

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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SWISS PHARMA INTERNATIONAL AG,  
Petitioner

v.

BIOGEN IDEC,  
Patent Owner

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Case IPR2016-00915  
Patent 8,349,321

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**PATENT OWNER PRELIMINARY RESPONSE  
PURSUANT TO 37 C.F.R. § 42.107**

## LIST OF EXHIBITS

EXHIBIT	DESCRIPTION
Ex. 2001	CURRENT TRENDS IN MONOCLONAL ANTIBODY DEVELOPMENT AND MANUFACTURING (Steven J. Shire, et al., eds., 2010)
Ex. 2002	Theodore W. Randolph & John F. Carpenter, <i>Engineering Challenges of Protein Formulations</i> , 53 AIChe J. 1902-07 (2007)
Ex. 2003	RATIONAL DESIGN OF STABLE PROTEIN FORMULATIONS: THEORY AND PRACTICE (John F. Carpenter & Mark C. Manning, eds., 2002)
Ex. 2004	Elizabeth R. Proos, et al., <i>Long-term Stability and in vitro Release of hPTH(1-34) from a Multi-reservoir Array</i> , 25(6) Pharm. Res. 1387-95 (2008)
Ex. 2005	HERCEPTIN <sup>®</sup> FDA Approved Drug Label, dated September 25, 1998
Ex. 2006	SYNAGIS <sup>®</sup> , in PHYSICIANS' DESK REFERENCE 2028-29 (2002)
Ex. 2007	XOLAIR <sup>®</sup> FDA Approved Drug Label, dated June 20, 2003
Ex. 2008	RAPTIVA <sup>®</sup> FDA Approved Drug Label, dated October 24, 2003
Ex. 2009	REMICADE <sup>®</sup> FDA Approved Drug Label, dated October 2, 2015
Ex. 2010	ENTYVIO <sup>®</sup> FDA Approved Drug Label, dated May 20, 2014
Ex. 2011	David Ouellette, et al., <i>Comparison of the in vitro and in vivo stability of a succinimide intermediate observed on a therapeutic IgG1 molecule</i> , 5(3) mAbs 432-44 (2013)
Ex. 2012	LH Stockwin & S Holmes, <i>Antibodies as therapeutic agents: vive la renaissance!</i> , 3(7) Expert Opin. Biol. Ther. 1133-52 (2003)
Ex. 2013	Robert G. Hamilton, THE HUMAN IGG SUBCLASSES (2001)
Ex. 2014	<i>The Generation of Antibody Diversity</i> , in MOLECULAR BIOLOGY OF THE CELL 1385-92 (Bruce Alberts, et al., eds., 4th ed. 2002)
Ex. 2015	PROTEIN FORMULATION AND DELIVERY (Eugene J. McNally, ed., 2000)
Ex. 2016	Wei Wang, <i>Instability, stabilization, and formulation of liquid protein pharmaceuticals</i> , 185 Int. J. Pharm. 129-88 (1999)
Ex. 2017	Samir Mitagotri, et al., <i>Overcoming the challenges in administering biopharmaceuticals: formulation and delivery strategies</i> , 13 Nat.

EXHIBIT	DESCRIPTION
	Rev. Drug Discov. 655-72 (2014)
Ex. 2018	Jeffrey L. Cleland, et al., <i>The Development of Stable Protein Formulations: A Close Look at Protein Aggregation, Deamidation, and Oxidation</i> , in CRITICAL REVIEWS IN THERAPEUTIC DRUG CARRIER SYSTEMS 307-77 (Stephen D. Bruck, ed., 1993)
Ex. 2019	Romain Rouet, et al., <i>Stability engineering of the human antibody repertoire</i> , 588 FEBS Lett. 269-77 (2013)
Ex. 2020	PHARMACEUTICAL FORMULATION DEVELOPMENT OF PEPTIDES AND PROTEINS (Sven Frokjaer & Lars Hovgaard, eds., e-Library ed. 2003)
Ex. 2021	Shihong Li, Christian Schöneich, et al., <i>Chemical Instability of Proteins</i> , 2(5) Pharm. News 12-16 (1995)
Ex. 2022	Olivier Mozziconacci, Christian Schöneich, et al., <i>Comparative Evaluation of the Chemical Stability of 4 Well-Defined Immunoglobulin G1-Fc Glycoforms</i> , 105 J. Pharm. Sci. 575-87 (2016)
Ex. 2023	<i>United States Top 25 Neurological Therapies</i> , 49(11) Medical Marketing & Media 38 (2014)
Ex. 2024	<i>Tecfidera Will Be Leading MS Drug In 2015</i> , BMI Research, May 6, 2015
Ex. 2025	Ingrid Loma & Rock Heyman, <i>Multiple Sclerosis: Pathogenesis and Treatment</i> , 9 Curr. Neuropharmacol. 409-16 (2011)
Ex. 2026	Prosecution History of U.S. Patent No. 8,349,321
Ex. 2027	REMICADE <sup>®</sup> approval letter from the FDA, dated August 24, 1998
Ex. 2028	Sumit Goswami et al., <i>Developments and Challenges for mAb-Based Therapeutics</i> , 2 Antibodies 452-500 (2013)
Ex. 2029	SIMULECT <sup>®</sup> , in PHYSICIANS' DESK REFERENCE 2399-401 (2002)
Ex. 2030	Reed J. Harris, et al., <i>Commercial Manufacturing Scale Formulation and Analytical Characterization of Therapeutic Recombinant Antibodies</i> , 61 Drug Dev. Res. 137-54 (2004)
Ex. 2031	RITUXAN <sup>®</sup> FDA Approved Drug Label, dated November 26, 1997
Ex. 2032	WJ Pan, et al., <i>Pharmacology of AMG 181, a human anti- <math>\alpha_4\beta_7</math> antibody that specifically alters trafficking of gut-homing T cells,</i>

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	169 Br. J. Pharmacol. 51-68 (2013)
Ex. 2033	Sampathkumar Krishnan, et al., <i>Development of Formulations for Therapeutic Monoclonal Antibodies and Fc Fusion Proteins</i> , in FORMULATION AND PROCESS DEVELOPMENT STRATEGIES FOR MANUFACTURING PHARMACEUTICALS 383-427 (Feroz Jameel & Susan Hershenson, eds., 2010)
Ex. 2034	Marco van de Weert & Theodore W. Randolph, <i>Physical Instability of Peptides and Proteins</i> , in PHARMACEUTICAL FORMULATION DEVELOPMENT OF PEPTIDES AND PROTEINS 107-29 (Lars Hovgaard, et al., eds., 2013)
Ex. 2035	Jasmin F. Sydow, et al., <i>Structure-Based Prediction of Asparagine and Aspartate Degradation Sites in Antibody Variable Regions</i> , 9(6) PLoS ONE e100736 (2014)
Ex. 2036	Josef Vlasak, et al., <i>Identification and characterization of asparagine deamidation in the light chain CDR1 of a humanized IgG1 antibody</i> , 392 Anal. Biochem. 14554 (2009)
Ex. 2037	<i>Genentech: Survivor Strutting Its Stuff</i> , The New York Times, Oct. 1, 2000
Ex. 2038	Jerry Cacia, et al., <i>Isomerization of an Aspartic Acid Residue in the Complementarity-Determining Regions of a Recombinant Antibody to Human IgE: Identification and Effect on Binding Affinity</i> , 35 Biochem. 1897-903 (1996)
Ex. 2039	Stuart Rudikoff, et al., <i>Single amino acid substitution altering antigen-binding specificity</i> , 79 Proc. Natl. Acad. Sci. USA 1979-83 (1982)
Ex. 2040	E. Morrey Atkinson & Wolfgang Klum, <i>Formulation Strategies for Biopharmaceuticals Ensuring Success to Market</i> , 4 IDrugs 557-60 (2001)
Ex. 2041	<i>Genentech, Xoma seeking FDA approval for psoriasis drug</i> , RBC News, Dec. 24, 2002
Ex. 2042	<i>CD18 trials disappoint again</i> , 18 Nat. Biotech. 817-20 (2000)
Ex. 2043	EP Patent Application No. 04709508.8, Grounds in Support of Appeal, Nov. 4, 2010
Ex. 2044	Wim Jiskoot, et al., <i>Protein Instability and Immunogenicity: Roadblocks to Clinical Application of Injectable Protein Delivery Systems for Sustained Release</i> , 101 J. Pharm. Sci. 946-54 (2012)

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## I. INTRODUCTION

Petitioner's allegations that the '321 patent merely claims "an old therapeutically active agent paired with a standard well-known formulation" and that all IgG antibodies can be "simply substituted" for one another is flatly contradicted by the prior art. As discussed in detail below, the art taught that formulation of proteins, including IgG antibodies, was highly complex because various degradation pathways, including deamidation, oxidation, aggregation, and denaturation, can result in loss of therapeutic effectiveness. Moreover, the art showed that IgG antibodies are an incredibly broad class of compounds that do not lend themselves to a generic approach to formulation. Most importantly, Petitioner completely ignores that developing a stable, high-concentration liquid antibody formulation, like the one claimed by the '321 patent, was a particularly difficult challenge.

Despite the complexities and unpredictability of antibody formulation development, Biogen was the first to invent and commercialize a stable, high-concentration liquid antibody formulation for use in treating multiple sclerosis ("MS"). The unique formulation contains natalizumab, a humanized monoclonal IgG<sub>4</sub> antibody, and is claimed by the '321 patent. It is commercialized as TYSABRI<sup>®</sup>, one of the top-selling neurology drugs in the United States to treat MS. *See* Ex. 2023 at 39; Ex. 2024. In MS, the patient's own immune system

attacks the central nervous system, causing a chronic condition with progressively devastating symptoms throughout a patient's lifetime. *See* Ex. 2025 at 409.

Before TYSABRI<sup>®</sup> launched in 2004, there were no antibody therapeutics available to treat MS, despite the long-felt need and recognition that antibody therapeutics would be of tremendous value for MS treatment due to their selectivity and potency compared to small molecule drugs. *See* Exhibit 2012 at 1134, 1136–37 (Table 1); Ex. 2001 at 103; Ex. 2017 at 655. The inventors of the '321 patent overcame substantial development obstacles to achieve a highly concentrated liquid antibody formulation, including facing complex degradation reactions in initial natalizumab formulations containing histidine as a buffer. *See* '321 patent at 11:15–25.<sup>1</sup> TYSABRI<sup>®</sup> is the first antibody formulation successfully

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<sup>1</sup> Petitioner argues that, during prosecution, applicant relied on pre-formulation study results to support unexpected results of the claimed formulation, and then “publicly admitted” during EP prosecution that the study results were inaccurate and not reproducible. Pet. at 2, 9, 57–59. But Petitioner mischaracterizes both the US and EP prosecution records where the pre-formulation study was cited to illustrate the level of experimentation required, and whether the study data could be reproduced or were described as “not accurate” is irrelevant. *See* Ex. 2026 at 145–52 ; Ex. 2043 at 10–12.

developed and approved to treat patients suffering from multiple sclerosis. *See* Ex. 2025 at 411 (Table 3). As recognized by experts at the Department of Neurology at the University of Pittsburgh Medical Center, TYSABRI<sup>®</sup> “has robust benefits on relapse rate, disability progression, and MRI activity.” Ex. 2025 at 412–13.

