

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SAMSUNG BIOEPIS CO., LTD.,
Petitioner,

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner.

Case IPR2025-00176

U.S. Patent No. 11,084,865

PETITION FOR *INTER PARTES* REVIEW

OF U.S. PATENT NO. 11,084,865

DECLARATION OF DR. ALPASLAN YAMAN

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1001	U.S. Patent No. 11,084,865 (“’865 Patent”)
1003	Yaman <i>Curriculum Vitae</i>
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I. INTRODUCTION

1. I have been retained by Quinn Emanuel Urquhart & Sullivan on behalf of Samsung Bioepis Co., Ltd. (“Petitioner”) to provide expert opinions regarding aflibercept formulations, their design, and the invalidity of U.S. Patent No. 11,084,865 (“’865 patent”) assigned to Regeneron Pharmaceuticals, Inc. (“Regeneron” or “Patent Owner”).

2. My opinions in this declaration are based on the documents I cite along with my education, experience and knowledge that I have acquired working in the area of Pharmaceutical Product Development from early formulations development through commercialization over the past 30 years. I am being compensated for my services as an expert at my standard consulting rate of \$650 per hour. My compensation is in no way contingent on the substance of my opinions or the outcome of this case.

3. My opinions and their underlying reasoning are explained in detail below.

II. BACKGROUND AND QUALIFICATIONS

4. My current *curriculum vitae*, which lists my degrees, experiences, activities, honors, and publications is attached as Exhibit 1003.

5. In 1984, I graduated from Drake University with a BA in chemistry and biology. I went on to get my Bachelor of Science in Pharmacy from Drake

University in 1987. I received a Ph.D. in Pharmaceutical Science (major in Industrial Pharmaceutics with minor in Physical Chemistry) from the University of Missouri, Kansas City, Missouri in 1992.

6. After I received my Ph.D., I was hired at Fujisawa as a Senior Scientist, Product Transfer in the Corporate Quality Assurance Department until the end of 1992. There, I scaled up and validated sterile pharmaceutical commercial processes, and I wrote and executed equipment and process validation protocols. Validation protocols are required by the U.S. Food and Drug Administration (“FDA”) in order to ensure that equipment is performing properly and as designed, and that the process is capable of consistently delivering quality product.

7. From 1992 to 1995, I was employed at the R.W. Johnson Pharmaceutical Research Institute at Johnson & Johnson as a Scientist in the parenterals section (non-oral drugs) and was promoted to senior scientist in 1995. While at the Institute, I was involved in the scale-up and validation of sterile pharmaceutical commercial processes. I also was involved with the set-up, design, and validation of parenteral manufacturing facilities in the United States and Europe. Finally, I was involved in the development of the Chemistry, Manufacturing, and Controls (“CMC”) section for applications to the FDA for new drugs for small molecule and biologic products.

8. From 1996 to 1997, I worked at Hoffmann-LaRoche as a Pharmaceutical Process Investigator, a management position, in the Process and Package Development Department. My responsibilities included the scale-up and validation of sterile pharmaceutical commercial processes. I was also involved with equipment acquisitions, the writing and reviewing of equipment specifications and related standard operating procedures (“SOPs”), and preparing and executing protocols for process and equipment validations. Likewise, I was involved in the development of the CMC section for New Drug Applications (“NDA”) and Biologics License Applications (“BLA(s)”), and with preapproval inspections. In addition, I was also involved as the chairman of the Co-Development Team and liaison to the International Project Team from the Pharmaceutical Operations area. This experience involved leading of multidisciplinary teams consisting of personnel from all departments associated with bringing products from Phase II clinical studies through validation and on to a commercial launch.

9. From 1997 until 1999, I was the Assistant Director in Process Research and Development and the Head of Liquids/Technical Life Cycle Management at Novartis Pharmaceuticals, Inc. I led and directed the liquids group through the scale-up and validation of liquid pharmaceutical commercial processes (oral liquids and sterile products). I was involved with equipment acquisitions, wrote and reviewed equipment specifications and related SOPs, and prepared and executed protocols for

process and equipment validations. I was also involved in the development of the CMC section for NDA and BLA submissions, and with preapproval inspections by the FDA.

10. In 1999, I became a Research Fellow II in Pharmaceutical Development at Novartis Pharmaceuticals, Inc. While there, I led and directed a group through the early development, scale-up, and validation of liquid pharmaceutical commercial processes (oral liquids and sterile products). I worked with multidisciplinary groups to assess the feasibility of new chemical entities. I was also involved with the identification of new technologies, equipment acquisitions, and the writing and reviewing of equipment specifications and related SOPs. I prepared and executed protocols for process and equipment validations, and I was also involved in the development of the CMC section for NDA and BLA submissions and with preapproval inspections.

11. From 1999 until 2001, I was the Assistant Director in Parenteral Technology Transfer, Parenteral Formulations at Purdue Pharma, L.P. While there, I led and directed the technology transfer group through the scale-up and validation of parenteral products. I was also involved with equipment acquisitions. I wrote and reviewed equipment specifications and related SOPs. I prepared and executed protocols for process and equipment validations (e.g., IQ, OQ, PQ) and was involved in the optimization of complex processes for the manufacture of injectable controlled

release formulations (microspheres). In addition, I was involved in the development of the CMC section for NDA and BLA submissions and with preapproval inspections.

12. From 2001 to 2005, I was a director in Pharmaceutical Technology Transfer, Global Technical Services at Schering-Plough. I led and directed technology transfer through the scale-up and validation of sterile and non-sterile liquid and semisolid pharmaceutical products. I prepared technology transfer plans, strategy plans, and GAP analysis for project transfers between development and operations or from one operating site to another. I also served as the Technical Operations representative member on the project team, the CMC sub-team, and the technology transfer team to ensure that the final process was commercially feasible and efficient.

13. From 2005 to 2008, I was employed at Johnson & Johnson Cordis Corp. First, from 2005 to 2007, I was the Executive Director, Process Engineering, Worldwide Technical Operations (April 2005–April 2007). While an Executive Director, I was responsible for three process engineering groups: Drug/Device Combination Products, Cardiology, and Endovascular/Neurovascular Device. My responsibilities included leading and directing technology transfer through PQ and PPQ of device and drug/device products, as well as process optimizations and base business support for the operational sites in the manufacturing of a wide variety of

medical device products. I prepared project strategy plans and was involved with design review, PMA submissions, and PAI readiness. I also served as the Technical Operations representative member on the project team to ensure that the final process was commercially feasible and efficient.

14. From 2007 to 2008, I was the Senior Research Fellow in Product Support/Technical Services at Johnson & Johnson Cordis Corp. My responsibilities included providing base business support as a Subject Matter Expert (“SME”) for drug/device combination products by directly leading or supporting the product improvement of commercial products and process optimizations for the operational sites in the manufacturing of a wide variety of medical device products.

15. From 2014 to 2018, I was a Vice President, Technical Operations and Manufacturing, at Edge Therapeutics, Inc. As Vice President, I was part of the senior leadership and reported to the CEO. I was responsible for the commercial manufacture and supply of both active pharmaceutical ingredients and the finished pharmaceutical product worldwide. I also negotiated commercial supply agreements with vendors and contract manufacturing organizations. I was also responsible for the Chemistry, Manufacturing, and Controls of all products in the pipeline from early concept through commercialization. I also supported product development with oversight through IND and NDA filings. Our lead product for which I worked to

develop the commercial process was a nimodipine encapsulated microsphere for direct injection into the ventricles of the brain.

16. Finally, since 2009, I have been a principal consultant at Biotech, Pharma & Device Consulting, LLC. I provide technical review and input technical review for the biotech, pharmaceutical, and medical device industries. In addition to providing technical consulting about development and commercialization of complex product and processes, I provide compliance support, which includes development of quality systems and remediation that is specific to the size and need of the company.

17. I have scaled up and validated more than 40 products ranging from sterile powders to lyophilized reconstituted products. I have experience working with both traditional and biotech (peptides, proteins and nucleotide) drugs and drug delivery systems such as liposomes, microspheres, emulsions, suspensions, and drug/device combination products.

18. I have served as a task force member in the validation of two facilities and am experienced with facilities in Sweden, Switzerland, France, Germany, Austria, Puerto Rico, Ireland, and Singapore. In addition, I am experienced with preapproval inspections both in the United States and in Europe (involving the FDA and the European Medicines Agency), third party CDMO and CMO manufacturers

and service providers (both in the arena of technical support and quality/compliance), and the performance of quality compliance audits.

19. For my work, I was selected as a SME by the International Society for Pharmaceutical Engineering (ISPE) in 2007. My recognized areas of expertise include: Pharmaceutical Product Development: pre-formulations, formulations, process development and scale-up (for sterile and non-sterile liquids and semisolid products such as complex emulsions and suspensions including controlled release, e.g. liposomes and microspheres); Tech transfer, Commercialization, Process Validation, and PAI Readiness and Support; Equipment Qualification, Process Automation, and Sterile Manufacturing; and cGMP and Regulatory Applications (specifically pertaining to CMC sections of IND, NDA, BLAs, and PMA).

20. I am also a J&J Certified Process Excellence (6-Sigma) Black Belt. I was invited to prepare examination questions for the ISPE Certification Program for their Pharmaceutical Engineering Certification program.

21. I was awarded the President's Award by Schering-Plough Research Institute (SPRI), the highest award at SPRI, for process improvements and scale up of a dual-chambered lyophilized protein.

22. I have received numerous leadership awards from both internal and external organizations, such as Johnson & Johnson and the American Association of Pharmaceutical Scientists (AAPS).

23. Over the course of my career, I have worked on various liposomal formulations, from the product formulation stage through process engineering and scale-up to commercial scale. I am familiar, and have routinely used, process engineering principles to achieve final products that meet the specified requirements of the formulation as described in the target patient profile, and that meet product performance expectations provided to product development groups by clinical and marketing departments. Further, I have extensive experience with complex formulations, sterile emulsions, nanoparticle suspensions, sterile and non-sterile suspensions.

