

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FRESENIUS KABI SWISSBIOSIM GMBH,
Petitioner,

v.
REGENERON PHARMACEUTICALS, INC.,
Patent Owner.

Case IPR2025-01268
U.S. Patent No. 11,084,865

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

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2. a vascular endothelial growth factor (VEGF) antagonist	24
3. an organic co-solvent	27
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5. a stabilizing agent	29
6. wherein said VEGF antagonist fusion protein is glycosylated and comprises amino acids 27-457 of SEQ ID NO:4	30

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TABLE OF EXHIBITS

Exhibit	Description
1001	U.S. Patent No. 11,084,865 (“’865 Patent”)
1003	Ramsey <i>Curriculum Vitae</i>
1004	File History of U.S. Application No. 16/739,559
1005	U.S. Patent No. 10,406,226 (“Dix ’226”)
1007	<i>Regeneron v. Mylan</i> , Memorandum Opinion and Order Following Bench

I. INTRODUCTION

1. I have been retained by ArentFox Schiff LLP on behalf of Fresenius Kabi Swssbiosim GmbH (“Petitioner”) to provide expert opinions regarding aflibercept formulations, their design, and the invalidity of U.S. Patent No. 11,084,865 (“’865 patent”) assigned to Regeneron Pharmaceuticals, Inc. (“Regeneron” or “Patent Owner”).

2. My opinions in this declaration are based on the documents I cite along with my education, experience and knowledge that I have acquired working in the areas of pharmaceutical development and research for nearly 25 years. I am being compensated for my services as an expert at my standard consulting rate. My compensation is in no way contingent on the substance of my opinions or the outcome of this case.

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

II. BACKGROUND AND QUALIFICATIONS

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

5. I am currently a Professor in the School of Chemical Engineering at Oklahoma State University in Stillwater, OK. I have been a faculty member at Oklahoma State University since 2008.

6. I received a Bachelor of Science in Chemical Engineering from Oklahoma State University in 2000, a Master of Science in Chemical Engineering from the University of Illinois in 2003, and a Ph.D. in Chemical and Biomolecular Engineering from the University of Illinois in 2006. I was a Postdoctoral Fellow in the Department of Pharmaceutical Chemistry at the University of Kansas, Lawrence, KS, in 2006-07.

7. My research in the areas of drug development, formulation, and delivery has been competitively funded by multiple awards from the National Institutes of Health, National Science Foundation, American Heart Association, and the Department of Defense, among others.

8. I have received the University's highest teaching honor, the Regents Distinguished Teaching Award (2023), and many awards and honors related to my research, including an endowed professorship in chemical engineering (2016-current), the President's Fellows Faculty Research Award (2019), a finalist for the Oklahoma Biosciences Researcher Recognition Award (2016), the National Science Foundation CAREER Award (2014), Journal of Pharmaceutical Sciences Top Reviewers (2007), and the PhRMA Foundation Postdoctoral Fellowship (2006-2007), among others. Exhibit 1003 at p. 2-3.

9. I am a licensed professional engineer, with emphases in chemical, biochemical, and biomedical/bioengineering. I am currently, or have been in the past,

a member of various professional societies, including the American Institute of Chemical Engineers (AIChE), Tau Beta Pi Engineering Society and Omega Chi Epsilon Chemical Engineering Honor Society. I am currently serving as the area co-chair of ‘Chemical Engineers in Medicine’ for the 2025 AIChE Annual Meeting and have previously served as chair or co-chair for AIChE sessions on topics including Drug Delivery, Nucleic Acid Delivery, and Pandemic Response, Public Health, and mRNA Vaccines, among others. I teach courses on topics that include drug delivery, and I serve or have served on numerous scientific review panels, including the National Institutes of Health, National Science Foundation, Quebec Consortium for Drug Discovery, and the Swiss National Science Foundation. I have also served as an ad hoc reviewer for numerous scientific journals, including the Journal of Pharmaceutical Sciences, Molecular Pharmaceutics, and Nanomedicine and Nanotechnology. Exhibit 1003 at p. 3-5.

10. I have authored more than sixty peer-reviewed journal articles and six book chapters, most of which are focused on the design, production, formulation, or delivery of pharmaceuticals. Exhibit 1003 at p. 6-18. My research has worked to improve the stability of retroviral gene vectors (Vu et al., 2007) and understand the relationships between intramolecular dynamics and the stability of immunoglobulins used as pharmaceutical therapeutics (Kamerzell et al., 2008; Ramsey et al., 2009). My work has also involved screening of excipients for improving the stability of

plasmid DNA therapeutics (Zeng et al., 2011), vaccines (Choudhari et al., 2013), and adenovirus vectors (Kupgan et al., 2014).

11. I have edited a book on drug delivery and formulation. Exhibit 1003 at p. 5. In addition to my publications, my research has been covered in more than 80 presentations at national and international conferences. Exhibit 1003 at p. 11 to 16.

12. I have filed for or received about seven United States and international patents or patent applications related to drug discovery, production or delivery. Exhibit 1003 at p. 17.

13. I am the co-founder of Multivate LLC, founded in 2017, which specialized in novel, single-use bioreactors for large-scale production of protein pharmaceuticals.

14. In the past five years, I have been involved in the following litigations:

□ *Allergan, Inc. v. Revance Therapeutics, Inc.*, C.A. No. 21-1411-RGA.

15. Over the course of my career, I have worked on pharmaceutical drug development and formulation of large molecules (i.e., viruses, plasmid DNA, proteins, including immunoglobulins, and peptides) for intravenous, intramuscular, intratumoral, subcutaneous, and oral delivery. I have worked from the product formulation stage through post-market formulation analysis. Further, I have extensive

experience with nanoparticle and microparticle formulations, liquid and lyophilized products.

III. INFORMATION RELIED UPON

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

17. The full list of information, in addition to my professional and academic experience, that I have relied upon in forming my opinions for this report is set forth throughout the report and in the Table of Exhibits. Where my conclusions are based on certain assumptions that I have adopted, I have stated such assumptions in this Declaration.

IV. RELEVANT LEGAL STANDARD

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

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

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

A. Person of Ordinary Skill in the Art

21. I have been informed that the claims of a patent are judged from the perspective of a hypothetical construct involving “a person of ordinary skill in the art” (“POSA”). The “art” is the field of technology to which the patent is related. I understand that the purpose of using a POSA’s viewpoint is objectivity. Thus, I understand that the question of validity is viewed from the perspective of a POSA. I have been informed that the claims of the ’865 Patent are interpreted as a POSA would have understood them at the relevant time period, which I have been asked to assume is June 16, 2006 unless and until Regeneron establish otherwise.

B. Claim Construction

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

23. I further understand that in the absence of a specific definition within the specification or the reliance on a specific meaning in the prosecution history, the

terms as used in the challenged claims of the '865 Patent are to be afforded their plain and ordinary meaning at the time of the invention.