Petitioner identifies no specific evidence from the prior art showing there would have been a reasonable expectation of success in formulating the claims that cover the TYSABRI<sup>®</sup> product—*i.e.*, a stable, high-concentration liquid formulation of natalizumab. Petitioner fails to identify *any* high-concentration natalizumab formulation. Further, neither Petitioner’s cited “Prior Art IgG mAb Formulations” (Orthoclone, Aversano, van Oosten, and Zenapax) nor the contemporaneous literature cited by both parties (*e.g.* Wang (Ex. 2016), McNally (Ex. 2015), and Frokjaer (Ex. 2020)) would have provided a reasonable expectation of success in achieving the claimed high-concentration formulation. The cited mAb formulations do not contain natalizumab and are not high-concentration, and the literature at the time taught that formulating antibodies at high-concentration in solution was unpredictable.

Petitioner instead resorts to hindsight, cherry-picking prior art without providing any reason why a person of ordinary skill in the art (“POSA”)<sup>2</sup> would have selected and combined those references as opposed to any of the numerous other prior art describing antibody products that did *not* contain components of the claimed invention. Petitioner then proceeds to make broad conclusions that each claim element is obvious because the identity, amount, or concentration of a particular component could have been achieved by “routine optimization of a result effective variable” and/or by “simple substitution.” Petitioner, however, fails to provide any evidence as to *why* the particular identity, amount, or concentration of a particular component was a “result-effective variable” that could be achieved through “routine optimization” and/or by “simple substitution.”

Recognizing that it has failed to meet its burden, Petitioner turns to numerous additional prior art references in an attempt to plug the holes in Grounds 1 and 2—*nineteen* and *seven* references, respectively. Despite relying on *twenty-two* prior art references for Ground 1 and *ten* prior art references for Ground 2, Petitioner still fails to demonstrate a reasonable likelihood that any

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<sup>2</sup> Patent Owner submits that any disagreement it may have with Petitioner’s definition of a POSA does not change the analysis below.

claim of the '321 patent is unpatentable. Simply put, Petitioner's allegations lack any merit and the Board should deny institution of the Petition.

## II. CLAIM CONSTRUCTION UNDER “BROADEST REASONABLE INTERPRETATION”

A claim subject to *Inter Partes* Review is given its “broadest reasonable construction in light of the specification of the patent in which it appears.” 37 C.F.R. § 42.100(b); *In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1278 (Fed. Cir. 2015), *aff'd*, 2016 WL 33699425 (U.S. June 20, 2016).

Under this standard, claim terms are given their ordinary and customary meaning as would be understood by a POSA at the time of the invention and in the context of the entire patent disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). If an inventor acts as his or her own lexicographer and provides a definition of a term, that definition will control. *See In re ICON Health and Fitness, Inc.*, 496 F.3d 1374, 1379 (Fed. Cir. 2007).

As Petitioner concedes:

The '321 patent expressly defines [stable] by stating that “[a] ‘stable’ formulation is one in which the protein therein essentially retains its physical stability and/or chemical stability and/or biological activity upon storage. By ‘stable’ is also meant a formulation which exhibits *little or no signs of instability*, including aggregation and/or deamidation.” (Ex. 1001 at 5:55–60.)

Pet. at 11 (emphasis added). Petitioner does not offer any reason why the explicit definition should not control. Petitioner, instead, simply asserts that stable “merely requires that the formulation retains any one of physical, chemical, or biological stability upon storage.” Pet. at 11. Petitioner’s interpretation of “stable” is flawed because it treats the definition above as “alternate definitions” rather than a single definition. *Id.* However, even if the Board adopts Petitioner’s definition, Petitioner still fails to establish that there is a reasonable likelihood it would prevail with respect to any of the challenged claims, as detailed below in Sections III.–VI.

### **III. PETITIONER FAILS TO DEMONSTRATE A REASONABLE LIKELIHOOD THAT ANY CLAIM OF THE ’321 PATENT IS UNPATENTABLE.**

#### **A. The prior art taught that antibody formulations were unpredictable, highly specific, and challenging to develop.**

Despite Petitioner’s allegations to the contrary, there was overwhelming scientific evidence in 2003, and still today, that achieving a stable liquid formulation of a monoclonal antibody was an unpredictable and highly antibody-specific challenge. As discussed in detail below, the art taught that liquid antibody formulations were difficult and that lyophilized formulations were preferred. The art also taught that IgG antibodies are an incredibly broad class of compounds that do not lend themselves to a generic approach to formulation such that they could be seen as “simple substitutes.” Most importantly, the art taught that stable, high-concentration (*e.g.*, 20 mg/mL) liquid antibody formulations, like



the formulations recited in the '321 patent, were particularly difficult to achieve. *See* Ex. 2004 at 1394 (reporting that therapeutic formulations having >10 mg/mL protein are considered highly concentrated); *infra* Sections III.A.1–4. Indeed, Petitioner all but admits this conclusion by failing to identify *any* stable, high-concentration antibody formulation in the prior art.

Ingredient	Claim	Orthoclone	Aversano	van Oosten	Zenapax
IgG mAb	20 mg/ml	1 mg/ml	5 mg/ml	10 mg/ml	5 mg/ml

Excerpt from Pet. at 16, Table 1, 1<sup>st</sup> row.

**1. The art taught that liquid antibody formulations were difficult and that lyophilized formulations were preferred.**

Formulating antibodies as liquids (as opposed to a lyophilized, or freeze-dried, formulation) is unpredictable and challenging because the protein must retain its physical and chemical stability in solution for months or years. *See* Ex. 2001 at 106–112. This unpredictability is further exacerbated with the high antibody concentrations claimed in the '321 patent (20 mg/mL). *Id.* at 110; Ex. 2002 at 1905.

These challenges are highlighted in the literature both before and after 2003. “[F]or most proteins maintaining physical and chemical stabilities in aqueous solution for an extended period of time is *extremely difficult*.” Ex. 2003 at 184

(emphasis added). In fact, “[i]t can be assumed that most proteins will not exhibit sufficient stability in aqueous solution to allow a liquid formulation to be developed.” *Id.* at 188. Even in 2007, four years *after* the priority date, it was understood that the “[d]evelopment of these [high protein concentration] formulations poses a number of serious obstacles to commercialization.” Ex. 2002 at 1905.

As a result of the challenges with liquid formulations, it was well-known just prior to the filing date that the primary way to stabilize protein formulations was lyophilization into powders. Ex. 2003 at 188. This was the case despite the fact that a POSA would have otherwise preferred liquid formulations due to “simple processing, less manipulation, and easy application.” Ex. 2016 at 175; *see also* Ex. 2001 at 112. Even after the filing date, lyophilization is the most prevalent method of stabilization. Ex. 2004 at 1394; *see also* Ex. 2001 at 112–114, 123. This is because “water is the common culprit” in antibody degradation events. Ex. 2001 at 112. Even the 2000 Frokjaer text relied upon by Dr. Schöneich and Petitioner teaches that lyophilization was the preferred method for stabilizing proteins. Only four (4) of the twenty-two (22) commercialized protein products reported in 2000 were formulated as liquids for storage. Ex. 1029 at 146. The remainder of the products at the time were lyophilized powders. *Id.*

In fact, Dr. Schöneich also provides direction toward the development of lyophilized formulations: “In designing a protein formulation, formulators generally *prefer to select excipients that have been used in marketed products....*” Ex. 1002 ¶ 38 (citing Ex. 1029 at 146–147) (emphases added). As Exhibit 1029 reports, the vast majority of marketed protein products were lyophilized formulations. Ex. 1029 at 146. And one excipient—histidine buffer—was predominantly used in the marketed lyophilized antibody formulations. *See* Ex. 2005 at 1; Ex. 2006 at 1; Ex. 2007 at 1; Ex. 2008 at 2; Ex. 2037; Ex. 2041.

The teachings toward lyophilization by Dr. Schöneich and others run contrary to Dr. Schöneich’s hindsight-driven assertions about achieving the stable formulation of the ’321 patent claims. For example, Dr. Schöneich states—with no citation support—that “the [van Oosten] formulation would have to remain stable at least for the length of time required to be shipped.” Ex. 1002 ¶ 96. But the reality was that developing a stable liquid antibody formulation, particularly at a high concentration, was extremely challenging. *See, e.g.,* Ex. 2001 at 110; Ex. 2002 at 1905. Indeed, the liquid antibody formulation of van Oosten was abandoned and replaced with a lyophilized formulation for commercial purposes, which Dr. Schöneich fails to recognize, despite his assertion that a formulator would look to marketed products. *See* Ex. 2009 at 1. Confirming the prevalence of lyophilized formulations even to this day, the only other approved  $\alpha 4$  integrin-

binding antibody, besides TYSABRI<sup>®</sup>, is ENTYVIO<sup>®</sup> (vedolizumab), a lyophilized formulation. *See* Ex. 2010 at 1.

The marketed products in early 2003, as well as the established literature, demonstrate the strong preference for high-concentration lyophilized formulations over liquid formulations.

**2. Antibodies are incredibly diverse, and small differences among antibodies result in profound functional changes.**

Therapeutic antibodies encompass a platform of glycoproteins with a tremendous array of variations resulting in exquisite specificity for target antigens. *See* Ex. 2011 at 432; Ex. 2012 at 1133–35. Human antibodies (immunoglobulins) consist of five different classes, IgA, IgD, IgE, IgG, and IgM, each evolved for different physiological roles. Ex. 2012 at 1134.

The IgG class of antibodies has been the focus for therapeutic antibody development. *See id.* One reason is due to the substantial versatility among IgG subclasses (IgG<sub>1-4</sub>). *Id.* at 1134–35; Ex. 2013 at 7–11. The amino terminal regions of the heavy and light chains contain highly variable amino acid compositions ( $V_H$  and  $V_L$  regions) that are involved in antigen binding. Ex. 2013 at 8. It was well-known that IgG antibodies contain major structural differences in other regions as well, which result in significant functional diversity. In different IgG subclasses, unique antigenic determinants are found in the constant fragment (Fc) region and hinge region. *Id.* at 8–9. Besides the protein components, another distinguishing

feature among IgG antibodies is the presence of different carbohydrates at the antibody's glycosylated sites, which participate in cell response events and affect clinical efficacies. *See* Ex. 2001 at 105; Ex. 2016 at 145 (“The effect of glycosylation on stability of proteins is highly protein-dependent.”). Additionally, although overlooked by Dr. Schöneich, *see infra* at Section III.A.2.f, there are differences in the higher-order three-dimensional structures among IgG antibodies, resulting in significant challenges to prevent unfolding and loss of physical stability. *See* Ex. 2013 at 7–9; Ex. 2015 at 28; Ex. 2001 at 243–44.

Dr. Schöneich contradicts this well-established art by asserting that IgG monoclonal antibodies are nothing more than “simple substitut[es].”<sup>3</sup> *See, e.g.*, Ex.

