Filed on behalf of: Celltrion, Inc.
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CELLTRION, INC.,
Petitioner,

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner.

Case No. IPR2025-00456
Patent No. 11,084,865

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

TABLE OF CONTENTS

Page

I. INTRODUCTION

Celltrion, Inc. ("Petitioner") respectfully requests *inter partes* review of claims 1-50 of US11,084,865 ("*US865*" EX1001), assigned to Regeneron Pharmaceuticals, Inc. ("Regeneron" or "PO"). The challenged claims are entitled, at best, to an effective filing date no earlier than October 12, 2018, and thus invalid over an earlier-published application in the same family, US2007/0293432 ("*US432*" EX1004). *US432* is the published application of US App. 11/818,463 ("*App463*" EX1016), an application in *US865*'s priority chain, which has the same specification as *US865*. *US865* is premised on formulating VEGF antagonists to provide for increased stability.

US865 is the eleventh patent to issue from a common specification that Regeneron filed on June 16, 2006, almost 20 years ago. This "thicket" of continuation patents is generally directed to the same "stable" formulation of aflibercept, with only trivial variations between the family members. That stable formulation comprises a VEGF antagonist like aflibercept in combination with a buffer, a sugar, and an organic co-solvent, which are excipients commonly used to stabilize therapeutic proteins. Most of the patents in the thicket are subject to terminal disclaimers over earlier-filed patent families claiming similar formulations of VEGF antagonist.

In a bid to wring more patent term for EYLEA from the same priority specification, Regeneron added two limitations to the challenged claims that it alleged distinguished them from the earlier-expiring formulation claims subject to the terminal disclaimers. These limitations require only that the VEGF inhibitor be "glycosylated,"[1] and that the formulation stabilize the VEGF inhibitor such that at least 98% (or, in certain dependent claims, 99%) of it remains in "native conformation" when measured by size-exclusion chromatography ("SEC") after storage for two months at 5ºC, or at least 98% remains in "native conformation" after storage for 24 months.

The specification, however, does not contain sufficient written description for these limitations. Despite the broad genus of glycosylated VEGF antagonist proteins covered by the challenged claims, *US865* mentions glycosylation only once, and only in the context of describing one specific glycosylated VEGF antagonist, aflibercept, which has a specific glycan structure.

Similarly, despite Regeneron's broad claims to a genus of VEGF antagonists containing a buffer, a sugar, and an organic co-solvent covered by the challenged claims, the specification discloses stability testing only for formulations containing a specific VEGF antagonist, aflibercept, and only for a handful of formulations

[1] Claims 14, 22, 39, and 47 specify a single glycosylated variant.

containing the specific buffer phosphate, the specific sugar sucrose, and the specific organic co-solvents polysorbate 20 and polyethylene glycol 3350 for specified lots of aflibercept.

Further, while the examples provide results for stability testing of this handful of formulations reporting a measured stability that falls within the claimed range of "at least 98% of the VEGF antagonist is present in native conformation following storage at 5° C for two months [or 24 months] as measured by size exclusion chromatography" ("SEC"), not all the examples test the stability at these time points. Notably, nothing in the general disclosure, or even in the text accompanying the examples, discloses these end points, much less these ranges.

Regeneron's gambit to include these two limitations in the challenged claims to gain patent term for its formulations, despite the lack of sufficient written description, renders the claims invalid for obviousness and lack of novelty over Regeneron's *US432* application published over a decade earlier, *which has the identical specification*.

To obtain issuance of the challenged claims, Regeneron argued that this common specification discloses formulations that support the claims of *US865*.

EX1006, 80. Based on that admission, the challenged claims must be anticipated by, or at a minimum, obvious[2] over, the specification of *US432*.

This is not the first time a patent in this family has been before the Board. Celltrion previously brought an IPR against US10,464,992, IPR2023-00462 ("*462IPR*"). The claims in that proceeding are very similar to the claims challenged here.[3] After institution, Regeneron disclaimed all claims of US10,464,992 and adverse judgment was entered. IPR2023-00462, Paper 37.

[2] While the claims are obvious over the disclosure of *US432*, which is identical to *US865*, such obviousness does not support written description. *Regents of University of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1567 (Fed. Cir. 1997) ("a description which renders obvious a claimed invention is not sufficient to satisfy the written description requirement of that invention.")

[3] The claims of US10,464,992, although specifying that the VEGF antagonist is made in CHO cells, do not specify that the VEGF antagonist is glycosylated. The POSA would have understood, however, that producing the VEGF antagonist in CHO cells, the only method of producing VEGF antagonist disclosed in the common specification, would naturally result in glycosylation. *See* Section VIII.A.1.

Petitioner respectfully submits this Petition and supporting expert declaration from Dr. Peter Tessier (EX1002), an expert in the formulation of injectable dosage forms with over 25 years of experience in the pharmaceutical industry. EX1002 ¶¶1-13; EX1003. For the reasons set forth herein and in the declaration, Petitioner has demonstrated that there is at least a reasonable likelihood that the claims are unpatentable, and respectfully requests that the Board institute this petition for *inter partes review* and cancel the challenged claims.

A. Brief Overview of *US865*

US865 describes the alleged innovation as "[s]table formulations of a VEGF-specific fusion protein antagonist" comprising a "VEGF 'trap' antagonist with a pharmaceutically acceptable carrier." EX1001, 2:14-17. Challenged independent claims 1 and 26 encompass ophthalmic formulations suitable for intravitreal administration comprising a VEGF antagonist that "is glycosylated and comprises amino acids 27-457 of SEQ ID NO:4," an organic co-solvent, a buffer, and a stabilizing agent, thereby achieving the claimed levels of stability. *Id.*, 19:29-41 (claim 1), 20:66-21:12 (claim 26). The challenged independent claims do not limit the VEGF antagonist concentration, or the type or amount of organic co-solvent, buffer, or stabilizing agent. EX1002 ¶133. In addition, not all the examples provide data for "% VEGF Trap Native Configuration," (i.e., "native conformation") at two months and/or 24 months. *See* EX1002 ¶¶45-46. Only

three of the examples drawn to liquid formulations provided data for the two-month time period, and only two present data for the 24 month time period.

B. Prosecution History

The underlying application (16/739,559, "*App559*") that issued as *US865* was filed on January 10, 2020, claiming benefit through a chain of applications to a provisional application filed on June 16, 2006. EX1001, 1. The priority chain includes ten issued patents and the 2006 provisional application. *Id.*

During prosecution, the Examiner rejected the then-pending claims (claims 12-20) for obviousness-type double patenting ("ODP") over Regeneron's earlier-issued patents. EX1006, 259-61. To extend patent protection for EYLEA, rather than file a terminal disclaimer, Regeneron added an unsupported glycosylation limitation, arguing that this additional limitation, along with the stability limitations added in parent application 16/582,486, rendered the claims non-obvious over the earlier-expiring patents. *Id.*, 281-82, 286-92.

Specifically, Regeneron amended independent claim 12, adding the limitation that the VEGF antagonist is generally glycosylated (*i.e.*, no limitation on number of residues or which residues are glycosylated) and comprises amino acids 27-457 of SEQ ID NO:4 ("general glycosylation limitation"). EX1006, 286. Regeneron also cancelled claims 13-20 and added new claims 21-83. *Id*., 286-92. Claim 12 and new independent claims 45 and 70 required "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" ("the at least 98% two-month stability limitation"), new claims 36, 43, 61, and 68 added a limitation that 99% of the VEGF antagonist is present in native conformation following storage at 5° C. for 24 months as measured by size exclusion chromatography" ("the at least 99% two-month stability limitation"), and new claims 37, 44, 62, and 69 added "wherein at least 98% of said VEGF antagonist…is present in native conformation following storage at 5° C. for 24 months as measured by size exclusion chromatography" ("the at least 98% 24-month stability limitation") (collectively, "the stability limitations"). *Id*. Regeneron then terminally disclaimed US8,092,803, which also contained formulation claims with the at least 98% two-month stability limitation, but argued that the claims of the other reference patents were patentably distinct because they did not include the same limitations relating to the rate of aggregation of the VEGF antagonist over time recited in the proposed claims. *Id.*, 293; EX1002 ¶101. The Examiner then allowed the claims.

C. Scope and Content of the Prior Art

1. Background

a. VEGF Antagonists

VEGF is a naturally-occurring protein that regulates "angiogenesis," the process by which new blood vessels are formed. EX1002 ¶50. VEGF functions by binding to specific VEGF receptors on the surface of cells responsible for angiogenesis, thereby increasing their activity. *Id.*¶¶50-51. VEGF inhibitors, such as aflibercept, are used to treat age-related macular degeneration, a disease characterized by proliferation of blood vessels in the retina of the eye. *Id.* ¶52.

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:

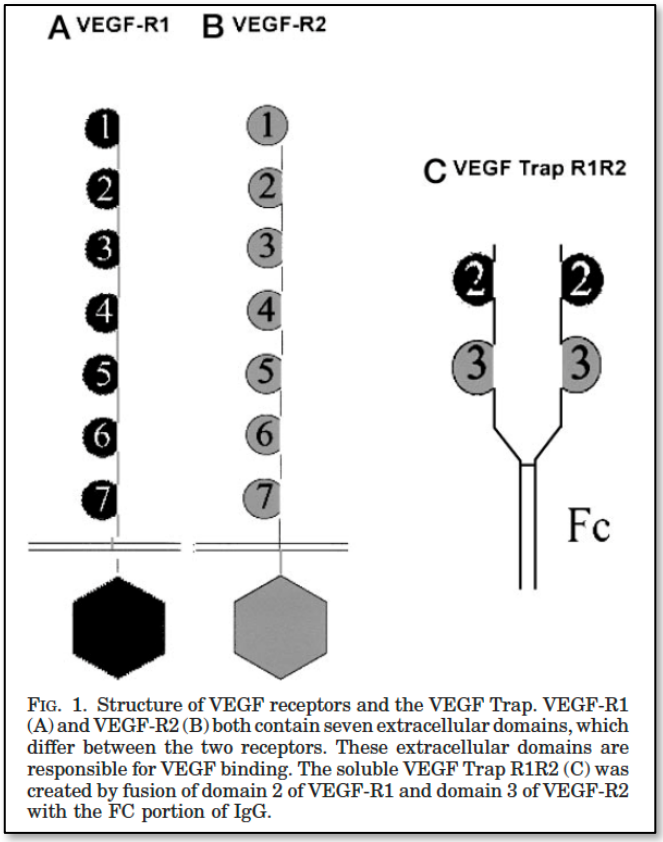

FIG. 1. Structure of VEGF receptors and the VEGF Trap. VEGF-R1 (A) and VEGF-R2 (B) both contain seven extracellular domains, which differ between the two receptors. These extracellular domains are responsible for VEGF binding. The soluble VEGF Trap R1R2 (C) was created by fusion of domain 2 of VEGF-R1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

EX1017, 2798, Fig. 1; EX1002 ¶53. Amino acid residues 27-457 of SEQ ID NO:4 of *US865* is the amino acid sequence of aflibercept, with amino acid residues 1-26 being a signal sequence that is not present in the mature protein. EX1018, ¶37; EX1002 ¶54. Aflibercept was known to be made in CHO cells and glycosylated at asparagine residues 62, 94, 149, 222, and 308. EX1018 ¶¶ 37, 45; *see also* EX1019, 9; EX1002 ¶55. Regeneron markets aflibercept under the trade name EYLEA. EX1002 ¶53. "EYLEA is supplied as a preservative-free, sterile, aqueous solution in a single-use, glass vial designed to deliver 0.05 mL (50 microliters) of EYLEA (40 mg/mL in 10 mM sodium phosphate, 40 mM sodium chloride, 0.03% polysorbate 20, and 5% sucrose, pH 6.2)." EX1019, 9; *see also*

EX1002 ¶85. Regeneron also supplies the above dose of EYLEA in a pre-filled syringe ("PFS").

b. Protein Stability

It was well known that proteins like aflibercept are subject to physical and chemical degradation via well-defined pathways and mechanisms. EX1020, 1; EX1002 ¶59.