24. I understand that the “plain and ordinary meaning” of a term means the ordinary and customary meaning given to the term by those of ordinary skill in the art at the time of the invention and that the ordinary and customary meaning of a term may be evidenced by a variety of sources, including the words of the claims, the specification, drawings, and prior art. I understand that in construing claims, all words in a claim must be considered in judging the patentability of that claim against the prior art.

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

C. Presumption of Validity

26. I understand that a granted patent is presumed to be valid. I understand that the presumption of validity can be overcome in district court litigation if clear and convincing evidence is presented that proves the patent is invalid. I understand

that the standard of proof for invalidating a patent in an *inter partes* review proceeding is a “preponderance of the evidence” (*i.e.*, greater than 50% chance of likelihood), which is a lower standard than the clear and convincing evidence standard.

D. Anticipation

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

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

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

only steps required to achieve the functional result are the same as those disclosed in the prior art. In other words, when the patent does not itself disclose any more than what is in the prior art regarding how to achieve a claimed functional result, then the functional result is inherently disclosed by the prior art. I understand that “post art” evidence (documents or other information created or published after the patent’s priority filing date) can be relied on to show that a claimed feature is necessarily present, or inherent, in the prior art.

30. I understand that, in an anticipation analysis, there is no need to consider secondary considerations, such as commercial success, unexpected results, failure of others, long-felt but unmet need, teaching away, or praise.

V. BACKGROUND OF THE ’865 PATENT

A. General Description

31. The ’865 patent is entitled “VEGF Antagonist Formulations Suitable for Intravitreal Administration.”

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

33. VEGF is a known protein that was known in the prior art to help grow blood vessels; VEGF traps are proteins designed to “trap” VEGF to decrease blood vessel growth, which helps treat ocular diseases like wet-AMD. The ’865 patent

admits that this class of compounds was already known in the prior art, and that the “VEGF antagonist of the methods and formulations of the invention can be prepared by any suitable method known in the art, or that comes to be known.” Exhibit 1001 at col. 6, ll. 40-42.

34. The '865 patent admits that “[i]n specific embodiments, the VEGF antagonist is expressed in a mammalian cell line such as a CHO cell and may be modified post-translationally,” and further notes that in “a specific embodiment, the fusion protein comprises amino acids 27-457 of SEQ ID NO:4 and is glycosylated at Asn residues 62, 94, 149, 222 and 308.” Exhibit 1001 at col. 6, ll. 32-38.

35. The '865 patent includes eight examples, which describe combinations of protein, buffer, stabilizer and one of two “organic co-solvents.” Seven of the eight examples include 20 to 50 mg/ml of “VEGF Trap (SEQ ID NO:4)” protein in combination with phosphate buffer, sodium chloride, and polysorbate 20 in varying combinations at a pH of 6.25 or 6.3. Exhibit 1001 at Examples 1, 3-8. Five of the examples additionally contain sucrose. *Id.*, Examples 1-4, 7. Six of the examples deal with liquid formulations (*Id.*, Examples 1-6), and two with lyophilized formulations (*Id.*, Examples 7-8).

36. The examples of the '865 patent report the formulation's stability after storage at 5 °C for certain periods of time. Turbidity at OD405 nm and “% VEGF Trap Native Configuration” as measured by size-exclusion chromatography are reported

after storage periods that run from zero to 24 months. *See, e.g.*, Exhibit 1001., Tables 1-8. The examples also provide the pH of the formulation over time. The range of concentrations for the VEGF Trap and excipients and their associated stability characteristics are summarized below:

	VEGF	Buffer	Tonicity	Co-solvent	Stabilizing	Stability
'865	20-50	5-10 mM	20-135	0.015-0.1%	0-5%	98.5%-
Examples	mg/mL	phosphate	mM	polysorbate	sucrose	99.3% at

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

B. Priority Date

38. The '865 patent claims priority to ten prior patent applications and one provisional application, which was filed on June 16, 2006. I have been informed that June 16, 2006 is the appropriate priority date, unless Regeneron establishes an earlier priority date.

C. Prosecution History

39. I have reviewed the '865 patent prosecution history, and the Examiner issued obviousness-type double patenting rejections. Ex.1004, '865 File History March 19, 2021 Office Action at pp. 4-5. Regeneron relied on the stability claim element regarding the percent of aflibercept remaining in native conformation to overcome the obviousness-type double patenting rejection. Exhibit 1004, '865 File History May 5, 2021 Response at p. 11-13. Regeneron did not argue, however, that obtaining the added stability limitation was unexpected or that it conferred any unexpected properties to the formulation or that it was not inherent.

D. Level of Ordinary Skill in the Art

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

41. The POSA at the time of the invention would have had a Ph.D. in pharmaceutical sciences or a similar field, with at least several years of experience in the development, manufacture and characterization of formulations of therapeutic proteins, including, for example, fusion proteins or antibodies. The POSA may also have had less education but substantially more practical relevant work experience. This individual would have understood how to combine proteins with compatible excipients such as surfactants, stabilizers, salts and buffers at different pH ranges, and

how to adjust these combinations in order to optimize their stability in liquid or solid form. This individual also would have been able to use state-of-the-art analytical methods, such as size-exclusion chromatography (“SEC”), to assess stability and compatibility.

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

VI. THE CHALLENGED CLAIMS

43. The Challenged Claims are generally directed to ophthalmic formulations, in either a vial or a pre-filled syringe, comprising a glycosylated VEGF antagonist that comprises amino acids 27-457 of SEQ ID NO:4, an organic co-solvent, a buffer, and a stabilizing agent, wherein the formulations have specific stability (turbidity and % “native conformation” measured by SEC). Exhibit 1001 at col. 19-22.

VII. PRIOR ART

44. Aflibercept was known, and so too were its suitable formulations, as later claimed in the '865 patent.

A. Background

1. Vascular Endothelial Growth Factor (“VEGF”)

45. I understand that Vascular Endothelial Growth Factor, also known as VEGF, is a naturally-occurring protein that mediates the formation of new blood vessels, or “angiogenesis.” VEGF binds to VEGF receptors on the cells responsible for angiogenesis. Ex. 1005 at col. 1, ll.43-60.

46. VEGF was shown to have a role in angiogenesis in tumors, and VEGF inhibitors had been developed as potential cancer therapies. *Id.*

2. Aflibercept

47. Aflibercept was a VEGF inhibitor, with different known names and known sequence identification. Aflibercept binds VEGF before it can trigger angiogenesis.

48. Aflibercept was known as a fusion protein, and the prior art identified what was known as aflibercept by Sequence Id No. and provided specific tested formulation examples. Exhibit 1005 (titled “Method Manufacturing VEGF Antagonist Fusion Proteins”). Because they refer to the same thing, I may refer to one or the other term in my declaration.

