

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CELLTRION, INC.,
Petitioner,

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner.

Case No. IPR2023-00462
Patent No. 10,464,992

**DECLARATION OF DR. RALPH TARANTINO IN SUPPORT OF
PETITION FOR *INTER PARTES* REVIEW OF
U.S. PATENT NO. 10,464,992**

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I. INTRODUCTION

1. I have been retained by counsel for Celltrion, Inc. (“Celltrion”) as a technical expert in connection with the above-identified proceeding. I have been asked to provide my opinions concerning the “novelty” and “obviousness” of the claims of U.S. Patent No. 10,464,992 (“the ’992 Patent”) (EX1001), which concern formulations of the protein aflibercept, in light of prior publications concerning such formulations. I understand my declaration will be submitted in support of Celltrion’s Petition for *Inter Partes* Review of the ’992 Patent against Regeneron Pharmaceuticals, Inc. (“Patent Owner” or “Regeneron”).

2. My opinions are based on my review of the ’992 patent (EX1001), its prosecution history (EX1004), the relevant prior art that I have identified and that I have been informed of, the other documents referred to in this declaration, and my decades of experience in industry with the formulation and packaging of biologics and drug products during the time period relevant to the questions I’ve been asked to consider.

3. I am being compensated for my time at my usual consulting rate of \$475 per hour. I am also being reimbursed for reasonable travel expenses related to my consultation. I do not have a personal or financial interest in the outcome of this proceeding nor is my compensation affected by its outcome.

II. BACKGROUND AND QUALIFICATIONS

4. I am currently the Principal and founder of Steritech Solutions, LLC. Steritech provides consulting services directly to the pharmaceutical industry and other business involved in pharmaceuticals. My work at Steritech has focused on injectable biologics and drug products, in particular peptide and protein formulation and processing, quality assurance, manufacturing, drug delivery via devices, and primary packaging issues.

5. I have an undergraduate degree in Pharmacy from Long Island University and a Ph.D. in Pharmaceutical Sciences from St. John's University. I am a registered pharmacist in the State of New York.

6. I joined Hoffman-La Roche, Inc. in Nutley, New Jersey after receiving my doctorate in 1989. I worked at Hoffman-La Roche until 2011, when I founded Steritech Solutions, LLC.

7. I have worked in the field of protein formulation development throughout my career at Roche, where I was the head of sterile clinical manufacturing for 17 years. My duties included peptide/protein pre-formulation, formulation development, and the manufacture and packaging of toxicology and clinical supplies for injectable products. I managed two Good Manufacturing Practice ("GMP") sterile suites and one Good Laboratory Practice ("GLP") sterile suite, which developed and guided the manufacture of formulations for Small

Volume Parenterals (“SVPs”), Large Volume Parenterals (“LVPs”), small organic molecules and polypeptides (“parenteral” is synonymous with “injectable”). I directed the formulation, manufacture and packaging of clinical parenterals within Roche and related activities by Roche’s outside contractors. I have personally performed and directed a wide variety of analytical tests to determine the stability, potency and purity of Roche parenteral products, including size-exclusion chromatography.

8. In 1995, I became Director of Clinical Manufacturing. In this capacity, I led the clinical manufacturing and packaging group for all Roche U.S. clinical supplies, sterile and oral dosage forms, including injectable proteins. In addition to leading the Preformulation Group, I also evaluated drug delivery systems and devices for investigational and marketed products. The Preformulation function performs physical and chemical characterization of drug substances intended for use in drug products.

9. The Peptide/Protein Preformulation Group conducted analyses such as HPLC, reverse-phase HPLC, size-exclusion chromatography, ion exchange chromatography, hydrophobic interaction chromatography, circular dichroism, laser light scattering analysis, and gel electrophoresis to characterize new peptide/protein products. The use of these chromatography techniques as well as ultrafiltration and diafiltration were employed to concentrate and/or purify

peptide/protein as needed for further development and in support of active pharmaceutical ingredient (“API”) processing and testing.

10. In 2000, I was appointed Co-Chair of the Roche Parenteral Technology International Working Group, which set global technical and scientific standards and policies for the development and manufacture of all Roche pharmaceutical sterile products, including injectable proteins. I was also appointed Research Director of Sterile Product Formulation & Clinical Manufacturing, where I led a group responsible for sterile formulations and packaging, including injectable protein products.

11. During this period, I led the formulation development of at least four new peptide/protein products, PEGASYS®, MIRCERA®, ZENAPAX®, and FUZEON®, and the development of multiple-line extensions and drug delivery systems for peptides and proteins. My formulation experience ranged from synthetic peptides to monoclonal antibodies, including fusion proteins such as TNFR-Ig fusion proteins. I was also appointed as an FDA trainer for “Protein Formulation and Stability,” an assignment involving the training of FDA inspectors on formulation and stability issues encountered during the development of therapeutic peptides and proteins.

12. In 2009, I became Research Director and Global Head of the Sterile Product Formulation Group. In that role, in addition to continuing the duties of my

previous position, I managed international technology transfer, harmonization processes, and clinical manufacturing outsourcing for sterile clinical products.

13. At Roche, I led the development of nine marketed parenteral drug products, including ready-to-use injectable products for infusion and lyophilizate products that required reconstitution prior to infusion. I worked on over 100 parenteral drug products that entered clinical trials and numerous preclinical parenteral drug formulations.

14. Early in my career, for about ten years, I personally performed and supervised the analytical testing of active pharmaceutical ingredients and dosage forms. I spent a significant portion of that time in the lab performing analytical tests on pharmaceutical formulations. Those analytical tests included size-exclusion chromatography, including state-of-the-art versions of that test method such as SE-HPLC. My responsibilities included reviewing and approving analytical methods.

15. I was also a “CMC” leader at Roche. “CMC” refers to the technical or Chemistry, Manufacturing and Control sections of New Drug Applications (“NDAs”) and Investigational New Drug applications (“INDs”), which are applications to the U.S. Food & Drug Administration (“FDA”) to test experimental drug and biologic products in humans. A CMC Leader leads a multidisciplinary team generating the data needed for an NDA or IND. The team includes

formulation, analytical chemistry, manufacturing, packaging, and quality control scientists. The CMC Leader ensures the data's scientific validity and interacts with regulatory agencies. In that role, I reviewed the entire technical submission—including several submissions related to parenteral formulations—for Biologics License Applications (“BLAs”), NDAs and INDs.

16. I am a member of the American Association of Pharmaceutical Scientists, the Parenteral Drug Association and the American Pharmacists Association. From 1990-1995, I was appointed Clinical Assistant Professor of Pharmaceutics at the Long Island University for my supervision of Pharmacy student research projects. From 1995-1996, I served as elected Chair of Basic Pharmaceutical Sciences at the American Pharmaceutical Association. I have authored or co-authored 27 published, peer-reviewed articles, abstracts, and presentations, most of which were related to parenteral dosage forms. I am also the named inventor on patents relating to parenteral dosage forms.

17. My curriculum vitae accompanies this declaration as EX1003.

III. LEGAL STANDARDS

18. I am not a lawyer. I have been informed by Celltrion's counsel of a number of legal principles to keep in mind when formulating my opinions as they relate to the patentability of the claims of the '992 patent. These are set forth below.

A. Claim Construction

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

20. I further understand that claims can be “independent” or “dependent.” An independent claim does not refer to or incorporate the elements of any other claim. A dependent claim refers to another claim and includes all of its limitations while also adding additional limitation(s). The ’992 patent contains two independent claims: claims 1 and 10. The remaining claims are dependent on these two claims.

21. In my review, I did not find that the named inventors in this case provided their own definition of any of the claim terms in the disclosure of the ’992 patent. Accordingly, I interpreted the claim terms consistent with their ordinary and customary meaning to a POSA. For clarity, I set forth below the ordinary and customary meaning of three terms relevant to my analysis.

22. I understand the term “native” in the phrase “native conformation” in claims 1, 2, 10 and 11 to refer to the fully-intact and functional conformation of the VEGF-antagonist protein referred to in the claims.¹

23. I understand the term “vial” in claims 1-9 to refer to a small closed or closable vessel, especially for liquids. *See EX1031 (Merriam Webster Vial Definition).*

24. I understand the term “multimerizing component” in claims 1 and 10 to refer to a protein moiety that joins two or more protein domains together to form a multimer, such as a dimer or trimer.

¹ As I explain later in this declaration, while the patent claims refer to the percentage of protein in “native conformation following storage at 5 °C for two months *as measured by size exclusion chromatography*,” in my view this usage presents a minor technical inconsistency. In size-exclusion chromatography (“SEC”), a protein in native conformation may co-elute with other substances, including degraded versions of that protein, that have a similar size, molecular weight or shape as the natively-conformed protein and thus migrate with it on the size-exclusion column being used.

B. Prior Art and Earliest Effective Filing Date

25. I have been asked to assume that the earliest possible filing date for the '992 patent is June 16, 2006, which I will sometimes refer to as the “priority date,” and that any printed publication published prior to that date should be considered “prior art” to the patent.

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

C. Anticipation

27. I understand that for a claimed invention to be patentable, it must be new, or “novel” over the prior art.

28. I understand that a patent claim is “anticipated” if a single prior art reference discloses every element of the claim to a POSA.

29. I understand that even if the prior art reference does not expressly disclose a particular claim element, the reference may still anticipate that element if it is “inherent” in the disclosure. A claim element is inherent if it is necessarily present in, or is the natural result of, subject matter disclosed in the reference. I understand that whether a claimed feature is necessarily present in, or is the natural result of, the prior art may not be established by probabilities or possibilities. I also understand that if a claim describes a functional result, it is considered

inherently disclosed in the prior art if the patent teaches that the only steps required to achieve the claimed result are the same as those disclosed in the prior art. In other words, when the patent does not itself disclose any more than what is in the prior art regarding how to achieve a claimed functional result, then the functional result is considered to be inherently disclosed by the prior art.

30. I also understand that while anticipation must be based on a single prior-art reference, additional references may be used to explain how a POSA would understand the anticipating reference or terms used within it, or to establish that a claimed feature is inherent. In particular, I understand that references published after the June 16, 2006 priority date may be used as evidence of the inherent properties of the subject matter referred to in an anticipating prior-art reference.

31. I understand that a prior-art publication must be “enabling” in order to anticipate a patent claim. Prior art is enabling if it describes the claimed invention sufficiently to allow a POSA to carry out the invention using nothing more than routine skill.

D. Obviousness

32. I have been informed by counsel that, for a patent claim to be patentable, it must be “non-obvious” over the prior art.

33. I understand that a patent claim is obvious if the differences between the claims and the prior art are such that the subject matter as a whole would have been obvious to a POSA at the time the invention was made. For purposes of my analysis, I have been asked to assume a date of invention of June 16, 2006.

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

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

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

37. I understand that “secondary” evidence may weigh against a finding that a claimed invention would have been obvious. Such secondary evidence may include: (i) commercial success of a product due to the merits of the features of the

product that are the subject of the patent claims; (ii) a long-felt but unsolved need for the solution provided by the patent claim; (iii) unsuccessful attempts by others to find the solution provided.

E. Burden of Proof

38. I understand that in an IPR, a claim is not patentable if a “preponderance of the evidence” establishes that the claim is anticipated by, or obvious from, the prior art. I understand “a preponderance of the evidence” means “more likely than not.”

F. The POSA

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

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

41. Here, the '992 patent concerns stable formulations of aflibercept and other VEGF inhibitor proteins. Based on my extensive experience as a protein

formulator and consultant in the biopharmaceutical industry, including first-hand knowledge of how protein formulation was carried out in 2006, 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 of various pH values, 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 SEC, to assess stability and compatibility.

42. This 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.

43. My opinions would not change even if a different definition of POSA is adopted.

IV. THE '992 PATENT

44. The '992 patent is entitled "VEGF Antagonist Formulations Suitable for Intravitreal Administration." The '992 patent, based on the information on the face of the patent, is assigned to Regeneron Pharmaceuticals, Inc.

45. I have reviewed the claims, specification, and prosecution history of the '992 patent. The patent describes the invention as "[s]table formulations of a VEGF-specific protein antagonist" comprising a "VEGF 'trap' antagonist with a pharmaceutically acceptable carrier." EX1001 ('992 Patent), 1:66-2:2. The patent explains that "VEGF antagonist" includes any "fusion proteins capable of trapping VEGF." *Id.*, 6:9-12. The term "pharmaceutically acceptable carrier" is defined as comprising "one or more organic co-solvent(s) ... a buffering agent ... and optionally...a stabilizing agent," but is not limited to any specific kind(s) of these ingredients. *Id.*, 2:19-24. According to the patent, a POSA can use this combination of ingredient types to prepare stable lyophilized and liquid formulations of VEGF antagonist using only routine skill and knowledge. *Id.*, 3:44-46, 6:22-24 (the "VEGF antagonist of the methods and formulations of the invention can be prepared by any suitable methods known in the art.").

46. The '992 patent includes eight examples, each of which contain the same combination 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, polysorbate 20 and sucrose at a pH of 6.3. *Id.*, 8:8-12:27. One of the examples contains polyethylene glycol 3350 instead of polysorbate 20. *Id.*, 8:36-61. The concentrations of protein, buffer, sodium chloride and polysorbate 20 vary somewhat in several of the examples, but only within relatively narrow ranges. *Id.*, 8:8-12:27, Examples 1-8.

