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 IPR2023-00999
U.S. Patent No. 9,725,504 B2
Issue Date: August 8, 2017

Title: TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 9,725,504 B2

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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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1037	Jette Wypych et al., *Human IgG2 Antibodies Display Disulfide-mediated Structural Isoforms*, 283 J. Biol. Chem. 16194 (2008) ("Wypych")
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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")
1048	Evelyn D. Lobo et al., *Antibody Pharmacokinetics and Pharmacodynamics*, 93 Journal of Pharmaceutical Sciences 2645 (2004) ("Lobo 2004")

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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)
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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)
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1064	Excerpt from The Merck Manual (17th ed. 1999)
1065	Health, United States, 2005 with Chartbook and Trends in the Health of Americans, U.S. Department of Health and Human Services, Centers for Disease Control and Prevention (2005)

Petitioner respectfully requests institution of *inter partes* review (IPR) of United States Patent No. 9,725,504 B2 ("'504 patent" or "EX1001") claims 1-10, as shown below.

I. INTRODUCTION

The '504 patent never should have issued. Its sole independent claim covers a method of treating the debilitating condition called paroxysmal nocturnal hemoglobinuria ("PNH") using the heavy and light chains of the antibody known as eculizumab as a pharmaceutical composition. But years before 2007, eculizumab was known as an anti-C5 antibody that was an effective treatment for PNH. And despite Alexion's recent efforts to argue that the scientific community did not know the amino acid sequence of eculizumab before the March 15, 2007 priority date, the sequence was in fact available to researchers long before that date. Several prior art publications disclose outright the exact sequence of eculizumab by providing a simple roadmap for its assembly, rendering the claimed sequence anticipated and obvious. It was also inherently anticipated by published Alexion patent applications and clinical trials using eculizumab. Various trivial limitations presented in the dependent claims add nothing of patentable significance to the basic method claim.

Arguments similar (but not identical) to those presented here were the basis of a previous IPR pursued by Amgen, Inc., which was instituted. That IPR never reached a final written decision because the parties settled and the IPR was

terminated. As explained below, IPR should again be instituted against the '504 patent to prevent Alexion from asserting the patent to an antibody sequence that was firmly in the public domain long before Alexion filed its patent application.

II. MANDATORY NOTICES UNDER §42.8(A)(1)

A. Real Party-In-Interest under §42.8.(b)(1)

Samsung Bioepis Co., Ltd. is the real party-in-interest to this IPR petition.

B. Related Matters under §42.8(b)(2)

The '504 patent is not currently involved in any litigation or Patent Office proceedings. An *inter partes* review of the '504 patent filed by Amgen, Inc. was instituted as IPR2019-00739 ("Amgen IPR"). (EX1024.) No final written decision was issued because the Amgen IPR was terminated following settlement. (EX1026.) The '504 patent is related to U.S. Patent Nos. 9,732,149, and 9,718,880, which Petitioner recently challenged in petitions for *inter partes* review IPR2023-00933 ('149) and IPR2023-00998 ('880).

C. Lead and Back-Up Counsel under §42.8(b)(3)

Petitioner provides the following designation of counsel.

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D. Service Information

This Petition is being served by Federal Express to the attorney of record for the '504 patent, NELSON MULLINS RILEY & SCARBOROUGH LLP, One Financial Center, Ste. 3500, Boston, MA 02111. Petitioner consents to electronic service at the addresses provided above for counsel.

III. FEE PAYMENT

Petitioner requests review of 10 claims, with a $41,500 payment.

IV. REQUIREMENTS UNDER §§ 42.104 AND 42.108

A. Standing

Petitioner certifies that the '504 patent is available for IPR and that Petitioner is not barred or otherwise estopped.

B. Identification of Challenge

Petitioner requests institution of IPR of claims 1-10 based on the following grounds:

Ground	Claim(s)	Basis for Challenge
1	1-5, 7-10	Obvious over Bell (EX1007), Bowdish (EX1004), and Evans (EX1005) in view of Tacken (EX1008) and Mueller PCT (EX1009)
2	6	Obvious over Bell, Bowdish, Evans, and Wang (EX1044) in view of Tacken and Mueller PCT
3	1-5, 7-10	Obvious over Bell, Evans, and Mueller PCT in view of Tacken
4	6	Obvious over Bell, Evans, Mueller PCT, and Wang in view of Tacken
5	1-5, 7-10	Anticipated by Bell

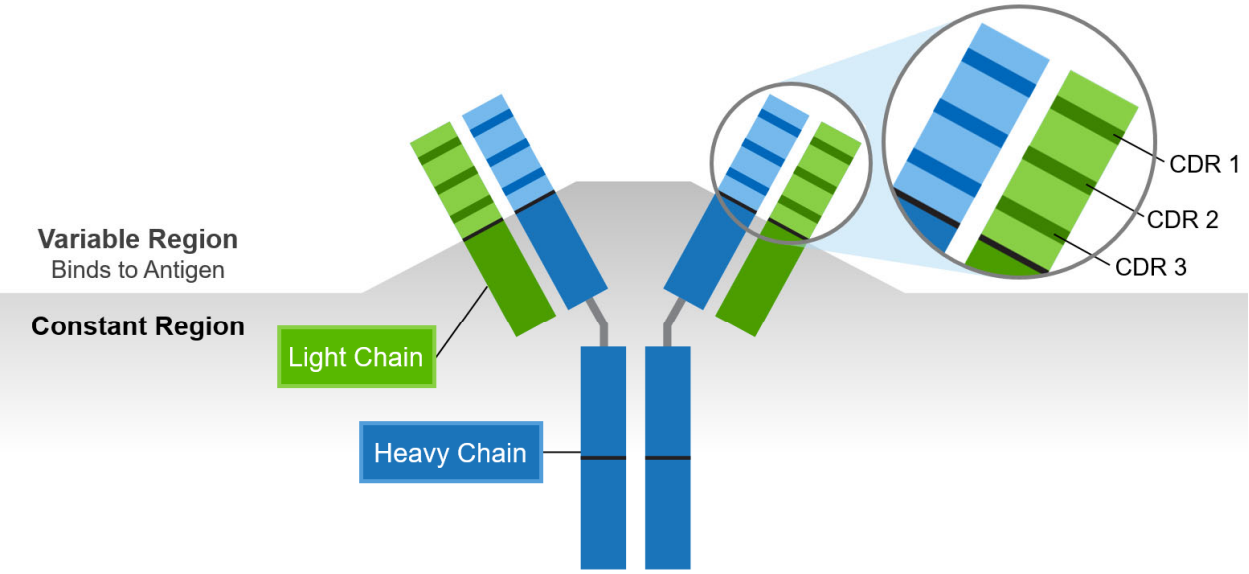
Submitted with this petition are the declarations of qualified experts Jeffrey V. Ravetch, M.D. Ph.D. and Cindy Ippoliti, Pharm.D. (EX1003, ¶¶1-14, Ex. A; EX1062, ¶¶1-10, Ex. A.)

V. FACTUAL BACKGROUND

A. Antibody Structure and Humanization of Antibodies

As relevant here, an antibody consists of two pairs of amino acid chains referred to as heavy and light chains. (EX1003, ¶¶35-36.) Each of these chains has a constant and a variable domain. (EX1003, ¶37; EX1046, 004-06.) The variable domains contain subportions responsible for antigen recognition called

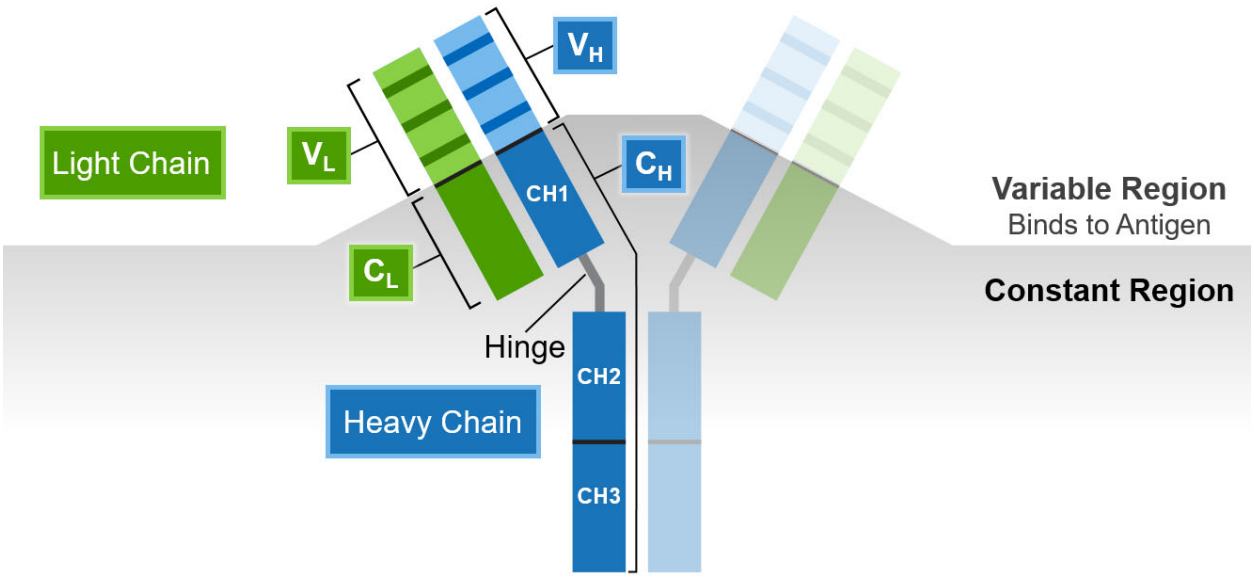
Complementarity-Determining Regions ("CDRs"); there are three CDRs each in the variable domains of each heavy and light chain, as shown below:



Basic domain structure of antibody

(EX1003, ¶38; EX1045, 055-57.)

The variable regions of the heavy and light chains are abbreviated as "V_H" and "V_L." The constant region of the heavy chain is broken up into subregions called CH1, CH2, and CH3. CH1 is separated from CH2 and CH3 by a hinge region, as shown below.



Basic domain structure of antibody

(EX1003, ¶¶40-44.) Well before 2007, the process of "humanization" of antibodies – in which mouse antibodies to human targets were converted into mostly human sequences while retaining target-binding function – was well known and routinely practiced by artisans developing antibodies for use as therapies in humans. (*Id.*, ¶¶49-54; EX1050, 010-12; EX1051; EX1052.)

B. Therapeutic Antibodies Were Routinely Used as Pharmaceutical Compositions by 2007

Before 2007, more than a dozen antibodies had been approved by the FDA for therapeutic use in humans, including several humanized antibodies. (EX1052; EX1003, ¶55; EX1062, ¶25.) Such antibodies were the basis of pharmaceutical compositions that were most commonly formulated in sterile, preservative-free single use dosage forms and administered by intravenous ("IV") infusion. (EX1003,

¶55; EX1062, ¶26; *see also* EX1055, 002.)

C. By 2007, the C5-Binding Antibody Called Eculizumab Was Known as a Treatment for PNH

PNH is a disease of blood cells caused by a genetic mutation that renders the cells more susceptible to destruction by the complement system. (EX1007, [0005]; EX1013, 009.) It is characterized by paroxysmal nocturnal (sudden attacks in the night) hemoglobinuria (hemoglobin in the urine, causing dark coloring). (EX1007, [0007]; EX1013, 009.) Other known clinical symptoms include anemia, fatigue, thrombosis, and pain. (EX1007, [0007]; EX1013, 009; EX1011, 004.) Inhibition of the complement cascade at the step in which C5 is converted to C5a and C5b was recognized as useful for inhibiting PNH symptoms, while retaining upstream complement system activity necessary for immune system function and clearance of microorganisms. (EX1013, 009; EX1011, 004; EX1003, ¶¶56-57; EX1062, ¶¶27-28.) Each of the Bell, Hill, and Hillmen references disclose the use of pharmaceutical compositions, namely antibody formulations delivered intravenously to PNH patients. (EX1007, [0062], [0082]; EX1013, 010; EX1011, 005.)

By March 15, 2007, one known inhibitor of C5 conversion was the anti-C5 antibody eculizumab. Indeed, more than a year before the ’504 patent was filed, several clinical publications disclosed that eculizumab was a useful treatment for PNH. (EX1007, [0052]; EX1013, 009; EX1011, 003; EX1003, ¶58; EX1062, ¶29;

see also EX1016; EX1017.) As shown in the table below, the prior art contained many express disclosures regarding the successful use of eculizumab as a treatment for PNH; several of these relate to the same eleven patient trial and various extensions of that trial. (*See* EX1007; EX1011; EX1012; and EX1013.)

Reference	Study Identifier	Description
EX1011	C02-001: Phase 2 Pilot	11 PNH patients
EX1013	E02-001: Phase 2, 1st Extension	11 PNH patients, 64 weeks
EX1012	X03-001: Phase 2, 2nd Extension	10 of 11 PNH patients, two years
EX1007	Phase 2, Second Extension	10 of 11 PNH patients, two years
EX1014	Phase 3 "TRIUMPH"	87 PNH patients
EX1015	Phase 3 "SHEPHERD	97 PNH patients

(*See* EX1003, ¶58; EX1002, 1314-15.)

D. As of the 2007 Priority Date, Alexion Believed the Sequence of Eculizumab Had Been Publicly Disclosed

By seeking a patent on the amino acid sequence of eculizumab, Alexion represented to the patent office that the sequence was novel and nonobvious, but this was not so. On the contrary, Alexion presumably intended to disclose the full amino acid sequence of eculizumab in 1999 and made a submission to Chemical Abstracts Services ("CAS") for that purpose. In Alexion's words to the European Patent Office, "the sequence for eculizumab was publicly available [before Feb. 3, 2004]," and the "sequence for eculizumab was submitted to [CAS] and entered into their STN database on 14 February 1999[.]" (EX1027, 277, 291 (5.1.2.); EX1003, ¶59.)

Alexion later claimed in an European counterpart patent application in this family that it was not until ten years later, in 2009, that Alexion "learned" that the sequence for eculizumab had "inadvertently" been submitted with errors in the sequences. (EX1028, 235-42, 280-81, 412-13, 522-23.)[1]

Even setting aside the implausibility of Alexion's ten-year delay in discovering that it had submitted erroneous sequence information to CAS, as discussed in Part VIII below, the prior art still anticipated and rendered these sequences obvious.

E. Eculizumab Development and Naming History

When first identified as a mouse antibody that specifically binds C5, Alexion scientists gave it the name "5G1.1." (EX1010, 006-07.) This mouse antibody was then "humanized," meaning that the CDR domains responsible for C5 binding were grafted into a human "framework" variable region, using techniques that were well-developed by the mid-1990s. (EX1010, 007-08; EX1003, ¶¶54, 61; EX1050, 010-12; EX1051; EX1052.) The resulting humanized antibody maintains fully mouse sequences in each of its six CDR domains, but otherwise uses human sequences for

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[1] The EPO refused to grant the application, in part based on its conclusion that "[e]culizumab is considered to have been available to the public before the filing date of the present application." (EX1028, 1444.)

the variable region to varying degrees; this antibody was given the name "h5G1.1" by Alexion. (EX1010, 010-12; *see also* EX1005, 43:6-14, 43:62-45:4.) After confirming that the humanized antibody variable domain retained its C5-binding function, Alexion scientists assembled it into a full-length antibody of the human IgG4 isotype, which they named "h5G1.1 HuG4." (EX1010, 013; EX1003, ¶61.)

Soon after creating this antibody, Alexion set about improving it by modifying the constant region to give it a hybrid IgG2/IgG4 backbone. (EX1006, 013-14; *see also* EX1009, 014, 097 (referencing "h5G1.1 G2/G4").) Alexion sought to reduce or eliminate binding by the constant region of the IgG4 isotype to other proteins such as FcR and C1q that are involved in human immune responses and the complement system, by replacing it with comparable IgG2 sequences. (EX1006, 015-16; EX1003, ¶¶45-48, 62; *see also* EX1048, 013-14.) Specifically, the improved antibody contained the CH1 and hinge region from IgG2 and the CH2 and CH3 regions from IgG4; Alexion again confirmed that this modification did not impact binding to C5. (EX1006, 015-16.) Alexion called this antibody "h5G1.1 HuG2/G4." (*Id*.; EX1003, ¶62.) In a companion patent application describing the same work, Alexion referred to this antibody interchangeably as "h5G1.1 G2/G4" and "h5G1.1 CO12 HuG2/G4." (EX1009, 014, 097; EX1003, ¶62.)

By 2002, Alexion had obtained a unique name for this antibody pursuant to the World Health Organization's guidelines for international nonproprietary names

("INNs"). Under INN rules in place since the 1990s, antibodies are named as follows: A random prefix of a few letters chosen by the product sponsor for uniqueness (in this case "ecu-") is followed by a "sub-stem" indicating its function (immunomodulators use "-li-"), followed by another sub-stem indicating humanization ("-zu-"), finally followed by the stem "-mab" applied to all monoclonal antibodies. (EX1019, 031-32.) Thus, Alexion's antibody received the nonproprietary name ecu-li-zu-mab. (EX1003, ¶63.)

