UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FORMYCON AG.,
Petitioner,

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner.

Case IPR2025-00233
U.S. Patent No. 11,084,865

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 11,084,865

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I. INTRODUCTION

Formycon AG ("Petitioner") petitions for *inter partes* review ("IPR") under 35 U.S.C. §§ 311-319 and 37 C.F.R. §§ 42 et seq., seeking cancellation of claims 1-12, 14-17, 19-20, 22-36, 39-42, 44-45, and 47-55 (the "Challenged Claims") of U.S. Patent No. 11,084,865 ("'865 patent") (Ex.1001), assigned to Patent Owner, Regeneron Pharmaceuticals, Inc. ("Regeneron" or "Patent Owner").

The Challenged Claims are generally directed to ophthalmic formulations, in either a vial or a pre-filled syringe ("PFS"), comprising the anti-VEGF molecule aflibercept, an organic co-solvent, a buffer, and a stabilizing agent. The claims recite the formulation's stability characteristics (percent "native conformation" of the protein and turbidity) under common storage conditions.

One subset of the Challenged Claims—1-12, 14-17, 19-20, 22-25, 51-53,and 55—recite that the formulation is stored in a vial. These claims are collectively referred to as the "Vial Claims" and are addressed in Ground I. A second subset of Challenged Claims—26-36, 39-42, 44-45, 47-50, 54—recite the same formulation stored in a PFS. These claims are collectively referred to as the "PFS Claims" and are addressed in Ground II.

Both sets of claims are rendered obvious by two publications—Fraser (Ex.1009) and Wulff (Ex.1016)—in combination with a small set of additional

references. Fraser and Wulff describe the same intravenous formulation of aflibercept. The Fraser/Wulff formulation was the only aflibercept formulation described in the prior art. It contained aflibercept formulated in a phosphate buffer, a polysorbate 20 co-solvent, and a sucrose stabilizer (Ex.1002, ¶¶88-94; Ex.1011, 96; Ex.1009, 1115; Ex.1016, 2798). These are the same excipients recited in the Challenged Claims, as shown below:

Fraser/Wulff Formulation	Challenged Claims Active Ingredients and Excipients
aflibercept	aflibercept
polysorbate 20	polysorbate 20 (an organic co-solvent)
phosphate buffer	phosphate buffer
sucrose	sucrose (a stabilizing agent)

The dependent Challenged Claims specify narrower concentration ranges for aflibercept and the excipients and are rendered obvious by Fraser/Wulff in combination with a series of presentations given by Patent Owner in February and March 2006 ("2006 Presentations") describing administering aflibercept intravitreally to treat angiogenic eye disorders. These presentations would have motivated a POSA to modify the intravenous Fraser/Wulff formulation–the only known aflibercept formulation—for intravitreal use. Taking simple, necessary steps to convert the intravenous Fraser/Wulff formulation into an intravitreal formulation leads directly to the claimed formulation.

Specifically, the 2006 Presentations teach using aflibercept to treat wet AMD, which is "a major cause of blindness in adults over 60." *See, e.g.*, Ex.1012, 19. According to Regeneron, aflibercept could be the "best in class" for wet AMD with the potential to achieve greater efficacy with a more convenient dosing regimen. *Id.* The presentations disclose that a "single intravitreal injection" of aflibercept showed "[r]apid, substantial, and prolonged (up to at least 4 weeks) reduction in retinal thickness"—necessary to treat wet AMD—and that a Phase 2 trial was set to begin with a Phase 3 trial planned for the following year. *See, e.g.*, Ex.1012, 23.

The presentations would have motivated a POSA to develop an intravitreal formulation of aflibercept for use in treating angiogenic eye disorders. Though the presentations tout aflibercept intravitreal injections, they do not give details on the formulation used. A POSA naturally would have looked to Fraser and Wulff, which describe the only known formulation of aflibercept, as a starting point.

Modifying the Fraser/Wulff formulation for intravitreal use would have only required a few simple steps:

(1) **Selecting the dosage**. The 2006 Presentations teach that the maximum safe and tolerated dose of aflibercept for intravitreal injections was 4 mg, so a POSA would have been motivated to select this dose for the treatment of angiogenic eye disorders.

(2) **Reducing the volume**. The 2 mL volume of the Fraser/Wulff formulation is far too large for the human eye. A POSA would have been motivated to reduce it to 0.1 mL, the known safe and tolerated volume for intravitreal injections, which was used in the most commonly administered intravitreal drugs.

(3) **Reducing sucrose**. The Fraser/Wulff formulation includes 20% sucrose, which results in a formulation with an extremely high concentration of dissolved particles in the fluid (its osmolality or osmolarity). Injecting the Fraser/Wulff formulation into the eye would have caused the eye to compensate by drawing water in from surrounding tissues, including the retina, risking substantial discomfort and even significant damage. To avoid this, a POSA would have been motivated to reduce the formulation's osmolarity to match that of the eye. As described further below, reducing sucrose from 20% to 10% or less was the only way to achieve this, given the composition of the formulation. Doing so, along with selecting the dose and reducing the volume, would have made the formulation suitable for intravitreal administration.

As set out below in Section VII.A, a POSA would have been motivated to make these minor, obvious modifications, leading directly to the formulation recited in the Challenged Claims, including the concentration ranges and amounts recited in the dependent claims. Storing the formulation in a vial or PFS would have been obvious.

The resulting formulation ("Modified Fraser/Wulff formulation") also would have had the claimed stability characteristics (percent "native conformation" and turbidity) under the recited storage conditions. While the stability of the Modified Fraser/Wulff formulation was not expressly taught in the prior art, the stability of the formulation is "the natural result of the combination of elements explicitly disclosed by the prior art." *PAR Pharmaceutical, Inc. v. TWI Pharmaceuticals, Inc.*, 773 F.3d 1186, 1195-96 (Fed. Cir. 2014). Regeneron's own testing on aflibercept formulations confirm that the Modified Fraser/Wulff formulation would have had the claimed stability. Regeneron discloses stability testing on a wide range of aflibercept formulations containing different concentrations of excipients, and the Modified Fraser/Wulff formulation falls within the ranges of the formulations Regeneron tested. That testing shows that the Modified Fraser/Wulff formulation will have the claimed stability. Testing an obvious formulation to ascertain protein aggregation and turbidity after storage at 5°C does not make that formulation patentable, because "the identification and characterization of a prior art material… does not make it novel." *In re Crish*, 393 F.3d 1253, 1258 (Fed. Cir. 2004).

Furthermore, the '865 Patent does not teach a POSA how to achieve the recited stability other than by simply making and testing the formulation. Indeed, where a Patent Owner claims a composition in terms of a property and the prior art teaches the same composition without disclosing that property, "the PTO can require

an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product." *In re Best*, 562 F.2d1252, 1255 (CCPA 1977). Further, a POSA would have been motivated to make the Modified Fraser/Wulff formulation as stable as possible and would have regarded achieving the stability recited in the claims to be obvious. Ex.1002, ¶¶149-157; Ex.1016, 2798.

Finally, discretionary denial is not appropriate here. None of the references cited in Petitioner's grounds were substantively discussed during prosecution.

The Board should institute an *inter partes* review of the Challenged Claims and find those claims unpatentable on the grounds presented herein.

II. MANDATORY NOTICES PURSUANT TO 37 C.F.R. § 42.8(A)(1)

A. Real Party-In-Interest (37 C.F.R. § 42.8(b)(1))

The real party-in-interest for Petitioner is Formycon AG.

B. Related Matters (37 C.F.R. § 42.8(b)(2))

The '865 patent is challenged in *Samsung Bioepis Co. Ltd. v. Regeneron Pharmaceuticals, Inc.*, IPR2025-00176 (P.T.A.B.), which was filed on November 20, 2024. The Board has not yet issued an institution decision in IPR2025-00176, which concerns precisely the same invalidity grounds raised by this Petition.

Petitioner conditionally seeks to join IPR2025-00176. *See* Conditional Motion for Joinder (filed concurrently). Petitioner submits "copycat" declarations from Dr. Laird Forrest, Dr. Zhaohui Zhou, and Dr. Todd Lefkowitz, on whom Petitioner will rely only in the event that trial in IPR2025-00176 is not instituted or

Samsung Bioepis is terminated from that proceeding. *Id.* at 6 n.2. The declarations submitted by Petitioner differ from those Samsung Bioepis filed in IPR2025-00176 (from Drs. Yaman, Butler, and Chaum, respectively), in that they have been updated to list the qualifications and personal experience of Drs. Forrest, Zhou, and Lefkowitz. *Id.*

The related '992 patent was challenged in *Chengdu Kanghong Biotechnology Co., Ltd. v. Regeneron Pharmaceuticals, Inc.*, IPR2021-00402 (P.T.A.B.), which the parties voluntarily terminated on June 25, 2021. The '992 patent was challenged in *Celltrion, Inc. v. Regeneron Pharmaceuticals, Inc.*, IPR2023-00462 (P.T.A.B.), which was instituted on July 20, 2023. Regeneron subsequently disclaimed all challenged claims in response to institution.

The '865 patent is currently being asserted in *Regeneron Pharmaceuticals, Inc. v. Formycon AG*, No. 1:23-cv-97 (N.D.W.Va.). A preliminary injunction was entered by the Court in that case, which is on appeal to the Federal Circuit in *Formycon AG v. Regeneron Pharmaceuticals, Inc.*, Appeal No. 24-2009. The West Virginia Court has not scheduled trial in that matter and discovery has not been conducted. Regeneron asserts the '865 patent as one of 52 patents.

To the best of Petitioner's knowledge, the following are additional judicial or administrative matters that potentially would affect, or be affected by, a decision in this proceeding:

- *Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals Inc.*, Nos. 24-

1965, 24-1966, 24-2002, 24-2009, 24-2019, 24-2058, 24-2082, 24-2083, 24-2147, 24-2156, 24-2351 (Fed. Cir.)

- *In re: Aflibercept Patent Litigation*, No. 1:24-md-3103 (N.D.W.Va.)
- *Regeneron Pharmaceuticals, Inc. v. Amgen, Inc.*, No. 2:24-cv-264 (C.D. Cal.)
- *Regeneron Pharmaceuticals, Inc. v. Amgen, Inc.*, No. 1:24-cv-39 (N.D.W.Va.)
- *Regeneron Pharmaceuticals, Inc. v. Samsung Bioepis Co., Ltd.*, No. 1:23-cv-106 (N.D.W.Va.)
- *Regeneron Pharmaceuticals, Inc. v. Samsung Bioepis Co., Ltd.*, No. 1:23-cv-94 (N.D.W. Va.)
- *Regeneron Pharmaceuticals, Inc. v. Celltrion, Inc.*, No. 1:23-cv-89 (N.D.W.Va.)
- *Regeneron Pharmaceuticals, Inc. v. Celltrion, Inc.*, No. 1:24-cv-53 (N.D.W.Va.)
- *Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals Inc.*, No. 1:22-cv-61 (N.D.W.Va.)
- *Regeneron Pharmaceuticals, Inc. v. Sandoz, Inc.*, No. 1:24-cv-85 (N.D.W.Va.)

C. Lead and Backup Counsel (37 C.F.R. § 42.8(b)(3)-(4)

Petitioner hereby identifies its lead and backup counsel as follows:

Lead Counsel	Backup Counsel
Louis E. Fogel (Reg. No. 54,731) Fish & Richardson P.C. 60 South Sixth Street, Suite 3200 Minneapolis, MN 55402 Tel: 202-783-5070 Fax: 877-769-7945 fogel@fr.com	Grace Kim (Reg. No. 71,977) Fish & Richardson P.C. 60 South Sixth Street, Suite 3200 Minneapolis, MN 55402 Tel: 202-783-5070 Fax: 877-769-7945 PTABInbound@fr.com

Pursuant to 37 C.F.R. § 42.10(b), a Power of Attorney has been filed herewith.

D. Service Information (37 C.F.R. § 42.8(b)(4))

Please send all correspondence to the lead and backup counsel at the addresses shown above. Petitioner consents to service by e-mail at IPR57795-0001IP1@fr.com.

E. Payment of Fees (37 C.F.R. §§ 42.103 and 42.15(a))

The requisite filing fee of $73,000 (request fee of $29,500, post-institution fee of $43,500) for a Petition for *Inter Partes* Review is submitted herewith. Claims 1-12, 14-17, 19-20, 22-36, 39-42, 44-45, 47-55 are being reviewed as part of this Petition. If any additional fees are due during this proceeding, the Office is authorized to charge such fees to Deposit Account No. 06-1050. Any overpayment or refund of fees may also be deposited in this Deposit Account.

