UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SAMSUNG BIOEPIS CO., LTD.,
Petitioner

v.

ALEXION PHARMACEUTICALS, INC.,
Patent Owner

Case IPR2023-01069
U.S. Patent No. 10,590,189 B2

PETITIONER'S REPLY IN SUPPORT OF PETITION

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1005	U.S. Patent No. 6,355,245 B1 issued to Mark J. Evans et al. (filed June 7, 1995, issued Mar. 12, 2002) ("Evans")
1006	John P. Mueller et al., *Humanized Porcine VCAM-Specific Monoclonal Antibodies with Chimeric IgG2/G4 Constant Regions Block Human Leukocyte Binding to Porcine Endothelial Cells*, 34 Molecular Immunology 441 (1997) ("Mueller 1997")
1007	U.S. Patent Application Publication No. 2005/0191298 A1 issued to Leonard Bell et al. (filed Feb. 3, 2005, published Sept. 1, 2005) ("Bell")
1008	Paul J. Tacken et al., *Effective induction of naive and recall T-Cell responses by targeting antigen to human dendritic cells via a humanized anti–DC-SIGN antibody*, 106 Blood 1278 (2005) ("Tacken")
1009	World Intellectual Property Organization International Publication No. WO 97/11971 issued to John P. Mueller et al. (filed Sept. 27, 1996, published Apr. 3, 1997) ("Mueller PCT")

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1010	Thomas C. Thomas et al., *Inhibition of Complement Activity By Humanized Anti-C5 Antibody and Single-Chain Fv*, 33 Molecular Immunology 1389 (1996) ("Thomas")
1011	Peter Hillmen et al., *Effect of Eculizumab on Hemolysis and Transfusion Requirements in Patients with Paroxysmal Nocturnal Hemoglobinuria*, 350 N. Engl. J. Med. 552 (2004) ("Hillmen 2004")
1012	Anita Hill et al., *Abstract# 2823: Sustained Control of Hemolysis and Symptoms and Reduced Transfusion Requirements over a Period of 2 Years in Paroxysmal Nocturnal Hemoglobinuria (PNH) with Eculizumab Therapy*, 104 Blood 772a (2004) ("Hill 2004")
1013	Anita Hill et al., *Sustained response and long-term safety of eculizumab in paroxysmal nocturnal hemoglobinuria*, 106 Blood 2559 (2005) ("Hill 2005")
1014	Peter Hillmen et al., *The Complement Inhibitor Eculizumab in Paroxysmal Nocturnal Hemoglobinuria*, 355 N. Engl. J. Med. 1233 (2006) ("Hillmen 2006")
1015	Neal S. Young et al., *Abstract# 971: Safety and Efficacy of the Terminal Complement Inhibitor Eculizumab in Patients with Paroxysmal Nocturnal Hemoglobinuria: Interim Shepherd Phase III Clinical Study*, 108 Blood 290a (2006) ("Young")
1016	Peter Hillmen et al., *Abstract# 154: Eculizumab, a C5 Complement-Blocking Antibody, Abolishes Hemolysis and Renders Hemolytic Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) Transfusion Independent*, 100 Blood 44a (2002) ("Hillmen 2002")
1017	Peter Hillmen et al., *Abstract# 1858: Eculizumab, a C5 Complement-Blocking Antibody, Controls Hemolysis in Paroxysmal Nocturnal Hemoglobinuria (PNH) with Responses Maintained Over a Prolonged Period of Therapy*, 102 Blood 509a (2003) ("Hillmen 2003")

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1020	Alexion Press Release, *Alexion Issued Key C5 Complement Inhibitor Patent for Inflammatory Diseases* (Mar. 15, 2002), https://web.archive.org/web/20030621141230/http://www.alxn.com/products/index.cfm
1021	World Intellectual Property Organization International Patent Publication No. WO 2005/007809 A2 issued to Russell P. Rother et al. (filed May 28, 2004, published Jan. 27, 2005)
1022	World Intellectual Property Organization International Patent Publication No. WO 2005/110481 A2 issued to Russell P. Rother et al. (filed May 16, 2005, published Nov. 24, 2005)
1023	Mariana Kaplan, *Eculizumab Alexion*, 3 Curr. Opin. Investig. Drugs 1017 (2002)
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1032	*Reserved*
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1037	Jette Wypych et al., *Human IgG2 Antibodies Display Disulfide-mediated Structural Isoforms*, 283 J. Biol. Chem. 16194 (2008) ("Wypych")

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1038	Stylianos Bournazos et al., *Fc-optimized* antibodies *elicit CD8 immunity to viral respiratory infection*, 588 Nature 485 (2020) ("Bournazos 2020")
1039	Stylianos Bournazos et al., *Human IgG Fc domain engineering enhances antitoxin neutralizing antibody activity*, 124 J. Clinical Investigation 725 (2014) ("Bournazos 2014")
1040	Lucie Baudino et al., *Impact of a Three Amino Acid Deletion in the CH2 Domain of Murine IgG1 on Fc-Associated Effector Functions*, 181 J. Immunology 4107 (2008)
1041	Toshiyuki Takai et al., *FcR γ Chain Deletion Results in Pleiotropic Effector Cell Defects*, 76 Cell 519 (1994)
1042	Falk Nimmerjahn & Jeffrey V. Ravetch, *Fcγ receptors as regulators of immune responses*, 8 Nat. Rev. Immunol. 34 (2008)
1043	Jeffrey V. Ravetch & Jean-Pierre Kinet, *Fc Receptors*, 9 Annu. Rev. Immunol. 457 (1991)
1044	U.S. Patent Application Publication No. 2005/0271660 A1 issued to Yi Wang (filed May 11, 2005, published Dec. 8, 2005) ("Wang")
1045	Charles A. Janeway, Jr. et al., *Chapter 1: Basis Concepts in Immunology*, and *Chapter 3: Antigen Recognition by B-cell and T-cell Receptors*, Immunobiology: the immune system in health and disease, pp. 1-34, 93-122 (5th ed. 2001)
1046	Excerpts from Pei-Show Juo, Ph.D., Concise Dictionary of Biomedicine and Molecular Biology (2nd ed. 2001)
1047	Tina Völkel et al., *Optimized linker sequences for the expression of monomeric and dimeric bispecific single-chain diabodies*, 14 Protein Engineering 815 (2001) ("Völkel")