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<sup>3</sup> Petitioner ignores the clear language of the claims and mischaracterizes the specification by asserting that “[t]he ’321 patent specification states that virtually all proteins are interchangeable in this [phosphate-buffer, polysorbate, and sodium chloride] formulation.” Pet at 7. The specification states “other proteins are contemplated,” yet the claims recite natalizumab, not “other proteins.” Thus, the scope of the claims does not encompass “other proteins.” And Petitioner’s unsupported leap from “other proteins” to “virtually all proteins” confirms the absurdity of its position. *Id.* Further, the quoted specification language is directed to “the formulations disclosed” in the patent specification, not only in the particular

1002 ¶ 14; *see also id.* ¶ 34 (“[A]ll IgG mAbs ... share up to 95% homology....”). While IgG antibodies are greater than 95% homologous in the *constant regions* of the heavy chains ( $C_H$ ), Ex. 2013 at 8, they encompass an enormous number of antibodies. Differences in the variable regions lead to antibodies with very different functions. For example, vedolizumab (commercialized as ENTYVIO<sup>®</sup> (Ex. 2010)) and natalizumab are both humanized monoclonal antibodies that target the same antigen, namely, the  $\alpha 4$  subunit of integrin proteins found on the surface of immunoregulatory cells. Ex. 2032 at 52. But while vedolizumab targets the  $\alpha 4\beta 7$  integrin subunit and is used to treat ulcerative colitis and Crohn’s disease, natalizumab targets both the  $\alpha 4\beta 7$  and  $\alpha 4\beta 1$  integrin subunits and treats multiple sclerosis, in addition to Crohn’s disease. *Id.*

Furthermore, the human body can likely make over ten trillion different types of antibodies due to the evolution of unique genetic mechanisms. *See* Ex. 2014. And molecular engineering made the vast spectrum of monoclonal IgG antibodies exponentially more complex and diverse. *See* Ex. 2001 at 105–06. Such

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formulation [containing phosphate-buffer, polysorbate, and sodium chloride] that Petitioner plucks from a different section of the specification. In other words, the specification does not teach using “virtually all proteins” in the claimed formulation. *Id.*

complexity and diversity are confirmed by Petitioner’s own prior art references Orthoclone, a murine (mouse) antibody, and van Oosten, a chimeric (mouse and human) antibody. *See* Ex. 1014; Ex. 1022. Murine and chimeric antibodies have much lower homologies, as only 60–75% of the murine variable domains are homologous to human domains. Ex. 2001 at 9. Put differently, the number of different IgG antibodies and their functions is limitless with the advent of molecular engineering.

As confirmed by the complete version of Dr. Schöneich’s own Exhibit 1031 (McNally), subtle changes in IgG antibodies have profound effects. Ex. 2015 at 119. Yet Petitioner and Dr. Schöneich omit from their McNally exhibit the entire chapter on chemical and physical protein stability considerations, apparently because it contradicts their scientifically flawed argument that all IgG antibodies are “simple substitut[es].” *See* Ex. 2015 at Chap. 2, 5–69; Ex. 1031. As reported in the omitted McNally chapter, “[t]he effects of various levels of [protein] structure—primary, secondary, and tertiary—are believed to be *complex and varied*. At present, *only primary structure effects* have been characterized in a systematic manner.” Ex. 2015 at 11 (emphases added). McNally further states that “the complex interplay of the molecular determinants that drive [maintenance of higher order three-dimensional structure] makes protein stabilization an interesting challenge for the protein formulator.” *Id.* at 28.

The reality at the time was that even a *single* amino acid change in an antibody's variable region (Fv) could result in dramatic differences in its antigen-binding specificity and function. Ex. 2039 at 1979, 1982; Ex. 2001 at 123 (citing Ex. 2039); *see also id.* at 11. Even years later, protein folding and physical instability remained “complex phenomena,” such that “[e]ven minor differences in amino acid sequence or posttranslational modification *may result in significantly different physical instability.*” Ex. 2034 at 125 (emphases added).

**3. Formulation of proteins, particularly antibodies, including IgGs, was (and remains) complicated and unpredictable.**

Try as it might, Petitioner cannot overcome the overwhelming scientific evidence that in 2003, achieving a stable liquid formulation of a monoclonal antibody was an unpredictable and highly antibody-specific challenge. At the core of the complexity and unpredictability of formulating a stable liquid antibody formulation is the uniqueness of every antibody. The structural complexity of antibodies makes them among “the most challenging molecules to formulate and deliver.” Ex. 2017 at 655. Due to their origination in the human body, antibodies have built-in features, such as protein residues prone to deamidation, that cause challenging stability problems during storage. Ex. 2001 at 122–23. The art recognized that loss of antibody activity during storage results in a “substantial burden on formulation technologies.” *Id.*



- a) **There was no direction as to which combination of formulation components would be successful for a specific antibody.**

“[T]he structural differences among different proteins are so significant that generalization of universal stabilization strategies has not been successful.” Ex. 2016 at 130. Indeed, “[e]ven for closely related proteins, the relative stability and major pathways for degradation might be quite different.” Ex. 2003 at 185–86. Even when they contain significant sequence homologies, monoclonal antibodies have been shown to display dramatically different physical characteristics that dictate stability. Ex. 2001 at 243–44.

Additionally, it was unclear in 2003 what components, parameters, and combinations thereof would have a stabilizing effect on a particular antibody. An excipient, such as a buffer or formulation parameter (*e.g.*, pH) that stabilizes one antibody may destabilize another antibody. *See* Ex. 2001 at 107–112. Moreover, components and parameters of a formulation do not work in isolation, but instead are interdependent. As Wang observes, “[p]rotein stability is a result of balancing between destabilizing and stabilizing forces. The destabilizing forces are mainly due to the large increase in entropy of unfolding, and the stabilizing forces are provided by a few non-covalent interactions.... Disruption of any of these interactions will shift the balance and destabilize a protein. Many factors can disrupt this delicate balance.” Ex. 2016 at 145. Accordingly, changing one or more

of these variables could and typically did profoundly affect the overall stability and suitability of a formulation. *See id.*

**b) It is critical to understand antibody properties and degradation pathways for successful development of a stable formulation.**

To develop a stable liquid formulation of an antibody therapeutic, it is critical to begin by analyzing the specific protein to be formulated, including its individual degradation pathways and their relative importance at various conditions. Ex. 2016 at 178 (“To develop a liquid protein pharmaceutical, the basic properties of a protein need to be examined first.”). As explained in Carpenter, such pre-formulation studies to determine “the relative importance of various degradation pathways and elucidation of instability mechanisms for a given protein are essential.” Ex. 2003 at 185. The major focus of such pre-formulation studies was “on the solubility and stability as a function of a number of extrinsic factors, such as pH, protein concentration, ionic strength, buffer composition and temperature.” *Id.* at 186. A POSA would not have known the degradation pathways, and their relative importance, for a specific protein, without conducting extensive biochemical and biophysical analyses. *See id.* at 185–86; Ex. 2001 at 243–44 (citing earlier articles).

A pharmaceutical formulator was faced with a variety of antibody degradation pathways including oxidation, deamidation, aggregation,

fragmentation, unfolding, and other forms of chemical and physical modification that lead to loss of function. *See* Ex. 2001 at 106–112; Ex. 2002 at 1902–03. As discussed in Carpenter, “determination of the relative importance of various degradation pathways” is essential. Ex. 2003 at 185. This hierarchy of degradation pathways was a complicated function of the protein itself, solution components, and the environmental factors. For example, by varying the last two, the formulator may be able to reduce some of the degradation pathways but concurrently exacerbate others due to interplay between the roles of various components and parameters. Ex. 2016 at 147. As a result, formulation development was an unpredictable and challenging process, as the number of formulation components and parameters available are “far too many” “to allow a purely empirical screening approach to be successful.” Ex. 2002 at 1902. Even the complete version of the McNally book cited by Dr. Schöneich teaches that protein degradation processes represent a “complex interplay of molecular determinants,” making stabilization a “challenge for the protein formulator.” Ex. 1031 at 28.

**c) A stable formulation of one antibody would not have been expected to work for a different antibody.**

Given the protein-specific nature of the formulation challenge, it was well-known that protein formulation “does not readily lend itself to a generic approach.” Ex. 2003 at 185; *see also* Ex. 2018 at 359 (“The effects of protein degradation such as deamidation or oxidation cannot be predicted *a priori* and

have to be determined for each protein.”). Indeed, “the structural differences among different proteins are so significant that *generalization of universal stabilization strategies has not been successful.*” Ex. 2016 at 130 (emphasis added). Dr. Schöneich’s McNally exhibit further confirms the understanding in 2003: “Every protein has *unique physicochemical characteristics* and the potential to *behave differently stability-wise* in the presence of a particular excipient.” Ex. 1031 at 145 (emphases added). As glycoproteins, antibodies present similar formulation issues. Ex. 2001 at 106. “Each antibody has its *own unique personality* related to its requirements for stability,” which renders an antibody incapable of routinely being formulated according to approaches used for other antibodies. *Id.* at 107 (emphasis added). “The interfacial surface of *each antibody drug is unique* and thus *requires specific formulation components* to provide maximal stability and retention of activity.” *Id.* (emphases added). Moreover, each antibody can have its own reasons for instability and be prone to select degradation events. Ex. 2033 at 386.

Deamidation was (and continues to be) a particularly challenging antibody-specific degradation event. *See* Ex. 2040 at 559; Ex. 2001 at 106–08 (“Deamidation events appear to be highly selective events for individual antibodies.”); Ex. 2036 at 145–46 (“Depending on the antibody sequence and/or structure, Asn . . . can undergo deamidation rapidly . . . . Deamidation . . . represents

a significant concern during the development of antibody-based therapeutics.”); Ex. 2035 at 1; *see also* Ex. 2038 at 1897, 1902. Further, even across IgG monoclonal antibodies with “significant sequence homology, it is clear that the differences present [due to the intrinsic nature of a particular antibody] can have a profound impact on [] various physical properties.” Ex. at 2001 at 243; *see also id.* at 106–112, 244.

Petitioner suggests that because Wang and Cleland discuss the challenges of formulating proteins generally without specifically addressing antibody formulation, those challenges somehow do not apply to antibodies. Pet. at 41–42. But antibodies are among the most complex proteins, and numerous references attest that the stability issues of protein formulations generally apply equally to antibody formulations. *See, e.g.*, Ex. 2019 at 269 (“Antibodies are complex multidomain proteins and mechanisms governing their thermodynamic and, in particular, colloidal stability are not fully understood.”); Ex. 2017 at 656 (discussing challenges in the design of biologic formulations, including antibodies as well as other protein therapeutics); Ex. 2034 at 119. These references demonstrate that the stability and formulation issues outlined in Wang and Cleland, and other references discussing proteins generally, also apply specifically to antibodies. Further, Dr. Schöneich himself cites references directed to proteins in

general. *E.g.*, Ex. 1002 ¶¶ 35, 36, 38 (citing Exs. 1029 (Frokjaer) and 1031 (McNally)).

Neither Petitioner nor Dr. Schöneich provides contrary evidence supporting the purported interchangeability of antibodies and formulations. Indeed, as late as 2014, the authors of one review explained that “[d]espite recent advances, the identification of suitable formulation conditions for a specific monoclonal antibody *remains challenging* and cannot be determined from its amino acid sequence.” Ex. 2019 at 271 (emphasis added).

**d) Developing stable, high-concentration liquid antibody formulations was particularly difficult to achieve.**

Formulation complexities for higher antibody concentrations were especially challenging. Indeed, Petitioner identifies no stable, liquid high-concentration antibody formulation in the prior art. The reality was that high concentrations increased antibody aggregation events, resulting in particularly difficult obstacles to achieving stability. *See* Ex. 2030 at 138–39 (reviewing challenges to antibody development and discussing antibody products approved by 2002); *see* Ex. 2016 at 152 (“Protein aggregation is generally concentration dependent.... Accelerated aggregation of proteins at high concentrations has been reported in many cases.”) Ex. 2018 at 311 (“[A]ssociation of the protein was observed at high protein concentrations[.]”).

Even by 2007, achieving stable high-concentration liquid antibody formulations remained very difficult. *See* Ex. 2002 at 1905 (“Development of [high antibody concentration] formulations poses a number of serious obstacles ... [including] undesirably high-solution viscosities, opalescence, and increased rates of aggregation.”); *see* Ex. 2001 at 110 (“As protein concentration and temperature goes up, so does the probability of [events] leading to aggregation....”). Randolph discusses the antibody therapeutic HERCEPTIN<sup>®</sup>, having a concentration of 21 mg/mL, as an example of a high-concentration protein formulation that presented complex stability challenges. *See* Ex. 2002 at 1905 (discussing HERCEPTIN<sup>®</sup>); Ex. 2005 at 1; *see also* Ex. 2004 at 1394 (highly concentrated protein formulations are over 10 mg/mL). HERCEPTIN<sup>®</sup> was developed and approved as a freeze-dried powder, consistent with the expectation that developing liquid antibody formulations of high concentrations would be extremely difficult. *See* Ex. 2005 at 1.