Publications and statements by Alexion and others before 2007 clearly disclosed that the humanized 5G1.1 antibody *with* a hybrid G2/G4 constant domain <u>was</u> eculizumab. The Tacken reference referring to eculizumab as Alexion's "potential product" specifically identified eculizumab as the h5G1.1 antibody with an "IgG2/IgG4 constant region." (EX1008, 010-11.) Tacken further cited to the Mueller 1997 article discussed above, which discloses the conversion of h5G1.1 to the HuG2/G4 form. (EX1008, 011, 017 (ref. 17); EX1003, ¶64.)[2] Similarly, in a

[2] Although Tacken includes an obvious typo in its spelling of eculizumab ("eculizamab"), under the INN guidelines discussed above there are no allowed names for antibodies with the stem "-zamab," and a POSA would know that a

2002 press release, Alexion announced the issuance of the Evans patent, which Alexion said "cover[s] the composition and use of Alexion's lead drug candidate[] eculizumab (formerly known as 5G1.1)." (EX1003, ¶65; *see also* EX1022, 18:7-13.) Alexion also disclosed in Bowdish that it used the 5G1.1 antibody as a framework to create antibodies for other targets. (EX1004, [0191].) Bell uses parentheses to equate the two terms: "h5G1.1-mAb (eculizumab)." (EX1007, [0012]; EX1003, ¶68.) Likewise, a 2002 review of eculizumab identified its "synonyms" as 5G1.1 and h5G1.1. (EX1023, 001; EX1003, ¶66; *see also* EX1018, 011.) *No* reference states that eculizumab has exclusively IgG4 constant domain. (EX1003, ¶¶66-69.) A figure of the publications that discussed development of the 5G1.1 antibody before 2007 is shown below:

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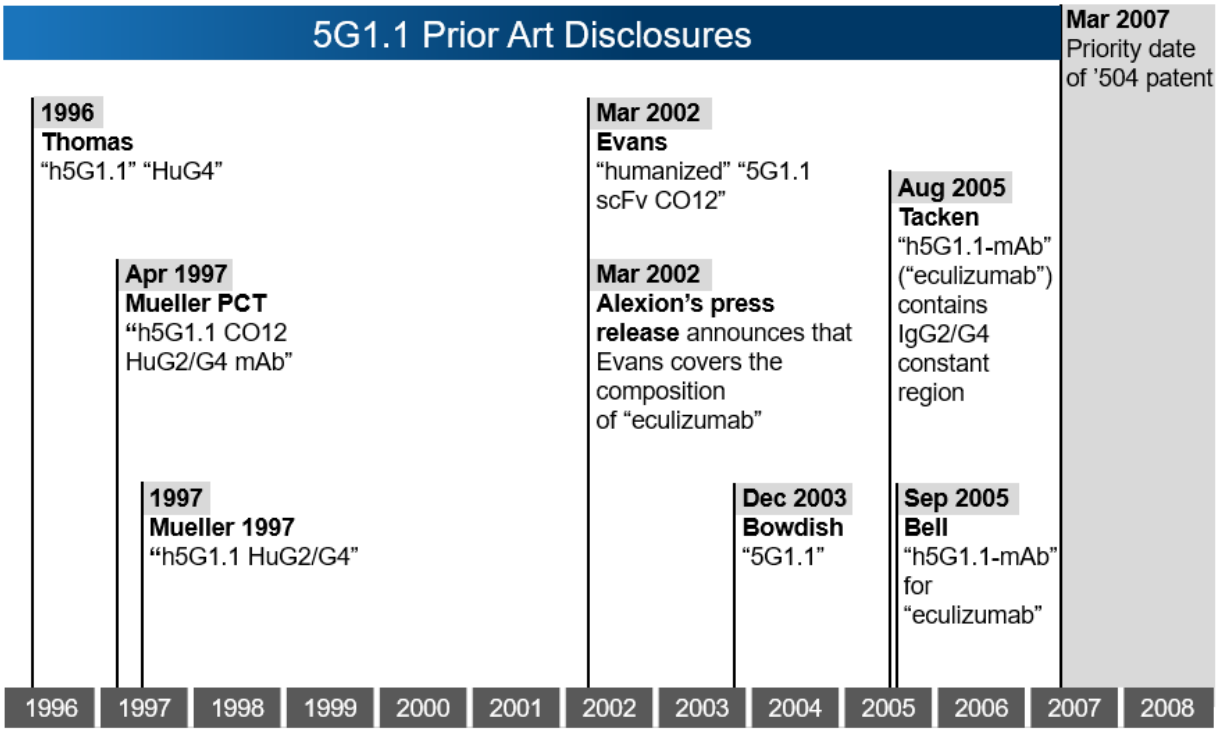
humanized antibody such as eculizumab would have the stem "-zumab." (EX1003, ¶64.)



Alexion admitted in other patent office proceedings that "it was well-known to one of ordinary skill in the art [as of 2002] that eculizumab has a G2/G4 Fc portion, i.e., a mutated Fc portion" and that "h5G1.1 … [was] well-known to one of ordinary skill in the art as eculizumab[.]" (EX1029, 010-11; *see also* EX1003, ¶70.) Alexion based these statements on the disclosures of the same Evans (EX1005) and Mueller 1997 (EX1006) references used by Petitioner in the Grounds below. (*See* EX1029, 010-11.)

Alexion also stated publicly that its eculizumab/Soliris product corresponds to the sequences disclosed in the Evans patent. For example, Alexion announced in a 2002 press release that the Evans patent "cover[s] the composition and use of … eculizumab (formerly known as 5G1.1)." (*See* EX1020, 001; EX1003, ¶65.) Having

to choose one patent for patent term extension for the eculizumab product (*see* 35 U.S.C. § 156(c)(4)), Alexion chose Evans, not the '504 patent at issue here. In its application for PTE, Alexion represented that "U.S. Patent 6,355,245 [Evans] claims the Approved Product [eculizumab]" and provided a claim chart comparing the Evans patent claims to eculizumab. (*See* EX1030, 004-07; EX1031 (granting term extension).)

VI. OVERVIEW OF THE '504 PATENT

The '504 patent has ten issued claims; only claim 1 is independent:

> 1. A method of treating a patient suffering from paroxysmal nocturnal hemoglobinuria (PNH) comprising administering to the patient a pharmaceutical composition comprising an antibody that binds C5, wherein the antibody comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.
>
> 2. The method of claim 1, wherein the pharmaceutical composition is administered by intravenous infusion.
>
> 3. The method of claim 1, wherein the antibody is administered to the patient at a dosage level of between 5 mg per kg and 50 mg per kg per patient per treatment.
>
> 4. The method of claim 1, wherein the pharmaceutical composition is in a single unit dosage form.
>
> 5. The method of claim 4, wherein the single unit dosage form is a 300 mg single unit dosage form.
>
> 6. The method of claim 1, wherein the pharmaceutical composition comprises a 300 mg single-use formulation of 30 ml of a 10 mg/ml

sterile, preservative free solution.

7. The method of claim 1, wherein the patient is anemic.

8. The method of claim 1, wherein the patient is dosed as follows: 600 mg of the antibody via intravenous infusion every 7±1 days for 4 doses; followed by 900 mg of the antibody via intravenous infusion 7±1 days later; followed by a maintenance dose of 900 mg of the antibody via intravenous infusion every 14±2 days.

9. The method of claim 1, wherein administration of the antibody results in an immediate and sustained decrease in mean levels of lactate dehydrogenase (LDH).

10. The method of claim 9, wherein the immediate decrease occurs within one week of administration of the antibody.

(EX1001, 39:2-32; EX1003, ¶71; EX1062, ¶30.)

A. Person of Ordinary Skill in the Art

A person of ordinary skill in the art ("POSA") would have knowledge of the scientific literature and have skills relating to the design and generation of antibodies, the complement system, and the application of antibodies as therapeutics before March 15, 2007. (EX1003, ¶¶16-20; EX1062, ¶¶15-19.) A POSA also would have knowledge of laboratory techniques and strategies used in immunology research, including practical applications of the same. (EX1003, ¶19; EX1062, ¶18.) Typically, a POSA would have had an M.D. and/or a Ph.D. in immunology, biochemistry, cell biology, molecular biology, pharmaceutics, or a related discipline, with at least two years of experience in the discovery, development, and design of

therapeutic antibodies for use as potential treatments in human disease. (*Id.*) Also, a POSA may have worked as part of a multidisciplinary team and drawn upon not only his or her own skills, but also taken advantage of certain specialized skills of others on the team, *e.g.*, to solve a given problem; for example, a clinician, a doctor of pharmacy, and a formulation chemist may have been part of a team. (*Id*.)

B. Overview of the Specification

The '504 patent describes the use of antibodies binding to the complement cascade protein C5 as a treatment for PNH. In particular, the '504 teaches that such antibodies "are known," and that a preferred antibody is disclosed in the Evans reference and "now named eculizumab." (EX1001, 12:28-31.) The patent describes details of the Phase 3 "TRIUMPH" clinical trial in which one such antibody, eculizumab, was evaluated in PNH patients. (*Id*., 19:53-28:38.) The patent also provides amino acid sequences for eculizumab's heavy and light chains as SEQ ID NOS:2 and 4, respectively. (*Id*., Cols. 30-35; EX1003, ¶¶72-73.)[3] The patent also provides details relating to the route of administration of eculizumab (IV infusion), the dose format (single use, sterile, preservative-free), the dose unit (300 mg), and

[3] In addition to these sequences, the '504 also repeats these sequences in Column 30, but with an error in SEQ ID NO:2, the eculizumab heavy chain, that was corrected by certificate. (EX1002, 1391-93.)

the formulation volume size and concentration (30 mL of a 10 mg/ml solution), although it makes no claims of novelty as to any of these conventional features. (EX1062, ¶¶32-33.)

C. '504 Prosecution History

Alexion originally sought claims 1-10 that issued as is in the '504 patent. Claims 1-2 and 7-10 were initially rejected as anticipated by Hillmen 2004 in view of Thomas. (EX1002, 1036-37.) Claims 1-4 and 7-10 were also rejected as obvious over Hillmen in view of Thomas and Evans, and all claims were rejected as obvious over Hillmen in view of Thomas, Evans and Wang. (*Id*., 1038-40.) In response, Alexion argued that the cited references do not disclose the "unique, non-naturally occurring, protein-engineered full heavy chain of eculizumab (including the CH1-hinge-CH2-CH3 regions)[,]" and "the complete structure of eculizumab was not disclosed prior to the March 15, 2007 effective filing date[.]" (*Id*., 1079-80.)

The Examiner then maintained two rejections: (1) claims 1-2 and 7-10 as anticipated by Hillmen in view of Thomas, and (2) claims 1-10 as obvious over Hillmen, in view of Thomas, Evans and Wang. The Examiner also requested additional information regarding sequences used in trials disclosed in various prior publications. (EX1002, 1123-24.)

In response, Alexion again asserted that "[n]either eculizumab nor its complete sequence, including the sequence of its unique, non-naturally occurring,

protein-engineered heavy chain, was in the public domain prior to the March 15, 2007 effective filing date of the present application[.]" (EX1002, 1296.) Alexion also submitted evidence that the clinical trial reported in Hillmen 2004 was conducted confidentially such that its participants could not reveal the sequence of eculizumab. (*Id*., 1296-98.)

The Examiner allowed the claims based on the belief that prior art did not "recite using an antibody which comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4 as currently recited and one of skill in the art would not have been easily guided to making antibodies with these recited sequences." (EX1002, 1347.) As explained in this Petition and further in Part X.B, this belief by the Examiner was erroneous and led to the issuance of unpatentable claims. (*See infra* X.B; EX1003, ¶¶176-179.) The Examiner did not address Wang or its teachings regarding eculizumab formulations.

On February 28, 2019, Amgen challenged all claims of the '504 patent in IPR2019-00739. The Board instituted *inter-partes* review. (EX1024.) The parties' submissions and Board's findings during the *inter-partes* review were submitted to the PTO during prosecution of the '504 patent's child application that issued as U.S. Patent No. 10,590,189 ("'189 patent").

VII. CLAIM CONSTRUCTION

Petitioner does not believe claim construction is necessary at this time.[4]

VIII. THE CHALLENGED CLAIMS ARE UNPATENTABLE

A. Prior Art References Cited in Proposed Grounds

The priority date of the '504 patent is March 15, 2007.[5] Each reference in Grounds 1-5 (*see supra* IV.B) qualifies as prior art under 35 U.S.C. § 102(b).

1. Bowdish [EX1004]

Bowdish is a U.S. patent application, published on December 18, 2003, and is thus prior art under 35 U.S.C. §102(b). Bowdish's 5G1.1 antibody discloses outright the light chain sequence (SEQ ID NO:4) in claim 1 of the '504 patent in Figure 13B. (EX1004, Fig. 13B; EX1003, ¶85.) Bowdish's 5G1.1 was also a

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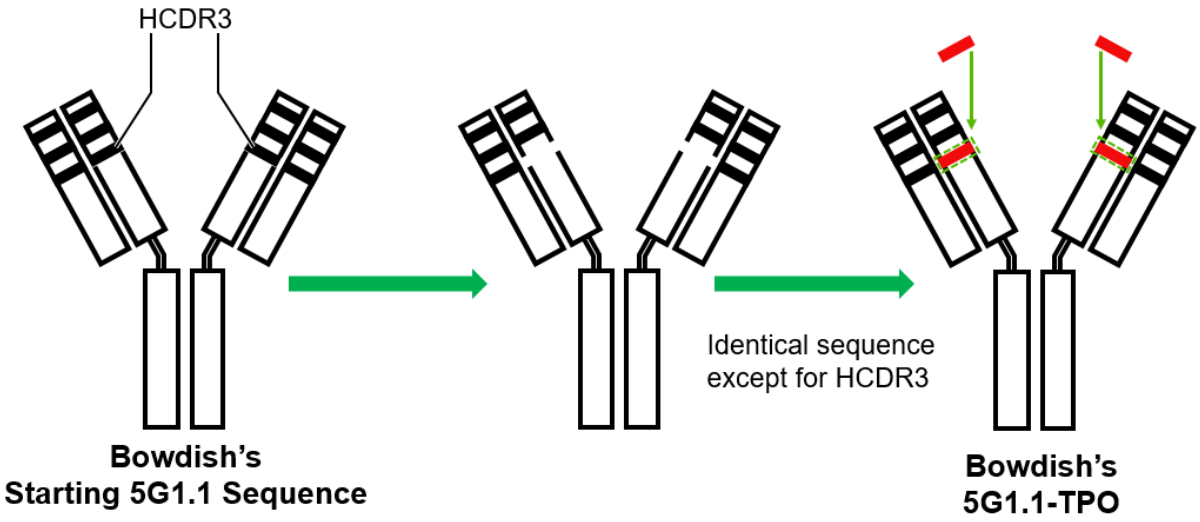
[4] In IPR2019-00739, the Board construed the "immediate" limitation of claims 9 and 10 to mean "within one week." (EX1024, 022-23.) Petitioner submits the term needs no construction and is disclosed by the prior art under any reasonable interpretation, including the construction adopted by the Board in the prior proceeding. (*See supra* VIII.C.)

[5] Petitioner assumes this date for this Petition without waiving its right to challenge this priority date.

starting point for making a new heavy chain that includes a "TPO mimetic peptide," as illustrated below. (EX1004, Fig. 13A & [0191]; EX1003, ¶82.)