47. Claims 1 and 10 of the '992 patent refer to formulations containing any amount of VEGF antagonist produced in a CHO cell, with any amount of three additional ingredients: “an organic co-solvent, a buffer, and a stabilizing agent”. The claims also require that “at least 98% of the VEGF antagonist is present in native conformation following storage at 5° C for two months as measured by size exclusion chromatography.” But the '992 patent specification does not state that the claimed 98-99% storage stability is critical to the invention or explain how to achieve it for any formulation other than the handful in the examples.

48. While the patent notes that the VEGF antagonist “is preferably substantially free of protein contaminants *at the time it is used to prepare the pharmaceutical formulation,*” a POSA reading the specification would understand that it does not describe any critical level of natively-conformed protein that the formulation must achieve over time during storage. *Id.*, 6:24-27 (emphasis added). The patent simply explains that “substantially free of protein contaminants” means

that preferably at least 90%, and most preferably at least 99%, “of the weight of protein of the of the VEGF-specific fusion protein antagonist *used for making a formulation* is VEGF fusion protein antagonist protein.” *Id.*, 6:26-32 (emphasis added). Similarly, while the patent explains that “[t]he fusion protein is substantially free of aggregates,” *id.*, 6:32-33, it further explains that “‘substantially free of aggregates’ means that at least 90% of the weight of fusion protein is not present in an aggregate *at the time the fusion protein is used to prepare the pharmaceutically effective formulation.*” *Id.*, 6:33-37 (emphasis added). A POSA would understand that these values pertain to the percentage of protein in “native conformation” *before* storage, and that the patent does not describe any critical percentage of protein in native conformation that must be achieved over time during storage.

49. I understand from reviewing portions of the prosecution history of the patent that the “at least 98%” stability limitation was added to the claims to overcome double-patenting rejections over Regeneron’s earlier patents on VEGF-antagonist formulations, which claimed formulations with similar ingredients. EX1004 (‘992 *Prosecution History*), 90-92, 93-34 (2019-07-22 Response to Office Action).

50. Dependent claims 2-9 and 11-18 further limit the percentage of protein in native confirmation left after storage at 5° C for two months, with the narrowest percentage being 99% in claims 2 and 11.

51. Dependent claims 3-5 and 12-14 further define the structure of the VEGF antagonist, including describing the antagonist in claims 4 and 13 as a fusion protein comprising amino acids 27-457 of SEQ ID NO:4, which a POSA would understand to be aflibercept.

52. A POSA reading the '992 patent would understand that it covers a broad recipe for formulating stable compositions of aflibercept and other VEGF-antagonists, using well-known and commonly used excipients including co-solvents, buffers, and stabilizers.

53. As I explain in more detail throughout this declaration, a POSA at the time of the invention would have been aware of Regeneron's existing formulation of aflibercept that used these well-known excipients, as well as highly-stable formulations of other complex proteins such as antibodies that used these same excipients. The POSA would have been able to create a highly-stable formulation of aflibercept by simply copying the Regeneron formulation and using nothing more than routine skill.

V. SCIENTIFIC BACKGROUND

A. VEGF Antagonists

54. Vascular endothelial growth factor or “VEGF” is a naturally-occurring protein in the body that helps to regulate “angiogenesis,” which is the process by which the body forms new blood vessels within tissues and organs. Blood vessels are required for tissues within the body to grow and thrive.

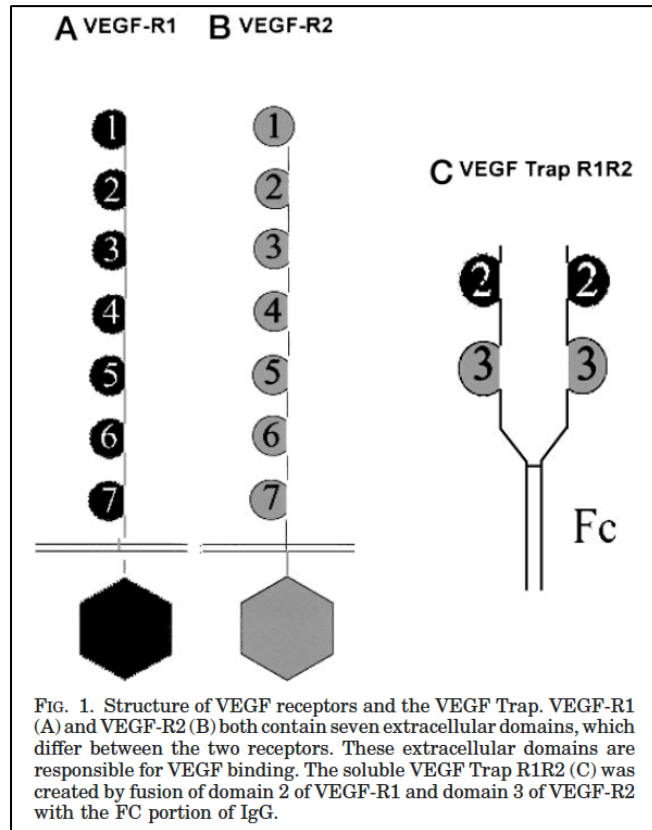
55. VEGF triggers angiogenesis by binding to VEGF receptors on the surfaces of cells involved in angiogenesis. As of 2006, two of the best-characterized VEGF receptors were VEGF receptor 1 (VEGFR1) also known as Flt1, and VEGF receptor 2 (VEGFR2) also known as Flk1. EX1015 (*Rudge*), 412. VEGFR1 and VEGFR2 both have seven extracellular domains, responsible for VEGF binding. EX1016 (*Wulff*), 2798. Upon binding to VEGF via its extracellular portion, the VEGF receptors form dimers. EX1015 (*Rudge*), 412.

56. By 2005, VEGF had also been identified as having a role in angiogenesis within tumors, with studies showing an upregulation of VEGF in various tumor types. EX1008, (*Ferrara 2005*), 968. Since angiogenesis is necessary for tumors to grow, anti-angiogenic VEGF inhibitors were identified as potential cancer therapies. Several had been developed and proven to be effective in clinical testing. *Id.*, 971. One of the first of these was bevacizumab, a humanized monoclonal antibody approved for the treatment of metastatic colon

cancer in combination with 5-fluoruracil. *Id.*, 967, 971. Another was ranibizumab, a modified fragment of the bevacizumab antibody. Ranibizumab had already been used to treat wet age-related macular degeneration (wet AMD), which is caused in part by the inappropriate proliferation of blood vessels in the retina of the eye, via monthly intraocular injections. EX1015 (*Rudge*), 411.

B. Aflibercept

57. Aflibercept is a VEGF inhibitor developed by Regeneron. It is also known to scientists by the names VEGFTrap_{R1R2} and VEGF Trap. Aflibercept is a dimeric fusion protein, consisting of the Ig domain 2 of human VEGFR1 and the Ig domain 3 of human VEGFR2 combined with a human IgG Fc fragment. The structure of aflibercept is depicted below, taken from Figure 1 of EX1016 (*Wulff*), 2798:



58. Aflibercept works by binding to VEGF and therefore “trapping it” before it can bind to VEGF receptors on the cell surface and exert its signal to up-regulate angiogenesis. Other VEGF antagonists, like bevacizumab and ranibizumab, work in a similar way.

59. Regeneron described its development of aflibercept in publications as early as 2002, along with *in vivo* experiments that showed its therapeutic promise over other approved and experimental VEGF antagonists. One such reference was *Holash*, in which Regeneron explained that aflibercept demonstrates “prolonged *in vivo* pharmacokinetics and pharmacodynamics, lacks nonspecific toxicities, and

can effectively suppress the growth and vascularization of a number of different types of tumors *in vivo*.” EX1010 (*Holash*), 11393.

60. In *Holash*, Regeneron also described early experiments it had conducted with an early, less-successful “parental VEGF-trap” fusion protein, where the first three extracellular domains of the human VEGFR1 receptor were fused to the Fc region of human IgG1. EX1010 (*Holash*), 11393. That VEGF-trap protein had poor pharmacokinetics, which Regeneron explained was due in part to the fact that certain of the extracellular domains of VEGFR1 were positively charged, which can lead to non-specific binding to negatively-charged components of the extracellular matrix at the site of injection, preventing the parental VEGF trap protein from reaching the bloodstream. *Id.*, 11394-95 & Fig. 1.

61. As a result of these problems, Regeneron swapped or removed the positively-charged extracellular domains to create less-positively-charged variants, which significantly improved pharmacokinetic performance. *Id.* The resulting variant, VEGF-Trap_{R1R2} (aflibercept), was found to have the best combination of anti-VEGF activity and *in vivo* pharmacokinetics, and showed favorable performance over other VEGF antagonists such as monoclonal antibodies.

62. As Regeneron explained in *Holash*, “[t]he combination of high-affinity and improved pharmacokinetics apparently contributes toward making VEGF-Trap_{R1R2} one of the most, if not the most, potent and efficacious VEGF

blocker available.” *Id.*, 11397. The authors concluded that “although the parental VEGF-Trap and its VEGF-Trap_{R1R2} derivative are quite comparable *in vitro*, the VEGF-Trap_{R1R2} performs much better *in vivo*, presumably because of its dramatically enhanced pharmacokinetic profile.” *Id.*, 11396. According to Regeneron, in comparison to existing antibody VEGF antagonists, “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.” *Id.*, 11396-97. Aflibercept had the additional advantage of being composed of “entirely human sequences”, which would “hopefully minimize the possibility that it might prove immunogenic in human patients.” *Id.* Because of these advantageous properties, Regeneron noted that “the VEGF-Trap [aflibercept] is currently in human clinical trials for several different types of cancer.” *Id.*

63. In 2005 and 2006, Regeneron had also published positive data from preclinical animal models, as well as initial positive data from human clinical trials. EX1015 (*Rudge*), 414-15 (referencing and citing publications by “Dupont et al. 2005; Mulay et al. 2006;” and “Rixe et al. 2006”). In Regeneron’s own words, these initial clinical trial results in human patients were “quite promising” and they noted that VEGFTrap_{R1R2} was “now entering more advanced clinical trials in vascular eye diseases.” *Id.*

64. The sequence of VEGFTrap_{R1R2}—aflibercept—was also widely published by Regeneron prior to the priority date of the '992 patent. In these publications, Regeneron sometimes referred to aflibercept by its earlier scientific names. But as Regeneron represented to the Patent Office during a request for patent term extension of its patent 7,374,758 (“the ’758 *Patent*”) based on regulatory approval of its product EYLEA®, the names aflibercept, VEGF trap, VEGF-trap, VEGF Trap-Eye and VEGF-TRAP_{R1R2}, all referred to the same sequence it previously published as VEGFR1R2-FcΔC1(a). *See* EX1020 (’758 *Patent PTE*), 2 (“The name of the active ingredient of EYLEA™ is aflibercept, also known as VEGF trap, VEGF-trap, VEGF Trap-Eye and VEGF-TRAP_{R1R2} ...[,] a fusion protein consisting of (a) a vascular endothelial growth factor (VEGF) receptor component having immunoglobulin-like (Ig) domains consisting of an Ig domain 2 of a first VEGF receptor that is human Flt1 and an Ig domain 3 of a second VEGF receptor that is human Flk1; and (b) an Fc portion of human IgG1.”). Regeneron also represented to the Patent Office that “aflibercept is described in [*Holash*] as VEGF-Trap_{R1R2}”, *Id.*, 5, and that the amino acid sequence of aflibercept is set forth in Figures 24A-24C of the ’758 *patent*. *Id.*, 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”).

65. Regeneron had published the nucleotide and amino acid sequences of VEGFR1R2-Fc Δ C1(a) as early as 2004, in at least three earlier patent publications. See EX1027 ('309 Publication), ¶5 and SEQ ID Nos. 1 and 2 (disclosing that VEGFR1R2-Fc Δ C1(a) is “also termed VEGF-Trap_{R1R2}”); EX1029 ('319 Publication), 12, 15 and Fig. 24A-24C; EX1028 ('061 Publication), ¶8 and SEQ ID Nos. 3 and 4. The '758 Patent, first published on November 3, 2005, also describes the protein with the amino acid sequence in Figs. 24A-24C, *i.e.*, aflibercept, as “VEGFR1R2-Fc Δ C1(a).” EX1019 ('758 Patent), 10:15-17.

66. In a number of prior-art publications, Regeneron also disclosed that its aflibercept was expressed in a CHO cell host vector system. For example, in EX1029 ('319 Publication), Regeneron disclosed that preferred compositions include those where the VEGF receptor is VEGFR1R2-Fc Δ C1(a), *id.*, 15 and Fig. 24A-24C, and a CHO cell host vector system is used, *id.* 12; *see also* EX1027 ('309 Publication), ¶22 (pointing the skilled artisan to the '319 Publication for “a complete description of VEGF-receptor based antagonists including VEGFR1R2-Fc Δ C1(a)” and incorporating the '319 Publication into the '309 Publication “by reference in its entirety.”).

67. Regeneron also confirmed in the *Wulff* reference that it produced VEGF-Trap_{R1R2} by expressing it in CHO cells. EX1016 (*Wulff*) at 2798 and n.1 (explaining that “[t]he VEGF Trap R1R2 used in these experiments ... was

expressed in CHO cells” and pointing the reader to the ‘319 *Publication* for a description of “the detailed molecular structure” of VEGF-Trap_{R1R2} and how it was created.”). Similarly, the *Holash* reference, which describes Regeneron’s creation and testing of VEGF-Trap_{R1R2} and related variants, explains that “[a]ll of the VEGF-Trap variants were produced and purified from Chinese hamster ovary cells.” EX1010 (*Holash*), 11394.