Chemical instability refers to processes, such as deamidation and oxidation, that break or form chemical bonds within the molecule. EX1002 ¶60. Physical instability refers to processes that change the protein conformation, including aggregation and denaturation. *Id*. When formulating protein therapeutics, inhibiting aggregation is a chief goal because aggregates can cause increased immunogenicity, alter protein serum half-life, and interfere with protein function or binding. EX1002 ¶¶61-67. It was also known that glycosylation can impart stability and preserve structural integrity. EX1002 ¶63; EX1021 ¶45, 56-58.

In the prior art, size exclusion chromatography ("SEC"), which measures differences in the size, molecular weight and shape of proteins, was a common technique for detecting formation of protein aggregates in a formulation over time. *E.g.*, EX1022 ¶278, Table 1; EX1023, 160; EX1002 ¶¶68-69. However, degradation products that have a similar molecular weight and shape to the native protein would not be detectable by SEC as they would co-elute with the protein in

native conformation. EX1002 ¶73; EX1021 ¶90. In addition, as Dr. Tessier explains, SEC only detects proteins that travel through and elute from the SEC column. Higher order aggregates may not make it through the frit at the beginning of the column and may also interact with the particles of the SEC column, thus failing to elute from the column. Smaller degradation products may move more slowly through the column. EX1002 ¶¶68, 126.

2. Key Prior Art

a. *US2007/0293432 (EX1004; "US432")*

US432 ("VEGF Antagonist Formulations Suitable for Intravitreal Administration") published on December 27, 2007, more than one year before *US865*'s earliest possible priority date of October 12, 2018, and is therefore prior art. Pre-AIA 35 U.S.C. §102(b); post-AIA 35 U.S.C. §102(a)(1).

US432 was filed by Regeneron and has the same inventors and specification as *US865*. EX1002 ¶¶81-82. *US432* discloses the same VEGF antagonists, formulations, examples, and stabilities as the specification of *US865*. EX1002 ¶82-83.

b. *WO 2017/129685 (EX1005; "WO685")*

WO685, titled "Liquid Formulation of a VEGF Antagonist, published on August 3, 2017, more than one year before *US865*'s earliest possible priority date

of October 12, 2018, and is prior art. Pre-AIA 35 U.S.C. 102(b); post-AIA 35 U.S.C. 102(a)(1).

WO685 discloses 40 mg/ml formulations of aflibercept comprising 10 mM L-histidine/histidine HCl buffer, 5% sucrose, 40 mM sodium chloride, and 0.03 wt% polysorbate 20, with a pH of 6.2. EX1005, 34, Table 9, Sample (a); EX1002 ¶86.

3. Level of Ordinary Skill in the Art

A POSA would have held an advanced degree, such as a Master's in a biopharmaceutical science, or a related discipline, such as chemical engineering, and several years of experience in the development of pharmaceutical formulations. Alternatively, the POSA could have had a Ph.D. in such a discipline and less experience. The POSA may collaborate with others, including a medical doctor with experience treating ophthalmic diseases. EX1002 ¶¶39-40.

II. THE BOARD SHOULD DECLINE TO EXERCISE ITS DISCRETION TO DENY INSTITUTION

A. The Board Should Not Exercise Its Discretion Under Section 325(d) to Deny Institution

PO may urge the Board to deny institution because "the same or substantially the same prior art or arguments previously were presented to the Office." In determining whether to exercise its discretion to deny institution under §325(d), the Board applies a two-part framework. *Advanced Bionics, LLC v.*

MED-EL Elektromedizinische Geräte GmbH, IPR2019-01469, Paper 6 (Feb. 13, 2020) (precedential). The first part assesses "whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office." *Id.*, 8. "[I]f either condition of [the] first part of the framework is satisfied," the second part assesses "whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of [the] challenged claims." *Id. Advanced Bionics* set forth factors that help inform whether the first part of the framework is satisfied. *Id.*, 9-10; *see also Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8, 17-18 (Dec. 15, 2017) (precedential).

This petition presents art and arguments that are materially different than those presented to the Office during prosecution of *US865*. Only ODP rejections were made during prosecution of the application that led to *US865*. EX1006, 259-61. Regeneron did not argue that achieving the added stability limitation was unexpected or conferred any unexpected properties to the formulation. *See generally id*., 279-84.

US865 claims priority to a series of applications. *See* Section VII.b. The prosecution histories of these applications do not contain any rejections over the prior art. Rather, the claims in the priority applications were rejected only for

ODP, written description, and indefiniteness. *See generally* EX1007-1016 (file histories and excerpts of file histories of aforementioned priority applications).

A review of the *Becton Dickinson* factors support institution. The challenges made herein are based on the fact that *US865* is not entitled to an effective filing date that is before the publication date of *US432*, which has the same disclosure as *US865*. As the effective filing date was not explored during prosecution, factors (a)-(d) support institution. And since Petitioner has explained why *US865* is not entitled to a filing date before the publication date of *US432* (*see* Section VII), factors (e)-(f) support institution. Moreover, it was error for the examiner not to consider whether the claim amendments satisfied §112, especially as Regeneron relied on the added stability limitations to differentiate the claims of *US865* from the claims of other patents issuing from the same specification.

Both parts of the Board's two-part framework are satisfied. The Board should thus decline to exercise its discretion under §325(d) to deny institution.

B. The Board Should Not Exercise Its Discretion under Section 314(a) to Deny Institution

PO may also urge the Board to exercise its discretion under §314(a) to deny institution because of copending litigation as well as the fact that *US865* is the subject of an IPR filed by Samsung Bioepis Co. LTD. ("SB"), challenging

different claims and presenting different grounds than are presented in this petition.[4]

The Board considers six factors when determining whether to deny institution under §314(a) based on a parallel district court proceeding. Consideration of these factors favors institution.

(1) Whether the court granted a stay or if one will be granted if trial is instituted is neutral. The possibility of a stay has not been raised in the litigation against Celltrion. Without "specific evidence" of how the court would rule on any stay motion, this factor is neutral. *Sand Revolution II LLC v. Continental Intermodal Group Trucking LLC*, IPR2019-01393, Paper 24, 7 (June 16, 2020) (informative).

(2) Proximity of the trial date to the PTAB's statutory deadline and (3) investment in the parallel proceeding by the court and parties, favors institution. *US865* was at issue in *Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals Inc., et al.*, 1:22-CV-61 (N.D.W.Va.) ("*Mylan* litigation"). Although the *Mylan* trial is complete as to *US865*, Celltrion was not a party and very different invalidity grounds were asserted. In the litigation against Celltrion,

[4] Formycon AG has filed a "copycat" petition and a conditional motion for joinder to SB's petition.

the district court has yet to enter a schedule, and it is likely this IPR will conclude before the district court reaches a final verdict. In addition, Regeneron is asserting multiple patents against Celltrion, and it is unlikely that Regeneron will assert all 50 claims Celltrion is challenging here.

(4) Overlap of issues between the petition and parallel proceeding and (5) whether the petitioner and defendant in the parallel proceeding are the same party favor institution. In the *Mylan* litigation, the district court found claims 4, 7, 9, 11, and 14-17 to be valid and infringed. The grounds raised in the *Mylan* litigation are different from those raised here, and this petition addresses claims that the district court did not address. Celltrion was not a party to *Mylan*. Celltrion also stipulates that if the IPR is instituted, Petitioner will not pursue the same grounds in the district court litigation. IPR2019-01393, Paper 24, 11-12 (June 16, 2020) (Informative). Accordingly, the Grounds presented in the instant IPR will be materially different from the grounds that will be presented in the district court, which dictates against discretionary denial.

As for factor (6), for the reasons herein, this Petition presents compelling evidence of unpatentability.

PO may also urge the Board to exercise its discretion under §314(a) to deny institution because this is the second petition filed requesting IPR of *US865*, as SB filed IPR2025-00176 challenging claims 1-12, 14-17, 19-20, 22-36, 39-42, 44-45,

and 47-55 of *US865*. When evaluating whether to deny institution of a "follow-on" petition, the Board generally looks at seven factors provided in *Gen. Plastic Indus. Co., Ltd. v. Canon Kabushiki Kaisha*, IPR2016-01357, Paper 19, 9-10.

The *General Plastic factors* weigh heavily in favor of institution. Factors (1) and (2) favor institution. This is the first petition filed by Celltrion against *US865*, and Celltrion was not a real-party-in-interest in IPR2025-00176. This petition relies on different prior art and different theories of invalidity than does IPR2025-00176. Factor (3)-(5) also favor institution. Celltrion had no say in the timing of the filing of IPR2025-00176, and this petition was filed before Regeneron filed a preliminary response to the IPR2025-00176 petition. Finally, factors (6)-(7) favor institution. Given the differences between the SB petition and the instant petition, the Board will not be using its resources to consider duplicative arguments. And Celltrion is not aware of any reason that would prevent the Board from meeting its one-year statutory requirement to issue a final written decision after institution.

III. GROUNDS FOR STANDING (37 C.F.R. §42.104(A))

Petitioner certifies that *US865* is available for IPR and that Petitioner is not barred or estopped from bringing this petition or challenging any claim of *US865* on the grounds identified herein. Petitioner has not filed a civil action challenging the validity of *US865*. Regeneron's summons in the West Virginia

district court action was served on Celltrion on October 16, 2024. 35 U.S.C. § 315(b).

IV. MANDATORY NOTICES UNDER 37 C.F.R. §42.8

Pursuant to 37 C.F.R. §§42.8(a)(1) and 42.8(b), the following mandatory notices are provided as part of this Petition.

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

Celltrion, Inc. is the real party in interest.

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

Celltrion challenged *US992* in *Celltrion, Inc. v. Regeneron Pharmaceuticals, Inc.*, IPR2023-00462 (P.T.A.B.), which was instituted on July 20, 2023. Regeneron disclaimed all of the challenged claims after institution. In addition, SB has filed a petition challenging claims 1-12, 14-17, 19-20, 22-36, 39-42, 44-45, and 47-55 of *US865*.