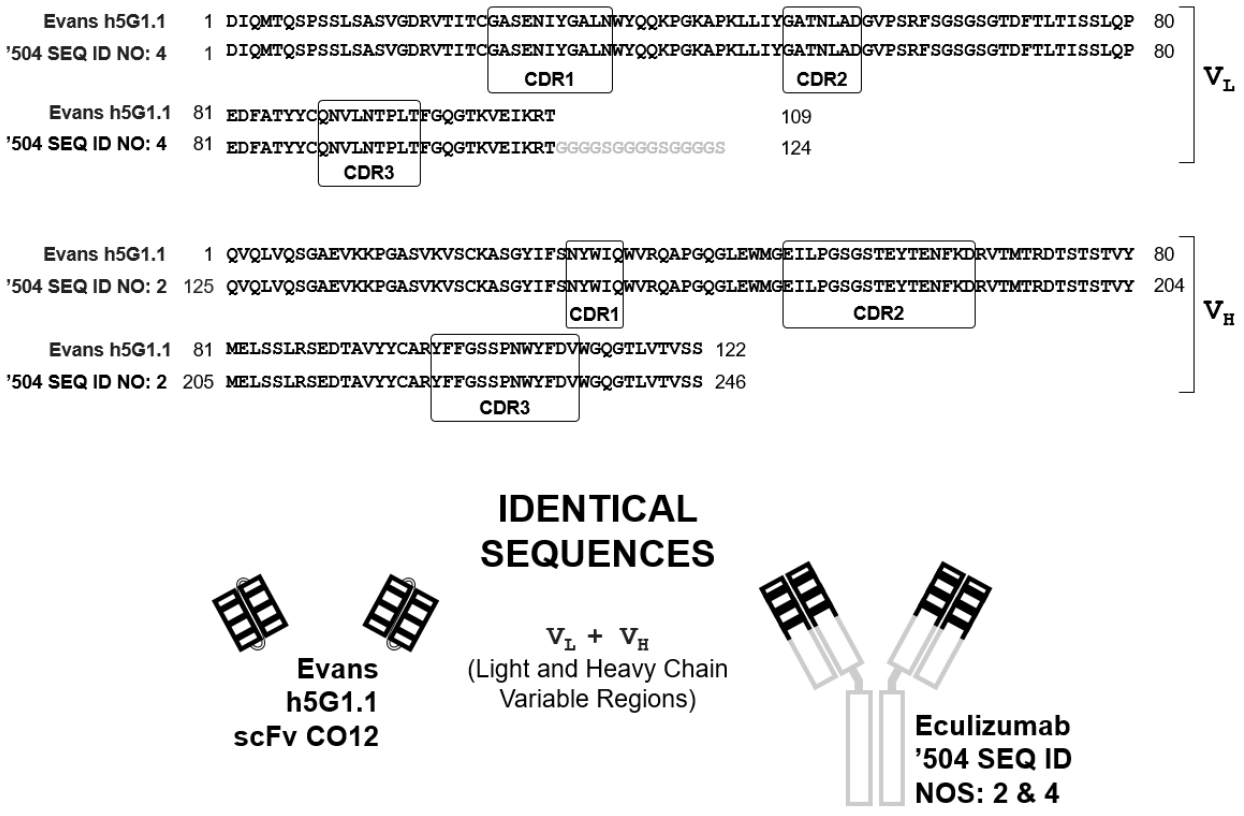
That starting heavy chain sequence is described as having the sequence of Figure 13A with a substituted heavy chain CDR3 ("HCDR3") domain reported by Evans, which is incorporated by reference. That original sequence is identical to SEQ ID NO:2 of claim 1. (EX1003, ¶¶82-87.)

Bowdish also teaches that its antibodies can be formulated as "pharmaceutical compositions," can be administered intravenously through known methods, and that such compositions "must be sterile" and that they can optionally include preservatives. (EX1004, [0148]-[0151]; EX1062, ¶¶36-37.)

2. Evans [EX1005]

Evans is a U.S. patent issued on March 12, 2002, based on Application number 08/487,283. It is prior art under 35 U.S.C. §102(b). Evans is titled "C5-

Specific Antibodies for the Treatment of Inflammatory Diseases." Example 11 provides eighteen constructs of "recombinant mAb-encoding DNAs." Of these, nine constructs provide sequences for humanized 5G1.1 single-chain variable fragments (scFv), which correspond to V_H and V_L domains joined by a short peptide linker and starting with the "MA" leader sequence. (EX1005, 43:6-14, 43:61-45:4 (Example 11 (2) and (11)-(18)); EX1003, ¶¶89-90.) The nine constructs disclose CDR sequences within the variable regions of humanized 5G1.1, and Evans' CO12 scFv construct discloses the light and heavy chain variable domains of SEQ ID NOS:2 and 4 of claim 1:



(EX1005, 44:4-14 (Example 11 (12)); EX1003, ¶91.) All nine constructs disclose the identical heavy chain CDR3 sequence of SEQ ID NO:2 of claim 1. (EX1003, ¶90, Appendix A.)

Evans also teaches that its anti-C5 antibodies can be administered "in a variety of unit dosage forms," and that doses are typically from 1 to 100 mg per kg and preferably 5 to 50 mg per kg of patient weight. (EX1005, 17:60-18:11.) Evans discloses that its antibodies will generally be administered intravenously in a formulation that "must be sterile" and which "may" contain preservatives. (EX1005, 18:29-43; EX1062, ¶¶38-39.)

3. Bell [EX1007]

Bell is a U.S. patent application published on September 1, 2005, and is thus prior art under 35 U.S.C. §102(b). Bell teaches that anti-C5 antibody known as "h5G1.1-mAb (eculizumab)" is a "particularly useful" treatment for PNH. (EX1007, [0012], [0052], [0081]-[0083], [0096], Fig. 3; EX1003, ¶¶94-98.) Bell also teaches that "[m]ethods for the preparation of" h5G1.1 "are described in" Evans (EX1005) and Thomas (EX1010), "the disclosures of which are incorporated [into Bell] in their entirety." (EX1007, [0052].)

Bell teaches that formulations of its anti-C5 antibodies "suitable for injection" "must be sterile" and may or may not contain preservatives. (EX1007, [0062].) Bell discloses human clinical studies in which eculizumab was administered

intravenously at a dose of 600 mg every 7±1 days for four weeks, followed by a 900 mg dose one week later and then a 900 mg maintenance dose every 14±2 days later. (EX1007, [0082]; *see also id*., [0088]; EX1003, ¶¶94-95; 41-42.)

Bell discloses that eculizumab is an effective treatment for PNH. (EX1007, [0081]-[0097], Figs. 1a, 1b, 3, 6a, 6b, 7-10.) Bell teaches that its anti-C5 antibodies such as eculizumab ameliorate the effects of PNH, including "anemia." (*Id.*, [0037].) Bell also discloses that the patients in its study were anemic, with mean hemoglobin levels of 10 g/dl, well below the levels which the American Society for Hematology defines anemia. (EX1064, 008; EX1003, ¶96; EX1062, ¶40.) Bell further teaches that when used as a treatment for PNH, eculizumab resulted in an immediate (i.e., within one week of administration) and sustained decrease in the mean levels of lactate dehydrogenase (LDH). (EX1005, [0085], Fig. 1b.)

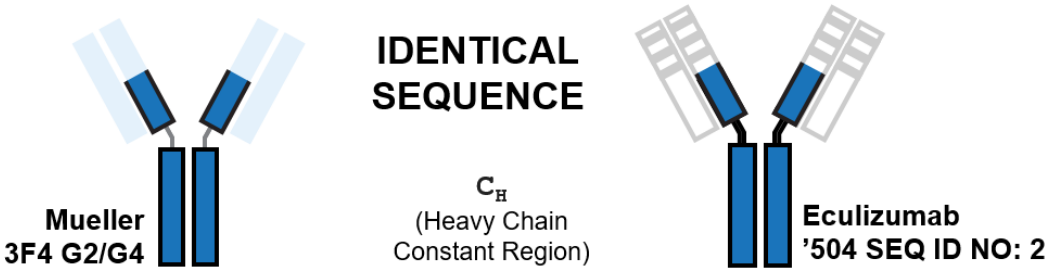
4. Tacken [EX1008]

Tacken is a journal article published on August 15, 2005, and is thus prior art under 35 U.S.C. §102(b). Tacken teaches that "h5G1.1-mAb" is "eculizamab [*sic*]." (EX1008, 011.) Tacken states that h5G1.1-mAb contains the "human hybrid IgG2/IgG4 constant domain," and further cites to the Mueller 1997 reference for these domains. (*Id.*; EX1003, ¶100.)

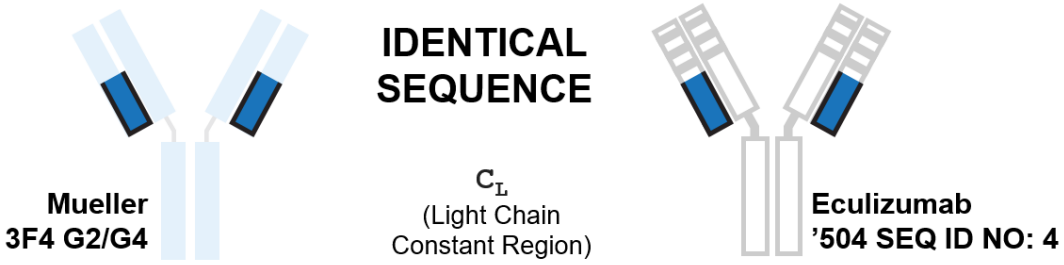
5. Mueller PCT [EX1009]

Mueller PCT, published on April 3, 1997, is the companion international patent application of the Mueller 1997 reference cited by Tacken. It is prior art under 35 U.S.C. §102(b). Mueller PCT discloses sequences for anti-pVCAM antibodies, including the full-length 3F4 HuG2/G4 antibody, which contains a hybrid IgG2/G4 heavy chain constant region with "the C1 and hinge regions of human IgG2 and the C2 and C3 regions of human IgG4[.]" (EX1009, 8:23-26, 12:23-27; EX1003, ¶103.) Mueller PCT refers to antibodies with this IgG2/G4 constant region as "**HuG2/G4 mAb**." (EX1009, 8:23-26; EX1003, ¶104.) Mueller PCT describes using "h5G1.1 CO12 **HuG2/G4 mAb**" and discloses the amino acid sequences for the constant regions of SEQ ID NOS:2 and 4 of claim 1:

Mueller 3F4 G2/G4 C_H	1	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQT	80
'504 SEQ ID NO: 2 C_H	1	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQT	80
Mueller 3F4 G2/G4 C_H	81	YTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG	160
'504 SEQ ID NO: 2 C_H	81	YTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG	160
Mueller 3F4 G2/G4 C_H	161	VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKN	240
'504 SEQ ID NO: 2 C_H	161	VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKN	240
Mueller 3F4 G2/G4 C_H	241	QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSL	320
'504 SEQ ID NO: 2 C_H	241	QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSL	320
Mueller 3F4 G2/G4 C_H	321	SLSLGK	326
'504 SEQ ID NO: 2 C_H	321	SLSLGK	326



Mueller 3F4 C_L	1	VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKH	80
'504 SEQ ID NO: 4 C_L	1	VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKH	80
Mueller 3F4 C_L	81	KVYACEVTHQGLSSPVTKSFNRGEC	105
'504 SEQ ID NO: 4 C_L	81	KVYACEVTHQGLSSPVTKSFNRGEC	105



(EX1003, ¶¶105-106, EX1009, 054-55, 058-59.)

6. Wang [EX1044]

Wang is a U.S. patent application, published on December 8, 2005, and is thus prior art under 35 U.S.C. § 102(b). Wang describes various methods and compositions for formulation of antibodies, including eculizumab, that inhibit activation of the complement system. (EX1044, Abstract, [0004].) Wang's teachings identify the anti-C5 antibody eculizumab as a preferred embodiment, citing to Evans. (*Id*., [0004], [0011], [0067].) Wang expressly teaches that eculizumab formulations "may be stable in a formulation at a concentration ranging from 1 mg/ml to 200 mg/ml." (*Id*., [0067].) Wang further provides specific examples disclosing that eculizumab can be effectively formulated in solutions with concentrations ranging from 1 mg/ml to 30 mg/ml while maintaining the integrity of the antibody. (*Id.*, Fig. 10, [0025], [0170]-[0173]; EX1003, ¶¶108-109; EX1062, ¶¶45-46.)

B. Overview of Proposed Grounds for IPR

Ground 1 is based on obviousness of claims 1-5 and 7-10 from combining Bell, Bowdish, and Evans in view of Tacken and Mueller PCT. (EX1003, ¶¶111-143; EX1062, ¶¶47-61.) A POSA would have been motivated to obtain the sequence of eculizumab (identical to SEQ ID NOS:2 and 4) by Bell, which teaches that eculizumab, also known as "h5G1.1," is a "particularly useful" antibody for treatment of PNH. Bell, like Bowdish, points to Evans for preparation of the h5G1.1 antibody. A POSA would have obtained SEQ ID NOS:2 and 4 from Bowdish and Evans. Bowdish provides the entire eculizumab amino acid sequence through SEQ ID NOS:67 and 69 and the incorporation by reference of the heavy chain CDR3 of Evans. Specifically, Bowdish provides the framework for the humanized IgG2/G4 eculizumab antibody and incorporates by reference the 13 amino acid heavy chain CDR3 for humanized 5G1.1 that Evans discloses to complete the eculizumab sequence. And Bowdish discloses the exact light chain of SEQ ID NO:4 outright. Thus, Bowdish and Evans as a single integrated document disclose the full sequence of Bowdish's 5G1.1 antibody, the exact antibody sequence recited in challenged claim 1 (SEQ ID NOS:2 and 4), as a pharmaceutical composition. Tacken and Mueller PCT provide additional guidance to a POSA to confirm that Bowdish's 5G1.1 antibody is Alexion's "potential product," known both as h5G1.1 and eculizamab (*sic*), which contains the IgG2/IgG4 constant region reported in the

Mueller 1997 reference (also disclosed in Mueller PCT). With this guidance, a POSA would have understood that the starting sequence used by Bowdish, having the heavy chain CDR3 of Evans, was eculizumab (SEQ ID NOS:2 and 4).

Bell and Evans also variously disclose the uninventive formulation, dosing regimen, and efficacy limitations of claims 2-5 and 7-10. Collectively, the limitations in these claims are nothing more than "the predictable use of prior art elements according to their established functions," and therefore add nothing of patentable significance. *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 417 (2007); *see also W. Union Co. v. MoneyGram Payment Sys., Inc*., 626 F.3d 1361, 1371-72 (Fed. Cir. 2010).

Ground 2 simply adds the Wang reference to the Ground 1 combination to address the uninventive 10 mg/ml solution limitation of claim 6. (EX1003, ¶¶144-150; EX1062, ¶¶47-61.)

Ground 3 is based on obviousness of claims 1-5 and 7-10 in combining Bell, Evans, and Mueller PCT in view of Tacken. (EX1003, ¶¶151-160; EX1062, ¶¶47-61.) Bell teaches that eculizumab, also known as "h5G1.1," is a "particularly useful" antibody for treatment of PNH. Bell points to Evans for the complete variable region sequences of eculizumab under the name "humanized 5G1.1," which correspond to the variable regions of SEQ ID NOS:2 and 4. Bell and Evans are combined with Mueller PCT, which teaches the constant regions of SEQ ID NOS:2 and 4. The

combination of Evans and Mueller PCT is directed by Tacken, which confirms the constant region of eculizumab is the IgG2/G4 type taught by Mueller PCT. In addition, Mueller PCT's disclosure of "h5G1.1 CO12 HuG2/G4" specifically teaches a POSA to combine with the CO12 variable domain from Evans, resulting in an antibody as a pharmaceutical composition that is a 100% match for SEQ ID NOS:2 and 4 as recited in challenged claim 1. As with Ground 1, Bell, Bowdish, and Evans also variously disclose the uninventive formulation, dosing regimen, and efficacy limitations of claims 2-5 and 7-10.

Ground 4, similar to Ground 2, adds the Wang reference to the Ground 3 combination to address the uninventive formulation limitation of claim 6. (EX1003, ¶161; EX1062, ¶¶47-61.)

Ground 5 is based on anticipation of claims 1-5 and 7-10 by Bell. (EX1003, ¶¶162-168.) As discussed above and as evidenced by multiple Alexion admissions to patent offices, the eculizumab antibody with the identical amino acid sequence of claim 1 was *necessarily* the exact antibody used in the PNH clinical studies described by Bell, and enabling disclosures for the claimed sequences were in the prior art. As such, Bell inherently anticipates the antibody sequence recited in claim 1. And Bell expressly discloses the remaining trivial limitations of dependent claims 2-5 and 7-10.

This petition is supported by the declarations of Dr. Jeffrey Ravetch, M.D., Ph.D., a renowned expert in antibody structure, modification of antibody domains, and development of therapeutic antibodies for a variety of human diseases (EX1003, ¶¶1-14, 19-20); and Dr. Cindy Ippoliti, Pharm.D., a skilled pharmaceutical scientist with over 30 years of experience in the administration of therapeutic antibody drugs to patients (EX1062, ¶¶1-9, 19).

C. Ground 1: Claims 1-5 and 7-10 Are Obvious Over Bell, Bowdish, and Evans in view of Tacken and Mueller PCT

1. Claim 1

Bell teaches that eculizumab is an effective treatment for PNH. Bell teaches that eculizumab, also referred to as h5G1.1, had been successful in the treatment of PNH. Bell discloses that a "particularly useful" treatment for PNH is the anti-C5 antibody known as "h5G1.1-mAb (eculizumab)." (EX1007, [0012], [0052], [0082]; EX1003, ¶111.) As Bell explains, by 2005 "[t]he antibody h5G1.1" carried the "tradename eculizumab." (EX1007, [0052].) Bell discloses human clinical trial evidence that eculizumab is an effective treatment for PNH. (*Id*., [0003], [0012], [0081]-[0097], Figs. 1a, 1b, 3, 6a, 6b, 7-10.)