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1048	Evelyn D. Lobo et al., *Antibody Pharmacokinetics and Pharmacodynamics*, 93 Journal of Pharmaceutical Sciences 2645 (2004) ("Lobo 2004")
1049	Neil S. Lipman et al., *Monoclonal Versus Polyclonal Antibodies: Distinguishing Characteristics, Applications, and Information Resources*, 46 ILAR Journal 258 (2005) ("Lipman 2005")
1050	Benny K.C. Lo, *Chapter 7: Antibody Humanization by CDR Grafting*, Methods in Molecular Biology, Vol. 248: Antibody Engineering: Methods and Protocols, pp. 135-159 (2004) ("Lo 2004")
1051	Lutz Riechmann et al., *Reshaping human antibodies for therapy*, 332 Nature 323 (1988) ("Riechmann")
1052	Janice M. Reichert, *Marketed therapeutic antibodies compendium*, 4 mAbs 413 (2012) ("Reichert")
1053	Bruce Alberts et al., *Chapter 12: Intracellular Compartments and Protein Sorting*, Molecular Biology of the Cell, pp. 551-98 (1994)
1054	Elisabeth E. Adderson et al., *Immunoglobulin Light Chain Variable Region Gene Sequences for Human Antibodies to Haemophilus influenzae Type b Capsular Polysaccharide Are Dominated by a Limited Number of V_κ and V_λ Segments and VJ Combinations*, 89 J Clin. Invest. 729 (1992)
1055	Genentech, Inc., Avastin 2004 Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/125085lbl.pdf
1056	Millennium, Campath 2001 Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2001/alemmil050701LB.htm

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1061	Ann L. Daugherty & Randall J. Mrsny, *Formulation and delivery issues for monoclonal antibody therapeutics*, 58 Advanced Drug Delivery Reviews 686 (2006)
1062	Declaration of Cindy Ippoliti, Pharm.D.
1063	Note for Guidance on Excipients, Antioxidants and Antimicrobial Preservatives in the Dossier for Application for Marketing Authorisation of a Medicinal Product, European Agency for the Evaluation of Medicinal Products (2003)
1064	*Reserved*
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1066	Excerpt from the File History of U.S. Patent No. 9,718,880, Response to Non-Final Office Action Under 37 C.F.R. § 1.111, dated May 12, 2017

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1101	Deposition of Arturo Casadevall, Jan. 24, 2020
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I. INTRODUCTION

Alexion's Response gives no reason for this Board to depart from its initial conclusions. First, the Response is unsupported by proper expert testimony: Alexion simply recycled old expert declarations from the 2019 Amgen IPRs and never submitted substantive responses to Samsung's arguments and expert opinions. Second, nearly all of Alexion's patentability arguments rest on the false premise that a POSA seeking to prepare the eculizumab antibody in 2007, though admittedly highly skilled, would have ignored the 2005 Tacken reference declaring eculizumab to be an IgG2/G4 antibody. Alexion insists a POSA would instead have believed that eculizumab was a IgG4 antibody, based on a 1996 Thomas reference, which describes a precursor antibody and never links that antibody to the term, "eculizumab." But Tacken is the only reference of record that expressly identifies an isotype for eculizumab, and it states definitively that eculizumab is an IgG2/G4 antibody. Third, Alexion's few remaining patentability arguments are based solely on attorney argument or rehash old positions from the Amgen IPRs that have been fully considered and discounted by this Board. Fourth and similarly, Alexion's secondary considerations arguments are baseless and repetitive of the already-rejected arguments Alexion previously made. A final written decision should issue declaring all challenged claims unpatentable.

II. ARGUMENT

A. Alexion's Response Is Unsupported Because Its Expert Declarations from the Amgen '149 and '504 IPRs Are Insufficient

1. This IPR Is Based on Different Grounds than Amgen's '149 and '504 IPRs

As a threshold matter, this Board's findings in its Institution Decision should be carried forward to its final written decision, because Alexion submitted no new evidence with its Response that is entitled to any weight. Alexion's expert declarations for this IPR merely reference old declarations from the Amgen IPRs of the '149 and '504 patents (not the '189 patent challenged here). Importantly, Samsung relies on different Grounds than Amgen did. For example, none of Amgen's Grounds rely on Tacken. *Amgen Inc. v. Alexion Pharms.*, No. IPR2019-00739, Paper 2, 23 (Feb. 28, 2019). Similarly, Samsung relied on new expert declarations specifically focused on the '189 patent, rather than attempting to rely on any Amgen arguments or expert testimony. And given that the '189 patent issued after Amgen's IPR was dismissed, Alexion's expert declarations do not address the Patent Examiner errors acknowledged by this Board. (Paper 9 ("ID"), 60-66.)

2. Alexion's Expert Testimony Recycled from Amgen's '149 and '504 IPRs Is Entitled to No Weight

Alexion's failure of proof is not cured by the handful of conclusory paragraphs submitted as new declarations. (ALXN2105, ¶¶7-10; ALXN2107, ¶¶7-8.) For example, Dr. Casadevall's declaration includes the conclusory statement that he

disagrees with the opinions of Samsung's experts Drs. Ravetch and Ippoliti, but he submits no facts, no evidence, and no explanation of any kind within his seven-page declaration to support that opinion. (ALXN2105, ¶¶8-9.)

Such conclusory statements are entitled to no weight. First, "[e]xpert testimony that does not disclose the underlying facts or data on which the opinion is based is entitled to little or no weight." 37 C.F.R. § 42.65(a). Second, conclusory expert statements that simply parrot the Patent Owner's briefing and arrive at the ultimate determination of validity without any explanation or support must be discounted. *See, e.g., Xerox Corp. v. Bytemark, Inc.*, No. IPR2022-00624, Paper 12, 5 (Feb. 10, 2023) (precedential) (Board was "correct in giving little weight" to expert testimony because the "declaration merely offered conclusory assertions without underlying factual support and repeated, verbatim … conclusory arguments."); *Upjohn Co. v. Mova Pharm. Corp.,* 225 F.3d 1306, 1311 (Fed. Cir. 2000).