24. I have worked on numerous projects/products that employed an emulsion step as part of the process to manufacture the final product. I have previous working experience with the process engineering and scale-up of liposomes.

III. INFORMATION RELIED UPON

25. In addition to my general knowledge gained as a result of my education and experience, I have reviewed and considered, among other things, the prior art of record discussed herein.

26. The full list of information, in addition to my professional and academic experience, that I have relied upon in forming my opinions for this report is set forth throughout the report and in the Table of Exhibits.

27. Where my conclusions are based on certain assumptions that I have adopted, I have stated such assumptions in this Declaration.

IV. RELEVANT LEGAL STANDARD

28. In forming my opinions and considering the patentability of the claims of the '865 Patent, I am relying upon certain legal principles that counsel for Petitioner have explained to me, as listed below.

29. I understand that for an invention claimed in a patent to be found patentable, it must be, among other things, new and not obvious in light of what came before it. Patents and publications which predated the invention are generally referred to as “prior art.”

30. For patent invalidity under an *inter partes* review, I understand the burden is on the party asserting unpatentability to prove it by a preponderance of the evidence. I understand that “a preponderance of the evidence” is evidence sufficient to show that a fact is more likely than not.

A. Person of Ordinary Skill in the Art

31. I have been informed that the claims of a patent are judged from the perspective of a hypothetical construct involving “a person of ordinary skill in the art” (“POSA”). The “art” is the field of technology to which the patent is related. I understand that the purpose of using a POSA’s viewpoint is objectivity. Thus, I understand that the question of validity is viewed from the perspective of a POSA

as of March 20, 2006, and not from the perspective of (a) the inventor, (b) a layperson, or (c) a person of extraordinary skill in the art. I have been informed that the claims of the '865 Patent are interpreted as a POSA would have understood them at the relevant time period, which I have been asked to assume is pre-March 21, 2006.

B. Claim Construction

32. I understand the first step in determining whether a patent claim is valid is to properly construe the claims. I understand that each claim of a patent subject to *inter partes* review is to be interpreted in light of the language of the claim, the written description, the figures, and the prosecution history of the patent.

33. I further understand that in the absence of a specific definition within the specification or the reliance on a specific meaning in the prosecution history, the terms as used in the challenged claims of the '865 Patent are to be afforded their plain and ordinary meaning at the time of the invention.

34. I understand that the “plain and ordinary meaning” of a term means the ordinary and customary meaning given to the term by those of ordinary skill in the art at the time of the invention and that the ordinary and customary meaning of a term may be evidenced by a variety of sources, including the words of the claims, the specification, drawings, and prior art.

35. I understand that in construing claims all words in a claim must be considered in judging the patentability of that claim against the prior art.

36. I understand that extrinsic evidence may be consulted for the meaning of a claim term as long as it is not used to contradict claim meaning that is unambiguous in light of the intrinsic evidence. I also understand that in construing claim terms, the general meanings gleaned from reference sources must always be compared against the use of the terms in context, and the intrinsic record must always be consulted to identify which of the different possible dictionary meanings is most consistent with the use of the words by the inventor.

C. Presumption of Validity

37. I understand that a granted patent is presumed to be valid. I understand that the presumption of validity can be overcome in district court litigation if clear and convincing evidence is presented that proves the patent is invalid. I understand that the standard of proof for invalidating a patent in an *inter partes* review proceeding is a “preponderance of the evidence” (i.e., greater than 50% chance of likelihood), which is a lower standard than the clear and convincing evidence standard.

D. Obviousness

38. I understand that even if a patent claim is not anticipated, it is still invalid if the differences between the claimed subject matter and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person of ordinary skill in the pertinent art.

39. I understand that a person of ordinary skill in the art provides a reference point from which the prior art and claimed invention should be viewed. This reference point prevents one from using his or her own insight or hindsight in deciding whether a claim is obvious.

40. I also understand that an obviousness determination includes the consideration of various factors such as (1) the scope and content of the prior art, (2) the differences between the prior art and the asserted claims, (3) the level of ordinary skill in the pertinent art, and (4) the existence of secondary considerations or objective indicia of obviousness or non-obviousness.

41. I understand that an obviousness determination can be based on a single prior art reference or a combination of multiple prior art references or the knowledge of one of ordinary skill in the art. I understand that the prior art itself may provide a suggestion, motivation, or reason to combine or modify the teachings of the prior art, or that such a reason may come from other sources, such as the knowledge of a person having ordinary skill in the art, common sense, and market forces. I understand that the following rationales may support a finding of obviousness:

- combining prior art elements according to known methods to yield predictable results;
- simple substitution of one known element for another to obtain predictable results;

- use of known technique to improve similar devices (methods, or products) in the same way;
- applying a known technique to a known device (method or product) ready for improvement to yield predictable results;
- “obvious to try” – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;
- known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art;
- some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

42. I understand that an obviousness determination requires a reasonable expectation of success in achieving the claimed invention.

43. I understand that the content of a patent or other printed publication (i.e., a reference) should be interpreted the way a person of ordinary skill in the art would have interpreted the reference as of the effective filing date of the patent application for the '865 Patent. I have assumed that the person of ordinary skill in the art is a hypothetical person who is presumed to be aware of all of the relevant art at the time

of the invention. The person of ordinary skill is not an automaton, and may be able to fit together the teachings of multiple patents employing ordinary creativity and the common sense that familiar items may have obvious uses in another context or beyond their primary purposes.

44. I understand that if an alleged invention is otherwise rendered obvious in view of the prior art, it is not patentable simply because the inventors discover an inherent property or a result that naturally flows from its application or use.

45. I understand that secondary considerations or objective indicia of obviousness or non-obviousness may include (1) a long felt but unmet need in the prior art that was satisfied by the invention of the patent; (2) commercial success or lack of commercial success of processes covered by the patent; (3) unexpected results achieved by the invention; (4) praise of the invention by others skilled in the art; (5) the taking of licenses under the patent by others; (6) deliberate copying of the invention; (7) teaching away; and (8) the simultaneous invention of the claimed subject matter. I also understand that there must be a relationship between any such secondary considerations and the invention. I further understand that contemporaneous and independent invention by others is a secondary consideration supporting an obviousness determination.

46. I understand that any secondary considerations or objective indicia must bear a nexus to the claimed invention. Where the offered secondary

consideration actually results from something other than what is both claimed and novel in the claim, there is no nexus to the merits of the claimed invention. I further understand that the patentee bears the burden of demonstrating that the relevant commercial success is attributable to the claimed invention, as opposed to other economic and commercial factors unrelated to the technical quality of the patented subject matter.

47. I understand that whether a prior art reference “teaches away” from the claimed invention is a fact to be considered in determining obviousness. I understand that it is improper to combine references where the references teach away from their combination. However, I understand that the nature of the teaching is highly relevant and must be weighed in substance—a known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use. Furthermore, I understand that the fact that mere disclosure of more than one alternative in the prior art does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed.

48. I understand that hindsight must not be used when comparing the prior art to the invention for obviousness.

V. BACKGROUND OF THE '865 PATENT

A. General Description

49. The '865 patent is entitled “VEGF Antagonist Formulations Suitable for Intravitreal Administration.”

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

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

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

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

additionally contain sucrose. *Id.*, Examples 1-4, 7. Six of the examples deal with liquid formulations (*Id.*, Examples 1-6), and two with lyophilized formulations (*Id.*, Examples 7-8).

54. The examples of the '865 patent report the formulation's stability after storage at 5 °C for certain periods of time. Turbidity at OD405 nm and “% VEGF Trap Native Configuration” as measured by size-exclusion chromatography are reported after storage periods that run from zero to 24 months. *See, e.g., Id.*, Tables 1-8. The examples also provide the pH of the formulation over time. The range of concentrations for the VEGF Trap and excipients and their associated stability characteristics are summarized below:

	VEGF Trap	Buffer	Tonicity	Co-solvent	Stabilizing agent	Stability
'865 Examples	20-50 mg/mL	5-10 mM phosphate	20-135 mM NaCl	0.015-0.1% polysorbate 20 or 3% PEG 3350	0-5% sucrose	98.5%-99.3% at 2-3 months

55. Other than making and testing the claimed formulations, the '865 patent does not teach how to achieve the claimed stability. The patent does not teach the effect of adjusting or optimizing the concentrations of the various excipients, other than what is taught in the handful of examples. The patent also does not teach whether any intravitreal formulations were safe and effective. It does not teach that any of the formulations were intravitreally injected, or whether they were tolerated if they were to be injected.

B. Priority Date

56. The '865 patent claims priority to ten prior patent applications and one provisional application, which was filed on June 16, 2006. Regeneron has previously contended the inventors of the '865 patent conceived and reduced to practice the alleged inventions therein by March 21, 2006. For the purposes of this declaration, I assume that is the relevant priority date.

C. Prosecution History

57. I have reviewed the '865 patent prosecution history, and the Examiner issued only obviousness-type double patenting rejections. Ex.1004, 256-62. Regeneron relied on the stability claim element to overcome the obviousness-type double patenting rejection. *Id.*, 279-284. Regeneron did not argue, however, that obtaining the added stability limitation was unexpected or that it conferred any unexpected properties to the formulation.

D. Level of Ordinary Skill in the Art

58. Based on my review of the patent and prior art, I have adopted the following definition of a POSA, which I understand is consistent with that proposed in a related IPR by Patent Owner:

59. The POSA at the time of the invention would have had a Ph.D. in pharmaceutical sciences or a similar field, with at least several years of experience in the development, manufacture and characterization of formulations of therapeutic proteins, including, for example, fusion proteins or antibodies. The POSA may also

have had less education but substantially more practical relevant work experience. This individual would have understood how to combine proteins with compatible excipients such as surfactants, stabilizers, salts and buffers at different pH ranges, and how to adjust these combinations in order to optimize their stability in liquid or solid form. This individual also would have been able to use state-of-the-art analytical methods, such as size-exclusion chromatography (“SEC”), to assess stability and compatibility.