These definitive clinical data would have more than motivated a POSA to obtain the structure of eculizumab. (EX1003, ¶111.) Although Bell's disclosure does not include the exact amino sequence of eculizumab, Bell teaches that the antibody h5G1.1 *is* eculizumab, and that "methods for the preparation of" h5G1.1

"are described in" Evans (EX1005) and Thomas (EX1010), both of which are incorporated into Bell in their entirety. (EX1007, [0052].) Based on Bell's reference to Evans for h5G1.1, and Evans' disclosure of humanized scFv sequences (discussed below), a POSA would have understood that Evans contains the variable region sequences for eculizumab. And as discussed further below, a POSA would not have wrongly concluded from Bell's citation to Thomas that the eculizumab disclosed in Bell would have an IgG4 isotype as discussed in the Thomas reference. (*See infra* this section; EX1003, ¶112, 130, 165.)

(a) Bowdish and the Incorporated Evans Reference Provide the Complete Sequence of h5G1.1

Bowdish is an Alexion patent publication that, through incorporation by reference of Evans, discloses both SEQ ID NOS:2 and 4, as claimed in the '504 patent. Bowdish's SEQ ID NO:69 discloses the light chain sequence of SEQ ID NO:4 in claim 1 of the '504 patent. (EX1004, Fig. 13B; EX1003, ¶¶113-114 (comparing sequences).)

```
Bowdish SEQ ID NO: 69   1 MDMRVPAQLLGLLLLWLRGARCDIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYGATNLADGV  80
'504 SEQ ID NO: 4       1 ----------------------DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYGATNLADGV  58
                                                          CDR1                    CDR2

Bowdish SEQ ID NO: 69  81 PSRFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNN 160
'504 SEQ ID NO: 4      59 PSRFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNN 138
                                                  CDR3

Bowdish SEQ ID NO: 69 161 FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC 236
'504 SEQ ID NO: 4     139 FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC 214
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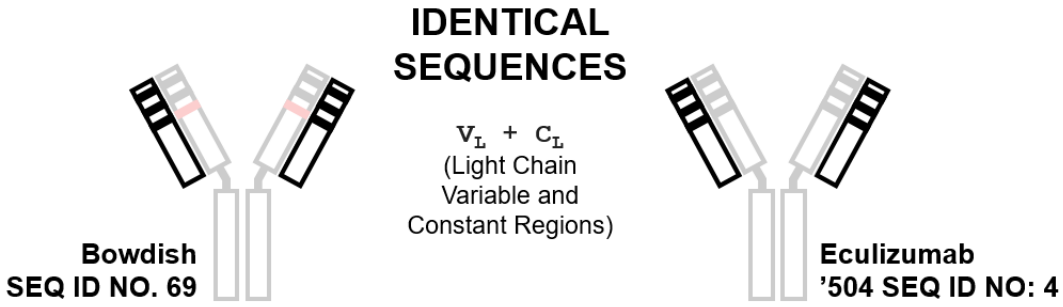
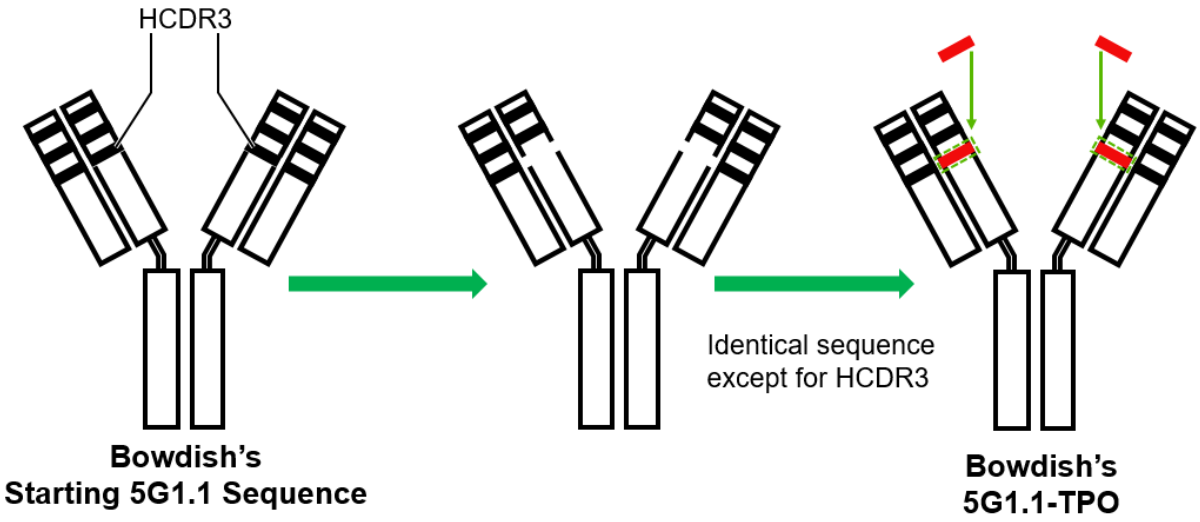
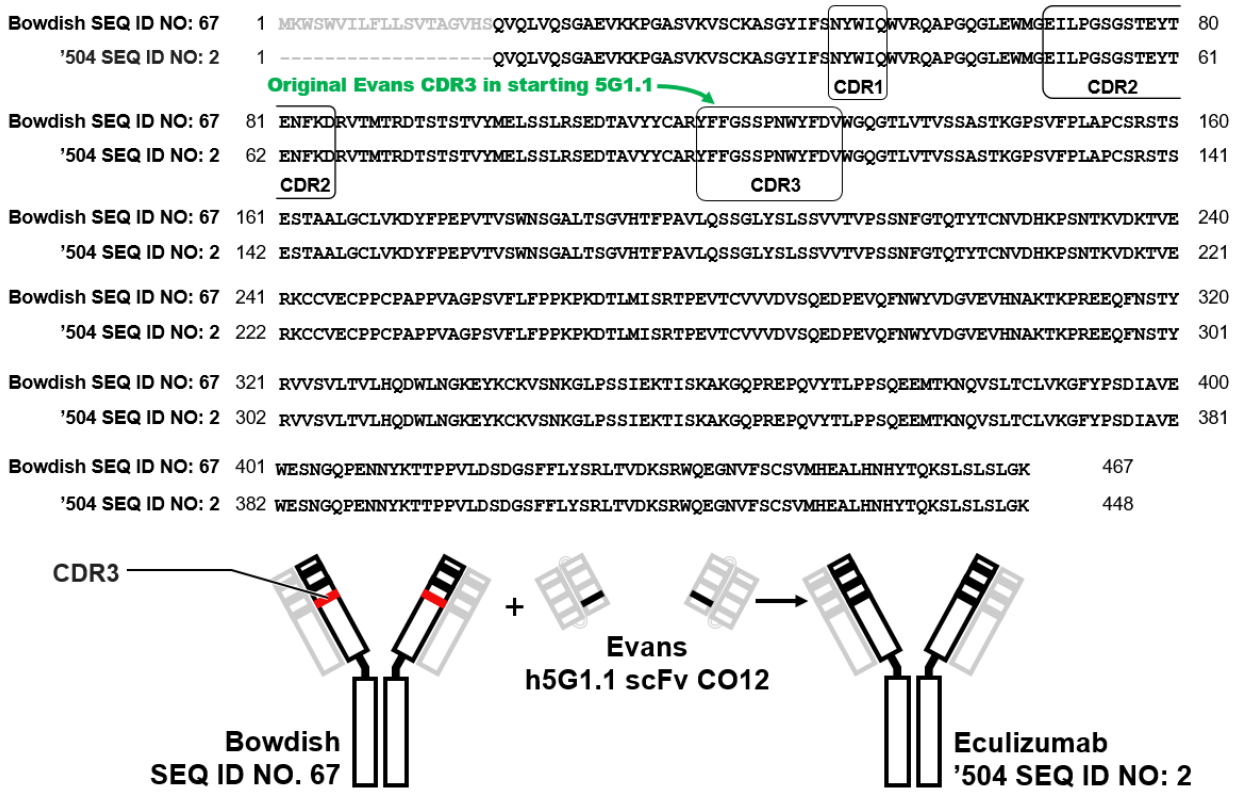


In addition, Bowdish explains that it created SEQ ID NO:67 from a starting heavy chain sequence that is identical to SEQ ID NO:2. Bowdish's SEQ ID NO:67 discloses all elements of the heavy chain sequence of SEQ ID NO:2 in claim 1, with the exception of the 13 amino acid "native CDR3" of "5G1.1" within SEQ ID NO:2. (EX1004, Fig. 13A, [0191]; EX1003, ¶115.) Bowdish explains that the "native CDR3" has been replaced with a TPO mimetic peptide and identifies the sequence of that peptide. (*Id.*) Critically, Bowdish identifies the Evans U.S. Application Ser. No. 08/487,283 (published in 2002 as Evans patent '245 (*see* EX1005, Cover) as disclosing the "native CDR3" and incorporates the Evans application by reference. (*See* EX1004, [0191]; EX1003, ¶¶116-117.) Accordingly, Bowdish identifies the

heavy chain sequence that had the "native CDR3" before it was replaced with the TPO peptide's HCDR3.



In other words, the original heavy chain of Bowdish's 5G1.1 antibody contained Evans' "native CDR3," YFFGSSPNWYFDV, before it was replaced with the TPO mimetic peptide, LPIEGPTLRQWLAARAPV, as shown in SEQ ID NO:67. (EX1003, ¶116; EX1004, [0191]; EX1005, Fig. 19, 43:6-14, 43:61-45:4; EX1003, ¶116.) Accordingly, the original heavy chain has the identical sequence as SEQ ID NO:2 of claim 1.



(EX1003, ¶116.) There can be no doubt that the 5G1.1 sequences taught in Evans encode antibodies that bind C5. (EX1005, Cover (Title), 7:60-64, 9:44-45, Fig. 8, Claim 19; *see also* EX1022, 16:10-12.) Bowdish's disclosure thus teaches the antibody sequence recited in claim 1, indeed, as the Board previously concluded, "Bowdish discloses a substantial portion of the anti-C5 antibody 5G1.1 and points to Evans as evidencing the remaining amino acid sequence." (EX1024, 045.)

A POSA following Bowdish's incorporation of Evans would have no difficulty immediately identifying the sequence Bowdish refers to as "the native CDR3." Evans' Example 11 teaches the construction of recombinant antibodies using the heavy and light chain CDRs of the 5G1.1 antibody. (EX1005, 42:56-

45:33; EX1003, ¶117.) In all, Evans' Example 11 provides eighteen constructs of "recombinant mAb-encoding DNAs." Of these, nine provide humanized single-chain variable domain structures ("scFvs") which correspond to the V_H and V_L domains of an antibody joined by a short peptide linker and starting with the "MA" leader sequence. (EX1005, 42:56-45:33; EX1003, ¶¶39, 117-119.) Importantly, the *identical* HCDR3 sequence is used in *every one* of these examples. (EX1005, 9:65-10:20, 42:56-45:33, 143:22-144:14, Figs. 18-19, Claim 19; EX1003, ¶120, Appendix A.) This is not surprising, since the CDR regions determine binding to target (here, C5), and are a fundamental component of the uniqueness of a particular antibody such as 5G1.1. (EX1003, ¶120.) Finally, Bowdish also expressly discloses a pharmaceutical composition as recited in challenged claim 1. (EX1004, [0148]-[0151]; EX1003, ¶120; EX1062, ¶37.)

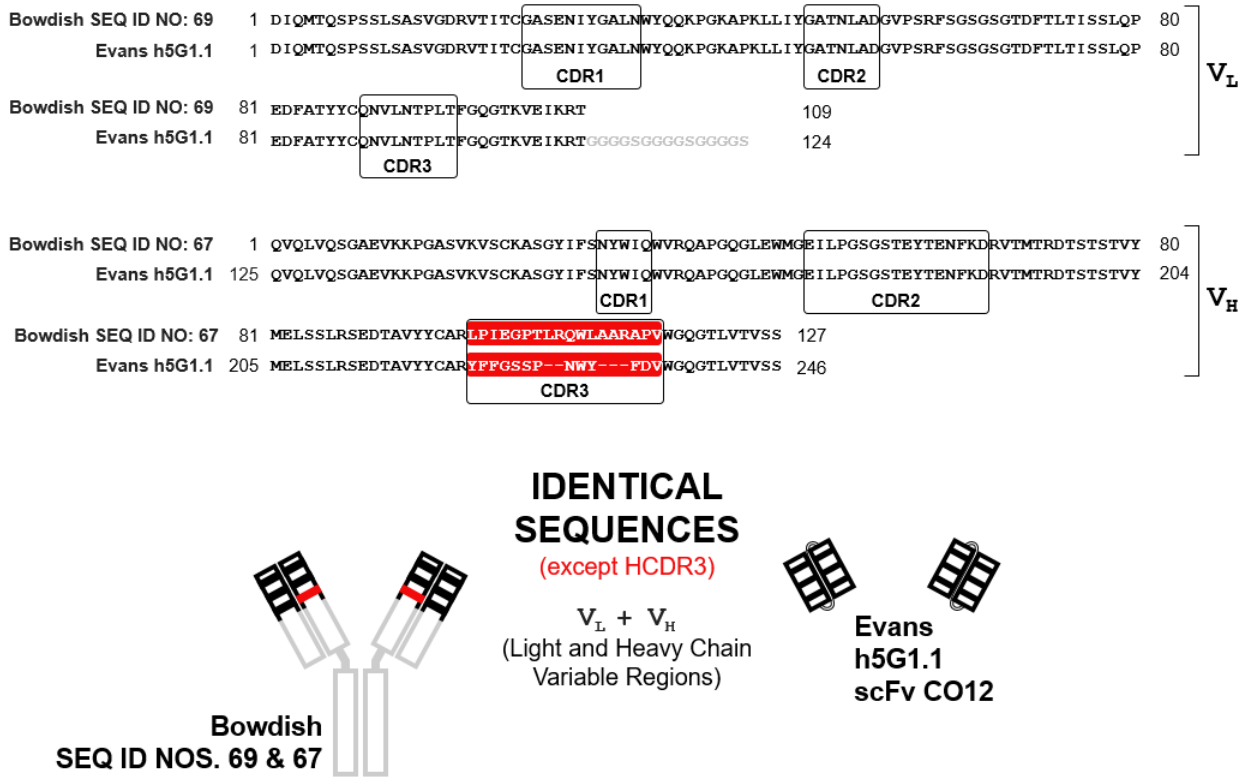
Bowdish's express incorporation by reference of Evans is operative to bring the entire disclosure of Evans within Bowdish "as if it were explicitly contained therein." *See Paice LLC v. Ford Motor Co.*, 881 F.3d 894, 906 (Fed. Cir. 2018). The disclosure in Bowdish specifically incorporates Evans for "[c]onstruction of 5G1.1." (EX1004, [0191]; EX1003, ¶121.) That is, Bowdish identifies specifically what material from Evans is being incorporated, and expressly incorporates those teachings without qualification. Accordingly, Bowdish and Evans must be treated as an integrated single reference. *Paice*, 881 F.3d at 906-07.

The disclosure of Bowdish and Evans as a single integrated document is also enabling. It does not matter whether either of the Bowdish or Evans inventors, on their own, actually made the assembled sequence of eculizumab. *See Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1380-81 (Fed. Cir. 2003) ("A reference may enable one of skill in the art to make and use a compound even if the author or inventor did not actually make or reduce to practice that subject matter."). It only matters that the Bowdish and Evans integrated document discloses sufficient information to make eculizumab. *Id; see also Novo Nordisk Pharms., Inc. v. Bio-Technology Gen. Corp*, 424 F.3d 1347, 1356 (Fed. Cir. 2005) (reference disclosed production of hGH protein in an enabling manner which, in combination with "standard recombinant DNA techniques" known to a POSA, could be used to produce the protein).

Further, a POSA looking to obtain the amino acid sequences for h5G1.1 (eculizumab) would have easily found Bowdish and considered it to be analogous art to Bell, and to the field of the challenged patent, because it provides express teachings about the structure of the antibody "5G1.1," identifies "Alexion Pharmaceuticals" as the inventors' addressee, and cites to the same Evans patent as does Bell for the structure of 5G1.1. (EX1004, Cover, [0191]; EX1003, ¶122.) These links are more than sufficient to meet the standard for analogous art. *See*

Unwired Planet, LLC v. Google Inc., 841 F.3d 995, 1000-01 (Fed. Cir. 2016); *In re GPAC Inc*., 57 F.3d 1573, 1577-79 (Fed. Cir. 1995).

Although Bowdish calls its antibody framework "5G1.1," a POSA would have understood that it is referring to h5G1.1 based on a comparison of Bowdish's and Evans' variable region sequences. (EX1003, ¶123.) Bowdish's SEQ ID NOS.67 and 69 disclose the sequences of "5G1.1" antibody framework, into which only the HCDR3 was replaced for the TPO mimetic peptide graft. (*See* EX1004, Figs. 13A & 13B.) A routine comparison of these sequences with Evans' constructs in Example 11 would have quickly revealed that Evans' SEQ ID NO:20 is identical to the variable regions in Bowdish's SEQ ID NO:69 & 67, except for the HCDR3 sequence:



(EX1003, ¶123.) Evans' SEQ ID NO:20 is designated "***humanized***" 5G1.1 scFv. Further, since Bowdish used an "anti-human IgG" in a binding assay to detect 5G1.1, it would have been evident to a POSA that Bowdish discloses humanized 5G1.1. (EX1003, ¶¶83, 124; EX1004, [0192].) Thus, a POSA would have understood that Bowdish's antibody framework sequences in SEQ ID NOS:67 and 69, including the constant region sequences, are indeed humanized 5G1.1 (*i.e.*, h5G1.1). (EX1003, ¶124.)

(b) Tacken and Mueller PCT Confirm that Bowdish's 5G1.1 Is Eculizumab

The Tacken reference would have further confirmed that Bowdish contains the desired constant regions of eculizumab. First, Tacken is yet another reference

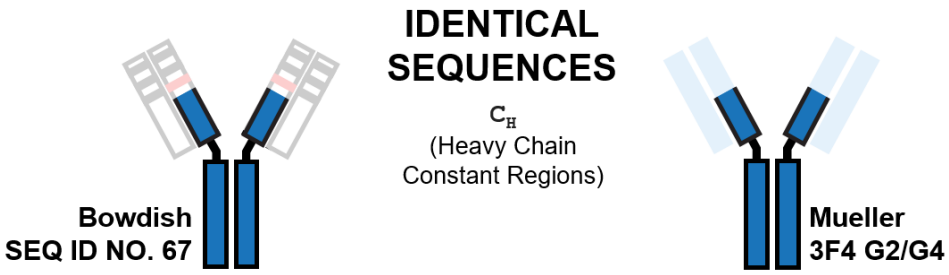
that equates h5G1.1 with eculizumab. (EX1008, 010; *see supra* VIII.A.) Second and critically, Tacken teaches that eculizumab contains an IgG2/IgG4 constant region that is "the same" as that disclosed in Tacken's reference 17, which is the Mueller 1997 article.

Recombinant antibodies

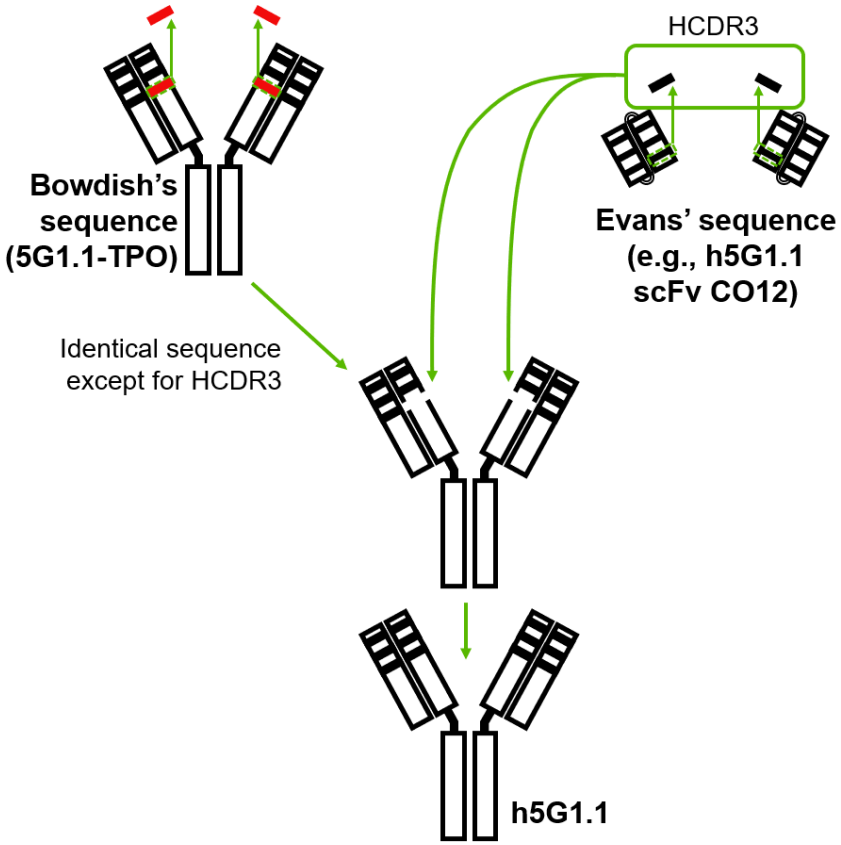
The humanized antihuman DC-SIGN antibody hD1V1G2/G4 (hD1) was generated by complementarity determining region (CDR) grafting of AZN-D1 hypervariable domains into human framework regions. The humanized variable heavy and variable light regions were then genetically fused with a human hybrid IgG2/IgG4 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); EX1003, ¶125.) Mueller PCT, the companion patent application for Mueller 1997, expressly discloses the full amino acid sequence for the IgG2/IgG4 constant domain heavy chain used in the "h5G1.1 HuG2/G4" antibody. (EX1009, 014, 058-59, 097; EX1003, ¶126.) A routine alignment of the IgG2/G4 constant domain heavy chain from Mueller PCT and Bowdish would have immediately confirmed that the antibody disclosed in Bowdish has *precisely* the sequence of eculizumab:

Bowdish SEQ ID NO: 67 C_H	1	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQT	80
Mueller 3F4 G2/G4 C_H	1	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQT	80
Bowdish SEQ ID NO: 67 C_H	81	YTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG	160
Mueller 3F4 G2/G4 C_H	81	YTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG	160
Bowdish SEQ ID NO: 67 C_H	161	VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKN	240
Mueller 3F4 G2/G4 C_H	161	VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKN	240
Bowdish SEQ ID NO: 67 C_H	241	QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSL	320
Mueller 3F4 G2/G4 C_H	241	QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSL	320
Bowdish SEQ ID NO: 67 C_H	321	SLSLGK	326
Mueller 3F4 G2/G4 C_H	321	SLSLGK	326



(EX1003, ¶¶126-127.) Just as easily, a POSA in March 2007 would have readily confirmed that Bowdish's starting 5G1.1 antibody had the desired IgG2/G4 constant regions as opposed to pure IgG2 or IgG4 constant regions by running Bowdish's 5G1.1 antibody through a protein sequence search. (EX1003, ¶128; *see also* EX1033, 005; EX1037, 005.) With this confirmation in hand, a POSA would have known to swap back into Bowdish's SEQ ID NO:67 the thirteen amino acid heavy chain CDR3 disclosed throughout Evans – as shown below:



(EX1003, ¶128.)

Tacken, like Bowdish, is analogous art to Bell and to the field of the challenged patent. Tacken is from the same field of study (humanized antibodies, including eculizumab) and is pertinent to the issue of the structure of eculizumab, which Tacken expressly identifies and describes as an anti-C5 antibody and Alexion's "potential product." (EX1008, 010-11; EX1003, ¶129.) A POSA seeking the sequence of eculizumab would have relied on Tacken, and its clear teaching from 2005 that eculizumab has an IgG2/IgG4 constant domain. (EX1003, ¶129.) A POSA reading Tacken would also have understood that Thomas—which was

published in 1996 and pre-dates Mueller PCT—discloses only an IgG4 isoform of 5G1.1, and was thus not eculizumab. (EX1010, 013; EX1003, ¶¶130, 165.) Moreover, Mueller PCT is itself analogous art to Bell, Bowdish, Evans, and Tacken, and to the field of the challenged patent, because like those references it is concerned with recombinant antibodies, expressly recites 5G1.1, is associated with Alexion Pharmaceuticals, and has Alexion scientist Mark Evans identified as an inventor on both Evans and Mueller PCT. (EX1009, Cover, 12:19-27; EX1005, Cover; EX1003, ¶131.)