C. Protein Stability

68. As of the priority date, it was well known that proteins were subject to several degradation pathways and mechanisms, which can be grouped into either physical or chemical instability. *See, e.g.,* EX1005 (*Andya 2003*), 1.

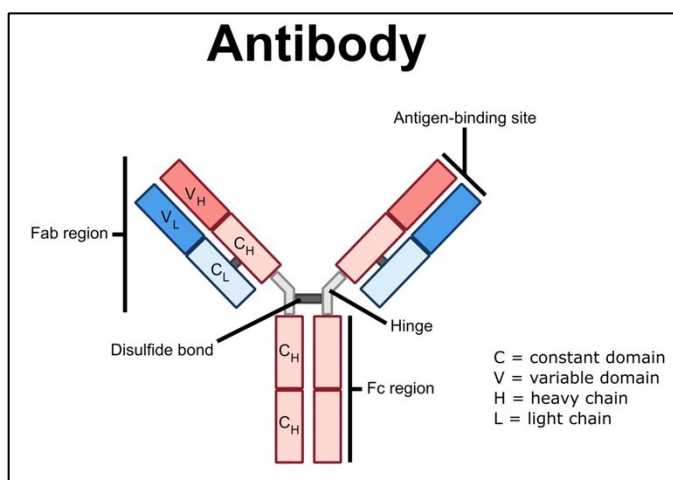
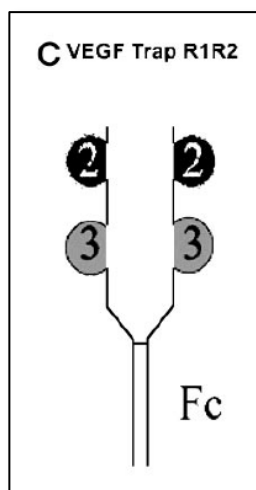
69. Chemical instability refers to processes that break or form chemical bonds within the molecule. Examples of this type of instability include deamidation and oxidation. Physical instability refers to processes that cause changes in the protein conformation, including aggregation or denaturation. The table below, reproduced from EX1006 (*Chang 2002*), provides a brief overview of some of the instabilities that may arise during development of a complex protein like aflibercept.

Table 6. Typical stability problems observed in protein pharmaceuticals.

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

70. I note that while some of the references I cite refer to proteins and others to antibodies, aflibercept and antibodies are both proteins. Moreover, aflibercept and antibodies have similar structures in that both are large, complex, multi-domain, recombinant proteins that are produced for therapeutic use in cell culture (usually CHO cells). Further, both are “Y” shaped and have two arms which specifically bind to a target ligand and that are linked together at their bases by an Fc immunoglobulin domain:²

² Antibody diagram obtained from <https://step1.medbullets.com/immunology/105060/antibodies>.



71. *Chang 2002* also provides a table, reproduced below, showing important components of protein formulations and their typical uses:

Table 7. Important components of protein formulations

Formulation Variables	Desired attributes	Examples
pH	Provides good physical properties of protein, minimize degradations	
Stabilizer	Inhibit degradations, effective at low concentrations	Surfactants, sugars, salts, antioxidants
Solubilizer	Improve the solubility, effective at low concentrations	Salts, amino acids, surfactants
Buffer	Good buffering capacity, stable to temperature change, stable to freezing, good safety record	Phosphate, acetate, histidine, glutamate
Tonicity modifier; bulking agent	Inert, good safety record	Sodium chloride, sorbitol, mannitol, glycine

72. In particular, protein aggregation was known to be an issue when developing formulations of antibodies which, as explained, are structurally similar to aflibercept. EX1005 (*Andya 2003*), 1. In general, protein aggregation leads to a

decrease in protein activity and may increase immunogenic reactions. EX1014 (*Parkins*), 131. When formulating protein therapeutics, inhibiting aggregation is always a chief goal since aggregates can cause increased immunogenicity, alter the serum half-life of the protein, and interfere with its function, *e.g.*, cause it to bind less well to its intended target at the site of disease. Accordingly, part of a formulator's job is to increase the stability of a formulation, including by minimizing aggregation, in order to achieve a safe and efficacious product that is stable under storage conditions.

73. As can be seen in Table 6 from *Chang 2002* reproduced above, one well-known way to reduce aggregation was through the use of surfactants. Aggregation is often caused by transient changes to the native, folded structure of a protein that result in "hydrophobic" (water-repelling) regions of the molecule to be exposed to the surrounding, aqueous environment. These hydrophobic regions will repel water but attract other hydrophobic substances, including hydrophobic regions on neighboring protein molecules. This attraction will tend to cause protein molecules to adhere. Surfactants are molecules with hydrophilic and hydrophobic ends that will orient their hydrophobic ends towards the hydrophobic portion of the protein to shield it from being exposed to other proteins, thus preventing adhesion. Polysorbate 20 and polysorbate 80 (also called "Tween 20" and "Tween 80") were commonly-used surfactants to achieve this goal. *See, e.g.*,

EX1014 (*Parkins*), Box 1. As of the priority date, a number of approved and commercially-available protein (antibody) biologics used polysorbate 20 or polysorbate 80 in their formulations. See EX1032 (*AVASTIN Label*), 2 (polysorbate 20); EX1034 (*REMICADE Label*), 1117 (polysorbate 80); EX1037 (*XOLAIR Label*), 1359 (polysorbate 20); EX1033 (*RAPTIVA Label*), 1350 (polysorbate 20); EX1036 (*HERCEPTIN Label*), 1338 (polysorbate 20).

74. Another known way to stabilize a solution by reducing aggregation was through the use of a stabilizer, such as sucrose. Solutions of protein therapeutic agents for administration by subcutaneous injection are often lyophilized (freeze-dried) to form solid powders in vials that can be reconstituted with suitable diluents such as saline prior to injection. They are also commonly prepared as liquid protein formulations that are ready for injection. As of the priority date, it was well known that “formulation with carbohydrate excipients, such as sucrose and trehalose, has proven to be effective in the stabilization of freeze-dried proteins.” EX1005 (*Andya 2003*), 1. These molecules tend to modify the structure of water around the protein in order to maintain a stabilizing environment. It was known that when water is removed during dehydration, excipients such as sucrose may substitute for water to maintain hydrogen bonds with surface-accessible polar sites on the protein. These hydrogen bonds stabilize the protein’s folding, which reduces the exposure of hydrophobic interior regions

of the protein and subsequent aggregation during storage. *Id.*, 2. The prior art taught that for optimum long-term stability, the use of disaccharides such as sucrose and trehalose were recommended. EX1014 (*Perkins*), 134; *see also* EX1005 (*Andya 2003*), 1 (“formulation with carbohydrate excipients, such as sucrose and trehalose, has proven to be effective in the stabilization of freeze-dried proteins.”). As of the priority date, a number of approved and commercially-available protein (antibody) biologics used disaccharides such as sucrose and trehalose in their formulations. *See* EX1032 (*AVASTIN Label*), 2 (trehalose); EX1034 (*REMICADE Label*), 1117 (sucrose); EX1037 (*XOLAIR Label*), 1359 (sucrose); EX1033 (*RAPTIVA Label*), 1350 (sucrose); EX1035 (*SIMULECT Label*), 2367 (sucrose); EX1036 (*HERCEPTIN Label*), 1338 (trehalose).

75. Another known consideration when stabilizing antibody formulations was pH. As can be seen in Table 6 from *Chang 2002* above, pH can have an effect on the major chemical protein degradation pathways of deamidation and oxidation. Optimization of pH will also provide physical stability. *Id.*, Table 7. As pH is adjusted away from a protein’s “isoelectric point” (the pH at which a protein carries no net positive or negative surface charge), there is increased electrostatic repulsion between molecules and thus less of a chance for aggregation. It was known that proteins are often stable against aggregation over narrow pH ranges and may aggregate rapidly in solutions with pH outside these ranges. EX1007

(*Chi*), 1326. Optimization of pH was also known to avoid other issues that could arise in formulation, such as electrostatic effects that can prevent proper protein folding. *Id.* Accordingly, keeping the pH within a certain range was a common technique to avoid degradation through these pathways.

76. One known, very common way to do this was through the use of a buffer. Buffers, which are mixtures of acid and base that tend to resist changes in pH, are used to maintain the pH of a protein formulation within a certain target range. “Buffering” a formulation to keep pH at a desired value was a common technique to avoid degradation through these pathways.

77. Phosphate was a very commonly-used buffer at the time. A number of antibody biologic products approved before the priority date utilized phosphate buffer in their formulations. *See* EX1032 (*AVASTIN Label*), 2; EX1034 (*REMICADE Label*), 1117; EX1035 (*SIMULECT Label*), 2367.

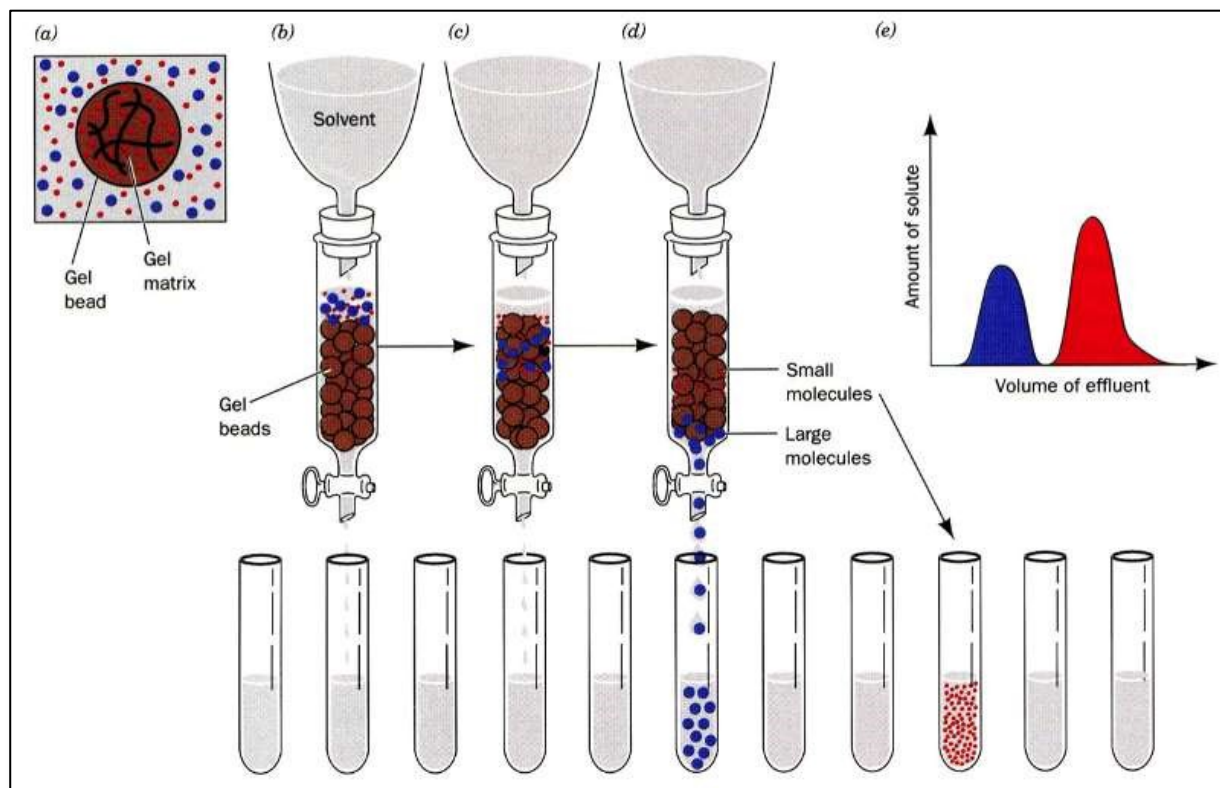
78. Protein formulations are typically refrigerated to avoid degradation, commonly at a temperature of 2-8 °C (which is known as “USP Standard Refrigerated Temperature Range”). Protein degradation pathways were well known to proceed more slowly at colder temperatures. As a result, therapeutic protein formulations are commonly refrigerated at 2-8 °C to maintain stability. *See* EX1032 (*AVASTIN Label*), 25 (storage at 2-8 °C); EX1034 (*REMICADE Label*), 1121 (storage at 2-8 °C); EX1037 (*XOLAIR Label*), 1362 (storage at 2-8 °C);

EX1033 (*RAPTIVA Label*), 1352 (storage at 2-8 °C); EX1035 (*SIMULECT Label*), 2369 (storage at 2-8 °C); EX1036 (*HERCEPTIN Label*), 1341 (storage at 2-8 °C).

In order to assess whether a formulation can be turned into a product with a commercially-viable shelf-life, it was common to test storage stability at these standard refrigeration conditions for a number of months or years, including, for example, 2 months. *See* EX1026 (*Liu*), ¶¶63, 280 (showing stability data for 1, 3, 14, 16, and 24 months).