60. The POSA may collaborate with others, including a medical doctor with experience treating ophthalmic diseases. The POSA also would have had access to other individuals typically employed in developing protein active pharmaceutical ingredients and products, including those involved in upstream and downstream manufacturing, analytical chemistry, pharmacokinetics, clinical testing, pharmaceutical packaging, and regulatory affairs. These diversely-qualified individuals would have worked together as needed during development.

VI. THE CHALLENGED CLAIMS

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

62. One subset of the Challenged Claims—1-12, 14-17, 19-20, 22-25, 51-53, and 55—recite the formulation is stored in a vial. Throughout this declaration, I refer to these claims collectively as the “Vial Claims.” The Vial Claims are the subject of Ground I. A second subset of Challenged Claims—26-36, 39-42, 44-45, 47-50, 54—recite the same formulation stored in a PFS. I refer to these claims collectively as the “PFS Claims.” The PFS Claims are the subject of Ground II.

VII. SCOPE AND CONTENT OF THE PRIOR ART

63. Below, I summarize the scope and content of the prior art, including the disclosures of the primary prior art references relied on in my analysis below. I also note that I have reviewed the Declarations of Dr. Edward Chaum and Dr. Michael Butler to further understand what was known and understood in the art at the time regarding the administration of intravitreal injections, compositions and presentations of prior art formulations, the development of aflibercept, and the known glycosylation sites of aflibercept. *See*, Exs.1005 and 1007.

A. Background

1. *Vascular Endothelial Growth Factor (“VEGF”)*

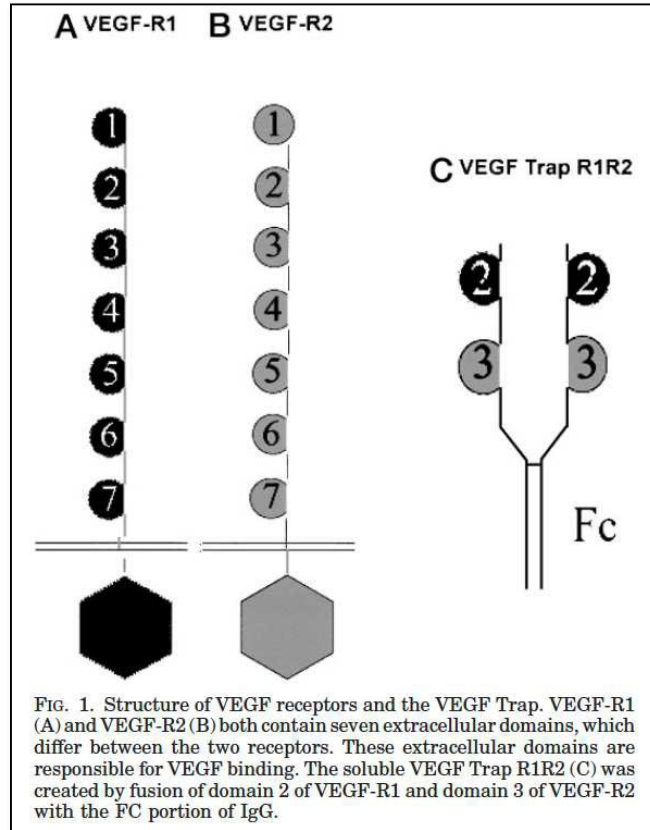
64. I understand that Vascular Endothelial Growth Factor, also known as VEGF, is a naturally-occurring protein that regulates the process by which new blood vessels are formed, known as “angiogenesis.” VEGF functions by binding to VEGF receptors on the surfaces of cells responsible for angiogenesis. Ex.1015, 412; Ex.1005, ¶45; Ex.1007 ¶¶18-19.

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

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

2. *Aflibercept*

67. I also understand that during this time, Regeneron developed aflibercept, another VEGF inhibitor, and that aflibercept was known as “VEGF-Trap_{R1R2},” “VEGFR1R2-FcΔC1(a),” and “VEGF Trap-Eye” at the time. Aflibercept is a fusion protein of domain 2 of the human VEGFR1 receptor and domain 3 of the human VEGFR2 receptor, linked via the Fc domain of a human IgG antibody as shown below:



Ex.1016, 2798, Fig. 1; Ex.1007, ¶18.

68. Aflibercept binds VEGF before it can trigger angiogenesis. *Id.*

69. I understand from the Declaration of Dr. Butler and my review of the literature that Regeneron publicized its development of aflibercept, including experiments demonstrating its therapeutic promise. Ex.1010; Ex.1007, ¶¶18-36. For instance, Regeneron claimed: “The combination of high-affinity and improved pharmacokinetics apparently contributes toward making VEGF-Trap_{R1R2} [aflibercept] one of the most, if not the most, potent and efficacious VEGF blocker available.” Ex.1010, 11397.

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

71. Regeneron also reported that “the [aflibercept] VEGF-Trap is currently in human clinical trials for several different types of cancer.” Ex.1010, 11397. In fact, by 2006, Regeneron published “quite promising” results for its first clinical trials of aflibercept. Ex.1015, 414-15.

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

73. Regeneron had also widely published the sequence of aflibercept prior to the priority date, although it referred to the protein by its earlier scientific names,

VEGF-Trap_{R1R2} and VEGFR1R2-FcΔC1(a), rather than the non-proprietary name “aflibercept” it coined later as the molecule neared regulatory approval.¹ I understand from Dr. Butler that by 2004, Regeneron had published the amino acid sequences of VEGFR1R2- FcΔC1(a) in various patent publications. *See* Ex.1027, ¶5, SEQ ID Nos. 1 and 2 (also disclosing that VEGFR1R2-FcΔC1(a) is “also termed VEGF- Trap_{R1R2}); Ex.1029, 12, 15, Fig. 24A-24C; Ex.1028, ¶8, SEQ ID Nos. 3 and 4; Ex.1007, ¶¶18-22. Regeneron also disclosed the sequence of VEGFR1R2-

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

FcΔC1(a) in the '758 *Patent*, first published on November 3, 2005. Ex.1019, 10:15-17, Figs. 24A-24C; *see* Ex.1007, ¶18.

74. Regeneron also disclosed in these publications that it used CHO cells to express aflibercept. *See, e.g.*, Ex.1029, 12, 15, Fig. 24A-24C, claims 9, 20 (describing production of VEGFR1R2-FcΔC1(a) in CHO cells); *see also* Ex.1027 ¶22 (directing POSA to the '319 *Publication* for “a complete description of VEGF-receptor based antagonists including VEGFR1R2-FcΔC1(a)” and incorporating the '319 *Publication* into the '309 *Publication* “by reference in its entirety.”). I understand from Dr. Butler that that it was well known and a POSA understood that when aflibercept is expressed in CHO cells it is glycosylated. Ex.1007, ¶¶18-36.

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

3. Protein Stability

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

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

78. When creating a formulation for a protein therapeutic, limiting aggregation is the chief goal since aggregates can cause immunogenicity, diminish half-life, and interfere with drug function.

79. There were many formulation techniques well known in the field that had proven to be effective in preventing protein aggregation. One common way was to include an organic co-solvent known as a “surfactant” in the formulation. *See* Ex.1018, Table 6. Polysorbate 20 and polysorbate 80 (which were sold under the brand names “Tween 20” and “Tween 80,” respectively) were commonly used surfactants to prevent aggregation in therapeutic protein formulations. *See, e.g.,* Ex.1097, Box 1. As of the priority date, a large number of FDA-approved and commercially-available protein therapeutics used polysorbate 20 or polysorbate 80 in their formulations to prevent aggregation. *See, e.g.,* Ex.1032, 2 (polysorbate 20); Ex.1034, 1117 (polysorbate 80); Ex.1037, 1359 (polysorbate 20); Ex.1033, 1350 (polysorbate 20); Ex.1036, 1338 (polysorbate 20).

80. POSAs commonly used phosphate as a buffer for proteins at the time to stabilize them further; a number of FDA-approved protein formulations were

formulated with phosphate buffer prior to the priority date. *See* Ex.1032, 2; Ex.1034, 1117; Ex.1035, 2367. Sodium phosphate is the most common of those buffers, and, along with citrate buffers, was commonly used in intravitreal formulations. Ex.1005, ¶¶32, 35-36, 44-45.

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

82. POSAs also routinely refrigerated protein therapeutics to avoid degradation because degradation proceeds slower at colder temperatures. Thus, POSAs commonly stored protein formulations at 2-8 °C to maintain stability. Ex.1032, 25; Ex.1034, 1121; Ex.1037, 1362; Ex.1033, 1352; Ex.1035, 2369; Ex.1036, 1341. To test whether a formulation can be safely stored for a reasonable shelf life, POSAs commonly tested storage stability for weeks or months under refrigeration at 2-8 °C. *See, e.g.*, Ex.1026, ¶¶63, 280 (showing stability data for 1, 3, 14, 16, and 24 months).

83. POSAs also commonly used SEC at the time to quantify the formation of protein aggregates in a formulation. *See, e.g.*, Ex.1026, ¶278, Table 1; Ex.1012, 160. SEC measures the percent monomer present in a formulation.

84. POSAs also understood how to optimize a therapeutic protein formulation to obtain as close to 100% stability over a reasonable shelf-life as possible. POSAs understood that very high levels of purity could be maintained during storage at 2-8 °C. *Id.* In fact, numerous publications reported antibody formulations preserving >98% of the protein in “native conformation” as measured by SEC during storage at 5 °C for two months.²

85. For instance, *WO '801* (Ex.1030) discloses lyophilized trastuzumab formulations that contained trehalose and polysorbate 20 and maintained >99% of the protein “intact” (*i.e.*, native conformation) as measured by SEC after storage at 5 °C for 2 weeks. Ex.1030, Table 4 (99.8% or 100.0% native conformation at 91 days), Table 5 (100.0% native conformation at 61 days), Table 6 (100.0% native conformation at 92 days), Table 7 (99.8% native conformation at 92 days).