49. The prior art also disclosed that it used CHO cells to express aflibercept. *See, e.g.*, Exhibit 1005 at col. 5, ll. 37-39 (“VEGF antagonist is expressed in a mammalian cell line such as a CHO cell and may be modified posttranslationally”). The prior art also made clear that “[i]n a specific embodiment, the fusion protein comprises amino acids 27-457 of SEQ ID NO:4 and is glycosylated at Asn residues 62, 94, 149, 222, and 308.”

50. The prior art also included detailed aflibercept formulation disclosures, as further discussed below. For example, aflibercept was formulated with phosphate buffer NaCl polysorbate 20 and sucrose. *See e.g.*, Exhibit 1005.

B. Dix '226

51. U.S. Patent No. 10,406,226 (“Dix '226”) is titled “Method of manufacturing VEGF antagonist fusion proteins.” It is my understanding that Dix '226 is considered prior art as it relies on a priority date of March 25, 2005 based on a provisional application (No. 11/387,246) and a utility patent application (60/665,125) filed on March 25, 2006, which is before the '865 patent's priority date of June 16, 2006 based on the filing of the provisional application 60/814,484.

52. Dix '226 is directed to VEGF antagonist formulations. The Dix '226 reference taught all of the elements of the claims of the '865 patent. Dix '226 also disclosed aflibercept formulations that are “suitable for intravitreal administration” as it discloses all of the excipients in amounts claimed in the challenged claims of

the '865 patent. Dix '226 contained this important teaching for the POSA to understand the formulations Regeneron itself had already purported to invent: "In a specific embodiment, the stable liquid formulation of a VEGF-specific fusion protein antagonist comprises 1-10 mM phosphate buffer, 1-10 mM citrate, 25-150 mM NaCl, 5-30% sucrose, 10-50 mg/ml of the fusion protein, at a pH of about 6-6.5." Exhibit 1005 at col. 2, ll. 20 to 25. While I discuss additional disclosures and examples, this statement would demonstrate to the POSA what Regeneron already considered workable ranges of formulations for aflibercept, and these are not relatively broad ranges in the art.

53. Dix '226 disclosed aflibercept formulations having each of the claimed excipients and stability. Dix '226 disclosed several embodiments of aflibercept formulations. Dix '226 disclosed polysorbate 20 as the preferred organic cosolvent. The preferable buffers are phosphate and citrate (Exhibit 1005 at col. 1, ll. 58-64; col. 2 ll. 3-6). It also has an embodiment using a histidine buffer (*Id.* at col. 2, ll. 16-21). Dix '226 disclosed sucrose as a preferred stabilizing agent or lyoprotectant. (*Id.* at col. 2, ll. 35-37). The aflibercept formulations of the Dix '226 patent were produced in a Chinese Hamster Ovary (CHO) cell (*Id.* at col. 5, ll. 13-14).

54. Dix '226 disclosed a 40 mg/ml pre-lyophilized formulation that was lyophilized and reconstituted to an 80 mg/ml solution. Dix also disclosed formulations with a range of sucrose that permitted lower amounts of sucrose. For example, Dix

disclosed an embodiment where the pre-lyophilized formulation comprises 5-50 mM histidine, 0.1-3.0% PEG, 0.25-3.0% glycine, 0.5-6.0% sucrose, and 5-75 mg/ml of the fusion protein, at a pH of about 6.0-6.5. Exhibit 1005 at col. 2, ll. 63-66.

55. In another embodiment, “the pre-lyophilized formulation consists of about 10 mM histidine, about 1.5% PEG 3350, about 0.75% glycine, about 2.5% sucrose, and about 50 mg/ml of the VEGF trap protein (SEQ ID NO:4), pH 6.3, and upon reconstitution claims 20 mM histidine, 3% PEG, 1.5% glycine, about 5% sucrose, and about 100 mg/ml VEGF trap protein.” (Exhibit 1005 at col. 3, ll. 27-34).

56. Example 1 disclosed a 50 mg/ml liquid formulation of VEGF trap protein containing 10 mM phosphate, 50 mM NaCl, 0.1% polysorbate 20, 20% sucrose, and 50 mg/ml VEGF trap (SEQ ID NO: 4, aflibercept) with pH 6.25. It disclosed a second formulation that has PEG 3350 as the organic co-solvent instead of polysorbate 20. (Exhibit 1005 at col. 7, ll. 62-65).

57. Thus, Dix '226 disclosed all of the claimed ingredients in the amounts in the '865 patent. The below table summarizes the pertinent disclosures from Dix '226:

	VEGF Trap (aflib)	Buffer	Tonicity agent	Co- solvent	Stabilizing agent	pH
Dix '226 Specification	10-50 mg/mL	1-10 phospha	25-150 mM	0.05- polysorb	5-30% sucrose	6.0- 6.5

	VEGF Trap (aflib)	Buffer	Tonicity agent	Co- solvent	Stabilizing agent	pH
(2:20-34)		1-10	NaCl	20		
Dix '226 Specification (Tables 1-6)	50 to 100 mg/mL	5-10 phospha 5 mM phos- phate	50 mM NaCl	0.1% polysorb 20	20% sucrose	6.0- 6.3
Narrowest '865 claims	40 mg/ml	5-25 buffer	tonicity agent	0.03- polysorb 20	1 to 7.5% sucrose	6.2- 6.3

58. Dix '226 disclosed VEGF trap formulations that meet the claimed stability of at least 98% native conformation as measured by size exclusion chromatography after storage at 5 °C.

59. Stability was determined by SE-HPLC (Size Exclusion High Performance Liquid Chromatography), which is a common type of size exclusion chromatography (SEC), with SE-HPLC being more sensitive and precise compared to standard SEC chromatography column. The core principle of both is to separate molecules based on their size, using a porous gel or bead-packed column. A POSA would have understood based on general knowledge that SE-HPLC disclosed in Dix '226 is a type of SEC. The results are shown in Tables 1 and 2. Both show that well over 98% of the VEGF trap was in native conformation after 2 months at 5 °C.

TABLE 1

Stability of 50 mg/ml VEGF Trap Protein When Stored at 5° C. (VGFT-SS065)					
Months	Visual Appearance	Turbidity	pH	% VEGF Trap Recovered	% VEGF Trap Native Configuration
0	Pass	0.00	6.2	100	99.0
3	Pass	0.00	6.2	102	98.8
6	Pass	0.01	6.2	103	98.7
9	Pass	0.01	6.3	102	98.2
12	Pass	0.01	6.3	106	98.6
18	Pass	0.00	6.3	103	98.4
24	Pass	0.00	6.2	93	98.3

TABLE 2

Stability of 50 mg/ml VEGF Trap Protein When Stored at 5° C. (VGFT-SS065)					
Months	Visual Appearance	Turbidity	pH	% VEGF Trap Recovered	% VEGF Trap Native Configuration
0	Pass	0.00	6.2	100	99.0
3	Pass	0.00	6.2	100	98.8
6	Pass	0.01	6.3	103	98.5
9	Pass	0.00	6.3	103	98.3
12	Pass	0.01	6.3	110	98.3
18	Pass	0.00	6.3	113	98.0
24	Pass	0.01	6.2	90	97.8

60. Example 5 tests the stability of formulation of aflibercept with 5 mM phosphate and 5 mM citrate as buffers, 0.1% polysorbate 20, 100 mM NaCl, 20% sucrose and 25mg/ml VEGF trap protein. Exhibit 1005 at col. 12, ll. 1-30.