Alexion's evidence also adds nothing new to the record. Alexion's recycled declarations from the Amgen IPRs were already submitted with its Preliminary Response and thus have already been considered and discounted by this Board. (Paper 6 ("POPR"), 3; ID, 11-12.) Even though Alexion "reserve[d] the right to submit one or more expert declarations specifically directed to Samsung's Petition if any Grounds are instituted." (POPR, 3 n.5.) Alexion never submitted additional substantive expert testimony with its Response. It has thus forfeited its opportunity

to introduce evidence that actually responds to Samsung's arguments and experts. As this Board warned Alexion, "**Patent Owner is cautioned that any arguments not raised in the response may be deemed waived**." (IPR2023-00933, Paper 10, 10.)

Alexion's contentions opposing Samsung's experts Drs. Ravetch and Ippoliti are not supported by expert evidence, because Alexion's experts never submitted declarations actually responding to Samsung's experts. Instead, Alexion's Response is pure attorney argument, again entitled to no evidentiary weight. *See, e.g., Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 424 F.3d 1276, 1284 (Fed. Cir. 2005) ("Attorney argument is no substitute for evidence."); *Wasica Fin. GmbH v. Cont'l Auto. Sys., Inc.*, 853 F.3d 1272, 1284-85 (Fed. Cir. 2017) ("a party's 'unsworn attorney argument . . . is not evidence' and thus cannot rebut record evidence.").

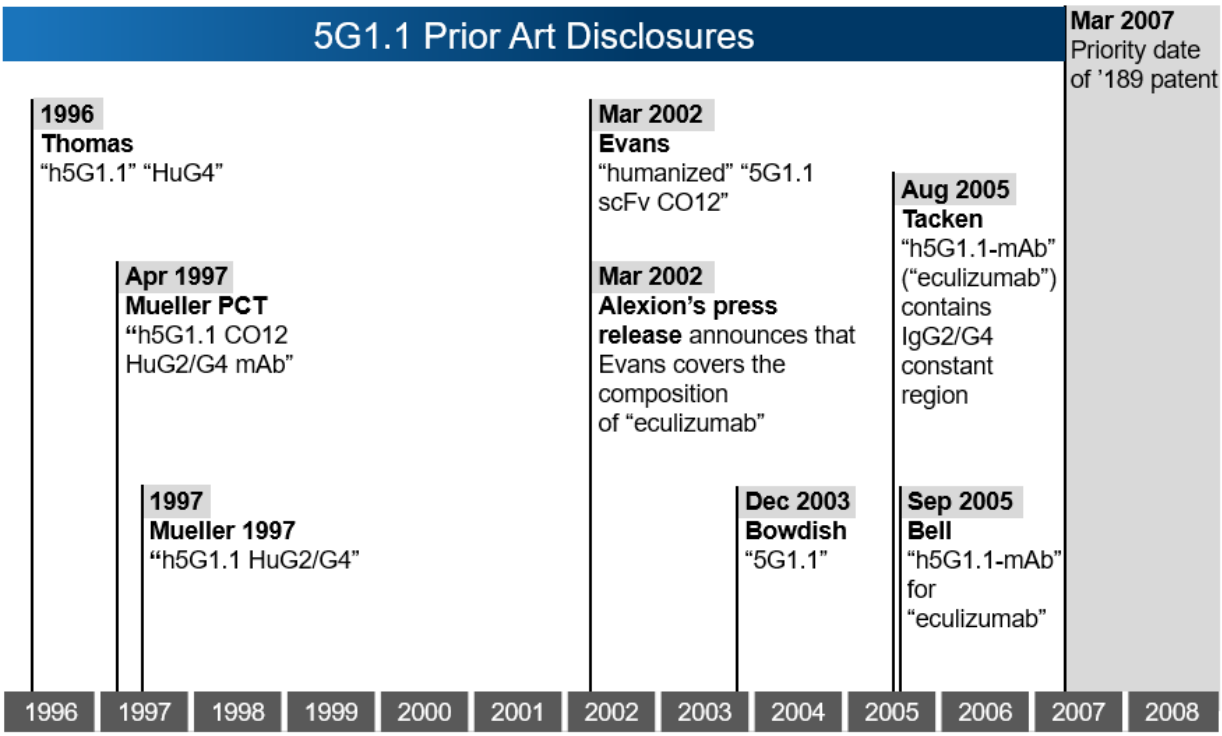
This reason alone is sufficient to dispense with Alexion's Response and affirm this Board's Institution Decision findings as a final written decision cancelling all the challenged claims. Nevertheless, Samsung replies to Alexion's Response arguments below. Samsung's Reply, unlike Alexion's Response, is supported by detailed expert evidence. (*See* EX1103 (Reply Declaration of Jeffrey Ravetch, M.D., Ph.D.).)

B. Alexion Mischaracterizes the Clear Teachings of Its Own Prior Art and the Import of Its Admissions

The crux of Alexion's Response is based on a singularly false premise. Alexion wrongly states that "the literature as of March 15, 2007 consistently identified 'eculizumab' as the antibody described in the 'Thomas' publication[.]" (Paper 13, ("POR") 2.) This is simply not true, as explained in detail in the Petition and again in this Reply. In truth, Thomas does not even contain the word "eculizumab." (EX1003, ¶160; EX1101, 186:19-22.) The only prior art that actually identifies eculizumab's constant domain, Alexion's own Tacken, unmistakably states that it is an IgG2/G4 antibody. (EX1008, 011; Paper 2, ("Pet."), 37; EX1003, ¶¶64, 98, 123, 127; EX1103, ¶¶10-12.) Alexion's narrative of the state of the art, in which a POSA would have ignored the more recent 2005 Tacken reference and believed that the "clinically safe and effective" antibody of Bell's clinical trial results was Thomas' IgG4 antibody as reported in 1996, is entirely counterfactual. (POR, 29; EX1103, ¶¶10-12.)

