

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

**DECLARATION OF DR. PETER TESSIER
IN SUPPORT OF PETITION FOR INTER PARTES REVIEW OF
U.S. PATENT NO. 11,084,865**

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I, Peter M. Tessier, Ph.D., declare as follows:

I. INTRODUCTION

1. I have been retained by counsel for Celltrion, Inc. (“Celltrion”) as a technical expert in connection with the above-identified proceeding. I have been asked to provide my opinions concerning the “novelty” and “obviousness” of claims 1-50 of U.S. Patent No. 11,084,865 (“*US865*”) (EX1001), which relate to “VEGF antagonist formulations suitable for intravitreal administration,” wherein the VEGF antagonist includes aflibercept. VEGF is short for Vascular Endothelial Growth Factor. I understand that my declaration will be submitted in support of Celltrion’s Petition for Inter Partes Review of *US865* patent against Regeneron Pharmaceuticals, Inc. (“Regeneron” or “Patent Owner”).

2. I am the same Peter M. Tessier who submitted a declaration in *Celltrion, Inc. v. Regeneron Pharms., Inc.*, No. IPR2023-00620, EX1002 (“IPR620 Declaration”), challenging claims of U.S. Patent No. 10,406,226 (“*US226*”). *US226* patent relates to methods of manufacturing aflibercept.

3. My opinions in this declaration are based on my review of *US865* (EX1001), its prosecution history (EX1006), the relevant prior art that I have identified and of which I have been informed, other documents referred to in this declaration, and my many years of experience in the industry with the development

of therapeutic protein products, including during the relevant time period for the questions I have been asked to consider.

4. I am being compensated for my time at my usual consulting rate of \$650 per hour. For live testimony, I am compensated at a rate of \$800 per hour. I am also being reimbursed for reasonable travel expenses related to my consultation. I do not have a personal or financial interest in the outcome of this proceeding nor is my compensation affected by its outcome.

II. BACKGROUND AND QUALIFICATIONS

5. I am currently the Albert M. Mattocks (Endowed) Professor in the Departments of Pharmaceutical Sciences, Chemical Engineering, and Biomedical Engineering at the University of Michigan. My research focuses on discovering, designing, characterizing, formulating, and delivering biologics ranging from peptides to proteins and antibodies. I have extensive experience in formulating peptides and proteins to optimize their stability, solubility, and viscosity. My formulation development work has included evaluating the impacts of excipients, pH, and other variables on their key formulation properties, including their solubility, aggregation, and viscosity. I and my lab have developed new screening assays for evaluating the self-association and/or aggregation of peptides and proteins in different formulation conditions to simplify the identification of optimal

formulation conditions and peptide or protein variants with optimal formulation properties.

6. I have a Bachelor of Science in Chemical Engineering from the University of Maine, where I was Co-Valedictorian, and a Ph.D. in Chemical Engineering from the University of Delaware.

7. After earning my Ph.D. in 2003, I became an American Cancer Society Post-Doctoral Fellow at the Whitehead Institute for Biomedical Research, at MIT, where I remained until 2007. After completing the fellowship, I joined the faculty at Rensselaer Polytechnic Institute (“RPI”), first as an Assistant Professor, then as an Associate Professor and then as a Richard Baruch M.D. Career Development (Endowed) Associate Professor and Professor. I remained at RPI until 2017, when I joined the University of Michigan in my current role.

8. I have extensive experience related to the discovery, engineering, expression, purification, biophysical characterization, and formulation of protein therapeutics, including antibodies and Fc-fusion proteins. My lab routinely expresses antibodies and Fc-fusion proteins in mammalian cells, purifies them using standard methods (including Protein A, size-exclusion chromatography and ion-exchange chromatography), and formulates them into various kinds of pharmaceutical formulations.

9. I have authored or co-authored more than 100 published, peer-reviewed articles. I am also named as an inventor on several patent applications and issued patents, all relating to antibodies and protein aggregation.

10. I have held positions on the Editorial Board of the Journal of Biological Chemistry, as a Review Editor for Frontiers in Molecular Biosciences, and as a Membership Chair for the American Chemical Society. I have acted as co-chair for a number of conferences on biotherapeutics and biomolecular engineering, and I am a Panelist for the National Science Foundation and the National Institutes of Health.

11. I have received over 50 grants to my laboratory since 2008, totaling over \$15 million. Members of my lab, including at the postdoctoral, graduate, and undergraduate level, have won a number of awards from organizations including the American Chemical Society, the National Institutes of Health, and the National Science Foundation.

12. I have been invited to give over 100 seminars since 2007, by a number of organizations, universities and pharmaceutical and biotechnology companies, including Regeneron.

13. My curriculum vitae accompanies this declaration as EX1003.

III. LEGAL STANDARDS

14. I do not hold any legal qualifications; however, Celltrion's counsel has informed me of a number of legal principles to consider when formulating my opinions relating to the validity of US865. These principles are set forth below.

A. Claim Construction

15. I understand that in an IPR proceeding, the terms in a patent claim are generally given their ordinary and customary meaning as understood by a "person of ordinary skill in the art" ("POSA") in the context of the entire patent disclosure. If, however, an inventor defines a claim term in the patent disclosure, then the inventor's definition applies. But if the inventor chooses to define a claim term, the inventor must do so with reasonable clarity, deliberateness, and precision.

16. I further understand that claims can be "independent" or "dependent." An independent claim does not refer to or incorporate the elements of any other claim. A dependent claim refers to another claim and includes all its limitations while also adding additional limitation(s). Claims 1-50 of *US865* include two independent claims: claims 1 and 26. Claims 2-25 and 27-50 depend directly or indirectly from claims 1 and 26, respectively.

B. Burden of Proof

17. I understand that in an IPR, a claim is not patentable if a "preponderance of the evidence" establishes that the claim is anticipated by, or

rendered obvious by, the prior art. I understand that “a preponderance of the evidence” means “more likely than not.”

C. Prior Art and Earliest Effective Filing Date

18. I understand that in order 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 enablement and written description.

19. As I discuss below in Section IX, the earliest effective filing date for *US865* is October 12, 2018. I have thus been asked to assume that any printed publication published prior to that date should be considered “prior art” to the patent.

20. I further understand that a document is considered a “printed publication” if it was published or otherwise made available such that a POSA exercising reasonable diligence could have located it.

D. Anticipation

21. I have been informed and understand that for a patent claim to be patentable, it must be novel.

22. I have been informed and understand that a patent claim is “anticipated” if a single prior art reference discloses every element of the claim to a POSA.

23. I have been informed that a member of a genus, that is, a species, anticipates a genus.

24. I have been informed and understand that even if the prior art reference does not expressly disclose a particular claim element, the reference may still anticipate that element if it is “inherent” in the disclosure. A claim element is inherent if it is necessarily present in, or is the natural result of, the subject matter disclosed in the reference. I understand that whether a claimed feature is necessarily present in, or is the natural result of, the prior art may not be established by probabilities or possibilities. I understand that, while other references cannot be used in combination in an anticipation analysis, other art may be relied upon to show what was inherent in the disclosure of the anticipating reference or the general knowledge in the field that a POSA would have known. I also understand that if a claim describes a functional result, it is considered inherently disclosed in the prior art if the patent teaches that the only steps required to achieve the functional result are the same as those disclosed in the prior art. In other words, when the patent does not itself disclose any more than what is in the prior art regarding how to achieve a claimed functional result, then the functional

result is inherently disclosed by the prior art. I understand that “post art” evidence (documents or other information created or published after the patent’s priority filing date) can be relied on to show that a claimed feature is necessarily present, or inherent, in the prior art.

25. I have been informed and understand that, in an anticipation analysis, there is no need to consider secondary considerations.

E. Obviousness

26. I understand from counsel that for a patent claim to be patentable, it must be “non-obvious” over the prior art.

27. I understand that a patent claim is obvious if the differences between the claims and the prior art are such that the subject matter as a whole would have been obvious to a POSA at the time the invention was made.

28. I understand that when assessing whether a claim is obvious, I should consider: (i) the scope and content of the prior art; (ii) the level of ordinary skill in the art; (iii) the differences between the prior art and what is claimed; and (iv) any “secondary” evidence that may indicate that the claims are not obvious.

29. I understand that a claimed invention may be obvious when, for example, there is some motivation, reason, or suggestion that would have led a POSA to modify a prior-art reference or to combine prior-art teachings to arrive at the claimed invention.

30. I also understand that when combining or modifying prior-art references to arrive at the claimed invention, the POSA must also have a reasonable expectation of success, given their general knowledge and what has been disclosed in the prior art. I understand that this success need only be reasonably expected and does not need to be guaranteed or proven.

31. I understand further that an obvious member of a genus, that is, a species, also renders obvious the genus.

32. I understand that “secondary” evidence may weigh against a finding that a claimed invention would have been obvious. Such secondary evidence may include: (i) commercial success of a product due to the merits of the features of the product that are the subject of the patent claims; (ii) a long-felt but unresolved need for the solution provided by the patent claim; and (iii) unsuccessful attempts by others to find the solution provided.

F. Written Description

33. I have been informed and understand that a patent specification must contain a written description of the invention sufficient to allow persons of ordinary skill in the art to recognize that the inventor actually invented (had possession of) what is claimed. An applicant shows that the inventor was in possession of the claimed invention by describing the claimed invention with all of

its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention.

34. I understand that the precise wording of the claims does not need to be present in the specification for the written description standard to be met. I also understand that what is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.

35. I understand that the purpose of the written description requirement is to ensure that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor's contribution to the field of art as described in the patent specification.

36. I understand that, in order to satisfy the written description requirement as to a range, the skilled artisan must be able to reasonably discern a disclosure of that range. I understand that this is a highly fact-dependent inquiry, but that in general, in order to claim a range, the written description must provide support for the full range, as opposed to a subset of points within the range.

37. I understand that for claims to be entitled to an earlier application's filing date, the patent specification must contain a written description of the invention sufficient to allow persons of ordinary skill in the art to recognize that the inventor actually invented (had possession of) what is claimed.

G. The POSA

38. I understand that claim construction, anticipation, obviousness, and written description must be judged from the perspective of the POSA to which the patent is directed. I understand that the POSA is a hypothetical person or persons that is presumed to have perfect knowledge of all the relevant prior art.

39. I understand that in determining who a POSA is the following may be considered: (1) the educational level of the inventor(s); (2) the type of problems encountered in the relevant technical field; (3) prior-art solutions to those problems; (4) rapidity with which innovations are made; and (5) the sophistication of the technology and educational level of active workers in the field.

40. Here, *US865* concerns formulations of a VEGF antagonist suitable for intravitreal administration. Based on my extensive experience in protein development, the POSA at the time of the invention would have held an advanced degree, such as a Master's in a pharmaceutical 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 a Ph.D. in such discipline and less experience. The POSA may collaborate with others, including a medical doctor with experience treating ophthalmic diseases.

IV. A BRIEF OVERVIEW OF *US865*

41. *US865* is titled “VEGF Antagonist Formulations Suitable for Intravitreal Administration.” EX1001. *US865*, based on the information on the face of the patent, is assigned to Regeneron Pharmaceuticals, Inc. *Id.*

42. I have reviewed the claims, specification, and portions of the prosecution history of *US865*. The patent describes the invention 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. The patent explains that “VEGF antagonist” includes “fusion proteins capable of trapping VEGF.” *Id.*, 6:27-30.

43. *US865* states that the “VEGF antagonist of the methods and formulations of the invention can be prepared by any suitable method known in the art, or that comes to be known.” EX1001, 6:40-42. It further states that the antagonist “is preferably substantially free of protein contaminants at the time it is used to prepare the pharmaceutical formulation.” *Id.*, 6:42-45. “Substantially free of protein contaminants” means that preferably at least 90%, and most preferably at least 99%, “of the weight of protein of the of the VEGF-specific fusion protein antagonist preparation used for making a formulation is VEGF fusion protein antagonist protein.” *Id.*, 6:45-50. Similarly, while the patent explains that “[t]he fusion protein is preferably substantially free of aggregates,” *id.*, 6:50-51, it further

explains that “‘substantially free of aggregates’ means that at least 90% of the weight of fusion protein is not present in an aggregate *at the time the fusion protein is used to prepare the pharmaceutically effective formulation.*” *Id.*, 6:51-55 (emphasis added).

44. A POSA would have understood that these values pertain to the percentage of protein in “native conformation” *before* storage, and that the patent does not describe any critical percentage of protein in native conformation that must be achieved during storage.

45. *US865* includes eight examples, each of which contain substantially similar combinations of protein, buffer, stabilizer and one of two “organic co-solvents.” Six of the examples deal with liquid formulations (Examples 1-6), and two with lyophilized formulations (Examples 7-8). *Id.*, Examples 1-8. The liquid examples include 40 or 50 mg/ml of “VEGF Trap (SEQ ID NO:4)” protein in combination with phosphate buffer, sodium chloride, and polysorbate 20 at a pH of 6.25 or 6.3. EX1001, Examples 1, 3-6. One of the examples contains polyethylene glycol 3350 instead of polysorbate 20. *Id.*, Example 2. Four of the liquid examples additionally contain sucrose. *Id.*, Examples 1-4. The concentrations of protein, buffer, sucrose, sodium chloride and polysorbate 20 vary in several of the examples, but only within relatively narrow ranges. *Id.*, Examples 1-8.

46. The examples of the patent report certain stability parameters of the formulations after storage at 5 °C for certain periods of time. Turbidity at OD₄₀₅ nm and “% VEGF Trap Native Configuration,” as measured by SEC, are reported after storage periods that run from zero to as many as 24 months. *See, e.g.*, EX1001, Tables 1-8. A POSA would have understood that “Native Conformation” can be used interchangeably with “Native Configuration.” *US865* provides two examples wherein the % VEGF Native Conformation was measured at 24 months, which were 50 mg/ml formulations that had 98.1% VEGF Trap Native Configuration (in Table 1 of Example 1) and 97.6% VEGF Trap Native Configuration (in Table 2 of Example 2). *US865* also provides examples of liquid formulations that exhibited 99.1 to 99.2% VEGF Trap Native Configuration at 2 months (in Tables 3, 4, 5) and one example of a lyophilized formulation that exhibited 99.3% VEGF Trap Native Configuration at 2 months (in Table 7). Table 6 indicates that there was 99.2% and 99.1% VEGF Trap Native Configuration at 1 and 3 months, respectively, which may imply that at two months, the % VEGF Trap Native Configuration was between those values.