The teachings of the prior art cited in this Ground provide a direct route to the sequence of eculizumab that renders challenged claim 1 obvious. A POSA would have been strongly motivated by Bell to obtain the sequence of eculizumab. Indeed, Bell is just one of many references in the prior art which taught that eculizumab was a useful treatment for PNH. (*See* EX1011; EX1013; EX1012; EX1014; EX1015; EX1003, ¶132.) A POSA further would have been informed by Tacken as to important details regarding the structure of eculizumab. From the combined teaching of Bowdish and Evans, a POSA could immediately confirm the correctness of the constant region against the teachings of Mueller PCT. (EX1003, ¶132.)

A POSA also would have had a reasonable expectation of success in assembling SEQ ID NOS:2 and 4 recited in challenged claim 1, since the prior art already confirmed each of the details necessary to create the heavy and light chains

of the antibody. A POSA would have understood how to make an anti-C5 antibody with SEQ ID NOS:2 and 4 using the teachings of Bowdish and Evans and standard, well-known molecular biology methods. (EX1004, [0069]-[0070], [0131]; EX1005, 45:24-33; EX1003, ¶133.)

2. Claim 2

Claim 2 adds the trivial limitation that the pharmaceutical composition be administered by intravenous infusion. This is expressly disclosed by each of Bell, Bowdish, and Evans. (*See* EX1007, [0060], [0062], [0082]; EX1004, [0148]-[0151]; EX1005, 18:29-43.) It was also conventional by 2007 to administer therapeutic antibodies by intravenous infusion. (EX1003, ¶134; EX1062, ¶49.)

3. Claim 3

Claim 3 depends from claim 1 and requires that the antibody be administered "at a dosage level of between 5 mg per kg and 50 mg per kg per patient per treatment." This is disclosed by Bell, which teaches a dosing regimen with 600 and 900 mg dose phase. Based on the CDC (Centers for Disease Control) disclosure that the average body weight for adult females and males in the United States was 74 kg and 87 kg, respectively, patients in Bell's study necessarily received doses ranging from 6.9 mg/kg to 12.2 mg/kg, fully within the range recited by claim 3. (EX1065, 061; EX1003, ¶135; EX1062, ¶50.)

The limitation of claim 3 is also expressly disclosed by Evans, which teaches that doses of its anti-C5 antibodies are typically from 1 to 100 mg per kg and "preferably between about 5 mg per kg and about 50 mg per kg per patient per treatment." (EX1005, 17:60-18:13.) A POSA would thus have been motivated to administer doses in the claimed range, and had a reasonable expectation of success, in light of these express teachings and Bell's disclosure that such doses successfully treated PNH. (EX1003, ¶136; EX1062, ¶51.)

4. Claim 4

Claim 4 depends from claim 1 and adds the trivial limitation that the pharmaceutical composition be in a "single unit dosage form." This limitation adds nothing of patentable significance. Bell discloses that its antibodies can be administered "in a variety of unit dosage forms." (EX1007, [0058].) A POSA would have known that single-use dosage units are the most convenient and appropriate for use in contexts such as intravenous infusion in which sterility must be maintained (and is considered compromised when a vial is opened). (EX1003, ¶137; EX1062, ¶53; EX1055-1060.)

5. Claim 5

Claim 5 specifies that the obvious single unit dosage form of claim 4 comprises a 300 mg amount. This was also obvious. Bell's report of the eculizumab clinical trial in PNH patients employed a dosing regimen with an initial 600 mg dose

phase followed by a 900 mg dose phase, with doses delivered by intravenous infusion. (EX1007, [0082].) Given Bell's express disclosure of a dosage regimen having 600 and 900 mg phases, a 300 mg unit dosage form would have been obvious. 300 is the highest common factor of 600 and 900, and thus the most convenient unit dose to use without the need to manufacture vials of differing quantities, and without causing unnecessary waste of costly antibody treatments. A POSA aware of Bell's teachings would be motivated to choose a 300 mg single-use dosage form above all other options given these considerations. (EX1003, ¶138; EX1062, ¶55.)

6. Claim 7

Claim 7 depends from claim 1 and specifies that the claimed patient is "anemic." In the clinical trial disclosed by Bell, the pre-treatment hemoglobin value for patients was 10.0 ± 0.4 g/dl. (EX1007, Fig. 1A.) Per American Society of Hematology guidelines, anemia is defined as a hemoglobin value of less than 14 g/dl in a man or less than 12 g/dl in a woman. (EX1064, 008; EX1003, ¶139.) A POSA would have recognized that the patients in Bell's PNH trial were anemic prior to treatment. Moreover, Bell expressly taught that symptoms of PNH, which include anemia, are "eliminated or decreased" by administration of anti-C5 antibodies such as eculizumab. (EX1007, [0037]; *see also id.* [0014], [0066], [0076]-[0077]; EX1003, ¶139.)

7. Claim 8

Claim 8 depends from claim 1 and recites the exact dosing regimen disclosed by Bell, namely "600 mg of the antibody via intravenous infusion every 7±1 days for 4 doses; followed by 900 mg of the antibody via intravenous infusion 7±1 days later; followed by a maintenance dose of 900 mg of the antibody via intravenous infusion every 14±2 days." Bell teaches this eculizumab dosing regimen, exactly.

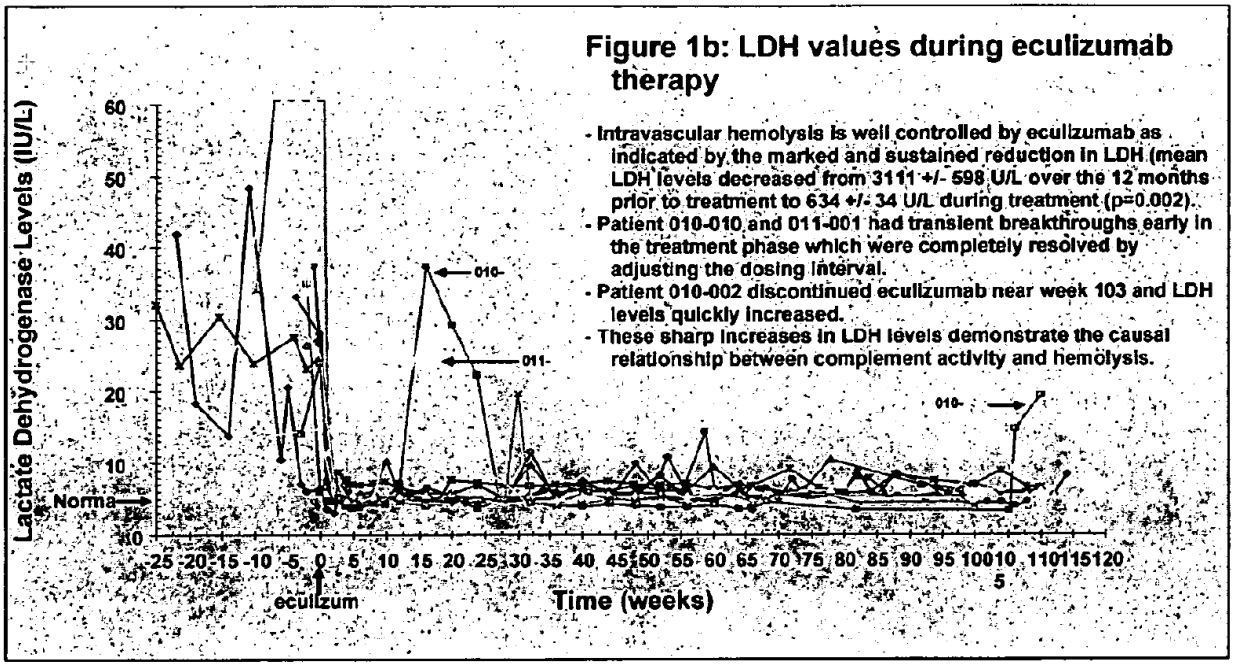
> **[0082]** Over the course of four weeks, each of 11 patients received a weekly 600 mg intravenous infusion of anti-C5 antibody for approximately thirty minutes. The specific anti-C5 antibody used in the study was eculizumab. Patients received 900 mg of eculizumab 1 week later then 900 mg on a bi-weekly basis.

(EX1007, [0082].) Bell also teaches that two patients received the maintenance dose every 12 days. (*Id.*, [0088].) A POSA would have been motivated to use, and would have expected success in, the exact dosing regimen for PNH that Bell had already disclosed. (EX1003, ¶140.)

8. Claims 9 and 10

Claim 9 depends from claim 1 and recites that "administration of the antibody results in an immediate and sustained decrease in mean levels of lactate dehydrogenase (LDH)." Claim 10 adds to Claim 9 the requirement that the "immediate decrease occurs within one week of administration." Based on the narrowing limitation of claim 10, the "immediate" decrease of claim 9 must cover at least a decrease that occurs within one week of administration of the antibody.

The limitations of claims 9 and 10 are both expressly disclosed by Bell. Bell teaches that eculizumab administration decreased LDH levels in PNH patients by more than 80%, and that this decrease was "marked and sustained." (EX1007, [0085], Figs. 1a-1b; EX1003, ¶142.) Bell's data further shows that this marked decrease in LDH was both immediate and sustained:



(EX1007, Fig. 1b, [0085]; EX1003, ¶142.) A POSA would have recognized from Bell's disclosure that LDH values in PNH patients treated with eculizumab immediately and markedly decreased to near-normal levels, and then remained low for the duration of eculizumab treatment. (EX1003, ¶142.) Bell's disclosure as shown in the above figure is further confirmed by the words of the Hillmen 2004 and Hillmen 2003 references, which both describe the same eleven patient Phase 2 PNH study. (*See supra* V.C.) These manuscripts confirm that eculizumab caused

an immediate and sustained decrease in LDH levels that "began after a single dose of eculizumab in all patients":

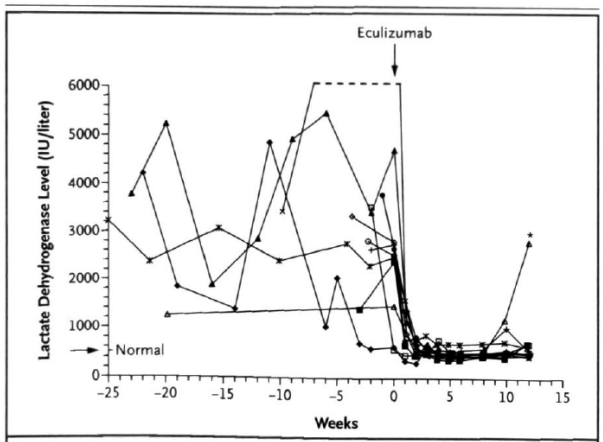


Figure 2. Analysis of Lactate Dehydrogenase Levels, a Biochemical Indicator of Hemolysis, in 11 Patients with Paroxysmal Nocturnal Hemoglobinuria up to 25 Weeks before and during 12 Weeks of Eculizumab Treatment.

The first dose of eculizumab is indicated by an arrow, as is the upper limit of the normal range of lactate dehydrogenase at the Leeds Teaching Hospital. The data point identified at week 12 by the asterisk represents a reading that was obtained from a duplicate serum sample since the original sample was lost. The dashed line represents off-scale points from one patient with a peak value of 12,100 IU per liter.

(EX1011, 005 (Fig. 2), 006; EX1003, ¶143.) Similarly, Hillmen 2003 states that "dramatic improvement in the biochemical parameters of hemolysis occurring in all patients within a week of starting therapy persists. Mean LDH decreased from 3111 +/- 598 U/L … to 670 +/- 69 U/L over 6 months following treatment[.]" (EX1017, 002; EX1003, ¶143.) And as Bell confirms, LDH levels are a biochemical parameter associated with hemolysis underlying PNH disease. (EX1007, [0064]; EX1003, ¶143.)

D. Ground 2: Claim 6 Is Obvious Over Bell, Bowdish, Evans, and Wang in view of Tacken and Mueller PCT

Claim 6 depends from claim 1 and adds the uninventive further limitations of "300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution." None of these claim elements are of patentable significance.

1. "sterile, preservative free"

Each of Bell, Bowdish, and Evans teaches that formulations of anti-C5 antibodies such as eculizumab "must be sterile." (EX1007, [0062]; EX1004, [0150]; EX1005, 18:29-43.) Each of Bell, Bowdish, and Evans also teach that use of a preservative is optional, and thus can be omitted from the formulation – express disclosure sufficient to teach the negative claim limitation of "preservative free." (EX1007, [0062]; EX1004, [0150]; EX1005, 18:29-43.) *See Upsher-Smith Lab'ys, Inc. v. PamLab, L.L.C.*, 412 F.3d 1319, 1320-21 (Fed. Cir. 2005) ("[A] prior art composition that 'optionally includes' an ingredient anticipates a claim for the same composition that expressly excludes that ingredient[.]").

These disclosures specific for eculizumab accord with the conventional teachings of the prior art for antibody pharmaceutical compositions in general. For example, several widely-prescribed FDA-approved antibodies (approved before 2007) were provided in sterile, preservative free formulations. (EX1003, ¶146; EX1062, ¶¶56-57; EX1052, 002-03; EX1055, 002; EX1056, 002, 013; EX1057, 001; EX1058, 001-02; EX1059, 001; EX1060, 001.)

2. "300 mg single-use dosage formulation"

This limitation is equivalent to the added limitation of Claim 5, and is unpatentable for the same reasons. (*See supra* VIII.C.5.) As discussed above, Bell discloses that its antibodies can be administered "in a variety of unit dosage forms." (EX1007, [0058].) A POSA would have known that single-use dosage units are the most convenient and appropriate for use in sterile IV infusion contexts. (EX1003, ¶147; EX1062, ¶55; *see also* EX1055-1060.) Further, given Bell's express disclosure of a dosage regimen having 600 and 900 mg phases, a POSA would have been motivated to make a 300 mg unit dosage formulation as obviously the most convenient and scalable to the appropriate target dose. (EX1003, ¶147; EX1062, ¶55.)

3. "30 ml of a 10 mg/ml … solution"

For convenience in handling and addition to IV bags for infusion, antibody therapies by 2007 were commonly supplied in a liquid solution that could easily be drawn into a syringe. (EX1003, ¶148; EX1062, ¶58.) Based on simple arithmetic, 30 ml of a 10 mg/ml solution provides a 300 mg total dose of antibody, which as explained above would be considered desirable by a POSA. (EX1003, ¶148; EX1062, ¶58.) A POSA would also know that eculizumab could be successfully and stably formulated in an aqueous solution at concentrations in the range of 1 to 30 mg/ml based on the express teachings of Wang, and thus eculizumab could be

formulated at 10 mg/ml. (EX1044, Fig. 10, [0025], [0067], [0170]-[0173]; EX1003, ¶148; EX1062, ¶59.) A POSA would also have known that 10 mg/ml was well within the known range of concentrations of a large number of FDA-approved antibody pharmaceutical compositions. (EX1003, ¶148; EX1062, ¶59; EX1061, 014 (Table 1); EX1056, 013; EX1057, 001; EX1058, 001-02; EX1059, 011; EX1060, 001.)

4. Manner, Motivation, and Rationale for Combination

A POSA would have been motivated to prepare pharmaceutical compositions matching the limitations of the challenged claims based on the express teachings of the prior art. For example, each of Bell, Bowdish, and Evans expressly teach formulations and compositions matching the limitations as discussed above. (*See supra* VIII.D.1-3.) Further, a POSA would have looked to Wang for its additional express disclosures about formulation methods and compositions that specifically pertain to eculizumab. (EX1044, [0004], [0011], [0067]; EX1003, ¶149; EX1062, ¶60.)

A POSA would also have had a reasonable expectation of success in arriving at the pharmaceutical compositions having the characteristics recited in challenged claim 6, because the Bowdish, Bell, and Evans prior art expressly disclosed these characteristics specifically in the context of eculizumab. Further, a POSA would have had a reasonable expectation of success in preparing a stable, non-aggregated