III. GROUNDS FOR STANDING (37 C.F.R. § 42.104(a); 37 C.F.R. §§ 42.101(a)-(c))

Petitioner certifies that the '865 patent is available for IPR and that Petitioner is not barred or estopped from requesting this review.

IV. IDENTIFICATION OF CHALLENGE AND RELIEF REQUESTED

A. Identification of Challenge (37 C.F.R. § 42.104(b))

Petitioner requests IPR of '865 patent claims 1-12, 14-17, 19-20, 22-36, 39-42, 44-45, 47-55 and that the Board cancel those claims as unpatentable.

B. Grounds of Challenge (37 C.F.R. § 42.204(b)(2))

Petitioner respectfully requests that the Board grant institution of IPR on the Challenged Claims based on the following grounds:

Statutory Grounds of Challenge		
Ground I	Claims **1/51**, 2-12, 14-17, 19-20, 22-25, 52-53, 55	Obvious over the combination of Fraser (Ex.1009), Wulff (Ex.1016), and the 2006 Presentations (Ex.1011-1013), in light of the '319 Publication (Ex.1029) and FDA Container Closure Guidance (Ex.1038).
Ground II	Claims **26**-36, 39-42, 44-45, 47-50, 54	Obvious over the combination of Fraser, Wulff, and the 2006 Presentations, in light of the '319 Publication, and Nayar (Ex. 1020).

V. THE '865 PATENT

A. Overview

The '865 patent is entitled "VEGF Antagonist Formulations Suitable for Intravitreal Administration."

The '865 patent describes the invention as "[s]table formulations of a VEGF-specific protein antagonist" comprising a "VEGF 'trap' antagonist with a pharmaceutically acceptable carrier." Ex.1001, 2:14-19.

The '865 patent states that the "VEGF antagonist of the methods and formulations of the invention can be prepared by any suitable method known in the art, or that comes to be known." *Id*., 6:40-42.

The '865 patent teaches that "[i]n specific embodiments, the VEGF antagonist is expressed in a mammalian cell line such as a CHO cell and may be modified post-translationally," and further notes that in "a specific embodiment, the fusion protein comprises amino acids 27-457 of SEQ ID NO:4 and is glycosylated at Asn residues 62, 94, 149, 222 and 308." *Id.*, 6:32-38. That is the only disclosure in the specification regarding glycosylation.

The '865 patent includes eight examples, which describe combinations of protein, buffer, stabilizer and one of two "organic co-solvents." Seven of the eight examples include 20 to 50 mg/ml of "VEGF Trap (SEQ ID NO:4)" protein in combination with phosphate buffer, sodium chloride, and polysorbate 20 in varying combinations at a pH of 6.25 or 6.3. *Id*., Examples 1, 3-8. Five of the examples additionally contain sucrose. *Id*., Examples 1-4, 7. Six of the examples deal with liquid formulations (*Id*., Examples 1-6), and two with lyophilized formulations (*Id*., Examples 7-8).

The '865 patent examples report the formulation's stability after storage at 5 °C for certain periods of time. Specifically, the patent reports turbidity data and "% VEGF Trap Native Configuration" (as measured by size-exclusion chromatography ("SEC")) after storage periods that run from zero to 24 months. *See, e.g.*, *Id*., Tables 1-8. The examples also provide the pH of the formulation over time.

Other than making and testing the claimed formulations, the '865 patent does not teach how to achieve the claimed stability. Ex.1002, ¶¶49-55. Apart from the handful of examples, the patent does not teach the effect of adjusting or optimizing the concentrations within the scope of what is claimed. *Id.*

The patent also does not teach whether the disclosed formulations are safe and effective for intravitreal administration. There is no disclosure that any of the formulations were intravitreally injected, or whether they were tolerated if they were to be injected.

B. Priority Date

The '865 patent claims priority to ten prior patent applications and one provisional application, which was filed on June 16, 2006. Regeneron has previously contended the inventors of the '865 patent conceived and reduced to practice the alleged inventions by March 21, 2006. For the purposes of this petition, Petitioner assumes March 21, 2006 is the relevant priority date. Ex.1002, ¶¶56, 63.

C. The Challenged Claims

The Challenged Claims are generally directed to ophthalmic formulations, in either a vial or a PFS, comprising a glycosylated VEGF antagonist that comprises amino acids 27-457 of SEQ ID NO:4, an organic co-solvent, a buffer, and a stabilizing agent, wherein the formulations have specific stability (turbidity and % "native conformation" measured by SEC). Ex.1002, ¶¶61-62.

D. Prosecution History

During prosecution of the '865 patent, the claims were rejected only for obviousness-type double patenting. Ex.1004, 256-62. To overcome the rejection, Regeneron relied on the stability limitations recited in the claims. *Id.*, 279-84. Regeneron did not argue, however, that the recited stability values were unexpected. Ex.1002, ¶57.

E. Level of Ordinary Skill in the Art

The POSA at the time of the invention would have had a Ph.D. in pharmaceutical sciences or a similar field, with at least several years of experience in the development, manufacture and characterization of formulations of therapeutic proteins, including, for example, fusion proteins or antibodies. Ex.1002, ¶¶58-60. The POSA may also have had less education but substantially more practical relevant work experience. *Id.* This individual would have understood how to combine proteins with compatible excipients such as surfactants, stabilizers, salts and buffers of various pH values, and how to adjust these combinations in order to optimize their stability in liquid or solid form. *Id.* This individual also would have been able to use state-of-the-art analytical methods, such as SEC, to assess stability and compatibility. *Id.*

The POSA may collaborate with others, including a medical doctor with experience treating ophthalmic diseases. *Id.* The POSA also would have had access

to other individuals typically employed in developing protein active pharmaceutical ingredients and products, including those involved in upstream and downstream manufacturing, analytical chemistry, pharmacokinetics, clinical testing, pharmaceutical packaging, and regulatory affairs. *Id.* These diversely-qualified individuals would have worked together as needed during development. *Id.*

VI. SCOPE AND CONTENT OF THE PRIOR ART

Petitioner summarizes the scope and content of the prior art, including the disclosures of its primary prior art references, below. All references discussed herein are prior art under both pre-AIA and AIA 35 U.S.C. § 102 and Petitioner's arguments are the same under both.

A. Background

1. *VEGF*

VEGF is a naturally-occurring protein that regulates the process by which new blood vessels are formed, known as "angiogenesis." Ex.1002, ¶64; Ex.1015, 412; Ex.1005, ¶¶43-45; Ex.1007 ¶¶18-19. VEGF functions by binding to VEGF receptors on the surfaces of cells responsible for angiogenesis. *Id.* (citing Ex.1015, 412; Ex.1005, ¶¶43-45; Ex.1007 ¶¶18-19). Two of the best-characterized VEGF receptors are VEGF receptor 1 (VEGFR1), known as Flt1, and VEGF receptor 2 (VEGFR2), known as Flk1. Ex.1015, 412; Ex.1002, ¶¶64-66.

By 2005, it was known that VEGF had a role in tumor angiogenesis, and a number of VEGF inhibitors had been developed as potential cancer therapies. Ex.1008, 968-971; Ex.1002, ¶65; Ex.1005, ¶¶33, 35, 43-45; Ex.1007, ¶¶18-22.

VEGF antagonists were also being used successfully to treat age-related macular degeneration (wet AMD). Bevacizumab and ranibizumab (a modified fragment of the bevacizumab antibody) are two examples. Ex.1015, 411; Ex.1002, ¶66; Ex.1005, ¶¶33-34, 36-37; Ex.1007, ¶18; Exs.1068-1077.

2. *Aflibercept*

During this time, Regeneron developed aflibercept, another VEGF inhibitor. Aflibercept was known as "VEGF-Trap$_{R1R2}$", "VEGFR1R2-FcΔC1(a)," and "VEGF Trap-Eye" at the time. Aflibercept is a fusion protein of domain 2 of the human VEGFR1 receptor and domain 3 of the human VEGFR2 receptor, linked via the Fc domain of a human IgG antibody as shown below:

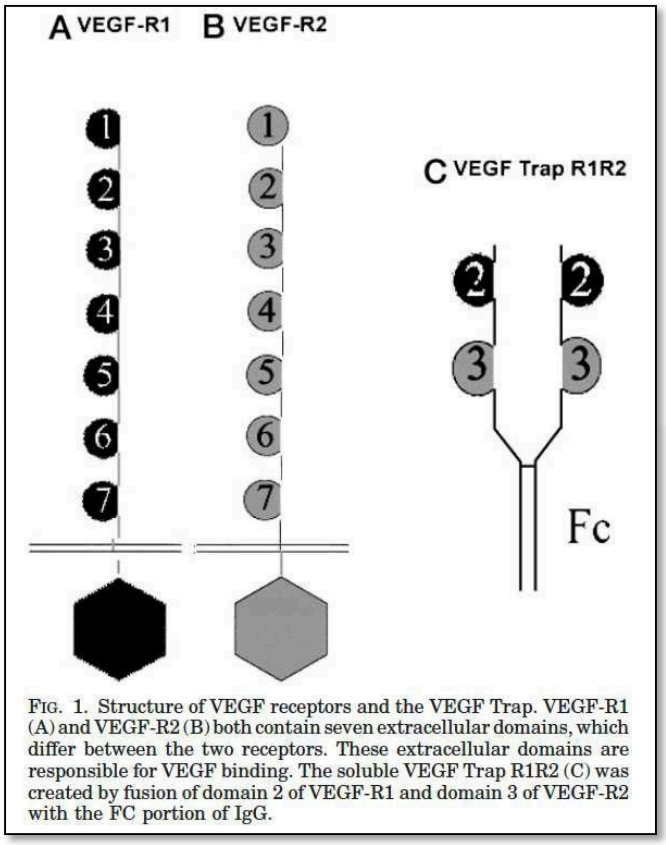

FIG. 1. Structure of VEGF receptors and the VEGF Trap. VEGF-R1 (A) and VEGF-R2 (B) both contain seven extracellular domains, which differ between the two receptors. These extracellular domains are responsible for VEGF binding. The soluble VEGF Trap R1R2 (C) was created by fusion of domain 2 of VEGF-R1 and domain 3 of VEGF-R2 with the FC portion of IgG.

Ex.1016, 2798, Fig. 1; Ex.1002, ¶67; Ex.1007, ¶18-22. Like bevacizumab and ranibizumab, aflibercept binds and "traps" VEGF before it can trigger angiogenesis. Ex.1002, ¶68.

Starting in 2002, Regeneron publicized its development of aflibercept, including *in vivo* experiments which demonstrated its therapeutic promise. Ex.1010. Though Regeneron had developed other VEGF traps, aflibercept was reported to have the best pharmacokinetic activity. Regeneron claimed: "The combination of high-affinity and improved pharmacokinetics apparently contributes toward making VEGF-Trap$_{R1R2}$ [aflibercept] one of the most, if not the most, potent and efficacious VEGF blocker available." Ex.1010, 11397.

Regeneron noted that aflibercept was comprised of "entirely human sequences," which would "hopefully minimize the possibility that it might prove immunogenic in human patients." Ex.1010, 11397. Regeneron also noted "far lower circulating levels of VEGF-Trap$_{R1R2}$ [aflibercept] are required for similar efficacy" and its "safety has recently been confirmed in toxicological studies in cynomolgus monkeys." Ex.1010, 11397.

Regeneron started its Phase I dose escalating trial using aflibercept for wet AMD in June 2005. Ex.1014. In a September 27, 2005 presentation at the UBS Global Life Sciences Conference, Regeneron stated that its VEGF Trap had the "[o]pportunity… to emerge as 'best-in-class' treatment for wet AMD" because of the "[p]otential for greater efficacy related to unique characteristics" and the "[p]otential for greater convenience by requiring less frequent injections." Ex.1022, 12. As discussed further below, Regeneron publicized the results of that initial clinical trial as well, including the success of the 4 mg dose. Exs.1011-1013.

Before the priority date, Regeneron also had widely published the aflibercept sequence, although Regeneron referred to aflibercept by its scientific names, VEGF-Trap$_{R1R2}$ and VEGFR1R2-FcΔC1(a), rather than the non-proprietary name

"aflibercept."[1] By 2004, Regeneron had published the amino acid sequence of VEGFR1R2-FcΔC1(a) in three patent publications. *See* Ex.1027, ¶5, SEQ ID Nos. 1 and 2 (disclosing that VEGFR1R2-FcΔC1(a) is "also termed VEGF-Trap$_{R1R2}$"); Ex.1029, 12, 15, Fig. 24A-24C; Ex.1028, ¶8, SEQ ID Nos. 3 and 4; Ex.1002, ¶73; Ex.1007, ¶¶18-22. Regeneron also disclosed the VEGFR1R2-FcΔC1(a) sequence in the *'758 Patent,* which published as U.S. Patent Application Publication No. 2005/0245447 on November 3, 2005. Ex.1019, 10:15-17, Figs. 24A-24C; Ex.1002, ¶73; Ex.1007, ¶18.