47. The specification of *US865* discloses buffers generally, but the only specific buffer disclosed by the specification is phosphate buffer. For example, the specification states: “In one or more specific embodiments, ... the buffering agent may be, for example, phosphate buffer. In a specific embodiment, the phosphate

buffer is a sodium phosphate buffer.” EX1001, 2:39-48. Likewise, the only buffer disclosed in the Examples is phosphate buffer. EX1001, 8:32-12:25 (Examples 1-8). The specification of *US865* does not describe any reason to exclude phosphate and does not disclose any specific alternative to phosphate.

48. I have reviewed portions of the prosecution history of *US865*. I discuss some of these portions below in the context of my analysis related to the effective filing date and my opinion that claims 1-50 of *US865* are not patentable because they are anticipated and/or obvious. *See* Section XI.A-D.

V. SCIENTIFIC BACKGROUND

49. I previously provided a declaration in support of Celltrion’s IPR regarding *US226*. *Celltrion, Inc. v. Regeneron Pharms., Inc.*, No. IPR2023-00620, EX1002 (“IPR620 Declaration”). I understand that during the pendency of that IPR, Regeneron disclaimed all claims of *US226*.

A. VEGF Antagonists and Aflibercept

50. VEGF is a naturally occurring protein that regulates “angiogenesis,” the process by which new blood vessels are formed. *See* EX1028 (*Holash*), 11393. VEGF binds to specific VEGF receptors on the surfaces of cells responsible for angiogenesis, initiating the VEGF pathway. *Id.* Two of the most well-known and best-characterized VEGF receptors are VEGF receptor 1 (VEGFR1), also known as Flt1, and VEGF receptor 2 (VEGFR2), also known as Flk1. *Id.*, *see also, e.g.*,

EX1029 (*WO319*), 58:8-9, 59:3. VEGFR1 and VEGFR2 both have an extracellular region consisting of seven domains to which VEGF binds. *See* EX1017 (*Wulff*), 2798, Fig. 1.

51. As early as 2002, VEGF had been identified as playing a key role in angiogenesis, which is necessary for tumor growth. *See* EX1028 (*Holash*), 11393; *see also* EX1030 (*Ferrara*), 968. By 2005-2006, a number of VEGF antagonists had been developed and explored as anti-cancer therapies given their potential to inhibit tumor growth. EX1030 (*Ferrara*), 971.

52. VEGF antagonists had also been developed to treat age-related macular degeneration (wet AMD), a disease characterized by proliferation of blood vessels in the retina of the eye. Aflibercept was developed for that purpose and was indicated “for the treatment of patients with Neovascular (Wet) Age-Related Macular Degeneration (AMD).” EX1019 (*PI2011*), 1.

53. Aflibercept is a VEGF antagonist developed by Regeneron and marketed under the trade name EYLEA. EX1019 (*PI2011*), 1. Aflibercept was known to be 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:

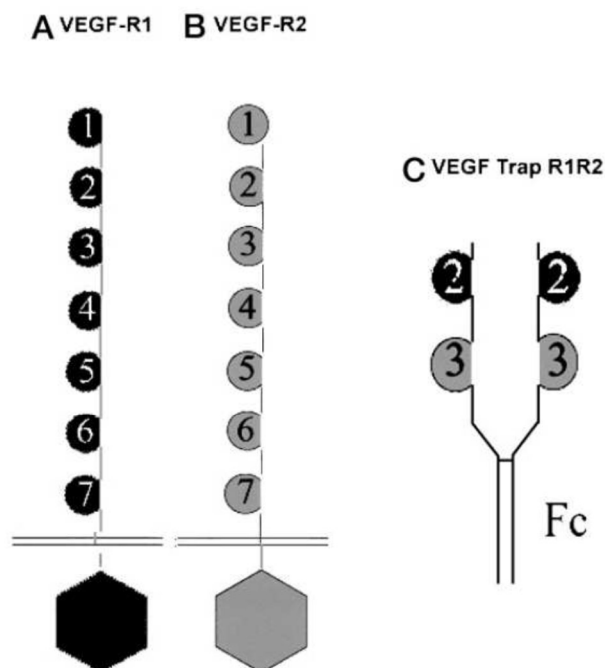


FIG. 1. Structure of VEGF receptors and the VEGF Trap. VEGF-R1 (A) and VEGF-R2 (B) both contain seven extracellular domains, which differ between the two receptors. These extracellular domains are responsible for VEGF binding. The soluble VEGF Trap R1R2 (C) was created by fusion of domain 2 of VEGF-R1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

See EX1017 (Wulff), 2798, Fig. 1. The Fc domain links two of these moieties together by disulfide bonds to form a “dimer,” that is, a molecule composed of two of the moieties containing the VEGF extracellular domains, as seen in the figure above. This Fc region contains a “multimerizing component,” as that term is used in US865, because it joins the two moieties to create a multimer (in this case, a dimer). See, e.g., EX1001 (US865), 2:20-26. Aflibercept works by binding to VEGF and “trapping” it before it can bind to cell-surface VEGF receptors, thereby preventing it from triggering angiogenesis (hence the name, VEGF Trap). See EX1028 (Holash), 11393.

54. Amino acid residues 27-457 of SEQ ID NO:4 in *US865* is the amino acid sequence of Aflibercept, with amino acids 1-26 being a signal sequence that is not present in the mature protein. EX1018 (*WO316*) ¶37; *see* Section VIII, below.

55. It was additionally known in the prior art that aflibercept was made in CHO (Chinese hamster ovary) cells and was glycosylated at asparagine residues 62, 94, 149, 222 and 308. *See* Section VIII, below; *see also* EX1043 (Daly) ¶64; EX1018 ¶¶37, 45; EX1019 (PI2011), 9.

B. Glycosylation

56. Glycosylation refers to the process where sugars or “glycans” are created, altered, and attached to proteins or other biomolecules. Protein glycosylation is one of the most common forms of post-translation modifications that can occur in a protein, particularly proteins expressed in CHO cells. There are two main types of glycosylation: N-linked glycosylation and O-linked glycosylation. N-linked glycosylation refers to the process where glycans are attached to the side-chain nitrogen atoms of asparagine residues, whereas O-linked glycosylation refers to the process where glycans are attached to the side-chain oxygen atoms of hydroxyl amino acids, particularly serine and threonine residues. N-linked glycosylation occurs at specific sequences of amino acids, known as “sequence motifs,” that have the sequence “asparagine-X-serine/threonine,” where the first residue after asparagine (“X”) can be any residue except proline and the

second residue after asparagine can be either serine or threonine. *See* EX1031 (*Liu 2015*), 1867; *see also* EX1032 (*Jefferis*), 13. Thus, a POSA would have been able to review a protein's amino acid sequence and understand where the N-linked glycosylation "sequence motifs" were.

57. The glycosylation of IgG antibodies, including the "Fc" portion of those antibodies, was well-characterized by the date of the provisional application, which was filed in 2006.¹ For example, N-linked glycosylation was well known to occur at a conserved asparagine residue in the CH2 domain (located in the Fc region) of the IgG molecule at position 297. *See* EX1032 (*Jefferis*), 12; EX1033 (*Krapp*), 980; EX1034 (*Mimura 2001*), 45539. This same Fc region of IgGs is commonly used for producing Fc fusion proteins, including for aflibercept and similar VEGF Traps. *See* EX1017 (*Wulff*), 2798, Fig. 1. Because the conserved Fc glycosylation site will be maintained in any Fc fusion protein produced in mammalian cells, such as in aflibercept and similar VEGF Traps, these fusion proteins will contain at least one N-linked glycan in the Fc region. In addition, Fc fusion proteins can also contain N-linked glycans in the non-Fc portion of the

¹ I am using the knowledge of a POSA at the earliest possible priority date as that is the date at which the application was written, and it would thus reflect the level of skill as of that date.

fusion protein, and as explained, these sites can be readily identified based on the sequence motif “asparagine-X-serine/threonine”.

58. Glycosylation of asparagine residues of the Fc region of IgG was also shown to be essential to the functions of the Fc region. *See* EX1032 (*Jefferis*), 11-13; EX1033 (*Krapp*), 979-981; EX1034 (*Mimura 2001*), 45539. For example, glycosylation of the Fc region is important for IgG and Fc-fusion protein binding to FcγRs, which results in various effector functions, such as antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). *See* EX1032 (*Jefferis*), 14-15; EX1033 (*Krapp*), 979-981; EX1034 (*Mimura 2001*), 45539.

C. Protein Stability

59. It was also well known that several degradation pathways and mechanisms impact proteins. Those degradation pathways and mechanisms can be grouped into either physical or chemical instability. *See, e.g.*, EX1020 (*Andya 2003*), 1.

60. Physical instability refers to processes that cause reduced solubility and/or changes in the protein conformation. Such processes include aggregation and denaturation. Chemical instability refers to processes that break or form chemical bonds within the protein. Such processes include deamidation and oxidation. The table below, reproduced from EX1038 (*Chang*), provides an

overview of typical stability problems observed during development of complex pharmaceuticals like aflibercept. EX1038, Table 6.

Table 6. Typical stability problems observed in protein pharmaceuticals.

Problems	Potential causes	Possible solutions
Non-covalent aggregation	Solubility, structural changes, heat, shear, surface, denaturants, impurities	pH, ionic additives, amino acids, surfactants, protein concentration, raw material purity
Covalent aggregation	Disulfide scrambling, other unknown mechanisms	pH, inhibit non-covalent aggregation
Deamidation	pH < 5.0 or pH > 6.0	pH optimization
Cyclic imide	pH around 5	pH optimization
Cleavages	Protease impurity, other unknown mechanisms	pH, product purity, inhibitors
Oxidation	Active oxygen species, free radicals, metals, light, impurity	Excipient purity, free-radical scavenger, active oxygen scavengers, methionine
Surface denaturation, adsorption	Low protein concentration, specific affinity, protein hydrophobicity	Surfactants, protein concentration, pH

61. It was well known that protein aggregation was an important issue to consider when developing pharmaceutical formulations of antibodies (or fusion proteins such as aflibercept), which share substantial structural similarity. *See* EX1020 (*Andya 2003*), 1-2. Inhibiting aggregation is important because an aggregated protein will be less able to bind to its intended target and may increase immunogenicity, thus affecting its efficacy as a pharmaceutical product. *See, e.g.*, EX1039 (*Parkins*), 131.

62. As of October 12, 2018, formulators had several methods available to them to inhibit aggregation. Aggregation often occurs because, if not stabilized in

solution, “sticky” patches such as hydrophobic and/or charged patches on proteins that are exposed to the surrounding solvent can attract other molecules with similar sticky patches, most commonly other molecules of the same protein.

63. As an initial matter, it was known that glycosylation imparts stability, preserves structural integrity, and improves binding activity of molecules like aflibercept. *See* EX1021 (*Klibanov Declaration*) ¶45. For example, numerous publications reported that glycosylation of immunoglobulin antibodies produced in mammalian cells, having similar structures and mechanisms of action as aflibercept as discussed above, is essential for binding recognition, activation, and self-association. *See* EX1033 (*Krapp*), 979 (finding “glycosylation of IgG-Fc is essential for recognition and activation of these ligands” and affects its protein conformation); EX1034 (*Mimura 2001*), 45539 (reporting that deglycosylation of IgG-Fc causes a more compact Fc structure, impairing its binding to the target antigen/ligand); EX1037 (*Panka*), 593 (finding that glycosylation of murine IgG3 affects solubility and influences self-association); EX1040 (*Mimura 2000*), 697 (reporting that “[g]lycosylation of IgG-Fc has been shown to be essential for efficient activation” of the target receptor).

64. One well-known way to combat aggregation was the use of a stabilizer, such as sucrose or trehalose. “Formulation with carbohydrate excipients, such as sucrose and trehalose, has proven to be effective in the

stabilization of freeze-dried proteins.” EX1020 (*Andya 2003*), 1. When water is removed from freeze-dried formulations, the carbohydrate, such as sucrose, helps to stabilize the protein by substituting the -OH moieties on the sucrose for those of water in the solution, thus maintaining the stabilizing hydrogen bonds that prevent the hydrophobic regions of the protein from interacting together in a way that would otherwise result in aggregation. In a liquid formulation, such excipients tend to stabilize by modifying the structure of water around the protein in order to maintain a stabilizing environment. The prior art particularly recommended disaccharides, such as sucrose and trehalose, for long-term stability. *See* EX1039 (*Parkins*), 134. As of October 12, 2018, it was known that the commercial EYLEA (aflibercept) formulation included sucrose. EX1019 (*PI2011*), 9.

65. Another well-known way to reduce aggregation was through the use of surfactants, such as polysorbate 20. Surfactants have both hydrophilic and hydrophobic ends and can thus “shield” the protein from aggregation by blocking the air-water interface or hydrophobic patches on protein surfaces or both. Polysorbate 20 was a commonly used surfactant to achieve this goal. *See, e.g.,* EX1039 (*Parkins*), Box 1. As of October 12, 2018, it was known that the commercial EYLEA (aflibercept) formulation included polysorbate 20. EX1019 (*PI2011*), 9.