79. One commonly-used technique to assess aggregation and other physical stability characteristics was SEC. *See, e.g.*, EX1026 (*Liu*) at ¶278, Table 1; EX1012 (*Kostanski 2004*), 160 (“Today, SEC is the most widely accepted and used analytical method for the measurement of molecular weight distribution and molecular weight averages of biopolymers and synthetic polymers.”). SEC employs a chromatography column containing a medium that separates proteins according to their molecular size and shape. This separation happens as smaller and more compact molecules tend to get trapped within the pores and other spaces of the medium, while larger molecules tend to avoid getting trapped and pass through the column more quickly. SEC can thus detect if two or more molecules have aggregated together to form a larger aggregate, a molecule has “denatured”

(unfolded and thus changed its shape), or a molecule has fragmented into smaller fragments. Below is a simplified diagram³ of how SEC works:



80. SEC is often not able to conclusively quantify, however, the percentage of protein that is present in a solution in undegraded or “native” conformation. A single peak in a SEC plot may include several different molecules, including certain degradation products, that have similar molecular size

³ Sourced from https://comis.med.uvm.edu/vic/coursefiles/MD540/MD540-Protein_Methods_Learning_Module_10400_593281210/Protein-methods/Protein_Methods5.html.

and shape. However, SEC may be used, and was used at the time—sometimes inappropriately—to estimate the percentage of protein in a sample that has not denatured, aggregated or fragmented in comparison to another sample.⁴ The '992 patent does this, and other prior art from that time does this as well, sometimes referring to this measurement as “native configuration” or “intact protein”. When I refer to the percentage of protein in “native conformation” in this declaration, I am using it in the way the '992 patent does, which is to say, the percentage of protein in native conformation **as measurable by SEC**.

81. In an ideal world, the target of a formulator is always a formulation that is 100% stable, *i.e.*, experiences no degradation of the active ingredient, whether physical or chemical. This is because degradation of the active ingredient is always a negative. It increases potentially problematic impurities and decreases the amount of fully-intact active ingredient available to exert its intended effect. In practice, it was well-known in 2005 that very high levels of purity can be maintained in a properly-formulated protein biologic product under various typical storage conditions, including over two months and even two years of storage at 5 °C.

⁴ Other methods such as RP-HPLC or circular dichroism more accurately quantify the percentage of protein in “native conformation.”

82. For example, as of the priority date, numerous publications reported formulations containing antibodies with >98% “native conformation” at the two-month mark after storage at 5 °C as measured by SEC. EX1030 (*WO '801*) provides a number of lyophilized formulations of humanized antibody protein (trastuzumab) that included trehalose and polysorbate 20 and maintained >99% of the protein intact (native conformation as measured by SEC) after storage at 5 °C for 2 weeks. EX1030 (*WO '801*), 20, Table 2. Moreover, after 12 months at 5 °C, “there was no change in the % intact protein for the trehalose formulation.” *Id.*, 19:37-38. Some of the formulations reported in *WO '801* had >99% native conformation even after storage for over 2 months at 5 °C and reconstitution. *Id.*, 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).

83. Similarly, *Kaisheva '316* reports data for three formulations of anti-IL-2 receptor antibody that utilized histidine, sucrose, and polysorbate 80. EX1024 (*Kaisheva '316*), ¶¶113-15, Fig 9A.

[0113] 1. Formulation I (FORM-I): 50 mg/mL anti-IL2 receptor antibody, 20 mM Histidine, 4% (117 mM) sucrose, 0.015% Tween® 80, pH 6.0. Vial configuration: 2 mL fill in 2 mL vial. Reconstituted with 1 mL WFI. Protein concentration post-reconstitution=100 mg/mL.

[0114] 2. Formulation II (FORM-II): 80 mg/mL protein, 20 mM Histidine, 6.5% (190 mM) sucrose, 0.025% Tween 80, pH 6.0. Vial configuration: 1.25 mL fill in 2 mL vial, Reconstituted with 1 mL WFI. Protein concentration post-reconstitution=100 mg/mL.

[0115] 3. Formulation III (FORM-III): 80 mg/mL protein, 20 mM Histidine, 4% sucrose, 0.015% Tween 80, pH 6.0. Vial configuration: 2 mL fill in 2 mL vial. Reconstituted with 1 mL WFI. Protein concentration post-reconstitution=160 mg/mL.

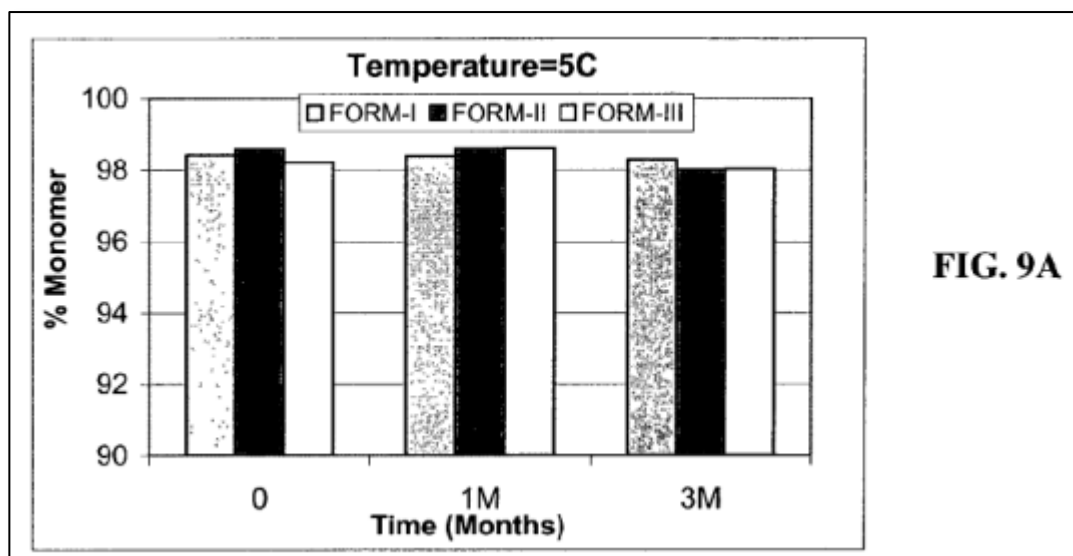


FIG. 9A

84. *Kaisheva '316* shows “percent monomer as a function of time” in all three formulations, confirming that at 3 months, all three formulations contained above 98% “monomer” as measured by SEC, *i.e.*, equivalent to the “native

conformation” of the ’992 patent. EX1024 (*Kaisheva* ’316), ¶¶ 22; 113-15, Fig 9A.

85. *Liu* similarly reports two liquid formulations of recombinant human antibody having >98% “monomer” (equivalent to native conformation) as measured by SEC after storage at 5 °C for 3 months (and even up to 16 months). Both formulations contain polysorbate 20, and one also contains trehalose. EX1026 (*Liu*), Table 1.

86. *Kaisheva* ’417 similarly reports a number of liquid formulations of daclizumab antibody with greater than 98% “monomer” as measured by SEC (*i.e.*, native conformation) after storage for 8 weeks (approximately two months) or longer. *See, e.g.*, EX1025 (*Kaisheva* ’417), Table 5 (reporting 98.3% native conformation at 8 weeks storage at 5 °C); Table 6 (reporting 99.26% 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).

87. Finally, the ’586 Patent (EX1018) similarly reports an antibody formulation containing polysorbate 20 and trehalose as having >98% “monomer” (*i.e.*, native conformation) after storage at 2-8 °C for two years, measured by SEC. *Id.*, Fig 28 and 5:35-40.

VI. ANALYSIS OF THE CHALLENGED CLAIMS

A. *Fraser* Expressly and Inherently Anticipates Claims 1-18

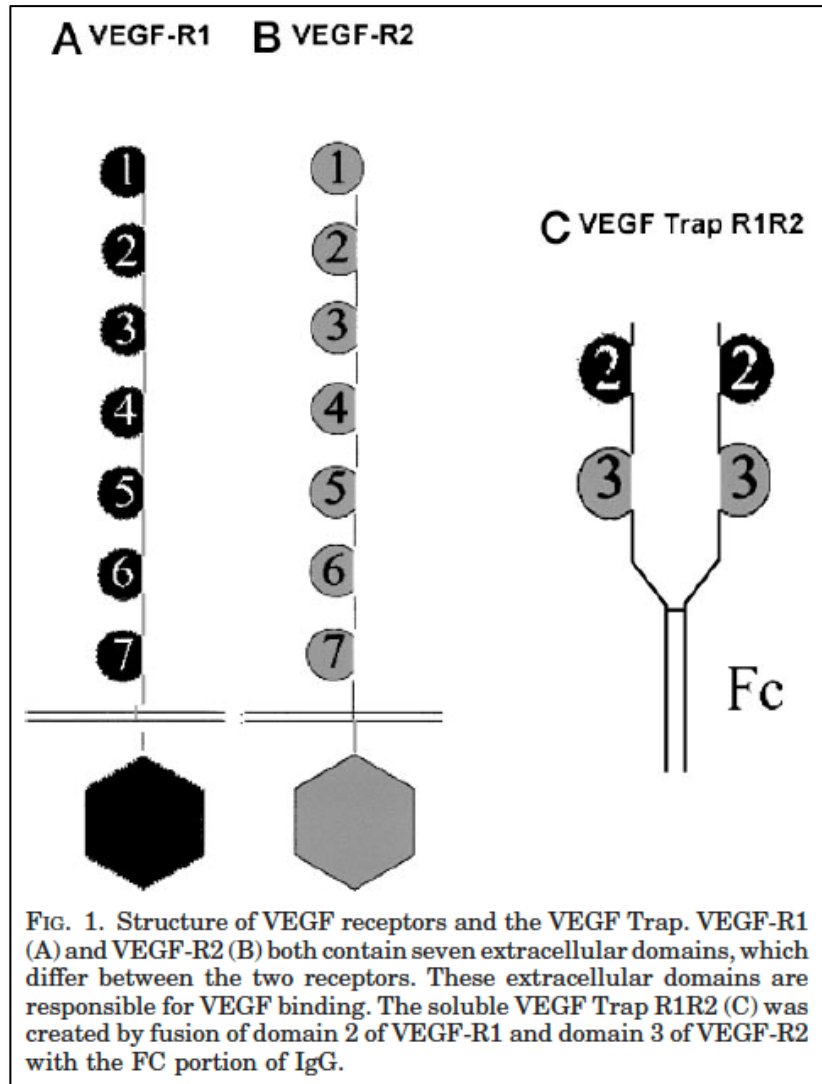
1. Claim 10

88. Claim 10 describes a formulation comprising the following elements: (1) a VEGF antagonist, (2) an organic co-solvent, (3) a buffer, and (4) a stabilizing agent, wherein (5) the VEGF antagonist is a fusion protein produced in a Chinese Hamster Ovary (CHO) cell, (6) the fusion protein comprising an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor and a “multimerizing component,” and (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. Every one of these elements is disclosed in *Fraser* (EX1009), either expressly or inherently.

89. *Fraser* is a Regeneron publication entitled “Single Injections of Vascular Endothelial Growth Factor Trap Block Ovulation in the Macaque and Produce a Prolonged, Dose- Related Suppression of Ovarian Function.” EX1009, 1114. *Fraser* was published in the Journal of Clinical Endocrinology & Metabolism in February 2005. *Id.* Accordingly, *Fraser* was available more than one year prior to the June 2006 priority date of the '992 patent.

90. *Fraser* describes a formulation of VEGFTrap_{R1R2}, *i.e.*, aflibercept, made by Regeneron. *Fraser* states that “VEGF was inhibited by administration of

VEGFTrap_{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.” *Id.*, 1115. The “Fc” referred to in *Fraser*’s description is a “Fragment crystallizable” region of a human IgG1 antibody, originally named for its propensity to crystallize readily. EX1011 (*Janeway*), 96. The Fc region connects the two “Fab” (fragment antigen binding) fragments of aflibercept to form the completed fusion protein, much like the Fc region connects the two Fab regions of an antibody that are responsible for binding antigen. A diagram from *Wulff* illustrates this:



EX1016 (*Wulff*), 2798 Fig. 1. Since the Fc region in VEGFTrap_{R1R2} acts as a multimerizing component by joining the two Fab fragments, a POSA would have understood that *Fraser* discloses a “fusion protein comprising an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component.”

91. The *Fraser* formulation also contains an “organic co-solvent, a buffer, and a stabilizing agent.” *Fraser* states that “VEGFTrap_{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. As discussed above, polysorbate 20 (also known to POSAs by the brand name Tween 20) is a common surfactant or “co-solvent,” phosphate is a common buffer, and both sucrose and glycerol are common stabilizers. *See supra* Section V.C.

92. While *Fraser* states that the formulation Regeneron provided contained “either 20% glycerol or 20% sucrose,” the evidence I have reviewed indicates that the formulation contained 20% sucrose. In statements and a declaration submitted during prosecution of *Dix*, another Regeneron patent, Regeneron explained that “the actual lot and formulation used in Fraser” contained “Lot# VGTF01001T (24.3 mg/ml VEGF Trap); “5 mM phosphate”; 5mM citrate”; 199mM NaCl”; “20% sucrose”; “0.1% Polysorbate 20”; and had “pH 6.05.” EX1022 (*Declaration of Dix et al.*), Exhibit C; EX1023 (*Nov 22 OA Response*), 2.

93. The VEGFTrap_{R1R2} disclosed in *Fraser* was created in CHO cells, and a POSA would have known as much when reading the term “VEGFTrap_{R1R2}” in the context of the whole *Fraser* article. *Fraser* notes that the VEGFTrap_{R1R2} “was provided” by Regeneron. *Id.*, 1115. *Fraser* references the *Holash* paper as part of its description of what VEGFTrap_{R1R2} is. *Fraser* states: “Compared with earlier

versions of receptor-based fusion proteins, the VEGFTrapR1R2 exhibits greater affinity for VEGF-A (affinity constant $\sim 1\text{pm}$) as well as improved bioavailability and pharmacokinetic properties (21).” *Id.*, 1115. Reference 21 is the *Holash* paper, an earlier Regeneron publication published in 2002.