61. Table 9 demonstrates that this formulation had greater than 99% remaining in native conformation after 24 months of storage at 5 °C.

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

62. Dix '226 also described the robustness of its formulations, even providing different forms and details for a variety of applications within the patent itself. Example 4 is even titled “Further Embodiments of Stable VEGF Trap Formulations” and discusses assorted approaches. Ex.1005 at col. 10. One approach is to use lyophilization, with both pre-lyophilized and post-lyophilization formulations disclosed. For example, Dix '226 disclosed a pre-lyophilized formulation containing 10 mM histidine, 1.5% PEG 3350, 0.75% glycine, 2.5% sucrose, 50 mg/ml VEGF trap protein, pH 6.3. After reconstitution, Dix '226 showed that the formulation concentration could be increased, to 20 mM histidine, 3% PEG 3350, 5% sucrose, 1.5% glycine, 5% sucrose and 100 mg/ml of VEGF trap protein, pH 6.3. (Exhibit 1005 at col. 3, ll. 28-34). Another approach is to use liquid formulations without lyophilization.

“One advantage of this liquid formulation is that it provides a higher concentration of VEGF trap without requiring the manufacture of a lyophilized product.” Ex.1005 at 10:30-33. Dix ’226 disclosed that formulations comprising 10 mM histidine, 50 mM NaCl, 5-20% sucrose, 50-100 mg/ml VEGF trap and one of 0.1% polysorbate 20 or TY[®] PEG 3350 were stable in Table 7. (Exhibit 1005 at col. 10, ll. 42-55). For example, a formulation with 50 mg/ml of VEGF trap and 0.1% polysorbate had only 0.7% degradation after 24 months.

TABLE 7

Stability of Liquid Formulation with 50-100 mg/ml VEGF Trap (VGFT-SS101)				
Incubation (months)	VEGF Trap (mg/ml)	% Polysorbate 20	% PEG 3350	% Degradation
24	50	0.1	—	0.7
24	50	—	3	1.3
15	75	0.1	—	1.5
15	75	—	3	2.0
15	100	0.1	—	1.9
15	100	—	3	2.6

63. Dix ’226 did not just test one concentration formulation, but also ranges of formulations including higher concentration formulations that would be useful for intravitreal administration because a higher concentration permits a lower administration volume. The 25 mg/ml example was one formulation concentration,

for which Dix '226 disclosed detailed formulation and express stability data. In addition, Dix '226 disclosed other, even higher concentrations as well.

64. Dix '226 further disclosed a 100 mg/ml example. After lyophilization and reconstitution, the formulation contained 20 mM histidine, 3% PEG 3350, 5% sucrose, 1.5% glycine and 100 mg/ml of VEGF trap protein (SEQ ID No: 4)—which is aflibercept. *See e.g.*, Exhibit 1005 at Example 4, col. 10, ll. 1 to 40.

65. Dix '226 also disclosed 50 mg/ml examples. One example used 10 mM histidine, 1.5% PEG 3350, 0.75% glycine, 2.5% sucrose, 50 mg/ml VEGF trap protein, pH 6.3, and is reconstituted to a formulation containing 20 mM histidine, 3% PEG 3350, 1.5% glycine, and 5% sucrose. *See e.g.*, Exhibit 1005, at Example 4 col. 10, ll. 1 to 54. A POSA reviewing Dix '226 would have thus recognized that higher concentrations were not a problem for aflibercept.

66. Dix '226 reported validating stability results for these higher-concentration 50100 mg/ml aflibercept formulations. The results were summarized in Table 7. Exhibit 1005 at col. 10, ll. 41 to 55.

TABLE 7

Stability of Liquid Formulation with 50-100 mg/ml VEGF Trap (VGFT-SS101)				
Incubation (months)	VEGF Trap (mg/ml)	% Polysorbate 20	% PEG 3350	% Degradation
24	50	0.1	—	0.7
24	50	—	3	1.3
15	75	0.1	—	1.5
15	75	—	3	2.0
15	100	0.1	—	1.9
15	100	—	3	2.6

67. As shown in Table 7, percent degradation was very low even after extended tested time periods. The first line in Table 7 shows a formulation with 50 mg/ml of aflibercept with 0.1% polysorbate faced only 0.7% degradation even after 24 months. *Id.*

VIII. INVALIDITY GROUND 1: ANTICIPATION BY DIX '226

68. In my opinion, the intravitreal formulation recited in the Challenged Claims is anticipated. Dix '226 disclosed all of the elements in the Challenged Claims and anticipates the Challenged Claims of the '865 patent. Again, as highlighted above, Dix '226 already disclosed useful formulations for aflibercept: “In a specific embodiment, the stable liquid formulation of a VEGF-specific fusion protein antagonist comprises 110 mM phosphate buffer, 1-10 mM citrate, 25-150 mM NaCl, 5-30% sucrose, 10-50 mg/ml of the fusion protein, at a pH of about 6-6.5.” Exhibit 1005 at col. 2, ll. 20-24. While I discuss additional disclosures and examples, this statement would demonstrate to the POSA what Regeneron already

considered workable ranges of formulations for aflibercept, and these are not relatively broad ranges in the art.

A. Claim 1 and 26

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

69. Independent claims 1 and 26 are identical except that claim 1 is directed to a vial while claim 26 is directed to a pre-filled syringe (PFS). Dix '226 disclosed a formulation that can be stored in a vial or PFS. Dix also disclosed a formulation that is suitable for intravitreal administration as it has the same excipients that are used in the example formulations of the '865 patent.

70. Dix '226 disclosed vials as a suitable storage container. (Exhibit 1005 at col. 3, ll. 52-58). The Dix '226 patent also disclosed an embodiment using a PFS. (col. 10, ll. 2741). Dix '226 disclosed that an advantage of using PFS is that it allows administration of a higher concentration in a shorter infusion time compared to IV infusion. *Id.* This advantage would encourage a POSA to use a PFS for intravitreal injection where a higher concentration needs to be administered in a small volume of 0.1 ml.

71. Further, the formulations disclosed in Dix '226 were “suitable for intravitreal administration” as an “ophthalmic formulation.” It is my understanding from counsel that the district court previously construed this claim term to mean formulations using excipients in the '865 patent's formulations or those other prior art

products for intravitreal administration. Ex.1007 at p. 205 to 206. The court agreed with Defendants' expert, Dr. Trout, who stated a POSA would look to literature and credited the disclosure that "[i]t is preferred to select excipients that have been used in marketed products with a relevant route of delivery." *Id.* at p. 209. Dix '226 meets this standard. Dix '226 disclosed formulations with the same excipients used in the '865 patent and for at least this reason are "suitable for intravitreal administration."