Alexion's efforts to rewrite the clear teachings of Tacken, or simply wish the reference out of existence, all fail. A POSA understood that by 2007, the prior art showed a simple, clear, and linear path <u>beginning with</u> Thomas' early 5G1.1 anti-C5 antibody and culminating with the IgG2/G4 as disclosed by Tacken and used in Bell. As explained in the Petition, the meaning of "5G1.1," including whether it refers to a mouse or a human antibody, is clear to a POSA from the context in which

it appears. (Pet., 9-13; EX1003, ¶¶61-70; EX1103, ¶¶13-16.) For example, a POSA understood whether a reference discussed "5G1.1" in the context early discovery and humanization of a mouse anti-C5 antibody, or instead used "5G1.1" in the context of the further development and modification of that antibody into an IgG2/G4 form used in clinical trials and called eculizumab. (*Id.*; ALXN2104, 188:12-192:1.)



Although the primary references are all directly associated with Alexion, Alexion attempts to paint its own publications charting the development of eculizumab as confusing or misleading to a POSA. (POR, 18, 24-37.) This supposed ambiguity is manufactured. A POSA would easily be able to interpret the art's use of terms like "5G1.1," "h5G1.1.," and "eculizumab" to arrive at the

sequence of eculizumab. For example, Alexion points to the fact that prior art such as Bell cites to Thomas, and argues that a POSA would have simply stopped there, ignoring the clear teachings of the much more current Tacken reference. (POR, 42-43, 54.) Alexion's view of a POSA as a simpleton, stopping at Thomas' IgG4 teachings, is legally unsound. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 402 (2007) ("[A] person of ordinary skill often will be able to fit the teachings of multiple patents together like pieces of a puzzle."). This is especially so since Alexion agrees that the level of skill in this art was high, even specifying that a POSA would have experience specifically in "engineering monoclonal antibodies for human therapeutic use." (POR, 40-41.) Indeed, as Dr. Ravetch explains, a POSA in this field was highly skilled and well-informed, would not have focused exclusively on the eleven-year-old Thomas reference, and could easily understand the meaning of the various 5G1.1 terms over the course of eculizumab development from context. (EX1003, ¶¶110, 128, 146, 160; EX1103, ¶17; ALXN2104, 34:6-35:7, 66:5-67:6.) As even Alexion admits, "the precise meaning of the various '5G1.1' terms depends on the context in which it appears[.]" (POR, 9.) A POSA would have been able to interpret the teaching of the prior art based on that context, contrary to Dr. Casadevall's views. (EX1103, ¶¶18-21.) Alexion's restricted view of the art focuses on individual references and impermissibly fails to "consider[] the prior art in context or in combination" as required for obviousness. *Janssen Pharms., Inc. v.*

Teva Pharms. USA, Inc., 97 F.4th 915, 928 (Fed. Cir. 2024) (rejecting "siloed and inflexible approach" for "inflating the significance of minor variations between the prior art and the claims").

Finally, as discussed in Ground 3 below, Alexion has repeatedly admitted not only that the eculizumab of the prior art was the same IgG2/G4 antibody recited in the challenged claims, but also that this fact was known before 2007. (*See infra* II.E.) There is no dispute, even in this case, that the eculizumab antibody reported in Alexion's clinical trial publications did indeed possess the amino acid sequences recited in SEQ ID NOS:2 and 4 of the '189 patent. Alexion's arguments against Ground 3 ultimately collapse to the same contention that a POSA would have mistakenly understood eculizumab to be an IgG4 antibody despite the clear teaching of Tacken – a false premise as shown in Grounds 1 and 2.

C. Ground 1: Claims 1-8 Are Obvious over Bell, Bowdish, Evans, and Wang in View of Tacken and Mueller PCT

1. There Is No Dispute that the Prior Art Taught Eculizumab Was an Effective PNH Treatment and that the Prior Art Sequences Read on the Challenged Claims

Alexion's Response does not dispute that (1) Bell teaches eculizumab as an effective treatment for PNH; (2) the sequence disclosed in the Bowdish/Evans integrated document expressly discloses the claimed sequences, as shown in alignments; and (3) the specific limitations in claims 2-8 are disclosed in the prior art. Alexion only disputes motivation to combine and reasonable expectation of

success. As discussed below, Samsung has met its burden to show obviousness by preponderance of the evidence in view of these factors.

2. A POSA Would Have Followed Samsung's Obviousness Rationale

The obviousness rationale proposed by Samsung and Dr. Ravetch was clear to a POSA, contrary to Alexion's narrow reading of the prior art where all roads lead to (and end with) the Thomas reference. Beginning with Bell's teaching that eculizumab (which it calls "the antibody h5G1.1" and "h5G1.1-mAb") is an effective treatment for PNH, a POSA would have been led first to Evans and Thomas, both of which are cited and incorporated by Bell for "methods of preparation" of h5G1.1. (Pet., 28-29, 40; EX1007, [0012], [0052], [0082]; EX1003, ¶¶109-110, 130; EX1103, ¶¶22-26.) A POSA would also have recognized that Evans provides variable region sequences for eculizumab and that Thomas' full-length IgG4 antibody is not eculizumab, based on the express (and more recent) teaching of Tacken that eculizumab has an IgG2/G4 domain. (Pet., 29; EX1003, ¶110; EX1103, ¶27.)

A POSA thus continuing to search for relevant literature of the 5G1.1 antibody discussed by Bell and Evans would have found Bowdish particularly relevant. Bowdish provides express teachings about the structure of the antibody "5G1.1," identifies "Alexion Pharmaceuticals" as the Correspondence Address and cites/incorporates the same Evans patent as does Bell for the structure of 5G1.1.

(EX1004, Cover, [0191]; EX1003, ¶120; EX1103, ¶28.) Alexion's argument that Bowdish is not analogous art thus fails. (POR, 44.) Furthermore, Alexion's argument that Thomas' IgG4 disclosure teaches away (POR, 47) fails because the art (including Thomas) did not "criticize, discredit, or otherwise discourage" the IgG2/G4 form – especially when Tacken expressly disclosed that eculizumab was an IgG2/G4. *Galderma Lab'ys, L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013); (EX1103, ¶29).