94. *Holash* describes VEGF-Trap_{R1R2} as follows: “VEGF-Trap_{R1R2} possesses the second Ig domain of VEGFR1 and the third Ig domain of VEGFR2 fused to the Fc portion of human IgG1.” EX1010 (*Holash*), 11394, Fig. 1. *Holash* additionally notes that “VEGF-Trap_{R1R2} was created by fusing the second Ig domain of VEGFR1 with the third Ig domain of VEGFR2. All of the VEGF-Trap variants were produced and purified from Chinese hamster ovary cells.” *Id.*, 11393-94. The reference by *Fraser* to VEGFTrap_{R1R2} being “provided” by Regeneron and directing the reader to *Holash* for a description of the protein would have informed the POSA that the VEGFTrap_{R1R2} in *Fraser* was made in CHO cells.

95. Another Regeneron publication, *Wulff*, also disclosed that Regeneron manufactured VEGFTrap_{R1R2} in CHO cells, and this article also would have informed the POSA’s understanding of that term in *Fraser*. See EX1016 (*Wulff*), 2798 (“The VEGF trap was expressed in CHO cells and was purified by protein A affinity chromatography followed by size-exclusion chromatography.”). *Wulff* further cites to the ’319 Publication (EX1029), stating that “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.” EX1016 (*Wulff*), 2798 n.1. As discussed above in Section V.B, the structure of VEGFTrap_{R1R2} had been disclosed in several Regeneron publications, including the '*319 Publication*'. The '*319 Publication*' also discloses that VEGFTrap_{R1R2} was made in CHO cells. EX1029 ('*319 Publication*') at 12, 15, Fig. 24A-24C and claims 9, 20 (describing and claiming the production of VEGFR1R2-FcΔC1(a) in CHO cells). Accordingly, the POSA would have understood that the VEGFTrap_{R1R2} referred to in *Fraser*, which, as discussed above, was the same VEGFTrap_{R1R2} referred to in *Wulff* and the '*319 Publication*', was generated in CHO cells.⁵

⁵ In my experience, once a protein biologic like aflibercept has entered human clinical trials, the manufacturer does not make substantial changes to the method of manufacture, *e.g.*, switching to an entirely new cell culture to express the protein. To do so would risk introducing altering the protein active pharmaceutical ingredient and having to redo the clinical trials. This is another reason why a POSA would have understood that Regeneron continued to use CHO cells to make the VEGFTrap_{R1R2} used in *Fraser*.

96. While *Fraser* does not explicitly disclose a percentage of the aflibercept (VEGFTrap_{R1R2}) that remained in native conformation in its formulation after storage at 5 °C for two months, stability is an inherent property of the *Fraser* formulation and Regeneron's own SEC test data show that greater than 99% of the aflibercept in the formulation will remain in native conformation (as measured by SEC) when stored at 5 °C for far longer than two months. *Dix*, another Regeneron publication that published *after* the priority date, provides SEC test data for a formulation with the same ingredients as the *Fraser* formulation. Those SEC data confirm that the *Fraser* formulation preserves greater than 99% of the aflibercept in native conformation (as measured by SEC) for over *two years* when stored at 5 °C.

97. *Dix* discloses a formulation “containing about 5 mM phosphate, 5 mM citrate, 100 mM NaCl, 0.1% polysorbate 20, 20% sucrose, and 25 mg/ml VEGF trap protein” with “pH ranged from 6.0-6.1.” EX1021 (*Dix*), 11:15-20, Example 5 and Table 9. The “VEGF trap protein” is disclosed as having amino acid sequence in “SEQ ID NO:4,” *id.* at 10:49-50, which is the same sequence as VEGFTrap_{R1R2}.

98. According to Regeneron, “the actual lot and formulation used in *Fraser*” contained “Lot# VGTF01001T (24.3 mg/ml VEGF Trap)”; “5 mM phosphate”; “5mM citrate”; “199mM NaCl”; “20% sucrose”; “0.1% Polysorbate 20”;

and had “pH 6.05.” EX1022 (*Declaration of Dix et al.*), Exhibit C; EX1023 (*Nov 22 OA Response*), 2.

99. The *Dix* formulation is, in all material respects, the same as the *Fraser* formulation.

100. *Dix* provides SEC test results for this *Fraser* formulation showing change over time when stored at 5 °C for three years. Table 9 of *Dix* shows that the “% Native Configuration” (another way of saying “native conformation”) after retained greater than 99% native conformation over a two-month period, and indeed over a *two-year* period:

TABLE 9				
Stability and Activity of Liquid Formulation (VGT-FS405)				
Months	% Native Configuration	Bioassay	Binding Assay	Protein Content mg/ml
0	99.7	106	72	25.0
1	99.9	119	4.4 pM*	25.2
2	99.6	102	5.4 pM*	25.1
3	99.6	97	88	25.1
6	99.6	101	106	25.0
9	99.4	89	126	25.4
12	99.5	85	95	25.2
18	99.4	99	81	25.5
24	99.3	75	95	25.6
36	98.8	109	79	25.6

EX1021 (*Dix*), 11:15-20, Example 5 and Table 9.

101. The only “differences” between the *Dix* formulation and the *Fraser* formulation are (1) *Dix* reporting the concentration of fusion protein as “25.0

mg/ml” at 0 months (versus *Fraser*’s “24.3 mg/mL”), and (2) *Dix* reporting the pH as ranging from “6.0-6.1” over the 36 months rather than *Fraser*’s value of “6.05.” But these are not in fact differences. In my experience, the recorded value of 24.3 mg/ml of aflibercept reported in *Fraser* is within normal measurement variability of the target value of 25 mg/ml in *Dix* Table 9. Indeed, as the “Protein Content” column of Table 9 in *Dix* shows, Regeneron’s measurement variability with respect to protein content was at least as high as +/-0.6 mg/ml. The same goes for pH. In my experience, the recorded pH values of *Dix* and *Fraser* are within normal measurement variability of each other and thus are the same.⁶

102. Even if these slight differences in measured values are real and not just measurement variation, they are trivial, and, based on my decades of experience, would not have had a material effect on the SEC results at 2 months. This is especially true given that the *Dix* formulation’s SEC results were above 99% for *two years*, indicating that the formulation was highly stable. Moreover, assuming the difference is not just measurement error, *Fraser*’s solution had a

⁶ The *Fraser* formulation and the *Dix* formulation have different lot numbers. The *Dix* formulation is “VGT-FS405” and the *Fraser* formulation is “VGTF01001T.” But the formulations are described as being part of the same project “VEGF-SS017.”

lower concentration of protein than *Dix*, and formulations with lower protein concentrations tend to exhibit *less* aggregation than ones with higher concentrations. *See, e.g.*, EX1006 (*Chang 2002*), Table 6 (noting that adjusting concentration of protein (antibody) is a potential solution to aggregation issues). Thus, the *Fraser* formulation inherently has the same stability (as measured by SEC) as the *Dix* formulation under the claimed storage conditions.

103. For all of the above reasons, the formulation of *Fraser* meets all of the limitations of the formulation of claim 10 and therefore anticipates claim 10.

2. Claim 1

104. Claim 1 is the same as claim 10 but additionally requires that the formulation be in a “vial.” *Fraser* inherently anticipates this limitation as well.

105. The description in *Fraser* inherently discloses to a POSA that Regeneron provided the *Fraser* formulation to the study authors in “vials”. *Fraser* notes that the formulation “was provided” by “Regeneron Pharmaceuticals, Inc., Tarrytown, NY... in 2-ml aliquots.” EX1009 (*Fraser*), 1115. To a POSA, an “aliquot” would have denoted an individually-filled volume for clinical use that is not intended for later subdivision. The design of the *Fraser* study indicates that

Regeneron provided a minimum of 14 of the aliquots.⁷ *Fraser* further explained that “[t]he compounds were stored at -20° C until required, at which time they were

⁷ That design involved a pilot study in which two macaque monkeys were each given “a single i.v. injection of 12.5 mg/kg” of VEGFTrap_{R1R2}. *Id.* Then, 12 monkeys were divided into three groups and each was administered either 4.0, 1.0 or 0.25 mg/kg of VEGFTrap_{R1R2}. *Id.* Later, four monkeys each received a dose of 1 mg/kg of VEGFTrap_{R1R2} to test the effect of the protein in the late follicular phase (“LFP”). *Id.* Assuming multiple doses were permitted from the same aliquot, the total number of 2 ml aliquots needed for the study, assuming no wastage or spares, was 14:

Fraser Dosing Protocol					
Dose (mpk)	Study Phase	Dose per macaque* (mg)	Number of Macaques Tested	Injection Volume (mL) per macaque	Volume needed for Phase (mL)
12.5	Pilot Study	162.5	2	6.7	13.4
0.25	Mid-follicular	3.3	4	0.1	0.5
1	Mid-follicular	13.0	4	0.5	2.1
4	Mid-follicular	52.0	4	2.1	8.6
1	Late-follicular	13.0	4	0.5	2.1
Total					26.7
*assuming average weight of 13 kg					

thawed,” and that “[a]ny compound remaining was stored at 4° C and used within 2wk.” *Id.* This would have indicated to a POSA that the multitude of individual aliquots were necessarily provided in individual vials, *i.e.*, a small closed or closable vessel, especially for liquids, otherwise they could not have been transported or stored in the freezer or refrigerator without being subject to spillage, evaporation/sublimation and contamination. Those vials also would have necessarily had to bear labels, to identify them and avoid confusion.

106. A POSA also would have understood that, since they were for use in *in vivo* studies in macaque monkeys, which are advanced primates, the aliquots would have been packaged in a form that adhered to Good Laboratory Practice for Nonclinical Laboratory Studies (“GLP”). This would have been reinforced by *Fraser’s* disclosure that “the study was approved by the local Primate Ethical Committee and carried out under a project license granted by the United Kingdom Home Office,” EX1009 (*Fraser*), 1115, two regulatory bodies that would have assured compliance with the highest applicable standards for primate clinical trials. GLP regulations dictate that for investigational drugs, “[d]istribution is made in a

If the authors used only one aliquot per dose, then 18 would have been required (one per macaque for this single-dose protocol).

manner designed to preclude the possibility of contamination, deterioration, or damage.” *See* 21 C.F.R. Part 58.107. The investigator must “[a]ssure that test and control articles or mixtures have been appropriately tested for identity, strength, purity, stability, and uniformity, as applicable.” 21 C.F.R. Part 58.31(d). This precludes the use of anything other than a hermetically-sealed vial capable of ensuring that the formulation remained free of contaminants and of a fixed composition, and could be stored in a freezer or refrigerator without being compromised. This is especially true for the *Fraser* formulation, which did not contain a preservative. The vials also would have required a label containing sufficient information to ensure accurate identification of the contents and study, and safe storage and administration (*e.g.*, lot numbers, expiration dates, directions for proper storage).

107. In my experience as Research Director of Sterile Product Formulation & Clinical Manufacturing at Roche from 2000 to 2009, in which I directed, *e.g.*, GLP manufacturing, protein formulation development and packaging in support of *in vivo* studies like *Fraser* at the relevant time period, a POSA would have understood from *Fraser* that Regeneron provided the formulation to the *Fraser* researchers in a specific kind of vial that would have prevented spillage, evaporation/sublimation and contamination, borne a label, and assured compliance with GLP: “vials for injection” made from plastic or glass. At Roche in 2004, the

year of the *Fraser* study, vials for injection were necessarily used to package sterile liquids for injection for studies in humans and advanced primates like the macaque monkey, given all of the ethical, regulatory and quality-assurance restraints governing such studies. A POSA would have understood that Regeneron also adhered to GLP or similarly high standards.

108. These “vials for injection” are familiar to anyone who has gotten a shot at the doctor. They are small, cylindrical vials with a synthetic rubber stopper hermetically sealed with an aluminum cap, to which an identifying label has been applied. Below is an example of a typical vial for injection containing a typical investigational drug label⁸:



⁸ Image sourced from <https://jnj-content-lab.brightspotcdn.com/dims4/default/dd2fe32/2147483647/strip/true/crop/795x539+2+0/resize/295x200!/quality/90/?url=http%3A%2F%2Fjnj-brightspot.s3.amazonaws.com%2F92%2F94%2Fdd0f121748678e4865957cb989d0%2Finset-2-jnj-vaccine-vials.jpg>.

A sterilized syringe is used to withdraw liquid from the vial through the synthetic rubber stopper. The stopper is resealable to a certain extent and allows multiple withdrawals from a single vial of an appropriate formulation, minimizing the risk of contamination. Withdrawal of drug and administration is essentially all conducted in a closed system. Such vials also greatly aid the filling of a syringe with an accurate dose while minimizing air bubbles. Since the *Fraser* study demanded that very small volumes from approximately 0.1 mL to 2 mL be administered, this would have been an important concern. Other kinds of containers would run the risk of contamination and injury, especially if used for multiple injections.

109. Even if the aliquots were not provided in vials for injection, a POSA would have understood that they would necessarily have been provided in sealed, resealable, labeled vials of some kind. The maintenance of sterility, especially in a primate study, would have been essential not only for reasons of animal safety but also as to not confound the results of the experiment (morbidity/ mortality due to microbial contamination can affect results). A resealable vial would also have been essential to maintain product integrity by reducing exposure to environmental oxygen and facilitate administration of the study formulation.