86. Similarly, *Liu* reports recombinant human antibody formulations had >98% “monomer” (*i.e.*, native conformation) after storage at 5 °C for 3 months (and even up to 16 months). Ex.1026, ¶¶279-280; Table 1. The *'586 Patent* (Ex.1018) similarly reports an antibody formulation containing polysorbate 20 and trehalose as

² I will use the term “native conformation” in my declaration as that term is used in the *'865 patent*, *i.e.*, to refer to the % native conformation as measurable by SEC.

having >98% “monomer” (*i.e.*, native conformation) as measured by SEC after storage at 2-8 °C for two years. Ex.1018, Fig 28, 5:34-39.

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

B. Key Prior Art

1. Fraser (Ex.1009)

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

89. *Fraser's* study evaluated aflibercept's effect on ovarian angiogenesis. *Id.*, 1114. The study used an aflibercept formulation comprising the excipients recited in the challenged claim: "VEGF Trap_{R1R2} (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." *Id.*, 1115. "Tween 20" is the brand name for polysorbate 20. Ex.1102.³

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

2. Wulff (Ex.1016)

91. *Wulff* is titled "Prevention of Thecal Angiogenesis, Antral Follicular Growth, and Ovulation in the Primate by Treatment with Vascular Endothelial

³ I understand that during prosecution of *Dix*, Regeneron represented that *Fraser's* formulation used sucrose, not glycerol. Ex.1098, 2 (noting that the "actual lot and formulation used in Fraser" contained "24.3 mg/ml VEGF Trap protein, 5 mM phosphate, 5 mM citrate, 100 mM NaCl, 20% sucrose, and 0.1 % polysorbate-20, pH 6.05.").

Growth Factor Trap R1R2.” Ex.1016. It was published in the journal *Endocrinology* in July 2002, prior to the ’865 patent’s alleged priority date of March 2006.

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

93. *Wulff* discloses the same formulation as *Fraser* but specifies that sucrose was used: “[c]ontrol animals were treated with vehicle containing 5mM phosphate, 5 mM citrate, 100 mM sodium chloride, 0.1% (wt/vol) Tween 20, and 20% (wt/vol) sucrose).” *Id.*

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

3. Feb. 3 and 8, 2006 and March 8, 2006 Presentations (“2006 Presentations”)

95. Prior to the alleged priority date of March 21, 2006, on February 3, 8, and March 8, 2006, Regeneron gave a series of similar presentations reporting on aflibercept’s use in early clinical trials to treat wet AMD. Ex.1011-13; Ex.1017.

96. Specifically, the 2006 Presentations promote the use of aflibercept to address wet AMD, which they note is “a major cause of blindness in adults over 60.” *See, e.g.*, Ex.1012, 19. They teach that aflibercept could be the “best-in-class” treatment for wet AMD, with potentially “greater efficacy related to unique characteristics” and potentially “greater patient convenience/safety.” *Id.* The presentations disclose that a “single intravitreal injection” of aflibercept showed “[r]apid, substantial, and prolonged (up to at least 4 weeks) reduction in retinal thickness,” which is necessary to treat wet AMD. *See, e.g.*, Ex.1012, 23. They also report that a Phase 2 trial was set to begin with initiation of a Phase 3 trial planned the following year. *See, e.g.*, Ex.1012, 23.

97. Further, these presentations more specifically reported that patients were being intravitreally injected with doses of 0.05, 0.15, 0.5, 1.0, 2.0, and 4.0 mg of aflibercept. Ex.1011, 13-22, Ex.1012, 19-23, Ex.1013, 21-24. The February 3, 2006 presentation reports, for instance, that the “maximum tolerated dose has not yet been reached (0.05 to 4.0 mg) and that there were “no ocular serious adverse events” and “no evidence of inflammation.” Ex.1011, 14; *see also* Ex.1012, 19-23,

Ex.1013, 21-24. It further reported the study “remains ongoing at 4 mg/eye dose level,” and patients showed a “[r]apid, substantial decrease in retinal thickness.” *Id.* The March 8, 2006 presentation reported the 4.0 mg dose had been completed and reported that there was “[c]onfirmed evidence of biological activity.” Ex.1013, 24.

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

98. Several container/closure systems using vials and prefilled syringes were available for protein-based therapeutics as of June 2006, and were also used for intravitreal products, as discussed by Dr. Chaum. Ex.1018, 4 Table 2; Ex.1005, ¶¶38-42. For instance, Chang 2002 lists “Vial/stoppers” and PFSs as options for “Container/closure” systems. Ex.1018, 6. In its Container Closure Guidance, published in 1999, the FDA specifically recommended that injectable formulations be packaged in vials. Ex.1038, 23-24; Ex.1031.

99. Similarly, at the time, POSAs understood that PFSs offered convenience for purposes of administration, including intravitreal administration, as they eliminate the step of withdrawing liquid from the vial and into a syringe. *Nayar*, titled “High Throughput Formulation: Strategies for Rapid Development of Stable Protein Products,” and published in Rational Design of Stable Protein Formulations 177, 183 (J.F. Carpenter & M.C. Manning eds., 2002) (“Nayar 2002”), explains that each dosage form “offers various advantages and disadvantages, in the speed of development, manufacturing, packaging and shipment logistics, and in

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

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

5. '319 Publication (Ex.1029)

101. WO 00/75319 A1 (“’319 Publication”/“Papadopoulos”) is a PCT publication published on December 14, 2000, prior to the ’865 patent’s alleged priority date.

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

6. '309 Publication (Ex.1027)

103. U.S. Patent Application Publication No. 2004/0265309 (*'309 Publication*) is a U.S. patent publication that was published on December 30, 2004, prior to the '865 patent's alleged priority date.

104. The *'309 Publication* discloses that VEGFR1R2-Fc Δ C1(a) is “also termed VEGFTrap_{R1R2}” and discloses its amino acid sequence. Ex.1027, ¶5, SEQ ID NOs: 1 and 2. The *'309 Publication* also points the skilled artisan to the *'319 Publication* for “a complete description of VEGF-receptor based antagonists including VEGFR1R2-Fc Δ C1(a)” and incorporates the *'319 Publication* “by reference in its entirety.” *Id.*, ¶22.

VIII. DETAILED GROUNDS FOR INVALIDITY: GROUND 1

105. In my opinion POSA would have found the intravitreal formulation recited in the Challenged Claims obvious. In particular, based on the 2006 Presentations, it would have been obvious to a POSA to modify the formulation described in the Fraser and Wulff references to produce a formulation suitable for intravitreal injection (which I refer to below as the “Modified Fraser/Wulff” formulation). In my opinion, this formulation renders all of the Challenged Claims obvious.

A. The Modified Fraser/Wulff Formulation

106. The 2006 Presentations discussing success using intravitreal aflibercept injections to treat angiogenic eye disorders would have motivated a POSA to

develop an intravitreal aflibercept formulation. *See, e.g.* Ex.1005, ¶¶43-48. The presentations disclose dosing amounts, including a maximum dose of 4 mg, but not a formulation. *See, e.g.*, Ex.1011, 14; *see also* Ex.1012, 19-23, Ex.1013, 21-24.

107. The POSA seeking to formulate aflibercept for intravitreal injection would not have started from scratch. The most natural starting point would have been intravenous formulation described in Fraser and Wulff, which I understand was the only known aflibercept formulation in the prior art. A POSA would have favored such a formulation, as it is likely to be compatible with the drug product and demonstrate stability.

108. In particular, Fraser and Wulff describe the same overlapping aflibercept formulation: an intravenous formulation of aflibercept at a concentration of 24.3 mg/ml, with a buffer of 5 mM phosphate⁴ and 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20 (polysorbate), with 20% sucrose.

109. In my opinion, a POSA starting from this formulation would have consulted with an ophthalmologist to determine key characteristics specific to the

⁴ A POSA would have understood this to be a sodium phosphate buffer, as the most commonly used phosphate buffer at the time, including in intravitreal injections. Ex.1005, ¶¶35-36.

intravitreal injection, such as dose, volume, and osmolality. While these factors are standard considerations in the development of any injectable pharmaceutical product, the consultation would focus on tailoring them and other relevant characteristics for intravitreal administration. I have reviewed the declaration of Dr. Chaum, which I understand summarizes many of these considerations, including the dose, volume, and osmolality specific to intravitreal use, each of which I discuss below.

110. First, a POSA starting from the Fraser/Wulff formulation would have understood it was necessary to select a dose for intravitreal injection specifically. The 2006 Presentations describing the intravitreal use of aflibercept teach a set of dosage amounts for treating angiogenic eye disorders such as wet AMD, including that the maximum tolerated dose reached was 4 mg. *See, e.g.*, Ex.1011, 14; Ex.1012, 19-23, Ex.1013, 21-24. The presentations describe these doses as effective in achieving a “[r]apid, substantial, and prolonged (up to at least 4 weeks) reduction in retinal thickness”—which I understand from Dr. Chaum treats wet AMD. Ex.1011, 15; Ex.1012, 20; Ex.1013, 22; Ex.1005, ¶47. They also explain that a Phase 2 trial was set to begin with initiation of a Phase 3 trial planned the following year. *See, e.g.*, Ex.1013, 22, 24. A POSA would have been motivated to select the known maximum tolerated dose of 4 mg for the treatment of wet AMD.