[1] When seeking PTE for U.S. Patent No. 7,374,758 ("the *'758 Patent*") based on EYLEA®, Regeneron represented to the Office that aflibercept is "also known as VEGF trap, VEGF-trap, VEGF Trap- Eye and VEGF-Trap$_{R1R2}$." Ex.1020, 2, 6-7; Ex.1002, ¶73, n.1. Regeneron also represented that "aflibercept is described in [*Holash*] as VEGF-Trap$_{R1R2}$", Ex.1020, 5, and that the amino acid sequence of aflibercept is set forth in Figures 24A-24C of the '758 patent. Ex.1020, 6-7 (noting that the "Flt1 Ig domain 2" of aflibercept "spans amino acid residues 27 through 129," "Flk1 Ig domain 3 spans amino acid residues 130 through 231," and "the Fc multimerizing component" spans amino acid residues 232 through 458"); Ex.1002, ¶73, n.1.

Regeneron also disclosed that it expressed aflibercept in CHO cells. *See, e.g.*, Ex.1029, 12, 15, Fig. 24A-24C, claims 9, 20 (describing production of VEGFR1R2-FcΔC1(a) in CHO cells); *see also* Ex.1027 ¶22 (directing POSA to *'319 Publication* for "a complete description of VEGF-receptor based antagonists including VEGFR1R2-FcΔC1(a)" and incorporating the *'319 Publication* into the *'309 Publication* "by reference in its entirety."); Ex.1002, ¶¶73-74; Ex.1010, 11394 (describing testing of VEGF-Trap$_{R1R2}$ and related variants; "[a]ll of the VEGF-Trap variants were produced and purified from Chinese hamster ovary cells."); Ex.1007, ¶¶18-22. *Wulff* also disclosed that Regeneron expressed VEGF-Trap$_{R1R2}$ in CHO cells. Ex.1016, 2798 and n.1 (explaining that "[t]he VEGF Trap R1R2 used in these experiments … was expressed in CHO cells"); Ex.1002, ¶¶91-94. It was well known and understood that when aflibercept is expressed in CHO cells, it is glycosylated. Ex.1007, ¶¶18-36; Exs.1079-1085, 1089-1093.

Regeneron also disclosed an intravenous formulation of aflibercept used in preclinical studies. In Fraser, aflibercept was formulated with 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose. Ex.1009, 1115. Wulff discloses the same formulation, but specifies that sucrose is used: 5mM phosphate, 5 mM citrate, 100 mM sodium chloride, 0.1% (wt/vol) Tween 20, and 20% (wt/vol) sucrose. Ex.1016, 2798. Ex.1002, ¶75.

3. *Protein Stability*

As of the priority date, it was well known that proteins like aflibercept degraded via known mechanisms. *See, e.g.* Ex.1096, 1; Ex.1002, ¶76.

Chemical instability refers to processes that break or form chemical bonds within the molecule, including deamidation and oxidation. Ex.1002, ¶77. Physical instability refers to changes in protein conformation—its three-dimensional structure—including aggregation. *Id.* Physical instability often leads to aggregation. Ex.1096, 1; Ex.1002, ¶77.

When formulating a protein therapeutic, POSAs seek to limit aggregation because it can cause immunogenicity, diminish half-life, and interfere with drug function. Ex.1002, ¶78.

Many well-known formulation techniques were proven to be effective in preventing protein aggregation. One common technique involved using an organic co-solvent known as a "surfactant." *See* Ex.1018, Table 6; Ex.1002, ¶79. Polysorbate 20 and polysorbate 80 (which are sold under the brand names "Tween 20" and "Tween 80," respectively) were commonly used surfactants to prevent aggregation in therapeutic protein formulations. *See, e.g.*, Ex.1097, Box 1; Ex.1002, ¶79. As of the priority date, many FDA-approved and commercially-available protein therapeutics used polysorbate in their formulations to prevent aggregation. *See, e.g.*, Ex.1032, 2 (polysorbate 20); Ex.1034, 1117 (polysorbate 80); Ex.1037,

1359 (polysorbate 20); Ex.1033, 1350 (polysorbate 20); Ex.1036, 1338 (polysorbate 20); Ex.1002, ¶79. These included intravitreal formulations. Ex.1005, ¶¶34, 36.

POSAs also commonly used phosphate as a buffer to stabilize protein formulations, and as of the priority date many FDA-approved protein formulations included a phosphate buffer. *See* Ex.1032, 2; Ex.1034, 1117; Ex.1035, 2367; Ex.1002, ¶80. Sodium phosphate was the most common phosphate buffer. Ex.1005, ¶¶35-36; Ex.1002, ¶80. Citrate buffers also had been used in intravitreal formulations at the time. *Id.*

Sucrose was also commonly used as a stabilizer in formulations, particularly for its cryoprotectant abilities. Ex.1002, ¶81; Ex.1096, 1. As of the priority date, sugars like sucrose and trehalose had been used in intravitreal formulations. *Id.*; Ex.1005, ¶¶34, 36, 44-45.

POSAs also routinely refrigerated protein therapeutics at 2-8 °C to minimize degradation; colder temperatures slow the degradation process. Ex.1002, ¶82; Ex.1032, 25; Ex.1034, 1121; Ex.1037, 1362; Ex.1033, 1352; Ex.1035, 2369; Ex.1036, 1341. POSAs commonly tested stability after storage for weeks ormonths at 2-8 °C. *See, e.g.*, Ex.1026, ¶¶63, 280 (showing stability data for 1, 3, 14, 16, and 24 months); Ex.1002, ¶82.

POSAs also commonly used SEC at the time to quantify protein aggregation. *See, e.g.*, Ex.1026, ¶278, Table 1; Ex.1012, 160; Ex.1002, ¶83. SEC measures the percent monomer present. Ex.1002, ¶83.

POSAs also knew how to optimize a therapeutic protein formulation to minimize aggregation over a reasonable shelf-life. Ex.1002, ¶84; Ex.1026, ¶278, Table 1; Ex.1012, 160. POSAs understood that very high levels of purity could be maintained following storage at 2-8 °C. *Id.* In fact, numerous publications reported antibody formulations with >98% "native conformation" following two months storage at 5 °C.[2] *Id.*

For instance, *WO '801* (Ex.1030) discloses lyophilized trastuzumab formulations that contained trehalose and polysorbate 20 and maintained >99% of the protein "intact" (*i.e.,* native conformation) as measured by SEC after two weeks storage at 5 °C. Ex.1030, Table 4 (99.8% or 100.0% native conformation at 91 days), Table 5 (100.0% native conformation at 61 days), Table 6 (100.0% native conformation at 92 days), Table 7 (99.8% native conformation at 92 days); Ex.1002, ¶85.

[2] The term "native conformation" will be used herein as that term is used in the '865 patent, *i.e.*, to refer to the % native conformation as measurable by SEC.

Similarly, *Liu* reports recombinant human antibody formulations that had >98% "monomer" (*i.e.*, native conformation) after storage at 5 °C for 3 months (and even up to 16 months). Ex.1026, ¶¶279-280; Table 1; Ex.1002, ¶86. The *'586 Patent* (Ex.1018) similarly reports that an antibody formulation containing polysorbate 20 and trehalose (a stabilizing agent) had >98% "monomer" (*i.e.*, native conformation) as measured by SEC following storage at 2-8 °C for two years. Ex.1018, Fig 28, 5:34-39; Ex.1002, ¶86.

Likewise, *Kaisheva '316* reports SEC data for three anti-IL-2 receptor antibody formulations containing histidine, sucrose, and polysorbate 80. Ex.1024, ¶¶113-15, Fig 9A; Ex.1002, ¶87. At 3 months, all three formulations contained above 98% "monomer" (*i.e.*, native conformation). Ex.1024, ¶22; ¶¶113-15, Fig 9A; Ex.1002, ¶87. *Kaisheva '417* also reports dacilizumab antibody formulations with greater than 98% "monomer" (*i.e.*, native conformation) after 8 weeks storage at 5 °C. *See, e.g.*, Ex.1025, Table 5 (98.24% native conformation following 8 weeks storage at 5 °C), Table 6 (99.24% native conformation following 8 weeks storage at 5 °C), Table 8 (99.1% native conformation following 3 months storage at 5 °C), Table 9 (98.9% native conformation following 7 months storage at 5 °C), *see also* Table 10-13 (reporting similar results); Ex.1002, ¶87.

B. Key Prior Art

1. *Fraser (Ex.1009)*

Fraser is titled "Single Injections of Vascular Endothelial Growth Factor Trap Block Ovulation in the Macaque and Produce a Prolonged, Dose-Related Suppression of Ovarian Function," and was published in the Journal of Clinical Endocrinology & Metabolism in November 2004, before the '865 patent's alleged March 2006 priority date. Ex.1009, 1114.

Fraser's study evaluated aflibercept's effect on ovarian angiogenesis. *Id.*, 1114. *Fraser* used an aflibercept formulation comprising the excipients recited in the challenged claims: "VEGF $Trap_{R1R2}$…was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." *Id.*, 1115. "Tween 20" is the brand name for polysorbate 20. Ex.1002, ¶¶88-90, 128; Ex.1102.[3]

[3] During prosecution of U.S. Patent No. 8,110,546 ("Dix"), Regeneron represented that *Fraser's* formulation used sucrose, not glycerol. Ex.1098, 2 (noting that the "actual lot and formulation used in Fraser" contained "24.3 mg/ml VEGF Trap protein, 5 mM phosphate, 5 mM citrate, 100 mM NaCl, 20% sucrose, and 0.1 % polysorbate-20, pH 6.05.").

Fraser reported that "VEGF was inhibited by administration of VEGF-Trap$_{R1R2}$, a recombinant, chimeric protein comprising Ig domain 2 of human VEGF-R1 and Ig domain 3 of human VEGF-R2, expressed in sequence with the human Fc." Ex.1009*,* 1115.

2. *Wulff (Ex.1016)*

Wulff is titled "Prevention of Thecal Angiogenesis, Antral Follicular Growth, and Ovulation in the Primate by Treatment with Vascular Endothelial Growth Factor Trap R1R2." Ex.1016. It was published in the journal Endocrinology in July 2002, before the '865 patent's alleged March 2006 priority date.

Wulff investigated the aflibercept's ability to inhibit thecal angiogenesis. *Id.*, 2798. *Wulff* noted that "[t]he VEGF Trap R1R2 used in these experiments is a recombinant chimeric protein comprising portions of the extracellular, ligand binding domains of the human VEGF receptors Flt-1 (VEGF-R1, Ig domain 2) and KDR (VEGF-R2, Ig domain 3) expressed in sequence with the Fc portion of human IgG (Fig. 1)." *Id*. *Wulff* further noted that "[t]he VEGF trap was expressed in CHO cells and was purified by protein A affinity chromatography followed by size-exclusion chromatography." *Id.*

Wulff discloses the same aflibercept formulation used in *Fraser*: "[c]ontrol animals were treated with vehicle containing 5mM phosphate, 5 mM citrate, 100 mM sodium chloride, 0.1% (wt/vol) Tween 20, and 20% (wt/vol) sucrose)." *Id.*

Wulff states that the *'319 Publication* (Ex.1029) discloses VEGF-Trap$_{R1R2}$'s structure: "the detailed molecular structure and how it was created are described in the patent REG 710-A-PCT, VEGF Trap Application published December 2000, Publication WO 00/75319 A1." *Id.*, n.1; Ex.1002, ¶¶91-94.

3. *Feb. 3 and 8, 2006 and March 8, 2006 Presentations ("2006 Presentations")*

Before the alleged priority date, on February 3, 8, and March 8, 2006, Regeneron gave a series of presentations reporting aflibercept's use in clinical trials to treat wet AMD. Ex.1011-13; Ex.1017.

Specifically, the 2006 Presentations teach that aflibercept could be the "best-in-class" treatment for wet AMD, with potentially "greater efficacy related to unique characteristics" and potentially "greater patient convenience/safety." *See, e.g.*, Ex.1012, 19. The presentations disclose that a "single intravitreal injection" of aflibercept showed "[r]apid, substantial, and prolonged (up to at least 4 weeks) reduction in retinal thickness," which treats wet AMD. *Id.*, 23. They also report that a Phase 2 trial was set to begin with a Phase 3 trial planned the following year. *See, e.g.*, Ex.1012, 23.