66. pH was another common consideration at the time to improve stability. It was known that using buffers to adjust pH could increase stability. Buffers are combinations of acids and bases that resist changes in pH by supplying an environment that can quickly neutralize small amounts of acid or base. Buffers were known to help stabilize proteins by keeping the pH away from a protein's isoelectric point (the point at which its net charge is zero). By doing this, electrostatic repulsion between protein molecules is increased, and aggregation is less favored. Moreover, pH optimization can reduce deleterious electrostatic effects, such as those that can prevent proper protein folding. Phosphate was a commonly used buffer at the time, and the commercial EYLEA (aflibercept) formulation included a phosphate buffer. EX1019 (*PI2011*), 9.

67. In order to maintain stability, it was typical at the time to store proteins between 2-8 °C (“USP Standard Refrigerated Temperature Range”), since proteins were known to degrade more slowly at colder temperatures. Many commercially available proteins carried instructions to store between 2-8 °C. As of October 12, 2018, it was known that the commercial EYLEA (aflibercept) product included instructions to store the product at 2-8 °C. EX1019 (*PI2011*), 14. To assess whether a formulation could be turned into a product with a viable shelf-life, it was common to test stability at these standard refrigeration conditions for

months or years. *See* EX1022 (*Liu*) ¶¶63, 280 (showing stability data for 1, 3, 6, 14, 16, and 24 months).

68. One of the ways that formulators at the time would have attempted to approximate the amount of aggregation present in a sample was through the use of size-exclusion chromatography (“SEC”). *See, e.g.,* EX1023 (*Kostanski 2004*), 160 (“Today, SEC is the most widely accepted and used analytical method for the measurement of molecular weight distribution and molecular weight averages of biopolymers and synthetic polymers.”); EX1022 (*Liu*) ¶278, Table 1. The reason that this technique can only approximate the amount of aggregation in a sample is due to the way size-exclusion chromatography works. As its name would suggest, size-exclusion chromatography separates molecules by their size and shape. The sample is dissolved in a liquid buffer or “mobile phase” and passed through a chromatographic column filled with a matrix that causes smaller molecules to migrate more slowly through the column relative to larger molecules. Only those molecules that elute from (emerge from the end of) the column pass through the detector and are measured. Very large aggregates cannot migrate through the column, which limits the ability of size-exclusion chromatography to accurately measure the amount of aggregated and non-aggregated (monomeric) protein. For example, large aggregates may not pass through the frit at the beginning of the column and may also stick to the SEC matrix of the column, and thus fail to elute

from the column. *See, e.g.*, EX1046 (*Ejima*), Abstract (noting that a major problem of SEC “is non-specific binding of applied proteins to the column matrix (stationary phase)”); EX1045 (*Yumioka*), Abstract (noting, *e.g.*, that “[l]oss of protein aggregates due to matrix protein interaction during SEC often causes underestimation of aggregate content in the quality control of pharmaceutical proteins.”); EX1047 (*Gandhi*), 2178 (noting, *e.g.*, that “numerous factors can cause problems with analysis of protein aggregates with SEC, and such problems have been recognized for more than 30 years.”). Accordingly, SEC was not, and is not, regarded as a method capable of accurately determining the percentage of a molecule in a composition that has resisted aggregation and/or degradation.

69. Despite this, size-exclusion chromatography was sometimes used at the time as a proxy to estimate the amount of protein in a composition that has not been degraded, such as by aggregation or denaturation, since these types of degradation often cause the protein to interact differently with the size-exclusion chromatography column. *US865* refers to “% VEGF Trap Native Configuration” in the tables of the Examples. *US865* clarifies that this measurement was made by size-exclusion chromatography. *See, e.g.*, EX1001 (*US865*), 8:40-43 (explaining that “purity” was measured by size-exclusion HPLC).

70. The POSA also would have been mindful of the turbidity of the formulation. It was known at the time that the presence of suspended particles like

insoluble protein aggregates and precipitates leads to an apparent increase in UV absorbance at all wavelengths due to scattering effects. *See* EX1041 (*Mahler 2005*), 409-10. It was common to measure turbidity using UV absorbance between 350 and 550 nm. *Id.* 405 nm was another common wavelength in this regard. *See, e.g.,* EX1042 (*Andersen 1990*), 53 (measuring change in turbidity of protein aggregates at 405 nm).

71. In *US865*, turbidity is measured using optical density (OD), which is the negative log of transmittance. *E.g.,* EX1001, Examples 1-8 (reporting turbidity at OD₄₀₅ nm). The higher the optical density, the more aggregates (large particles) are likely present, that are causing the UV light to be scattered. A formulator would have viewed low values for an optical density turbidity test as an indication that one type of aggregation (formation of large particles) was being minimized.

VI. CLAIM CONSTRUCTION

72. I interpreted the claim terms consistent with their ordinary and customary meaning to a POSA, or (where indicated below) how the POSA would have understood a term in light of the specification and any applicable prosecution history. For clarity, I set forth below the ordinary and customary meaning of terms relevant to my analysis.

73. I understand the term “native” in the phrase “native conformation” was construed in *Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals Inc.*,

et al., 1:22-CV-61 (N.D. WV) (“the Mylan Case”) to refer to the fully-intact and functional conformation of the VEGF-antagonist protein referred to in the claims. As explained below, while the claims refer to the percentage of protein in “native conformation following storage at 5 °C” for two or 24 months “as measured by size exclusion chromatography,” this usage presents a technical inconsistency. In size-exclusion chromatography (“SEC”), a protein in native conformation may co-elute with other substances that have a similar size, molecular weight or shape. For example, the protein in native conformation may co-elute with a degraded version (or versions) of that protein, that have a similar size, molecular weight or shape. *See, e.g.*, EX1021 (Klibanov Declaration) ¶90. While SEC may allow for an estimate of the amount of aggregate, which may be viewed as a way to approximate the amount of protein in native conformation, it does not provide an accurate measurement of the amount of protein in its native conformation.

74. In addition, the claims require that “at least” 98% or 99% of the VEGF antagonist “is present in native conformation after ... storage at 5° C.” “[T]he VEGF antagonist” refers back to the VEGF antagonist that is present in native conformation prior to storage at 5° C. A POSA would have understood that the VEGF antagonist used in the formulation refers to a fully-intact and functional conformation of the VEGF-antagonist protein, excluding any protein that had already degraded and/or aggregated and thus no longer acts as a VEGF antagonist.

The “at least” 98% or 99% of “the VEGF antagonist” present after storage at 5° C would be relative to that initial amount of the fully-intact and functional conformation of a VEGF-antagonist protein at time zero, and not the total amount of VEGF protein used in making the formulation. A POSA would thus have understood the claim to be describing a rate of degradation and/or aggregation of the non-aggregated/degraded VEGF antagonist in the formulation over time.

75. This construction is consistent with the specification of *US865*, which discloses that the “invention includes liquid pharmaceutical formulations having increased stability.” EX1001, 1:49-50. As I discuss above, *US865* also states that the VEGF traps are “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 protein is substantially free of contaminants or aggregates. *Id.* Because *US865* teaches that the % VEGF trap in native conformation is measured by SEC, a POSA would have understood the specification as preferably requiring that at least 90% of the total weight of the protein used in making the formulation is not aggregated at time zero. Stated differently, a POSA would have understood the disclosure as stating that approximately at least 90% of the weight of the protein is VEGF antagonist, that is, at least 90% of the weight of the protein is the fully-intact and functional conformation of the VEGF-antagonist protein at time zero.

76. A POSA would have understood that any initial measurement of the % VEGF trap in native conformation at time zero 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, as I discuss in paragraph 127 and 130, a POSA would have understood that once a protein is aggregated, it rarely un-aggregates. *See* EX1049 (Testimony of Kenneth S. Graham), 1707:9-22 (Regeneron expert, Kenneth S. Graham, PhD, testifying on direct that “when a protein aggregates, it’s like rolling a ball downhill. It goes – the level of purity goes down. It doesn’t roll back up.”). Measuring the stability of an aggregated protein after 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 can un-aggregate to re-assume its functional conformation.

77. To the extent that Regeneron argues that the claim phrase “at least” 98% or 99% of the VEGF-antagonist “is present in native conformation after ... storage at 5° C” should be construed as requiring that at least 98% of the total weight of the protein that was used to make the formulation is present in its intact functional conformation after storage, that is, consistent with the absolute amounts reported in the Tables, as I discuss above paragraphs 74-76, that is not consistent with how a POSA would construe “a VEGF antagonist” that is used in making the formulation.

78. Claims 1 and 26 claim a vial and a pre-filled syringe (“PFS”) comprising an ophthalmic formulation suitable for intravitreal administration, respectively. Each of the claimed ophthalmic formulations comprises a VEGF antagonist fusion protein that is glycosylated and comprises amino acids 27-457 of SEQ ID NO:4. I have been informed by counsel that the term “comprises” means “includes.” Therefore, the VEGF antagonist required by the claims encompasses a protein having only amino acids 27-457 but also encompasses proteins that may include additional amino acids at either end. Thus, I construe the claims as encompassing a VEGF antagonist fusion protein that has a sequence that only has the amino acids as found at residues 27 to 457 of SEQ ID NO:4. But the sequence can also include additional amino acids at either end, so long as it still binds VEGF to some degree. Accordingly, the claims encompass a VEGF antagonist fusion protein having the sequence of amino acids 27-457 of SEQ ID NO: 4, as well as a sequence that matches the full amino acid sequence of SEQ ID NO:4, i.e. amino acids 1 to 458 of SEQ ID NO:4.

79. I understand that in the *Mylan* Case, Regeneron asserted *US865* against Mylan. I further understand that the parties in the *Mylan* Case stipulated that the term “glycosylated” in claim 1 means “containing at least one amino acid residue with an attached carbohydrate.” EX1024, 50. I thus use this construction in rendering my opinions in this declaration.

80. Regardless of the claim construction adopted, the claims are only entitled to the effective filing dates discussed in Section IX, X.A.1, and the claims are still unpatentable over the anticipation and obviousness grounds over *US432*, which has the same specification as *US865*, asset forth below in Sections XI.A-D.

VII. OVERVIEW OF THE PRIOR ART

A. US 2007/0293432 (“*US432*,” EX1004)

81. US 2007/0293432, titled “VEFG Antagonist Formulations Suitable for Intravitreal Administration” (“*US432*”) published on December 20, 2007, and therefore was a printed publication available before *US865*’s earliest possible priority date of October 12, 2018.

82. *US432* is the publication of Application No. 11/818,463 (“*App463*”), filed by Regeneron on June 14, 2007, which issued as U.S. Patent No. 7,608,261, and names the same inventors as *US865*. The face of *US865* indicates that it is related to *App463* through only divisional and continuation applications. I have been informed that *US865* and *App463* (and its published form as *US432*) have identical specifications (except for the cross-references to related applications). I have confirmed for myself that this is the case.

83. Because *US432* and *US865* have the same specification, they disclose the same formulations, examples and stability. Thus, *US432*, like *US865*, discloses the following:

- “Ophthalmic formulations of a vascular endothelial growth factor (VEGF)-specific fusion protein antagonist are provided suitable for intravitreal administration to the eye” (EX1004, Abstract; EX1001, Abstract);
- “The present invention is directed to pharmaceutical formulations suitable for intravitreal administration” (EX1004 ¶3; EX1001, 1:45-46).
- “The invention further features ophthalmic formulations provided in a pre-filled syringe or vial, particularly suitable for intravitreal administration” (EX1004 ¶39; EX1001, 5:23-25).
- “A liquid formulation containing 40 mg/ml VEGF Trap (SEQ ID NO:4), 10 mM phosphate, 40 mM NaCl, 0.03% polysorbate 20, 5% sucrose, and pH 6.3, was stored at 5 °C. in 3 ml glass vials and samples tested at 0.5, 1, 2, 3, and 4 months. Stability results are shown in Table 3. Turbidity, percent recovered protein and purity was determined as described above.” Turbidity and “% VEGF Trap Native Configuration” as reported in Table 3 for the formulation after 2 months storage were 0.00 and 99.2%, respectively (EX1004 ¶62; EX1001, 9:19-44);
- “A liquid formulation containing 40 mg/ml VEGF trap (SEQ ID NO:4), 10 mM phosphate, 40 mM NaCl, 0.03% polysorbate 20, 5% sucrose, and pH 6.3, was stored at 5 °C. in 1 ml prefilled luer glass syringe ... and

- samples tested at 0.5, 1, 2, 3, and 4 months. Stability results are shown in Table 4. Turbidity, percent recovered protein and purity was determined as described above.” Turbidity and “% VEGF Trap Native Configuration” as reported in Table 4 for the formulation after 2 months storage was 0.0 and 99.1%, respectively (EX1004 ¶63; EX1001, 9:45-10:12);
- “An ophthalmic liquid formulation containing 50 mg/ml VEGF Trap (SEQ ID NO:4), 10 mM phosphate, 50 mM NaCl, 0.1% polysorbate 20, 5% sucrose, and pH 6.25, was stored at 5 °C. in 3 ml glass vials and samples tested at 3, 6, 9, 12, 18 and 24 months.” % VEGF Trap Native Configuration “was determined by SE-HPLC[.] The results are shown in Table 1. Turbidity was measured at OD₄₀₅ nm; and percent recovered protein and purity by size exclusion HPLC.” The “% VEGF Trap [in] Native Configuration” as reported in Table 1 at 24 months was 98.1% (EX1004 ¶60; EX1001, 8:32-58);
 - A liquid formulation containing 50 mg/ml VEGF Trap (SEQ ID NO:4), 10 mM phosphate, 50 mM NaCl, 3% polyethylene glycol 3350, 5% sucrose, and pH 6.25, was stored at 5 °C. in 3 nil [sic] glass vials and samples tested at 3, 6, 9, 12, 18 and 24 months. Stability results are shown in Table 2. Turbidity, percent recovered protein and purity was

- determined as described above.” The “% VEGF Trap [in] Native Configuration” as reported in Table 2 at 24 months was 97.7% (EX1004 ¶61; EX1001, 8:59-9:4);
- “Unless stated otherwise, the phosphates employed are sodium phosphates” (EX1004 ¶49; EX1001, 6:55-56);
 - “In a specific embodiment, the fusion protein comprises amino acids 27-457 of SEQ ID N0:4 and is glycosylated at Asn residues 62, 94, 149, 222 and 308” (EX1004 ¶48; EX1001, 6:34-37);
 - “In one or more specific embodiments ... the buffering agent may be, for example, phosphate buffer” (EX1004 ¶11; EX1001, 2:39-48).