111. Second, a POSA also would have inquired into the proper injection volume for an intravitreal injection, and would have been motivated to reduce the

volume of the original Fraser/Wulff formulation to 0.1 mL. Fraser and Wulff teach the use of 2 mL aliquots. Ex.1009, 1115; Ex.1016, 2798. I understand from Dr. Chaum that this volume is far too large for the human eye, which was understood to be able to safely receive only a 0.1 mL injection. Ex.1005, ¶¶23-26. I further understand that the most common intravitreally injected drug at the time was given in volumes of 0.1 mL. *Id.* A POSA thus would have been motivated to reduce the injection volume to 0.1 mL, as that was the known, safe injection volume.

112. I note that a 4 mg dose in 0.1 mL is a 40 mg/mL concentration (4 mg in 0.1 mL of volume). I understand this is consistent with the volume and concentration of the most common intravitreally injected drug at the time, Kenalog, and was the maximum known, safe tolerated concentration for an intravitreal injection. Ex.1005, ¶¶23-26. I also understand that, based on the maximum intravitreal volume taught in the art (0.1 mL) and the maximum dose taught in the 2006 presentations (4 mg), a POSA would have understood that aflibercept had previously been formulated at 40 mg/mL, likely in a similar formulation to that taught by Fraser and Wulff. They would have reasonably expected this concentration to work in the modified formulation.

113. Third, based on information provided in Dr. Chaum's declaration (Ex.1005, ¶¶19-22), in my opinion a POSA would have understood that matching the osmolality of the human eye (around 285-310 mOsm) is important for an

intravitreal formulation. That is because osmolality and tonicity are critical factors in formulating any injections. Ex.1005, ¶¶19-22. The osmolality of the Fraser/Wulff formulation fell far outside this range. I understand this would have presented significant risks to a patient. *Id.*, ¶¶20-21.⁵

114. As set out by Dr. Chaum, a POSA informed by an ophthalmologist would have understood that ensuring the solution's osmolality is appropriately matched not only improves patient comfort but also helps preserve the eye's physiological balance, reducing the risk of side effects and unintended outcomes. Ex.1005, ¶¶19-22. While there would be some range of tolerance, getting the formulation close to the eye's osmolality would have been important.

115. In fact, as Dr. Chaum explains (Ex.1005, ¶22), I understand that intravitreal injections at the time were typically formulated to match the osmolality

⁵ Osmolality refers to the total concentration of solutes in a solution, while tonicity focuses specifically on how those solutes affect water movement across cell membranes. Osmolality and tonicity are interconnected; both work together to ensure that the solute concentration is balanced with the body's fluids to prevent unwanted water movement across cell membranes.

of the vitreous humor (i.e., to be iso-osmotic). Ex.1005.⁶ At the time of the patent, the osmolarity of two primary FDA-approved intravitreal preparations were known: Macugen, supplied in a PFS with an osmolality of roughly 280-360 mOsm, and Vitravene, supplied in a vial with an osmolality of roughly 290 mOsm. Ex.1045, 2; Ex.1046, 3; Ex.1005, ¶22. Matching the osmolality would have been consistent with normal practice.

116. I have calculated the osmolality of the Fraser/Wulff formulation below. Osmolality is measured in units of osmol (Osm) per kg of solvent. An osmol “is related to a mole (gram molecular weight) of the molecules or ions in solution.” Ex.1103, 456. For example, one mole of glucose dissolved in 1 kg water has an osmolality of 1 Osm, or 1000 mOsm/kg. *Id.* By contrast, 1 mole of NaCl which dissociates into sodium and chloride ions in water, has an osmolality of 2 Osm when dissolved in 1 kg water.

⁶ I understand from Dr. Chaum that anti-VEGF agents like Macugen and Avastin, as well as other known intravitreal agents, were all formulated with an osmolality of 280–360 mOsm/kg to closely match the environment of the eye and avoid adverse reactions following injection. Ex.1005, ¶22.

117. To calculate the osmolality of the Fraser/Wulff formulation, I must first determine the concentration in mM of the components of the formulation. Fraser/Wulff provide this information for phosphate (5 mM), citrate (5 mM) and NaCl (100 mM), but I must calculate it for aflibercept, sucrose and Tween 20.

118. Fraser/Wulff teach that the concentration of aflibercept is 24.3 mg/mL, or 24.3 g/L. The molecular weight of aflibercept is 115 kDa (Ex.1099, ¶36), which is 115,000 g/mol. To obtain the millimolar concentration of aflibercept, I multiply 24.3 g/L by 1 mol/115,000 (*i.e.*, I divide 24.3 by 115,000), and obtain 0.000211 mol/L, which is 0.211 mM.

119. Fraser/Wulff teach that the concentration of sucrose is 20%. 20% wt/v means 20 g/100 mL, or 200 g/L. The molecular weight of sucrose is 342.29 g/mol. Ex.1100, 308. To obtain the millimolar concentration of sucrose, I multiply 200 g/L by 1 mol/342.29 (*i.e.*, I divide 200 by 342.29), and obtain 0.584 mol/L, which is 584 mM.

120. Fraser/Wulff teach that the concentration of Tween 20 is 0.1%. 0.1% wt/v means 0.1 g/100 mL, or 1 g/L. The molecular weight of Tween 20 is 1,225 g/mol. Ex.1102, 1. To obtain the millimolar concentration of Tween 20, I multiply 1 g/L by 1 mol/1,225 (*i.e.*, I divide 1 by 1,225), and obtain 0.000816 mol/L, which is 0.816 mM.

121. Now that I have the millimolar concentration of all components in the solution, I can determine the osmolality. The solvent for this formulation is water. The osmolality of each component is calculated based on the number of molecules or ions in solution for each solute when dissolved in water.

Component	Amount (mM)	mOsm
Aflibercept	0.211	0.211
Sucrose	584	584
NaCl	100	200
Phosphate	5	10
Citrate	5	10
Polysorbate	0.816	0.816
Total:		805.027

122. As shown above, the formulation has total osmolarity of above 800 mOsm. Each component contributes some osmolality to the formulation. But sucrose contributes by far the largest amount—so much so that even if a POSA entirely eliminated any other component of the formulation, the formulation still would not have approached the osmolality of the human eye. It is necessary to reduce sucrose to half to even approach that amount.

123. Accordingly, in my opinion, a POSA would have been motivated to modify the Fraser/Wulff formulation because, with an osmolarity above 800 mOsm,

it would not be considered safe for intravitreal injection, and, as Dr. Chaum explains, likely would have drawn water out of cells around the eye, leading to dehydration of those cells, cell shrinkage, and tissue damage to delicate ocular structures like the retina. Ex.1005, ¶20. A POSA would have been motivated to modify the Fraser/Wulff intravenous formulation to approximate the osmolarity of the human eye, or at the very least, to approximate the ranges of the FDA approved intravitreal formulations, which would have been considered a useful guide.

124. In view of the chart above, a POSA would have understood that the sucrose level of the formulation had to be reduced to at least 10%, down from 20% sucrose. That is because the osmolarity of sucrose is so high (584 mOsm) that it alone puts the formulation well outside the desired range. Thus, a POSA would need to cut the sucrose amount at least in half in order to approach the desired range for a 40 mg/mL aflibercept formulation, as shown in the chart below. *Id.* I note that in the chart below, I used a 40 mg/mL aflibercept dosage, which translates to 0.347 mM.

Component	Amount (mM)	mOsm
Aflibercept	0.347	0.347
Sucrose	292 (or 10% sucrose, reduced from 584 mM/20%)	292
NaCl	100	200

Phosphate	5	10
Citrate	5	10
Polysorbate	0.816	0.816
Total:		513.163

125. But, as shown above, cutting the sucrose concentration in half, by itself, is not sufficient and a POSA would need to further optimize the formulation by either further reducing sucrose (*e.g.*, to 5%) or reducing NaCl in order to achieve an iso-osmotic solution. As shown below, both of these approaches would bring the osmolarity of the injection to within safe and tolerable limits for the human eye and would have been a matter of routine optimization. No matter how the POSA proceeds with this further optimization, the resulting solution practices the claims.

Component	Amount (mM)	mOsm
Aflibercept	0.347	0.347
Sucrose	146 (or 5% sucrose)	146
NaCl	100	200
Phosphate	5	10
Citrate	5	10
Polysorbate	0.816	0.816
Total:		367.163

Component	Amount (mM)	mOsm
Aflibercept	0.347	0.347
Sucrose	292 (or 10% sucrose)	292
NaCl	25	50
Phosphate	5	10
Citrate	5	10
Polysorbate	0.816	0.816
Total:		363.163

126. I note that the calculations above provide the osmolarity (mOsm/L) of the Modified Fraser/Wulff formulation. Osmolality is measured in Osm/kg of solvent, and because the solvent is water, which has a density of 1 kg/L, the osmolarity of the Modified Fraser/Wulff formulation is the same as the osmolality.

127. Also, the Fraser/Wulff formulation has a pH of 6.0, and the Modified Fraser/Wulff formulation would have this same pH as the starting point. However, a POSA would have been motivated, as a matter of routine optimization, to make and test the Modified Fraser/Wulff formulation at a range of pH values, including, at the higher pH values of 6.1-6.3, in order to determine the effect of pH changes that may occur naturally. This is because, due to standard measurement error and variations in commercial manufacture, the pH of a formulation will vary to some degree. It would be standard practice to make sure that a formulation can withstand

small variations in pH to ensure stability for commercial manufacture. It thus would have further been obvious to adjust the pH of the Modified Fraser/Wulff formulation to 6.1, 6.2 or 6.3 as part of this work.

128. Finally, a POSA would need to select a presentation for the formulation. I understand from Dr. Chaum that there were two known presentations for intravitreal formulations at the time—a vial and a PFS. Both had known benefits. A POSA would have been motivated to use either presentation, consistent with the intravitreal formulations on the market at the time, which were presented in vials and PFSs. While vials are generally simpler to develop, PFSs are generally more commercially desirable. *See generally* Ex.1005, ¶40.