110. Indeed, the lot of formulation used to supply the aliquots to the *Fraser* authors was stored at Regeneron in vials. As explained, during prosecution of

another patent, Regeneron provided a copy of a notebook page that it described as referring to “the actual lot and formulation used in *Fraser*.” EX1023 (*Nov 22 OA Response*), 2. That notebook page is entitled “Receipt of Protein” and is dated January 30, 2001, which is about three and-a-half years before Regeneron submitted the *Fraser* paper to the publisher (on August 1, 2004). EX1022 (*Declaration of Dix et al.*), Exhibit C; EX1009 (*Fraser*), 1122. The notebook page tabulates the “# of vials” and the “vol/vial” that were “[r]eceived from the Process Development Group.” EX1022 (*Declaration of Dix et al.*), Exhibit C. Four “vials” of lot number VGTF01001T, which is the same formulation described in *Fraser*, were received and then “frozen at -80° C as received”. *Id.* Thus, Regeneron’s own notebook shows that Regeneron stored the same lot of formulation used in *Fraser* in sealed tubes that it called “vials” to avoid contamination, spillage, and other problems during transport and storage.

111. Thus, it is clear that even if Regeneron departed from GLP and did not package the aliquots in vials for injection, it nevertheless would have necessarily provided the aliquots in vials of some kind, consistent with its own internal handling and packaging procedures.

112. For the foregoing reasons, *Fraser* inherently discloses that the aflibercept formulation used in the study was contained within vials.

113. For the foregoing reasons, as well as all of the reasons given for claim 10, *Fraser* expressly and inherently discloses all of the elements of claim 1 and therefore anticipates that claim.

3. Claims 2 and 11

114. Claims 2 and 11 depend from claims 1 and 10 respectively, and further require that “about 99% or more of the weight of the fusion protein is in native conformation.” EX1001 (*'992 patent*), 19:44-45, 20:41-43.

115. As discussed, the aflibercept in the *Dix* Table 9 formulation exhibited >99% native conformation at 2 months, and even at 24 months. *See supra* ¶100. As explained above with respect to claim 10, since the *Fraser* formulation is materially identical to *Dix*’s formulation and, if not, would be *more* stable, *Fraser* inherently discloses this limitation as well.

116. For these reasons and all of the reasons expressed regarding claims 1 and 10, *Fraser* expressly and inherently discloses all of the elements of claims 2 and 11 and therefore anticipates those claims.

4. Claims 3 and 12

117. Claims 3 and 12 depend from claims 1 and 10 respectively, and further recite “the first VEGF receptor is human Flt1 and the second VEGF receptor is selected from the group consisting of human Flk1 and the human Flt4.” *Id.*, 19:46-48, 20:44-47.

118. As discussed above, VEGF-R1 is encoded by the Flt1 gene, while VEGF-R2 is encoded by the Flk1 gene. *See supra*, Section V.A. The VEGF Trap_{R1R2} of *Fraser* comprises “Ig domain 2 of human VEGF-R1 and Ig domain 3 of human VEGF-R2.” EX1009 (*Fraser*), 1115. Therefore, *Fraser* discloses a VEGF antagonist fusion protein in which the first VEGF receptor is human Flt1 and the second VEGF receptor is selected from the group consisting of human Flk1 and the human Flt4.

119. For these reasons and all of the reasons expressed regarding claims 1 and 10, *Fraser* expressly and inherently discloses all of the elements of claims 3 and 12 and therefore anticipates those claims.

5. Claims 4 and 13

120. Claims 4 and 13 depend from claims 3 and 12 respectively, and further recite “the fusion protein comprises amino acids 27-457 of SEQ ID NO: 4.” EX1001 (*'992 patent*), 19:51-52, 20:49-50.

121. As explained above with respect to claim 10, Regeneron had published the sequence of VEGFTrap_{R1R2} in multiple places, including, *e.g.*, the *'319 Publication*. *See supra* ¶65. All of those references disclose an identical sequence to SEQ ID NO:4.

122. *Fraser*, by using VEGFTrap_{R1R2} in its formulation, inherently discloses amino acids 27-457 of SEQ ID NO: 4 of the '992 patent. Further, a POSA reading *Fraser* would have known that VEGFTrap_{R1R2} had this sequence.

123. For these reasons and all of the reasons expressed regarding claims 3 and 12, *Fraser* expressly and inherently discloses all of the elements of claims 4 and 13 and therefore anticipates those claims.

6. Claims 5 and 14

124. Claims 5 and 14 depend from claims 4 and 13 respectively, and further recite “the VEGF antagonist is a dimer of the fusion protein.” EX1001 (*'992 patent*), 19:51-52, 20:51-52.

125. As discussed above, VEGFTrap_{R1R2}, used in *Fraser*, is a dimer. *See supra* ¶57. A POSA reading *Fraser* would have known as much.

126. For these reasons and all of the reasons expressed regarding claims 4 and 13, *Fraser* expressly and inherently discloses all of the elements of claims 5 and 14 and therefore anticipates those claims.

7. Claims 6 and 15

127. Claims 6 and 15 depend from claims 5 and 14 respectively, and further recite “the organic co-solvent is selected from the group consisting of polysorbate 20, polysorbate 90, polyethylene glycol (PEG), PEG3350, and propylene glycol.” *Id.*, 19:53-56, 20:53-56.

128. As discussed above, *Fraser* discloses a formulation containing “0.1% wt/ vol Tween 20.” EX1009 (*Fraser*), 1115; *supra* ¶91. “Tween 20” is a commercial brand name for polysorbate 20.

129. For these reasons and all of the reasons expressed regarding claims 5 and 14, *Fraser* expressly and inherently discloses all of the elements of claims 6 and 15 and therefore anticipates those claims.

8. Claims 7 and 16

130. Claims 7 and 16 depend from claims 6 and 15 respectively, and further recite “the stabilizing agent is selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol.” EX1001 (‘992 *patent*), 19:57-59, 20:57-59.

131. As discussed above, *Fraser* discloses a formulation containing “either 20% glycerol or 20% sucrose.” EX1009 (*Fraser*), 1115. Regeneron later disclosed that “the actual lot and formulation used in Fraser” contained “20% sucrose.” EX1022 (*Declaration of Dix et al.*), Exhibit C; EX1023 (*Nov 22 OA Response*), 2.

132. For these reasons and all of the reasons expressed regarding claims 6 and 15, *Fraser* expressly and inherently discloses all of the elements of claims 7 and 16 and therefore anticipates those claims.

9. Claims 8 and 17

133. Claims 8 and 17 depend from claims 1 and 10 respectively, and further recite “the organic co-solvent is polysorbate 20 and the stabilizing agent is sucrose.” EX1001 (*'992 patent*), 19:60-61, 20:59-61.

134. As discussed above with respect to claims 1, 7 and 16, Regeneron has disclosed that the *Fraser* formulation contained “20% sucrose, and 0.1% polysorbate-20.” EX1023 (*Nov 22 OA Response*), 2.

135. For these reasons and all of the reasons expressed regarding claims 1, 7, 10 and 16, *Fraser* expressly and inherently discloses all of the elements of claims 8 and 17 and therefore anticipates those claims.

10. Claims 9 and 18

136. Claims 9 and 18 depend from claims 1 and 10 respectively, and further recite “the organic co-solvent is polysorbate 20, the buffer is phosphate, and the stabilizing agent is sucrose.” EX1001 (*'992 patent*), 19:62-64, 20:63-65.

137. As discussed above with respect to claims 1, 7, 8, 10, 16 and 17, Regeneron has disclosed that the *Fraser* formulation contained “5 mM phosphate ... 20% sucrose, and 0.1% polysorbate-20.” EX1023 (*Nov 22 OA Response*), 2.

138. For these reasons and all of the reasons expressed regarding claims 1, 7, 8, 10, 16 and 17, *Fraser* expressly and inherently discloses all of the elements of claims 9 and 18 and therefore anticipates those claims.

B. Claims 1-18 are Obvious Over the Combination of *Fraser*, *Holash*, and *Wulff*, in view of the '319 Publication, the '309 Publication, *McNally 2000*, and *FDA Container Closure Guidance*

139. As discussed previously, *Fraser* expressly discloses a formulation containing VEGFTrap_{R1R2}, a co-solvent, a buffer and a stabilizer, and the remaining limitations of the independent claims (namely, manufacture in CHO cells, purity level, and placement in a vial) are inherent in *Fraser*'s disclosure. *See supra* Section VI.A. However, even if *Fraser* does not inherently disclose these limitations, they would have been trivially obvious to a POSA from *Fraser*, in view of the other prior art at the time.

1. Claim 10

140. As discussed, VEGFTrap_{R1R2} was, at the time of the priority date, a well-known VEGF antagonist comprising an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component. *See supra* ¶57. In fact, Regeneron had already published, in several places, the full amino acid sequence and overall structure of VEGFTrap_{R1R2}. *See, e.g.*, EX1029 ('319 Publication) (disclosing structure of VEGFR1R2-FcΔC1(a); EX1027 ('309 Publication) (disclosing that VEGFR1R2-FcΔC1(a) was "also known as VEGFTrap_{R1R2}"); EX1016 (*Wulff*), 2798 and Fig. 1 (disclosing overall structure of VEGFTrap_{R1R2}). Regeneron had also published papers that disclosed production of VEGFTrap_{R1R2} in CHO cells. *See* EX1016

(*Wulff*), 2798 (disclosing VEGFTrap_{R1R2} and that “the VEGF Trap was expressed in CHO cells); EX1010 (*Holash*) 11393-94 (disclosing VEGFTrap_{R1R2} and that “[a]ll of the VEGF-Trap variants were produced and purified from Chinese hamster ovary cells.”).

141. A POSA would have been motivated by Regeneron’s own prior-art publications to develop a formulation of VEGFTrap_{R1R2} to make use of these advantages. *Holash* explains that VEGFTrap_{R1R2} “was designed to overcome the poor *in vivo* pharmacokinetic properties of an earlier soluble VEGF decoy receptor,” *id.*, 11393, and that the VEGF Trap has “markedly enhanced pharmacokinetic properties” and “effectively suppresses tumor growth and vascularization *in vivo*.” *Id.* Moreover, 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.” EX1029 (‘319 Publication), 1, 10.

142. Furthermore, Regeneron had already published, in *Fraser*, *Wulff*, and *Holash*, a number of *in vitro* and *in vivo* studies demonstrating the therapeutic potential of its “VEGF-trap” fusion protein inhibitors as human anti-angiogenesis agents. As previously discussed, Regeneron had described VEGFTrap_{R1R2} as “one of the most, if not the most, potent and efficacious VEGF blocker available,” and had touted the advantages of VEGFTrap_{R1R2}, including being composed of

“entirely human sequences” and the low levels required for comparable efficacy and safety compared to other VEGF antagonists. *See supra*, ¶62. As further noted above, *in vivo* tests were already published with “quite promising” results with further clinical trials on the horizon. *See supra*, ¶63.

143. To make a formulation of VEGFTrap_{R1R2}, the POSA would have started by sourcing Regeneron’s VEGFTrap_{R1R2} or, barring that, expressing VEGFTrap_{R1R2} in CHO cells. Considering the numerous Regeneron publications that already disclosed that Regeneron expressed its VEGFTrap_{R1R2} in CHO cells, the POSA would have tried this approach first, and would have had a reasonable expectation of success in this approach. Indeed, at the time, CHO cells were the dominant mammalian cell line in which to express recombinant human proteins for therapeutic use. *See, e.g.*, EX1017 (*Wurm 2004*), 1396 (“CHO cells now dominate the domain of mass production of recombinant protein products because of their capacity for single-cell suspension growth.”).

144. Moreover, the POSA would have known that expression in a different mammalian cell type carried at least some risk of producing additional host cell protein and/or DNA impurities, and would wish to avoid this risk as much as possible by sticking to a proven method that was already shown to have worked (*i.e.*, cultivation in CHO cells). These sorts of impurities were well known as of the priority date, and as early as 1999, FDA had published guidance instructing

formulators to minimize such impurities “by the use of appropriate, well-controlled manufacturing processes.” *See* EX1047 (*FDA Specifications Guidance*), 12.

145. The POSA also would have understood that expression in cell culture different than CHO cells might result in somewhat different post-translational processing of the protein, which could affect its properties *in vivo*. This would have provided additional motivation to stick to CHO cells.

146. When selecting the amount of VEGFTrap_{R1R2} to include in the formulation, as well as the types and amounts of excipients and the pH, the POSA would naturally have started with the formulation that Regeneron itself published in the *Fraser* reference. This formulation would have served as a natural starting point.