72. Dix also disclosed amounts of aflibercept, stabilizer, buffer, tonicity agent and organic co-solvent that are suitable for intravitreal administration. Dix '226 discloses a range of 10-50 mg/ml and a pre-lyophilized formulation that is precisely 40 mg/ml, that is in claim 2 of the '865 patent. In addition, Examples 1 and 4 use phosphate buffer, sucrose stabilizer and polysorbate, which are the same as the '865 patent's Example 1 ingredients. Under the district court's claim construction, which is assumed to be applicable here as a reasonable construction, these Dix '226 formulations are considered "suitable for intravitreal administration" at least for the reason that they contain the same excipients used in the '865 patent's claimed formulation. Ex.1007 at p. 209.

73. The challenged dependent claims (2-5, 7-25, 27-30, 32-50) focus on the specific aflibercept concentration or the types and amounts of excipients in the formulation. Dix '226 discloses ranges that encompass the amounts claimed in the '865 dependent claims or it discloses embodiments that fall squarely within the

claimed ranges of the '865 dependent claims. Dix '226 also describes several aflibercept formulations in the prior art, such as (1) a 40 mg/ml pre-lyophilized aflibercept formulation (Exhibit 1005 at col. 3, ll. 60-62) and (2) a formulation containing 25 mg/ml aflibercept, a buffer of 5 mM phosphate and 5 mM citrate, 100 mM NaCl (pH 6.0)), 0.1% wt/vol polysorbate 20, with 20% sucrose (Exhibit 1005, col. 12, ll. 1-10), or 50 mg/ml aflibercept, a buffer of 10 mM phosphate, 50 mM NaCl, 0.1 wt/vol polysorbate 20, with 20% sucrose, Exhibit 1005, col. 7, ll. 60-68 (Table 1)). It also provides stability data for several prior art aflibercept formulations.

74. Dix '226 discloses that sucrose can range from about 5% to about 30%, which overlaps with the narrowest claimed range of 1 to 7.5% of the '865 patent. It also discloses embodiments using histidine buffer and PEG 3350 co-solvent and optionally polysorbate 20 where the pre-lyophilized amount of sucrose is 2.5% and a reconstituted sucrose amount of 5%. For these histidine embodiments, Dix '226 discloses the sucrose is in a range of 0.5-6.0%, 5-50 mM histidine, 0.13.0% PEG, 0.25-3.0% glycine, 5-75 mg/ml of the fusion protein, pH of 6-6.5 and may optionally contain polysorbate 20. Exhibit 1005, col. 2, l. 63-col. 3: l. 3. A POSA would have understood from Dix '226's inclusion of a range that goes down to 5% sucrose to disclose a formulation that is suitable for intravitreal use.

2. a vascular endothelial growth factor (VEGF) antagonist

75. Dix '226 disclosed formulations with a VEGF antagonist (aflibercept). Specifically, it disclosed “more preferably, SEQ ID NO: 4,” which corresponds to aflibercept. Exhibit 1005, col. 5, ll. 37-42. Dix '226 also disclosed specific examples of formulations comprising a VEGF antagonist: Example 1 of Dix '226 disclosed “[a] liquid formulation containing 10 mM phosphate, 50 mM NaCl, 0.1% polysorbate 20, 20% sucrose, and **50 mg/ml VEGF trap (SEQ ID NO:4)**, pH 6.25” Exhibit 1005 at Example 1 (emphasis added). Example 3 disclosed “[a] liquid formulation containing 10 mM phosphate, 50 mM NaCl, 0.1% polysorbate 20, 20% sucrose, and **100 mg/ml VEGF trap (SEQ ID NO:4)**, pH 6.25” *Id.*, Example 3 (emphasis added). Example 4 disclosed “a stable liquid VEGF-binding fusion protein (VEGF trap) formulations comprising 5 mM phosphate, 5mM citrate, 100 mM NaCl, 0.1% Polysorbate 20, 20% sucrose, **25 mg/ml VEG F Trap protein**, pH 6.0.” *Id.* at Example 4 (emphasis added). Example 5 disclosed “[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.**” *Id.* at 12:1-3 (emphasis added).

76. Dix '226 also explicitly provides the glycosylated asparagine residues that are claimed in the '865 patent.

77. Moreover, a POSA would have understood that a VEGF antagonist produced in CHO cells would necessarily be glycosylated at the claimed asparagine

residues of the '865 patent, and Dix '226 also expressly disclosed using a CHO cell line. Ex.1005 at 5:37-42.

3. an organic co-solvent

78. The Dix '226 disclosed embodiments with 0.1% wt/vol of an organic co-solvent (polysorbate 20). It also disclosed embodiments containing a PEG 3350 co-solvent. In particular, Example 1 of Dix '226 disclosed “[a] liquid formulation containing 10 mM phosphate, 50 mM NaCl, **0.1% polysorbate 20**, 20% sucrose, and 50 mg/ml VEGF trap (SEQ ID NO:4), pH 6.25” Ex.1005 Example 1 (emphasis added). Example 3 disclosed “[a] liquid formulation containing 10 mM phosphate, 50 mM NaCl, **0.1% polysorbate 20**, 20% sucrose, and 100 mg/ml VEGF trap(SEQ ID NO:4), pH 6.25” *Id.*, Example 3 (emphasis added). Example 4 disclosed “a stable liquid VEGF-binding fusion protein (VEGF trap) formulations comprising 5 mM phosphate, 5mM citrate, 100 mM NaCl, **0.1% Polysorbate 20**, 20% sucrose, 25 mg/ml VEG F Trap protein, pH 6.0.” *Id.* at Example 4 (emphasis added). Example 5 disclosed “[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.” *Id.* at 12:1-3 (emphasis added).

4. a buffer

79. The Dix '226 formulations disclosed examples with 50/50 5mM phosphate and 5mM citrate as buffers, or 10 mM phosphate alone or 10 mM histidine

alone. Ex.1005, Examples 1, 3, 4 and 5, col. 10, ll. 15-25. In particular Example 1 of Dix '226 disclosed “[a] liquid formulation containing **10 mM phosphate**, 50 mM NaCl, 0.1% polysorbate 20, 20% sucrose, and 50 mg/ml VEGF trap (SEQ ID NO:4), pH 6.25” Ex.1005 Example 1 (emphasis added). Example 3 disclosed “[a] liquid formulation containing **10 mM phosphate**, 50 mM NaCl, 0.1% polysorbate 20, 20% sucrose, and 100 mg/ml VEGF trap (SEQ ID NO:4), pH 6.25” *Id.* at Example 3 (emphasis added). Example 4 disclosed “a stable liquid VEGF-binding fusion protein (VEGF trap) formulations comprising **5 mM phosphate, 5 mM citrate**, 100 mM NaCl, 0.1% Polysorbate 20, 20% sucrose, 25 mg/ml VEG F Trap protein, pH 6.0.” *Id.* at Example 4 (emphasis added). Example 5 disclosed “[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.” *Id.* at 12:1-3 (emphasis added).