129. Following the modifications required to develop the Fraser and Wulff formulation for intravitreal use would lead to a 0.1 mL vial or PFS consisting of aflibercept in a 40 mg/mL concentration, with 10% or less sucrose, 5 mM phosphate and 5 mM citrate buffer, 0.1% wt/vol polysorbate.

130. A POSA would have expected this formulation to succeed as an intravitreal injection—aflibercept had been successfully injected in the amount and at (maximum) the concentration in question, and the remainder of the excipients were common ingredients used in other intravitreal injections within ranges known to be tolerated by the human eye.

131. I further address the claims on a limitation-by-limitation basis below.

B. Claim 1

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

132. A POSA would have been motivated to develop an intravitreal aflibercept formulation suitable for intravitreal administration based on the 2006 Presentations, which describe the successful use of intravitreal injections of aflibercept to treat angiogenic eye disorders.

133. As just discussed, a POSA would have been motivated to make a set of obvious modifications to the Fraser/Wulff formulation to make it suitable for intravitreal administration: reducing the volume to 0.1 mL (the known safe and tolerated dose), selecting from the doses used in the presentations to treat angiogenic eye disorders, including the 4 mg dose which was the maximum tolerated dose described (resulting in a 40mg/mL concentration), and reducing the osmolality of the formulation to match the eye and remove risks associated with hyperosmotic formulas.

134. Also, in my opinion, it would have been obvious to use a vial to store the Modified Fraser/Wulff formulation. Neither Fraser or Wulff explain specifically how the formulation was stored. An ophthalmic formulation must be packaged in some type of container. Vials are one such container and well known and commonly used, rendering their use obvious. Ex.1018, 6; Ex.1038, 23-24.

135. In particular, vials were one of two common presentations for intravitreal formulations. Ex.1005, ¶38. In fact, as of the priority date, of the two approved intravitreal preparations, one (Macugen) was supplied in a PFS, and the other (Vitravene) was supplied in a vial. Ex 1045, 1; Ex.1046, 9. Similarly, Chang 2002 lists “Vial/stoppers” and PFSs as options for “Container/closure” systems. Ex.1018, 6.

136. A POSA would have been motivated to select a vial as one of the storage options. A POSA would have understood that vials were commonly and successfully used for storage of such formulations. Ex.1018, 6. For example, in its Container Closure Guidance, published in 1999, the FDA specifically recommended that injectable formulations be packaged in vials. Ex.1038, 23-25. The FDA’s guidance taught vials reduce potential interactions between the drug substance and material because they consist of a single material. *Id.*

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

2. a vascular endothelial growth factor (VEGF) antagonist

138. Wulff and Fraser disclose the use of a VEGF antagonist (VEGF Trap R1R2) in the claimed formulation. Ex.1009, 1115; Ex.1016, 2798.

3. an organic co-solvent

139. The Wulff/Fraser formulation contains an organic co-solvent in the form of Tween 20 (polysorbate), present at 0.1% wt/vol. Ex.1009, 1115; Ex.1016, 2798.

4. a buffer

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

5. a stabilizing agent

141. The Wulff/Fraser formulation contains a stabilizing agent in the form of sucrose. Ex.1009, 1115; Ex.1016, 2798.

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

142. A POSA would have understood that the aflibercept used in the modified Fraser/Wulff formulation is glycosylated and comprises amino acids 27-457 of SEQ ID NO:4. I understand from Dr. Butler that the sequence and glycosylation of aflibercept were known in the art at the time and would have been obvious. Ex.1005, ¶¶18-36.

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

(a) The stability limitations are inherent in the formulation

143. The resulting formulation also would have had the claimed stability characteristics (percent “native conformation” of the protein and turbidity) under the recited storage conditions. While the stability of the Modified Fraser/Wulff formulation was not taught in the art, a formulation’s stability is a product of the interaction between its active ingredient, excipients, and storage conditions. Thus, it is a property of the formulation.

144. Moreover, I note that the Dix reference (Ex.1021) teaches that the original (unmodified) Fraser/Wulff formulation had the claimed stability, as shown in the chart below.

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

145. Based on the teachings of the '865 patent, a POSA would have understood the Modified Fraser/Wulff formulation would also have the requisite stability. The Examples in the specification teach a range of concentrations for the VEGF Trap and excipients, and their associated stability characteristics. Based on

my review of the '865 patent, it teaches that formulations with higher and lower concentrations of aflibercept, with varying concentrations of NaCl, with varying concentrations (and types) of co-solvent, with varying amounts of stability agent, and over the pH range 6-6.3 all have two month stability values well over 98%. *See* Ex.1001, 6-8. The Modified Fraser/Wulff formulation⁷ falls squarely within these ranges.

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

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

146. Furthermore, as shown below, Regeneron's Dix patent provides stability data for even more formulations with different excipients and concentrations. The Dix formulations that contain 50 mg/mL or less aflibercept have two-three month stability values well over 98%, just like the '865 formulations. The only formulations that did not achieve that stability had 75 mg/mL or 100 mg/mL aflibercept. The Modified Fraser/Wulff formulation falls well within the ranges of formulations tested in the '865 patent and Dix that achieve better than 98% stability at two months, which shows that the Modified Fraser/Wulff formulation will have the claimed stability.

	VEG F Trap	Buffer	Tonicity	Co-solvent	Stabilizing agent	pH	Stability
'865 Examples	20-50 mg/mL	5-10 mM phosphate	20-135 mM NaCl	0.015-0.1% polysorbate 20 or 3% PEG 3350	0-5% sucrose	6.25-6.3	98.5-99.3% at 2-3 months
Dix (50 mg/mL or less)	25-50 mg/mL	10 mM phosphate or 5 mM phosphate and 5 mM citrate	50-100 mM NaCl	0.1% polysorbate or 3% PEG 3350	20% sucrose	6.0-6.25	98.8-99.6% at 2-3 months
Dix (75 mg/mL or more)	75-100 mg/mL	10 mM phosphate or 20 mM histidine	0-50 mM NaCl	0.1% polysorbate or 1.5-3% PEG 3350	20% sucrose or 2.5% sucrose and	6.25	95.7-98.6 at 2-3 months

					0.75% glycine		
Modified Fraser/Wulff	40 mg/mL	5 mM phosphate 5 mM citrate	100 mM NaCl	0.1% polysorbate	5% sucrose	6.0- 6.3	

147. In formulation science, it is a fundamental principle that once a product's stability is established using defined ranges, any formulation within those ranges will exhibit the same inherent stability. Because the Modified Fraser/Wulff formulation falls within the described ranges of aflibercept and excipients that the patent teaches have the claimed stability, the Modified Fraser/Wulff formulation has the claimed stability.

148. Establishing a formulation's stability involves testing variations in excipient concentrations, amounts, pH, and other parameters to define an acceptable range around the final formulation. Since testing every possible value or iteration for each excipient is neither practical nor possible, a range of discrete points is tested. This method ensures that stability can be reliably determined despite inevitable measurement variations or fluctuations in concentrations and amounts during commercial manufacturing. It is widely accepted that formulations within these tested ranges will inherently share the stability of the tested formulations. Therefore, I disagree with any argument that variations in certain unclaimed elements, such as pH, NaCl concentrations, or the inclusion of a citrate buffer, between the discrete

examples and the Modified Fraser/Wulff formulation preclude a finding of inherency.

(b) The claimed level of stability is obvious and does not distinguish the claimed formulation from the prior art

149. Further, a POSA would have been motivated to make the Modified Fraser/Wulff formulation as stable as possible and would have regarded achieving the stability recited in the claims as obvious, including through making any additional adjustments to the formulation necessary.

150. A POSA would have been motivated to make an aflibercept formulation that was as stable as possible. The more stable a formulation is, the longer its “shelf life.” A POSA would have understood a longer shelf life to be more desirable because a manufacturer and its customers, including pharmacies, healthcare providers and patients, would end up discarding fewer doses due to product expiration.

151. Moreover, a POSA also would have been motivated to reduce the aggregation (and associated turbidity) of aflibercept in the formulation as much as possible. Aggregates can cause undesirable immunogenicity and can reduce the quality and activity of a biologic product. As a result, POSAs understood and were motivated to reduce aggregates as much as possible, starting with as pure a product as possible and maintaining that purity.

152. Indeed, Wulff and Fraser discuss purifying the formulation. Ex.1016, 2798. In particular, POSAs would have been very familiar with SEC tests that measure the formation of aggregates and other impurities by after storage for two months at 5° C, as these were among the most common in the industry as of 2006. A POSA would have viewed these test conditions as being routine and generally accepted when assessing aggregate formation in the aflibercept formulation.

153. A POSA thus would have understood that preserving at least 98% of the aflibercept in native conformation after storage for two months at 5° C as measured by SEC as being an obvious goal to which they were motivated (and a level of 99% or greater to be even more desirable). A POSA would have done so by formulating the Modified Fraser/Wulff formulation and then engaging in routine SEC stability testing which, as the patent data itself shows, would have demonstrated the formulation met and exceeded the 99% threshold after storage for two months at 5° C.

154. Moreover, even if a lower level of stability was initially achieved, a POSA would have had a reasonable expectation of success in making any minor optimizations to the formulation to achieve the claimed stability levels. POSAs possessed a high degree of skill in stabilizing protein therapeutics. To the extent Patent Owner argues that the inclusion of unclaimed excipients (5 mM citrate or NaCl) would have changed the stability or that the pH of the formulation differs

from those in the patent, a POSA would have been able to make incremental adjustments to the concentrations/pH and observed their impact on stability, adjusting to achieve at least the level shown in the claims.

155. The design and execution of such experiments was routine and well within ordinary skill, and “step-by-step, how-to” protocols to “enable the formulation scientist to proceed through a protein solution formulation development study” were available. Ex.1013, 156, 157 (teaching detailed three-step protocol that sets forth the “natural sequence to the order in which individual [formulation] parameters are investigated” and how to investigate them).