Moreover, a POSA in 2003 would have understood that various additional factors could “disrupt this delicate balance” of protein stability, adding to the multifaceted complexity of developing high-concentration antibody formulations. Ex. 2016 at 145; *id.* at 138 (“Protein aggregation may be induced by a variety of physical factors, such as temperature, ionic strength, vortexing, surface/interface adsorption, etc.). Yet Dr. Schöneich declares—without any citation support—that

“[o]ne of ordinary skill would have simply calculated the appropriate concentration of natalizumab” to achieve the uniquely concentrated and stable formulations of natalizumab in the ’321 patent inventions. Ex. 1002 ¶ 106; *see also id.* ¶ 145. Dr. Schöneich fails to identify a stable, liquid antibody formulation of high-concentration in the prior art. Dr. Schöneich does not even attempt to address the well-established body of literature teaching that high-concentration liquid antibody formulations presented complex stability challenges. *See, e.g.*, Ex. 2030 at 138–39; Ex. 2002 at 1905; Ex. 2004 at 1394; Ex. 2001 at 110; *id.* at 242; *id.* at 244. In reality, achieving stable liquid antibody formulations, particularly those at high concentrations, was extremely difficult, and sometimes impossible. *See, e.g.*, Ex. 2019 at 271 (“[A] considerable proportion of human monoclonal antibody candidates *fail formulation studies.*”) (emphasis added).

**e) Reference pages omitted by Petitioner and Dr. Schöneich show that antibody formulation components were not routine.**

One example of the serious complexities presented by antibody formulation components in 2003 was phosphate-buffer, which is recited in the ’321 patent claims. Phosphate-buffer had been reported to catalyze reactions that lead to protein deamidation. Ex. 2003 at 186–87. The pages omitted from Dr. Schöneich’s own Exhibit 1031 (McNally) also taught that phosphate-buffers may promote oxidation. Ex. 2015 at 20. Additionally, in their Frokjaer exhibit, Petitioner and Dr.



Schöneich exclude the pages demonstrating that formulating proteins in liquid solutions required achieving precise formulation components, parameters, and combinations specific to a particular protein. *See* Ex. 1029 (omitting pp. 148–149; 153–159; 166–170); *see* Ex. 2020 at 155–158; 166–170).

Confirming that Dr. Schöneich uses impermissible hindsight, he does not address the vast number of other known components, parameters, and combinations as formulation options. For example, Frokjaer states that choosing an effective antioxidant for liquid protein formulations “*must be practised* in formulation development.” Ex. 2020 at 154 (emphasis added). Yet Dr. Schöneich does not even mention an antioxidant as a component that a POSA would have considered. On the other hand, Dr. Schöneich states that the claimed phosphate-buffer component would be routine, notwithstanding the significant concerns recognized in the prior art. Dr. Schöneich’s sole focus on the components claimed in the ’321 patent demonstrates his hindsight-driven analysis.

**f) Dr. Schöneich’s own work confirms that the unique structures of antibodies render their successful formulation unpredictable.**

Dr. Schöneich has recognized and expressed the expectation in 2003 that developing a liquid antibody formulation was a complex endeavor based in large part on the unique characteristics of each antibody. For example, an article Dr. Schöneich co-authored in 1995 about the chemical instability of proteins states:

[P]roteins ... have the disadvantage of being unstable during . . . formulation. ... The development of a protein into a marketable pharmaceutical product requires a careful design of processing and formulation conditions. It is well recognized that chemical instability of a protein is not only *dependent on its intrinsic structure*, but is also influenced by exogenous factors such as pH, temperature, buffer species and other components in formulations.”

Ex. 2021 at 12–15 (emphasis added).

Another article Dr. Schöneich co-authored in 2016 about the chemical stability of IgG glycoforms states, “any chemical change, which would modify the primary or higher order structure of an IgG [antibody], could affect not only its stability but also its potency and immune potential.” Ex. 2022 at 575. Furthermore, the article reported that degradation of antibodies was “*glycan dependent....* Our data will show that different glycans not only *affect chemical degradation differently* but also do lead to *different impurity profiles*, which can affect chemical degradation.” *Id.* at Abstract (emphasis added).

Contradicting his own research and countless references describing the challenges of obtaining a stable, high-concentration liquid antibody formulation, Dr. Schöneich declares—without any citation support—that “[i]t is this similarity in structural characteristics that allows one IgG mAb to be compatible with the excipients used in a different known, stable, aqueous formulation of another IgG mAb.” Ex. 1002 ¶ 34. Dr. Schöneich apparently references the “largely constant

remaining [non-variable] domains,” as well as the alleged “identical” secondary, tertiary, and quaternary structures “of all IgG mAbs,” to support this overly simplistic generalization. *Id.* However, Dr. Schöneich misstates the degree of similarity among higher order IgG antibody structures, in addition to ignoring the various diverse IgG components besides the amino acids of the variable region. As discussed above, it was known that there were differences in higher order (secondary, tertiary, and quaternary) structures among IgG antibodies. *See supra* Section III.A.2; Ex. 2013 at 7–9; Ex. 2015 at 28; Ex. 2001 at 243–44. Further, diversity in the antibodies’ constant fragment (Fc) regions, hinge regions, and glycosylation result in distinct biophysical characteristics among IgG antibodies. *See* Ex. 2013 at 8–9; Ex. 2001 at 105; Ex. 2016 at 145 (“The effect of glycosylation on stability of proteins is highly protein-dependent”). Dr. Schöneich ignores all of this in his simplistic, unsupported analysis.

**B. The inventions claimed by the ’321 patent are not merely a compilation of “result-effective variables” subject to routine optimization.**

Petitioner attempts to fill gaps in its obviousness allegations by asserting that the elements claimed by the ’321 patent are merely “result-effective variables subject to routine optimization.” *See, e.g.,* Pet. at 27, 46 (arguing that natalizumab concentration is a result-effective variable). However, the Petition is void of *any* mention of what the desired “result” would be for each alleged result-effective

variable, and, therefore, fails to establish that the prior art disclosed the relationship between the variable and the result in the prior art. Moreover, as explained further in Section III.B.3, *infra*, the circumstances here are distinguishable from cases applying the results-effective variable doctrine. For instance, the '321 patent does not claim a *range* of natalizumab concentrations but instead a “20 mg/ml” natalizumab concentration. *C.f. In re Aller*, 220 F.2d 454, 456 (C.C.P.A. 1955) (“No invention is involved in discovering optimum ranges of a process by routine experimentation.”) (emphasis added). As discussed below, Petitioner’s conclusory statements fail to support a finding of obviousness.

**1. Petitioner fails to show that protein concentration of liquid antibody formulations is a result-effective variable.**

Petitioner not only neglects to articulate the desired “result,” but also disregards the threshold step of properly identifying the result-effective variables. Petitioner relies on the rule from *In re Aller*: “where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.” Pet. at 22 (quoting *In re Aller*, 220 F.2d at 456). But in order for routine optimization of reaction conditions to be considered obvious, the prior art must *first* recognize that the conditions are result-effective variables—*i.e.*, variables that are “known to affect a particular desirable result[.]” *In re Haase*, 542 Fed. App’x 962, 967 (Fed. Cir. 2013); *see In re Applied Materials, Inc.*, 692 F.3d 1289, 1295 (Fed. Cir. 2012) (the *Aller* rule is “limited to

cases in which the optimized variable is a ‘result-effective variable’” (citation omitted)); *In re Antonie*, 559 F.2d 618, 620 (C.C.P.A. 1977) (finding exception to the *Aller* rule “where the parameter optimized was not recognized to be a result-effective variable”).

Here, Petitioner fails to present *any* evidence to show that natalizumab concentration is a result-effective variable. This stands in stark contrast to *In re Applied Materials*, relied on by Petitioner, where the Federal Circuit held that “substantial evidence” proved that groove dimensions on a polishing pad were result-effective variables. 692 F.3d at 1297 (noting one prior art reference which “clearly disclose[d] that *pitch* affects the polishing rate and uniformity”).

Petitioner’s failure to provide any evidence is not surprising because antibody concentration in a formulation is *not* a result-effective variable. More specifically, achieving a stable, liquid high-concentration antibody formulation, like the formulation claimed by the ’321 patent, was not recognized to be routine. As explained in Section III.A.3.d, *supra*, formulating proteins as an aqueous solution is unpredictable and challenging, and those challenges only become greater as antibody concentration increases. *See, e.g.*, Ex. 2001 at 110 (“As protein concentration and temperature goes up, so does the probability of [events] leading to aggregation....”). This is why at the time of the ’321 patent inventions,

lyophilized powders were the most common protein formulation, as discussed *supra* at Section III.A.1.

**2. Petitioner fails to show that buffer, salt, and polysorbate 80 concentrations are result-effective variables.**

Petitioner also makes numerous assertions that the excipients (*i.e.*, sodium chloride, phosphate-buffer, and polysorbate 80 concentrations) are result-effective variables. *See, e.g.*, Pet. at 28; *id.* at 32; *id.* at 52; *see also id.* at 33 (asserting that the “pH of a formulation containing natalizumab” is a result-effective variable subject to routine optimization). These conclusory assertions are not true.

It is recognized even today that the stabilizing effects of excipients vary significantly from protein to protein because “there is no single pathway to follow in formulating [a liquid protein] product. Proteins must be evaluated on a case-by-case basis” based upon their individual structures and properties prior to formulation. *See Ex. 2016 at 178.* Furthermore, the excipients of a formulation are not discrete, optimizable variables that work in isolation, but instead are interdependent upon one another. *Id.* at 175 (“Both the type and level of excipients can significantly affect protein stability.... When multiple excipients are used, they should not interact with one another, and, more importantly, should not adversely affect protein stability. Thus, compatibility studies should be conducted.”) Accordingly, changing one or more of these variables can profoundly affect the

overall stability of the protein in the formulation and the overall viability of the formulation as a therapeutically-effective composition. *See* Ex. 2001 at 107–112.

**3. Petitioner’s arguments further fail because the result-effective variable doctrine does not apply in these circumstances.**

Even if protein concentration were a result-effective variable, the circumstances here are distinguishable from cases applying the result-effective variable doctrine because (1) the ’321 patent does not claim a *range* of natalizumab concentrations and (2) the prior art references do not disclose “the general conditions of a claim[.]” *Aller*, 220 F.2d at 456

On this point, Petitioner’s reliance on *In re Peterson* (Pet. at 27) is ill-founded. In *In re Peterson*, the Federal Circuit merely reiterated the uncontroversial rule that “[a] *prima facie* case of obviousness typically exists when the *ranges* of a claimed composition overlap with the ranges disclosed in the prior art.” 315 F.3d 1325, 1329 (Fed. Cir. 2003) (emphasis added). Further, the Court noted that “*each range* listed in Peterson’s claim 5 *lies within* the corresponding range disclosed in [the prior art].” *Id.* (emphasis added). Here, claim 1 of the ’321 patent requires a “20 mg/ml” natalizumab concentration and does not claim a range of concentrations. Moreover, Petitioner fails to cite *any* prior art reference that discloses a “20 mg/ml” natalizumab concentration. For example, van Oosten and Zenapax (Ground 1) include antibody concentrations of 10 mg/mL and 5 mg/mL,

respectively. Gordon, Orthoclone, and Aversano (Ground 2) disclose antibody concentrations of 5 mg/mL, 1 mg/mL, and 5 mg/mL, respectively. These low-concentration levels are nowhere close to the claimed high concentration of 20 mg/mL. In particular, Gordon (Ex. 1017 at 7), which discloses a natalizumab formulation, is four times *less* concentrated than the claimed level of 20 mg/mL. Pet. at 46; *see also In re Patel*, 566 Fed. App'x 1005, 1010 (“[E]ven small differences in formulations can be meaningful ... [and] proximity alone is not enough to establish ... obviousness.”). Petitioner also fails to cite any combination of prior art that provides a motivation to combine natalizumab with the claimed combination of excipients at the claimed concentrations.