US865 is being asserted by Regeneron against Celltrion in *Regeneron Pharmaceuticals, Inc. v. Celltrion, Inc.*, No. 1:23-cv-89 (N.D.W. Va.) and *Regeneron Pharmaceuticals, Inc. v. Celltrion, Inc.*, No. 1:24-cv-53 (N.D.W. Va.). The district court entered a preliminary injunction in those cases, which is currently on appeal to the Federal Circuit in *Celltrion, Inc. v. Regeneron Pharmaceuticals, Inc.*, Appeal Nos. 2024-2058, 2024-2147. The West Virginia

Court has not scheduled a *Markman* hearing or trial in that matter, and discovery has not been conducted.

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. 24-2002, 24-2009, 24-2019, 24-2058, 24-2082, 24-2083; 23-1395; 23-1396; 24-1402; 24-1405, 24-1564; 24-1567 (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. Formycon AG*, No. 1:23-cv-97 (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. Samsung Bioepis Co., Ltd.*, No. 1:24-cv-106 (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 Back-Up Counsel and Service Information (37 C.F.R. §42.8(b)(3), (4))

Lead counsel is Lora M. Green (Reg. No. 43,541). Back-up counsel are Robert Cerwinski (to be admitted *pro hac vice*), Michael Johnson (Reg. No. 63,731), Keith A. Zullow (Reg. No. 37,975), Michael Cottler (Reg. No. 79,455), Yahn-Lin (Franklin) Chu (Reg. No. 75,946), and Aviv Zalcenstein (to be admitted *pro hac vice*).

Petitioner hereby consents to electronic service. Please direct all correspondence to lead and back-up counsel at the contact information below. A power of attorney accompanies this petition.

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

The required fees are submitted herewith. If any additional fees are due at any time during this proceeding, the Office is authorized to charge such fees to Deposit Account No. 604962.

V. OVERVIEW OF CHALLENGE AND PRECISE RELIEF REQUESTED

A. Challenged Claims and Relief Requested

Petitioner requests institution of IPR against claims 1-50 of *US865* and cancellation of these claims as unpatentable.

B. Statutory Grounds of Challenge

Each of the following prior art references and/or combinations of references renders the challenged claims unpatentable:

Ground	35 U.S.C.	References	Claims
1	§102	Anticipated by *US432* (EX1004)	1-17, 19-42, 44-50
2	§103	Obvious over *US432*	1-50
3	§103	Obvious over combination of *US432* and *WO685* (EX1005)	18, 43

Petitioner's full statement of the reasons for the relief requested is set forth in greater detail below, as supported by the declaration of Dr. Peter M. Tessier (EX1002).

VI. CLAIM CONSTRUCTION

Claim terms should be given their ordinary and customary meaning consistent with the specification, as a POSA would have understood them. 37 C.F.R. § 42.100(b); *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-13 (Fed. Cir. 2005) (*en banc*). Accordingly, the terms of the challenged claims should be given their plain and ordinary meaning. Four claim terms are specifically discussed below, none of which are defined in the patent, and all of which should be given their plain and ordinary meaning to a POSA. EX1002 ¶¶72-80. Regardless of the claim construction adopted, the challenged claims are anticipated by, or obvious over, *US432*, which shares a common specification with *US865*.

A. Wherein the VEGF Antagonist Fusion Protein Comprises Amino Acids 27-457 of SEQ ID NO:4

Claims 1 and 26 claim a formulation comprising a VEGF antagonist, wherein the VEGF antagonist fusion protein "comprises amino acids 27-457" of SEQ ID NO:4. The accepted legal meaning of the open-ended transitional phrase "comprises" is "includes," and therefore the claims are not limited to a protein comprising only amino acids 27-457 of SEQ ID NO:4. *Mars Inc. v. H.J. Heinz Co.*, 377 F.3d 1369, 1376 (Fed. Cir. 2004). In other words, the claims encompass

proteins including amino acids 27 to 457 of SEQ ID NO:4, as well as proteins that have additional amino acids on either end, provided they still bind VEGF to some degree. EX1002 ¶78.

B. Native Conformation as Measured by SEC

The POSA would have understood that the term "native" in the phrase "native conformation" or "native configuration" refers to the fully intact and functional conformation of the protein, which is the construction adopted by the district court in the *Mylan* litigation. EX1024, 50. But as explained by Dr. Tessier, while the patent claims refer to the percentage of protein in "native conformation" following storage at 5 °C for two months or 24 months "*as measured by size exclusion chromatography*," this usage presents a technical inconsistency. EX1002 ¶73. Protein in native conformation may co-elute with other substances, including degraded protein, that have a similar size, molecular weight, or shape as the natively-conformed protein, as such substances may migrate with it on the size-exclusion column being used, inflating the amount protein in native conformation. In addition, SEC can only measure the protein that travels through the column and is eluted from it. Because SEC only detects aggregate that elutes from the column, it only provides a rough approximation of the amount of protein in native conformation. It is not a true measurement of the amount of protein in native conformation or the amount of aggregate. *Id.*

C. Wherein at Least 98 or 99% of the VEGF Antagonist is Present in Native Conformation Following Storage at 5°C. for Two Months as Measured by SEC

The claim phrase "wherein at least 98% [or 99%] of the VEGF antagonist is present in native conformation following storage at 5° C. for two [or 24] months as measured by size exclusion chromatography" should be construed in a way that is most consistent with the specification, that is, that "at least 98%" or "at least 99%" is in comparison with the amount of VEGF trap in native conformation reported at time zero. EX1002 ¶¶44, 74. That is, the claim permits a maximum of 1% or 2% of the VEGF antagonist initially present in intact functional form at time zero to have aggregated (or otherwise degraded) during the specified storage period.

This construction is consistent with the specification of *US865*. *Id.* ¶¶74-75. Specifically, *US865* discloses that the "invention includes liquid pharmaceutical formulations having increased stability." EX1001, 1:49-50. *US865* also states that the VEGF antagonists used for making the formulation are preferably "substantially free of protein contaminants" or "substantially free of aggregates." *Id.*, 6:42-55. *US865* defines "substantially free" as at least 90% of the *weight* of the fusion protein used *in making* the formulation is substantially free of contaminants or aggregates. *Id*; EX1002 ¶43. As *US865* teaches that the % VEGF antagonist in native conformation is measured by SEC, a POSA would understand that at least 90% of the total amount of the weight of the VEGF protein used in

making the formulation is not aggregated. Stated differently, approximately at least 90% of the weight of the initial amount of protein is VEGF antagonist, that is, at least 90% of the weight of the protein used in making the formulation is the fully-intact and functional conformation of the VEGF antagonist protein. EX1002 ¶75.

A POSA would understand that any initial measurement of the amount of a VEGF antagonist would not include the amount of aggregated protein that may have been included in the weight of the VEGF antagonist that was used in making the formulation because a POSA would understand once a protein is aggregated, it rarely un-aggregates. EX1002 ¶76. Measuring the native conformation of an aggregated protein that was already aggregated before storage is thus an oxymoron—an aggregated protein is not present in its intact functional conformation, and there is little possibility that an aggregated protein could revert to its native, functional conformation. Accordingly, this claim phrase should be construed such that the "at least 98% or 99%" is in comparison with the amount of VEGF antagonist that is in intact functional form at time zero. *Id.* ¶¶74-75

Regeneron may argue, as it did at the district court, that the that the claim phrase "at least" 98% or 99% of the VEGF-antagonist "is present in native conformation after … storage at 5º C as measured by SEC" should be construed as requiring that at least 98 or 99% of the total amount of protein used to make the

formulation is present in its intact functional conformation after storage, i.e., the absolute amounts disclosed in the Tables. As discussed above, this construction is not consistent with the teachings of the specification. EX1002 ¶77.

Regardless of how this claim term is construed, the claims are only entitled to an effective filing date as discussed in Section VII and are still anticipated and/or rendered obvious by *US432*, which has the same disclosure as *US865*.

D. Glycosylated

In *Mylan*, the parties stipulated that the term "glycosylated" in claim 1 means "containing at least one amino acid residue with an attached carbohydrate." EX1024, 50. As Regeneron stipulated to this construction at the district court, this construction is adopted for purposes of this petition. EX1002 ¶79.

VII. EFFECTIVE FILING DATE OF *US865*

A. Legal Standard

To obtain the benefit of an earlier filed application, including a provisional application, the later-filed application must claim an invention that is also disclosed in the prior application *and* the disclosure of the invention in the prior- and later-filed applications must satisfy the requirements of pre-AIA 35 U.S.C. §112, first paragraph, *i.e.*, enablement and written description. 35 U.S.C. §§119, 120; *see also Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1571 (Fed. Cir. 1997) (noting that to receive "the benefit of the filing date of an earlier application under

35 U.S.C. § 120, each application in the chain leading back to the earlier application must comply with the written description requirement of 35 U.S.C. § 112.").

The written description of an invention "must 'clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.'" *Ariad Pharmaceuticals, Inc. v. Eli Lilly and Co.*, 598 F.3d, 1336, 1351 (Fed. Cir. 2010) (alteration original). "In other words, the test for sufficiency is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession *of the claimed subject matter* as of the filing date." *Id.* (emphasis added). Although *ipsis verbis* support for the claim language is not required, there must be sufficient "blaze marks" in the specification pointing the skilled artisan to the claimed invention. *Regents of the Univ. Minn. v. Gilead Sciences Inc.*, 61 F.4th 1350, 1357 (Fed. Cir. 2023); *see also Purdue Pharma L.P. v. Faulding, Inc.*, 230 F.3d 1320, 1323 (Fed. Cir. 2000). "[T]he level of detail required [in the specification] to satisfy the written description requirement varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology." *Ariad Pharmaceuticals., Inc. v. Eli Lilly and Co*., 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). As discussed below in Sections VII.C-D, the stability and general glycosylation limitations of the challenged claims are not supported by the common specification, and, thus, at

best, are entitled to the filing date of the application in which claims containing those limitations were added.

B. Effective Filing Date of *US865*

US865 is not entitled to an effective filing date before the publication date of *US432*. 35 USC §§119(e), 120. The table below lists the applications and patents to which *US865* claims priority.

Priority Document	Filing Date	Exhibit Number of Prosecution History/Provisional Filing
16/582,486, now US11,066,458	09/25/2019	1007
16/159,269, now US10,464,992	10/12/2018	1008
15/879,294, now US10,400,025	01/24/2018	1009
15/095,606, now US9,914,763	04/11/2016	1010
14/330,096, now US9,340,594	07/14/2014	1011
13/914,996, now US8,802,107	06/11/2013	1012
13/329,770, now US8,481,046	12/19/2011	1013
12/833,417, now US8,092,803	07/09/2010	1014
12/560,885, now US7,807,164	09/16/2009	1015
11/818,463, now US7,608,261	06/14/2007	1016
60/814,484	06/14/2006	1025

The above listed utility applications all have the same specification (except for the continuity statement). EX1002 ¶¶93-94, 154.