These presentations also teach that patients received intravitreal doses of 0.05, 0.15, 0.5, 1.0, 2.0, and 4.0 mg aflibercept. Ex.1011, 13-22, Ex.1012, 19-23, Ex.1013, 21-24. The February 3, 2006 presentation reports that the maximum tolerated dose has not yet been reached (0.05 to 4.0 mg) and that there were "no

ocular serious adverse events" and "no evidence of inflammation." Ex.1011, 14; *see also* Ex.1012, 19-23, Ex.1013, 21-24. It further reported the study "remains ongoing at 4 mg/eye dose level," and patients showed a "[r]apid, substantial decrease in retinal thickness." *Id*.; Ex.1012, 23. The March 8, 2006 presentation reported that the 4.0 mg dose had been completed and there was "[c]onfirmed evidence of biological activity." Ex.1013, 24; Ex.1002, ¶¶95-97.

4. *Container Closure Systems (FDA Guidance and Nayar)*

As of the priority date, vials and PFSs were among the known container/closure systems that could be used with protein-based therapeutics. Ex.1018, 4 Table 2. For instance, Chang 2002 lists "Vial/stoppers" and PFSs as options for "Container/closure" systems. Ex.1018, 6. In its 1999 Container Closure Guidance, the FDA specifically recommended packaging injectable formulations in vials. Ex.1038, 23-24; Ex.1031.

Similarly, at the time, POSAs understood that PFSs were convenient modes of administering formulations, including intravitreal formulations, because they eliminate the step of withdrawing liquid from the vial and into a syringe. *Nayar,* titled "High Throughput Formulation: Strategies for Rapid Development of Stable Protein Products, published in Rational Design of Stable Protein Formulations 177, 183 (J.F. Carpenter & M.C. Manning eds., 2002) ("Nayar 2002") explains that each dosage form "offers various advantages and disadvantages, in the speed of

development, manufacturing, packaging and shipment logistics, and in administration of the product to the patient." Ex.1020, 183; Ex.1005, ¶¶38-42. It also explains that the "most preferred" dosage form for a therapeutic protein product was "a solution formulation that is typically stored in the refrigerator and preferably in a pre-filled syringe." *Id*., 183; Ex.1005, ¶41.

As of the priority date, there were two FDA approved intravitreal preparations. One (Macugen) was supplied in a PFS, and the other (Vitravene) was supplied in a vial. Ex.1045, 1; Ex.1046, 9; Ex.1005, ¶42; Ex.1002, ¶¶98-100.

5. *'319 Publication* (Ex.1029)

WO 00/75319 A1 ("*'319 Publication"*/"Papadopoulos") is a PCT publication published on December 14, 2000, before the '865 patent's alleged March 2006 priority date.

The *'319 Publication* teaches "Flt1 receptor polypeptides that have been modified in such a way as to improve their pharmacokinetic profile." Ex.1029*,* 1:14-16; 10:3-4. It discloses the development of aflibercept in more detail, including expression in CHO cells. *See id.*, Examples 17-21. It refers to aflibercept as VEGFR1R2-FcΔC1(a), which Regeneron represented is another name for VEGF-Trap$_{R1R2}$. Section VI.A.2. It also discloses the amino acid sequence and structure of VEGFR1R2-FcΔC1(a). Ex.1029, 11:14-12:1, 15:19-27, Fig. 24A-24C; Ex.1002, ¶¶101-102.

6. *'309 Publication* (Ex.1027)

U.S. Patent Application Publication No. 2004/0265309 (*'309 Publication*) published on December 30, 2004, before the '865 patent's alleged March 2006 priority date.

The *'309 Publication* discloses that VEGFR1R2-FcΔC1(a) is "also termed $VEGFTrap_{R1R2}$" and discloses its amino acid sequence. Ex. 1027, ¶5, SEQ ID NOs: 1 and 2. The *'309 Publication* also points the skilled artisan to the *'319 Publication* for "a complete description of VEGF-receptor based antagonists including VEGFR1R2-FcΔC1(a)" and incorporates the *'319 Publication* "by reference in its entirety." *Id.*, ¶22; Ex.1002, ¶¶103-104.

VII. DETAILED GROUNDS FOR INVALIDITY: GROUND 1

A POSA would have found the claimed intravitreal formulation obvious. It would have been obvious to a POSA to modify the Fraser/Wulff formulation to produce a formulation suitable for intravitreal injection, and this formulation meets all of the Challenged Claims.

A. The Modified Fraser/Wulff Formulation

A POSA reading the 2006 Presentations, which discuss successfully using intravitreal aflibercept injections to treat angiogenic eye disorders, would have been motivated to develop an intravitreal aflibercept formulation. Ex.1002, ¶106; Ex.1005, ¶¶43-48. Despite the fact the Presentations do not disclose a specific aflibercept formulation, a POSA would not have had to start from scratch.

First, the Presentations disclose successful dosing amounts, including a maximum dose of 4 mg. *See, e.g.*, Ex.1011, 14; *see also* Ex.1012, 19-23, Ex.1013, 21-24. The Presentations describe these doses as effective in achieving a "[r]apid, substantial, and prolonged (up to at least 4 weeks) reduction in retinal thickness"—necessary to treat wet AMD. Ex.1011, 15; Ex. 1012, 20; Ex.1013, 22. They also explain that a Phase 2 trial was set to begin and a Phase 3 trial also was planned. Ex.1013, 22, 24. A POSA would have been motivated to select the known maximum tolerated dose (4 mg) to treat wet AMD.

For the remaining excipients, a POSA would have used as a starting point the intravenous formulation described in Fraser and Wulff. Ex.1002, ¶¶106-131; Ex.1005, ¶¶43-48. Fraser and Wulff describe the only known aflibercept formulation in the prior art: an intravenous formulation containing 24.3 mg/ml aflibercept, a buffer of 5 mM phosphate[4] and 5 mM citrate, 100 mM NaCl (pH 6.0)), and 0.1% wt/vol Tween 20 (polysorbate), with 20% sucrose. Ex.1009, 1115; Ex.1016, 2798. This formulation would have been a natural starting point for a POSA. Ex.1002, ¶¶107-109.

[4] As Dr. Forrest explains, a POSA would have understood that a sodium phosphate buffer was used because this was most commonly used phosphate buffer at the time. Ex.1002, ¶108, n.4; Ex.1005, ¶¶35-36.

A POSA starting from a 4 mg dose and the Fraser/Wulff formulation would have understood three obvious modifications were necessary to obtain an intravitreal preparation. Ex.1002, ¶¶109-130. As set out below on a claim-by-claim basis, these modifications result in a formulation that meets the Challenged Claims.

First, a POSA would have been motivated to select an injection volume of 0.1 mL, resulting in a 40 mg/mL concentration. Ex.1002, ¶129. While Fraser and Wulff teach 2 mL aliquots, a POSA would have understood that this volume is far too large for the human eye, for which 0.1 mL was known to be the maximum safe injection volume. Ex.1005, ¶¶23-37; Ex.1002, ¶111; Ex.1009, 1115; Ex.1016, 2798. The most common intravitreally injected drug at the time was given in volumes of 0.1 mL. Ex.1005, ¶¶23-26.

Selecting the known, safe 0.1 mL injection volume and a 4 mg dose leads to a 40 mg/mL concentration (4 mg in 0.1 mL of volume). Ex.1002, ¶112. This is consistent with the volume and concentration of the most common intravitreally injected drug at the time, Kenalog, and was the maximum known, safe tolerated concentration for an intravitreal injection. Ex.1005, ¶¶23-26, 31; Ex.1002, ¶112.

Second, a POSA would have been motivated to reduce the 20% sucrose content of the Fraser and Wulff formulation to below 10%. The Fraser/Wulff formulation had a high concentration of dissolved particles in the fluid (*i.e,* osmolarity), particularly due to its high sucrose content (20% wt/vol). Ex.1002,

¶¶121-126; Ex.1005, ¶43-48. Injecting the unmodified Fraser/Wulff formulation into the eye would have caused concentration of particles in the eye's vitreous fluid to increase, and the eye would have sought to compensate by drawing water in from surrounding tissues, including the retina, to reduce the concentration, risking substantial patient discomfort and significant damage. Ex.1005, ¶¶19-22. A POSA would have been motivated to match the formulation's concentration of dissolved particles to that of the eye to avoid this. *Id*.; Ex.1002, ¶123.

More specifically, the osmolality of the human eye is around 288-323 mOsm.[5] Ex.1005, ¶¶19-22; Ex.1103, 456. Accordingly, intravitreal injections at the time were typically formulated to match the osmolality of the vitreous humor (i.e., to be iso-osmotic). Ex.1005, ¶22; Ex.1002, ¶115 ("osmolarity of two primary FDA-approved intravitreal preparations were known: Macugen, supplied in a PFS with an osmolality of roughly 280-360 mOsm, and Vitravene, supplied in a vial with an osmolality of roughly 290 mOsm"); Ex.1045, 2; Ex.1041, 126. POSAs understood that ensuring a formulation is iso-osmotic improves patient comfort and helps preserve the eye's physiological balance, reducing the risk of side effects and unintended outcomes. Ex.1005, ¶¶19-22.

[5] Osmolality is a measure of the dissolved particles relative to weight and osmolarity is a measure of the dissolved particles relative to volume. Ex.1005, ¶19.

The Fraser/Wulff formulation has an osmolarity far outside this range—a total osmolarity of above 800 mOsm. Ex.1002, ¶¶117-122; Ex.1099, ¶36; Ex.1100, 308; Ex.1102, 1. This would not have been considered safe for intravitreal injection, and likely would have drawn water out of cells around the eye, leading to dehydration of those cells, cell shrinkage, and tissue damage to delicate ocular structures like the retina. Ex.1005, ¶19-22; Ex.1042, 3; Ex.1044, 60; Exs.1050-1057.

Of the components of the Fraser/Wulff formulation, the sucrose contributes by far the most to the high osmolarity value (sucrose accounts for nearly three-fourths of the total osmolarity). Ex.1002, ¶¶117-124. Accordingly, the only way to obtain an iso-osmotic formulation and avoid the attendant physiological risks is to reduce the sucrose concentration. *Id.* As a first step, sucrose must be reduced to at least below 10%, but that is not sufficient. Ex.1002, ¶¶117-125. In addition, it is necessary to either further reduce the sucrose concentration (for example, to around 5%) or reduce the concentration of another component. After sucrose, NaCl has the next highest contribution to osmolarity, so reducing NaCl would have been the obvious alternative choice. Ex.1002, ¶¶125-126. This would have approximated the osmolality of the human eye, and, relatedly, approximated the ranges of the FDA approved intravitreal formulations. Ex.1002, ¶¶125-126. This would have been a matter of routine optimization, and no matter how the POSA proceeds with this

further optimization, the resulting solution practices the claims as set out further below. *See generally* Ex.1002, ¶¶106-126.

The Fraser/Wulff formulation has a pH of pH 6.0, and the modified formulation would likewise have this pH. However, as Dr. Forrest explains, a POSA would have been motivated, as a matter of routine optimization, to make and test the Modified Fraser/Wulff formulation at a range of pH values, including at pH values of 6.1-6.3, in order to determine the effect of pH variation on the formulation. Ex.1002, ¶127. That is because, due to standard measurement error and variations in commercial manufacture, the pH of a formulation will vary to some degree. *Id.* It would be standard practice to make sure that a formulation can withstand small variations in pH to ensure stability for commercial manufacture. *Id.* It thus would have been obvious to adjust the pH of the Modified Fraser/Wulff formulation to 6.1, 6.2 or 6.3 as part of this work. *Id.*

Finally, a POSA would select a presentation for the formulation. There were two known presentations for intravitreal formulations at the time—a vial and a PFS. Both had known benefits. A POSA would have been motivated to use either presentation, consistent with the intravitreal formulations on the market at the time, which were presented in vials and PFSs. While vials are generally simpler to develop, PFSs are generally more commercially desirable. *See generally* Ex.1002, ¶¶128-129; Ex.1005, ¶38-42.

Following the modifications required to develop the Fraser/Wulff formulation for intravitreal use would lead to a 0.1 mL vial or PFS consisting of aflibercept in a 40 mg/mL concentration, with 10% or less sucrose stabilizer, 5 mM sodium phosphate buffer, 5 mM citrate buffer and 0.1% wt/vol polysorbate. Ex.1002, ¶¶128-129. A POSA would have expected this formulation to succeed as an intravitreal injection—aflibercept had been successfully injected in the amount in question, and the remainder of the excipients were common ingredients used in other intravitreal injections within ranges known to be tolerated by the human eye. *See generally* Ex.1002, ¶¶130-131.