#### **IV. PETITIONER FAILS TO SHOW THE CHALLENGED CLAIMS ARE UNPATENTABLE OVER VAN OOSTEN OR ZENAPAX IN VIEW OF SORBERA.**

Petitioner fails to meet its burden to show that the combination of van Oosten (Ex. 1014) or Zenapax (Ex. 1024) in view of Sorbera (Ex. 1019) renders the challenged claims unpatentable. As discussed in detail below, none of these references discloses a formulation with an antibody concentration of 20 mg/ml nor do they disclose stable liquid formulations. Petitioner does not show that a POSA, with the knowledge of the unpredictable and highly antibody-specific formulation art, would have had a reasonable expectation of success in obtaining a stable, high-



concentration liquid natalizumab formulation based on these references. Instead, Petitioner relies merely on hindsight.

van Oosten discloses humanized IgG1 monoclonal anti-TNF antibody cA2 (Ex. 1014 at 4), also known as infliximab, an antibody that is separate and distinct from natalizumab—a humanized IgG4 monoclonal  $\alpha$ 4 integrin-binding antibody. van Oosten reports that treatment with infliximab resulted in improvement for patients with Crohn’s Disease (“CD”) but “treatment of MS patients ... may ... be harmful...” (*Id.* at 6.) Unlike the invention claimed by the ’321 patent, the formulation disclosed in van Oosten was a low-concentration formulation—10 mg/mL of infliximab. van Oosten also provides no data about the stability of a high concentration antibody formulation and does not suggest that any IgG antibody could be “simply substituted” for infliximab—much less natalizumab.<sup>4</sup>

Zenapax relates to a humanized IgG<sub>1</sub> monoclonal antibody, an antibody that is also separate and distinct from natalizumab. Ex. 1024 at 2. Zenapax was indicated for the prophylaxis of organ rejection in patients receiving renal transplants. (*Id.* at 3.) Similar to van Oosten, the formulation disclosed in Zenapax

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<sup>4</sup> The liquid antibody formulation van Oosten discloses was abandoned and replaced with a lyophilized formulation for commercial purposes. *See supra*, Section IV.B.1.

is a low-concentration formulation—5 mg/mL of antibody. Zenapax also provides no data on the stability of a high concentration formulation and does not suggest that any other IgG antibody could be “simply substituted” for Zenapax—much less natalizumab.

Sorbera discloses that natalizumab can be used to treat patients with CD or MS. But, as Petitioner appears to admit, Sorbera does not disclose a stable *high-concentration* formulation of natalizumab as claimed by the '321 patent. Pet at 27–28.

Petitioner attempts to fashion Ground 1 as simply the combination of van Oosten or Zenapax in view of Sorbera. Petitioner, however, implicitly concedes that those reference cannot render the challenged claims unpatentable by relying on no less than *nineteen* additional prior art references in Ground 1 in an attempt to plug holes in a sinking ship. *See* Pet. at 20–42 (citing Exs. 1010; 1016; 1017; 1020; 1021; 1022; 1023; 1025; 1027; 1028; 1029; 1030; 1031; 1032; 1033; 1034; 1035; 1036; 1037). By citing to additional prior art throughout its discussion of Ground 1, Petitioner has failed to identify the challenge that is Ground 1 with the specificity required by 37 C.F.R. § 42.104(b). Ground 1 is defective and should be denied.

**A. van Oosten, Zenapax, and Sorbera fail to disclose a stable, high-concentration liquid formulation of any antibody.**

Even if a POSA were to combine van Oosten, Zenapax, and Sorbera, this combination could not render the claims of the '321 patent unpatentable because it does not disclose all claim elements. Indeed, Petitioner concedes that van Oosten, Zenapax, and Sorbera do not disclose a formulation with an antibody concentration of 20 mg/mL—*i.e.*, a high-concentration liquid formulation. Pet. at 16, 26–28. In fact, the only reference disclosing natalizumab, Sorbera, does not disclose *any* concentration other than to say that natalizumab was administered by IV infusions. Ex. 1019 at 3. And the most concentrated formulation, van Oosten, is half as concentrated as the least concentrated formulation claimed by the '321 patent.<sup>5</sup>

Using hindsight, Dr. Schöneich figures that a 3 mg/kg dose somehow translates to a 20 mg/mL concentration of natalizumab. Ex. 1002 ¶¶ 106–108. But Dr. Schöneich fails to provide any evidence to support his superficial characterization that only dosing determines formulated antibody concentrations. Instead, Dr. Schöneich states that “[a]rriving at a natalizumab concentration of 20 mg/ml is nothing more than a routine optimization of a result effective variable” and that “[o]ne of ordinary skill would have simply calculated the appropriate

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<sup>5</sup> The concentration of the formulation claimed by the '321 patent is at least 4 times as concentrated as the formulation disclosed in Zenapax.

concentration of natalizumab.” *Id.* ¶ 106. As discussed below, these conclusory statements are without merit and should be given little or no weight. 37 C.F.R. § 42.65(a).

As explained in Section III.C, *supra*, there is simply no evidence that concentration of an antibody formulation is a result-effective variable. Tellingly, Dr. Schöneich does not even attempt to address the well-established body of literature teaching that high-concentration liquid antibody formulations presented complex stability challenges. *See supra* Section III.A.3.d. And Dr. Schöneich cites *no* high-concentration liquid IV antibody products. *Id.*

In an apparent attempt to plug holes in Ground 1, Dr. Schöneich cites to Gordon (Ex. 1017) and Cummins (Ex. 1021) for the proposition that IgG formulations between 5 and 50 mg/mL were known. Ex. 1002 ¶ 106. But this last ditch effort by Dr. Schöneich also fails. As explained in Section V.A, *infra*, Gordon does not disclose a high-concentration formulation of natalizumab. Cummins discloses hyperimmune globulin against (HIV-1), which is a mixture of IgG antibodies against HIV-1. One lot is brought to 50 mg/mL in saline for *in vitro* testing. Ex. 1021 at 7. Cummins, however, does not provide any information about natalizumab, a buffer, pH, or the need for polysorbate 80, let alone the amount, or concentration of a particular component claimed by the ’321 patent. Thus it is not surprising that Petitioner identifies no evidence indicating the experimental 50

mg/mL IgG lot in Cummins is stable. Petitioner has therefore failed to meet its burden because there is no evidence that van Oosten, Zenapax, or Sorbera disclose a high-concentration liquid formulation of any antibody, let alone a 20 mg/mL liquid formulation of natalizumab.

Petitioner also fails to present evidence that van Oosten, Zenapax, or Sorbera discloses a high-concentration liquid formulation that is “*stable*” (*see* claim 1), including a high-concentration liquid formulation, let alone one that is “*stable* when stored at about 5°C to about 8°C *for greater than 6 months*” (*see* claim 3). As described above, van Oosten and Zenapax disclose low-concentration formulations, and Sorbera makes no mention of any formulation other than to say that a formulation was administered. Petitioner completely fails to address the stability issues surrounding high-concentration liquid formulations. *See supra* Section III.A.3.d. Petitioner has therefore also failed to meet its burden because there is no evidence that van Oosten, Zenapax, or Sorbera discloses a stable, high-concentration liquid formulation of any antibody, let alone a 20mg/mL liquid formulation of natalizumab that is stable “for greater than 6 months” (*see* claim 3).

**B. Petitioner relies on impermissible hindsight.**

Petitioner alleges the “prior art is replete with IgG and IgG mAb formulations having the same excipients as those in the Challenged Claims at the same or similar concentrations.” Pet. at 14. But Petitioner relies on hindsight to

cherry-pick from the prior art. Furthermore, Petitioner fails to identify any reason to modify van Oosten, Zenapax, and Sorbera to arrive at the claimed invention.

**1. Petitioner fails to show why a POSA would have had reason to select the formulation of van Oosten or Zenapax over other possible formulations and combinations of components (Ground 1).**

Petitioner points to no reason why a POSA would have selected the formulations of van Oosten or Zenapax. van Oosten discloses a formulation for cA2 (also known as infliximab, *see* Ex. 1015 at 4). *See* Ex. 1014 at 6. While van Oosten mentions that cA2 was reported to provide improvement in Crohn's disease, van Oosten does not disclose the formulation used in such treatment. *See* Ex. 1014 at 4; Pet. at 23 (assuming without support that the formulation disclosed in van Oosten was also the formulation reported to be effective in treating CD). Thus, nothing in van Oosten itself would have directed a POSA to select its formulation for a different antibody, natalizumab, to obtain the formulations claimed in the '321 patent.

In addition, almost two years after van Oosten but more than four years before the priority date, cA2 (infliximab) was marketed in a formulation different from van Oosten's formulation. Infliximab was and continues to be sold as a lyophilized powder, not an aqueous solution. *See* Ex. 2009 (FDA Approval Label); Ex. 2027 (FDA Approval Letter). Petitioner fails to explain why a POSA would

have chosen the aqueous formulation of van Oosten, knowing that the manufacturer of infliximab pursued a different formulation.

Neither of the other Ground 1 references—Zenapax and Sorbera—provides the missing reason. Zenapax (daclizumab) is a low-concentration formulation indicated for the prophylaxis of organ rejection, and Petitioner provides no reason why a POSA would have sought to increase the concentration and substitute natalizumab into its formulation. Ex. 1024 at 2. Sorbera, which, as Dr. Brod explains, discloses a natalizumab formulation effective in treating MS (*see* Ex. 1011 ¶¶ 17, 19), would not have provided any reason to search for a new formulation for natalizumab, let alone to select the formulation in van Oosten or Zenapax specifically. *See also* Ex. 1011 (Brod Decl.) ¶ 21 (“The precise formulation of the antibody [natalizumab] should not have an effect on the treatment of MS as long as the formulation provides stability, which means it does not significantly affect the therapeutic activity of the protein upon storage.”). Moreover, *even if* a POSA had a reason to deviate from the natalizumab formulation in Sorbera, Sorbera did not disclose its formulation, and thus a POSA would not have even known whether, and if so how, Sorbera’s formulation differed from other formulations (including van Oosten and Zenapax), and thus would not have known what changes to make to arrive at a different formulation.

Petitioner further ignores that the state of the art provided reasons against selecting the formulations in van Oosten and Zenapax. For example, the antibodies in van Oosten and Zenapax are both IgG1 antibodies, whereas natalizumab is an IgG4 antibody. *See* Exs. 1014; 1024; 1001 at 7:11–13. Petitioner does not explain why a POSA, knowing about the differences among IgG subclasses and across antibodies even within the same subclass (*see supra* Section III.A.2), would have nonetheless chosen the formulation used in van Oosten or Zenapax for natalizumab, especially when Sorbera taught successful use of a natalizumab formulation (even if not identifying its formulation).

Petitioner also overlooks that the antibody concentrations of van Oosten and Zenapax are low—10 mg/mL and 5 mg/mL, respectively. *See* Ex. 1014 at 5; Ex. 1024 at 2. Petitioner fails to explain why a POSA would have chosen either formulation when designing a formulation containing a much higher antibody concentration as claimed in light of the unique challenges in designing high-concentration antibody formulations. *See, e.g.*, Exs. 2040; 2003; *see also supra* Section III.A.3.d.