App559, which issued as *US865*, was filed with claims drawn to a PFS, wherein the VEGF antagonist is produced in a CHO cell and requiring the stability limitations. *See* EX1006, 47-48. On March 24, 2021, the examiner rejected the claims for ODP. *Id.*, 256-262. Regeneron amended the claims on May 5, 2021, to drop the CHO cell limitation, and added a limitation that the VEGF antagonist is glycosylated, without specifying the sites of glycosylation, and comprises amino acids 27-457 of SEQ ID NO:4.[5] EX1006, 279-292. The claims were also amended to include claims to a vial, PFS, and a formulation. *Id*. After the filing of a terminal disclaimer (*id.*, 293), the examiner allowed the amended claims. *Id*., 305-308. Thus, at best, the general glycosylation limitation is entitled to the filing date of *App599*, January 10, 2020.

App486 was filed with claims drawn to a vial and a formulation in which the VEGF antagonist is produced in CHO cells, containing no limitations drawn to stability or glycosylation. EX1007, 15. The day after filing, Regeneron added

[5] As-issued dependent claims 15, 23, 40, and 48 add the limitation that the "formulation is capable of providing a turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5º C." EX1001, claims 15, 23, 40, 48. This limitation suffers the same deficiencies as the stability limitations, but because it only applies to a small number of claims, Petitioner does not focus on it here.

claims drawn to a vial containing a VEGF antagonist formulation and containing the at least 98% and 99% two-month stability limitations, asserting that no new matter had been added. EX1007, 51-55. A second preliminary amendment was submitted on July 13, 2020, with claims drawn to a glass vial and a PFS, wherein the claims contained the stability limitations. In addition, claims drawn to VEGF antagonist glycosylated at asparagine residues 62, 94, 149, 222, and 308 were added, but without a general glycosylation limitation. *Id*., 254-58. The examiner rejected the claims for ODP, and Regeneron filed a terminal disclaimer as to certain patents but not others, arguing that the claims of the patents to which it had not filed terminal disclaimers did not contain the stability limitations. *Id.*, 295-312. The claims were allowed soon thereafter. *Id*., 392.

App269 was filed with claims drawn to a vial and a formulation in which the VEGF antagonist is produced in CHO cells, and contains no limitations drawn to stability or glycosylation. EX1008, 2-4. Thus, as of the October 12, 2018, filing date of *App269*, there was no written description support for the stability limitations or the general glycosylation limitation. *See* Sections VII.C-D. The claims were rejected for ODP. *Id*., 75-80. In response, on July 22, 2019, Regeneron amended the claims to recite the stability limitations, asserting that no new matter had been added, and filed terminal disclaimers as to one of the patents that were the basis of the ODP rejections. *Id*., 89-95. As to the remaining

rejections, Regeneron argued that the newly-added stability limitations were not included in the claims in the patents over which the claims had been rejected for ODP. *Id*., 93-94. The claims were then allowed. *Id*., 104. Thus, at best, the stability limitations are entitled to an effective filing date that is the filing date of *App269*, *i.e.*, October 12, 2018. *See* Section VII.C; EX1002 ¶105.

The claims of the remaining applications listed above did not contain the stability limitations (*see* EX1009-EX1013, EX1015-EX1016), except for *App417*, which was filed July 9, 2010. *App417* issued as US8,092,803 with claims that contained the limitation "wherein at least 99% of the VEGF antagonist is present in native conformation following storage at 5° C. for 2 months as measured by size exclusion chromatography," which was part of the claims as originally filed with *App417*. EX1014, 23-25. US8,092,803 issued on January 10, 2012, and thus was not co-pending with *App559*, *App486*, or *App269*. EX1002 ¶¶108-109. Accordingly, the claims of US8,092,803 cannot serve as written description support for the claims of *US865*. *In re Hogan*, 559 F.2d 595, 609 (C.C.P.A. 1977) ("[T]here has to be a continuous chain of copending applications each of which

satisfies the requirements of §112 with respect to the subject matter presently claimed.").[6]

C. The *App559* Disclosure Lacks Written Description Support for the Stability Limitations

The challenged claims of *US865* all contain stability limitations, which, as discussed above, were added during prosecution of *App269*. Regeneron did not, and could not, explain to the examiner how the disclosure as filed provides written description support for the added stability limitations, because it does not. The only portion of the specification that discusses the stability of the formulation after storage is in the examples, and that is only through the reporting of specific data points for a VEGF antagonist described as SEQ ID NO:4, which Regeneron has acknowledged is aflibercept. *See* EX1048, 7-8, EX1024, 195-96. There is no discussion of a desired level of stability after a specified time of storage or the lower 98 and 99% end points (reflecting a maximum change in the amount of native VEGF antagonist from time zero of 2 or 1%), much less the currently claimed ranges, in the general disclosure or the text accompanying the examples. EX1002 ¶112, 141; *Purdue Pharma*, 230 F.3d at 1326-27 ("As *Ruschig* makes

[6] Even if Regeneron were to argue it is entitled to claim priority back to the July 9, 2010, filing of *App417*, *US432* was still published over a year before that priority date.

clear, one cannot disclose a forest in the original application, and then later pick a tree out of the forest and say here is my invention. In order to satisfy the written description requirement, the blazemarks directing the skilled artisan to that tree must be in the originally filed disclosure.").

According to the disclosure as filed, the "invention includes liquid pharmaceutical formulations having increased stability …," linking the stability to the formulation. EX1001, 1:49-52; EX1006, 4. The disclosure, however, does not define the term "stability."[7] *E.g.*, EX1001, 6:60-7:24, EX1006, 11-12. As Regeneron argued in the *462IPR*, a POSA would not necessarily read "stability" in this context as requiring 98% or 99% stability. EX1026, 56-58 (Regeneron's POR in the *462IPR*, noting that multiple FDA-approved products were known to have less than 98% of the product present in native conformation); EX1021 ¶¶164, 168-174. Nor does the disclosure as filed point to obtaining any specific stability at two months or twenty-four months, much less a general disclosure of the 98 and 99% lower limits of the claimed stability limitations for the broadly claimed

[7] The specification provides a lower limit of 90% for the amount of aggregates used in making the formulation, but as Dr. Tessier notes, that section of the specification addresses the preparation of the formulation, and not its stability over time. EX1002 ¶¶117-118.

formulations. Thus, the disclosure of "increased stability" does not support the 98 and 99% lower limits of the claimed stability limitations. EX1002 ¶¶114-118.

Moreover, the plain and ordinary meaning of the claim phrase "at least 98%" is a range encompassing 98-100%, and of "at least 99%" is a range encompassing 99-100%. *Quantum Corp. v. Rodime, PLC*, 65 F.3d 1577, 1581 (Fed. Cir. 1995) (reading in an implicit range when interpreting "at least 600 tpi" as a range, i.e. 600 tpi and up). The disclosure as filed, however, does not disclose, discuss, or suggest these ranges or their end-points, and thus again fails to provide support for the claim limitation in which at least 98% (or 99%) of a glycosylated VEGF antagonist comprising amino acids 27-457 is present in native conformation following storage at 5ºC for two months (or twenty-four months) as measured by SEC for the broadly claimed formulations. EX1002 ¶¶111-113.

Moreover, the examples do not provide data that allow the skilled artisan to derive the lower 98% and 99% end points of the claimed ranges. Nothing in the general disclosure, the text accompanying the examples, the data, or anything else in the specification provide blaze marks to the % claimed stability limitations including the 98 and 99% lower end or 100% upper end of the claimed range. The specification does not provide disclosure from which a POSA would understand that Regeneron possessed the currently claimed stability limitations at the time of filing of the disclosure. *Purdue Pharma*, 230 F.3d at 1326. As in *Purdue Pharma*,

Regeneron has merely picked a characteristic that it will argue is encompassed by its examples, "a characteristic that is not even discussed in passing in the disclosure, and then make it the basis of claims that cover not just [the exemplified formulations], but any formulation that has that characteristic." *Id.* at 1327. As the court noted in *Purdue Pharma*, "[t]his is exactly the type of overreaching the written description requirement was designed to guard against." *Id.*

The data points reported in the Tables from the very closely related formulations of the examples in the absence of a specific definition for the term "stability" are not sufficient for a POSA to recognize that Regeneron invented what is now claimed. And a POSA reading the narrow examples would not understand that the inventors possessed the broadly claimed formulations having the claimed stability range after storage for a defined amount of time given only the specifically reported data points of the examples having very similar formulations. EX1002 ¶¶122-125, 133. In fact, Regeneron has argued that the stability limitations reported in the examples should be limited to the specific lot of aflibercept used. Specifically, in response to an inherency argument in SB's brief appealing the district court's grant of Regeneron's motion for a preliminary injunction that claim 5 of US9,340,594, which claims the EYLEA commercial formulation but does not expressly describe the VEGF antagonist as being glycosylated or as having the stability over time as recited by the challenged

claims, Regeneron argued that "claim 5 [of *US594*] (unlike Example 3) is not directed to a particular lot of aflibercept…; accordingly, the formulations of claim 5 do not always achieve the 98% native conformation after 2 months achieved in Example 3 and required by the asserted claims, foreclosing a finding of inherency." EX1048, 50. A sufficient written description requires a statement of an invention, not an invitation to go on a hunting expedition to cobble together, after the fact, a synthetic definition of an invention. *Indivior UK Ltd. v. Dr. Reddy's Labs. S.A.*, 18 F.4th 1323, 1329 (Fed. Cir. 2021) (finding that PO's range was not described but was merely "cobbling together numbers after the fact").

During prosecution of *App559*, when introducing claims reciting these stability limitations via preliminary amendment, Regeneron pointed to ¶37 and Example 6 of the disclosure for support. EX1006, 45. Paragraph 37, however, merely states that "[t]he invention further features ophthalmic formulations provided in a pre-filled syringe or vial, particularly suitable for intravitreal administration." EX1006, 9. No explanation was offered as to how ¶37 provides written description support for the stability limitations. EX1002 ¶120, 140.

Example 6 of the disclosure measures the stability of a specific 40mg/ml "VEGF Trap Protein" liquid formulation stored at 5ºC in a 1ml pre-filled glass syringe. EX1006, 16. Table 6, reproduced below, shows the stability results when stored at 5ºC:

Table 6. Stability of 40 mg/ml VEGF Trap Protein (VGFT-SS203)

Months	Visual Appearance	Turbidity	pH	% VEGF Trap Recovered	% VEGF Trap Native Configuration
0	Pass	0.00	6.3	100	99.2
0.5	Pass	0.01	6.3	101	99.2
1	Pass	0.00	6.3	101	99.2
2	Pass	0.00	6.3	-	-
3	Pass	0.01	6.3	102	99.1
4	Pass	0.01	6.3	103	98.8
5	Pass	0.00	6.3	99	98.9

Id. Table 6 does not present two-month or 24-month stability data, and the results presented are limited to a specific formulation. Even assuming that the two-month stability data were around 99.1 or 99.2% (the reported three month and one month stability, respectively, having no change or a 0.1% change from time zero), this example does not provide the necessary written description support for the claimed lower limit of 98%, much less ranges of 98-100% or 99-100%. EX1002 ¶¶121-122. There are no blaze marks pointing the skilled artisan to the claimed stability ranges or indicating that the data points would also apply to the broad range of formulations encompassed by the claims. The formulation of Example 6 contained 40 mg/ml VEGF Trap, 10mM phosphate, 135mM NaCl, 0.03% polysorbate 20, at a pH of 6.3. EX1006, 16 (Table 6). None of the challenged claims recite a formulation at that level of detail. EX1002 ¶122.