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

157. Thus, to the extent Patent Owner argues the stability properties are not inherent, they would have been obvious.

C. Claim 2

158. Dependent claim 2 is obvious for the same reasons as claim 1. Claim 2 recites the concentration of the formulation (40 mg/mL) and specifies the organic co-solvent comprises polysorbate. As set out above in Section VIII.A, the concentration of the VEGF antagonist fusion protein in the Modified Fraser/Wulff formulation is 40 mg/ml, and the organic co-solvent in that formulation comprises polysorbate. Specifically, a POSA would have been motivated to make the following two modifications to the Fraser/Wulff formulation leading to the recited concentration.

159. ***Reduce the volume to 0.1 mL.*** As described in Fraser, the formulation was stored in 2 mL aliquots. A POSA would have understood that 2 mL was far too large of an injection volume for the human eye, as explained in the declaration of Dr. Chaum. Injecting that volume would have carried significant risks to patients.

160. Instead, 0.1 mL injection volumes were understood at the time to be safe, and indeed were the most commonly used volume. As taught in the art, “intravitreal injection of a small volume (such as 0.01 ml or less) represent[ed] a much more reasonable approach for drug administration” than injections of larger amounts. Ex.1049, 106; *see also* Ex.1048, 932; Ex.1005, ¶¶22-24. Accordingly,

the most common intravitreal injection at the time, for Triamcinolone (Kenalog), used primarily for retinal diseases such as macular edema and wet AMD, was given in a 0.1 mL dose (at a concentration of 40 mg/mL). Ex.1005 ¶¶25, 31; Exs. 1059-1061.

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

162. *Set the concentration at 40 mg/mL.* The 2006 Presentations report a dose escalation study with a maximum dose of 4 mg. *See, e.g.*, Ex.1011, 14; Ex.1012, 19-23, Ex.1013, 21-24. The Presentations teach that the formulation was effective and that the maximum safe tolerated dose had not been reached. Exs. 1011-1013. A POSA would have understood from this disclosure that the 4 mg dose was safe and effective and would have been motivated to use it. Ex.1005, ¶¶47-48.

163. A POSA would have been motivated to select this dose for a second reason. Using a 0.1 mL injection volume and 4 mg dose leads to a concentration of 40 mg/mL. As set out in the declaration of Dr. Chaum, a concentration of 40 mg/mL was a commonly used concentration for intravitreal injections and was generally accepted as the limit for intravitreal injections for ensuring patient safety. A number of approved intravitreal drugs and drugs in clinical trials as of March 2006 used a 40 mg/mL concentration. Ex.1005, ¶¶24-25, 31.

164. A POSA would have particularly been motivated to use the established safe maximum concentration in an intravitreal injection to potentially extend the time between any repeat injections. Ex.1005, ¶26.

D. Claims 3-5

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

E. Claims 6-7

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

F. Claims 8-9

167. Dependent claims 8-9 depend from claim 5 and recite that the buffer comprises a pH between “about 5.8-7” in claim 8 and further specify a pH of “about 6.2-6.3” in claim 9.

168. Wulff discloses that the pH of the unmodified formulation is 6.0, which falls within the range recited in claim 8. Additionally, a POSA would have

understood that the measured pH of 6.0 falls within the narrower “*about* 6.2-6.3” range recited in claim 9.

169. First, the term “about 6.2-6.3” must encompass a broader range than the precise recited values of 6.2-6.3; otherwise, the inclusion of “about” would be superfluous. Specifically, I understand that “about” is generally understood in patent claims to mean “approximately,” reflecting the level of precision achievable in the field and the scientific context at the relevant time. It does not imply a precise, fixed limit. Specifically, a POSA would have recognized that the measurement error for pH meters at the time was typically within +/- 0.1-0.2 pH, meaning “about 6.2” would reasonably include values down to at least 6.0. *See generally*, Ex.1104; Ex.1105; *see also*, Ex.1106, 1845-1846; Ex.1107, 1; Ex.1108, 3. In view of this known variation, a POSA would have understood a reported pH of 6.0, as described in Fraser and Wulff, to represent a range from 5.8 to 6.2, further highlighting the overlap between these ranges.

170. Specifically, the '865 patent examples confirm my opinion that the measured pH may vary by +/- 0.1-0.2 pH units, including over time. Each example specifies the pH of the formulation, and then the pH is measured over time, starting at 0 months and then following storage. In the chart below, the specified pH for each example formulation is shown on the left, and the actual pH variation measured in each Example on the right.

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

171. The difference between the described pH and the measured variations covers a range from 6.1-6.4 for formulations described as having pHs of 6.25-6.3. For instance, Example 2 describes the formulation as having a pH of 6.25, but the measured pH to vary between 6.1 and 6.3. Similarly, Example 3 specifies that the pH is 6.3, but the measured pH varies between 6.2 and 6.4.

172. In view of the above, a POSA would understand that a formulation with a pH of 6.25, right in the middle of the recited range can have a measured pH of between 6.1 and 6.3. Even though a pH of 6.25 rounds up to 6.3, the measured value of that solution can drop as low as 6.1. A solution with a pH of 6.3 can therefore have a measured pH of 6.2-6.4. This fluctuation is consistent with the error of standard pH meters at the time. In view of the fluctuation taught in the patent and

inherent in the measurement tools available at the time, the POSA would have understood a pH of 6.0 to fall within the scope of “about 6.2-6.3.”

173. Further, as discussed above, a POSA would have been motivated, as a matter of routine industry practice, to make and test the Modified Fraser/Wulff formulation at both higher and lower pHs, including the range of 6.1 to 6.3, in order to establish the formulation’s characteristics across a broader range of values. That is because, due to standard measurement error and variations in commercial manufacture, pH will vary in a formulation. As a result, it is standard practice to make and test formulations having a broader range of pHs to ensure stability for commercial manufacture. Thus, it would have been obvious to adjust the pH of the Modified Fraser/Wulff formulation to 6.1, 6.2 or 6.3. A pH of 6.1 is “about 6.2-6.3.”

G. Claims 10-11, 19-20

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

175. As set out above, the POSA would have been motivated to use the Fraser/Wulff formulation as a starting point. *Id.* A POSA would have been motivated to modify that formulation for intravitreal administration, however, by reducing the sucrose (and possibly the NaCl) to achieve an iso-osmotic solution. *Id.*

The POSA would have been motivated to do this order to match the osmolality of the eye and minimize the chance of causing an adverse reaction, including damage to the retina or surrounding tissues. *Id.*

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

H. Claim 12

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

178. As explained above, a POSA would have been motivated to modify the Fraser/Wulff formulation for intravitreal administration by reducing sucrose to achieve an iso-osmotic solution. Section VIII.A. A POSA would have initially reduced the sucrose concentration to below 10% and further lowered the sucrose or NaCl concentration to approximate the osmolarity of the human eye, consistent with the osmolarity ranges of the FDA approved intravitreal formulations. *Id.* Opting to reduce sucrose further (e.g., to 5%) instead of NaCl would have been a matter of routine optimization (*id.*), rendering claim 12 obvious.

I. Claims 14, 22

179. These claims are obvious for the same reasons as claims 1, 5. They specify that the VEGF antagonist fusion protein is glycosylated at asparagine

residues corresponding to asparagine residues 62, 94, 149, 222 and 308 of SEQ ID NO: 4. As noted above, the glycosylation sites of the aflibercept used in the Modified Fraser/Wulff formulation was known in the art and would have been obvious. Section VIII.A, Ex.1007, ¶¶26-36.

J. Claims 15, 23

180. The stability limitations of these claims reciting the turbidity of the formulation are obvious for the same reasons set out in Section VIII.A.

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

182. Based on the teachings of the '865 patent, the Modified Fraser/Wulff formulation will have the requisite turbidity, just as they will have the requisite stability. As explained above and shown in the table below, the Examples in the specification teach a range of concentrations for the VEGF Trap and excipients, and the Modified Fraser/Wulff formulation falls squarely within these ranges.

	VEG F Trap	Buffer	Tonici ty	Co-solvent	Stabili zing agent	pH	Turbidi ty
'865 Examples	20-50 mg/m L	5-10 mM phospha te	20-135 mM NaCl	0.015- 0.1% polysorbat e 20 or 3% PEG 3350	0-5% sucrose	6.25- 6.3	0.0-0.01 at 2-3 months
Modified Fraser/W ulff	40 mg/m L	5 mM phospha te 5 mM citrate	100 mM NaCl	0.1% polysorbat e	5% sucrose	6.0- 6.3	

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

	VEG F Trap	Buffer	Tonicit y	Co- solvent	Stabilizi ng agent	pH	Turbidi ty
'865 Examples	20-50 mg/m L	5-10 mM phospha te	20-135 mM NaCl	0.015- 0.1% polysorba te 20 or 3% PEG 3350	0-5% sucrose	6.25 -6.3	0.0-0.01 at 2-3 months
Dix (50 mg/mL or less)	50- 100 mg/m L	10 mM phospha te	50 mM NaCl	0.1% polysorba te or 3% PEG 3350	20% sucrose	6.25	0-0.01 at 2-3 months

Modified Fraser/Wulff	40 mg/mL	5 mM phosphate 5 mM citrate	100 mM NaCl	0.1% polysorbate	5% sucrose	6.0-6.3	
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184. As with the native conformation stability limitation, the '865 patent does not teach any way of obtaining the claimed turbidity besides making and testing the formulation. And the Modified Fraser/Wulff formulation falls in the genus of Example formulations that achieved the claimed turbidity. Thus, based on the teachings of the '865 patent Modified Fraser/Wulff formulation meets these claims.

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

K. Claims 16, 24

186. The stability limitations of these claims reciting 99% stability at 2 months are obvious for the same reasons set out in Section VIII.B.

L. Claims 17, 25

187. The stability limitations of these claims reciting 98% stability at 24 months are obvious for the same reasons set out in Section VIII.B.

