expect Lam's formulations to work for D2E7, citing Wang (Ex. 1017) for the principle that "success with one type of protein could not be reasonably expected to lead to success with another type of protein." *See* Ex. 2011 at 14 (citing Ex. 1017 at 175); *see also* Ex. 2012 at 11; Ex. 2013 at 7-8.

Recognizing that essentially the same arguments were overcome during prosecution of the parent patents to the '158, (Pet. at 27-31), Petitioner first falls back on its unsupported and hindsight-driven assertion that "the development of a new protein formulation was not a complex process as of August 16, 2002." Pet. at 28. This is simply false, as discussed in Section IV.A.3. Next, Petitioner attempts to distinguish the three prior art references (Exs. 1044-1046) that Patent Owner

submitted during prosecution of family member patents because, according to Petitioner, they each "involve altering the antibody itself to observe the effect of mutations on stability, rather than altering the excipients with which it interacts." Pet. at 29. But the fact that the antibodies were altered in no way detracts from the basic truth that a POSA would expect antibodies with different CDRs *to require different formulations*. *See, e.g.*, Ex. 2014 at 6; Ex. 2004 at 125; Ex. 2015 at 8 (citing Ex. 1017 at 130); *see also* Section IV.A.3. Simply put, Petitioner falls far short of unseating the PTO's correct assessment when it ultimately withdrew arguments that parallel those that Petitioner now advances for Lam and Barrera.

When its cited art was previously considered by the PTO, a Petition must advance new issues to support institution. *See Integrated Global Concepts, Inc. v. Advanced Messaging Techs., Inc.*, No. IPR2014-01028 (P.T.A.B. Dec. 22 2014), Paper 13 at 8 (denying institution where "Examiner explicitly considered the same argument that the claimed subject matter would have been obvious over that same prior art."). The instant Petition adds nothing meaningful to the information and arguments already overcome during prosecution. Rather, the Petition merely relies on—and extensively incorporates by reference—unsupported assertions in Dr. Randolph's Declaration to suggest that antibody formulation was "predictable" and "routine," and that individual antibody formulations were essentially interchangeable. However, the Board should not credit Petitioner's allegations or

Dr. Randolph's unsupported assertions in this regard, not only because they are conclusory, but also, as detailed in Section IV.A.3, because they are directly contradicted by the scientific literature and by numerous prior statements by Petitioner and Dr. Randolph. *See, e.g.*, Ex. 2015 at 8.

Accordingly, because the Petitioner's obviousness arguments were previously considered and overcome, and the Petition adds nothing new, the Board should reject the Petition under 35 U.S.C. § 325(d). *See Integrated Global Concepts*, Paper 13 at 7-9; *see also Microboards Tech., LLC v. Stratasys Inc.*, No. IPR2015-00288 (P.T.A.B. May 28, 2015), Paper 13 at 16 n.1; *Merial Ltd. v. Virbac*, No. IPR2014-01279 (P.T.A.B. Jan. 22, 2015), Paper 13 at 23-28; *Excelsior Med. Corp. v. Lake*, No. IPR2013-00494 (P.T.A.B. Feb. 6, 2014), Paper 10 at 20.

V. CONCLUSION

The Board should deny institution of the Petition because the asserted grounds are driven by hindsight and are contradicted both by Petitioner's prior statements and those of its expert. The Petition fails to show that any challenged claim is obvious: It fails to identify a reference formulation, fails to present any motivation to combine references, and fails to set forth any reasonable expectation of success in doing so. The flaws in Petitioner's argument are still more dramatic for dependent claims, such as claims 3, 15, 24 and 26. The Petition also resorts to improper gap-filling of its incomplete combinations with purportedly "routine"

modification and through recourse to long lists of non-asserted prior art. For all these reasons, the Petition fails to raise a reasonable likelihood that even one challenged claim is unpatentable.

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Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on this 19th day of October 2015, true and correct copies of the foregoing PATENT OWNER'S PRELIMINARY RESPONSE AND EXHIBITS THERETO were served by electronic mail upon the following counsel of record for Petitioner Amgen Inc.:

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