Examples 1-5[8] fare no better. Again, as demonstrated below, the formulations of those examples are drawn to narrow ranges of essentially the same excipients as Example 6. Specifically, Example 5 uses the same formulation as Example 6, while Examples 3 and 4 use 40mM NaCl (as opposed to 135 mM in Example 6) and add 5% sucrose. EX1006, 14-16. Examples 1 and 2 both contain 50mg/ml VEGF Trap, 50 mM NaCl, and 5% sucrose, while Example 1 uses 0.1% polysorbate 20, and Example 2 uses 3% polyethylene glycol 3350. *Id.* Examples 1

[8] Examples 7 and 8 are not addressed as they relate to lyophilized formulations and are thus not relevant to the formulations claimed in *US865*. Even if considered, they do not support the 98-100% or 99-100% ranges added by amendment. The buffers in which the VEGF Trap was lyophilized were very similar to the other examples, and the text accompanying these examples does not disclose the idea of a range, much less the claimed range. In addition, as further discussed below, the "% VEGF Trap Recovered" at time 0 was 100%, which actually went up in both examples to 106 or 105%, respectively, at 1 month, and 103% for both examples at 2 months. As both "% VEGF Trap Recovered" and "% VEGF Trap Native Config." is measured by SEC, a POSA would understand from the increase in "% VEGF Trap Recovered" from the 100% at time 0 that using SEC introduces error into the data obtained using SEC. EX1002 ¶¶124-125.

and 2 do not provide data for two months. Examples 3 and 4 reported two-month % VEGF Trap Native Configurations of 99.2% and 99.1%, respectively. As for twenty-four months (claims 17, 25, 42 and 50), Examples 1 and 2 reported 98.1 and 97.6%, respectively, and Examples 3-8 did not report a 24-month value. *See* EX1006, 13-17.

Regeneron never explained how any example provided support for the added at least 98% (i.e., a range of 98-100%) or at least 99% (99-100%) two-month limitations or the at least 98% 24-month limitation. In fact, the lowest change in % native conformation from time zero to two months reported by *US865* for a non-lyophilized formulation is 0.3%, and it is for the single, specific formulation of Examples 3 and 4. EX1006, 14-15 (Examples 3 (99.5% VEGF Trap Native Configuration at Time 0 and 99.2% at two months) and 4 (99.4% at Time 0 and 99.1% at two months)). Regeneron also never explained how the very similar formulations of the Examples provide written description support for these limitations given the broad range of formulations encompassed by the claims. For example, many of the challenged claims depend from claim 5 of *US865*, which encompasses a formulation having 40mg/ml VEGF Trap and 0.01%-3% polysorbate 20. Other claims add a buffer, or a stabilizing agent, or specify the glycosylated residues, but none of the challenged claims specify narrowed ranges of all of these excipients at the same time in the same claim.

The examples provide specific measurements for very specific formulations, and not all the examples report SEC results at two and/or 24 months. There are no "blaze marks" in the general disclosure or in the text accompanying the examples leading the skilled artisan to the claimed range end points of 98% or 99% at the low end, and 100% at the high end for the narrow set of formulations in the examples, much less the broader set of formulations encompassed by the challenged claims. EX1002 ¶134. In fact, there are no "blaze marks" in the general disclosure or the text accompanying the examples that would have directed the skilled artisan to understand that ranges of a VEGF antagonist that is present in native conformation following storage at 5°C. at 2 or 24 months as measured by SEC is an aspect of the invention. And at even a higher level, there are no "blaze marks" pointing the skilled artisan to the understanding that the use of SEC data at 2 months and/or 24 months was part of Regeneron's invention. While the claims do not need *in haec verba* support, "the specification must indicate with some clarity what the claim recites." *Indivior*, 18 F.4th at 1328. As the *Indivior* court noted, "[i]n the case of a claimed range, a skilled artisan must be able to reasonably discern a disclosure of that range."

The level of description required is also dependent on the complexity and predictability of the relevant art. Notably, in the *462IPR* challenging claims of *US992*, which has the same specification as *US865,* Regeneron characterized the

art as highly unpredictable. For example, Dr. Klibanov testified in the *462IPR* that as of 2006, "it was known that even small structural differences between two proteins of the same class can lead to significant stability differences," and as noted above in Section I.C.1.a, the claims encompass VEGF trap proteins having additional amino acids at either or both of the C- and N-termini. EX1027 ¶63 (the declaration of Regeneron's own expert submitted in support of its Preliminary Response in the *462IPR*); *see also id*. ¶¶64-69. Dr. Klibanov also testified that other factors that can affect stability include glycosylation (EX1021 ¶45), excipients (*id.* ¶46), and protein concentration (*id.* ¶47). According to Dr. Klibanov, "it was known that even a minor change in any of the aforementioned variables could affect whether a protein remains in its native conformation over time," asserting that "the magnitude of the effect would be impossible to predict based on theory alone." *Id.* ¶50. Here, as already discussed, the examples all use the same or very similar formulations, whereas the claims encompass a much broader range of formulations. The complexity and unpredictability of the art asserted by Regeneron through Dr. Klibanov further support the conclusion that the skilled artisan would not read the limited examples as demonstrating that the inventors have possession of the claimed invention. EX1002 ¶132.

There is yet further reason that the 98 and 99% lower stability limitations do not have written description support in the specification. All the Tables of the examples not only report "% VEGF Trap Native Configuration" and "Turbidity," which are concepts that are included in the claims, but also report "% VEGF Trap Recovered." "% VEGF Trap Recovered," like "% VEGF Trap Native Configuration," was measured using SEC. EX1001, 8:40-43; EX1002 ¶126. As would be understood by the POSA, SEC will only measure the protein that travels through and is eluted from the SEC column. *Id.*; *see also* Section I.C.1.b. The patent asserts that VEGF Trap that is in native configuration—that is, fully intact and functional conformation of the protein—will pass through the column. Degradants that are approximately size and shape as VEGF Trap in its native configuration may co-elute with VEGF trap in its native configuration. And, as Dr. Tessier explains, certain aggregates and degradants will not pass through the column. EX1002 ¶¶126-127. This is reflected in the Tables of the examples. All the examples have 100% VEGF Trap recovered at time zero. That does not reflect that 100% of the protein used in the formulation was recovered, but, as Dr. Tessier explains, is most likely the amount of protein that was eluted from the column at time zero and normalized to 100% VEGF Trap recovered. *Id*.

Looking at Table 3 specifically, the "% VEGF Trap Recovered" goes from 100%, 99%, 98%, to 95% at 0, 0.5, 1, and 2 months, respectively. The

specification does not address this change, but a POSA would attribute it to loss of protein that failed to make it through the column due to degradation and/or aggregation. Thus, the POSA would understand that the loss of the % of VEGF Trap in native configuration is not just the 0.1 or 0.3% at times 0.5 and 2 months, but would include the decreases from 100% of the %VEGF Trap Recovered at those times of 1% and 5%, respectively. Thus, the POSA would understand that the total loss would be higher than 1 and 5%, respectively, with the amount of loss at 2 months thus being greater than the maximum of 1 or 2% allowed by the claims. EX1002 ¶128.

Table 5 demonstrates further why a POSA would not read the data in the examples as providing written description support for the claimed ranges of "at least 98%" or at least "99%." The "% VEGF Trap Recovered" at time points 0, 0.5, 1, 2, 3, 4, and 5 is 100, 87, 88, 103, 88, 85, and 84, respectively. Just between 0 and two months the % VEGF Trap Recovered goes down to 87% and then back up to 103%. The 87% either represents loss of protein due to degradation and/or aggregation of up to 13%, while 103% would suggest an increase of 3% from time zero. And in Table 2, the "% VEGF Trap Recovered" is reported to be as high as 113%. EX1002 ¶129. Aggregation is known to be essentially irreversible. EX1002 ¶¶76, 127, 130. The data presents no margins of error, and the specification and text accompanying the examples do not explain why amounts of

% VEGF Trap Recovered over 100% were obtained. But, as Dr. Tessier explains, a POSA would most likely assume that the 103% reported value is due to measurement error. EX1002 ¶¶130-131. Thus, when the inventors measured "% VEGF Trap Recovered" by SEC, the data suggest their assay produced measurement errors of at least 3%, and maybe as high as 13%. And when it comes to measuring "% VEGF Trap Native Configuration" neither the specification nor the text accompanying the examples explains whether and how the SEC method used to measure "% VEGF Trap Native Configuration" is different from that used to measure "% VEGF Trap Recovered." A POSA would thus read the specification as indicating that there is a margin of error in measuring the amount of VEGF trap by SEC, and a change from time zero of up to two percent of VEGF antagonist in native conformation as claimed is well below a possible margin of error of 3-13%. *Id.*

The lack of written description for these added ranges is further highlighted by Regeneron's addition of claims 17, 25, 42, and 50 reciting the at least 98% 24-month stability limitation. Each of those claims requires 40 mg/ml VEGF antagonist. As noted above, only Examples 1 and 2 contain 24-month data, but neither Example 1 nor 2 is a 40 mg/ml formulation, and only Example 1 is reported to be above 98%. EX1002 ¶¶135-139. The SEC value reported for Example 2 in Table 2 is 97.6%. EX1002 ¶¶46, 123, 136. To the extent Regeneron's

construction for "wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5° C. for 24 months as measured by [SEC]" as being the absolute amount reported by the Tables is adopted, the 97.6% reported stability in Table 2 fails to meet that limitation.[9] Reciting one or two data points within a range, wherein neither results from a formulation covered by the claims, is not sufficient to support the claimed stability range of 98-100% at 24 months. *Indivior UK Ltd.*, 18 F.4th at 1329 (disclosure of four points does not constitute disclosure of a range).

D. Claims 1-13, 15-21, 23-38, 40-46, and 48-50 Lack Written Description Support for the General Glycosylation Limitation

Independent claims 1 and 26 require the VEGF Trap to be glycosylated without specifying the type of glycosylation or which residues are glycosylated. But as to glycosylation, the disclosure states:

> A VEGF antagonist…includes fusion proteins capable of trapping VEGF. In a preferred embodiment, the VEGF antagonist is the fusion protein of SEQ ID NO:2 or 4; more preferably, SEQ ID NO:4. In specific embodiments, the VEGF antagonist is expressed in

[9] If Celltrion's claim construction is adopted, this data point would fall within the claimed range, as the reported stability at time 0 is 98.9%, reflecting a change from time 0 to 24 months of 1.3%.