84. As mentioned above, Examples 3 and 4 of *US432* (and *US865*) indicate that “[t]urbidity, percent recovered protein and purity was determined as described above.” EX1004 ¶¶62-63; EX1001, 9:28-30, 54-56. A POSA would have understood that these statements refer to Example 1, which states that “[t]urbidity was measured at OD₄₀₅ nm; and percent recovered protein and purity by size exclusion HPLC” (EX1004 ¶60; EX1001, 8:42-44) because this is the only disclosure “above” regarding how to measure turbidity and the only specific disclosure of how a purity was determined.

85. I have also been informed that Regeneron has acknowledged that the formulations used in Examples 3 and 4 of the specification are its EYLEA

formulation: “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).

B. WO 2017/129685 (EX1005; “WO685”)

86. WO685, titled “Liquid Formulation of a VEGF Antagonist, published on August 3, 2017, and therefore was a printed publication available before US865’s earliest possible priority date of October 12, 2018. 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 % polysorbate 20, with a pH of 6.2, as well as the favorable stability achieved. EX1005, 14 (Table 9, Sample (a)), 43.

VIII. VEGF Trap as Used in US865

87. Claim 1 of US865 recites: “A vial comprising an ophthalmic formulation suitable for intravitreal administration that comprises: a vascular endothelial growth factor (VEGF) antagonist, an organic co-solvent, a buffer, and a stabilizing agent; wherein said VEGF antagonist fusion protein is glycosylated and comprises amino acids 27-457 of SEQ ID NO: 4; and 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.”

88. Claim 1 uses the term “wherein said VEGF antagonist fusion protein is glycosylated and comprises amino acids 27-457 of SEQ ID NO:4.” EX1001, 19:35-37. I have been asked to opine on how the POSA would have understood this term in claim 1 of *US865*.

89. As mentioned above, I understand that it is permissible to use the specification of the patent to understand how the POSA would have understood a claim term used in that patent. In the case of the term “wherein said VEGF antagonist fusion protein is glycosylated and comprises amino acids 27-457 of SEQ ID NO:4,” the POSA would have understood that this term refers to a molecule that comprises amino acids 27-457 of SEQ ID NO:4 (but can include other amino acids) and is glycosylated at asparagine residues 62, 94, 149, 222, and 308. In fact, the only time that the specification of *US865* mentions amino acids 27-457 of SEQ ID NO:4 also states that it is glycosylated at asparagine residues 62, 94, 149, 222, and 308. EX1001, 6:30-37.

90. *US865* discusses SEQ ID NO:4 in several places. For example, when generally describing the VEGF antagonist that may be used in the invention, the patent states that, in a particular embodiment, “the fusion protein has the amino acid sequence of SEQ ID NO:2 or SEQ ID NO:4. Preferably, the VEGF antagonist is a dimer comprising two fusion proteins of SEQ ID NO:4.” EX1001, 2:29-32. Later, when describing ophthalmic formulations, the patent again refers

multiple times to SEQ ID NO:4. *See, e.g.*, EX1001, 2:53-3:24 (listing formulations involving SEQ ID NO:4); *see also, e.g.*, 3:53-4:6 (same). The examples also refer to “VEGF Trap (SEQ ID NO:4),” which is the only protein described or tested in any of the examples. *See* EX1001, Examples 1-8.

91. As noted above, the patent only once (other than claim 1, 26, 51 and their dependent claims) refers to “amino acids 27-457 of SEQ ID NO:4.” This truncated sequence appears one time in the specification. *Id.*, 6:34-37. This portion of the specification states that “[i]n 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 a mammalian cell line such as a CHO cell and may be modified post-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.” EX1001, 6:30-37.

92. The POSA would have understood that amino acids 1-26 of SEQ ID NO:4, is a “signal sequence,” which is a portion of the amino acid sequence whose function is to target the molecule for secretion by a eukaryotic cell. It was known in the prior art that VEGFR1R2-Fc Δ C1(a) (known later as aflibercept) had an amino acid sequence that was contained within what later became known as SEQ ID NO:4 in *US865*, and that amino acids 1-26 of SEQ ID NO:4 are a signal

sequence that gets cleaved off when aflibercept is expressed in CHO cells. *See* EX1043 (*Daly*) ¶¶23, 32, 64, Example 8; *see also* EX1029 (*WO319*), Figs. 24A-24C. When aflibercept is expressed in a mammalian (eukaryotic) cell such as a CHO cell, which is the only method of producing the VEGF Trap disclosed in *US865*, this signal sequence is cleaved off by an enzyme (signal peptidase) as a post-translational modification. The same signal sequence would not direct the molecule for secretion out of the cell if the protein were expressed in a prokaryotic cell, such as *E. coli*. Moreover, if aflibercept were expressed in, for example, *E. coli*, which is never even mentioned in *US865*, the POSA would have expected the signal sequence to remain attached and that the molecule would not be secreted out of the cell. Accordingly, when the patent refers to this truncated sequence, the POSA would have understood that it is truncated specifically because it was expressed in a CHO cell and the signal sequence was cleaved off post-translationally, especially because the only disclosed method for producing the VEGF Trap in the patent is in CHO cells. A POSA would have understood that this post-translational processing would also glycosylate the truncated sequence at the N-glycosylation sequence motifs that were readily identifiable in SEQ ID NO:4 at asparagine residues 62, 94, 149, 222, and 308.

IX. THE EFFECTIVE FILING DATE OF *US865*

93. *US865* states on its face, and in column 1, that it claims priority from the following applications (and patents):

Priority Document	Filing Date	Exhibit Number of Prosecution History / Provisional Filing
16/582,486, now US11,066,458	Sep. 25, 2019	1007
16/159,269, now US10,464,992	Oct. 12, 2018	1008
15/879,294, now US10,400,025	Jan. 24, 2018	1009
15/095,606, now US9,914,763	Apr. 11, 2016	1010
14/330,096, now US9,340,594	Jul. 14, 2014	1011
13/914,996, now US8,802,107	Jun. 11, 2013	1012
13/329,770, now US8,481,046	Dec. 19, 2011	1013
12/833,417, now US8,092,803	Jul. 9, 2010	1014
12/560,885, now US7,807,164	Sep. 16, 2009	1015
11/818,463, now US7,608,261	Jun. 14, 2007	1016
60/814,484		1025

94. All of the above utility applications have the same specification (except for the statement of continuity), thus when I refer to the disclosure as originally filed, I am referring to the disclosure as originally filed in 11/818,463 (“*App463*”).

95. I have reviewed excerpts of the file histories of each of these applications.

96. Challenged claims 1-50 of *US865* each require that “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”). EX1001. Claims 16, 24, 41 and 49 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” (“the at least 99% two-month stability limitation”). *Id.* Claims 17, 25, 42 and 50 also 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” (“the at least 98% 24-month stability limitation”). *Id.* I collectively refer to these limitations as “the stability limitations.”

97. Claims 1-13, 15-21, 23-38, 40-46, and 48-50 each require that “said VEGF antagonist protein is glycosylated and comprises amino acids 27-457 of SEQ ID NO:4.” The claims do not limit the type of glycosylation (*e.g.*, O-glycosylation or N-glycosylation), the number of residues that are glycosylated or which residues are glycosylated. I refer to this limitation as “the general glycosylation limitation.”

98. US865 issued from the Application No. 16/739,559 (*App559*), which was filed on January 10, 2020. EX1001.

99. *App559*, as filed, claimed a prefilled syringe suitable for intravitreal administration containing a VEGF antagonist produced in CHO cells. EX1006 (January 10, 2020 Preliminary Amendment), 3. When introducing claims reciting these stability limitations via preliminary amendment, Regeneron pointed to ¶37 and Example 6 of the disclosure for support. EX1006, 45. The claims as of the filing date did not include the general glycosylation limitation. *Id.*

100. On March 24, 2021, the examiner rejected the claims for obviousness-type double patenting (“ODP”) over claims of US8,092,803, US7,608,261, US9,340,594, and US9,914,763. EX1006 (March 24, 2021 Office Action), 256-262.

101. On May 5, 2021, Regeneron amended the claims to remove the CHO cell limitation and add the general glycosylation limitation, stating that support for the amendment could be found “throughout the originally filed application, such as, for example, at ¶[0046].” EX1006 (May 5, 2021 Response), 280. The applicants also added claims to a vial, a prefilled syringe, and a formulation, and added claims with the stability limitations. Claim 12 was amended to include the at least 98% two-month stability limitation, and new independent claims 45 and 70 also included that limitation. New claims 36, 43, 61, and 68 included the at least

99% two-month stability limitation. New claims 37, 44, 62, and 69 included the at least 98% 24-month stability limitation. Applicants said that support for the amendment could be found “throughout the originally filed application” without specifically identifying any support. EX1006 (May 5, 2021 Response), 280. The applicants also filed a terminal disclaimer over US8,092,803 and argued to the examiner that the claims US7,608,261, US9,340,594 and US9,914,763 do not include the stability limitations. EX1006 (May 5, 2021 Terminal Disclaimer), 293; *Id.* (May 5, 2021 Response), 281-282. The Examiner then allowed the claims. EX1004 (June 9, 2021 Notice of Allowance), 301-303.

102. *App559* is a continuation of Application No. 16/582,486 (“*App486*”), filed on September 25, 2019. EX1001. As filed, *App486* claimed a vial and a formulation in which the VEGF antagonist is produced in CHO cells. The original claims did not have any stability or glycosylation limitations. EX1007, September 25, 2019 Application as Filed, 15.

103. On September 26, 2019, applicants filed a preliminary amendment in *App486* that added claims to a vial containing a VEGF antagonist formulation, including claims requiring “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 size exclusion chromatography,” stating that the new claims “are supported in the original application” without specifically identifying any

particular portion of the specification for support. EX1007 (September 26, 2019 Preliminary Amendment), 49, 51-55. On July 13, 2020, applicants filed a preliminary amendment that included claims to include a vial and a PFS, claims with the stability limitations, and claims requiring that the VEGF antagonist is glycosylated at asparagines 62, 94, 149, 222, and 308. These claims did not include a general glycosylation limitation. Applicants stated that support for the amendment could be found “throughout the originally filed application” without specifically identifying any support. EX1007 (July 13, 2020 Preliminary Amendment), 254-259.

104. The examiner rejected these claims for ODP over claims of US8,092,803, US7,608,261, US9,340,594, US9,914,763, US10,400,425, and US10,464,992. EX1007 (January 6, 2021 Rejection), 266-272. Applicants amended the claims to specifically indicate that the claimed formulation is an ophthalmic formulation suitable for intravitreal administration. Applicants also filed terminal disclaimer over US8,092,803 and US10,464,992 and argued to the examiner that the claims of US7,608,261, US9,340,594, US9,914,763, and US10,400,425 do not include the stability limitations. EX1007 (March 2, 2021 Response), 295-312; *id.* (Terminal Disclaimer), 313. The claims were allowed soon thereafter. EX1007 (May 12, 2021 Notice of Allowance), 392-394.

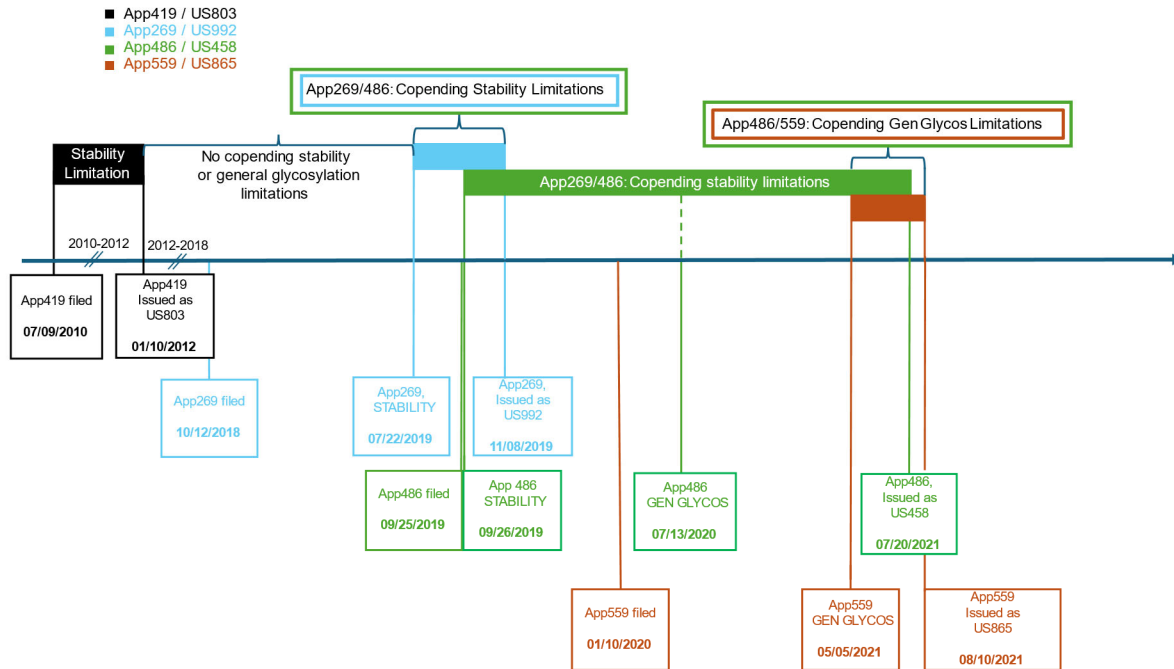
105. *App486* is a continuation of Application No. 16,159,269 (“*App269*”), filed on October 12, 2018. EX1001. *App269*, as filed, claimed a vial and a formulation in which the VEGF antagonist is produced in CHO cells. EX1008 (October 12, 2018 Preliminary Amendment), 2-4. The claims of *App269*, as filed, did not contain the stability limitations or the general glycosylation limitation. *Id.* As explained below (Section X.A.2.), at best, the challenged claims are entitled to the filing date of October 12, 2018, which is the filing date of *App269*.