5. a stabilizing agent

80. The Dix '226 formulations contained a stabilizing agent (sucrose) in an amount of 0.6-6% or 5 to 30%. It disclosed embodiments with 20% sucrose using phosphate buffer, as well as other aflibercept embodiments with 2.5 or 5% sucrose when using histidine buffer and PEG with polysorbate 20. Ex.1005. In particular Example 1 of Dix '226 disclosed “[a] liquid formulation containing 10 mM phosphate, 50 mM NaCl, 0.1% polysorbate 20, **20% sucrose**, and 50 mg/ml VEGF trap (SEQ ID NO:4), pH 6.25” Ex.1005 Example 1 (emphasis added). Example 3 disclosed “[a]

liquid formulation containing 10 mM phosphate, 50 mM NaCl, 0.1% polysorbate 20, **20% sucrose**, and 100 mg/ml VEGF trap(SEQ ID NO:4), pH 6.25” *Id.* at Example 3 (emphasis added). Example 4 disclosed “a stable liquid VEGF-binding fusion protein (VEGF trap) formulations comprising 5 mM phosphate, 5mM citrate, 100 mM NaCl, 0.1% Polysorbate 20, **20% sucrose**, 25 mg/ml VEG F Trap protein, pH 6.0.” *Id.* at Example 4 (emphasis added). Example 5 disclosed “[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.” *Id.* at 12:1-3 (emphasis added).

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

81. The VEGF antagonist fusion protein comprises amino acids 27-457 of SEQ ID NO:4. Dix ’226 discloses “more preferably, SEQ ID NO:4,” which corresponds to aflibercept. (Exhibit 1005 at col. 5, 37-42). Dix ’226 then described the claimed glycosylation and residue descriptions. The sequence and glycosylation of aflibercept were known in the art at the time. In particular, Dix ’226 explained that aflibercept (referred to as “VEGF Trap” or “VEGF Trap R1R2”) comprises amino acids 27-457 of SEQ ID NO:4 and is glycosylated at Asn residues 62, 94, 149, 222 and 308. (col. 5, ll. 37-42).

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

82. The Dix '226 formulations also meets the claimed stability characteristics (percent “native conformation” of the protein and turbidity). The claimed stability would be inherent, as a property associated with the Dix '226 anticipatory formulation. That is especially true for the Dix '226 aflibercept anticipatory formulation that meets the dependent claims below, including 5% sucrose and 40 mg/ml aflibercept. Post-prior art data confirms the stability for this Dix '226 formulation, and shows why the stability is an inherent property: nothing other than formulation components was sufficient to obtain the claimed property. Of course, Dix '226 itself already disclosed very high stability for aflibercept formulations falling within the scope of the '865 patent claims, and that further supports my opinion that the '865 patent reflects merely additional testing for the alleged invention Regeneron already disclosed in Dix '226.

83. Table 9 disclosed in Dix '226 reports that the “native configuration” for “[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.” *Id.* at 12:1-3. Table 9 disclosed that the “native configuration” was above 99% after 24 months and still above 98% after 36 months at 5 °C as measured by SE-HPLC, which is a type of size exclusion chromatography (SEC). (Dix '226, Table 9).

84. The stability properties of percent remaining in native conformation or turbidity levels are inherent properties of the formulation, and reflects a standard test result for a formulation. The stability results are associated hand-in-hand with the

formulation components. I understand that one may rely on post-prior art information for data regarding inherency. The '865 patent itself reported testing using the claimed formulation, and attributed the claimed stability properties to nothing more than the formulation components. The stability is therefore an inherent property, and it is permissible to use the data in the '865 patent itself to show inherency.

85. In sum, the claimed 98 or 99% “native conformation” at 2 months would have been inherent to the formulation in Dix '226, and the '865 patent data confirms the results corresponding to that inherent property.

B. Dependent Claims 2 and 27: “wherein the concentration of said VEGF antagonist fusion protein is 40 mg/ml, and wherein said organic co-solvent comprises polysorbate.”

86. Claims 2 and 27 recite a 40 mg/mL aflibercept concentration and specify the organic co-solvent comprises polysorbate. Dix '226 disclosed “[a] preferred liquid formulation comprises phosphate buffer, an organic co-solvent, and one or more thermal stabilizers to minimize formation of aggregates and low molecular weight products when stored, and *about 10 mg/ml to about 50 mg/ml fusion protein*, wherein the formulation is from about pH 6.0-6.5.” *Id.* at 7:5-10 (emphasis added). The claims 40 mg/ml VEGF antagonist fusion protein falls squarely within the range of 10 to 50 mg/ml aflibercept disclosed in Dix '226.

87. In addition, and as an independent basis to show that Dix '226 disclosed a 40 mg/ml aflibercept concentration, Dix '226 disclosed a pre-lyophilized aflibercept formulation with 40 mg/ml aflibercept. The fact that it was pre-lyophilized does not put the formulation outside the scope of Claim 2 or 27 of the '865 patent.

88. A pre-lyophilized formulation is “suitable for intravitreal administration” as that term is used in claims 2 and 27. It has the same excipients used in the '865 patent, and it is in liquid form ready to be injected. In fact, the '865 patent and its claims include lyophilized formulations as being suitable for intravitreal administration. Examples 7 and 8 of the '865 patent disclose stable lyophilized aflibercept formulations. (Exhibit 1001 at Examples 7 and 8).

89. The Dix '226 anticipatory 40 mg/ml formulation would necessarily meet the stability limitations. The '865 patent's data demonstrates that the 40 mg/ml formulation would indeed necessarily meet the claimed stability limitations demonstrating over 99% VEGF remaining in native conformation after storage at the claimed conditions. (*See e.g.* Exhibit 1001 at Tables 3-5).

90. The 40 mg/ml formulation also has not been shown to be critical to meeting the claimed stability properties. Dix '226 discloses a useful range, with particular examples, and 40 mg/ml is a useful concentration within the range, and therefore anticipates values within the range 10-50 mg/ml. While the district court

opinion suggested that any range necessarily includes an infinite number of values, because of decimal places, a POSA would consider this range primarily as referencing each step of 5 mg/ml along the range as that is a common approach. The Dix '226 data show that various concentrations from 25 mg/ml to 75 mg/ml are able to meet the claimed stability limitations. (*See e.g.* Exhibit 1005 at Tables 7 and 9).