pharmaceutical composition of eculizumab at a concentration of 10 mg/ml based on the Wang reference, which teaches stable eculizumab formulations at concentrations as high as 30 mg/ml. (EX1003, ¶150; EX1062, ¶61; EX1061, 009.) Collectively, the dose form and formulation limitations in claims 1 and 3 are nothing more than "the predictable use of prior art elements according to their established functions," and therefore add nothing of patentable significance. *KSR*, 550 U.S. at 417; *see also W. Union*, 626 F.3d at 1371-72.

E. Ground 3: Claims 1-5 and 7-10 Are Obvious Over Bell, Evans, and Mueller PCT in view of Tacken

1. Claim 1

A POSA would also have been directed by Bell and Tacken to Evans and Mueller PCT to use an antibody with SEQ ID NOS:2 and 4 to treat PNH. As explained in Ground 1, a POSA would have been strongly motivated by Bell to obtain the amino acid sequence of the anti-C5 antibody eculizumab as a method of treatment of PNH—the subject matter of Claim 1. (*See supra* VIII.C.) Bell points directly to Evans and Thomas for this information and incorporates both by reference. (*Id.*) As discussed above, a 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. (*See supra* VIII.C.) A POSA examining Evans, entitled "C5-Specific Antibodies for the Treatment of Inflammatory Diseases" would readily understand that it teaches the critical CDR sequences for

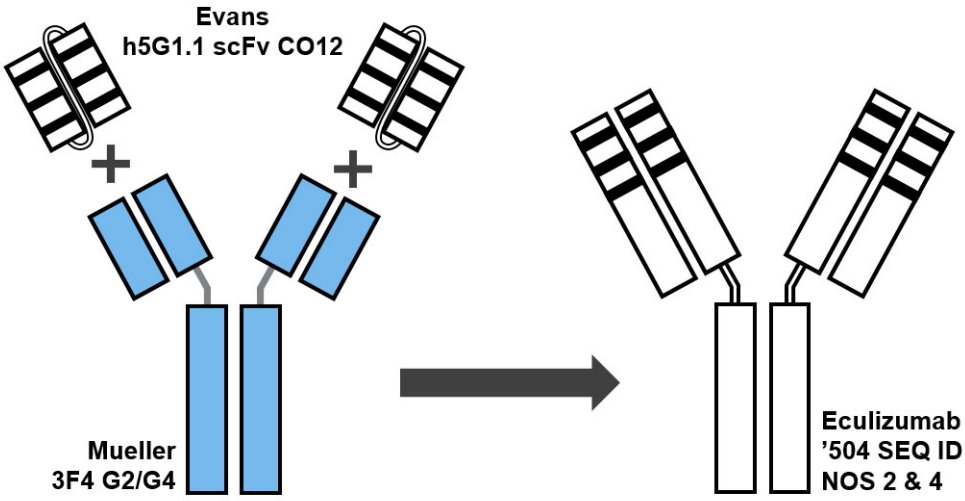
the heavy and light chains of the original mouse antibody 5G1.1, which binds C5, as well as variable domain sequences for humanized forms of 5G1.1. (EX1005, 1:1-3, 9:65-10:20, 42:56-45:23, 143:22-144:14, Figs. 18-19, Claim 19; EX1003, ¶¶151-152.)

Evans' Example 11 teaches the construction of recombinant antibodies using the heavy and light chain CDRs of the 5G1.1 antibody. (EX1005, 42:56-45:33; EX1003, ¶152; *see supra* VIII.C.) In all, Evans' Example 11 provides eighteen "recombinant mAb-encoding DNAs" constructs. Of these, nine provide humanized single-chain variable domain structures ("scFv") which correspond to the V_H and V_L domains of an antibody joined by a short peptide linker. (EX1005, 42:56-45:33; EX1003, ¶152.) Evans then explains that "one each of the various L1, L2, and L3 CDRs" and "one each of the various H1, H2, and H3 CDRs" disclosed in Example 11, assembled into "matched pairs of the variable regions (e.g., a VL and a VH region) … may be combined with constant region domains by recombinant DNA or other methods known in the art to form full length antibodies *of the invention*." (EX1005, 45:5-33 (emphasis added); EX1003, ¶152.)

A POSA would have been motivated to build antibodies using *each* of the sequences labeled "5G1.1." Even if Evans does not identify the specific sequence used in eculizumab by name, it explains that *each* of the nine disclosed sequences include V_H and V_L domains with the CDRs of 5G1.1. (EX1005, 42:56-45:33;

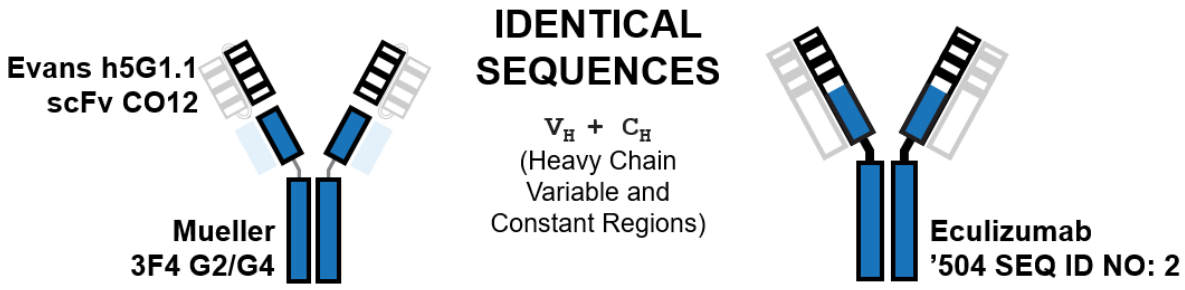
EX1003, ¶¶153-154.) Bell points to Evans for its teaching of the structure of 5G1.1, thus a POSA would have known to try any of these sequences. *See Merck & Co. v. Biocraft Lab'ys, Inc.,* 874 F.2d 804, 807 (Fed. Cir. 1989) ("That the [asserted prior art] discloses a multitude of effective combinations 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.

Even if a POSA wished to prioritize among the nine constructs providing a humanized V_H and V_L disclosed in Evans' Example 11 to choose, Mueller PCT would have guided POSA to the sequence in part 12 of Example 11, identified as "CO12." (*See* EX1005, 44:4-14; EX1009, 014; EX1003, ¶155.) The only 5G1.1 discussed in Mueller PCT is referred to as "h5G1.1 **CO12** HuG2/G4," thus a POSA would have been particularly motivated to assemble a full length G2/G4 antibody using the variable region employed in the CO12 example of Evans. (EX1009, 14 (emphasis added); EX1003, ¶155.) This assembly with the constant G2/G4 regions of Mueller PCT and variable regions of Evans results in the claimed sequences:

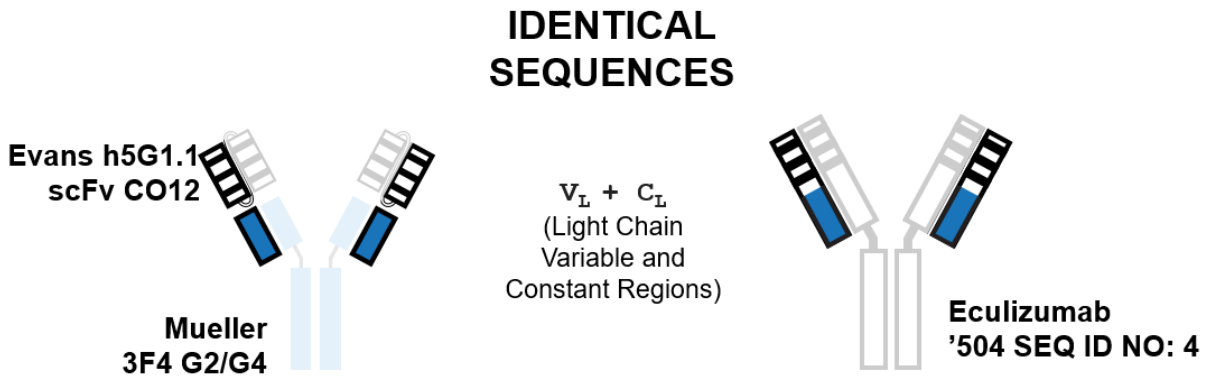


(EX1003, ¶155.) The resulting antibody is a perfect match to SEQ ID NOS:2 and 4 recited in challenged claim 1, which corresponds to eculizumab:

Evans + Mueller	1	QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEYTENFKDRVTMTRDTSTSTVY	80
'504 SEQ ID NO: 2	1	QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEYTENFKDRVTMTRDTSTSTVY	80
		← Evans | Mueller →	
Evans + Mueller	81	MELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT	160
'504 SEQ ID NO: 2	81	MELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT	160
Evans + Mueller	161	VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPS	240
'504 SEQ ID NO: 2	161	VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPS	240
Evans + Mueller	241	VFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEY	320
'504 SEQ ID NO: 2	241	VFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEY	320
Evans + Mueller	321	KCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD	400
'504 SEQ ID NO: 2	321	KCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD	400
Evans + Mueller	401	SDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK	448
'504 SEQ ID NO: 2	401	SDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK	448



Evans + Mueller	1	DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYGATNLADGVPSRFSGSGSGTDFTLTISSLQP	80
'504 SEQ ID NO: 4	1	DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYGATNLADGVPSRFSGSGSGTDFTLTISSLQP	80
		← Evans | Mueller →	
Evans + Mueller	81	EDFATYYCQNVLNTPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ	160
'504 SEQ ID NO: 4	81	EDFATYYCQNVLNTPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ	160
Evans + Mueller	161	ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	214
'504 SEQ ID NO: 4	161	ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	214



(EX1003, ¶156.)

Also as explained in Ground 1, Tacken specifically teaches that eculizumab has an IgG2/IgG4 constant region, and refers to the Mueller 1997 reference for this point. (*See supra* VIII.C.) A POSA would thus have been motivated by the express teachings of Tacken to create an antibody using the variable domain for 5G1.1 disclosed in Evans and the constant region discussed in Mueller 1997 and expressly taught in Mueller PCT. (*See supra id.*) Indeed, the same disclosure in Evans providing instructions for how to combine 5G1.1 variable regions with constant region domains to form a full-length antibody *expressly* 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, ¶157.)

Although these disclosures provided ample motivation for a POSA to use Evans and Mueller PCT to use the antibody having the sequences recited in claim 1 for treatment of PNH, the art provides still further motivation. 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, ¶158.) A POSA would have immediately recognized these benefits as useful in the context of a therapeutic antibody intended for use to block part of the complement system, and arrived at an antibody that is an IgG2/IgG4 hybrid sequence like the constant region of SEQ ID NO:2 of claim 1. (EX1003, ¶158.) Thus, a POSA would have been motivated to use the humanized 5G1.1 variable domains of Evans and combine them with constant regions from Mueller PCT to make the antibody of claim 1. (*Id*.) Still other disclosures in the prior art similarly taught that antibodies with hybrid IgG2/IgG4 constant regions conferred benefits such as reduced inflammation and activation of the complement system. (EX1021; EX1003, ¶158.)

The same disclosures would also have provided a POSA with a reasonable expectation of success, since a POSA would know from Tacken that such assemblies

had already been made to form eculizumab, which had itself already been validated as a PNH treatment as shown in Bell and other studies. *See KSR*, 550 U.S. at 416 ("combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results"); (EX1003, ¶159).

2. Claims 2-5 and 7-10

As set forth in the context of Ground 1 based on Bell, Bowdish, and Evans in view of Tacken and Mueller PCT, Bell and Evans also variously disclose the uninventive formulation, dosing regimen, and efficacy limitations of claims 2-5 and 7-10. (*See supra* VIII.C.) These same disclosures render the challenged claims obvious in the context of the Ground 3 combination of Bell, Evans, and Mueller PCT in view of Tacken. The relevant prior art teachings and motivation to combine with reasonable expectation of success for each challenged dependent claim are set forth above. (*See id.*; EX1003, ¶160.)

F. Ground 4: Claim 6 Is Obvious Over Bell, Evans, Mueller PCT, and Wang in view of Tacken

Ground 4, similar to Ground 2, adds the Wang reference to the Ground 3 group to address the uninventive formulation limitation of claim 6. As explained above, Wang in combination with the teachings of Bell discloses all of the additional limitations recited by claim 6. (*See supra* VIII.D.) Those same disclosures apply to the Bell, Evans, and Mueller PCT combination of Ground 3 to render the claim obvious. (EX1003, ¶161.)

G. Ground 5: Claims 1-5 and 7-10 Are Anticipated by Bell

As discussed above, Bell discloses clinical trials that show the utility of using eculizumab as a treatment for PNH. (*See supra* VIII.A.) Indeed, Bell is just one of several references that discloses the same eleven patient trial in which eculizumab was given to transfusion-dependent PNH patients; Hillmen 2004 discloses initial results while Bell and Hill 2005 supplement the record with longer-term follow up data. (*Id.*; *see supra* V.C; EX1011; EX1013; EX1003, ¶162.)

1. Claim 1

(a) Bell Necessarily Discloses SEQ ID NOS:2 and 4, the Anti-C5 Antibody Known as Eculizumab

What is equally clear from Bell is that patients were treated with the antibody known as eculizumab. And as noted above, there is no doubt that disclosure of eculizumab, by name, unambiguously refers to the h5G1.1 IgG2/IgG4 molecule that is exactly identical to the antibody sequence recited in challenged claim 1. Even though appreciation of an inherent disclosure by a POSA at the time of the disclosure is not required, *Schering*, 339 F.3d at 1377, a POSA would have known that eculizumab has the same sequence as the sequences in claim 1, SEQ ID NOS:2 and 4. As explained above in Grounds 1 and 3, before 2007 a POSA would have understood the amino acid sequence of eculizumab. The teachings of at least Bowdish and Evans, and Evans and Mueller PCT, all in view of Tacken, provided POSA with multiple direct routes to that sequence. (*See supra* VIII.C&E.) Alexion

sought to claim through the '504 patent what it says is the "novel" sequence of eculizumab, but because the prior art necessarily disclosed eculizumab, Alexion cannot obtain a patent on "the identification and characterization of a prior art material[.]" *In re Crish*, 393 F.3d 1253, 1258 (Fed. Cir. 2004).

Indeed, Alexion cannot dispute these facts, because Alexion has admitted to the Patent Office that the C5-binding antibody used in the study described by Bell *was necessarily* eculizumab, which has the same structure of the antibody of claim 1. For example, the 11 patient Phase 2 pilot study ("C02-001") and the extensions of that study ("E02-001" and "X03-001") were submitted by Alexion during prosecution with the statement that "the antibody (eculizumab) used in each of the studies … contained the heavy and light chain sequences of SEQ ID NOs: 2 and 4." (*See* EX1002, 1320-27, ¶¶5-6; *see also id.*, 1316; EX1003, ¶¶163-164.)

Alexion reconfirmed these admissions in the previously-instituted Amgen IPR, where it admitted to this Board that "it is known today that SOLIRIS® as used in these studies had the claimed sequence of SEQ ID NOs: 2 and 4." (EX1025, 041.) Of course, it is not necessary for inherent anticipation for a POSA to have appreciated the precise amino acid sequence of eculizumab at the time of Bell's publication. *Schering*, 339 F.3d at 1377. But Bell inherently anticipates because (1) Alexion admits that the "eculizumab" disclosed in Bell was *necessarily* of the same sequence as recited by challenged claim 1; and (2) the prior art available to a POSA

fully enabled the preparation of eculizumab as of no later than the 2005 (the publication date of Tacken). (EX1003, ¶164.)

Alexion's admissions on this subject are binding, disposing of the need for the Board to engage in factfinding on this issue. *See Southwall Techs., Inc. v. Cardinal IG Co*., 54 F.3d 1570, 1578 (Fed. Cir. 1995); *see also Gillette Co. v. Energizer Holdings, Inc*., 405 F.3d 1367, 1374 (Fed. Cir. 2005) (holding party to "blatant admission" in argument made to EPO); *Apple Inc. v. Motorola, Inc*., 757 F.3d 1286, 1313 (Fed. Cir. 2014), *overruled on other grounds sub nom. Williamson v. Citrix Online, LLC*, 792 F.3d 1339 (Fed. Cir. 2015).