106. The examiner rejected the claims of *App269* for ODP over US8,092,803, US7,608,261, US9,340,594, and US9,914,763, and over a pending application. EX1008 (April 2, 2019 Rejection), 74-80.

107. In its July 22, 2019, response, applicants amended the claims to add the at least 98% and 99% two-month stability limitations. EX1008 (July 22, 2019 Response), 90-92. Applicants said that the amendments “are supported in the originally filed application” but did not identify any specific support. *Id.*, 93. Applicants also filed a terminal disclaimer over US8,092,803, and said that US7,608,261, US9,340,594, and US9,914,763 and the pending application did not contain the stability limitations. *Id.*, 93-94; *id.* (Terminal Disclaimer), 96. The claims were then allowed. EX1008 (August 21, 2019 Notice of Allowance), 104-106.

108. The claims of Application Nos. 15/879,294, 15/095,606, 14/330,096, 13/914,996, 13/329,770, 12/560,885, and 11/818,463 never included any of the stability limitations or the glycosylation limitations. *See* EX1009-EX1013, EX1015-EX1016.

109. The claims of Application No. 12/833,417 (“*App417*”), filed July 9, 2010, included the at least 99% two-month stability limitation as filed. EX1014 (July 9, 2010 Application as Filed), 23-25. *App417* issued on January 10, 2012, as US8,092,803. EX1014 (Issue Notification), 189. Therefore, *App417* was never copending with *App269*, *App486*, or *App559*, which were filed on October 12, 2018, September 25, 2019 and January 10, 2020, respectively. EX1001; *see also* chart below demonstrating the overlap (or lack of overlap) of the pendency of applications *App419*, *App269*, *App486*, and *App559*.



X. THE CLAIMS OF *APP559* LACK WRITTEN DESCRIPTION SUPPORT

110. I have been asked to consider whether there is sufficient written support in *App559* for the stability limitations (claims 1-50). I was also asked to consider whether there is sufficient written support in *App559* for the general glycosylation limitation (claims 1-13, 15-21, 23-38, 40-46, and 48-50), and for the “no phosphate” limitation (claims 18 and 43). As I address below, I conclude there is not.

A. *App559* Lacks Written Description Support for the Stability Limitations

111. To start, to a POSA, the language “at least” in the stability limitations denotes a range starting at the recited value and going as high as 100%. Therefore, where the native conformation is described as being “at least 98%,” the claimed

range is 98%-100%, and where the native conformation is described as being “at least 99%,” the claimed range is 99%-100%.

112. Based on my review of the disclosure as originally filed, the ranges of “at least 98%” (i.e., 98-100%) and “at least 99%” (i.e., 99-100%) of VEGF antagonist present in native conformation at the recited time points is not disclosed in the application. I understand that a patentee is not required to explicitly recite a range for there to be written description. But if the range is not stated, there must be data points within and representative of that range in the specification that would allow a POSA to understand that the inventors had possession of the claimed invention. I am informed that the POSA must be able to reasonably discern a disclosure of that range from the disclosure as filed.

113. There is only one place in the patent where the specification provides information concerning % native conformation at different time points, and that is in the Examples. In particular, stability data for liquid formulations of aflibercept are provided in Examples 1-6 and corresponding Tables 1-6, and stability data for lyophilized formulations are presented in Examples 7-8 and corresponding Tables 7-8. I have reviewed the data and other information disclosed in the specification, and given this review a POSA would not have been able to reasonably discern a disclosure of any of the claimed ranges.

1. The at Least 98 or 99% Two-Month Stability Limitation

114. As an initial matter, I note that the specification states that “invention includes liquid pharmaceutical formulations having increased stability”

EX1001, 1:49-52; EX1006, 4. The specification does not define the term “stability.” *E.g.*, EX1001, 6:60-7:24, EX1006, 11-12. I have been informed that Regeneron argued in IPR2023-00462 (“*462IPR*”) that a POSA would not read “stability” in the context of pharmaceutical formulations as requiring 98 or 99% stability, i.e. reflecting a change from time 0 of no more than 1 to 2%. EX1026, 56-58 (Regeneron’s Patent Owner Response 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. Thus, a POSA would not read the specification’s teaching of pharmaceutical formulations having increased stability as informing the POSA that the inventor’s had possession of formulations limited to “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” as required by the challenged claims.

115. Further, “at least 98%” or “at least 99%” should be read as being a range of 98-100% or 99-100%, which is, again, no more than a 2% or 1% change in the amount of protein in “native” form as compared to time 0. That reading is consistent with how a POSA would read those terms. The specification, however,

does not discuss a desired level of stability at a specific time point, or what that level of stability should be at 2 months, or 24 months as required by challenged claims 17, 25, 42, and 50.

116. In addition, as discussed above, all the formulations of the examples contain essentially the same excipients, wherein the concentrations of the excipients of the examples fall within a narrow range. Even assuming that the specific data points provided in the Tables of the examples for the formulations that have this narrow range of excipients using a single VEGF trap somehow provide support for the reported points for the exemplified formulations, there is still nothing in the specification that would point the skilled artisan to the added stability limitations as required by the challenged claims. These limitations are not discussed in the general disclosure of the specification or in the text accompanying the Tables of the examples.

117. In rendering my opinion, I have also been asked to consider the portion of the specification that states as follows:

VEGF Antagonists

[0046] A VEGF antagonist is a compound capable of blocking or inhibiting the biological action of vascular endothelial growth factor (VEGF), and 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 a mammalian cell line such as a CHO cell and may be modified post-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 composed of two fusion proteins of SEQ ID NO:4.

[0047] The VEGF antagonist of the methods and formulations of the invention can be prepared by any suitable method known in the art, or that comes to be known. The VEGF antagonist is preferably substantially free of protein contaminants at the time it is used to prepare the pharmaceutically acceptable formulation. By “substantially free of protein contaminants” is meant, preferably, that at least 90 % of the weight of protein of the VEGF-specific fusion protein antagonist preparation used for making a formulation is VEGF fusion protein antagonist protein, more preferably at least 95%, most preferably at least 99%. The fusion protein is preferably substantially free of aggregates. “Substantially free of aggregates” means that at least 90% of the weight of fusion protein is not present in an aggregate at the time the fusion protein is used to prepare the pharmaceutically effective formulation. Unless stated otherwise, the phosphates employed are sodium phosphates and a desired buffering pH is achieved by mixing appropriate amounts of mono- and dibasic sodium phosphate.

EX1006 (January 10, 2020 Application as Filed ¶¶ 46-47), 11.

118. Nothing in that portion of the specification changes my opinion. The excerpt merely addresses the preparation of VEGF antagonist-containing formulations, and it explains the inventors’ preference that the VEGF antagonist be “substantially” free of protein contaminants and substantially free of aggregates “at the time the ... protein is used to prepare the pharmaceutically effective formulation.” It does not address the stability of the VEGF antagonist, or how much of the VEGF antagonist remains in native conformation over time during

storage. As a result, it does not inform a POSA anything about the amount of aflibercept in native conformation after two months of storage under the claimed conditions.

119. In addition, during prosecution of *App559*, in a preliminary amendment filed the same day as the application, applicants amended the claims to add the at least 98% and 99% two-month stability limitations. EX1006 (September 26, 2019 Preliminary Amendment), 3.

120. Applicant stated that support for the new claims could be found “in original paragraph [0037] and in example 6.” EX1006 (January 10, 2020 Preliminary Amendment), 45. Original paragraph 37 states: “The invention further features ophthalmic formulations provided in a pre-filled syringe or vial, particularly suitable for intravitreal administration.” EX1006 (January 10, 2020 Application as Filed ¶37), 9; EX1001, 5:23-25. Applicants did not explain how Paragraph 37 provides support for the added at least 98% and 99% two-month stability limitations. Paragraph 37 does not provide any support for the stability limitations.

121. Example 6 of the application is titled “Stability of 40 mg/ml VEGF Trap Liquid Formulation Stored at 5°C in 1ml Pre-Filled Glass Syringe.” The formulation used in Example 6 had 40 mg/ml VEGF trap (SEQ ID NO:4), 10 mM

phosphate, 135 mM NaCl, 0.03% polysorbate 20, and pH 6.3. Table 6 of Example 6, reproduced below, shows the stability results:

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

EX1006 (January 10, 2020 Application as Filed ¶63), 16. Table 6 does not provide any two-month (or 24 month) stability results.

122. A POSA would not understand from Example 6 that the inventors had possession of the claimed lower limits of 98% or 99%, or ranges of 98-100% or 99-100%. The specification does not point a POSA to these added limitations, especially given the small number of specific formulations tested as compared to the breadth of the challenged claims. The formulation in Example 6 contained 40 mg/ml VEGF Trap, 10mM phosphate, 135mM NaCl, 0.03% polysorbate 20, at a pH of 6.3, but none of the challenged claims are limited to that specific formulation.

123. I have also reviewed Examples 1-5 to determine if they provide support for the added stability limitations. Examples 1-5 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; EX1001, 9:19-10:40. 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. EX1006, 13-14; EX1001, 8:33-9:19. Examples 1 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; EX1001, 8:33-12:25. The reported results for these examples also would not point a POSA to the added stability limitations.

124. I did not address Examples 7 and 8 in the previous paragraph given that they relate to lyophilized formulations, and a POSA would not consider them to be applicable to the liquid formulations of the challenged claims. But even if they were considered to be applicable to the liquid formulations of the challenged claims, they do not support the stability limitations added by amendment. The formulations that were lyophilized were very similar to the formulations of the other examples. The formulation of Examples 7 that was lyophilized contained 20 mg/ml VEGF Trap (SEQ ID NO: 4), 5 mM phosphate, 20 mM phosphate, 20 mM

NaCl, 0.015% polysorbate 20, and 2.5% sucrose at a pH of 6.3. EX1006, 17; EX1001, 11:5-8. The Example 8 formulation that was lyophilized only differed from the formulation of Example 7 in that it had 67 mM NaCl and no sucrose. EX1006, 17; EX1001, 12:6-9. Both were reconstituted to a VEGF trap concentration of 40 mg/ml. EX1006, 17; EX1001, 11:9-11, 12:10-12.

125. There is no disclosure in the text accompanying Examples 7 and 8 that would have allowed a POSA to understand that the inventors were in possession of the idea of a range, much less the ranges of the stability limitations added by amendment.

126. I note additionally that all the Tables of the examples drawn to liquid formulations 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 size exclusion HPLC, i.e., SE-HPLC or SEC. EX1006, 13-14; EX1001, 8:40-43. As would be understood by the POSA, SEC will only measure the protein that migrates through and is eluted from the SEC column. As I discuss above in paragraph 68, certain aggregates and degradants will not pass through the column. Degradants that are approximately the size and shape as VEGF Trap in its native configuration may co-elute with VEGF trap in its native configuration. Smaller aggregates will also pass through the column, but

larger aggregates may get caught in the frit and/or not be able to pass through the particles of the column and elute. *See* EX1047 (*Gandhi* 2017), 2178. This behavior is reflected by the “% VEGF Trap Recovered” reported in the Tables of the examples. All the examples report 100% “VEGF Trap Recovered” at time zero. A POSA would not have understood that the reported value of 100% for each of the examples as reflecting that 100% of the protein used in the formulation was recovered. Rather, a POSA would have understood that the amount of native protein that was eluted from the column at time zero was normalized to 100% VEGF trap recovered.

127. That is, the amount of “% VEGF Trap Recovered” measured at time 0 would be essentially the amount of unaggregated VEGF trap used in making the formulation that passes through the column. As I discuss above at paragraph 76, once a protein aggregates, it rarely deaggregates. A POSA would thus not expect the “% VEGF Trap Recovered” to increase over time, since that would suggest that the amount of unaggregated VEGF trap is increasing, i.e., that aggregated VEGF Trap is deaggregating. Rather, a POSA would have understood that the increase in “% VEGF Trap Recovered” at time periods after time 0 is most likely due to measurement error.

128. For example, for the data presented in Table 3, the “% VEGF Trap Recovered” goes from 100% at Time 0, 99%, 98%, and 95% at 0.5, 1, and 2

months, respectively. The specification does not address this change. A POSA would have attributed this change to a loss of protein that failed to make it through the column due to degradation and/or aggregation. Thus, the POSA would have understood that the loss of the % of VEGF Trap in native configuration is not just the difference in value from time 0 to the values reported in Table 3 of 0.1 or 0.3% at times 0.5 and 2 months, but would include the decreases from 100% at those times of 1% and 5%, respectively. In my view, a POSA would thus have further understood the total loss to be greater than the 1% and 5% reported losses for VEGF trap recovered at 0.5 and 2 months, respectively, with the amount of loss at 2 months thus being greater than the maximum of 1 or 2% allowed by the claim.

129. Table 5 demonstrates further why a POSA would not have 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. Between 0 and two months, the % VEGF Trap Recovered goes down to 87% at 0.5 months and then back up to 103% at two months. The specification does not explain these down-then-up changes for the reported amounts of % VEGF Trap Recovered measured by SEC. A POSA, however, would have reasonably understood that the 13 % change in % VEGF Trap Recovered (from 100% to 87%) represents either loss of protein due to

degradation/aggregation of up to 13% or measurement error. The reported value for % VEGF Trap Recovered of 103% would suggest an increase in the amount of native VEGF trap recovered of 3% from time zero or measurement error.

Reviewing the other Examples, in Table 2 the “% VEGF Trap Recovered” is reported to be as high as 113% over the reported amount of 0% VEGF Trap Recovered at time 0. As explained below, A POSA would have concluded that the reported value of 113% VEGF Trap Recovered is likely due to measurement error.