Lastly, Petitioner ignores that there were other IgG antibodies being marketed and developed at the time, in formulations different from the van Oosten and Zenapax formulations. Such antibody products include HERCEPTIN<sup>®</sup> (Ex. 2005), RITUXAN<sup>®</sup> (Ex. 2031), SIMULECT<sup>®</sup> (Ex. 2029), and SYNAGIS<sup>®</sup> (Ex.



2006). *See also* Ex. 2001 at 116–17 (Table 8-1).<sup>6</sup> All of these formulations contain IgG antibodies in a formulation having a different combination of excipients than the combinations in van Oosten or Zenapax—or in any of the four formulations Petitioner selected. Petitioner does not explain why a POSA—assuming a POSA would have been searching for a new formulation for natalizumab in the first instance—would have selected the particular formulation for infliximab or daclizumab over such other formulations containing IgG antibodies.

**2. Petitioner fails to show why a POSA would have had reason to select the antibody and excipient concentrations claimed in the '321 patent based on Sorbera, van Oosten, and Zenapax.**

In addition to Petitioner's failure to show any reason to modify Sorbera, and to go a step further and select the van Oosten or Zenapax formulation for such a modified formulation, Petitioner fails to demonstrate why a POSA would have selected the particular antibody and excipient concentrations claimed in the '321 patent. Petitioner relies only on hindsight, using the claims as a starting point.

For example, with respect to antibody concentration, Petitioner relies on van Oosten and Zenapax—low concentration antibody formulations of different antibodies (Pet. at 16)—but ignores the known difficulties of achieving a stable

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<sup>6</sup> At least SIMULECT<sup>®</sup>, SYNAGIS<sup>®</sup>, and HERCEPTIN<sup>®</sup> are lyophilized. *See* Exs. 2005; 2006; 2029.

high-concentration liquid formulation and the fact that a POSA would not view IgG antibodies as “simple substitutes.” *See supra* Sections III.A.3.d; III.A.2. Petitioner instead asserts that “[o]ne of ordinary skill in the art would have simply calculated the appropriate concentration of natalizumab for storage in vials over a range of volumes,” pointing to the dose of natalizumab used in the Sorbera clinical studies (but not the product volume, as Sorbera does not disclose that volume). *See* Pet. at 27; Ex. 1002 ¶¶ 106–108. Petitioner additionally attempts to rely on two non-asserted references, in combination with Zenapax, to show the volume of various packaging vials. Pet. at 28. Yet Petitioner does not explain why a POSA would have selected a particular lower volume vial that would just so happen to result in a higher concentration of fluid. *See id.* (citing Exs. 1024; 1027; 1028).

Moreover, Petitioner never alleges that the dose administered in Sorbera provides a reason to design a high-concentration natalizumab formulation as claimed. In fact, Petitioner’s expert Dr. Brod states “the concentration of natalizumab is not important from the stand-point of administration as partial, single or multiple vials can be added to an intravenous bag in order to administer an efficacious dose.” Ex. 1011 ¶ 20. According to Dr. Brod, dosing—which is the amount of antibody per unit weight of the patient (*e.g.*, mg per kg)—would not have directed a POSA to a particular formulation concentration—which is the amount of antibody per unit volume of the formulation (*e.g.*, mg per ml). Dr.

Brod's statement, which is in accord with Dr. Schöneich's opinion (*see* Ex. 1002 ¶ 108 ("I do not think any single concentration is critical...")), demonstrates the failure of Petitioner to show any reason to seek a high natalizumab concentration.

With respect to the concentration of excipients, Petitioner simply asserts that a POSA would have arrived at the claimed concentrations through routine optimization, and that the concentrations are not critical to the formulation. *See* Pet. at 28–30–31, 32–33. But the prior art, including Dr. Schöneich's own Frokjaer exhibit, taught that both the type *and amount* of excipients *are* critical to the stability of antibody formulations. *See, e.g.*, Ex. 1029 at 150 ("In the pH range of 7–12, buffer concentration can have a significant effect on the rate of deamidation indicating general acid-base catalysis."); *id.* at 163 ("[T]he choice of surfactant and the final concentration optimal for stabilization is quite dependent on a variety of factors including other formulation ingredients, protein concentration, headspace in the container, the type of container, and test methodology."). Moreover, selecting the appropriate excipients, and their amounts, is not routine optimization. Rather, for some antibodies no stable formulation has been identified. *See, e.g.*, Ex. 2019 at 271. Thus, to the extent the claimed concentrations differ from the concentrations in the Ground 1 references (*see* Pet. at 16, Table 1), Petitioner fails to identify any reason for modifying the concentrations to arrive at the claimed invention.

**C. The documents cited by Petitioner for Ground 1 fail to establish a reasonable expectation of success of achieving the claimed invention.**

Petitioner fails to provide any specific evidence showing 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.” *Procter & Gamble v. Teva Pharm.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (quotation omitted). Petitioner offers no evidence showing *why* a POSA would have expected to successfully obtain a stable, high-concentration natalizumab formulation—including such a formulation that is stable “for greater than 6 months (*see* claim 3; Pet. at 36–37)—by selecting the antibody of Sobera and combining it with the formulation components of van Oosten or Xenapax. Petitioner instead merely points to two approved liquid antibody products—hand-picked from numerous other liquid and lyophilized products having entirely different formulations—as well as other references not even asserted in Petitioner’s statutory grounds.

**1. Petitioner fails to establish a reasonable expectation of success of achieving a stable, high-concentration liquid formulation of natalizumab.**

In apparent support of expecting to achieve a high-concentration formulation of natalizumab that was stable, Petitioner merely asserts that stable antibody formulations were “well-known in the prior art and approved by FDA.” Pet. at 39.

It references Orthoclone and Zenapax, but fails to provide any explanation about why a POSA would have expected to achieve a liquid high-concentration antibody formulation, much less one that has overcome well-known stability obstacles, given that both references are directed to *low-concentration* formulations of *different* antibodies. Further, its reliance on Orthoclone is improper because that reference is not part of its statutory ground for this challenge. Petitioner also improperly relies on Cummins and White, which are not part of either statutory ground in the Petition. *Id.* at 39. The Board should therefore disregard Petitioner's offer of Orthoclone, Cummins, and White as support. *See* 37 C.F.R. § 42.104(b)(2).

Nothing in the prior art supports that a POSA would have taken such a generic approach to formulation or have expected such approach to work. As explained in Section III.A.2, *supra*, each antibody is unique, with particular chemical and physical properties that result in numerous different degradation pathways required to be evaluated. *See, e.g.*, Ex. 2003 at 13. Such complexities are confirmed by Dr. Schöneich's own work and his Declaration exhibits. *See supra* Sections III.A.1; III.A.2; III.A.3.e; III.A.3.f. Formulating antibodies as a liquid (as opposed to a lyophilized, or freeze-dried, formulation) was especially unpredictable and challenging because the complex antibody structure must retain its physical and chemical stability for months or years, *see* Ex. 2016 at 148, 152,

163, 178, 164; Ex. 2001 at 106–112 (citing Exs. 2030; 2040), and “several chemical degradation pathways (*e.g.*, hydrolysis and deamidation) are mediated by water,” Ex. 2003 at 110.

Petitioner has not explained why a POSA would have even *attempted* a stable liquid antibody formulation, since “most proteins will not exhibit sufficient stability in aqueous solution to allow a liquid formulation to be developed.” Ex. 2003 at 188. The challenge of developing a stable liquid formulation is underscored by the prevalence of lyophilized (*i.e.*, freeze dried) formulations, which are not subject to the same degradation concerns. *See id.* at 184 (“Most protein pharmaceuticals currently on the market are sold as lyophilized formulations.”); Ex. 2004 at 1394 (“The issue of longer-term stability was addressed according to the most prevalent method for preservation of polypeptides, lyophilization.”); Ex. 2001 at 112–114, 123. Indeed, it was understood that “lyophilization should be considered as a primary mode for product development,” given the stability complications with aqueous formulations. Ex. 2003 at 110.

The unpredictability of aqueous formulations is further exacerbated with high (20 mg/mL) protein concentrations. Ex. 2002 at 1905 (“Development of [high antibody concentration] formulations poses a number of serious obstacles ....[including] undesirably high-solution viscosities, opalescence, and increased rates of aggregation.”); Ex. 2001 at 110 (“As protein concentration and

temperature goes up, so does the probability of [events] leading to aggregation....”); Ex. 2001 at 242 (citing earlier articles), 244.

Additionally, it was unclear in 2003 what components, parameters, and combinations thereof would have a stabilizing effect on a particular protein. *See* Ex. 2016 at 178. An excipient, such as a buffer, or formulation parameter, such as pH, that stabilizes one protein may destabilize another protein. *Id.* at 145, 147. Even in 2007, four years *after* the priority date, it was understood that the “[d]evelopment of these [high antibody concentration] formulations poses a number of serious obstacles to commercialization.” Ex. 2002 at 1905.

In the face of the wide body of literature directed to the antibody-specific stability challenges both before and after 2003 for high-concentration formulations, Petitioner cannot meet its burden by merely selecting two approved low-concentration liquid antibody products that happen to contain sodium phosphate and polysorbate 80. *See* Ex. 1022 at 4. A POSA in 2003 would have readily appreciated that high-concentration antibody formulations presented special stability problems. Yet both Petitioner and Dr. Schöneich entirely ignore this issue.

For the same reasons, then, Petitioner’s reliance on Cummins and White (Pet. at 24, 36–37), also directed to *different* antibodies, fails to provide specific evidence showing an expectation of successfully obtaining a stable, high-concentration liquid natalizumab formulation. Dr. Schöneich points to Cummins’

report of “extended stability” for 50 mg/mL of donor plasma hyperimmune IgG against HIV (HIVIG) in sodium chloride. Ex. 1002 at ¶ 128. Dr. Schöneich fails to explain why a POSA would in any way have regarded plasma HIVIG similar to natalizumab, a humanized monoclonal antibody. He then asserts—with no citation support—that adding phosphate-buffer and polysorbate 80 to the product “would only enhance the stability of natalizumab.” *Id.*<sup>7</sup> Clearly such conclusory assertions do not meet Petitioner’s burden. This is especially true in view of Dr. Schöneich’s own work confirming that the unique structures of antibodies render successful formulations unpredictable. *See supra* Section III.A.3.f.

Overall, Dr. Schöneich cites no prior art that gives “[any] indication of which parameters were critical [to formulating natalizumab] or [any] direction as to which of many possible choices is likely to be successful.” *In re Cyclobenzaprine*, 676 F.3d 1063, 1070–71 (Fed. Cir. 2012). Indeed, Dr. Schöneich

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<sup>7</sup> Once again failing to meet the particularity requirements, Petitioner does not identify any portion of Cummins that reports stability for an antibody at 50 mg/mL. *See* Pet. at 39 (citing Ex. 1021 at 8); *see also* Ex. 1002 at ¶ 128 (citing Ex. 1021 at 8). Petitioner cites to Cummins’ only report of stability at page 8, yet this report refers to an IgG donor lot, and Petitioner identifies no connection between the stability of that lot to the 5% protein solution reported on page 6.



opines that concentration is *not* critical. Ex. 1002 ¶ 108 (“I do not think any single concentration is critical....”). He also ignores the vast number of possibilities showing the myriad of directions for combatting complex antibody degradation pathways. Ex. 1002 ¶¶ 106–108. Thus, without such guidance on how a high-concentration of natalizumab might reasonably be formulated, a POSA is left “merely throw[ing] metaphorical darts at a board in hopes of arriving at a successful result.” *In re Cyclobenzaprine*, 676 F.3d at 1071 (internal quotation marks and citation omitted).