B. Claim 1

1. A vial comprising an ophthalmic formulation suitable for intravitreal administration that comprises:

A POSA would have been motivated to develop an aflibercept formulation suitable for intravitreal administration based on the 2006 Presentations, which describe successfully using aflibercept intravitreal injections to treat angiogenic eye disorders. Ex.1002, ¶132.

As set out above and further below for each relevant limitation, a POSA would have been motivated to make a set of obvious modifications to the Fraser/Wulff formulation to make it suitable for intravitreal administration: reducing the volume to 0.1 mL (the known safe and tolerated intravitreal dose), selecting the maximum

tolerated dose of 4 mg described in the 2006 Presentations (resulting in a 40 mg/mL concentration), and reducing the osmolarity to match that of the eye. Ex.1002, ¶133.

Finally, it would have been obvious to use a vial to store the Modified Fraser/Wulff formulation. Ex.1002, ¶134. Neither Fraser nor Wulff explain how the formulation was stored. An ophthalmic formulation of course must be packaged in some type of container. Vials are well known and commonly used, so it would have been obvious to use a vial. Ex.1018, 6; Ex.1038, 23-24. Vials were one of two common presentations for intravitreal formulations; as of the priority date, of the two approved intravitreal preparations, one (Macugen) was supplied in a PFS, and the other (Vitravene) was supplied in a vial. Ex 1045, 1; Ex.1046, 9; Ex.1005, ¶38; Ex.1002, ¶135. And the FDA's 1999 specifically recommended packaging injectable formulations in vials. Ex.1038, 23-25; Ex.1002, ¶136; Ex.1018, 6.

Finally, to the extent limiting, a POSA would have understood the Modified Fraser/Wulff formulation was "suitable for intravitreal administration." The 2006 Presentations teach that 4 mg aflibercept could be safely injected. *See, e.g.*, Ex.1011, 14; Ex.1005, ¶¶47-48; Ex.1002, ¶137; *see also* Ex.1012, 19-23, Ex.1013, 21-24. Further, the volume of the Modified Fraser/Wulff formulation was known to be safe, and the excipients in the formulation were commonly used in intravitreal injections. Ex.1005 ¶¶24-26, 29-37, 46-48.

2. a vascular endothelial growth factor (VEGF) antagonist

The Modified Fraser/Wulff formulation includes a VEGF antagonist (aflibercept). Ex.1009, 1115; Ex.1016, 2798; Ex.1002, ¶138.

3. an organic co-solvent

The Modified Fraser/Wulff formulation contains 0.1% wt/vol of an organic co-solvent (polysorbate 20). Ex.1009, 1115; Ex.1016, 2798; Ex.1002, ¶139.

4. a buffer

The Modified Fraser/Wulff formulation contains 5 mM phosphate buffer and 5 mM citrate buffer. Ex.1009, 1115; Ex.1016, 2798; Ex.1002, ¶140.

Dr. Forrest further explains that while citrate buffers had been used in intravitreal formulations (Ex.1002, ¶108; Ex.1005, ¶¶44-45), a POSA would have considered it a matter of routine optimization to replace the 5 mM citrate buffer with another 5 mM of phosphate buffer for simplicity and to match the more commonly used intravitreal formulations. This meets the claim element as well; the claim does not specify a particular buffer.

5. a stabilizing agent

The Modified Fraser/Wulff formulation contains a stabilizing agent (sucrose). Ex.1009, 1115; Ex.1016, 2798; Ex.1002, ¶141.

6. wherein said VEGF antagonist fusion protein is glycosylated and comprises amino acids 27-457 of SEQ ID NO:4

A POSA would have understood that the aflibercept used in the Modified Fraser/Wulff formulation is glycosylated and comprises amino acids 27-457 of SEQ ID NO:4.

The sequence and glycosylation of aflibercept were known in the art at the time. Ex.1007, ¶¶18-36. In particular, Wulff explains that aflibercept (referred to as "VEGF Trap" or "VEGF Trap R1R2") was "a recombinant chimeric protein comprising portions of the extracellular, ligand binding domains of the human VEGF receptors Flt-1 (VEGF-R1, Ig domain 2) and KDR (VEGF-R2, Ig domain 3) expressed in sequence with the Fc portion of human IgG (Fig. 1)." Ex.1016, 2798.

While Wulff does not disclose aflibercept's sequence, it refers directly to the '319 Publication as explaining aflibercept's "detailed molecular structure and how it was created." *Id*. The '319 Publication discloses aflibercept's amino acid sequence. Ex.1029, 11:14- 12:1, 15:19-27, Fig. 24A-24C; *see also* Ex. 1080, 89, SEQ ID No. 10; *see also* Ex. 1081, [0085], Example 20. The sequence recited in the claim (amino acids 27-457 of SEQ ID NO:4) is the same aflibercept amino acid sequence disclosed in the '319 Publication. Ex.1007, ¶¶18-36.

Although Wulff does not expressly teach glycosylated aflibercept, Wulff does teach that "[t]he VEGF trap was expressed in CHO cells…." Ex.1016, 2798. The '319 Publication also teaches that aflibercept was expressed in CHO cells. *See*

Ex.1029, Examples 17-21; Ex.1016, 2798; Ex.1007, ¶¶18-36. It was well-known by the priority date that when aflibercept is expressed in a CHO cell it will be glycosylated, and more specifically that it will be glycosylated at five asparagine residues: 62, 94, 149, 222 and 308. Ex.1039, [0013], [0064], Example 8, 8; Ex.1007, ¶¶23-36.

For example, Daly discloses the same aflibercept sequence (SEQ ID NO:8 (amino acids 27-457)) as the '319 Publication, and Daly teaches that when SEQ ID NO:8 is expressed in a CHO cell, it "***is glycosylated at Asn residues 62, 94, 149, 222 and 308***." Ex.1039, [0013] (emphasis added). Daly's Example 8 teaches that aflibercept expressed in CHO cells was "analyzed further to determine glycosylation patterns and oligosaccharide content." *Id*, at [0064]. The results showed that aflibercept was "glycosylated at the Asn residues of positions 62, 94, 149, 222, and 308." *Id.*; *see also* [0080-0084].

Moreover, as Dr. Zhou explains, even if the aflibercept glycosylation sites were not known, the POSA would have understood from the aflibercept sequence that expressing it in a CHO cell would result in a protein glycosylated at those five sites. Ex.1007, ¶¶26-36. When proteins are expressed in CHO cells, they are glycosylated at specific locations in particular repeating patterns ("motifs") of amino acids. *Id*.; Ex.1086, 688-689; Ex.1087, 1867; Ex.1088, 13. The asparagine residues at positions 62, 94, 149, 222, and 308 in the aflibercept sequence

are part of those known motifs, so the POSA would expect aflibercept to be glycosylated at those five sites. Ex.1007, ¶¶23-36; Ex.1002, ¶142.

7. wherein at least 98% of the VEGF antagonist is present in native conformation following storage at 5 °C. for two months as measured by size exclusion chromatography

(a) The stability limitations are inherent

The Modified Fraser/Wulff formulation also would have had the claimed stability characteristics (percent "native conformation" of the protein and turbidity). A formulation's stability is a product of the interaction between its active ingredient, excipients, and storage conditions. Thus, it is a property of the formulation. Ex.1002, ¶¶143-148.

While the Modified Fraser/Wulff formulation's stability was not taught in the art, it is "the natural result of the combination of elements explicitly disclosed by the prior art" and inherency can be used to supply a missing limitation in such a situation. *PAR*, 773 F.3d at 1195-96; Ex.1002, ¶¶143-148. Testing a formulation for stability does not make that formulation patentable: "the identification and characterization of a prior art material also does not make it novel." *In re Crish*, 393 F.3d at 1258. Indeed, a long line of cases confirms that one cannot establish novelty by claiming a known or obvious composition by its properties. *See e.g.*, *In re Spada,* 911 F.2d 705, 708 (Fed. Cir. 1990) ("The discovery of a new property or use of a previously known composition, even when that property and use are unobvious from

prior art, cannot impart patentability to claims to the known composition."); *Titanium Metals Corp. of Am. v. Banner*, 778 F.2d 775, 782 (Fed. Cir. 1985) (composition claim reciting a newly discovered property of an old alloy did not satisfy section 102 because the alloy itself was not new); *In re Pearson*, 494 F.2d 1399, 1403 (CCPA 1974) (intended use of an old composition does not render composition claim patentable); *In re Benner*, 36 C.C.P.A. 1081, 174 F.2d 938, 942 (1949) ("no provision has been made in the patent statutes for granting a patent upon an old product based solely upon discovery of a new use for such product").

Where a Patent Owner claims a prior art composition and specifies a particular characteristic of that composition not expressly disclosed in the prior art, "the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product." *In re Best*, 562 F.2d at 1255 (where a prior art composition is identical or substantially identical in structure or composition to a claimed one, a prima facie case of either anticipation or obviousness has been established with respect to claims directed to the properties of the claimed composition).

Here, Patent Owner claims the result of storing the Modified Fraser/Wulff formulation for a standard time and at a typical temperature. If storing an obvious composition and measuring the resulting percent native conformation (or turbidity)

can produce a patentable claim, then any and all compositions can be stored and measured for "new" properties and thereby made novel.

Further, Regeneron cannot show the stability of the Modified Fraser/Wulff formulation was not inherent. Another Regeneron patent, Dix,[6] teaches that the original (unmodified) Fraser/Wulff formulation had the claimed stability, as shown in the chart below.

	VEGF Trap	**Buffer**	**Tonicity**	**Co-solvent**	**Stabilizing agent**	**pH**	**Stability**
Dix Example 5	25 mg/mL	5 mM phosphate 5 mM citrate	100 mM NaCl	0.1% polysorbate 20	20% sucrose	6.0-6.1	99.6% at two months

Ex.1002, ¶144.

Also, based on the '865 patent disclosure, the Modified Fraser/Wulff formulation would have the requisite stability. Ex.1002, ¶145. The '865 patent examples teach formulations with a range of aflibercept and excipient concentrations and their stability characteristics. *Id.* The patent teaches that formulations with varying concentrations of aflibercept, with varying concentrations of NaCl, with

[6] U.S. Patent No. 8,110,546 ("Dix") issued on February 7, 2012 with an earliest effective priority date of March 25, 2005. Similar to the '865 patent, Dix discloses several aflibercept formulations and their stability characteristics. *See*, Ex.1021, Examples 1-5.

varying concentrations (and types) of co-solvent, with varying amounts of stability agent, and over the pH range 6.25-6.3 all have two month stability values well over 98%. *See* Ex.1001, 6-8; Ex.1002, ¶145. The Modified Fraser/Wulff formulation[7] falls squarely within these ranges, making it, at a minimum, a species of the described genre.

	VEGF Trap	**Buffer**	**Tonicity**	**Co-solvent**	**Stabilizing agent**	**pH**	**Stability**
'865 Examples	20-50 mg/mL	5-10 mM phosphate	20-135 mM NaCl	0.015-0.1% polysorbate 20 or 3% PEG 3350	0-5% sucrose	6.25-6.3	98.5-99.3% at 2-3 months
Modified Fraser/ Wulff	40 mg/mL	5 mM phosphate 5 mM citrate	100 mM NaCl	0.1% polysorbate	5% sucrose	6.0-6.3	

Ex.1002, ¶145.

As shown below, Dix provides stability data for even more formulations with different excipients and concentrations. The Dix formulations with 50 mg/mL or

[7] As explained above, to obtain an acceptable osmolarity in the Modified Fraser/Wulff formulation, the POSA would first reduce the sucrose to around 10% and then would either further reduce the sucrose to around 5% or would reduce the NaCl. In this chart and those that follow, the Modified Fraser/Wulff formulation has 5% sucrose.

less aflibercept have two to three month stability values well over 98%, just like the '865 formulations. The only formulations that did not achieve that stability had 75 mg/mL or 100 mg/mL aflibercept.

	VEGF Trap	Buffer	Tonicity	Co-solvent	Stabilizing agent	pH	Stability
Dix (50 mg/mL or less)	25-50 mg/mL	10 mM phosphate or 5 mM phosphate and 5 mM citrate	50-100 mM NaCl	0.1% polysorbate or 3% PEG 3350	20% sucrose	6.0-6.25	98.8-99.6 % at 2-3 months
Dix (75 mg/mL or more)	75-100 mg/mL	10 mM phosphate or 20 mM histidine	0-50 mM NaCl	0.1% polysorbate or 1.5-3% PEG 3350	20% sucrose or 2.5% sucrose and 0.75% glycine	6.25	95.7-98.6 % at 2-3 months
Modified Fraser/ Wulff	40 mg/mL	5 mM phosphate 5 mM citrate	100 mM NaCl	0.1% polysorbate	5% sucrose	6.0-6.3	

Ex.1002, ¶145.