Alexion has previously argued that Bell does not *necessarily* disclose SEQ ID NOS:2 and 4 (eculizumab), because of ambiguity as to whether "eculizumab" referred to a version of the antibody in its IgG4 form, as originally reported in Thomas 1996. (*See* EX1010; EX1003, ¶165.) But the prior art plainly dispels this manufactured ambiguity. No prior art reference anywhere states that "eculizumab" has an IgG4 isotype. On the contrary, the only disclosure in the prior art as to the constant domain structure of "eculizumab" is Tacken, which unambiguously states that it has the IgG2/IgG4 structure. (EX1008, 010-11; EX1003, ¶165; *see also supra* V.E.) This is not a question of "probabilities or possibilities." *MEHL/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1365 (Fed. Cir. 1999). Instead, as Tacken makes

clear, Bell's disclosure of the PNH clinical trial of eculizumab *necessarily* discloses SEQ ID NOS:2 and 4 of challenged claim 1. (EX1003, ¶165.)

By teaching that eculizumab is an efficacious treatment for PNH based on human clinical trial data, Bell expressly discloses the remaining limitations of a method of treating a patient suffering from PNH recited by challenged claim 1. (*See supra* VIII.A, VIII.C; EX1003, ¶166.)

(b) The Prior Art Enabled the Eculizumab Sequences Inherently Disclosed in Bell

The disclosures in the inherently anticipating Bell reference also meet the relevant test for enablement. To the extent Alexion argues that the reference is not, by itself, "enabling" for the amino acid sequence of eculizumab, this argument is unavailing. The prior art can and does provide sufficient information for a POSA to make the claimed subject matter that is inherently disclosed. (*See supra* VIII.C-E); *Schering*, 339 F.3d at 1380-81 (prior art is enabling if it discloses sufficient information to make the claimed subject matter). In this context, the art includes not just the inherently anticipating reference in isolation, but also a POSA's knowledge of the relevant art. *See In re Elsner*, 381 F.3d 1125, 1128 (Fed. Cir. 2004) (proper test is "whether [a POSA] could take the description of the invention in the printed publication *and combine it with his own knowledge of the particular art* and from this combination be put in possession of the invention" (emphasis added)); *see also In re Donohue*, 766 F.2d 531, 533 (Fed. Cir. 1985).

As explained throughout Grounds 1 and 3 above, the prior art provided enabling disclosures for creation of the same antibody (eculizumab) that is claimed in challenged claim 1. (*See supra* VIII.C&E; EX1003, ¶167.) A POSA in possession of the relevant prior art would have had multiple clear paths to making the exact antibody that is recited by challenged claim 1. Thus, the mere use of the word "eculizumab" by Bell provides an anticipating disclosure, because before 2007 a POSA had "the ability to make" eculizumab, and thus was in possession of the subject matter of challenged claim 1. *See In re Gleave*, 560 F.3d 1331, 1337 (Fed. Cir. 2009).

2. Claims 2-5 and 7-10

As explained in Ground 1 above, Bell expressly discloses each of the trivial formulation, administration, and efficacy limitations of dependent claims 2-5 and 7-10. (*See supra* VIII.C.) Based on Bell's inherent anticipation of the antibody sequences recited in claim 1, its express disclosure of the remaining method of treatment limitations of claim 1, and its express disclosures of added limitations of the dependent claims, Bell anticipates challenged claims 2-5 and 7-10. (EX1003, ¶168.)

IX. NO SECONDARY CONSIDERATIONS OF NONOBVIOUSNESS

There are no secondary considerations that would weigh against the strong case of obviousness set forth in Grounds 1-4. (EX1003, ¶¶169-174.) Secondary

considerations must be tied to what is *novel* in the claim, indeed any secondary considerations evidence that is not "both claimed *and* novel in the claim" cannot be said to have a nexus to the claimed invention. *In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011) (emphasis modified).

To the extent Alexion will argue that secondary considerations evidence can be derived from commercial success of its drug Soliris (the brand name of eculizumab), any such evidence must fail as evidence of nonobviousness because the use of eculizumab as a treatment for PNH was *indisputably* in the prior art and thus not novel in the claim. Several prior art publications expressly disclosed the utility of eculizumab as a treatment for PNH, including the Bell, Hillmen 2004, and Hill 2005 references. (*See supra* V.C & VIII.A.) *See Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1312 (Fed. Cir. 2006). Similarly, the fact that eculizumab was not commercially approved as a treatment for PNH until March 2007 is of no moment to the secondary considerations analysis, because the use of eculizumab as a PNH therapy is undisputed prior art to the '504 patent. *See Novartis AG v. Torrent Pharms. Ltd.*, 853 F.3d 1316, 1330-31 (Fed. Cir. 2017). (*See also* EX1024, 056-57; EX1003, ¶¶169-170.)

There is also no presumption of nexus, because any evidence based on Soliris sales must be due to the claimed invention specifically, not Alexion's other efforts such as marketing, *and* not contributions from the prior art. *See, e.g., Prometheus*

Lab'ys, Inc. v. Roxane Lab'ys, Inc., 805 F.3d 1092, 1101 (Fed. Cir. 2015); *In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996). Moreover, as explained above, Alexion has long identified the prior art Evans patent, not the challenged '504 patent, with the invention of eculizumab, and indeed sought to apply patent term extension under 35 U.S.C. § 156 for Soliris to the Evans patent. (*See supra* V.E.) Given the extensive disclosures of methods of treating PNH with eculizumab having the sequence disclosed in the prior art, Alexion cannot establish that commercial success based on Soliris's product launch in 2007 is relevant. (EX1003, ¶170.)

Similarly, Alexion cannot argue that the methods of treating PNH in the challenged claims solved a long-felt and art-recognized need, as required, because prior art published two to three years before the priority date of the '504 disclosed eculizumab as a treatment for PNH. Thus, judged against the priority date, as it must be, it cannot be said that as of March 2007 the long-felt need addressed by Soliris still existed. *See Nike, Inc. v. Adidas AG*, 955 F.3d 45, 55 (Fed. Cir. 2020); *Celgene Corp. v. Peter*, 931 F.3d 1342, 1352 (Fed. Cir. 2019). (EX1003, ¶171.)

Nor is there any competent evidence of industry praise. Any industry recognition following the launch of Soliris as a beneficial therapy for the rare disease PNH has no nexus with anything inventive in the challenged claims. As with the considerations of commercial success and long-felt need, by March 2007 there was nothing *novel* about the use of eculizumab to treat PNH. Further, any prizes awarded

to Alexion relating to the use of Soliris as a PNH treatment have no nexus because there is nothing to suggest that the prize was awarded due to anything other than the previously known methods of treating PNH with eculizumab. *See S. Ala. Med. Sci. Found. v. Gnosis S.P.A*., 808 F.3d 823, 827 (Fed. Cir. 2015); *see also Genentech, Inc. v. Hospira, Inc*., 946 F.3d 1333, 1342 (Fed. Cir. 2020). (EX1003, ¶172.)

Finally, Alexion cannot rely on Petitioner's intent to develop a biosimilar of Soliris as evidence of "copying," because the biosimilar statutes and regulations *require* that any biosimilar of Soliris be "highly similar to the reference product." *See* 42 U.S.C. §262(i)(2); *see also Adapt Pharma Operations Ltd. v. Teva Pharms. USA*, 25 F.4th 1354, 1374 (Fed. Cir. 2022) ("evidence of copying in the ANDA context is not probative of nonobviousness."). (EX1003, ¶173.)

Petitioner reserves the right to rebut any evidence of secondary considerations that Alexion asserts in this proceeding.

X. THE BOARD SHOULD REACH THE MERITS OF THE PETITION

No basis exists under either § 314(a) or § 325(d) for discretionary denial, as explained below.

A. § 314(a)

The '504 patent has never been asserted in any litigation.

B. § 325(d)

The Board assesses § 325(d) under the two-part *Advanced Bionics* framework: (1) whether the same or substantially the same art was previously presented to the Office, and if so (2) whether Petitioner has demonstrated that the Examiner erred in a manner material to the patentability of challenged claims. *Advanced Bionics, LLC v. Med-El Elektromedizinische Geräte GMBH*, IPR2019-01469, Paper 6 at 8 (PTAB Feb. 13, 2020). Examples of "material error" could be "misapprehending or overlooking specific teachings of the relevant prior art where those teachings impact patentability of the challenged claims" or misapplying the law in a material way. *Id.* at 8-9 n.9.

This Petition should be instituted in light of the *Advanced Bionics* framework and the art and arguments presented during prosecution of the '504 patent and its child '189 patent. Part (1) of the framework is not satisfied because the Examiner did not consider critical art and arguments presented in this Petition. To the extent certain art or arguments were considered, Part (2) is satisfied because the Examiner materially erred by overlooking specific teachings of the prior art, accepting without challenge Alexion's incorrect characterizations of the art; and by misapplying the law with respect to secondary considerations.

1. Evaluation of Art and Arguments During '504 Prosecution

Part (1) of the *Advanced Bionics* framework is not satisfied because the arguments and evidence presented herein were not before the Examiner during '504 prosecution, and therefore, do not constitute "the same or substantially the same prior art or arguments" under §325(d). During '504 prosecution, the Examiner rejected claims 1-2 and 7-10 as being anticipated by Hillmen in view of Thomas, and all claims as obvious over Hillmen in view of Thomas, Evans and Wang. The Examiner cited disclosures of Evans and Thomas for eculizumab sequence information. (EX1002, 1118-23.) Although Evans and Wang were cited in the rejections, this Petition presents those references in a different light. Petitioner combines Evans with Tacken, Bell, Bowdish, and Mueller PCT, which teach the IgG2/IgG4 constant domain of eculizumab, i.e., the very domain that Alexion argued was the "unique, non-naturally occurring, protein-engineered full heavy chain" missing in the prior art. (EX1002, 1079-81; *see also id.*, 1298.) The Examiner did not evaluate the combinations presented in this Petition with respect to Evans and Wang.

Part (1) also does not apply to Tacken and Mueller PCT because they are new references that were not identified anywhere during '504 prosecution. Tacken discloses that eculizumab has the IgG2/G4 constant domain, and Mueller PCT

provides that sequence.[6] (*See supra* VIII.A.) Grounds 1-4 in this Petition rely on Tacken and Mueller PCT as primary references. (*See* VIII.C-F.) And for Ground 5, Tacken and Mueller PCT inform the state of the art and a POSA's knowledge regarding the eculizumab sequence as of March 2007. (*See supra* VIII.G.)

Further, although Bell and United States Patent No. 7,482,435 (parent of Bowdish) were cited in Information Disclosure Statements during prosecution, there is no evidence that the Examiner considered these references. (EX1002, 1057-58.) When a reference is not the basis of rejection, and merely cited in an IDS, it weighs "strongly against" exercising discretionary denial, especially where there is a credible showing of Examiner error. *See, e.g., CODE200, UAB v. Bright Data Ltd.*, IPR2022-00353, Paper 8 at 10 (PTAB July 1, 2022); *Whitewater W. Indus., Ltd. v. Am. Wave Machs., Inc.*, IPR2022-01034, Paper 8 at 34-35 (PTAB Nov. 22, 2022); *Advanced Energy Indus. Inc. v. Reno Techs. Inc.*, IPR2021-01397, Paper 7 at 7-8

[6] Mueller PCT is not cumulative of the Mueller 1997 article for purposes of §325(d), because Mueller PCT has the complete IgG2/G4 constant domain, whereas Mueller 1997 does not expressly disclose the sequence for the CH3 region of that constant domain. (EX1009, 058-59; EX1006, 014.)

(PTAB Feb. 16, 2022); *Samsung Elecs., Co. v. G+ Commc'ns, LLC,* IPR2022-01598, Paper 10 at 13 (PTAB Apr. 4, 2023).