**2. Petitioner fails to establish a reasonable expectation of success that natalizumab can be “simp[ly] substitute[d]” for the antibodies disclosed by van Oosten or Zenapax.**

Petitioner postulates that a reasonable expectation of success existed for substituting natalizumab for infliximab because “[i]nfliximab and natalizumab qualify as simple substitutes because their functions, i.e., treatment of CD, was well-known in the art.” Pet. at 25. Petitioner is wrong. As Petitioner concedes, while both infliximab and natalizumab are approved to treat CD, their approved formulations are very different—*i.e.*, infliximab is formulated as a lyophilized powder whereas natalizumab is a stable, liquid high-concentration formulation. Pet at 25 n.4. To overcome this deficiency, Petitioner asserts that substitution of infliximab with natalizumab “would have yielded [] predictable results.” Pet. at 25.

This statement is a conclusion without any evidentiary support and should be given little or no weight. 37 C.F.R. § 42.65(a).

Contrary to the hindsight-driven assertion by Petitioner (Pet. at 24–28) and Dr. Schöneich (Ex. 1002 ¶¶ 98–108), the prior art as of 2003 showed that a POSA would not have reasonably expected formulations designed for different antibodies to be able to be successfully adapted to natalizumab. *See supra* Section III.A.3.c. For example, the prior art taught that “each antibody drug is unique and thus requires specific formulation components to provide maximal stability and retention of activity.” Ex. 2001 at 107. Carpenter stated that “[e]ven for closely related proteins, the relative stability and major pathways for degradation might be quite different.” Ex. 2003 at 185–86. Wang further states that “generalization of stabilization strategies has not been successful.” Ex. 2016 at 130. Indeed, even Dr. Schöneich’s own publications demonstrate that antibodies cannot be simply substituted from one formulation to another. For example, prior to involvement in these proceedings, Dr. Schöneich stated that “each protein has unique physicochemical properties and degradation pathways, and . . . the impact of degradation on efficacy and safety is unique to each therapeutic protein product[.]” Ex. 2044 at 952. Thus, a POSA would have had no way of knowing whether natalizumab could have been successfully “substituted” into the formulation disclosed in van Oosten.

Similarly, a POSA would not have known if natalizumab could have been successfully “substituted” into the formulation disclosed in Zenapax. Like for van Oosten, Petitioner asserts that substitution of infliximab with natalizumab would have “yield[ed a] predictable result[.]” Pet. at 27. This too is a conclusion without any evidentiary support and should be given little or no weight. 37 C.F.R. § 42.65(a). As described above, the prior art showed a POSA would not have reasonably expected formulations designed for different antibodies to be able to be successfully adapted to natalizumab. *See supra* Section III.A.3.c. As a result, a POSA would have had no way of knowing whether natalizumab could have been successfully “substituted” into the formulation disclosed in Zenapax.<sup>8</sup>

**V. PETITIONER FAILS TO SHOW THE CHALLENGED CLAIMS ARE UNPATENTABLE OVER GORDON IN VIEW OF ORTHOCLONE OR AVERSANO.**

Petitioner fails to meet its burden that the combination of Gordon (Ex. 1017) in view of Orthoclone (Ex. 1022) or Aversano (Ex. 1023) renders the challenged claims unpatentable. These references do not disclose an antibody concentration of 20 mg/mL nor do any of them disclose a stable high-concentration liquid

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<sup>8</sup> Accordingly, the mere “existence of these formulations” does not show a “reasonable expectation of success” in substituting natalizumab in place of the antibodies disclosed in the formulations, as Petitioner alleges. *See* Pet. at 58.

formulation. Once again, Petitioner also does not show that there would have been any reasonable expectation of success in obtaining a stable, high-concentration liquid natalizumab formulation based on the disclosures in these references, coupled with the knowledge of a POSA about the unpredictable and highly antibody-specific formulation art.

Gordon discloses a low-concentration 5 mg/mL formulation of natalizumab in a solution of 50 mmol/L histidine buffer, 0.02% polysorbate 80 adjusted to pH 6. Ex. 1017 at 7. Gordon demonstrated that remission of CD symptoms occurred in a greater portion of patients treated with this low-concentration liquid formulation of natalizumab than those treated with placebo. *Id.* at 10. Notably, Gordon provides no data on stability and does not suggest that a phosphate-buffer could be “simply substituted” for histidine. Moreover, the Examiner considered Gordon in the prosecution of the related ’321 patent, ultimately finding that the claimed invention was not obvious. Pet. at 8.

Orthoclone relates to a non-humanized murine monoclonal IgG2a monoclonal antibody to CD3 antigen of human T. Ex. 1022 at 2. Orthoclone is a *murine* antibody that is separate and distinct from natalizumab—a *humanized* IgG4 monoclonal  $\alpha 4$  integrin-binding antibody. Orthoclone is indicated for the treatment of acute allograft rejection in renal transplant patients. *Id.* at 3. Similar to all the other references relied on by Petitioner, the formulation disclosed in Orthoclone is

a low-concentration formulation—1 mg/mL of antibody. Orthoclone also provides no data on the stability of a high-concentration formulation and does not suggest that any other antibody—much less natalizumab—could be “simply substituted” for Orthoclone.

Aversano relates to a chimeric monoclonal IgG4 monoclonal antibody CLB54 directed against CD18, and thus CLB4 is separate and distinct from natalizumab. Ex. 1023 at 2. Aversano investigated whether CLB54 could have therapeutic potential by “reducing the neutrophil-mediated component of reperfusion injury.” *Id.* at 4. Although Aversano reports that CLB54 “reduce[d] infarct size in a baboon model of 90 min ischemia followed by 4 h of reperfusion,” it was never approved as a commercial product. *See* Ex. 2042 at 817–18. The formulation disclosed in Aversano is another low-concentration formulation—5 mg/mL of antibody. Aversano also provides no data on the stability of a high-concentration formulation and does not suggest that any other antibody—much less natalizumab—could be “simply substituted” for CLB54.

Similar to its approach to Ground 1, Petitioner characterizes Ground 2 as simply the combination of Gordon in view of Orthoclone or Aversano. Petitioner, however, implicitly concedes that those reference cannot render the challenged claims unpatentable by relying on no less than *seven* additional prior art references in Ground 2 in an attempt fill in the gaps. *See* Pet. at 42–55 (citing Exs. 1010;

1014; 1018; 1024; 1026; 1029; 1030; 1032). By citing to additional prior art throughout its discussion of Ground 2, Petitioner has failed to identify the challenge that is Ground 2 with the specificity required by 37 C.F.R. § 42.104(b). As a result, Ground 2 is defective and should be denied.

**A. Gordon, Orthoclone, and Aversano fail to disclose a stable, high-concentration liquid formulation of any antibody.**

Even if a POSA were to combine Gordon in view of Orthoclone or Aversano, the combination could not render the claims of the '321 patent obvious because certain claim elements are missing. Indeed, Petitioner concedes that Gordon, Orthoclone, and Aversano do not disclose a formulation with an antibody concentration of 20 mg/mL—*i.e.*, a high-concentration liquid formulation. Pet. at 16, 45–46. In fact, Dr. Schöneich does not testify that a POSA would have arrived at the natalizumab concentration of the claimed invention from the disclosure in Orthoclone or Aversano. Ex. 1002 ¶ 145. Dr. Schöneich, instead, relies solely on Gordon to conclude that the “difference in concentration [between Gordon and the claimed invention] represents nothing more than routine optimization of a result effective variable.” *Id.* Yet the formulation in Gordon is *four times* less concentrated than the least concentrated formulation claimed in the '321 patent. Dr. Schöneich’s conclusion is driven by hindsight and is devoid of any evidentiary support. Dr. Schöneich’s conclusory statements are therefore without merit and should be given little or no weight. 37 C.F.R. § 42.65(a).

As discussed in Section III.C.2, there is no evidence that concentration of an antibody formulation is a result-effective variable. Dr. Schöneich identifies no prior art reference that discloses a stable, liquid-high-concentration antibody formulation. *See supra* Section III.A.3.d. Dr. Schöneich also does not even attempt to address the well-established body of literature teaching that high-concentration liquid antibody formulations presented complex stability challenges. *Id.* Petitioner has therefore failed to meet its burden because there is no evidence that Gordon, Orthoclone, or Aversano discloses a high-concentration liquid formulation of any antibody, let alone a 20 mg/mL liquid formulation of natalizumab as claimed in the '321 patent.

Petitioner also fails to present evidence that Gordon, Orthoclone, or Aversano disclose a high-concentration liquid formulation that is “*stable*” (*see* claim 1), including one that is “*stable* when stored at about 5°C to about 8°C *for greater than 6 months*” (*see* claim 3). As described above, Gordon, Orthoclone, and Aversano disclose low-concentration formulations. Petitioner completely fails to address the stability issues surrounding high-concentration liquid formulations. *See supra* Section III.A.3.d. Petitioner has therefore also failed to meet its burden because there is no evidence that Gordon, Orthoclone, or Aversano disclose a stable, high-concentration liquid formulation of any antibody, let alone a 20

mg/mL liquid formulation of natalizumab that is stable “for greater than 6 months” (*see* claim 3).

**B. Petitioner relies on impermissible hindsight.**

Petitioner once again relies on hindsight to cherry-pick Gordon, Orthoclone, and Aversano from the prior art. Furthermore, Petitioner fails to identify any reason to modify Gordon, Orthoclone, and Aversano to arrive at the claimed invention.

**1. Petitioner fails to show why a POSA would have had reason to select the formulation of Orthoclone or Aversano over other possible formulations and combinations of components (Ground 2).**

Petitioner points to no reason why a POSA would have selected the formulation of Orthoclone or Aversano for natalizumab. Orthoclone is a formulation for a murine mAb, IgG<sub>2a</sub> subclass, against CD3. The antibody in Orthoclone is not humanized like natalizumab, and is of a different IgG subclass. Petitioner does not explain why a POSA, knowing about the differences between murine and humanized mAbs and the IgG subclasses (*see supra* Section III.A.2) nonetheless would have chosen the formulation of Orthoclone for natalizumab, and deviate from the formulation disclosed in Gordon. Similarly, Aversano describes a chimeric CLB54 mAb, IgG<sub>4</sub> subclass, against CD18 that is completely different from natalizumab. Petitioner provides no reason why a POSA would have nonetheless selected the particular formulation in Aversano for natalizumab.



In addition, and like the formulations in van Oosten and Zenapax, the formulations in Orthoclone and Aversano are low-concentration formulations—only 1 mg/mL and 5 mg/mL, respectively. Petitioner fails to explain why a POSA would have chosen either formulation when designing a formulation containing a much higher antibody concentration as claimed in the '321 patent. *See supra* Sections III.A.3.d.