The Modified Fraser/Wulff formulation falls well within the ranges of formulations tested in the '865 patent and Dix that achieve better than 98% stability at two months, which shows that the Modified Fraser/Wulff formulation will have the claimed stability. Ex.1002, ¶146. This is confirmed by the fact that the '865 Patent does not teach a POSA how to achieve the recited stability other than by simply making and testing the formulation. Patent Owner cannot contest that a formulation falling within the set of Examples provided to show written description support would not have the claimed stability. If that were the case, the claims would

lack sufficient written description support. Patent Owner should not be allowed to rely on the minor variations between the Modified Fraser/Wulff formulation (which meet the claims) and the precise Examples in the patent to prevent a finding of inherency.

Patent Owner may argue that variations in certain unclaimed elements between the patent examples and the Modified Fraser/Wulff formulation prevent a finding of inherency (such as pH, NaCl concentration, or a citrate buffer). But Dr. Forrest explains why a POSA would understand that, based on standard industry principles, the Modified Fraser/Wulff formulation would have the recited stability even with those differences. Ex.1002, ¶¶148-156.

It is common in the industry to perform stability testing on formulations with varying excipients in varying concentrations over a range of pH values in order to establish a range around the eventual formulation. Not every value can be tested, so a range of discrete points is tested instead. *Id*. It is important for POSAs to establish stability over a range of variations because there will inevitably be measurement variations or variations in concentrations and amounts during commercial manufacture. *Id*. It is commonly accepted that a formulation falling within these ranges will have the established stability of the tested formulations. *Id*.

(b) The claimed stability is obvious

Further, a POSA would have been motivated to make the Modified Fraser/Wulff formulation as stable as possible and would have regarded achieving the stability recited in the claims as obvious. Ex.1002, ¶¶148-156. A POSA would have been motivated to maximize stability. The more stable a formulation is, the longer its "shelf life." Ex.1002, ¶¶149-150. A POSA would have understood a longer shelf life to be more desirable, in general, because it would result in fewer discarded doses due to product expiration. *Id.*

Consistent with this goal, a POSA would have been motivated to reduce the aggregation (and associated turbidity) of aflibercept in the formulation as much as possible. Ex.1002, ¶151. Aggregates can cause undesirable immunogenicity and can reduce the quality and activity of a biologic product. *Id.* To accomplish this goal, a POSA would start with as pure a product as possible and then maintain that purity over time. *Id*. Indeed, Wulff and Fraser discuss purifying the formulation. Ex.1016, 2798.

A POSA thus would have been motivated to obtain a formulation with at least 98% of the aflibercept in native conformation after storage for two months at 5º C as measured by SEC (with 99% or more even more desirable). Ex.1002, ¶153. A POSA would have accomplished this by formulating the Modified Fraser/Wulff formulation and then engaging in routine SEC stability testing which, as the patent

itself shows, would have demonstrated the formulation met and exceeded the 98% threshold after storage for two months at 5º C. *Id.*

Moreover, even if the POSA initially achieved a lower level of stability the POSA would have had a reasonable expectation of success in obtaining the recited stability by making minor optimizations to the formulation, including modifying pH or the buffer. Ex.1002, ¶154. POSAs possessed a high degree of skill in stabilizing protein therapeutics. *Id.*

To the extent Patent Owner argues that including unclaimed excipients (5 mM citrate or NaCl) would have changed the stability or that the pH of the formulation differs from the patent examples, a POSA would have been able to make incremental adjustments to the concentrations/pH and observed their impact on stability, adjusting to achieve at least the level recited in the claims. *Id.* Such experiments were routine and well within ordinary skill, and "step-by-step, how-to" protocols to "enable the formulation scientist to proceed through a protein solution formulation development study" were available. Ex.1002, ¶155; Ex.1013, 156, 157 (teaching detailed three-step protocol that sets forth the "natural sequence to the order in which individual [formulation] parameters are investigated" and how to investigate them); *see E.I. Dupont de Nemours v. Synvina C.V.*, 904 F.3d 996, 1006 (Fed. Cir. 2018) (routine experiments that may be required to determine the optimum concentrations

of ingredients in an otherwise old or obvious formulation does not make the optimized formulation inventive).

In fact, the '865 patent assumes that such optimization is well within a POSA's ability. Ex.1002, ¶156. The patent broadly claims formulations containing varying amounts of a wide variety of VEGF antagonist proteins, organic co-solvents, buffers, and stabilizers, but only discloses a relative handful of specific embodiments in the examples, each of which contain polysorbate 20 or polyethylene glycol 3350, phosphate buffer and sucrose. *Id.* The patent assumes a POSA can adjust the specific amounts of these ingredients—and a broad range of others that fall within the claims—to achieve the claimed level of stability. *Id.* All a POSA would have had to do to arrive at the claimed invention would be to apply the very same routine adjustments required by the '865 patent to the prior art. That is not inventive.

Furthermore, Patent Owner cannot show—because the '865 patent itself does not support it—that the claimed stability limitations were unexpected. *See, e.g.*, *Southwire Company v. Cerro Wire LLC*, 870 F.3d 1306 (Fed. Cir. 2017) (affirming an obviousness finding because the prior art disclosed the identical process steps, and although the prior art did not quantify the amount of force reduction, the patentee had not produced any evidence that a 30% reduction was unexpected).

C. Claim 2

Dependent claim 2 is obvious for the same reasons as claim 1. Claim 2 recites a 40 mg/mL concentration and specifies the organic co-solvent comprises polysorbate. As set out above in Section VII.A, the Modified Fraser/Wulff formulation contains 40 mg/ml aflibercept, and the organic co-solvent in that formulation comprises polysorbate. Specifically, a POSA would have been motivated to make two modifications to the Fraser/Wulff formulation leading to the recited concentration:

Reduce the volume to 0.1 mL. As described in Fraser, the formulation was stored in 2 mL aliquots. A POSA would have understood that 2 mL was far too large an injection volume for the human eye, as Dr. Lefkowitz explains. Ex.1005, ¶¶23-26.

Instead, the 0.1 mL injection volume was understood to be safe, and indeed was the most commonly used intravitreal injection volume. As taught in the art, "intravitreous injection of a small volume (such as 0.01 ml or less) represent[ed] a much more reasonable approach for drug administration" than injections of larger amounts. Ex.1049, 106; see also Ex.1048, 932; Ex.1005, ¶¶22-26. The most common intravitreal injection at the time, triamcinolone (Kenalog), was administered in a 0.1 mL dose (at a concentration of 40 mg/mL). Ex.1005 ¶¶23-26, 31; Exs.1058-1067, 1078, 1094, 1095.

A POSA would have been motivated to select the commonly accepted and safe 0.1 mL injection volume for intravitreal injection of the Modified Fraser/Wulff formulation.

Set the concentration at 40 mg/mL. The 2006 Presentations report a dose escalation study with a maximum dose of 4 mg. *See, e.g.*, Ex.1011, 14; *see also* Ex.1012, 19-23, Ex.1013, 21-24. The Presentations teach that the formulation was effective and that the maximum safe tolerated dose had not been reached. Ex.1011-1013. A POSA would have understood from this disclosure that the 4 mg dose was safe and effective and would have been motivated to use it. Ex.1005, ¶¶23-26.

A POSA would have been motivated to select this dose for a second reason. Using a 0.1 mL injection volume and 4 mg dose leads to a concentration of 40 mg/mL. As Dr. Lefkowitz explains, 40 mg/mL was a commonly used concentration for intravitreal injections and was generally accepted as the upper limit for safe intravitreal injections. Ex.1005, ¶¶23-26. A number of approved intravitreal drugs and drugs in clinical trials as of March 2006 used a 40 mg/mL concentration. *Id.*,

¶¶24-25, 31.

A POSA would have been motivated to use as a high concentration as possible in an effort to lengthen the time between any repeat injections. Ex.1005, ¶26. Intravitreal injections were understood to carry significant risks at the time, including the risk of endophthalmitis, a known complication of intravitreal

injections. *Id.* Given these risks, a POSA would have been motivated to minimize the number of injections a patient would have to undergo. By injecting a higher concentration, a POSA would have expected that injections could potentially be given less frequently. *Id.*; Ex.1002, ¶¶158-164. And as explained above, 40 mg/mL was known to be the upper limit for intravitreal injections.

D. Claims 3-5

Dependent claims 3-5 are obvious for the same reasons as claims 1 and 2. These claims recite the organic co-solvent is polysorbate in various ranges from 0.01% to 3%. The Modified Fraser/Wulff formulation contains an organic co-solvent—polysorbabe 20—present at 0.1% wt/vol, rendering claims 3-5 obvious. Ex.1009, 1115; Ex.1016, 2798; Ex.1002, ¶165.

E. Claims 6-7

Dependent claims 6-7 are obvious for the same reasons as claims 1 and 5. These claims recite that the buffer is a phosphate buffer and specify that the buffer comprises 5-25 mM buffer. The Modified Fraser/Wulff formulation contains a 5 mM phosphate buffer, rendering claims 6-7 obvious. Ex.1009, 1115; Ex.1016, 2798; Ex.1002, ¶166.

F. Claims 8-9

Dependent claims 8-9 depend from claim 5. Claim 8 requires that the buffer comprises a pH between "about 5.8-7" and claim 9 requires a pH of "about 6.2-6.3."

Fraser discloses that the pH of the unmodified formulation is 6.0, which falls within the range recited in claim 8. As Dr. Forrest explains, a POSA would have understood that the measured pH of 6.0 falls within the "***about*** 6.2-6.3" range recited in claim 9. Ex.1002, ¶¶167-173.

First, "about 6.2-6.3" must be broader than the recited range of 6.2-6.3. Otherwise the term "about" would be superfluous. *See Modine Mfg. Co. v. United States Int'l Trade Comm'n*, 75 F.3d 1545, 1554 (Fed. Cir. 1996); *Britesmile, Inc. v. Discus Dental, Inc.*, 2005 WL 6225190 (N.D. Cal 2005). Specifically, "about" means "approximately" in a patent claim and takes into account the level of precision available to those working in the art and the scientific and technical background at the time. *Id.* It does not generally encompass a precise limit. *Id*. A POSA would have understood that measurement error for pH meters at the time ranged from +/- 0.1-0.2 pH units and thus would have understood "about 6.2" to encompass at least a 6.0 pH. Ex.1002, ¶169; *see generally* Ex.1104; Ex.1105; *see also* Ex.1106, 1845-1846; Ex.1107, 1; Ex.1108, 3. Because the measurement error ranged from +/- 0.1-***0.2*** pH, a POSA would have understood that the measured pH of 6.0 described in Fraser corresponds to an actual pH 6.0 +/- 0.2 (*i.e.,* 5.8-6.2). *Id.* Thus, the measured pH of 6.0 disclosed in Fraser is "about 6.2-6.3" as required by claim 9.

The '865 patent examples confirm that the measured pH may vary by +/- 0.1-0.2 pH units, including over time. Ex.1002, ¶170. Each example specifies the pH

of the formulation, and then the pH is measured over time, starting at 0 months and then again following storage. In the chart below, the specified pH is shown on the left, and the measured pH is shown on the right.

Example	pH disclosed in the Example	Measured pH range
1	6.25	6.2-6.3
2	6.25	6.1-6.3
3	6.3	6.2-6.4
4	6.3	6.3-6.4
5	6.3	6.2-6.3
6	6.3	6.3
7	6.3	6.2-6.3
8	6.3	6.2-6.3

Ex.1002, ¶170.

As shown in the chart above, the formulations described as having pHs of 6.25-6.3 had measured pHs of 6.1-6.4. Ex.1002, ¶171. For instance, Example 2 describes the formulation as having a pH of 6.25, but the measured pH varies between 6.1 and 6.3. *Id.* Similarly, Example 3 specifies that the pH is 6.3, but the measured pH varies between 6.2 and 6.4. *Id.*

In view of the above, a POSA would understand that a formulation with a pH of 6.25, right in the middle of the recited range, can have a measured pH of between

6.1 and 6.3. Similarly, a solution with a pH of 6.3 can have a measured pH of 6.2-6.4. In view of the fluctuation taught in the patent and inherent in the measurement tools available at the time, the POSA would have understood a pH of 6.0 to fall within the scope of "about 6.2-6.3." Ex.1002, ¶172.