C. Claims 3 and 5 and 28-30: “organic co-solvent comprises 0.01% to 3% polysorbate”, “organic co-solvent comprises about 0.03% to about 0.1% polysorbate 20”, “organic co-solvent comprises 0.01% to 3% polysorbate 20”

91. Dependent claims 3-5 depend from claim 2. Claims 28 to 30 depend from claim 27. These claims further specify that the organic co-solvent is polysorbate or polysorbate 20 and the narrowest of these claims requires polysorbate in a range of about “0.03 to about 0.1%.” Dix '226 satisfies these requirements. In particular, Example 1 of Dix '226 disclosed “[a] liquid formulation containing 10 mM phosphate, 50 mM NaCl, **0.1% polysorbate 20**, 20% sucrose, and 50 mg/ml VEGF trap (SEQ ID NO:4), pH 6.25” Ex.1005 Example 1 (emphasis added). Example 3 disclosed “[a] liquid formulation containing 10 mM phosphate, 50 mM NaCl, **0.1% polysorbate 20**, 20% sucrose, and 100 mg/ml VEGF trap (SEQ ID NO:4), pH 6.25” *Id.* at Example 3 (emphasis added). Example 4 disclosed “a stable liquid VEGF-binding fusion protein (VEGF trap) formulations comprising 5 mM phosphate, 5mM citrate, 100 mM NaCl, **0.1% Polysorbate 20**, 20% sucrose, 25 mg/ml VEG F Trap protein, pH 6.0.” *Id.* at Example 4 (emphasis added). Example 5 disclosed “[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.” *Id.* at 12:1-3 (emphasis added). Thus, Dix ’226 expressly disclosed polysorbate 20 and did so at 0.1% wt/vol.

92. The formulations with 40 mg/ml and polysorbate 20 in the claimed amounts would inherently meet the stability limitations of claim 1 for the reasons explained above for claim 2 rendering claims 3-5 and 28-30 anticipated. Ex.1001.

D. Claims 7 and 32: “buffer comprises 5-25 mM buffer”

93. Claim 7 depends from claim 5 and claim 32 depends from claim 5. These claims require the buffer be in an amount that is 5 – 25 mM. Dix ’226 contains embodiments with about 10 mM phosphate or histidine buffer. In particular Example 1 of Dix ’226 disclosed “[a] liquid formulation containing **10 mM phosphate**, 50 mM NaCl, 0.1% polysorbate 20, 20% sucrose, and 50 mg/ml VEGF trap (SEQ ID NO:4), pH 6.25” Ex.1005 Example 1 (emphasis added). Example 3 disclosed “[a] liquid formulation containing **10 mM phosphate**, 50 mM NaCl, 0.1% polysorbate 20, 20% sucrose, and 100 mg/ml VEGF trap (SEQ ID NO:4), pH 6.25” *Id.* at Example 3 (emphasis added). Example 4 disclosed “a stable liquid VEGF-binding fusion protein (VEGF trap) formulations comprising **5 mM phosphate**, **5 mM citrate**, 100 mM NaCl, 0.1% Polysorbate 20, 20% sucrose, 25 mg/ml VEG F Trap protein, pH 6.0.” *Id.* at Example 4 (emphasis added). Example 5 disclosed “[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.” *Id.* at 12:1-3 (emphasis added). Phosphate in the amount of 5 mM and 10 mM; and citrate in the amount of 5 mM fall squarely within the claimed range of 5-25 mM.

E. Claims 8-9 and 33-34: “buffer comprises a pH between about 5.8-7.0”, “said buffer comprises a pH about 6.2-6.3.”

94. These claims depend from claim 5 and recite the pH is about 6.2-6.3. Dix ’226 discloses formulations that fall within this range. In particular, Example 1 of Dix ’226 disclosed “[a] liquid formulation containing 10 mM phosphate, 50 mM NaCl, 0.1% polysorbate 20, 20% sucrose, and 50 mg/ml VEGF trap (SEQ ID NO:4), *pH 6.25*” Ex.1005 Example 1 (emphasis added). Example 3 disclosed “[a] liquid formulation containing 10 mM phosphate, 50 mM NaCl, 0.1% polysorbate 20, 20% sucrose, and 100 mg/ml VEGF trap (SEQ ID NO:4), *pH 6.25*” *Id.*

F. Claims 10-11, 19, 35-36 and 44: “stabilizing agent comprises a sugar”, “said sugar is selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol”, “formulation does not contain trehalose”

95. These claims require that the stabilizing agent is sucrose and not trehalose. Dix ’226 discloses formulations using sucrose only as a stabilizer without any trehalose. In particular Example 1 of Dix ’226 disclosed “[a] liquid formulation containing 10 mM phosphate, 50 mM NaCl, 0.1% polysorbate 20, *20% sucrose*, and 50 mg/ml VEGF trap (SEQ ID NO:4), pH 6.25” Ex.1005, Example 1 (emphasis

added). Example 3 disclosed “[a] liquid formulation containing 10 mM phosphate, 50 mM NaCl, 0.1% polysorbate 20, **20% sucrose**, and 100 mg/ml VEGF trap (SEQ ID NO:4), pH 6.25” *Id.* at Example 3 (emphasis added). Example 4 disclosed “a stable liquid VEGF-binding fusion protein (VEGF trap) formulations comprising 5 mM phosphate, 5 mM citrate, 100 mM NaCl, 0.1% Polysorbate 20, **20% sucrose**, 25 mg/ml VEG F Trap protein, pH 6.0.” *Id.* at Example 4 (emphasis added). Example 5 disclosed “[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.” *Id.* at 12:1-3 (emphasis added).

G. Claims 12, 20, 37 and 45: “stabilizing agent comprises 1.0-7.5% of sucrose”, “stabilizing agent comprises 1.0-10% of sucrose”

96. These claims require a sucrose amount of 1.0% up to 10%. Dix ’226 disclosed embodiments with a sucrose range of 5 to 30% for formulations with 10-50 mg/ml VEGF antagonist (including those comprising amino acids 27-457 of SEQ ID NO:4), phosphate buffer, and 0.01% to 3 % of polysorbate 20. In particular, Dix ’226 disclosed “[i]n a specific embodiment, the stable liquid formulation of a VEGF-specific infusion protein antagonist comprises 1-10 mM phosphate buffer, 1-10 mM citrate, 25-150 mM NaCl, 5-30% sucrose, 10-50 mg/ml fusion protein, at a pH of about 6-6.5.” *Id.* at 2:20-24. 5-30% sucrose overlaps with the claimed 1.0-10% sucrose.

97. Dix '226 also disclosed a stable embodiment of 50 mg/ml aflibercept with 0.1% polysorbate 20 and 5-20% sucrose that retained 99.3% native conformation at 24 months in Table 7. Based on this data in Dix '226 and the stability data in the '865 patent, the claimed stability would necessarily be present at the claimed sucrose amounts.