A POSA would have had still other reasons to conclude that the starting sequence of Bowdish, having the heavy chain CDR3 of Evans, was eculizumab. A POSA would have been able to tell that the heavy chain sequences disclosed in Bowdish's SEQ ID NO: 67 were of a human hybrid subclass, as Tacken taught eculizumab had. Using routine sequence alignment with the sequences of Mueller PCT, a POSA would have confirmed that SEQ ID NO: 67 was the desired IgG2/G4 type – just as Tacken described. (EX1003, ¶¶123-126; EX1103, ¶30; ALXN2104, 150:13-152:24.) Nor would a POSA have been confused by Bowdish's use of the term "5G1.1" because it was not preceded by an "h." A POSA would have recognized that Bowdish's 5G1.1 discloses humanized rather than mouse sequences based on the amino acid sequences themselves. (EX1003, ¶¶81, 121-122; EX1103, ¶31; ALXN2104, 142:17-145:6.) As Samsung showed, and Alexion does not dispute, the Bowdish/Evans sequence is identical to SEQ ID NOS: 2 and 4 of the

challenged claims. (Pet., 29-32; EX1003, ¶¶111-114.) A POSA would have been able to identify the correct human sequences in Evans for combination with Bowdish to arrive at Bowdish's starting antibody. (EX1103, ¶¶33-37.)

Alexion's argument that Samsung relied on "hindsight" by supposedly working backwards from the claimed sequences is wrong. Alexion complains that Samsung's Petition included alignments showing that the antibody sequences taught by the prior art, when combined, align perfectly with the claimed sequences. (POR, 48.)[1] But alignments are compelled by the obviousness inquiry, which requires a comparison of the claims against the closest prior art. *KSR,* 550 U.S. at 399 ("differences between the prior art and the claims at issue are . . . ascertained" in obviousness analysis (quoting *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966))). Indeed, Dr. Ravetch carefully avoided hindsight by beginning with the motivation from Bell to make the anti-C5 antibody eculizumab and the disclosure from Tacken that eculizumab had an IgG2/G4 constant domain. From there, Dr.

[1] Similarly, Alexion unfairly accuses this Board of "reverse engineering" by working backwards from the claimed sequences (POR, 24), but this Board did no such thing. The Board merely described what a POSA would easily do to determine Bowdish's starting antibody by working back from the 5G1.1+TPO antibody and using Evans' HCDR3 sequence, exactly as directed to by Bowdish. (ID, 31; EX1003, ¶¶113-114.)

Ravetch identified sequences from the prior art that would be considered by a POSA to be eculizumab in light of the art's guidance. (EX1003, ¶¶24, 109-130; EX1103, ¶32; ALXN2104, 55:19-56:12, 93:7-21, 155:9-156:3.) To support his obviousness opinions, Dr. Ravetch also included sequence comparisons against SEQ ID NOS:2 and 4, (EX1003, ¶¶112-114), which was proper to prove the prior art sequences exactly match the claimed ones. *See, e.g.*, *Pfizer, Inc. v. Uniqure Biopharma B.V.*, IPR2021-00926, Paper 50, 36-51 (PTAB Nov. 15, 2022) (rejecting patentee's hindsight arguments and finding claims obvious based on combining amino acid sequences from multiple references and comparing them with the claims).

3. A POSA Would Have Had a Reasonable Expectation of Success

A POSA would have had a reasonable expectation of success that the sequences provided by the prior art would possess the known anti-C5 properties of eculizumab, contrary to Alexion's unsupported concerns of unpredictability. (POR, 47.) First, a POSA already knew that eculizumab had an IgG2/G4 constant region, thus a POSA would not have any concern that they were testing a different antibody from what had already been successfully tested as a PNH therapy as shown in Bell and other references. (Pet., 39-40; EX1003, ¶¶110, 123, 125-126, 130-131; EX1103, ¶38.)

And even if a POSA thought there was anything experimental about an IgG2/G4 antibody, they would have had a reasonable expectation of success for

several reasons. First, antibodies with an IgG2/G4 constant region were already known in the art. (Pet., 10; EX1003, ¶¶48, 62; EX1103, ¶39; EX1006, 011, 013, 015-016; EX1009, 014, 097; EX1021, 011, 019, 028.) Second, the art including Mueller taught that a hybrid constant region made of G2 and G4 subclass components was desirable for lower activation of the complement system. (EX1003, ¶48; EX1103, ¶40; EX1006, 011, 013, 015-016; EX1009, 014, 097.) Third, the art including Evans expressly encouraged construction of 5G1.1 antibodies with varied constant regions, including constant regions made of hybrids of different antibody classes. (EX1005, 45:29-33; EX1003, ¶152; EX1103, ¶41.) For example, both Thomas and Mueller confirm that antibodies with altered subclasses retained target binding activity. (*See infra* II.D.2.)

Dr. Casadevall's concerns regarding potential loss of C5 binding activity are speculative and not based on any examples relevant to an IgG2/G4 antibody. (EX1101, 191:7-12 ("Q: Do any of those antibodies tested in McLean have a human hybrid IgG2-IgG4 constant region? A: None of those antibodies have a hybrid IgG2-IgG4 constant region."), 192:6-12, 193:23-194:11, 196:16-197:7, 198:22-199:8, 200:13-202:11, 203:20-205:7, 208:10-209:18; EX1103, ¶42.) Dr. Casadevall's examples are drawn from antibodies that recognize a unique class of antigens with repetitive carbohydrate epitopes. However, as Dr. Ravetch explains, a POSA would not generalize these few examples, especially since the prior art contained

eculizumab-specific disclosures that would have been considered far more relevant than Dr. Casadevall's examples. (EX1103, ¶¶43-56; ALXN2104, 57:21-58:8 ("we knew quite a bit more about eculizumab than this generic discussion that Dr. Casadevall is presenting.").) Based on Dr. Ravetch's review of the literature, "switching the constant region domain of the heavy chain or light chain has not impacted on the binding specificity or affinity of the original Fab domains." (ALXN2104, 60:13-61:22.) Dr. Casadevall's immunogenicity concerns are similarly speculative and contradicted by the specific teachings of the eculizumab clinical studies. (EX1103, ¶57; EX1013, 013.)