130. But as I discuss above in paragraph 76, aggregation is known to be essentially irreversible. Regeneron presents no margins of error for the data presented, and the specification and text accompanying the examples do not explain why amounts of % VEGF Trap Recovered over 100% were obtained. A POSA would have concluded that the most likely explanation is that the 103% reported value is due to measurement error. Thus, a POSA would have concluded that the “% VEGF Trap Recovered” measurements reported by the inventors in the patent are subject to measurement errors of at least 3%, and maybe as high as 13% as reported in Table 2. In addition, 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 have read the specification as indicating that there is a margin of error in measuring the amount of VEGF trap

by SEC. A POSA would have understood that a change from time zero of up to two percent of VEGF antagonist in native conformation as required by the challenged claims is well below a possible margin of error of 3-13%.

131. I also reviewed Examples 7 and 8, which are drawn to lyophilized formulations. The “% VEGF Trap Recovered” at time 0, like all of the other examples, was 100%. It then went up in both examples to 106 or 105%, respectively, at 1 month, and 103% for both examples at 2 months. A POSA would have viewed an increase in the amount of “% VEGF Trap Recovered” at later time points after time 0 as further reinforcing that using SEC introduces error into the data obtained using SEC.

132. I have also been informed that the level of description required is also dependent on the complexity and predictability of the relevant art. But I have also been informed that in the *462IPR* challenging claims of the '992 patent, which has the same specification as *US865*, Regeneron characterized the art as being highly unpredictable. I note, for example, that Dr. Klibanov testified 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.” EX1027 ¶¶63 (the declaration of Regeneron’s own expert submitted in support of its Preliminary Response in the *462IPR*); *see also id.* ¶¶64-69. But as I explain above (paragraph 78), the claims include VEGF trap proteins having additional amino acids at either or both of the

C- and N-termini. I understand that Dr. Klibanov also testified that other factors that can affect stability include glycosylation (EX1021 ¶45), excipients (*id.* ¶46), and protein concentration (*id.*, ¶47). I also understand that Dr. Klibanov testified that “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.

133. As I discuss in paragraphs 45 and 133, the examples all use the same or very similar formulations, whereas the claims encompass a much broader range of formulations. That is, while 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,” the claims merely require an organic co-solvent, a buffer, and a stabilizing agent to achieve the claimed levels of stability. *Id.*, 19:35-37 (claim 1), 21:6-8 (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. Thus, the complexity and unpredictability mentioned by Dr. Klibanov further support my conclusion that the POSA would not have read the limited examples as demonstrating that the inventors have possession of the

stability limitations added to the broadly claimed formulations of the challenged claims.

134. Because the examples provide specific measurements for very specific formulations, and not all the examples report SEC results at two and/or 24 months, there is nothing in the disclosure pointing a POSA 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 tested in the examples, much less the broader set of formulations encompassed by the challenged claims. Further, there is nothing 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 there is also no disclosure pointing a POSA to the understanding that the use of SEC data at 2 months and/or 24 months was part of Regeneron's invention.

2. The at Least 98% 24-Month Stability Limitation

135. Challenged claims 17, 25, 42, and 50 contain a limitation that “at least 98%” of the VEGF antagonist be present in native conformation, as measured by SEC, after storage at 5 °C for 24 months. As discussed above, Examples 1-2 disclose the stability data for the VEGF-Trap formulations at a concentration of 50 mg/ml, not 40 mg/ml as claimed; Examples 5-6 disclose the stability data for the

VEGF-Trap formulations without a stabilizer; and Examples 7-8 disclose the stability data for the lyophilized VEGF-Trap formulations. Examples 3-4 disclose the stability data for the VEGF-Trap formulations encompassed by claims 17, 25, 42, and 50 only up to four months.

136. Accordingly, the specification of *US865* includes no examples with stability data at 24 months for the VEGF-Trap formulations recited in claims 17, 25, 42, and 50. The only disclosure of any stability data at 24 months is in Examples 1-2 for a different formulation comprising 50 mg/ml VEGF-Trap. Specifically, Table 1 of Example 1 reports 98.1% native configuration at 24 months; Table 2 Example 2 reports 97.6% native configuration. Thus, under Regeneron's possible claim construction that the at least 98% native conformation at 24 months is an absolute amount, even considering the stability data of Examples 1-2, *US865* discloses only one data point in the range of at least 98% native conformation at 24 months, and that is 98.1%, while the other data point is below 98%. I understand, however, that under Celltrion's proposed claim construction, Example 2 may meet the added stability limitation as the amount of VEGF only decreased 1.3% from time 0 to twenty-four months.

137. Regardless, given the difference in the amount of VEGF-Trap in the formulation of Examples 1 and 2, i.e., 50 mg/ml, and the amount of VEGF-Trap required by the claims, i.e., 40 mg/ml, no disclosure in *US865* supports the stability

range of, “at least 98%” for the claimed formulation having 40 mg/ml of the at 24-month timepoint. And as I discuss above in paragraphs 114-134, the disclosure fails to provide any guidance for this added stability limitation.

138. Moreover, these data points are not representative of the claimed range, “at least 98%” in native conformation after 24 months’ storage at 5 °C.

139. Similarly, as with the at least 98% two-month limitation, the portion of the specification set forth in *App559* ((EX1006, January 10, 2020 Application as Filed ¶¶46-47), 11) does not change my opinion, for the same reasons set forth above. *Supra* Section X.A.1.

140. As explained above, applicants stated that support for the “at least 98% 24-month stability” limitation could be found “in original paragraph [0037] and in example 6.” EX1006 (January 10, 2020 Preliminary Amendment), 45. For the same reasons as set forth above with respect to the ‘at least 98% two-month stability’ limitation, paragraph 37 and Example 6 do not support the added at least 99% two-month stability limitation. *Supra* Section X.A.1.

141. For the above reasons, claims 1-50 lack written description support in the disclosure as originally filed. Thus, I have been informed that based on the lack of written description and based on the timing of the amendments during prosecution when the stability limitations were introduced, at best, the claims are entitled to the filing date of October 12, 2018, which is the filing date of *App269*.

B. Wherein Said VEGF Antagonist is Glycosylated

142. Challenged claims 1-13, 15-21, 23-38, 40-46, and 48-50 contain the limitation “wherein said VEGF antagonist is glycosylated,” without specifying which residues or the number of residues that are glycosylated.

143. The following is the only disclosure in the specification regarding glycosylation:

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 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.

EX1006 (January 10, 2020 Application as Filed ¶46), 11; EX1001, 6:27-39.

144. The Examples use a VEGF Trap having SEQ ID NO:4, but do not specify the glycosylation state of the VEGF Trap having SEQ ID NO:4.

145. The specification only mentions glycosylation once, and only mentions one glycosylated VEGF antagonist variant (also called a VEGF trap

variant), and that one glycosylated VEGF antagonist variant is glycosylated at each of ASN residues 62, 94, 149, 222, and 308.

146. I understand that in the Mylan litigation, the parties stipulated that the term “glycosylated” in claim 1 means “containing at least one amino acid residue with an attached carbohydrate.” EX1024, 50; *see also* ¶79 above. The only disclosure in the specification of a glycosylated VEGF antagonist is a VEGF antagonist having glycosylation at each of ASN residues 62, 94, 149, 222, and 308. EX1006, 11; EX1001, 6:27-39. Accordingly, the claim term “wherein said VEGF antagonist is glycosylated” lacks written description support in the disclosure as originally filed if it encompasses anything other than a VEGF antagonist that comprises amino acids 27-457 of SEQ ID NO:4 having glycosylation at each of ASN residues 62, 94, 149, 222, and 308.

147. For the above reasons, claims 1-13, 15-21, 23-38, 40-46, and 48-50 lack written description support in the disclosure as originally filed. Thus, I have been informed that based on the lack of written description and based on the timing of the amendments during prosecution when the stability limitations were introduced, at best, these challenged claims are entitled to the filing date of January 10, 2020, which is the filing date of *App559*.

C. The “No Phosphate” Limitation (Claims 18 and 43)

148. Claims 18 and 42 of *US865* include the limitation “wherein said formulation does not contain phosphate” (the “no phosphate” limitation). This limitation was introduced during the prosecution of *App559* in the amendment submitted on May 5, 2021. EX1006 (May 5, 2021 Amendment, new claims 38, 63), 286-292.

149. I understand that this is a negative limitation, and that to support such a limitation the specification must provide an alternative for phosphate or provide a reason to exclude phosphate.

150. However, the disclosure as originally filed does not provide any reason to exclude phosphate, provide a specific alternative to phosphate, or even describe a formulation that does not include phosphate.

151. While the specification teaches buffers generally, the only specific buffer noted, and the only buffer used in the examples, is phosphate. *See generally* EX1006 (January 10, 2020 Application as Filed), 1-17. For example, the specification states: “In one or more specific embodiments, ... and the buffering agent may be, for example, phosphate buffer.” EX1006 (January 10, 2020 Application as Filed, ¶9), 5. Such statements provide no disclosure of excluding phosphate, no reason to exclude phosphate, and no alternative to using phosphate.

152. For the above reasons, claims 18 and 43 lack written description support in the disclosure as originally filed. Accordingly, I have been informed that based on the lack of written description and based on the timing of the amendments during prosecution when these limitations were introduced, at best, the claims are entitled to the filing date of January 10, 2020, which is the filing date of *App559*.

XI. ANALYSIS OF THE CHALLENGED CLAIMS

153. For the reasons set forth above as to why the claims lack written description support in the disclosure as originally filed, I have been told to assume that *US865* is not entitled to a priority date before October 12, 2018.

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

154. Claims 1-17, 19-42, and 44-50 are anticipated by Regeneron's own prior art published application, *US432*. *US432* was published on December 20, 2007, and is therefore a printed publication available more than a year before the October 12, 2018, earliest priority date of prior art to *US865*. *US432* is the publication of Regeneron's '463 application. EX1004 (cover page). *US432* has the same specification as *US865* except for the listing of priority applications in column 1. Compare EX1001, col. 1-2 and EX1004 ¶¶1-19.

1. Claims 1 and 26 are Anticipated by US432

155. Claim 1 of *US865* requires the following elements:

- (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,
- (e) a stabilizing agent 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.

156. Claim 26 of *US865* claims a PFS comprising the same formulation and with the same limitations as the vial of claim 1.

157. As explained below, *US432* disclosed every element of independent claims 1 and 26, either expressly or inherently.

158. *US432* states that “[t]he invention...features ophthalmic formulations provided in a pre-filled syringe or vial, particularly suitable for intravitreal administration.” EX1004 ¶39; *see also* ¶3 (“[t]he present invention is directed to pharmaceutical formulations suitable for intravitreal administration.”). In view of these statements, a POSA would have understood that the formulations used in the Examples are also ophthalmic formulations for intravitreal administration.

EX1004 ¶¶3, 39, 60-65. Therefore, *US432* expressly disclosed formulations in vials and PFS that meet the respective vial/PFS, ophthalmic formulation and intravitreal administration limitations in element (a) of claims 1 and 26.

159. The Examples of *US432* all state that “VEGF Trap (SEQ ID NO:4)” was used. EX1004 ¶¶60-65. The examples do not specify that only amino acid residues 27-457 of SEQ ID NO:4 were used, but my understanding (*supra* Section III) is that because claims 1 and 26 of *US865* use the term “comprising,” they do not exclude the use of the full SEQ ID NO:4 (*i.e.* residues 1-458).

160. Moreover, the only method of producing the VEGF antagonist specifically disclosed in *US432* is to express the VEGF antagonist in CHO cells. EX1004 ¶48. In the *462IPR*, Regeneron’s expert, Dr. Klibanov, noted that in the final VEGF protein produced by CHO cells, amino acids 1-26 of SEQ ID NO:4 are a signal sequence that is cleaved off. EX1021 ¶121 (citing EX1043 ¶32), EX1027 ¶54. A POSA would have understood that when SEQ ID NO:4 is expressed in CHO cells the signal sequence is cleaved-off post-translationally, leaving amino acids 27-457. *Supra* Section VIII.

161. Although *US432* discloses that the VEGF antagonist “may be glycosylated at Asn residues 62, 94, 149, 222 and 308,” the examples of *US432* do not specifically disclose the glycosylation state of the VEGF antagonist. EX1004 ¶48. A POSA would have understood that the natural result flowing from post-

translational processing in CHO cells would be glycosylation at Asn residues 62, 94, 149, 222, and 308 of SEQ ID NO:4 as used in the Examples. *Supra* Section V, VIII. In addition, it is my understanding that Regeneron has acknowledged that the VEGF Trap used in the examples was aflibercept, which has amino acids 27-457 of SEQ ID NO: 4 and is glycosylated at Asn residues 62, 94, 149, 222, and 308.

162. Accordingly, the examples of *US432* inherently met the glycosylation limitation of element (b) of claims 1 and 26 of *US865*.

163. Examples 3 and 4 in *US432* 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 [i.e., % VEGF in Native Configuration] determined “as described above.” EX1004 ¶¶62-63. A POSA would have understood from the specification 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 have understood to be size exclusion chromatography (“SEC”) as used in the claims. EX1004 ¶¶60, 62-63. Tables 3 and 4 disclose that at 2 months, 99.2% and 99.1%, respectively, of the VEGF antagonist had its native configuration, reflecting a change from time zero of 0.3% for both examples as the amount of VEGF Trap in Native Configuration was reported to be 99.5% and 99.4%, respectively, at time 0. EX1004 ¶¶62-63. Accordingly, Examples 3 and 4 of *US432* expressly disclose

formulations with the purity, that is, the stability limitation, required by element (f) of claims 1 and 26 of *US865*.