TABLE 7

Stability of Liquid Formulation with 50-100 mg/ml VEGF Trap (VGFT-SS101)				
Incubation (months)	VEGF Trap (mg/ml)	% Polysorbate 20	% PEG 3350	% Degradation
24	50	0.1	—	0.7
24	50	—	3	1.3
15	75	0.1	—	1.5
15	75	—	3	2.0
15	100	0.1	—	1.9
15	100	—	3	2.6

98. This is illustrated by Dix's Table 7 and Table 9 and then further confirmed by the examples in the '865 patent itself. For example, Tables 1 to 8 of the '865 patent provide stability data for various aflibercept formulations with concentrations of 40 mg/ml, 50 mg/ml and sucrose levels of 5% or even lower. Exhibit 1005 at Tables 1 to 8. The data in the '865 patent demonstrates that a 40 mg/ml Dix formulation using a sucrose amount of about 5 or 7.5% from the lower end of the 5 to 30% disclosed range in Dix '226 would necessarily result in a stability where the formulation meets the at least 99% native conformation after 2 months at the claimed temperature or turbidity of less than 0.01. *See e.g.* Exhibit 1005 at Table

3 to 8 demonstrating over 98% native conformation and less than 0.01 turbidity at 2 months or longer at 5 degrees C.

H. Claims 14, 22, 39 and 47. “wherein said VEGF antagonist fusion protein is glycosylated at asparagine residues corresponding to asparagine residues 62, 94, 149, 222 and 308 of SEQ ID NO: 4”

99. These claims specify the glycosylated asparagine residues at 62, 94, 149, 222 and 308 of SEQ ID NO:4. These are explicitly disclosed in Dix ’226. In particular, Dix ’226 disclosed that “[i]n a specific embodiment, the fusion protein comprises amino acids 27-457 of SEQ ID NO:4 and is glycosylated at Asn residues 62, 94, 149, 222, and 308.” Exhibit 1005 at 5:39-42.

I. Claims 15, 23, 40 and 48. “wherein said formulation is capable of providing a turbidity of 0.01 or lower at OD405 after 2 month storage at 5° C”, “capable of providing a turbidity of 0.01 or lower at OD405 after 2 month storage at 5° C”

100. These claims require a turbidity of 0.01 or lower at OD405 after 2 months storage at 5 °C. Turbidity, like the other stability property above, is an inherent property of the claimed formulation disclosed in Dix ’226.

101. As shown in the table below, the ’865 patent and Dix ’226 examples teach a range of concentrations for the VEGF Trap and excipients that achieve the recited turbidity values, and the 40 mg/ml formulation in dependent claims 15, 23, 40 and 48 would be necessarily have a turbidity below 0.01.

	VEGF Trap	Buffer	Tonicity	Co-solvent	Stabilizing agent	pH	Turbidity
'865 Examples	20-50 mg/mL	5-10 mM phosphate	20-135 mM NaCl	0.015-0.1% polysorbate 20 or	0-5% sucrose	6.25-6.3	0.0-0.01 at 2-3 months
Dix Specification	10-50 mg/mL	1-10 mM phosphate, 1-10 mM	25-150 mM NaCl	0.05-0.15% polysorbate 20	5-30% sucrose	6.0-6.5	
Dix '226 Tables 1 to 6	50 to 100 mg/mL	5-10 mM phosphate/ 5 mM phosphate and 5 mM citrate	50 mM NaCl	0.1% Polysorbate 20	20% sucrose	6.0-6.3	0.0 to 0.01 for up to 15 months to 24 months
Narrowest amounts in '865 claims 15, 23, 40 & 48	40 mg/ml	5-25 mM buffer,	Tonicity agent	0.03 to 0.1% polysorbate 20	1 to 7.5% sucrose	6.2-6.3	0.0 to 0.01 for up to 2 months

Furthermore, Dix '226 provided turbidity data for even more formulations with different excipients and concentrations. Ex.1005 at Tables 1 to 6. All of the Dix '226 formulations meet the recited turbidity limitations. *Id.* The '865 patent's formulations with sucrose at the lower end of the disclosed range in Dix also achieved the claimed turbidity values. Thus, a POSA would know that the Dix '226 formulation with sucrose at 5% (*e.g.* within the claimed ranges) will necessarily have the claimed turbidity.

102. As with the native conformation stability limitation, the '865 patent does not separately teach obtaining the claimed turbidity other than by the formulation itself. And a 40 mg/ml aflibercept formulation with polysorbate disclosed

in Dix '226 falls in the range of Example formulations that achieved the claimed turbidity. *Id.* Thus, based on the teachings and data of the '865 patent and Dix '226, a 40 mg/ml aflibercept formulation with the claimed amount of polysorbate 20 would necessarily meet the turbidity limitation expressly and inherently. *Id.*

J. Claims 16, 24, 41 and 49. “wherein at least 99% of said VEGF antagonist fusion protein is present in native conformation after 2 month storage at 5° C. as measured by size exclusion chromatography.”

103. Claims 16 and 24 depend from claim 5 and claims 41 and 49 depend from claim 45. These claims further require that a formulation with 40 mg/ml aflibercept and 0.03% to 0.1% polysorbate 20, and 1 to 10% sucrose have 99% native conformation at 2 months. A 40 mg/ml aflibercept formulation with the claimed amounts of polysorbate 20 and sucrose would necessarily meet the 99% native conformation stability requirement at 2 months.

K. Claims 17, 25, 42 and 50. “wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5° C. for 24 months as measured by size exclusion chromatograph.”

104. Claims 17, 25, 42 and 50 require 98% native conformation at 24 months.

105. As shown in the table below, the 40 mg/ml aflibercept Dix '226 formulation with sucrose between 1.0-10% would necessarily have the claimed stability because that Dix '226 formulation falls within the described ranges of

aflibercept and excipients tested in the '865 patent and Dix '226 for stability. Therefore, the Dix '226 formulations, although already disclosed, were tested to demonstrate their associated and inherent stability properties in the '865 patent. *See e.g.*, Exhibit 1001 at Tables 3 to 6. I understand that merely testing the inherent property and reporting it does not make an anticipated formulation patentable.

	VEGF Trap	Buffer	Tonicity	Co-solvent	Stabilizing	pH	Stability
Dix '226 '865 patent Examples	25-50 mg/mL	10 mM phosphate or 5 mM phosphate and 5	50-100 mM NaCl	0.1% polysorbate	5-20% sucrose	6.0- 6.25	99.3% at 24 months
Dix '226 Included Values	40 mg/mL	5 mM phosphate 5 mM citrate	100 mM NaCl	0.1% polysorbate	5%	6.0- 6.3	

IX. CONCLUSION

106. This declaration, along with the materials considered, is based on my present assessment of information currently available to me.

107. I hereby declare that all statements made herein of my own knowledge are true and that all statements made herein on information and belief are believed to be true. Further, these statements were made with the knowledge that willful false statements and the like so made are punishable by fine, imprisonment, or both, under

Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the above-identified patent.

July 10, 2025

Date

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