Part (2) of *Advanced Bionics* is also satisfied for Bell and Bowdish because the Examiner materially erred in overlooking specific disclosures of these references regarding the eculizumab sequence, corresponding to SEQ ID NOS:2 and 4. In the Office Action, the Examiner only focused on Evans and Thomas for eculizumab sequence information. (EX1002, 1118-21.) Alexion responded, misleadingly, that "[n]either eculizumab nor its complete sequence … was in the public domain prior to the March 15, 2007 effective filing date[.]" (EX1002, 1296; *see supra* V.D & VI.C; EX1003, ¶177.) As a result, the Examiner committed error when he accepted Alexion's mischaracterization of the art, and failed to appreciate other pre-priority date references, such as (1) Tacken, which discloses that eculizumab contains the IgG2/G4 constant domain, (2) Mueller PCT that discloses the IgG2/G4 constant domain sequence, and (3) Bowdish, which discloses the sequence for antibody 5G1.1, including the complete sequence for IgG2/G4 constant domain. (*See supra* VIII.C&E.) Indeed, Tacken, Mueller PCT and Bowdish teach the very thing that the Examiner mistakenly concluded was missing from the prior art. (*See* 1002, 1347.) They are also enabling prior art for Bell. Thus, the prosecution history reflects a significant gap in Examiner's evaluation of art and arguments regarding the known

IgG2/G4 constant domain in SEQ ID NO:2 that is recited in claim 1. (EX1003, ¶178.)

Further, though the Examiner cited Wang in the rejections, the Examiner erred in overlooking Wang's disclosures regarding the claimed formulations, as evidenced by the lack of any discussion regarding Wang in the Notice of Allowance. *See Advanced Bionics*, Paper 6 at 10 ("[I]f the record of the Office's previous consideration of the art is not well developed or silent, then a petitioner may show the Office erred by overlooking something persuasive under factors (e) and (f)."); *Apple, Inc. v. Koss Co.*, IPR2021-00381, Paper 15 at 26, 28-29 (PTAB July 2, 2021) ("Koss"). (*See also* EX1003, ¶179.)

2. Evaluation of Art and Argument During Prosecution of '189 Child Patent

The prosecution record of the '189 patent also does not preclude institution of this Petition because the '189 claims are different from the '504 claims, and the Examiner materially erred in his evaluation of the asserted art and arguments during '189 prosecution.[7] The Board has declined to exercise denial under §325(d) over art

[7] To the extent that Patent Owner argues that Amgen's IPR2019-00739 raised the same art and arguments, the Board should still institute this Petition because (1) it

and arguments considered during a child patent's prosecution with "separate and distinct claims" where Petitioner has shown that the Examiner erred. *See Apple Inc. v. Seven Networks, LLC*, IPR2020-00285, Paper 10 at 28–31 (PTAB July 28, 2020) ("*Seven Networks*"); *SharkNinja Operating LLC v. iRobot Corp.*, IPR2021-00545, Paper 11 at 13-14 (PTAB Sept. 8, 2021). The Board should similarly decline to exercise discretionary denial here because the Examiner erred during prosecution of the '189 patent for the following reasons:

(a) Error 1: The Examiner Overlooked Tacken and Mueller PCT

First, the Examiner materially erred in overlooking the significance of Tacken or Mueller PCT. Both Tacken and Mueller PCT were identified in an IDS, and cited in Amgen's three IPR petitions that were submitted in an IDS. (EX1032, 027, 038, 048 (Nos. 4-6).) As described above, Tacken expressly teaches that eculizumab contains the IgG2/G4 constant region, and Mueller PCT discloses that sequence.

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provides different arguments based on Tacken (*see, e.g., supra* VIII.C-F) and additional motivations to use the IgG2/G4 constant domain (*see, e.g., supra* VIII.C), and (2) "the present Petitioner is different from the prior [P]etitioner." *See Medtronic Xomed, Inc. v. Neurovision Med. Prods., Inc.*, IPR2016-01405, Paper 12 at 8-9 (PTAB Dec. 29, 2016).

(*See supra* VIII.C.) But the Examiner overlooked Tacken's or Mueller PCT's disclosure, as evidenced by his failure to address either reference in the Office Action or Reasons for Allowance. (EX1034; EX1035; EX1003, ¶181.) *See Seven Networks*, Paper 10 at 28–31; *RTI Surgical, Inc. v. LifeNet Health,* IPR2019-00573, Paper 20 at 26-27 (PTAB Aug. 12, 2019).

It is not surprising that the Examiner overlooked Tacken and its teachings because Alexion mischaracterized the literature regarding the sequence of eculizumab. (EX1003, ¶182.) In its Response to an Office Action, Alexion stated:

> [T]he literature as of March 15, 2007 … ***consistently*** identified "eculizumab" as the antibody described in the "Thomas" publication …. Accordingly, a person of ordinary skill in the art as of March 15, 2007 would have had ***no doubt*** that "eculizumab" was Thomas's IgG4-isotype humanized antibody, because the pertinent literature ***consistently and unambiguously*** said so[.]

(EX1036, 006 (emphasis added).) Alexion then listed several references that purportedly referred to eculizumab as an IgG4 antibody.[8] But Alexion failed to provide a complete account of the literature, including the Tacken article, published in 2005 by its own employees. (EX1003, ¶182.) Given Tacken's 2005 disclosure

[8] In its list, Alexion mischaracterized Kaplan 2002, which expressly refers to Evans for the composition of eculizumab.

that eculizumab contains IgG2/G4 isotype, a POSA would have found it unambiguous that eculizumab has Mueller PCT's IgG2/G4 constant region, not the IgG4 constant region described by Thomas in 1996. (*See supra* VIII.C.) But, as a result of Alexion's inaccurate statements, the Examiner overlooked these critical disclosures of Tacken and Mueller PCT. (*See also* EX1003, ¶182.)

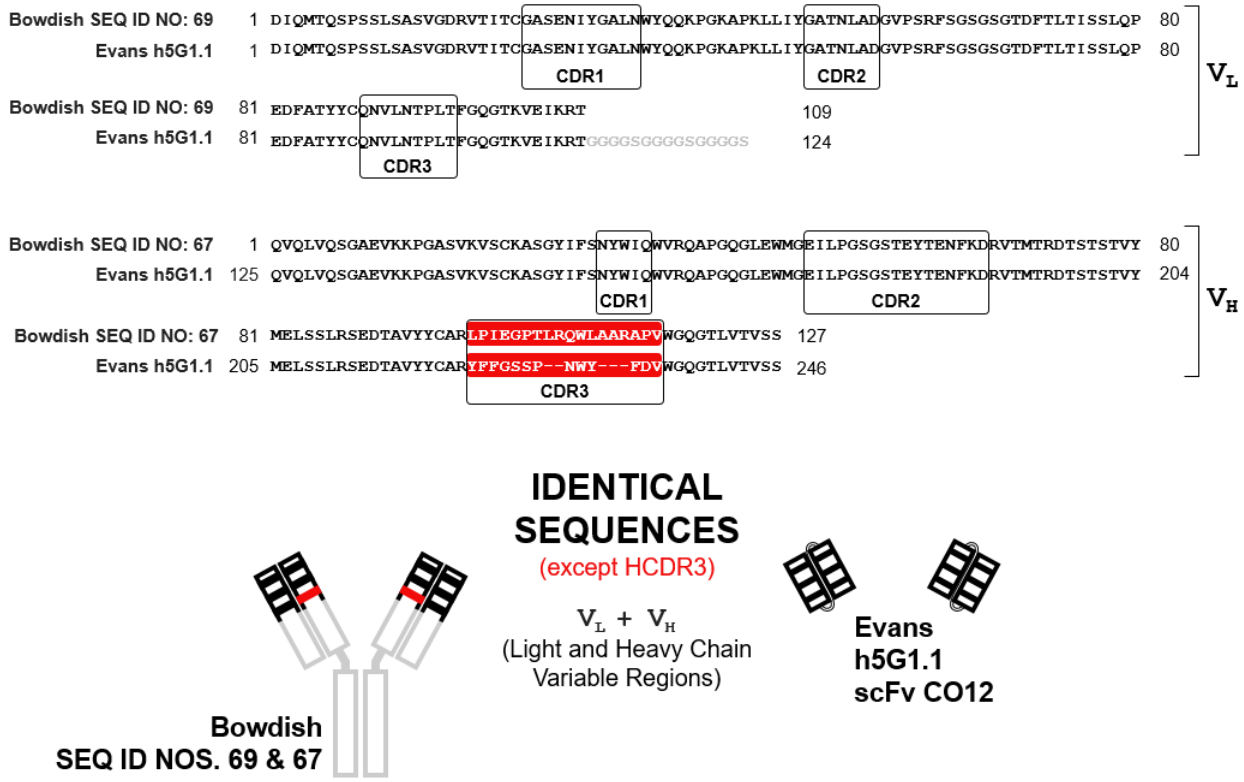
(b) Error 2: The Examiner Erred in Evaluating Bowdish and Evans

Second, the Examiner erred in evaluating Bowdish and Evans by relying on Alexion's misleading comparison of Bowdish's IgG2/G4 TPO-mimetic compound, which is a humanized antibody, with Evans' *mouse* 5G1.1 sequence. *See Liquidia Techs., Inc. v. United Therapeutics Corp.,* IPR2020-00770, Paper 7 at 14-15 (PTAB Oct. 13, 2020). During prosecution, Alexion provided an alignment of Evans' 5G1.1 *mouse* antibody variable regions with Bowdish's sequence rather than using Evans' 5G1.1 *humanized* variable region. This, unsurprisingly, revealed a mismatch. (EX1036, 014.) Persuaded by Alexion's comparison, the Examiner noted:

> Evan's [*sic*] scaffold 5G1.1 mouse antibody variable regions or the whole 5G1.1 mouse antibody with the sequences for Bowdish's TPO mimetic compound would still have revealed a mismatch in amino acids beyond those that Bowdish identified as the TPO mimetic peptide insert.

(EX1035, 006-07; EX1003, ¶183.) In fact, a comparison of Evans' *humanized* sequence with Bowdish's sequence—which is the correct, apples to apples,

comparison for the humanized 5G1.1 antibody that a POSA would make—would have shown the Examiner that there is no mismatch beyond the HCDR3 region of the TPO mimetic peptide insert:



(EX1003, ¶184.) Indeed, a proper comparison would have shown the Examiner that the starting variable region sequence used by Bowdish is identical to the Evans sequence, and that Bowdish swapped out the HCDR3 region of Evans for the TPO mimetic peptide. Thus, a POSA could reconstruct *humanized* 5G1.1 by reversing this step. (*See id.*) Tellingly, Alexion did not share any such alignments with the Examiner.

Alexion also misled the Examiner that Bowdish's "[c]onstruction of 5G1.1"

would have directed a POSA only to Evans' mouse antibody in Examples 7-10. (EX1036, 013.) Alexion's argument conveniently ignores the express description of other examples in Evans. Specifically, Evans' Example 11 expressly teaches humanized 5G1.1 scFv **constructs** and is entitled "**Construction** and Expression of Recombinant mAbs." (EX1005, 42:56-45:33 (emphasis added).) Example 11 also states: "Recombinant DNA **constructions** … are prepared by conventional recombinant DNA methods[.]" (*Id*., 42:59-62 (emphasis added).) Evans also discloses "CDR sequences that are useful in the **construction** of the humanized antibodies[.]" (*Id*., 8:50-54 (emphasis added).) By comparison, Alexion focused the Examiner on Example 7, entitled "Preparation of anti-C5 Monoclonal Antibodies," which discloses preparing (not constructing) the parent 5G1.1 mouse antibody from prior art mouse hybridomas. (*Id*., 37:34-39:30.) Alexion's misdirection is relevant because a POSA considering Bowdish's "construction of 5G1.1" by recombinant means would have referred to Evans' construction of the humanized 5G1.1 scFv constructs detailed in Example 11, not Example 7. (*See also supra* VIII.C; EX1003, ¶185.)

Further, the Examiner misapprehended Evans by relying on Alexion's mischaracterization that Evans discloses "multiple options" for HCDR3 sequence. In its Response, Alexion argued that even if a POSA were to consider Evans "for its disclosure of heavy chain CDR3 sequences, Evans *et al.* allows for multiple options,

and nothing in Bowdish *et al.* or Evans *et al.* indicates which, if any, were used in the 'scaffold' antibody used to produce Bowdish *et al.*'s TPO-mimetic peptide[.]" (EX1036, 018.) This is a blatant misrepresentation of Evans — all nine humanized scFv sequences of Evans have only one unique HCDR3 sequence (YFFGSSPNWYFDV), not "multiple options." (*See* EX1005, 42:56-45:33; *see also supra* VIII.C; EX1003, ¶186, Appendix A.) Alexion's misinformation regarding Evans' unique HCDR3 sequence for h5G1.1 misled the Examiner into allowing the claims.

(c) Error 3: The Examiner Misapplied the Law in Evaluation of Secondary Considerations

Third, the Examiner materially erred by misapplying the law in evaluating the evidence of secondary considerations submitted by Alexion during prosecution. *Advanced Bionics*, Paper 6 at 8-9 n.9. In Reasons for Allowance, the Examiner noted: "some of the secondary considerations are evidence of nonobviousness, particularly the invention as claimed satisfies a long felt need and that there is objective evidence of copying." (EX1035, 007.) However, Alexion's arguments for these secondary considerations are insufficient evidence as a matter of law. (EX1003, ¶187.)

For long-felt need, the Examiner erred in accepting Alexion's evidence because Alexion incorrectly derived its evidence from the success of its drug Soliris that was indisputably in the prior art as a PNH therapy. (EX1036, 024-26; *see supra*

IX; EX1003, ¶¶171, 187.) For copying, the Examiner also misapplied the law in accepting Alexion's evidence of four biosimilars. (EX1036, 026-27.) Biosimilars, however, as with Hatch-Waxman/ANDA cases, cannot be probative of nonobviousness because a showing of bioequivalence is required for FDA approval. *See, e.g.*, *Adapt Pharma Operations Ltd. v. Teva Pharms. USA, Inc.*, 25 F.4th 1354, 1374 (Fed. Cir. 2022). "Copying" by biosimilar applicants is entitled to no weight as a secondary consideration. (*See supra* IX.) The Examiner therefore erred in considering development of biosimilars as evidence of copying. (EX1003, ¶¶173, 187.)

(d) Error 4: The Examiner Erred in Evaluating Wang

Fourth, the Examiner erred in evaluating Wang's disclosures that unequivocally teach and render obvious the claimed eculizumab formulation. Although the Examiner cited Wang in a rejection, its pertinent disclosures were not discussed substantively in the Notice of Allowance. *Koss*, Paper 15 at 26, 28-29 (finding examiner erred in evaluating prior art reference that was not discussed substantively in the Notice of Allowance but "unequivocally" taught claimed features). This is not surprising given Alexion's mischaracterization that Wang's formulations are about "unrelated 'anti-C5 antibodies'" (EX1036, 018-19) when in fact Wang expressly discloses that "eculizumab" is a "preferred embodiment" for its anti-C5 antibodies, and specifically teaches the 1-30 mg/ml concentration in the

context of "eculizumab" formulations. (EX1044, [0004], [0170]-[0173]; EX1003, ¶¶188-189.) Wang even calls out "eculizumab" as an "embodiment" for antibodies that are "stable" in a formulation of 1-200 mg/ml. (EX1044, [0067].) Alexion's mischaracterizations of Wang evidently led the Examiner to err and fail to appreciate the strength of its teachings as prior art.

XI. CONCLUSION

Petitioner respectfully requests institution of IPR based on the grounds set forth and described above.

Dated: May 31, 2023

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE WITH WORD COUNT

Pursuant to 37 C.F.R. § 42.24(d), I certify that this petition complies with the type-volume limits of 37 C.F.R. § 42.24(a)(1)(i) because it contains 13,996 words, according to the word-processing system used to prepare this petition, excluding the parts of this petition 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 **PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 9,725,504 B2,** including all exhibits (**Nos. 1001-1065**) and related documents, are being served via Federal Express on the May 31, 2023, 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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