> a mammalian cell line such as CHO cells and may be modified translationally. 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. Preferably, the VEGF antagonist is a dimer compound of two fusion proteins of SEQ ID NO:4.

EX1001, 6:27-39; EX1006, 11.

The disclosure mentions glycosylation only once, and only mentions one glycosylated VEGF antagonist variant. EX1002 ¶¶97, 99, 142-145. That one variant is glycosylated at each of Asn residues 62, 94, 149, 222, and 308. EX1001, 6:27-39; EX1006, 11.

The parties in *Mylan* stipulated that the term "glycosylated" in claim 1 means "containing at least one amino acid residue with an attached carbohydrate." EX1024, 50. Thus, to the extent that glycosylation in claim 1 is construed to mean anything other than glycosylation at each of Asn residues 62, 94, 149, 222, and 308, such as in the construction adopted by the district court (*see* Section VI.D.), the term "glycosylated" lacks written description support, and at best, such clams are only entitled to the filing date of *App559*, *i.e.*, January 10, 2020. EX1002 ¶¶146-147.

E. Claims 18 and 43 Lack Written Description Support for the "No Phosphate" Limitation

Demonstrating the lengths Regeneron has gone to stretch the disclosure to cover possible competitors, Regeneron also added claims reciting "wherein said formulation does not contain phosphate" (the "no phosphate limitation") in an amendment filed on May 5, 2021, during prosecution of *App559*. EX1006, 286-92. For the disclosure to support this negative limitation, it must disclose a reason to exclude or an alternative. *Novartis Pharms. Corp. v. Accord Healthcare, Inc.*, 38 F.4th 1013, 1016-17 (Fed. Cir. 2022). Although the specification discloses buffers generally, the only specific buffer noted, and the only buffer used in the examples, is phosphate. EX1006, 5-6. The disclosure provides no possible reason to exclude phosphate and identifies no alternative, and therefore lacks written description support for this limitation. EX1002 ¶¶47, 148-151. Accordingly, at best, these claims are entitled to a filing date of January 10, 2020, which is the filing date of *App559*. EX1002 ¶152.

VIII. GROUNDS FOR UNPATENTABILITY

As noted by Judge Rader in *AK Steel Corp. v. Sollac*, when an applicant files a continuing application, and that later application contains new matter such that the later application cannot claim priority to the earlier application, the earlier application can become anticipatory prior art. 344 F.3d 1234, 1245-46 (Fed. Cir. 2003) (Judge Rader, concurring). As noted above, (a) *US432* is the published

application of the first utility application in *US865*'s priority chain and has the same specification as *US865*, and (b) the earliest possible priority date that any of the claims of *US865* may be entitled is October 12, 2018. EX1002 ¶153. Since *US432* was published on December 20, 2007, it is prior art to *US865*. And although the common specification does not provide written description support for the broad challenged claims, it anticipates those claims by disclosing a species that is encompassed by those broad claims. *See* PGR2021-00088, Paper 16 at 7 (Vidal, August 16, 2023).

A. Ground 1: Claims 1-17, 19-42, and 44-50 are Anticipated by *US432*

1. Claims 1 and 26

Claim 1 requires (a) a vial containing an ophthalmic formulation suitable for intravitreal administration, (b) a glycosylated VEGF antagonist comprising amino acids 27-457 of SEQ ID NO:4, (c) an organic co-solvent, (d) a buffer, and (e) a stabilizing agent, all in unspecified amounts, and (f) wherein at least 98% of the VEGF antagonist must be present in native conformation following storage at 5°C. for two months as measured by SEC. Claim 26 claims a PFS comprising the same formulation with the same limitations as vial claim 1. EX1002 ¶¶155-156. *US432*, which has the same specification and thus provides the same support for the claims as *US865*, expressly or inherently discloses every element of claims 1 and 26. EX1002 ¶157.

US432 discloses "ophthalmic formulations provided in a PFS or vial suitable for intravitreal administration," meeting these limitations. EX1004 ¶¶3, 39. Accordingly, the disclosed formulations meet the respective vial/PFS, ophthalmic formulation and intravitreal administration limitations of claims 1 and 26. Moreover, a POSA would have understood that the formulations used in the Examples are also ophthalmic formulations for intravitreal administration. EX1004 ¶¶39, 60-65; EX1002 ¶158.

The Examples of *US432* all state that "VEGF Trap (SEQ ID NO:4)" was used. EX1004 ¶¶60-65; EX1002 ¶159. The examples do not specify that amino acid residues 27-457 of SEQ ID NO:4 were used, but the use of "comprising" in the claims does not exclude the use of the full SEQ ID NO:4. The only method of producing the VEGF antagonist specifically disclosed in *US432* is expression in CHO cells. EX1004 ¶48; EX1002 ¶¶159-160. As Regeneron's expert Dr. Klibanov noted in the 462IPR, amino acids 1-26 of SEQ ID NO:4 are a signal sequence,[10] which would be cleaved off in the final VEGF protein produced by CHO cells. *See* EX1021 ¶121; EX1027 ¶54**;** EX1002 ¶160. A POSA would have

[10] A signal sequence enables a protein to find its correct location outside the cell membrane by tagging the protein for transport through the cell membrane and out of the cell. EX1027 ¶48 n.19.

understood that when SEQ ID NO:4 is expressed in CHO cells the signal sequence would be cleaved-off post-translationally, leaving amino acids 27-457.

Although *US432* discloses the VEGF antagonist "may be glycosylated at Asn residues 62, 94, 149, 222 and 308" (EX1004 ¶48), the examples of *US432* do not specifically disclose the glycosylation state of the VEGF antagonist (EX1004 ¶¶60-65). EX1002 ¶¶161-162. A POSA would have understood, however, that post-translational processing in CHO cells would result in glycosylation at Asn residues 62, 94, 149, 222, and 308 of SEQ ID NO:4 as used in the Examples. *Id*. The POSA would also would have understood that only the examples report the % VEGF antagonist present after storage, and given that the only disclosed method of making the VEGF antagonist is in CHO cells, the VEGF antagonist of the examples comprised amino acids 27-457 of SEQ ID NO:4 that was glycosylated at Asn residues 62, 94, 149, 222 and 308. EX1002 ¶¶87-92. Moreover, Regeneron has acknowledged that Examples 3 and 4 of *US865*, and thus *US432*, "disclose the liquid formulation having the same components as the formulation now marketed as EYLEA: '40 mg/ml VEGF Trap (SEQ ID NO:4), 10 mM phosphate, 40 mM NaCl, 0.03% polysorbate 20, 5% sucrose.'" EX1048, 7-8; *see also* EX1024, 195-96 (citing Example 3 in finding EYLEA is an embodiment of the claims).

Examples 3 and 4 disclose that the respective formulations were stored at 5°C. in 3 ml glass vials or PFS, respectively, and tested at 2 months, with purity

determined "as described above." *See, e.g.*, EX1004 ¶¶62-63; EX1002 ¶163. A POSA would have understood that "as described above" refers to the following statement in Example 1 of *US432*: "purity [was measured] by size exclusion HPLC," which a POSA would understand to be size exclusion chromatography ("SEC"). EX1004, ¶60; EX1002 ¶163. Tables 3 and 4 of Examples 3 and 4, respectively, disclose that at 2 months, 99.2% and 99.1%, respectively, of the VEGF antagonist had its native configuration. EX1004 ¶¶62-63; EX1002 ¶163. In addition, the % VEGF Trap Native Configuration at time zero was 99.5 and 99.4 in Examples 3 and 4, respectively. Thus, the change in % VEGF Trap Native Configuration from time zero to two months for both examples is 0.3%. Accordingly, regardless of how the claim phrase "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" is construed, Examples 3 and 4 of *US432* disclose embodiments of formulations with the native configuration required by claims 1 and 26 of *US865*.

As to the remaining limitations, Example 3 of *US432* discloses a stability study of a liquid VEGF antagonist stored in a vial that has the following: a VEGF antagonist (VEGF Trap); 0.03% polysorbate 20, an organic cosolvent; 10 mM phosphate, a buffer; and 5% sucrose, a stabilizing agent. EX1004 ¶62; EX1002

¶164. Example 4 discloses the same formulation elements for a PFS. EX1004 ¶63; EX1002 ¶164.

Accordingly, *US432* discloses every element of claims 1 and 26, arranged as in the claim, anticipating those claims. EX1002 ¶¶162, 165.

2. Claims 2-5 and 27-30

Claims 2-5 and 27-30 depend from claims 1 and 26, respectively, and further require that the VEGF antagonist has a concentration of 40 mg/ml (claims 2 and 27) and that the organic co-solvent comprises: polysorbate (claims 2 and 27); 0.01-3% polysorbate (claims 3 and 28); about 0.03% to about 0.1% polysorbate 20 (claims 4 and 29); or 0.01%-3% polysorbate 20 (claims 5 and 30). EX 1001, 19:42-50, 21:13-23. Examples 3 and 4 of *US432* disclose formulations that have 40 mg/ml concentrations of VEGF antagonist and 0.03% polysorbate 20 organic cosolvent. EX1004 ¶¶62-63. For these reasons and those explained above as to claims 1 and 26, *US432* anticipates claims 2-5 and 27-30 of *US865*. EX1002 ¶¶166-167; *see also* Section VIII.A.1.

3. Claims 6-9 and 31-34

Claims 6-9 and 31-34 depend from claim 5 and 30, respectively, and further require that the buffer comprises phosphate buffer (claims 6 and 31) that comprises 5-25mM buffer (7 and 32), wherein the buffer comprises a pH of about 5.8-7.0 (claims 8 and 33) or about 6.2-6.3 (claims 9 and 34). EX1001, 19:51-58, 21:24-31.

The formulation disclosed in Examples 3 and 4 of *US432* has 10 mM sodium phosphate buffer and a pH of 6.3, which meets the added limitations of claims 6-9 and 31-34. EX1004 ¶¶62-63. For this reason and those explained above, *US432* anticipates claims 6-9 and 31-34. EX1002 ¶168; *see also* Section VIII.A.1.

4. Claims 10-13 and 20-21, and Claims 35-38 and 45-46

Claims 10-13 and 20-21 depend directly or indirectly from claim 5 and claims 35-38 and 45-56 depend directly or indirectly from claim 30. These claims further require that the stabilizing agent comprises a sugar (claims 10 and 35) wherein the sugar can be sucrose (claims 11 and 36), that the stabilizing agent comprises 1.0-7.5% sucrose (claims 12 and 37) or 1.0-10% sucrose (claims 20 and 45), and that the formulation further comprises a tonicity agent (claims 13, 21, 38 and 46). EX1001, col. 19-22. The formulation disclosed in Examples 3 and 4 of *US432* has 5% sucrose (a sugar) and 40 mM NaCl (a tonicity agent), which meet the added limitations of these claims. EX1004 ¶¶62-63. For this reason and those explained above as to claims 1, 5, 26, and 30, *US432* anticipates claims 10-13, 20-21, 35-38 and 45-46. EX1002 ¶169; *see also* Section VIII.A.2.