4. Dose and Formulation Limitations

Alexion's patentability arguments for the dosing and formulation limitations of the challenged claims fare no better. First, any supposed concern about stability of eculizumab formulations for injection is exaggerated and contradicted by the evidence. Alexion ignores that Bell expressly discloses "[f]ormulations" of eculizumab "suitable for injection" (referencing the Remington's standard) and reports on their successful use in the clinic. (EX1007, [0062]; Pet. 21-22; EX1003, ¶¶92-96, 132-137; EX1062, ¶32; EX1103, ¶¶58-59.) Wang also taught stable eculizumab formulations at concentrations as high as 30 mg/ml, and 10 mg/mL was known to be a commonly used concentration for antibody formulations. (EX1044, Fig. 10, [0025], [0067], [0170]-[0173]; EX1061, 014; EXS1056-1060; EX1003,

¶¶135, 139; EX1103, ¶60.) Alexion also fails to identify even a single published instance of any concerns relating to the stability of eculizumab in any of the many prior art publications reporting on the PNH clinical trials, some of which ran for two years. (EX1003, ¶58.) A POSA thus would have no reason for concern that the eculizumab reported in Bell and other clinical trials, which Tacken taught was an IgG2/G4 antibody, would be difficult to stably formulate. (Pet., 43-44; EX1003, ¶¶138-139; EX1103, ¶61.) And in any event, none of the challenged claims recite a "stable" formulation, or require any particular level of stability. Accordingly, Alexion's arguments impermissibly go beyond "the objective reach of the claim." *Janssen*, 97 F.4th at 926.

Second, as to the 30 mL (10 mg/mL) and 300 mg limitations, the best Alexion can do is argue that those are individual choices from many options the prior art taught were available to a POSA. (POR, 51-52.) But, of course, the prior art can render obvious more than one possible option, and mere selection of a single option within a known range does not confer patentability absent some evidence of unexpected results or evidence of criticality. *See, e.g., Pfizer Inc. v. Sanofi Pasteur Inc.*, 94 F.4th 1341, 1347-48 (Fed. Cir. 2024) ("[W]here 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."); (EX1103, ¶62). Alexion resorts to attorney argument mischaracterizing Dr. Ippoliti's testimony as unsupported, (POR,

52), ignoring that Dr. Ippoliti based her opinions on her fifteen years of experience in accepted practices in medicine and pharmaceutical products. (ALXN2106, 19:20-23:13, 68:11-70:11, 32:15-36:2.) Dr. Ippoliti confirmed that stability would be considered important over ease of administration, (ALXN2106, 56:17-23), but Alexion never established that a POSA had any need to prioritize stability concerns over ease of administration, given that eculizumab had been successfully formulated and used in clinical trials. (Pet., 41-44; EX1003, ¶134; EX1062, ¶28; EX1103, ¶63.) Ultimately, Alexion did not bother to submit any expert testimony specifically rebutting the opinions of Dr. Ippoliti or Dr. Ravetch as to why the dosing and formulation limitations were obvious. (EX1062, ¶¶47-56; EX1003, ¶¶132-139; EX1103, ¶64; *see supra* Part II.A.1.) The declaration of Dr. Trout recycled from the Amgen '504 IPR does not support Alexion's nonobviousness arguments for the dose and formulation limitations, for the same reasons explained above. (EX1103, ¶¶65-73.)

D. Ground 2: Claims 1-8 Are Obvious over Bell, Evans, Mueller PCT, and Wang in View of Tacken

As with Ground 1, there is no dispute that Bell taught a POSA that eculizumab was a useful treatment for PNH, and there is no dispute that the amino acid sequences in the combined disclosures of Evans and Mueller PCT read on SEQ ID NOS:2 and 4 of the challenged claims. (Pet., 50-52; EX1003, ¶151.) Also as with Ground 1,

Alexion raises no disputes relating to any of the specific limitations found in challenged claims 2-8.

1. A POSA Would Have Followed Samsung's Obviousness Rationale

A POSA reading Bell would have looked to Evans and Mueller PCT, and would have combined them to obtain the desired sequences. Bell points directly to Evans and Thomas for the amino acid sequence of the anti-C5 antibody eculizumab and incorporates both by reference. (Pet., 48-49; EX1003, ¶¶146-148.) As discussed above, POSA would not have concluded that eculizumab was an IgG4 antibody from this reference to Thomas in view of the later teachings of Tacken and Mueller PCT. (*Id.*) A POSA would have understood the well-known distinction between variable and constant regions of an antibody, and would have used Evans for the C5-binding variable regions of eculizumab, as directed by Bell, and would have used Mueller PCT for the IgG2/G4 constant domains, as directed by Tacken and taught by Mueller PCT. (Pet., 49-52; EX1003, ¶¶148-151; EX1103, ¶75.)

Even if Tacken's IgG2/G4 disclosure didn't exist, as Alexion would like to have it, other prior art contained ample motivation to modify the constant region of the Thomas IgG4 antibody. For example, the same Evans disclosure provides instructions to combine 5G1.1 variable regions with constant region domains to form a full-length antibody and <u>expressly</u> suggests that it is "[p]articularly preferred" to use "a mixture of constant domains from IgGs of various subtypes" – exactly like

the IgG2/IgG4 disclosure of Tacken and Mueller PCT. (EX1005, 45:29-33; EX1003, ¶152; EX1103, ¶76.) Similarly, the Mueller 1997 reference associated with Mueller PCT provides general motivation to convert IgG4 isotype antibodies to the "HuG2/G4 design" in any human antibody intended for therapeutic use "where elimination of FcR binding and C activation may be desirable." (EX1006, 016; EX1003, ¶¶47-48, 153.) A POSA would have recognized these benefits as useful in the context of a therapeutic antibody intended to block part of the complement system. (EX1003, ¶153; EX1103, ¶77; ALXN2104, 169:5-18, 171:12-173:7.)

Alexion focuses on the Amgen IPR institution decision, complaining that this Board reached a different conclusion regarding the Mueller/Evans combination in that prior case. (POR, 7, 53-54.) Alexion even bizarrely contends that the unique grounds and unique expert testimony of this case somehow still present "the same record" as the Amgen IPR. (*Id.*) But if anything, the different outcome in the Amgen and Samsung IPRs only underscores the significant substantive differences between the proceedings. This is the very reason Alexion's recycled declarations from the Amgen IPRs fail to support Alexion's arguments in <u>this</u> proceeding.