147. In general, a POSA would assume that the originator of a biologic molecule would have a general level of familiarity with the properties of that molecule, and would naturally gravitate towards formulation that the originator had provided. In this case, as explained, the formulation in *Fraser* contained polysorbate 20, phosphate, and sucrose. *See* EX1009 (*Fraser*), 1115. The POSA’s confidence in the formulation would have been bolstered by the fact that *Wulff* disclosed and used *the same formulation*. *Wulff* disclosed that the marmosets involved in the study received VEGFTrap_{R1R2} “at a dose of 25 mg/kg” via “sc [subcutaneous]” injection, and that “[c]ontrol animals were treated with vehicle

containing 5 mM phosphate, 5mM citrate, 100mM sodium chloride, 0.1% (wt/vol) Tween 20, and 20% (wt/vol) sucrose.” EX1016 (*Wulff*), 2798. A POSA would have understood this as meaning that both the study and control marmosets received the same “vehicle,” but the vehicle contained VEGFTrap_{R1R2} only for the study marmosets. This is because the VEGFTrap_{R1R2} requires a vehicle to be injected subcutaneously, and there would have been no point in injecting the control animals with something the study animals were not. Moreover, I am not aware of any other formulation of VEGFTrap_{R1R2} that had been disclosed for *in vivo* use as of the ’992 patent’s priority date. Thus, this formulation would have been an easy—indeed the singular—starting point for the POSA.⁹

148. The POSA also would have been encouraged by *Fraser*’s disclosure that this formulation was at least stable enough to be used *in vivo* for a period of two weeks after being thawed and stored at 4° C. EX1009 (*Fraser*), 1115 (“The compounds were stored at -20 C until required, at which time they were thawed. Any compound remaining was stored at 4 C and used within 2 wk.”).

⁹ To the extent that *Fraser*’s reference to the use of “either 20% glycerol or 20% sucrose” would have presented the POSA with a choice, EX1009 (*Fraser*), 1115, *Wulff*’s disclosure of 20% sucrose would have led the POSA to choose that first.

149. The POSA also would have assumed that the Regeneron-provided VEGFTrap_{R1R2} formulation was at least reasonably stable from the fact that *Fraser* administered the VEGFTrap_{R1R2} to primates (macaque monkeys), EX1009 (*Fraser*), 1115, and the protein was already in clinical testing in humans as early as 2002. *See, e.g.*, EX1010 (*Holash*), 11397. In my experience, institutional review boards (“IRBs”) must approve studies like *Fraser* in primates, and both the FDA and IRBs must approve human clinical trials. In fact, *Fraser* expressly states that “the study was approved by the local Primate Ethical Committee and carried out under a project license granted by the United Kingdom Home Office.” EX1009 (*Fraser*), 1115. In both primate and human testing, these regulatory bodies require that the formulation for subcutaneous or intravenous injection be thoroughly tested, well-defined, and unlikely to produce any harmful side effects at the local site of injection or systemically. A POSA would have understood that because of these requirements, Regeneron’s formulation development was relatively advanced and that any aflibercept formulation it was using for *in vivo* testing was reasonably stable.

150. Accordingly, the POSA would have simply started with Regeneron’s published formulation rather than starting from scratch. This would have obviated the need for much of the routine trial-and-error testing that typically goes into developing formulations when nothing is known about the molecule.

151. As for stability, as discussed, the claimed stability is an inherent property of Regeneron's *Fraser/Wulff* formulation. *See supra* Section VI.1. The POSA would have conducted routine stability testing after selecting the *Fraser/Wulff* formulation as the logical starting point, including routine SEC testing. For commercial embodiments of protein biologics, a common target was storage at around 2-8 °C for a number of months. *See supra*, ¶78. As *Dix* shows, SEC testing during storage at 5 °C for three years would have revealed that the formulation stabilizes the VEGFTrap_{R1R2} to the extent that greater than 99% of it will remain in native conformation over a *two-year* period: EX1021 (*Dix*), 11:15-20, Example 5 and Table 9. A POSA would have considered this to be a very successful outcome.

152. Moreover, even if the POSA never tested the *Fraser/Wulff* formulation, using that formulation would have been obvious. Thus, using a formulation that inherently has the claimed stability would have been obvious.

153. However, even if this stability is not inherent, and even if the POSA achieved less stability than indicated in *Dix* Table 9, they would have been motivated to optimize *Fraser's* formulation for stability. As discussed above, in an ideal world, the POSA is constantly striving for assay or native conformation near 100%. *See supra*, ¶81. Indeed, the art disclosed numerous embodiments of antibody formulations that had 98 or 99% native conformation after being stored at

2-8 °C for 2 months, or even longer. *See supra*, ¶¶79, 82-87. Moreover, for a commercial product, the more stable a formulation is, the longer its “shelf life” or period between manufacture and expiry. Shelf life must take into consideration manufacturing, packaging, distribution and storage of a pharmaceutical product. All FDA-approved medications have an approved expiration date, beyond which the product cannot be sold or dispensed in the U.S. A POSA would have regarded a formulation of aflibercept with a longer shelf life to be more desirable than one with a shorter shelf life because a manufacturer and its customers, including pharmacies, healthcare providers and patients, would end up discarding fewer doses due to product expiration. Accordingly, the POSA would have been motivated to achieve as close to 100% native conformation as possible when designing a formulation for VEGFTrap_{R1R2}, and would have had a reasonable expectation of success in doing so, based on success of similar formulations of structurally-similar antibody proteins already known in the art.

154. Indeed, the POSA would have been motivated to reduce aggregation as much as possible. As explained above, aggregates can cause undesirable immunogenicity and reduce both the quality and potency of a protein biologic product. *See supra* ¶¶72-74. Accordingly, a POSA would have been motivated to reduce aggregates of all sizes as much as possible.

155. Optimizing the *Fraser/Wulff* formulation to achieve this level of native conformation after storage for two months at 5° C would have been routine for the POSA. As of 2006, formulators possessed a relatively high degree of skill in stabilizing protein therapeutics and whole textbooks had been published as of the priority date that gave detailed instructions to guide POSAs in undertaking this sort of routine optimization.

156. For example, EX1013 (*McNally 2000*) is a chapter in a textbook published in 2000. I have personal knowledge that *McNally 2000* was published prior to 2005 because I had it in my personal library prior to that date. *McNally 2000* sets forth instructions on how to conduct a “well-designed formulation study” to guide the optimization of protein formulations. EX1013 (*McNally 2000*), 139. *McNally 2000* gives specific guidance to POSAs on how to investigate possible problems and solutions to those problems. *See id.*, 139-140 (noting that problems such as aggregation may occur during fermentation, harvesting, and purification of a protein, and giving examples of solutions to these problems, including pH adjustment, adjusting buffer components, or adjusting physical processing steps such as diafiltration, and noting that “feedback from these experiences can be used to design formulation experiments to gain insight on how to avoid, minimize, or explain process problems” and “the results from these formulation experiments can

aid in refining the purification process as well as in guiding future formulation development to address specific potential stability problems.”)

157. *McNally 2000* also instructs the POSA on the importance of analytical techniques such as SEC for characterizing the physicochemical properties of the protein. *Id.*, 140. *McNally 2000* gives a roadmap for formulation optimization that includes solubility studies, isotonicity concerns, solution stability studies, the effect of specific buffers and pH, the use of different excipients, and many other considerations that were part of routine optimization of biologic formulations at the time. *Id.*, 141-153.

158. *McNally 2000* also sets forth a detailed three-step protocol for formulation optimization. *McNally 2000* notes that “while it is important to address all aspects of protein solution formulation, there is a natural sequence to the order in which individual parameters are investigated.” *Id.*, 156. *McNally 2000* then presents a three-step roadmap for optimization that looks at concentration, pH, and other excipients, which then allows for further “refin[ing] and narrow[ing] of future experiments” to optimize and stabilize the solution. *Id.*, 156-57. This is a very typical strategy and would have been very routine for a POSA to undertake.

159. Regarding specific steps that the POSA would undertake to optimize the *Fraser/Wulff* formulation, a POSA would have been able to make incremental

adjustments to the concentrations of polysorbate 20, phosphate buffer, aflibercept, NaCl and pH, observed their impact on stability, and then made additional adjustments as necessary until they achieved maximum stability. To reduce aggregation over time, the POSA would have focused in particular on the concentration of polysorbate 20 and pH, for the reasons set forth above. *See supra* ¶¶73, 75. While this might have required a series of experiments designed to determine the optimal value for each of these variables, the design and execution of such experiments would have been routine and well within ordinary skill.

160. Accordingly, claim 10 would have been obvious to a POSA from *Fraser's* disclosure, in view of the disclosures in *Wulff*, *Holash*, the '319 *Publication*, the '309 *Publication*, and *McNally 2000*, as well as the general knowledge and skill of the POSA.

2. Claim 1

161. As discussed above, a POSA would have understood that any formulation to be administered to humans and primates should be placed within a vial for injection, to be in compliance with GLP, for ease of use and safety, and to protect the formulation from being compromised during storage, transport or use. *See supra* , ¶¶106-109.

162. Common sense would dictate that such formulations be placed into vials to avoid contamination and spillage. Aflibercept was also known to be

administered parenterally (i.e., via injection), and as discussed, these sorts of formulations are most often provided in vials for injection, to, e.g., adhere to good laboratory practice, preserve the integrity of the formulation during use and storage, and aid administration. *See supra*, ¶¶107-08. Such vials are also by far the most practical means to store solid lyophilized protein formulations for reconstitution prior to injection: they could also be coated or made of materials to minimize interaction of the protein with the container. Indeed, long before the priority date, FDA had released guidance regarding the storage of parenteral formulations of proteins like aflibercept, where it stated that small-volume (100 mL or less) or large volume (>100 mL) parenteral drugs may be stored in, *inter alia*, a vial. *See EX1038 (FDA Container Closure Guidance)*, 23-24 (“An SVP may be packaged in a disposable cartridge, a disposable syringe, a vial, an ampule or a flexible bag. An LVP may be packaged in a vial, a flexible bag, a glass bottle or, in some cases, as a disposable syringe.”).

163. Since the ultimate goal of the POSA would have been to formulate VEGFTrap_{R1R2} so that it could be used as a human therapeutic, administered by IV or subcutaneous injection as in *Fraser* and *Wulff*, it would have been starkly obvious to the POSA to place their formulation in a vial.

164. Accordingly, claim 1 would have been obvious to a POSA from *Fraser*’s disclosure, in view of the disclosures in *Wulff*, *Holash*, the ’319

Publication, the '309 *Publication*, *McNally 2000* and *FDA Container Closure Guidance*, as well as the general knowledge and skill of the POSA.

3. Claims 2 and 11

165. Claims 2 and 11 depend from claims 1 and 10, respectively and further specify that “about 99% or more of the weight of the fusion protein” be “in native conformation.” As discussed, the POSA would ideally strive for 100% native conformation after storage for several months at 5 °C. *See supra* ¶81. As discussed, the prior art disclosed >99% native conformation after similar storage conditions. *See supra*, ¶82. For the same reasons expressed with respect to claims 1 and 10, the POSA would have been motivated to reach this 99% stability level and would have had a reasonable expectation of success in doing so. *See supra* Sections VI.B.1 and VI.B.2.

166. Further, as explained, it would have been obvious to use the formulation disclosed in *Fraser* and *Wulff*, which Regeneron later showed in *Dix* met this claimed level of stability. Thus, it would have been obvious to use a formulation that inherently met the claimed level of stability.

167. For all of these reasons and those expressed with respect to claims 1 and 10, claims 2 and 11 would have been obvious to a POSA.

4. Claims 3 and 12

168. Claims 3 and 12 depend from claims 1 and 10 respectively, and further require that “the first VEGF receptor” be “human Flt1” and “the second VEGF receptor” be “selected from the group consisting of human Flk1 and the human Flt4.” EX1001, 19:46-48, 20:44-47. As explained, VEGF-R1 is encoded by the Flt1 gene, while VEGF-R2 is encoded by the Flk1 gene. *See supra* Section V.A. The VEGF Trap_{R1R2} molecule of *Fraser* comprises “Ig domain 2 of human VEGF-R1 and Ig domain 3 of human VEGF-R2.” EX1009 (*Fraser*), 1115; EX 1016 (*Wulff*), 2798 and Fig. 1. Since, as explained, it would have been obvious from *Fraser*, *Wulff* and *Holash* to select VEGFTrap_{R1R2}, *see supra*, ¶¶140-42, it would have been obvious to select a VEGF antagonist in which the first VEGF receptor is human Flt1 and the second VEGF receptor is selected from the group consisting of human Flk1 and the human Flt4.

169. For these reasons and all of the reasons expressed regarding claims 1 and 10, claims 3 and 12 would have been obvious to a POSA.

5. Claims 4 and 13

170. Claims 4 and 13 depend from claims 3 and 12 respectively, and further require that “the fusion protein comprise[] amino acids 27-457 of SEQ ID NO: 4.” EX1001, 19:51-52, 20:49-50. As explained, it would have been obvious from *Fraser*, *Wulff* and *Holash* to select VEGFTrap_{R1R2}, and SEQ ID NO:4 is an

inherent property of VEGFTrap_{R1R2}. *See supra*, ¶¶65, 122, 141-142. Therefore, selecting a VEGF antagonist with SEQ ID NO:4 would have been obvious.

171. Further, Regeneron had published the sequence of VEGFTrap_{R1R2} in multiple places, including, *e.g.*, the '319 Publication and '309 Publication. *See supra*, ¶¶64-65. A POSA formulating VEGFTrap_{R1R2} would have wanted to understand its amino acid sequence and other structural features to determine whether there was anything they should take into account during formulation, and would have looked to one of these prior art references to provide the sequence. Thus, in choosing VEGFTrap_{R1R2} as the VEGF antagonist to formulate, the POSA would have understood they were choosing a VEGF antagonist with SEQ ID NO:4.

172. For these reasons and all of the reasons expressed regarding claims 3 and 12, claims 4 and 13 would have been obvious to a POSA.