5. Claims 14, 22, 39, and 47

Claims 14, 22, 39, and 47 depend from claims 5, 20, 30, and 45, respectively, and further require that the VEGF antagonist is glycosylated at

asparagine residues corresponding to asparagine residues 62, 94, 149, 222, and 308 of SEQ ID NO:4. EX1001, col. 20-22.

As noted above as to claims 1 and 26 (Section VIII.A.1), *US432* specifically teaches that the VEGF antagonist "may be glycosylated at Asn residues 62, 94, 149, 222 and 308." EX1004 ¶48. As explained above, a POSA would understand that post-translational processing in CHO cells would result in glycosylation at Asn residues 62, 94, 149, 222, and 308 of SEQ ID NO:4 as used in the Examples. EX1002 ¶171. For this reason and those explained above as to claims 1, 5, 20, 26, 30, and 45, *US432* anticipates claims 14, 22, 39, and 47. EX1002 ¶¶170-172; *see also* Section VIII.A.4.

6. Claims 15, 23, 40, and 48

Claims 15, 23, 40, and 48 depend from claims 5, 20, 30, and 45, respectively, and further require that the formulation is "capable of providing turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5° C." EX1001, col. 20-22. Examples 3 and 4 of *US432* disclose formulations that were stored in a glass vial or PFS, respectively, and both had turbidities of 0.00 when tested after two months of storage at 5°C. EX1004 ¶¶62-63. Examples 3 and 4 indicate that turbidity was determined as described above, which a POSA would have understood would be through measurement at OD_{405} nm, as described in Example 1. EX1004 ¶¶60, 62-63; EX1002 ¶¶70-71, 173. For this reason and those

explained above as to claims 1, 5, 20, 26, 30, and 45, the formulations disclosed in Examples 3 and 4 of *US432* anticipate claims 15, 23, 40, and 48. EX1002 ¶173; *see also* Section VIII.A.4.

7. Claims 16, 24, 41, and 49

Claims 16, 24, 41, and 49 depend from claims 5, 20, 30, and 45, respectively, and further require that "at least 99% of said VEGF antagonist fusion protein is present in native conformation after 2 month storage at 5° C. as measured by size exclusion chromatography." EX1001, col. 20-22. Examples 3 and 4 of *US432* disclose formulations that were stored in a glass vial or PFS, respectively, and had 99.2% and 99.1% VEGF antagonist in native configuration after 2 months of storage at 5°C., when measured by SEC, which, as discussed above as to claims 1 and 26 (Section VIII.A.1), is a change in the %VEGF Trap Native Conformation of 0.3%. EX1004 ¶¶60, 62-63; EX1002 ¶174. For these reasons and those explained above as to claims 1, 5, 20, 26, 30, and 45, the formulations disclosed in Examples 3 and 4 of *US432* anticipate claims 16, 24, 41, and 49, regardless of how the claim phrase "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" is construed. EX1002 ¶174; *see also* Section VIII.A.4.

8. Claims 17, 25, 42, and 50

Claims 17, 25, 42, and 50 depend from claims 5, 20, 30, and 45, respectively, and further require that "at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5° C. for 24 months as measured by size exclusion chromatography." EX1001, col. 20-22. *US432*, which has the same specification as *US865*, does not provide results for the amount of VEGF antagonist in native conformation of any 40 mg/ml VEGF antagonist formulations following storage at 5°C for 24 months. Example 1 discloses an embodiment within the scope of claim 17 except that it has a concentration of 50 mg/ml rather than the claimed 40 mg/ml. EX1004 ¶60. Specifically, *US432* discloses, in Table 1, that after storage for 24 months at 5°C., 98.1% of the VEGF antagonist was in native configuration, reflecting a change from Time 0 (98.8%) to 24 months of 0.7%. EX1004 ¶60; EX1002 ¶175.

A POSA would have understood that formulations having lower concentrations of VEGF antagonist, like the formulation used in Example 3, are as stable or more stable than formulations with higher concentrations, like the formulation used in Example 1. *E.g.*, EX1027 ¶25 (Regeneron's expert, Dr. Klibanov, testifying that "raising the concentration of a protein in a liquid formulation typically also raises the likelihood of aggregation"). Accordingly, the formulation used in Example 3 would inherently meet the added limitation of

claims 17 and 25, regardless of how the claimed stability limitation is construed. EX1002 ¶175.

Moreover, in view of the similarity in the amount of VEGF antagonist in native conformation for the identical formulations used in Examples 3 and 4, when stored at 5°C. for 2 months in a vial and PFS, respectively, the formulation of Example 4 inherently meets the added limitations of claims 42 and 50 for the same reasons as the formulation of Example 3 inherently meets the added limitations of claims 17 and 25. EX1002 ¶176.

For these reasons and those explained above as to claims 1, 5, 20, 26, 30, and 45, the formulations disclosed in Examples 3 and 4 of *US432* anticipate claims 17, 25, 42, and 50. EX1002 ¶¶175-177; *see also* Section VIII.A.4.

9. Claims 19 and 44

Claims 19 and 44 depend from claims 5 and 30, respectively, and further require that the formulation does not contain trehalose. EX1001, col. 20-21. The formulations disclosed in Examples 3 and 4 of *US432* do not contain trehalose, meeting the added limitations of these claims. EX1004 ¶¶62-63; EX1002 ¶178. For this reason and those explained above as to claims 1, 5, 26, and 30, *US432* anticipates claims 19 and 44. *Id.*; *see also* Section VIII.A.

B. Ground 2: Claims 1-50 are Obvious Over *US432*

If the prior art renders a species of a genus obvious, it renders the genus obvious as well. *See, e.g., Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1300-3 (Fed. Cir. 2007) (finding an isolated isomer obvious over a mixture, thus holding the genus obvious as well). To the extent that claims 1-17, 19-42, and 44-50 are deemed not to be anticipated by *US432*, they are rendered obvious by it, as are claims 18 and 43. EX1002 ¶179.

1. Claims 1 and 26

For the reasons set forth above (Section VIII.A.1), all the limitations of claims 1 and 26 are expressly disclosed in *US432* except for the glycosylation status of the VEGF antagonist used in Examples 3 and 4. However, as explained, glycosylation of the VEGF antagonist is an inherent property of the protein. Section VIII.A. To the extent it is deemed that glycosylation of the VEGF antagonist used in Examples 3 and 4 is not inherent, a POSA would have found it obvious to use a glycosylated VEGF antagonist based on the disclosures of *US432*. EX1002 ¶¶180-182.

US432 discloses 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." EX1004 ¶48. *US432* discloses that "[i]n 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" ("specifically disclosed glycosylated VEGF antagonist") and this is the only fusion protein identified with any specificity by *US432*. EX1004 ¶48; EX1002 ¶¶183-184.

These disclosures would have motivated a POSA to use CHO cells to prepare the specifically disclosed glycosylated VEGF antagonist because:

(a) the only specific method identified for expressing the VEGF antagonist is in a CHO cell line in which the protein may be modified post-translationally and a POSA would have known that such post-translational modification refers to glycosylation (EX1004 ¶48; EX1002 ¶185);

(b) the only fusion protein identified with any specificity is glycosylated at Asn residues 62, 94, 149, 222, and 308 and comprises amino acids 27-457 of SEQ ID NO:4 (EX1004 ¶48); and

(c) the VEGF antagonist used in all the Examples has SEQ ID NO:4, which comprises amino acids 27-457 of SEQ ID NO:4 (EX1004 ¶¶60-65).

A POSA would have reasonably expected to be able to use the specifically disclosed glycosylated VEGF antagonist to achieve the stability achieved in, for example, Examples 3 and 4, because the examples provide neither specificity regarding the VEGF antagonist other than that it has SEQ ID NO:4 nor any alternate VEGF antagonist(s) to use. In addition, it was known that glycosylation of a protein can obstruct aggregation. Accordingly, a POSA would have

reasonably expected that any VEGF antagonist with SEQ ID NO:4, including the specifically disclosed glycosylated VEGF antagonist, when used with the formulation in, for example, Example 3 or 4, would achieve the same stability/purity results as achieved by the examples. EX1002 ¶186.

For the above reasons, the disclosures of *US432* would have rendered claims 1 and 26 obvious to a POSA. EX1002 ¶¶180-187; *see also* Section VIII.A.

2. Claims 2-13, 19-21, 27-38, and 44-46

Claims 2-13 and 27-38 depend directly or indirectly from claims 1 and 26, respectively and add limitations relating to the ophthalmic formulation of claims 1 and 26 as follows: 40 mg/ml VEGF antagonist (claims 2 and 27); limiting the organic co-solvent, most narrowly to about 0.03 to about 0.1% polysorbate 20 (claims 2-5 and 27-30); limiting the buffer to phosphate (claims 6 and 31), 5-25 mM (claims 7 and 32), and limiting the pH, most narrowly to about 6.2-6.3 (claims 8-9 and 33-34); limiting the stabilizing agent, most narrowly to 1.0-7.5% sugar (claims 10-12, 20, 35-37, and 45); requiring a tonicity agent (claims 13, 21, 38, and 46); and specifying that there is no trehalose in the formulation (claims 19 and 44). As explained above (Sections VIII.A.2-4, 9), the formulations disclosed in Examples 3 and 4 expressly meet all these limitations. For these reasons and the reasons set forth above regarding claims 1 and 26, *US432* renders obvious claims

2-13, 19-21, 27-38, and 44-46. EX1002 ¶¶188-194, 211; *see also* Sections VIII.A.1, VIII.B.1.

3. Claims 14, 22, 39, and 47

Claims 14, 22, 39, and 47 depend from claims 5, 20, 30, and 45, respectively, and further require that the VEGF antagonist is glycosylated at asparagine residues corresponding to asparagine residues 62, 94, 149, 222, and 308 of SEQ ID NO:4. For the same reasons as set forth with respect to claims 1, 5, 20, 26, 30, and 45 above, a POSA would have been motivated to use a VEGF antagonist that is glycosylated at asparagine residues corresponding to asparagine residues 62, 94, 149, 222 and 308 of SEQ ID NO:4 with a reasonable expectation of success. For these reasons and the reasons set forth above regarding claims 1, 5, 20, 26, 30, and 43, *US432* renders obvious claims 14, 22, 39, and 47. EX1002 ¶¶195-196; *see also* Sections VIII.A.4, VIII.B.2.

4. Claims 15, 23, 40, and 48

Claims 15, 23, 40, and 48 depend from claims 5, 20, 30, and 45, respectively, and further require that the formulation is "capable of providing turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5° C." As explained above (Section VIII.A.6), the formulations of Examples 3 and 4 of *US432* expressly meet this limitation. For these reasons and the reasons set forth above

regarding claims 1, 5, 20, 26, 30, and 45, *US432* renders obvious claims 15, 23, 40, and 48. EX1002 ¶¶197-198; *see also* Sections VIII.A.4, VIII.B.2.