Further, as explained above, a POSA would have been motivated, as a matter of routine optimization, to make and test the Modified Fraser/Wulff formulation at both higher and lower pHs, including pH values of 6.1-6.3, in order to determine the formulation's tolerance to pH changes. Ex.1002, ¶173. Doing so would yield the claimed formulation. The 6.2 and 6.3 pH values fall squarely in the claimed range. Because "about 6.2 to 6.3" must include values outside that range, "about 6.2 to 6.3" must encompass a pH of 6.1. *E.g.*, *Allergan, Inc. v. Sandoz Inc.,* 796 F.3d 1293, 1311 (Fed. Cir. 2015) ("Moreover, if 'about 7.3' is to mean anything other than 7.3, it is not clearly erroneous for it to include a value that differs from it by only one decimal place."). Thus, it would have been obvious to make the Modified Fraser/Wulff formulation with the pH recited in claim 9.

G. Claims 10-11, 19-20

These claims are obvious for the same reasons as claims 1 and 5. Dependent claims 10-11 and 19-20 recite that the stabilizing agent is a sugar, including sucrose (and not containing trehalose), and further specify sucrose in the range of 1-10% sucrose. Ex.1002, ¶¶174-176.

As set out above, the POSA would have been motivated to use the Fraser/Wulff formulation as a starting point. *Id.* A POSA would have been motivated to modify that formulation for intravitreal administration by reducing the amount of sucrose to achieve an iso-osmotic solution in order to minimize the chance of causing an adverse reaction, including damage to the retina or surrounding tissues. *Id.*

The Modified Fraser/Wulff formulation contains sucrose at a concentration between 1-10%, as described above, rendering these claims obvious. Ex.1009, 1115; Ex.1016, 2798; Ex.1002, ¶¶174-176.

H. Claim 12

Claim 12 is rendered obvious for the same reasons as claims 1 and 5. Dependent claim 12 specifies that the stabilizing agent comprises 1-7.5% sucrose. Ex.1002, ¶¶177-178.

As explained above, a POSA would have been motivated to modify the Fraser/Wulff formulation for intravitreal administration by reducing sucrose to achieve an iso-osmotic solution. Section VII.A. A POSA would have first reduced the sucrose concentration to below 10% and further decreased the sucrose or NaCl concentration to approximate the osmolality of the human eye. *Id.* Choosing to reduce sucrose further (*e.g.*, to 5%) to obtain an iso-osmotic solution would have been a matter of routine optimization, rendering claim 12 obvious. *Id.*

I. Claims 14, 22

These claims are obvious for the same reasons as claims 1, 5. They specify that the VEGF antagonist fusion protein is glycosylated at asparagine residues corresponding to asparagine residues 62, 94, 149, 222 and 308 of SEQ ID NO: 4. Ex.1002, ¶179. As set out in Section VII.A, the aflibercept in the Modified Fraser/Wulff formulation is glycosylated at these sites. Ex.1007, ¶¶23-36; Ex.1002, ¶179.

J. Claims 15, 23

The turbidity requirements of these claims are obvious for the same reasons set out in Section VII.B.

These claims require a turbidity of 0.01 or lower at OD 405 after 2 months storage at 5 °C. Turbidity, like stability, is an inherent property of formulation. As explained above, it would have been obvious to make the Modified Fraser/Wulff formulation and test it for stability, including for turbidity. Ex.1002, ¶¶180-185.

Based on the teachings of the ’865 patent, the Modified Fraser/Wulff formulation will have the requisite turbidity, just as it would have the requisite stability. *Id.* As shown in the table below, the ’865 patent examples teach a range of concentrations for the VEGF Trap and excipients that achieve the recited turbidity values, and the Modified Fraser/Wulff formulation falls squarely within these ranges.

	VEGF Trap	Buffer	Tonicity	Co-solvent	Stabilizing agent	pH	Turbidity
'865 Examples	20-50 mg/mL	5-10 mM phosphate	20-135 mM NaCl	0.015-0.1% polysorbate 20 or 3% PEG 3350	0-5% sucrose	6.25-6.3	0.0-0.01 at 2-3 months
Modified Fraser/Wulff	40 mg/mL	5 mM phosphate 5 mM citrate	100 mM NaCl	0.1% polysorbate	5% sucrose	6.0-6.3	

Ex.1002, ¶182.

Furthermore, Dix provides turbidity data for even more formulations with different excipients and concentrations. Ex.1002, ¶183. All of the Dix formulations meet the recited turbidity limitations. *Id.* The Modified Fraser/Wulff formulation falls well within the ranges of formulations tested in the '865 patent and Dix that achieve the recited turbidity values, which shows that the Modified Fraser/Wulff formulation will have the claimed turbidity. *Id.*

	VEGF Trap	Buffer	Tonicity	Co-solvent	Stabilizing agent	pH	Turbidity
'865 Examples	20-50 mg/mL	5-10 mM phosphate	20-135 mM NaCl	0.015-0.1% polysorbate 20 or 3% PEG 3350	0-5% sucrose	6.25-6.3	0.0-0.01 at 2-3 months
Dix (50 mg/mL or less)	50-100 mg/mL	10 mM phosphate	50 mM NaCl	0.1% polysorbate or 3% PEG 3350	20% sucrose	6.25	0-0.01 at 2-3 months
Modified Fraser/Wulff	40 mg/mL	5 mM phosphate 5 mM citrate	100 mM NaCl	0.1% polysorbate	5% sucrose	6.0-6.3	

Ex.1002, ¶183.

As with the native conformation stability limitation, the '865 patent does not teach any way of obtaining the claimed turbidity besides making and testing the formulation. Ex.1002, ¶184. And the Modified Fraser/Wulff formulation falls in the genus of Example formulations that achieved the claimed turbidity. *Id.* Thus, based on the teachings of the '865 patent, the Modified Fraser/Wulff formulation meets this limitation. *Id.*

Alternatively, it would have been obvious to achieve the requisite turbidity. It is desirable for intravitreal formulations to be as transparent as possible, and not turbid. Ex.1002, ¶185. Thus, the skilled person would have been motivated to minimize turbidity to the greatest extent possible to avoid a cloudy appearance. *Id.*

K. Claims 16, 24

The stability limitations of these claims—99% stability at 2 months— are obvious for the same reasons set out in Section VII.B. Ex.1002, ¶186.

L. Claims 17, 25

The stability limitations of these claims— 98% stability at 24 months—are obvious for the same reasons set out in Section VII.B. Ex.1002, ¶187.

Furthermore, the 24 month stability data in the '865 patent examples and Dix confirm that the Modified Fraser/Wulff formulation will have the requisite stability. Specifically, aflibercept formulations with the same ingredients as the Modified Fraser/Wulff formulation, and specifically those that include polysorbate 20 like the

Modified Fraser/Wulff formulation, achieved greater than 98% stability after 24 months. *See, e.g.,* Ex.1021, Tables 1 and 9 (disclosing 98.3 and 99.3% native conformation at 24 months); Ex.1001, Table 1 (disclosing 98.1% native conformation at 24 months); Ex.1002, ¶¶188-189. The only formulations that did not achieve that stability had polyethylene glycol as the surfactant. *See* Ex.1001, Table 2 (disclosing 97.6% native conformation at 24 months); Ex.1021, Table 2 (disclosing 97.8 % native conformation at 24 months); Ex.1002, ¶¶188-189.

As shown below, the Modified Fraser/Wulff formulation has the claimed stability because the Modified Fraser/Wulff formulation falls within the described ranges of aflibercept and excipients that the '865 patent and Dix teach have the claimed stability.

	VEGF Trap	**Buffer**	**Tonicity**	**Co-solvent**	**Stabilizing agent**	**pH**	**Stability**
Dix and '865 patent Examples	25-50 mg/mL	10 mM phosphate or 5 mM phosphate and 5 mM citrate	50-100 mM NaCl	0.1% polysorbate	5-20% sucrose	6.0-6.25	98.1-99.3 % at 24 months
Modified Fraser/Wulff	40 mg/mL	5 mM phosphate 5 mM citrate	100 mM NaCl	0.1% polysorbate	5% sucrose	6.0-6.3	

Ex.1002, ¶188.

Furthermore, Patent Owner cannot show the formulation lacks the claimed stability. *See In re Best*, 562 F.2d at 1255; Ex.1002, ¶189.

M. Claim 51

1. An ophthalmic formulation comprising

The Modified Fraser/Wulff formulation is an ophthalmic formulation suitable for intravitreal injection as described above regarding claim 1. *See* Sections VII.A and VII.B; Ex.1002, ¶190.

2. (a) 40 mg/ml of a glycosylated VEGF antagonist fusion protein comprising amino acids 27-457 of SEQ ID NO:4

The Modified Fraser/Wulff formulation contains 40 mg/ml of a glycosylated VEGF antagonist fusion protein comprising amino acids 27-457 of SEQ ID NO:4 as described above for claim 1. *See* Sections VII.A and VII.B; Ex.1002, ¶191.

3. (b) 0.03% to 0.1% polysorbate

The Modified Fraser/Wulff formulation includes 0.03% to 0.1% polysorbate as described above regarding claim 1. *See* Sections VII.A and VII.B; Ex.1002, ¶192.

4. (c) 5-40 mM of sodium phosphate buffer, pH between 5.8-7.0

The Modified Fraser/Wulff formulation discloses 5-40 mM of sodium phosphate buffer, and a pH between 5.8-7.0 as described above regarding claims 1 and 6-9. *See* Section VII.A. A POSA would have understood that the phosphate buffer in Fraser/Wulff is a sodium phosphate buffer. Ex.1002, ¶193; Section VII.A.

5. (d) sucrose

The Modified Fraser/Wulff formulation contains sucrose, as described above regarding claim 1. *See* Sections VII.A and VII.B; Ex.1002, ¶194.

6. wherein the ophthalmic formulation is suitable for intravitreal administration

The Modified Fraser/Wulff formulation is an ophthalmic formulation suitable for intravitreal injection as described above regarding claim 1. *See* Sections VII.A and VII.B; Ex.1002, ¶195; Ex.1011, 14; Ex.1005, ¶¶23-26; *see also* Ex.1012, 19-23, Ex.1013, 21-24.

7. wherein at least 98% of the VEGF antagonist is present in native conformation following storage at 5 °C. for 2 months as measured by size exclusion chromatography

The Modified Fraser/Wulff formulation discloses this limitation for the same reasons described above regarding claim 1. *See* Sections VII.A and VII.B; Ex.1002, ¶196.

N. Claim 52

The Modified Fraser/Wulff formulation comprises at least 5% sucrose as described above regarding claim 1. *See* Sections VII.A and VII.B; Ex.1002, ¶197.

O. Claim 53

The Modified Fraser/Wulff formulation comprises 1-10% sucrose as described above regarding claim 1. *See* Sections VII.A and VII.B; Ex.1002, ¶198.

P. Claim 55

The Modified Fraser/Wulff formulation comprises a vial suitable for intravitreal administration comprising the formulation of claim 51 as described above regarding claims 1 and 55. *See* Sections VII.A and VII.B; Ex.1002, ¶199.

Q. There Are No Secondary Considerations

Finally, though it is not Petitioner's burden, Patent Owner cannot establish secondary considerations that would support a finding of non-obviousness, and particularly it cannot overcome the strong *prima facie* case of obviousness presented in Grounds IV-IX. *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010); Ex.1002, ¶200.

In particular, Patent Owner cannot establish a nexus to the "merits of the claimed invention" of the '865 patent because the art discloses all of the claimed elements. *Novartis AG v. Torrent Pharms. Ltd.*, 853 F.3d 1316, 1330–31 (Fed. Cir. 2017) (citing *In re Huai-Hung Kao,* 639 F.3d 1057, 1068 (Fed. Cir. 2011)). There is no "novel combination or arrangement of known individual elements" in the recited limitations—rather, they are routine as set out above. Ex.1002, ¶200.

Moreover, Patent Owner cannot credibly rely on factors such as commercial success. It has previously taken the position in a separate proceeding that Eylea's dosing regimen, and no other factor, drives demand. Patent Owner's economic expert in multiple IPR proceedings (Dr. Richard Manning) previously opined regarding what does ***and what does not*** drive consumer demand for Eylea—and it was not the subject matter of the '865 patent that drove demand. *See, e.g.,* Ex.1101. Rather, Dr. Manning opined that Eylea's commercial success "***cannot be explained*** by factors" other than dosing frequency (*id.*, 122-132) (emphasis added). Given this

testimony, Regeneron cannot credibly allege that the '865 patent's subject matter, which is unrelated to dosing frequency, drives demand for Eylea.