6. Claims 5 and 14

173. Claims 5 and 14 depend from claims 4 and 13 respectively, and further require that “the VEGF antagonist” be “a dimer of the fusion protein.” EX1001, 19:51-52, 20:51-52. As discussed above, a POSA would have understood that VEGFTrap_{R1R2} is a dimer. EX1009 (*Fraser*), 1115; EX 1016 (*Wulff*), 2798 and Fig. 1; *supra* ¶¶57, 124-126. Thus, in choosing VEGFTrap_{R1R2}

as the VEGF antagonist to formulate, the POSA would have understood they were choosing a VEGF antagonist that is a dimer.

174. For these reasons and all of the reasons expressed regarding claims 4 and 13, claims 5 and 14 would have been obvious to a POSA.

7. Claims 6 and 15

175. Claims 6 and 15 depend from claims 5 and 14 respectively, and further require that “the organic co-solvent” be “selected from the group consisting of polysorbate 20, polysorbate 90, polyethylene glycol (PEG), PEG3350, and propylene glycol.” EX1001, EX1001, 19:53-56, 20:51-52. As discussed above, *Fraser* discloses a formulation containing “0.1% wt/ vol Tween 20.” EX1009 (*Fraser*), 1115; *supra*, ¶¶91, 128. “Tween 20” is a commercial brand name for polysorbate 20. As explained, the POSA would have been motivated to start with the formulation that Regeneron itself had published in both *Fraser* and *Wulff*. See *supra*, ¶151.

176. For these reasons and all of the reasons expressed regarding claims 5 and 14, claims 6 and 15 would have been obvious to a POSA.

8. Claims 7 and 16

177. Claims 7 and 16 depend from claims 6 and 15 respectively, and further require that “the stabilizing agent” be “selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol.” EX1001, 19:57-59, 20:57-

59. As discussed above, *Fraser* discloses a formulation containing “either 20% glycerol or 20% sucrose.” EX1009 (*Fraser*), 1115. *See supra*, ¶¶91, 131. *Wulff* discloses the same formulation containing 20% sucrose. *See supra*, ¶147. The POSA would have been motivated to start with the sucrose formulation that Regeneron itself had published in *Fraser* and *Wulff*. *See supra*, ¶151.

178. Further, as discussed above, Regeneron subsequently explained that the *Fraser* formulation contained “20% sucrose, and 0.1% polysorbate-20.” EX1023 (*Nov 22 OA Response*), 2. *See supra*, ¶92. Since it would have been obvious to use the formulation of *Fraser*, it would have been obvious to use a formulation that inherently contained 20% sucrose.

179. Even if the POSA did not select 20% sucrose first, the POSA would have selected and tested both 20% sucrose and 20% glycerol. Selecting two slightly different prior-art Regeneron formulations to proceed with does not rise to the level of undue experimentation.

180. For these reasons and all of the reasons expressed regarding claims 6 and 15, claims 7 and 16 would have been obvious to a POSA.

9. Claims 8, 9, 17 and 18

181. Claims 8 and 17 depend from claims 1 and 10 respectively, and further requires that “the organic co-solvent” be “polysorbate 20” and “the stabilizing agent” be “sucrose.” EX1001, 19:60-61, 20:59-61.

182. Claims 9 and 18 depend from claims 1 and 10 respectively, and further recite “the organic co-solvent is polysorbate 20, the buffer is phosphate, and the stabilizing agent is sucrose.” EX1001, 19:62-64, 20:63-65.

183. As discussed above, *Fraser* discloses a formulation containing phosphate buffer, polysorbate 20 and “either 20% glycerol or 20% sucrose.” EX1009 (*Fraser*), 1115. *See supra*, ¶¶91, 131. *Wulff* discloses the same formulation containing phosphate buffer, polysorbate 20 and 20% sucrose. *See supra*, ¶147. The POSA would have been motivated to start with the sucrose-containing formulation that Regeneron itself had published in *Fraser* and *Wulff*. *See supra*, ¶151.

184. Even if the POSA did not select 20% sucrose first, the POSA would have selected and tested both 20% sucrose and 20% glycerol. Selecting two slightly different prior-art Regeneron formulations to proceed with does not rise to the level of undue experimentation.

185. For these reasons and all of the reasons expressed regarding claims 1, 10, 9 and 18, claims 8, 9 17 and 18 would have been obvious to a POSA.

VII. SECONDARY EVIDENCE OF NON-OBVIOUSNESS

186. I am not aware of any relevant “secondary” evidence that would relate to the particular elements of the claims of the ’992 patent. I may respond to any secondary evidence I may become aware of in the future.

VIII. AUTHENTICATION OF EXHIBITS

187. In preparing my declaration I downloaded and reviewed several publications that were available publicly on the FDA's website. One of these was a label (for AVASTIN), and two of these were guidance documents published by FDA. In my experience, the dates that these documents were publicly available corresponds with the publication dates given on FDA's website.

188. EX1032 (*AVASTIN Label*) is a copy of the publicly available labeling that issued with the approval of AVASTIN in February of 2004. I obtained this labeling by visiting the Drugs @ FDA website¹⁰, and searching for AVASTIN. This brought up the FDA's summary page for BLA 125085 for AVASTIN (bevacizumab). From here, I was able to see that the original approval date for AVASTIN was February 26, 2004. The labeling associated with that original approval was available for download by clicking the link to "Review" and then clicking on "Printed Labeling", and that labeling is EX1032. In my experience, the labeling available on Drugs @ FDA that is associated with a particular original approval date corresponds with the labeling that was published on the date of that approval. Thus, this labeling was available more than a year prior to the '992 patent priority date of June 2006.

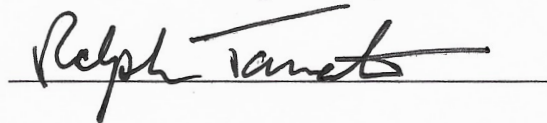
¹⁰ <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm>.

189. EX1038 (*FDA Container Closure Guidance*) and EX1047 (*FDA Specifications Guidance*) are guidances that I obtained through FDA's website. Both of these guidances are dated from 1999. In my experience, the FDA will regularly publish guidances for industry, and the dates on these guidances are the dates on which the guidance becomes publicly available. These guidances arose from the ICH (International Committee on Harmonisation). I was part of the Roche Committee for Injectables at the time, and had input on the substance of these Guidances. Accordingly, I have personal knowledge of the availability of these Guidances at the time. In this case, both EX1038 and EX1047 were available to the public as of 1999, significantly before the '992 priority date of June, 2006.

190. In preparing my declaration I also downloaded and reviewed a definition for the term "vial" that is publicly available in the online version of the Merriam Webster dictionary. I did this by visiting merriam-webster.com and searching for "vial." The resulting entry is saved as a PDF in EX1031. As can be seen on the PDF version, this definition for "vial" was last updated on January 13, 2023.

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

Respectfully Submitted,

A handwritten signature in dark ink, appearing to read "Ralph Tarantino", is written over a horizontal line.

Ralph Tarantino, Ph.D.

APPENDIX – LIST OF EXHIBITS

Exhibit No.	Description
1001	U.S. Patent No. 10,464,992 (“’992 patent”)
1003	Dr. Ralph Tarantino <i>curriculum vitae</i>
1004	File History of U.S. Application No. 16/159,269 (“’992 prosecution history”)
1005	James D. Andya et al., <i>Mechanisms of Aggregate Formation and Carbohydrate Excipient Stabilization of Lyophilized Humanized Monoclonal Antibody Formulations</i> , 5(2) AAPS PHARMSCI (Apr. 4, 2003) (“Andya 2003”)
1006	Byeong S. Chang & Susan Hershenson, <i>Practical Approaches to Protein Formulation Development</i> in RATIONALE DESIGN OF STABLE PROTEIN FORMULATIONS – THEORY AND PRACTICE, 1-25 (J.F. Carpenter and M.C. Manning eds., 2002) (“Chang 2002”)
1007	Eva Y. Chi et al., <i>Physical Stability of Proteins in Aqueous Solution: Mechanism and Driving Forces in Nonnative Protein Aggregation</i> , 20 PHARMACEUTICAL RESEARCH 9, 1325-1336 (Sept. 2003) (“Chi”)
1008	Napoleone Ferrara & Robert S. Kerbel, <i>Angiogenesis as a Therapeutic Target</i> , 438 NATURE 967-74 (Dec. 15, 2005) (“Ferrara 2005”)
1009	Hamish M. Fraser et al., <i>Single Injections of Vascular Endothelial Growth Factor Trap Block Ovulation in the Macaque and Produce a Prolonged, Dose-Related Suppression of Ovarian Function</i> , 90(2) J. CLIN. ENDOCRINOL. & METAB. 1114-1122 (Feb. 2005) (“Fraser”)
1010	Jocelyn Holash et al., <i>VEGF-Trap: A VEGF Blocker with Potent Antitumor Effects</i> , 99 (17) PNAS 11393-11398 (Aug. 20, 2002) (“Holash”)
1011	Janeway et al., <i>The Structure of a Typical Antibody Molecule</i> in IMMUNOBIOLOGY: THE IMMUNE SYSTEM IN HEALTH AND DISEASE, 5th ed., 94-100 (2001) (“Janeway”)

1012	Leopold K. Kostanski et al., <i>Size-exclusion Chromatography – a Review of Calibration Methodologies</i> , 58 J. BIOCHEM. BIOPHYS. METHODS 159-186 (2004) (“Kostanski 2004”)
1013	Paul McGoff & David S. Scher., <i>Solution Formulation of Proteins/Peptides</i> in PROTEIN FORMULATION AND DELIVERY vol. 99, 139-58 (2000) (“McNally 2000”)
1014	Dave A. Parkins & Ulla T. Lashmar, <i>The Formulation of Biopharmaceutical Products</i> , 3(4) PHARM. SCI. & TECH. TODAY 129-137 (Apr. 4, 2000) (“Parkins”)
1015	J.S. Rudge et al., <i>VEGF Trap as a Novel Antiangiogenic Treatment Currently in Clinical Trials for Cancer and Eye Diseases, and VelociGene®-based Discovery of the Next Generation of Angiogenesis Targets</i> , 70 COLD SPRING HARBOR SYMPOSIA ON QUANTITATIVE BIOLOGY 411-418 (2005) (“Rudge”)
1016	Christine Wulff et al., <i>Prevention of Thecal Angiogenesis, Antral Follicular Growth, and Ovulation in the Primate by Treatment with Vascular Endothelial Growth Factor Trap R1R2</i> , 143(7) ENDOCRINOLOGY 2797-2807 (Jul. 2002) (“Wulff”)
1017	Florian M. Wurm, <i>Production of Recombinant Protein Therapeutics in Cultivated Mammalian Cells</i> , 22 NATURE BIOTECHNOLOGY 1393-1398 (Nov. 2004) (“Wurm”)
1018	U.S. Patent No. 6,171,586 to Lam et al. (“’586 Patent”)
1019	U.S. Patent No. 7,374,758 to Papadopoulos et al. (“’758 Patent”)
1020	Application for Extension of Patent Term to U.S. Patent No. 7,374,758 (“’758 PTE”)
1021	U.S. Patent No. 8,110,546 to Dix et al. (“Dix”)
1022	Declaration Pursuant to 37 C.F.R. § 1.131 of Daniel B. Dix, Kelly Frye, and Susan Kautz in Support of U.S. Application No. 12/835,065 (Declaration of Dix et al.)
1023	Response to Office Action of July 13, 2011 in U.S. Application No. 12/835,065 (“Nov 22 OA Response”)
1024	U.S. Patent Publication No. 2003/0113316 to Kaisheva et al. (“Kaisheva ’316”)

1025	U.S. Patent Publication No. 2003/0138417 to Kaisheva et al. (“Kaisheva ’417”)
1026	U.S. Patent Publication No. 2004/0197324 to Liu et al. (“Liu”)
1027	U.S. Patent Publication No. 2004/0265309 to Kandel et al. (“’309 Publication”)
1028	U.S. Patent Publication No. 2005/0112061 to Holash et al. (“’061 Publication”)
1029	International Publication No. WO 00/75319 to Papadopoulos et al. (“’319 Publication”)
1030	International Publication No. WO 97/04801 to Andya et al. (“WO ’801”)
1031	<i>Vial</i> , Merriam-Webster.com, https://merriam-webster.com/dictionary/vial (last visited Jan. 16, 2023) (“ <i>Merriam Webster Vial Definition</i> ”)
1032	AVASTIN [®] , <i>Approved Labeling</i> , CENTER FOR DRUG EVALUATION AND RESEARCH (2004) (“AVASTIN label”)
1033	RAPTIVA [®] , <i>Physicians’ Desk Reference</i> (59th ed. 2005) (“RAPTIVA label”)
1034	REMICADE [®] , <i>Physicians’ Desk Reference</i> (59th ed. 2005) (“REMICADE label”)
1035	SIMULECT [®] , <i>Physicians’ Desk Reference</i> (59th ed. 2005) (“SIMULECT label”)
1036	HERCEPTIN [®] , <i>Physicians’ Desk Reference</i> (59th ed. 2005) (“HERCEPTIN label”)
1037	XOLAIR [®] label, <i>Physicians’ Desk Reference</i> (59th ed. 2005) (“XOLAIR label”)
1038	Food & Drug Administration, <i>Guidance for Industry, Container Closure Systems for Packaging Human Drugs and Biologics</i> (May 1999) (“FDA Guidance”)
1047	U.S. Department of Health and Human Services, Food & Drug Administration, <i>Guidance for Industry, Guidance for Industry</i> (Aug. 1999) (“ <i>FDA Specification Guidance</i> ”)