5. Claims 16, 24, 41, and 49

Claims 16, 24, 41, and 49 depend from claims 5, 20, 30, and 45, respectively, and further require that "at least 99% of said VEGF antagonist fusion protein is present in native conformation after 2 month storage at 5° C. as measured by size exclusion chromatography." As explained above (Section VIII.A.7), Examples 3 and 4 of *US432* expressly disclose formulations that meet those limitations. For these reasons and the reasons set forth above regarding claims 1, 5, 20, 26, 30, and 45, *US432* renders obvious claims 16, 24, 41, and 49. EX1002 ¶¶199-200; *see also* Sections VIII.A.4, VIII.B.2.

6. Claims 17, 25, 42, and 50

Claims 17, 25, 42, and 50 depend from claims 5, 20, 30, and 45, respectively, and further require that "at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5° C. for 24 months as measured by size exclusion chromatography." *US432* does not provide purity results for any 40 mg/ml VEGF antagonist formulations following storage at 5°C. for 24 months. Example 1 discloses a formulation within the scope of claim 17 except that it has a concentration of 50 mg/ml rather than the claimed 40 mg/ml. *US432* discloses, in Table 1, that after storage for 24 months at 5°C., 98.1% of the

VEGF antagonist was in native configuration, reflecting a change from Time 0 (98.8%) to 24 months of 0.7%. EX1004 ¶¶60; EX1002 ¶¶201-202. A POSA would have known that formulations having lower concentrations of VEGF antagonist, like the formulation used in Example 3, are as stable or more stable than formulations with higher concentrations, like the formulation used in Example 1. EX1002 ¶203. Accordingly, a POSA would have reasonably expected that the formulation used in Example 3, which is stored in a vial, would meet the added limitation of claims 17 and 25. *Id*.

Moreover, *US432* provides, in Examples 3 vs. 4 and 5 vs. 6, comparisons of the stability of identical formulations in vials vs. PFS, respectively. EX1004, ¶¶62-65. At every timepoint, the absolute difference in % VEGF Trap Native Configuration between the vial and PFS was 0.1% (except for 0.5 months for Examples 5 and 6, wherein the absolute difference was 0%). EX1002 ¶204. Accordingly, a POSA would have reasonably expected that the formulation of Example 4 stored in a PFS would have the stability recited in claims 42 and 50. EX1002 ¶¶204-205.

Finally, a POSA also would have reasonably expected that routine optimization could be used to obtain a formulation that meets the at least 98% 24-month stability limitation given the results reported in Examples 3-6, all of which

had less than a 1% change in % VEGF Trap Native Configuration at all reported time points compared to Time 0. EX1002 ¶¶203-205.

For these reasons and those explained above, *US432* renders obvious claims 17, 25, 42, and 50. EX1002 ¶¶201-206; *see also* Sections VIII.A.4, VIII.B.2.

7. Claims 18 and 43

Claims 18 and 43 depend from claims 5 and 30, respectively, and further require that the formulation does not contain phosphate. EX1001, 20:43-44, 21:56-57. As explained above, *US432* discloses that the buffer can be, but does not have to be, a phosphate buffer. EX1004 ¶¶10-11, 18. Because the formulations disclosed in paragraphs 10 and 18 of *US432* do not specify the buffer, a POSA would reasonably expect that any buffer could be used, and optimized, to obtain the desired stability. EX1002 ¶209. For these reasons and the reasons set forth above regarding claims 1, 5, 26, and 30, the *US432* renders obvious claims 18 and 43. EX1002 ¶¶207-210; *see also* Sections VIII.A.2, VIII.B.2.

C. Ground 3: Claims 18 and 43 are Obvious Over the Combination of *US432* and *WO685*

Even if *US432* by itself does not render obvious claims 18 and 43, which it does (*see* Section VIII.B.7), the combination of *US432* and *WO685* would have rendered those limitations obvious to a POSA. EX1002 ¶¶212-219.

Claims 18 and 43 depend from claims 5 and 30, respectively, and further require that the formulation does not contain phosphate, and thus require the use of a buffer that is not phosphate.

US432 states that "[i]n one or more specific embodiments,…the buffering agent may be, for example, phosphate buffer." EX1004 ¶11; EX1002 ¶214. The preferred pH of *US432* is 6.2-6.3, and the formulations of all the non-lyophilized examples all have a pH over time of 6.1-6.4. EX1004 ¶¶15-17, 60-65. Accordingly, *US432* discloses that embodiments can use non-phosphate buffer, wherein the buffer preferably has a pH of about 6.2-6.3. EX1002 ¶215.

WO685 discloses formulations of aflibercept that use a histidine hydrochloride/L-histidine buffer, include the other excipients of claims 5 and 30, and do not include a phosphate buffer. EX1002 ¶216. For example, *WO685* discloses a formulation having 40 mg/mL aflibercept, 10 mM L-histidine/histidine hydrochloride buffer (a non-phosphate buffer), 5% (w/v) sucrose (a stabilizing agent), 40 mM sodium chloride, 0.03% (w/v) polysorbate 20 (an organic cosolvent), and a pH of 6.2. EX1005, 34, Table 9, Sample (a); EX1002 ¶216**.**

As explained above, *US432* discloses, in Examples 3 and 4, formulations that are very similar to sample (a) in Table 9 of *WO685*; both have 40 mg/ml of a VEGF antagonist comprising amino acids 27-451 of SEQ ID NO:4, 10 mM buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 20, and pH of 6.2-6.3 at the different

time points at which purity was measured. EX1002 ¶¶216-217; *supra* Section VIII.A. The formulations differ in that sample (a) in Table 9 of *WO685* uses a L-histidine/histidine hydrochloride buffer and has a pH of 6.2 (EX1005, 34, Table 9, Sample (a)) while Examples 3 and 4 of *US432* use a phosphate buffer and have a pH of 6.3 at time 0 (EX1004 ¶¶62-63). Examples 3 and 4 of *US432* also do not explicitly identify the VEGF antagonist used, other than stating the VEGF Trap is SEQ ID NO:4. EX1004 ¶¶62-63.

In view *US432* teaching the general use of a buffer at a pH of about 6.2-6.3, *WO685* teaching the use of a histidine at pH 6.2, the similarity in the formulations of sample (a) in Table 9 of *WO685* and Examples 3 and 4 of *US432*, and the equal or better stability achieved by the non-phosphate examples in sample (a) in Table 9 of *WO685* compared to the phosphate examples (*see* EX1005, 43; EX1002 ¶¶86, 217), a POSA would have been motivated to replace the phosphate buffer in the formulations of Examples 3 and 4 of *US432* and would have had a reasonable expectation of achieving the same stability/purity results seen in Examples 3 and 4 of *US432*. EX1002 ¶¶217-218.

For these reasons and those explained above as to claims 1, 5, 26 and 30, the combination of *US432* and *WO685* renders obvious claims 18 and 43. EX1002 ¶¶212-219; *supra* Section VIII.A.2., VIII.B.7.

D. Objective Indicia of Non-Obviousness

Petitioner is not aware of any relevant objective indicia of non-obviousness that have a nexus to, or are commensurate in scope with, any of the challenged claims. EX1002 ¶220. Petitioner reserves the right to respond to any allegations that objective indicia support the validity of the challenged claims.

IX. CONCLUSION

For the reasons set forth above, claims 1-50 of *US865* are unpatentable. Petitioner requests that an *inter-partes* review of these claims be instituted and that the claims be cancelled.

Respectfully submitted,

Dated: January 15, 2025

/ Lora M. Green /
Lora M. Green, Lead Counsel
Reg. No. 43,541

X. CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. §42.24(d), the undersigned certifies that this Petition complies with the type-volume limitation of 37 C.F.R. §42.24(a). The word count application of the word processing program used to prepare this Petition indicates that the Petition contains 13,895 words, excluding the parts of the brief exempted by 37 C.F.R. §42.24(a).

Respectfully submitted,

Dated: January 15, 2025

/ Lora M. Green /
Lora M. Green, Lead Counsel
Reg. No. 43,541

XI. APPENDIX – LIST OF EXHIBITS

Exhibit No.	Description
1001	U.S. Patent No. 11,084,865 ("*US865*")
1002	Declaration of Dr. Peter Tessier in Support of IPR Petition
1003	Dr. Peter Tessier *curriculum vitae*
1004	U.S. Patent Publication No. 2007/0293432 ("*US432*")
1005	International Publication No. WO 2017/129685 ("*WO685*")
1006	Prosecution history of U.S. Application No. 16/739,559, now U.S. Patent No. 11,084,865
1007	Prosecution history of U.S. Application No. 16/582,486, now U.S. Patent No. 11,066,458
1008	Prosecution history of U.S. Application No. 16/159,269, now U.S. Patent No. 10,464,992
1009	Excerpts from prosecution history of U.S. Application No. 15/879,294, now U.S. Patent No. 10,400,025
1010	Excerpts from prosecution history of U.S. Application No. 15/095,606, now U.S. Patent No. 9,914,763
1011	Excerpts from prosecution history of U.S. Application No. 14/330,096, now U.S. Patent No. 9,340,594
1012	Excerpts from prosecution history of U.S. Application No. 13/914,996, now U.S. Patent No. 8,802,107
1013	Excerpts from prosecution history of U.S. Application No. 13/329,770, now U.S. Patent No. 8,481,046
1014	Prosecution history of U.S. Application No. 12/833,417, now U.S. Patent No. 8,092,803
1015	Excerpts from prosecution history of U.S. Application No. 12/560,885, now US 7,807,164
1016	Excerpts from prosecution history of U.S. Application No. 11/818,463, now U.S. Patent No. 7,608,261
1017	Christine Wulff et al., *Prevention of Thecal Angiogenesis, Antral Follicular Growth, and Ovulation in the Primate by Treatment with Vascular Endothelial Growth Factor Trap R1R2*, 143(7) ENDOCRINOLOGY 2797-2807 (Jul. 2002) ("*Wulff*")
1018	International Publication No. WO 2018/094316 ("*WO316*")

Exhibit No.	Description
1019	EYLEA® Prescribing Information, November 2011 ("*PI2011*")
1020	James D. Andya et al., *Mechanisms of Aggregate Formation and Carbohydrate Excipient Stabilization of Lyophilized Humanized Monoclonal Antibody Formulations*, 5(2) AAPS PHARMSCI (Apr. 4, 2003) ("*Andya 2003*")
1021	Declaration of Alexander M. Klibanov submitted in support of Regeneron's Patent Owner Response in IPR2023-00462 (Nov. 2, 2023)
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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§42.6(e) and 42.105(a), this is to certify that I caused to be served a true and correct copy of the foregoing Petition for Inter Partes Review (and accompanying Exhibits 1001-1034 and 1037-1049) by overnight courier (Federal Express or UPS), on this 15 day of January, 2025, on the Patent Owner at the correspondence address of the Patent Owner Counsel as follows:

A&P – Regeneron
Attn: IP Docketing
601 Massachusetts Avenue, N.W.
Washington, DC 20001

Respectfully submitted,

Dated: January 15, 2025

/ Lora M. Green /
Lora M. Green, Lead Counsel
Reg. No. 43,541