164. As to the remaining limitations, *i.e.*, the organic co-solvent, buffer and stabilizing agent limitations of elements (c), (d) and (e) of claims 1 and 26 of *US865*, Example 3 of *US432* discloses a stability study of a liquid VEGF antagonist stored in a vial that has the following: “VEGF trap”, a VEGF antagonist; 0.03% polysorbate 20, an organic cosolvent; 10 mM phosphate, a buffer; and 5% sucrose, a stabilizing agent. EX1004 ¶62. Example 4 discloses the same formulation elements for a PFS. EX1004 ¶63. Accordingly, *US432* expressly disclosed the organic co-solvent, buffer and stabilizing agent limitations of elements (c), (d) and (e) of claims 1 and 26 of *US865*.

165. Accordingly, *US432* disclosed every element of claims 1 and 26, either expressly or inherently, and anticipated those claims.

2. Claims 2-5 and 27-30 are Anticipated by *US432*

166. 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. Accordingly, *US432* disclosed each of the added limitations in claims 2-5 and 27-30 of *US865*.

167. For this reason and the reasons explained above, *US432* disclosed every element of claims 2-5 and 27-30 of *US865* and anticipated those claims.

3. Claims 6-9 and 31-34 are Anticipated by *US432*

168. Claims 6-9 and 31-34 depend from claims 5 and 30, respectively, and further require that the buffer comprises: phosphate buffer (claims 6 and 31); 5-25 mM buffer (7 and 32); a pH of about 5.8-7.0 (claims 8 and 33); or a pH of about 6.2-6.3 (claims 9 and 34). EX 1001, 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 met the added limitations of claims 6-9 and 31-34. EX1004 ¶¶62-63. For this reason and the reasons explained above, *US432* disclosed every element of claims 6-9 and 31-34 of *US865* and anticipated those claims.

4. Claims 10-13 and 20-21, and Claims 35-38 and 45-46, are Anticipated by *US432*

169. 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, and 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 is 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). *See* EX 1001, 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 met the added limitations of these claims. EX1004 ¶¶62-63. For this reason and those explained above, *US432* disclosed every element of claims 10-13, 20-21, 35-38 and 45-46 of *US865* and anticipated those claims.

5. Claims 14, 22, 39, and 47, are Anticipated by *US432*

170. 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. *See* EX 1001, col. 20-22.

171. As noted above as to claims 1 and 26 (Section XI.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 have understood 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. *Supra* Section VIII. Accordingly, *US432* disclosed each of the added limitations in claims 14, 22, 39, and 47 of *US865*.

172. For this reason and the reasons explained above, *US432* disclosed every element of claims 14, 22, 39, and 47 of *US865* and anticipated those claims.

6. Claims 15, 23, 40, and 48 are Anticipated by US432

173. 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 OD₄₀₅ after 2 month storage at 5° C.” See EX 1001, col. 20-22. Examples 3 and 4 of *US432* disclose formulations that were stored in a glass vial or PFS, respectively, and had turbidities of 0.00 when tested after 2 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 OD₄₀₅ nm, as described in Example 1. EX1004 ¶¶60, 62-63. The formulations disclosed in Examples 3 and 4 of *US432* therefore met the added limitations of claims 15, 23, 40, and 48. For this reason and the reasons explained above, *US432* disclosed every element of claims 15, 23, 40, and 48 of *US865* and anticipated those claims.

7. Claims 16, 24, 41, and 49 are Anticipated by US432

174. 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.” See EX 1001, 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

conformation after 2 months of storage at 5° C, when measured by SEC, representing a change of 0.3% from time 0, which had 99.5 and 99.4% VEGF antagonist in native conformation, respectively. EX1004 ¶¶60, 62-63.

Accordingly, the formulations disclosed in Examples 3 and 4 of *US432* met the added limitations of claims 16, 24, 41, and 49, regardless of the claim construction that is adopted. For this reason and the reasons explained above, *US432* disclosed every element of claims 16, 24, 41, and 49 of *US865* and anticipated those claims.

8. Claims 17, 25, 42, and 50 are Anticipated by *US432*

175. 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.” See EX 1001, col. 20-22. *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 VEGF of 50 mg/ml rather than the claimed 40 mg/ml. EX1004 ¶60. *US432* discloses, in Table 1, that after storage for 24 months at 5° C., 98.1% of the VEGF antagonist was in native conformation, with a difference from time 0, wherein 98.8% of the VEGF antagonist was in native conformation, of 0.7%. EX1004 ¶60. A POSA would have understood that formulations having lower concentrations, 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. Accordingly, the formulation used in Example 3 would have inherently met the added limitation of claims 17 and 25.

176. Moreover, in view of the similarity in the stability results for the identical formulations used in Examples 3 and 4, when stored but stored at 5° C. for 2 months in a vial and PFS, respectively, the formulation of Example 4 inherently met the added limitations of claims 42 and 50 for the same reasons as the formulation of Example 3 inherently met the added limitations of claims 17 and 25.

177. For this reason and the reasons explained above, *US432* disclosed every element of claims 17, 25, 42, and 50 of *US865* and anticipated those claims

9. Claims 19 and 44 are Anticipated by *US432*

178. Claims 19 and 44 depend from claims 5 and 30, respectively, and further require that the formulation does not contain trehalose. *See* EX 1001, col. 20-21. The formulations disclosed in Examples 3 and 4 of *US432* do not contain trehalose and therefore meet the added limitations of these claims. EX1004 ¶¶62-63. For this reason and those explained above, *US432* disclosed every element of claims 19 and 44 and anticipated those claims.

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

179. As explained above (Section XI.A), *US432* expressly or inherently discloses all the limitations of claims 1-17, 19-42, and 44-50 of *US865*. As explained below, based on the disclosures of *US432*, a POSA would have found the subject matter of claims 1-17, 19-42, and 44-50 obvious, and also would have found the subject matter of claims 18 and 43 obvious. Accordingly, as explained below, claims 1-50 would have been obvious over Regeneron's own prior art published application, *US432*.

1. Claims 1 and 26 are Obvious over *US432*

180. As explained above (Section XI.A.1), *US432* expressly discloses all of the limitations of claims 1 and 26 except for the glycosylation limitation, which is an inherent property of the VEGF antagonist used in the formulations of Examples 3 and 4. To the extent that Regeneron argues that glycosylation is not an inherent property of the VEGF antagonist used in the formulations of Examples 3 and 4, a POSA would have found it obvious to use a glycosylated VEGF antagonist based on the disclosures in *US432*.

181. Because *US865* expressly discloses the following limitations of claims 1 and 26, a POSA also would have found it obvious to prepare a VEGF formulation meeting these limitations:

- a vial/PFS containing an ophthalmic formulation suitable for intravitreal administration,
- an organic co-solvent,
- buffer,
- stabilizing agent in unspecified amounts, and
- 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.

182. As explained below, a POSA would have found it obvious to use a glycosylated VEGF antagonist based on the disclosures in *US432*.

183. *US432* discloses only one specific way to make a VEGF antagonist: “[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.

184. *US432* discloses only one VEGF antagonist fusion protein with any specificity, and that specifically disclosed VEGF antagonist is glycosylated: “[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.” EX1004 ¶48. In addition, the VEGF antagonist used in all the *US432* Examples has SEQ ID NO:4, which comprises amino acids 27-457 of SEQ ID NO:4. EX1004 ¶¶60-65.

185. A POSA would have been motivated to use CHO cells to prepare the only specifically disclosed VEGF antagonist (*i.e.*, comprising amino acids 27-457 of SEQ ID NO:4 and glycosylated at Asn residues 62, 94, 149, 222, and 308) because the only specific method identified for expressing the VEGF antagonist is in a CHO cell line. EX1004 ¶48. Moreover, *US432* states that the protein expressed in the CHO cell may be modified post-translationally. *Id.* A POSA would have known that one post-translational modification in CHO cells is glycosylation, and that a protein comprising amino acids 27-457 of SEQ ID NO:4 would be glycosylated at Asn residues 62, 94, 149, 222, and 308. *Supra* Section VIII. In view of the knowledge that CHO cells glycosylate proteins and the fact that the only VEGF antagonist that *US432* discloses with any specificity is glycosylated and comprises amino acids 27-457 of SEQ ID NO:4, a POSA would have understood that *US432*'s reference to post-translational modification is a reference to glycosylation.

186. A POSA would have reasonably expected to be able to use the only specifically disclosed VEGF antagonist (*i.e.*, comprising amino acids 27-457 of SEQ ID NO:4 and glycosylated at Asn residues 62, 94, 149, 222, and 308) to achieve the stability achieved in, for example, Examples 3 and 4 for the following reasons. First, none of the examples provide any specificity regarding the VEGF antagonist being tested other than that it has SEQ ID NO:4. EX1004 ¶¶60-67.

Second, neither the examples nor the specification provide any specificity regarding any alternate VEGF antagonist(s) to use. *See* EX1004. Third, a POSA would have known that glycosylation can help stabilize a protein by reducing aggregation. *Supra* Section V.C. For at least these reasons, 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 Example 3 and 4.

187. For the above reasons, the disclosures of *US432* would have rendered independent claims 1 and 26 obvious to a POSA.

2. Claims 2-5 and 27-30 are Obvious over *US432*

188. 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).

189. Examples 3 and 4 of *US432* disclose formulations that have 40 mg/ml concentrations of VEGF antagonist and 0.03% polysorbate 20 organic cosolvent and therefore met these added limitations. EX1004 ¶¶62-63.

190. For this reason and the reasons explained above with respect to claims 1 and 26, a POSA would have had motivation and a reasonable expectation of success in achieving the stability required by claims 2-5 and 27-30 of *US865*. Therefore, the disclosures of *US432* would have rendered claims 2-5 and 27-30 obvious to a POSA.

3. Claims 6-9 and 31-34 are Obvious over *US432*

191. 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); 5-25 mM (7 and 32); a pH of about 5.8-7.0 (claims 8 and 33); or a pH of about 6.2-6.3 (claims 9 and 34). Examples 3 and 4 of *US432* disclose formulations that have 10 mM sodium phosphate buffer and a pH of 6.3, which met the added limitations of claims 6-9 and 31-34. EX1004 ¶¶62-63.

192. For this reason and the reasons explained above with respect to claims 1, 5, 26 and 30, a POSA would have had motivation and a reasonable expectation of success in achieving the stability required by claims 6-9 and 31-34 of *US865*. Therefore, the disclosures of *US432* would have rendered claims 6-9 and 31-34 obvious to a POSA.

4. Claims 10-13, 20-21, 35-38, and 45-46, are Obvious over *US432*

193. 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, and

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 is 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). The formulation disclosed in Examples 3 and 4 of *US432* has 5% sucrose, a sugar, and 40 mM NaCl, a tonicity agent, which meets the added limitations of these claims. EX1004 ¶¶62-63.

194. For this reason and the reasons explained above with respect to claims 1, 5, 26 and 30, a POSA would have had motivation and a reasonable expectation of success in achieving the stability required by claims 10-13, 20-21, 35-38 and 45-46 of *US865*. Therefore, the disclosures of *US432* would have rendered claims 10-13, 20-21, 35-38 and 45-46 obvious to a POSA.

5. Claims 14, 22, 39, and 47 are Obvious over *US432*

195. 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.

196. 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 in achieving the stability required by claims 14, 22, 39, and 47. Therefore, the disclosures of *US432* would have rendered claims 14, 22, 39, and 47 obvious to a POSA.

6. Claims 15, 23, 40, and 48 are Obvious over US432

197. 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 OD₄₀₅ after 2 month storage at 5° C.” As explained above (*supra* Section XI.A.6), Examples 3 and 4 of *US432* disclose formulations that met these added limitations.

198. For this reason and the reasons explained above with respect to claims 1, 5, 20, 26, 30, and 45, a POSA would have had motivation and a reasonable expectation of success in achieving the stability required by claims 15, 23, 40, and 48 of *US865*. Therefore, the disclosures of *US432* would have rendered claims 15, 23, 40, and 48 obvious to a POSA.

7. Claims 16, 24, 41, and 49 are Obvious over US432

199. 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.” 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 explained above in paragraphs 163 and 174, is a change of 0.3% from time 0. EX1004 ¶¶60, 62-63. Accordingly, the formulations disclosed in Examples 3 and 4 of *US432* met the added limitations of claims 16, 24, 41, and 49, regardless of how the claims are construed.

200. For this reason and the reasons explained above with respect to claims 1, 5, 20, 26, 30, and 45, a POSA would have had motivation and a reasonable expectation of success in achieving the stability required by claims 16, 24, 41, and 49 of *US865*. Therefore, the disclosures of *US432* would have rendered claims 16, 24, 41, and 49 obvious to a POSA.

8. Claims 17, 25, 42, and 50 are Obvious over *US432*

201. 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.” While *US432* does not provide purity results for any 40 mg/ml VEGF antagonist formulations following storage at 5° C. for 24 months, the disclosures of *US432* would have made a formulation with such stability obvious to a POSA.

202. 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. EX1004 ¶60. US432 discloses, in Table 1, that after storage for 24 months at 5° C., 98.1% of the VEGF antagonist of Example 1 was in native configuration, which, as explained above in paragraph 175, is change of 0.7% from time 0. EX1004 ¶60. Seeing that such purity over time was achievable, a POSA would have been motivated to prepare a formulation that had no more than a change of 2% from time 0 in the amount of VEGF antagonist fusion protein present in native conformation following storage at 5° C. for 24 months.

203. A POSA would have reasonably expected that the formulation of Example 3, stored in a vial, would have no more than a loss of 2% from time 0 in the amount of VEGF antagonist fusion protein present in native conformation following storage at 5° C. for 24 months because a POSA would have known that all other things being equal, formulations having lower concentrations, like the 40 mg/ml formulation used in Example 3, are as stable or more stable than formulations with higher concentrations, like the 50 mg/ml formulation used in Example 1. EX1004 ¶¶60, 62. Moreover, a POSA would have reasonably expected that, to the extent necessary, the desired stability could be achieved through routine optimization.