In any event, Samsung explained in detail why a POSA would have combined Evans and Mueller PCT. (Pet., 48-53; EX1003, ¶¶146-151; EX1103, ¶78.) Thus, there would not have been guesswork on POSA's part about which amino acids would be used, as Alexion argues without evidentiary support. (POR, 17.) Mueller

PCT, as confirmed by Mueller 1997, clearly showed exactly how to construct an IgG2/G4 hybrid, by combining the C1 region and hinge of IgG2 with the C2 and C3 regions of IgG4. (EX1009, 8:23-26, 12:23-27; EX1006, 011, 013; EX1003, ¶¶48, 101.) Once again, Tacken gave all the direction a POSA might need, explaining that eculizumab contains an IgG2/G4 constant region that is "the same" as that disclosed in Tacken's reference 17, which is the Mueller 1997 article – more than sufficient disclosure to lead a POSA to Mueller PCT for the needed constant domain sequences. (EX1003, ¶¶98, 152-153; EX1103, ¶79.)

Recombinant antibodies

The humanized antihuman DC-SIGN antibody hD1V1G2/G4 (hD1) was generated by complementarity determining region (CDR) grafting of AZN-D1 hypervariable domains into human framework regions. The humanized variable heavy and variable light regions were then genetically fused with a human hybrid IgG2/IgG4 constant domain[17] and a human kappa chain constant domain, respectively. This construct was cloned into a mammalian expression vector and the final construct transfected into NSO cells. Stable transfectants were obtained using glutamate synthetase (GS) selection (Lonza Biologics, Portsmouth, NH). Supernatants containing hD1 were purified over a protein A column. An isotype control antibody, h5G1.1-mAb (5G1.1, eculizamab; Alexion Pharmaceuticals) containing the same IgG2/IgG4 constant region, is specific for the human terminal complement protein C5.[19]

(EX1008, 011 (citing EX1006) (highlighting added).)

Alexion argues that a POSA would not have been able to discern among Evans' multiple variable structures relating to 5G1.1 and instead would have focused on the disclosed mouse antibody sequence, even though Bell makes clear that eculizumab is a humanized antibody. (POR, 53-54.) Alexion again commits legal error by failing to examine the prior art through the lens of the highly skilled POSA.

(*See supra* II.B.) And in any event, the prior art gave a direct path to a POSA. Evans' Example 11, entitled "Construction and Expression of Recombinant mAbs," provides a finite set of clearly-identified CDRs that bind C5, more than sufficient guidance to a POSA – especially since the already-relevant Mueller PCT disclosure specifically highlights the "CO12" sequence as the only one investigated in that reference. (Pet., 49-50; EX1003, ¶¶147-150; EX1103, ¶80.) *See Merck & Co. v. Biocraft Lab'ys, Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989) ("That the [asserted prior art] discloses a multitude of effective combinations does not render any particular formulation less obvious."). When, as here, there are a "finite number of identified, predictable solutions," a POSA has good reason to pursue them and the resulting combinations are obvious ones. *See KSR*, 550 U.S. at 421. Dr. Casadevall's arguments against motivation to combine Evans and Mueller and contentions that a POSA would not have known how to do so are thus baseless. (EX1103, ¶¶82-92.)

Alexion's hindsight complaints for Ground 2 are again wrong. (POR, 56.) Dr. Ravetch began with motivation from Bell and knowledge from Tacken, combining the teachings of Evans and Mueller PCT, and only then performed a confirmatory alignment. (EX1003, ¶151 ("[t]he <u>resulting</u> antibody, as shown in the comparisons below, shows a perfect match [with] … the claimed SEQ ID NOS:2 and 4" (emphasis added)); EX1103, ¶81.)

2. A POSA Would Have Had a Reasonable Expectation of Success

A POSA would have had a reasonable expectation of success that the Mueller/Evans antibody would retain C5 binding. Dr. Casadevall's arguments regarding possible loss of C5 binding when subclass-switching from IgG4 to IgG2/G4 are speculative and contradicted by the art. For example, Thomas reported that a change in the heavy chain constant domain when going from Fab fragments to full length did not affect C5 binding. (EX1010, 013; ALXN2104, 70:15-71:4, 176:11-25; EX1103, ¶¶93-94.) Similarly, Mueller's G4 to IgG2/G4 subclass switch had no effect on target binding. (EX1006, 015-016; EX1009, 014; ALXN2104, 62:13-63:8, 175:8-25; EX1103, ¶95.) A POSA would thus have had a reasonable expectation of success that the Evans/Mueller antibody would retain C5 binding. (EX1003, ¶¶147-150, 154; EX1103, ¶96; ALXN2104, 175:8-177:4.) Indeed, Alexion's supposed concerns were contradicted by Dr. Casadevall's own admissions. (EX1101, 191:7-12, 192:6-12, 193:23-194:11, 196:16-197:7, 198:22-199:8, 200:13-202:11, 203:20-205:7, 208:10-209:18.) Alexion's immunogenicity concerns associated with the IgG2/G4 form are equally illusory. (POR, 39.) The prior art already confirmed that eculizumab, disclosed by Tacken as a humanized IgG2/G4 antibody, did not trigger an immunogenic response. (EX1003, ¶¶48, 58; EX1013, 013; EX1103, ¶97.) And as with the Bowdish/Evans ground, Dr. Casadevall's arguments against reasonable expectation of success with the

Evans/Mueller combination are again unfounded, based on extrapolation of rare examples involving unusual antigens and ignoring the specific teachings of the prior art relevant to eculizumab and IgG2/G4 antibodies. (EX1103, ¶¶98-100.)

Alexion makes no unique arguments for Ground 2 that relate to the dose and formulation limitations of the claims. As explained in connection with Ground 1, those limitations add nothing of patentable significance. (*See supra* II.C.4; EX1103, ¶101.)

E. Ground 3: Claims 1-8 Are Obvious Over Bell And Wang

Alexion argues that inherent disclosures cannot support an obviousness argument, (POR, 8, 57-58), but that is plainly wrong. *See, e.g., Persion Pharms. LLC v. Alvogen Malta Operations Ltd.*, 945 F.3d 1184, 1191 (Fed. Cir. 2019) ("Inherency may supply a missing claim limitation in an obviousness analysis."). And, in any event, Samsung only relies on inherency for the specific limitations relating to the claimed sequences, which were inherently disclosed by the art and which Alexion has admitted were publicly known and used in the study reported by Bell. (Pet, 54-59; EX1003, ¶¶157-163; EX1103, ¶102.) Samsung makes an obviousness combination only to address the dose and formulation limitations which were taught by Wang. (Pet., 58; EX1003, ¶161.) This Board correctly applied *Crish* and *Nichols* to find that Bell inherently anticipates the claimed sequences. (ID, 50-

54.) Analogizing to *Crish*, this Board explained that "Crish [was] claiming what Crish earlier disclosed[.]" (ID, 51.)