VIII. DETAILED GROUNDS FOR INVALIDITY: GROUND 2

The Ground 2 Challenged Claims recite storing the formulation in a PFS (instead of a vial). That is the only difference between the Ground 1 and Ground 2 Claims. POSAs at the time understood that PFSs offered convenience for purposes of administration, including intravitreal administration, because they eliminate the step of withdrawing liquid from the vial and into a syringe. For example, Nayar 2002 teaches that the "most preferred" dosage form for a therapeutic protein product was "a solution formulation that is typically stored in the refrigerator and preferably in a ***pre-filled syringe***." Ex.1020, 183 (emphasis added); Ex.1005, ¶¶38-42. Patent Owner has previously taken the position that a PFS was the preferred presentation prior to the '865 patent's alleged priority date of March 2006. Ex.1109, 51-52.

Accordingly, the Ground II claims are obvious for the same reasons as described above regarding the Ground I claims. Ex.1002, ¶¶201-202.

A. Claim 26

Claim 26 is identical to claim 1, except that claim 26 recites storing the formulation in a PFS rather than a vial. As discussed in Section VI.B.4 and VIII, it would have been obvious for the POSA to store the Modified Fraser/Wulff formulation in a PFS.

All other limitations of claim 26 are rendered obvious for the same reasons as set forth in Section VII with respect the Vial Claims. Therefore, claim 26 is rendered obvious. Ex.1002, ¶¶203-204.

B. Claim 27

Dependent claim 27 is obvious for the same reasons as claims 1 and 26. Claim 27 recites the concentration of the formulation (40 mg/mL) and specifies the organic co-solvent comprises polysorbate. As set out above in Section VII.A, the Modified Fraser/Wulff formulation contains 40 mg/ml aflibercept and polysorbate. Ex.1002, ¶205.

C. Claims 28-30

Dependent claims 28-30 are obvious for the same reasons as claims 1-2 and 27. These claims recite the organic co-solvent is polysorbate in various ranges from 0.01% to 3%. As explained in Section VII.A, the Modified Fraser/Wulff formulation contains 0.1% polysorbate 20. Ex.1009, 1115; Ex.1016, 2798; Ex.1002, ¶206.

D. Claims 31-32

Dependent claims 31-32 are obvious for the same reasons as claims 1, 5-7, and 30. These claims recite that the buffer is a phosphate buffer and specify that the buffer comprises 5-25 mM buffer. As explained in Sections VII.A and VII.B, the Modified Fraser/Wulff formulation contains a 5 mM phosphate buffer. Ex.1009, 1115; Ex.1016, 2798; Ex.1002, ¶207.

E. Claims 33-34

Dependent claims 33-34 depend from claim 30 and recite that the buffer comprises a pH between "about 5.8-7" in claim 33 and "about 6.2-6.3" in claim 34. As set out in Section VII.F above, in view of the variation taught in the patent and inherent in the measurement tools available at the time, the POSA would have understood that the Modified Fraser/Wulff formulation's pH of 6.0 falls within the scope of "about 6.2-6.3." Ex.1002, ¶208. Additionally, it would have been obvious to vary the pH of the formulation as part of standard testing, including to achieve a pH of 6.1, 6.2 or 6.3. *Id*. Claims 33-34 are therefore rendered obvious.

F. Claims 35-36, 44-45

These claims are obvious for the same reasons as claims 1, 5 10-11, 19-20, and 30. These claims recite that the stabilizing agent is a sugar, including sucrose (and not containing trehalose), and further require 1-10% sucrose. The Modified Fraser/Wulff formulation contains 10% or less sucrose, rendering these claims obvious. Ex.1009, 1115; Ex.1016, 2798; Ex.1002, ¶209.

G. Claims 39, 47

These claims are obvious for the same reasons as claims 1, 5. The claims specify that the VEGF antagonist fusion protein is glycosylated at asparagine residues 62, 94, 149, 222 and 308 of SEQ ID NO: 4. As set out in Section VII.B, the glycosylation sites of the aflibercept used in the Modified Fraser/Wulff formulation were known in the art and would have been obvious. Ex.1002, ¶210.

H. Claims 40, 48

The stability limitations of these claims, which require specified turbidity values, are obvious for the same reasons set out in Section VII.A and VII.J. Ex.1002, ¶211.

I. Claims 41, 49

The stability limitations of these claims (99% stability at 2 months) are obvious for the same reasons set out in Section VII.B. Ex.1002, ¶212.

J. Claims 42, 50

The stability limitations of these claims (98% stability at 24 months) are obvious for the same reasons set out in Section VII.B. Ex.1002, ¶213.

K. Claim 54

Claim 54 is obvious for the same reasons as claims 51 and 26. Claim 54 depends from claim 26 and recites a PFS suitable for intravitreal administration comprising the formulation of claim 51. As set out above in relation to claim 26, it would have been obvious to use a PFS container with the Modified Fraser/Wulff formulation. Section VIII.A; Ex.1002, ¶214.

L. There Are No Secondary Considerations

For the same reasons recited above for Ground I, there are no secondary considerations supporting non-obviousness. Ex.1002, ¶215.

IX. DISCRETIONARY DENIAL IS UNWARRANTED

A. The Becton Dickinson Factors Do Not Favor Denial Under 35 U.S.C. § 325(d)

The Board uses a two-part framework to analyze whether denial under § 325(d) is proper. The Board considers several nonexclusive factors ("*Becton Dickinson* factors") within this framework to provide useful insight into how to apply each prong, each of which is discussed below. *Id.*, 4; *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8, 17-18 (Dec. 15, 2017) (precedential as to Section III.C.5, first paragraph).

Becton Dickinson factors (a), (b), and (d) relate to whether the art or arguments presented in the Petition are the same or substantially the same as those previously presented to the Office. *Advanced Bionics, LLC v. Med-El Elektromedizinische Geräte GMBH*, IPR2019-01469, Paper 6, 10 (P.T.A.B. Feb. 13, 2020) (precedential). Factors (c), (e), and (f) are only considered if the same or substantially the same art or arguments were previously presented to the Office. *Id*.

1. *Becton Dickinson* Factors (a), (b), and (d)

Petitioner's arguments and prior art here are neither the same nor substantially the same art or arguments previously before the Office during prosecution of the '865 patent.

First, as set out in Section V.D, the Examiner only issued non-statutory double patenting rejections during prosecution. The Examiner did not issue any anticipation

or obviousness rejections based on prior art. Furthermore, Petitioner asserts combinations involving references never considered during prosecution that provide additional, non-cumulative disclosures, including Wulff, Daly, and the 2006 Presentations. Additionally, Fraser and the '319 Publication were not substantively considered. In other words, the art and arguments presented here were neither "involved" nor "evaluated" during prosecution; and therefore, they are not the same or substantially the same as that previously considered by the Office. *Becton, Dickinson*, IPR2017-01586, Paper 8, 17; 35 U.S.C. § 325(d).

Patent Owner may argue that references such as Fraser and the '319 Publication were identified on the Information Disclosure Statements along with hundreds of other references. But the Examiner did not consider any combination of the art and arguments presented here, opting instead only to issue obviousness-type double patenting rejections over prior Regeneron patents. *See* Section V.C. "The Board has consistently declined exercising its discretion under Section 325(d) when[, as here,] the only fact a Patent Owner can point to is that a reference was disclosed to the Examiner during the prosecution." *Amgen Inc. v. Alexion Pharms., Inc.*, IPR2019-00739, Paper 15, 62 (Aug. 30, 2019).

2. *Becton Dickinson* Factors (c), (e), and (f)

Because Petitioner presents new arguments and combinations herein, analysis of *Becton Dickinson* factors (c), (e), and (f) is unnecessary. Even if the grounds

presented herein somehow were considered to have been previously presented to the Office, the Examiner made clear errors in evaluating the art.

In particular, as discussed in Section V.D, the Examiner issued obviousness-type double patenting rejections but failed to make an obviousness rejection over, for instance, Fraser and Wulff. Applicants thus obtained the claims without ever addressing a substantive obviousness rejection. This was clear error.

B. The *General Plastic* and *Valve* Do Not Support Denial under 35 U.S.C. §314(a)

Under the relevant factors governing discretionary denial under 35 U.S.C. § 314(a), the Petition should be instituted. *See General Plastic Industrial Co., Ltd. v. Canon Kabushiki Kaisha*, IPR2016-01357, Paper 19 (P.T.A.B. Sept. 6, 2017) (§ II.B.4.i precedential); *Valve Corp. v. Electronic Scripting Products, Inc.*, IPR2019-00062, Paper 11 (P.T.A.B. April 2, 2019) (precedential).

Petitioner has never previously filed a petition directed to any claim of the ’865 patent. As described above, Samsung Bioepis is the only party to have filed an IPR petition challenging the ’865 patent in IPR2025-00176. Here, Petitioner is “neither the same party” as Samsung Bioepis, “nor possess[es] a significant relationship” with Samsung Bioepis, and thus, “exercising discretion to deny the Petition is not justified.” *Videndum Prod. Sols., Inc. v. Rotolight Ltd.*, IPR2023-01218, Paper 12 at 7 (P.T.A.B. April 19, 2024) (Dir. Decision).

Like Samsung Bioepis, Petitioner is facing allegations of infringing the same

'865 patent. However, that by itself is insufficient to create the type of "significant relationship" under *Valve* that weighs against institution. *See Ford Motor Co. v. Neo Wireless LLC*, IPR2023-00763, Paper 28 at 9-10 (P.T.A.B. Mar. 22, 2024). Petitioner and Samsung Bioepis are all defendants in a multidistrict litigation, but each are defending "different allegedly infringing products." *Id.* at 10. This is also not a case like *Valve*, where "both petitioners were accused of infringing the same patent based upon the same product for which they had an ongoing licensing relationship." *Id.* Petitioner here does not have "any interactions or agreements regarding the . . . their respective accused products." *Id.*

Moreover, Petitioner "had no involvement with, much less input into, [Samsung Bioepis'] IPR." *Id.* at 5. Petitioner was not even aware that Samsung Bioepis would be filing its petition in IPR2025-00176 until it was filed with the Board. Accordingly, this Petition does not implicate the types of serial-petitioning concerns addressed in *Valve* and *General Plastic*. Samsung Bioepis is not a "real party in interest" or a "privy" of Formycon.

C. *Fintiv* Does Not Support Denial Under 35 U.S.C. § 314(a)

Petitioner stipulates that, should the Board institute review, Petitioner will not pursue in the parallel district court proceeding the same grounds as in the Petition or any grounds that could have reasonably been raised in the petition. Thus, the Board should not exercise discretion to deny institution under § 314(a). *See* INTERIM PROCEDURE FOR DISCRETIONARY DENIALS IN AIA POST GRANT

PROCEEDINGS WITH PARALLEL DISTRICT COURT LITIGATION, 7 (USPTO Dir. June 21, 2022).

X. CONCLUSION

For the foregoing reasons, Petitioner has established a reasonable likelihood that claims 1-12, 14-17, 19-20, 22-36, 39-42, 44-45, and 47-55 are unpatentable. Petitioner therefore respectfully requests that *inter partes* review of the '865 patent be granted.

DATED: November 29, 2024 Respectfully submitted,

By /Louis E. Fogel/

Louis E. Fogel (Reg. No. 54,731)
Fish & Richardson P.C.
60 South Sixth Street, Suite 3200
Minneapolis, MN 55402
T: 202-783-5070
F: 877-769-7945

Attorney for Petitioner Formycon AG

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(a) and (d), the undersigned hereby certify that the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 11,084,865 complies with the type-volume limitation of 37 C.F.R. § 42.24(a)(1)(i) and (b)(1)(i) permitting a petition of up to 14,000 words because, exclusive of the exempted portions, it contains 13,982 words as counted by the word processing program used to prepare the paper.

Date: November 29, 2024

Respectfully submitted,

By: /Louis E. Fogel/

Louis E. Fogel (Reg. No. 54,731)
Fish & Richardson P.C.
60 South Sixth Street, Suite 3200
Minneapolis, MN 55402
T: 202-783-5070
F: 877-769-7945

Attorney for Petitioner

CERTIFICATE OF SERVICE

Pursuant to 37 CFR §§ 42.6(e)(4)(i) *et seq.* and 42.105(b), the undersigned certifies that on November 29, 2024, a complete and entire copy of this Petition for *Inter Partes* Review of U.S. Patent No. 11,084,865, Power of Attorney, and all supporting exhibits were provided via Federal Express to the Patent Owner at the correspondence address of record as follows:

A&P - Regeneron (Prosecution)
601 Massachusetts Ave., NW
Washington, DC, 20001

/Anastasia Renard/
Anastasia Renard
Fish & Richardson P.C.
60 South Sixth Street, Suite 3200
Minneapolis, MN 55402
renard@fr.com