204. US432 discloses two comparisons of identical formulations stored in vials and PFS: Example 3 (vial) vs. Example 4 (PFS); and Example 5 (vial) vs. Example 6 (PFS). EX1004 ¶¶ 62-65. As shown in the tables below, at every timepoint, formulations stored in PFS have a percent VEGF Trap Native Configuration that differs by an absolute value of no more than 0.1% from that of the formulation stored in a vial.

Comparison of US432 Examples 3 and 4

Months	Example 3 (vial)	Example 4 (PFS)	Absolute Difference
0	99.5	99.4	0.1
0.5	99.4	99.3	0.1
1	99.5	99.4	0.1
2	99.2	99.1	0.1

Comparison of US432 Examples 5 and 6

Months	Example 5 (Vial)	Example 6 (PFS)	Absolute Difference
0	99.3	99.2	0.1
0.5	99.2	99.2	0.1
1	99.1	99.2	0.1
2	99.2	NA	NA
3	99.0	99.1	0.1
4	98.9	98.8	0.1
5	99.0	98.9	0.1

205. Based on these disclosures in US432, a POSA would have reasonably expected that the formulation of Example 4 stored in PFS (which is the same as the formulation of Example 3) would lose no more than 2% of VEGF antagonist

fusion protein present in native conformation following storage at 5° C. for 24 months. Moreover, a POSA would have reasonably expected that, to the extent necessary, the desired stability could be achieved through routine optimization. Given that the specification of *US432* and *US865* are the same, the claims would have been obvious over *US432* regardless of the claim construction adopted.

206. For this reason and the reasons explained above with respect to claims 1, 5, 20, 26, 30, and 45, a POSA would have had motivation and a reasonable expectation of success in achieving the stability required by claims 17, 25, 42, and 50 of *US865*. Therefore, the disclosures of *US432* would have rendered claims 17, 25, 42, and 50 obvious to a POSA.

9. Claims 18 and 43 are Obvious over US432

207. 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.

208. *US432* discloses that the buffer can be, but does not have to be, a phosphate buffer. EX1004 ¶11 (“In on or more specific embodiments, ...the buffering agent may be, for example, phosphate buffer”).

209. *US432* discloses several formulations that do not specify the buffer to use. For example, paragraphs 10 and 18 disclose formulations that use “5-40 mM of a buffering agent” without specifying the buffering agent. EX1004 ¶¶10, 18.

Because the formulations disclosed in paragraphs 10 and 18 do not specify the buffer, a POSA would understand *US432* as teaching that buffers other than phosphate could be used and optimized to obtain the desired stability.

Accordingly, a POSA would have reasonably expected one could obtain the desired stability through the use of a buffer other than phosphate and use of routine optimization.

210. For this reason and the reasons explained above with respect to claims 1, 5, 26, and 30, a POSA would have had motivation and a reasonable expectation of success in achieving the stability required by claims 18 and 43 of *US865*. Therefore, the disclosures of *US432* would have rendered claims 18 and 43 obvious to a POSA.

10. Claims 19 and 44 are Obvious over *US432*

211. Claims 19 and 44 depend from claims 5 and 30, respectively, and further require that the formulation does not contain trehalose. The formulations disclosed in Examples 3 and 4 of *US432* do not contain trehalose and therefore meet the added limitations of these claims. EX1004 ¶¶62-63. For this reason and the reasons explained above with respect to claims 1, 5, 26, and 30, a POSA would have had motivation and a reasonable expectation of success in achieving the stability required by claims 19 and 44 of *US865*. Therefore, the disclosures of *US432* would have rendered claims 19 and 44 obvious to a POSA.

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

212. As discussed above, *US432* (EX1004) renders obvious the subject matter of claims 1-50. To the extent that *US432* fails to render obvious the “no phosphate” limitation in claims 18 and 43, any deficiency is remedied by *WO685* (EX1005).

213. Claims 18 and 43 depend from claims 5 and 30, respectively, and further require that the claimed formulation does not contain phosphate. A POSA would have understood that the claimed formulations would therefore include a buffer other than phosphate.

214. As discussed above, *US432* discloses that the buffer can be, but does not have to be, a phosphate buffer. EX1004 ¶11 (“In on or more specific embodiments, ... the buffering agent may be, for example, phosphate buffer”).

215. As explained above, a POSA would have known that buffers can be used to adjust pH and thereby improve stability. *See* Section V.C. *US432* discloses specific preferred embodiments have a pH of 6.2-6.3. *See, e.g.*, EX1004 ¶¶15-17. In addition, all the Examples have a starting pH of 6.25-6.3 and a pH of 6.2-6.3 at zero months. EX1004 ¶¶60-67. Accordingly, a POSA would understand that *US432* teaches that VEGF antagonist formulations can use a non-phosphate buffer, and that when doing so, the preferred pH is 6.2-6.3.

216. As discussed above, *WO685* discloses, as Sample (a) in Table 9, a 40 mg/ml formulation 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)). The formulation in Sample (a) is the same formulation as used in Examples 3 and 4 of *US432* except that the Sample (a) formulation has 10mM L-histidine/histidine HCl as the buffer rather than the 10mM phosphate buffer used in Examples 3 and 4 of *US432*, and the formulation in Sample (a) has a starting pH of 6.2 while the formulations of Examples 3 and 4 have a starting pH of 6.3. EX1004 ¶¶62-63. Thus, the *WO685* Sample (a) formulation does not contain phosphate.

217. A POSA would have been motivated to replace the phosphate buffer in the formulations of Examples 3 and 4 of *US432* with the histidine buffer of sample (a) in Table 9 of *WO685* because: (a) *US432* and *WO685* both relate to liquid VEGF antagonist formulations; (b) *US432* teaches the general use of a buffered formulation at a pH of about 6.2-6.3 and *WO685* teaches the use of a histidine buffered formulation at pH 6.2; (c) the formulations of sample (a) in Table 9 of *WO685* and Examples 3 and 4 of *US432* are very similar other than the buffer; and (d) the histidine buffered formulation of sample (a) in Table 9 of *WO685* achieved equal or better stability achieved compared to the phosphate buffered formulations in *WO685* (see Section VII.B; see EX1005, 43).

218. In addition, a POSA would have had a reasonable expectation that replacing the phosphate buffer in the formulations of Examples 3 and 4 of *US432* with the histidine buffer of sample (a) in Table 9 of *WO685* would achieve the same stability results seen in Examples 3 and 4 of *US432* because the histidine buffered formulation of sample (a) in Table 9 of *WO685* achieved equal or better stability achieved compared to the phosphate buffered formulations in *WO685*, including the commercial EYLEA formulation. EX1005, 35 (Table 9, Sample (a)), 43.

219. For this reason and the reasons explained above with respect to claims 1, 5, 26 and 30, a POSA would have had motivation and a reasonable expectation of success in achieving the stability required by claims 18 and 43 of *US865*. Therefore, the disclosures of *US432* would have rendered claims 18 and 43 obvious to a POSA.

D. Secondary Evidence of Non-Obviousness

220. I am not aware of any relevant “secondary” evidence of non-obviousness that would relate to the particular elements of claims 1-50 of *US865*. I may respond to any secondary evidence I may become aware of in the future.

XII. CONCLUDING STATEMENTS

221. In signing this declaration, I understand that the declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I acknowledge that I may be subject to cross-examination in this case and that cross-examination will take place within the United States. If cross-examination is required of me, I will appear for cross-examination within the United States during the time allotted for cross-examination.

222. I declare that all statements made herein of my knowledge are true, and that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: January 14, 2025


Peter M. Tessier, Ph.D.

XIII. APPENDIX – LIST OF EXHIBITS CITED

Exhibit No.	Description
1001	U.S. Patent No. 11,084,865 (“US865”)
1003	Dr. Peter Tessier <i>curriculum vitae</i>
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., <i>Prevention of Thecal Angiogenesis, Antral Follicular Growth, and Ovulation in the Primate by Treatment with Vascular Endothelial Growth Factor Trap R1R2</i> , 143(7) ENDOCRINOLOGY 2797-2807 (Jul. 2002) (“Wulff”)
1018	International Publication No. WO 2018/094316 (“WO316”)
1019	EYLEA® Prescribing Information, November 2011 (“PI2011”)

Exhibit No.	Description
1020	James D. Andya et al., <i>Mechanisms of Aggregate Formation and Carbohydrate Excipient Stabilization of Lyophilized Humanized Monoclonal Antibody Formulations</i> , 5(2) AAPS PHARMSCI (Apr. 4, 2003) (“ <i>Andya 2003</i> ”)
1021	Declaration of Alexander M. Klibanov submitted in support of Regeneron’s Patent Owner Response in IPR2023-00462 (Nov. 2, 2023)
1022	U.S. Patent Publication No. 2004/0197324 to Liu et al. (“ <i>Liu</i> ”)
1023	Leopold K. Kostanski et al., <i>Size-exclusion Chromatography – a Review of Calibration Methodologies</i> , 58 J. BIOCHEM. BIOPHYS. METHODS 159-186 (2004) (“ <i>Kostanski 2004</i> ”)
1024	Memorandum Opinion and Order Following Bench Trial (Dec. 27, 2023) in <i>Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals Inc., et al.</i> , 1:22-CV-61 (N.D. WV)
1025	U.S. Provisional Application No. 60/814,484
1026	Regeneron’s Patent Owner Response in IPR2023-00462
1027	Declaration of Alexander M. Klibanov submitted in support of Regeneron’s Preliminary Response in IPR2023-00462 (Apr. 25, 2023)
1028	Jocelyn Holash et al., <i>VEGF-Trap: A VEGF Blocker with Potent Antitumor Effects</i> , 99 (17) PNAS 11393-11398 (Aug. 20, 2002) (“ <i>Holash</i> ”)
1029	International Publication No. WO 00/75319 (“ <i>WO319</i> ”)
1030	Napoleone Ferrara & Robert S. Kerbel, <i>Angiogenesis as a Therapeutic Target</i> , 438 NATURE 967-74 (Dec. 15, 2005) (“ <i>Ferrara</i> ”)
1031	Liming Liu, <i>Antibody Glycosylation and its Impact on the Pharmacokinetics and Pharmacodynamics of Monoclonal Antibodies and FC-fusion Proteins</i> , 104(6) J. PHARM SCI 1866-1884 (Apr. 14, 2015) (“ <i>Liu 2015</i> ”)
1032	Royston Jefferis, <i>Glycosylation of Recombinant Antibody Therapeutics</i> , 21 Biotechnol. Prog. 11-16 (2005) (“ <i>Jefferis</i> ”)
1033	S. Krapp et al., <i>Structural Analysis of Human IgG-Fc Glycoforms Reveals a Correlation Between Glycosylation and Structural Integrity</i> , 325(5) J. MOL. BIOL. 979-89 (Jan. 31, 2003) (“ <i>Krapp</i> ”)

Exhibit No.	Description
1034	Y. Mimura et al., <i>Role of Oligosaccharide Residues of IgG1-Fc in gamma RIIB Binding</i> , 276(49) J. BIOL. CHEM. 45539-47 (Sep. 20, 2001) (“Mimura 2001”)
1037	David J. Panka, Glycosylation is Influential in Murine IgG3 Self-Association, 34 (8-9) MOLECULAR IMMUNOLOGY 593-98 (June 1997) (“Panka”)
1038	Byeong S. Chang & Susan Hersenson, Practical Approaches to Protein Formulation Development in RATIONALE DESIGN OF STABLE PROTEIN FORMULATIONS – THEORY AND PRACTICE, 1-25 (J.F. Carpenter and M.C. Manning eds., 2002) (“Chang”)
1039	Dave A. Parkins & Ulla T. Lashmar, <i>The Formulation of Biopharmaceutical Products</i> , 3(4) PHARM. SCI. & TECH. TODAY 129-137 (Apr. 4, 2000) (“Parkins”)
1040	Y. Mimura et al., <i>The influence of glycosylation on the thermal stability and effector function expression of human IgG1-Fc: properties of a series of truncated glycoforms</i> , 37 (2000) MOLECULAR IMMUNOLOGY 697-706 (Sept. 2000) (“Mimura 2000”)
1041	Hanns-Christian Mahler et al., <i>Induction and Analysis of Aggregates in a Liquid IgG1-antibody Formulation</i> , 59(2005) EURO. J. PHARMA. BIOPHARM 407-17 (Jan. 19, 2005) (“Mahler 2005”)
1042	Ib Anderson, <i>Determination of Specific Proteins by FIA Principle</i> , 12(2) J. AUTO. CHEM. 53-59 (Apr. 1990) (“Anderson 1990”)
1043	U.S. Patent Publication No. 2006/0058234 (“Daly”)
1044	U.S. Patent Publication No. 2005/0175610 (“Wiegand”)
1045	Ryosuke Yumioka et al., <i>Mobile Phase Containing Arginine Provides More Reliable SEC Condition for Aggregation Analysis</i> , 99(2) J. PHARM SCI 618-620 (June 30, 2009) (“Yumioka”)
1046	Daisuke Ejima et al., <i>Arginine as an effective additive in gel permeation chromatography</i> , J. CHROMATOGR. A 1094 49-55 (Oct. 5, 2005) (“Ejima”)
1047	Aditya V. Gandhi et al., <i>Some Lessons Learned From a Comparison Between Sedimentation Velocity Analytical Ultracentrifugation and Size Exclusion Chromatography to</i>

Exhibit No.	Description
	<i>Characterize and Quantify Protein Aggregates</i> , 106 J. PHARM SCI 2178-2186 (2017) (“ <i>Gandhi</i> ”)
1048	Nonconfidential Brief of Appellee Regeneron Pharmaceuticals, Inc. in <i>Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals Inc. et al.</i> , Doc. 36, Case Nos. 24-1965, 24-1966, 24-2082, 24-2083 (Fed. Cir., Aug. 26, 2024)
1049	Testimony of Kenneth S. Graham in <i>Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals Inc., et al.</i> , 1:22-CV-61 (N.D. WV)