In addition, like in *Nichols*, there is no dispute that the antibody used in Bell's clinical trial possessed the exact sequences the inventors claimed were novel after Bell's publication. (ID, 52-53.) This Board was correct to distinguish this case from *Endo Pharms.* In that case, the petitioner failed to prove that the prior art necessarily used the material pertinent to the challenged claims. Not so here, where Alexion has repeatedly and unequivocally admitted to Patent Offices that the eculizumab antibody used in the prior art clinical studies such as Bell is identical to the antibody of the challenged claims. (Pet., 13, 56-57; EX1003, ¶¶70, 158; EX1103, ¶¶103-105.) Disclaiming these admissions, Alexion's brief now mysteriously characterizes its own statements as something Alexion "inadvertently incorrectly" said. (POR, 64.) Such unsupported attorney argument is entitled to no weight and should be dismissed out of hand. Ultimately, it is undisputed that "eculizumab, as disclosed by Bell, *is* the claimed antibody." (ID, 54.) Accordingly, *Crish* and *Nichols*, and not *Endo Pharms*., apply.

Alexion's remaining arguments against Ground 3 fail because they relitigate old issues from the Amgen IPRs, and because they are all ultimately based on Alexion's incorrect argument that a POSA would have ignored Tacken and been misled by Thomas into thinking eculizumab was an IgG4 antibody. (*See supra* II.B,

II.C.2; POR, 59-66.) Alexion challenges the applicability of *Nichols* by citing to a recycled Amgen expert declaration, but this testimony, too, simply rehashes Alexion's Thomas-IgG4 argument. (POR, 66 (citing ALXN2022, ¶¶174-184).) Indeed, there is nothing in Alexion's Response relating to this Ground that differs from the arguments it already made unsuccessfully in its POPR, accordingly the Board should confirm its initial determination.

Alexion raises no disputes for Ground 3 relating to any of the specific limitations found in challenged claims 2-8, nor do they make any arguments relating to the dose and formulation limitations that differ from their arguments already addressed in connection with Ground 1. (*See supra* II.C.4.) Those claims are also invalid as obvious under Ground 3.

F. Alexion Failed to Show Any Secondary Considerations of Non-Obviousness

Alexion's Response presents halfhearted secondary considerations arguments. These contentions are purely attorney argument, however, unsupported by any expert evidence. They were also already fully considered by this Board during the institution phase. Alexion raises the same four considerations and relies on the same exhibits as it did in its Preliminary Response. (*Compare* POPR, 70-72, *with* POR, 67-70, both citing only ALXN2018-2021.) This Board indicated its willingness to re-evaluate evidence of secondary considerations "on a full trial record," but Alexion provided no new evidence for the Board to consider. (ID, 25-

29.) These same arguments should therefore be rejected again. *See, e.g.*, *Target Corp. v. Proxicom Wireless, LLC,* IPR2020-00934, Paper 31, 20-21 (Nov. 30, 2021) ("remain[ing] persuaded" by the Petitioner when the Patent Owner "repeat[ed] substantively the same arguments that [the Board] found unpersuasive in the Institution Decision.").

Alexion's commercial success arguments fail because "the feature that creates the commercial success [or other secondary considerations] was known in the prior art." (ID, 27 (citing *Ormco Corp. v. Align Tech.*, 463 F.3d 1299, 1312 (Fed. Cir. 2006)).) It is undisputed that the prior art disclosed that eculizumab was a useful treatment for PNH and, as Samsung has shown, the sequence of eculizumab was obvious to a POSA. Relatedly, Alexion's other purported secondary considerations of industry praise and solving a long-felt need fail because they have no nexus with any novel elements of the challenged claims. (EX1103, ¶¶106-113.) *See Novartis v. Torrent Pharms.*, 853 F.3d 1316, 1331 (Fed. Cir. 2017).

Alexion has also given this Board no reason to disturb its determination that evidence of copying is not probative of nonobviousness in the context of a BPCIA-regulated biological product, and certainly is not sufficient to outweigh Samsung's strong evidence of obviousness. (ID, 28 (citing *Adapt Pharma Operations v. Teva Pharms.,* 25 F.4th 1354, 1374 (Fed. Cir. 2022))); *see also Janssen*, 97 F.4th at 933 n.9.

In sum, Alexion's weak and unsupported secondary considerations arguments fail to show nonobviousness. *See, e.g., Tokai Corp. v. Easton Enters., Inc.*, 632 F.3d 1358, 1371 (Fed. Cir. 2011) ("A strong case of prima facie obviousness . . . cannot be overcome by a far weaker showing of objective indicia of nonobviousness.").

III. CONCLUSION

The Board should find all challenged claims unpatentable.

Dated: June 10, 2024

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CERTIFICATE OF COMPLIANCE WITH WORD COUNT

Pursuant to 37 C.F.R. § 42.24(d), I certify that this reply complies with the type-volume limits of 37 C.F.R. § 42.24(c)(1) because it contains 5,585 words, according to the word-processing system used to prepare this reply, excluding the parts of this reply that are exempted by 37 C.F.R. § 42.24(a) (including the table of contents, a table of authorities, mandatory notices, a certificate of service or this certificate word count, appendix of exhibits, and claim listings).

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CERTIFICATE OF SERVICE

I hereby certify, pursuant to 37 C.F.R. Sections 42.6 and 42.105, that a complete copy of the attached **PETITIONER'S REPLY IN SUPPORT OF PETITION,** including all exhibits and related documents, are being served via Federal Express on June 10, 2024, the same day as the filing of the above-identified document in the United States Patent and Trademark Office/Patent Trial and Appeal Board, upon Patent Owner by serving the correspondence address of record with the USPTO as follows:

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