Petitioner's only alleged reason to deviate from the formulation in Gordon is based on a 2001 poster abstract by Subramanian *et al.* (Ex. 1026), which is not cited as part of Ground 2. *See* Pet. at 19, 43, 47 (asserting Subramanian directed a POSA away from using histidine buffers as in Gordon). Petitioner's reliance on Subramanian is improper and should therefore be disregarded by the Board. *See* 37 C.F.R. § 42.104(b)(2). In any case, Petitioner is incorrect that "Subramanian taught those of ordinary skill that histidine buffer combined with polysorbate 80 caused accelerated degradation of IgG mAb actives" generally. Pet. at 47; *see also* Pet. at 58 (arguing Subramanian "discloses accelerated potency loss of IgG mAb actives attributable to histidine buffers in the presence of polysorbate 80"). Subramanian only tested one antibody, and specifically an IgG<sub>2</sub> mAb; Subramanian did not test multiple or even several "IgG mAb actives." Thus, a POSA "reviewing Gordon"

would not have known about “the problematic histidine buffer” based on Subramanian. *See* Pet. at 46–47.<sup>9</sup>

Nor would a POSA, based on Gordon and Subramanian, have been directed to “incorporate phosphate buffer in place of histidine” (Pet. at 47), as nothing in Gordon or Subramanian even mentions phosphate-buffer or suggests its use. Notably, Subramanian observed potency loss in *both* histidine and citrate buffers and did not test any other buffers; Petitioner does not explain why potency loss in both histidine and citrate buffers would have directed a POSA specifically to phosphate-buffer, instead of simply teaching a POSA that Subramanian’s particular antibody was difficult to formulate (*see* Ex. 2019 at 271) and might also be unstable in other buffers, including phosphate. Moreover, and contrary to Petitioner’s assertion, there were more than “only a few buffers” (Pet. at 19, 48) available to a POSA; in fact, Frokjaer (Ex. 1029 at 151) provides twelve different buffers (including histidine and phosphate) that are used in protein formulations, at least half of which are suitable for use “at pH of about 6.0[.]” Pet. at 47 (referring

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<sup>9</sup> Indeed, even years after Subramanian, in a 2013 review, histidine is stated to be “the primary buffer of choice” and “extremely useful in formulating several mAb-based commercial products.” *See* Ex. 2028 at 460 (discussing buffers as well as surfactants such as polysorbate 20 and 80).

to the pH of the formulation in Gordon). The mere existence of phosphate-buffer says nothing about the desirability or reason to include it in a high-concentration natalizumab formulation, much less with any expectation of success.

Similarly, even assuming Subramanian directed a POSA away from using histidine and polysorbate together in a formulation (*see* Pet. at 43), Petitioner fails to explain how Subramanian pointed a POSA to the specific formulations in Orthoclone or Aversano over other possible combinations of excipients. For example, Petitioner overlooks that a POSA would have considered other formulation options, including adding an antioxidant (*see supra* Section III.A.3.e), *if* Subramanian had indeed taught that histidine and polysorbate together are generally “problematic” (*see* Pet. at 47). Petitioner fails to explain why a POSA would have turned to the formulations in Orthoclone or Aversano, when a POSA could have looked to any of the other number of possible excipients and formulations available at the time, including the preferred lyophilized formulations.

**2. Petitioner fails to show why a POSA would have had reason to select the antibody and excipient concentrations claimed in the '321 patent based on Gordon, Orthoclone, and Aversano.**

As with the Ground 1 references, Petitioner again relies on hindsight and simply asserts that a POSA would have arrived at the claimed concentrations through routine optimization, and further asserts that the concentrations are not

critical to the formulation. *See* Pet. at 49, 51–52. But, as explained above, the prior art taught that both the type *and amount* of excipients *are* critical to the stability of antibody formulations. *See supra* Section IV.B.2. Moreover, selecting the appropriate excipients, and their amounts, is not routine optimization. Rather, for some antibodies no stable formulation has been identified. *See id.* Thus, to the extent the claimed concentrations differ from the concentrations in the Ground 2 references (*see* Pet. at 16, Table 1), Petitioner fails to identify any reason for modifying the concentrations to arrive at the claimed invention.

**C. The documents cited by Petitioner for Ground 2 fail to establish a reasonable expectation of success of achieving the claimed invention.**

Petitioner offers no specific evidence showing *why* a POSA would have expected to successfully obtain a stable, high-concentration natalizumab formulation by selecting the antibody of Gordon to combine with the formulation components of van Oosten or Aversano. Once again, Petitioner merely references the same two hand-picked products and non-asserted references cited in Ground 1, not even approaching a showing of a reasonable expectation of success.

**1. Petitioner fails to establish a reasonable expectation of success of achieving a stable, high-concentration liquid formulation of natalizumab.**

Petitioner cites its assertions from Ground 1 in apparent support for its conclusion that a POSA “recognized that the claimed formulation could be made

and would work[.]” Pet. at 55. For the same reasons detailed in Section IV.B.1, *supra*, then, Petitioner has not met its burden for establishing that the claims of the ’321 patent are unpatentable. In particular, Petitioner fails to provide any explanation about why a POSA would have expected to achieve a liquid high-concentration antibody formulation, much less one that has overcome well-known stability obstacles, given that both Orthoclone and Aversano are directed to *low-concentration* formulations of *different* antibodies. In addition, Petitioner’s reliance on Cummins and White is improper because they are not part of Petitioner’s statutory ground and should therefore be disregarded by the Board. *See* 37 C.F.R. § 42.104(b)(2). And even if Orthoclone, Aversano, Cummins, and White references were considered, as discussed above, none teaches any critical parameters to formulating natalizumab, or any direction as to which of the vast array of possible formulation component choices could successfully achieve stability. *See In re Cyclobenzaprine*, 676 F.3d at 1070–71.

**2. Petitioner fails to establish a reasonable expectation of success that natalizumab can be “simply substituted” for the antibodies disclosed in Orthoclone or Aversano.**

Petitioner again assumes, without evidentiary support, that antibodies and formulations can be seen as simple substitutes, notwithstanding that reference after reference in the prior art only stated the opposite. *See supra* Sections III.A.3.c; IV.B.2. For the same reasons detailed in Section IV.B.2, *supra*, Petitioner

has not met its burden to show that a POSA would have had a reasonable expectation of success in combining Gordon with Orthoclone or Aversano to arrive at a stable, high-concentration natalizumab formulation.

Contrary to Petitioner's conclusory and hindsight-driven assertions, the prior art shows that a POSA would not have reasonably expected formulations designed for lower concentrations of different antibodies to yield a stable, high-concentration formulation for natalizumab. Petitioner simply ignores that the stability issues associated with formulating antibodies were, and continue to be, unpredictable and antibody-specific. *See supra* Section III.A.3. For example, chemical degradation of an antibody's amino acid residues is a frequently occurring degradation reaction in proteins. *See id.* Such degradation at residues involved in antigen recognition—a *part of the antibody that differs* for natalizumab and the antibodies in Orthoclone and Aversano—can lead to potency loss. *See* Ex. 2035 at 1; Ex. 2001 at 108. Thus, contrary to Petitioner's assertion that “many of the amino acids changes are conservative and would not affect the behavior of the IgG mAb actives within the same formulation,” Pet. at 40 (citing Ex. 1002 ¶ 34), the prior art taught a POSA that the complementary determining regions (CDRs) alone posed stability concerns. As the art at the time demonstrates, different antibodies—even different antibodies that are all IgG antibodies—have different

degradation profiles and present unique stability issues. *See supra* Section III.A.3.c.

Petitioner's other assertion—that “simple substitution of histidine with sodium phosphate would have led to the predictable result of a stable formulation” Pet. at 48 (citing Ex. 1002 ¶ 149)—is also without merit. The fact that prior art formulations of different antibodies had used “the combination of excipients polysorbate 80, sodium chloride and sodium phosphate buffer” (*id.*; *see also id.* at 39; Ex. 1002 ¶ 149) would not have told a POSA that natalizumab—especially a high-concentration of natalizumab—could be used successfully in a formulation containing polysorbate 80 with phosphate-buffer and sodium chloride. Even the antibody in Subramanian (*see* Pet. at 47) was never shown to be stable in phosphate-buffer; Subramanian only demonstrated that its antibody was *unstable* in formulations containing polysorbate and histidine or citrate. While Subramanian's antibody was unstable in both histidine and citrate, nothing would have told a POSA to expect success by switching to a different buffer, and specifically phosphate-buffer.

As explained above in Section III.A, *supra*, designing a formulation requires balancing stabilizing and destabilizing forces, and changing one factor will alter this balance. In fact, several references taught that deamidation—one of several stability issues associated with protein formulations—occurred faster in phosphate-

buffer. *See, e.g.*, Ex. 2018 at 338; Ex. 2003 at 186–87; Ex. 2015 at 20. In other words, even if a POSA would have been motivated to use a different buffer (and specifically phosphate-buffer) to solve one stability problem, other stability problems might have arisen due to the switch, and thus a POSA would not have had a reasonable expectation of success in simply substituting one buffer for another.

## **VI. THE PETITION FURTHER LACKS ARTICULATED REASONING SUPPORTED BY EVIDENCE FOR ADDITIONAL CLAIM ELEMENTS.**

Beyond the deficiencies in the Petition as a whole, for additional claim elements, Petitioner’s conclusory, cherry-picking statements are inadequate and fail to raise a reasonable likelihood that any challenged claim is unpatentable. As an illustrative example, dependent claim 3 requires that the formulation “is stable when stored at about 5° C. to about 8° C. for greater than 6 months.” ’321 patent at 18:58–60. Petitioner asserts, without any citation support, that “Petitioner’s modified natalizumab formulations, which satisfy all limitations of claim 1, are stable under these conditions.” Pet. at 37; *see also id.* at 54. But Petitioner provides no evidence of a stable, high-concentration liquid formulation of any antibody, let alone a 20mg/mL liquid formulation of natalizumab that is stable “for greater than 6 months” (*see* claim 3). *See supra* Sections IV.A and V.A. Thus, Petitioner’s conclusory statements about stability are unsubstantiated.



## VII. CONCLUSION

As detailed above, Petitioner fails to identify *any* stable, high-concentration liquid antibody formulation, let alone a stable, high-concentration liquid formulation of natalizumab, and particularly any such formulation that is stable for “greater than 6 months.” Petitioner instead relies on hindsight, cherry-picking the prior art to arrive at the unsupported conclusion that the claims of the ’321 patent are unpatentable. But Petitioner provides no reason why, in a highly complex and unpredictable prior art landscape, a POSA would have selected and combined its selected references as opposed to any of the numerous other antibody formulations that did *not* contain components of the claimed invention. Moreover, Petitioner’s broad conclusions that each of the claims is unpatentable are based on generalities such as “routine optimization of a result effective variable” and/or by “simple substitution,” and are not supported with any evidence. Petitioner has failed to show a reasonable likelihood of prevailing on any claim in the asserted grounds, and the Board should deny institution of the Petition.

Date: July 20, 2016

Respectfully submitted,

By 

Andrea G. Reister

Registration No. 36,253

Jennifer L. Robbins

Registration No. 61,163

Jessica L. Parezo

Registration No. 50,286

COVINGTON & BURLING LLP

One CityCenter, 850 Tenth Street, NW

Washington, DC 20001

(202) 662-6000

Attorneys for Patent Owner

**CERTIFICATION UNDER 37 C.F.R. § 42.24(d)**

I certify that the foregoing complies with the type-volume limitation of 37 C.F.R. § 42.24 and contains 13,900 words based on the word count indicated by the word-processing system used to prepare the paper, and excluding those portions exempted by §§ 42.24(a) and (b).

Date: July 20, 2016

A handwritten signature in cursive script, reading "Andrea G. Reister". The signature is written in black ink and is positioned above a horizontal line.


Andrea G. Reister, Esq.  
Reg. No.: 36,253

## CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6, I hereby certify that on this 20th day of July 2016, the foregoing Patent Owner Preliminary Response Pursuant to 37 C.F.R. § 42.107 was served by electronic mail, by agreement of the parties, and Exhibits 2001–2044 were served by FedEx, a means at least as fast and reliable as Priority Mail Express®, on the following counsel of record for petitioner.

Jeremy Lowe  
Jonathan A. Harris  
Jason W. Balich  
Axinn, Veltrop & Harkrider LLP  
90 State House Square, 9th Floor  
Hartford, CT 06103

Date: July 20, 2016

  
Andrea G. Reister, Esq.  
Reg. No.: 36,253