188. Moreover, Dix and the '865 patent show that aflibercept formulations with the same ingredients as the Modified Fraser/Wulff formulation, specifically

those that include polysorbate 20 like the Modified Fraser/Wulff formulation, achieved 98% or more native conformation after 24 months as summarized in the table below. *See, e.g.*, Ex.1021, Tables 1 and 9 (disclosing 98.3 and 99.3 % native conformation at 24 months); Ex.1001, Table 1 (disclosing 98.1 % native conformation at 24 months). The only formulations that did not achieve that stability had polyethylene glycol as the surfactant. *See* Ex.1001, Table 2 (disclosing 97.6% native conformation at 24 months); Ex.1021, Table 2 (disclosing 97.8 % native conformation at 24 months).

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

189. Consistent with my conclusion in Section VIII.B, the Modified Fraser/Wulff formulation has the claimed stability because the Modified Fraser/Wulff formulation falls within the described ranges of aflibercept and excipients that the '865 patent and Dix teach have the claimed stability.

M. Claim 51

1. An ophthalmic formulation comprising

190. The Modified Fraser/Wulff formulation is an ophthalmic formulation for suitable for intravitreal injection as set out in relation to claim 1. *See* Section VIII.A and VIII.B.

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

191. The Modified Fraser/Wulff formulation discloses 40 mg/ml of a glycosylated VEGF antagonist fusion protein comprising amino acids 27-457 of SEQ ID NO:4 as set out in relation to claim 1. *See* Section VIII.A and VIII.B.

3. (b) 0.03% to 0.1% polysorbate

192. The Modified Fraser/Wulff formulation discloses 0.03% to 0.1% polysorbate as set out in relation to claim 1. *See* Section VIII.A and VIII.B.

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

193. The Modified Fraser/Wulff formulation discloses 5-40 mM of sodium phosphate buffer, pH between 5.8-7.0 as set out in relation to claims 1 and 6-9. *See* Section VIII.A. A POSA would have understood Fraser/Wulff's disclosure of a phosphate buffer to include sodium phosphate. *Id.* A POSA would have understood that sodium phosphate buffers were a commonly used type of phosphate buffer at the time. *Id.*

5. (d) sucrose

194. The Modified Fraser/Wulff formulation discloses sucrose, as set out in relation to claim 1. *See* Section VIII.A and VIII.B.

6. wherein the ophthalmic formulation is suitable for intravitreal administration

195. The Modified Fraser/Wulff formulation is an ophthalmic formulation for suitable for intravitreal injection as set out in relation to claim 1. *See* Section VIII.A and VIII.B. Finally, a POSA would have understood the modified Fraser/Wulff formulation was suitable for intravitreal administration. The 2006 Presentations teach that 4 mg aflibercept could be safely injected. *See, e.g.*, Ex.1011, 14; Ex.1012, 19-23, Ex.1013, 21-24; Ex.1005, ¶¶47-48. Further, the excipients in the formulation were commonly used in intravitreal injections. *Id.*

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

196. The Modified Fraser/Wulff formulation discloses this limitation for the same reasons set forth in relation to claim 1. *See* Section VIII.A and VIII.B.

N. Claim 52

197. The Modified Fraser/Wulff formulation comprises at least 5% sucrose as set forth in relation to claim 1. *See* Section VIII.A and VIII.B.

O. Claim 53

198. The Modified Fraser/Wulff formulation comprises 1-10% sucrose as set forth in relation to claim 1. *See* Section VIII.A and VIII.B.

P. Claim 55

199. The Modified Fraser/Wulff formulation comprises a vial suitable for intravitreal administration comprising the formulation of claim 51 for the reasons set forth in relation to claims 1 and 55. *See* Section VIII.A and VIII.B.

Q. There Are No Secondary Considerations

200. Finally, I have considered factors such as long felt need, failure of others, and commercial success. I am not aware of any evidence of secondary considerations at this time.

IX. DETAILED GROUNDS FOR INVALIDITY: GROUND 2

201. I understand that only difference between the Ground 2 Challenged Claims and those of Ground 1 is that Ground 2 Challenged Claims recite storing the formulation in a PFS, rather than a vial. POSAs at the time understood that PFSs offered convenience for purposes of administration, including intravitreal administration, because they eliminated the step of withdrawing liquid from the vial and into a syringe. *Nayar*, titled “High Throughput Formulation: Strategies for Rapid Development of Stable Protein Products, was published in *Rational Design of Stable Protein Formulations* 177, 183 (J.F. Carpenter & M.C. Manning eds., 2002) (“*Nayar 2002*”), and explains that each dosage form “offers various advantages and

disadvantages, in the speed of development, manufacturing, packaging and shipment logistics, and in administration of the product to the patient.” *Id.* It further explains that the “most preferred” dosage form for a therapeutic protein product was “a solution formulation that is typically stored in the refrigerator and preferably in a pre-filled syringe.” Ex.1020, 183. Patent Owner has previously taken the position that a PFS was the preferred presentation as of 2006. Ex.1109, 51-52.

202. Accordingly, the Ground II claims are obvious for the same reasons set forth above in relation to claim 1. *See* Section VIII.A and VIII.B.

A. Claim 26

203. Claim 26 is identical to claim 1, except that claim 26 recites storing the formulation in a PFS rather than a vial. As discussed in Section III.B.4, POSAs at the time understood that PFSs offered convenience for purposes of administration, including intravitreal administration, because they eliminate the step of withdrawing liquid from the vial and into a syringe. In fact, Nayar explained that the “most preferred” dosage form for a therapeutic protein product was “a solution formulation that is typically stored in the refrigerator and preferably in a *pre-filled syringe*.” Ex.1020, 183; Ex.1005, ¶41. Patent Owner also agreed that a PFS was the preferred presentation at the time of the patent. Ex.1109, 51-52. A POSA would have thus found obvious and been motivated to store the claimed formulation in a PFS.

204. All other limitations of claim 26 are rendered obvious for the same reasons as set forth in Section VIII with respect the Vial Claims. Therefore, claim 26 is rendered obvious.

B. Claim 27

205. Dependent claim 27 is obvious for the same reasons as claims 1 and 26. Claim 27 recites the concentration of the formulation (40 mg/mL) and specifies the organic co-solvent comprises polysorbate. As set out above in Section VIII.A, the concentration of the VEGF antagonist fusion protein in the Modified Fraser/Wulff formulation is 40 mg/ml, and the organic co-solvent in that formulation comprises polysorbate.

C. Claims 28-30

206. Dependent claims 28-30 are obvious for the same reasons as claims 1-2 and 27. *See* Section VIII.A and VIII.B. These claims recite the organic co-solvent is polysorbate in various ranges from 0.01% to 3%. The Fraser/Wulff formulation contains an organic co-solvent in the form of Tween 20 (polysorbate), present at 0.1% wt/vol, rendering claims 3-5 obvious. Ex.1009, 1115; Ex.1016, 2798.

D. Claims 31-32

207. Dependent claims 31-32 are obvious for the same reasons as claims 1, 5-7, and 30. *See* Section VIII.A and VIII.B. These claims recite that the buffer is a phosphate buffer and specify that the buffer comprises 5-25 mM buffer. The

Fraser/Wulff formulation contains a 5 mM phosphate buffer, rendering claims 6-7 obvious. Section VIII.A; Ex.1009, 1115; Ex.1016, 2798.

E. Claims 33-34

208. Dependent claims 33-34 depend from claim 30 and recite that the buffer comprises a pH between “about 5.8-7” in claim 33 and further specify a pH of “about 6.2-6.3” in claim 34. As set out in Section VIII.F above, in view of the variation taught in the patent and inherent in the measurement tools available at the time, the POSA would have understood a pH of 6.0 in the Fraser/Wulff formulation to fall within the scope of “about 6.2-6.3.” Alternatively, it would have been obvious to modify the pH of the Fraser/Wulff formulation to obtain a pH of 6.2-6.3 as part of routine formulation optimization. Claims 33-34 are therefore rendered obvious for the same reasons set forth in Section VIII.F with respect to claims 8-9.

F. Claims 35-36, 44-45

209. These claims are obvious for the same reasons as claims 1, 5 10-11, 19-20, and 30. These claims recite that the stabilizing agent is a sugar, including sucrose (and not containing trehalose), and further specify sucrose in the range of 1-10% sucrose. The Modified Fraser/Wulff formulation contains sucrose at a concentration of less than 10% rendering these claims obvious. Section VIII.A; Ex.1009, 1115; Ex.1016, 2798.

G. Claims 39, 47

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

H. Claims 40, 48

211. The stability limitations of these claims reciting the turbidity of the formulation are obvious for the same reasons set out in Sections VIII.A and VIII.J.

I. Claims 41, 49

212. The stability limitations of these claims reciting 99% stability at 2 months are obvious for the same reasons set out in Section VIII.B.

J. Claims 42, 50

213. The stability limitations of these claims reciting 98% stability at 24 months are obvious for the same reasons set out in Section VIII.B.

K. Claim 54

214. Claim 54 is obvious for the same reasons as claims 51 and 26. Claim 54 depends from claim 26 and recites a pre-filled syringe suitable for intravitreal administration comprising the formulation of claim 51. As set out above in relation

to claim 26, use of a PFS container would have been obvious with the Modified Fraser/Wulff formulation, which discloses the formulation of claim 51. Section V.A.

L. There Are No Secondary Considerations

215. For the same reason recited in relation to Ground I, there are no secondary considerations supporting non-obviousness.

X. CONCLUSION

216. This declaration, along with the attached appendices, is based on my present assessment of material and information currently available to me.

217. I hereby declare that all statements made herein of my own knowledge are true and that all statements made herein on information and belief are believed to be true. Further, these statements were made with the knowledge that willful false statements and the like so made are punishable by fine, imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the above-identified patent.

20 November 2024

Date


Alpaslan Yaman, Ph.D