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 B2

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 11,084,865 B2

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I. INTRODUCTION

Fresenius Kabi SwissBioSim GmbH ("Fresenius" or "Petitioner") petitions for *inter partes* review ("IPR") under 35 U.S.C. §§ 311-319 and 37 C.F.R. §§ 42 et seq., seeking cancellation of claims 1-5, 7-30, and 32-50 (the "Challenged Claims") of U.S. Patent No. 11,084,865 ("'865 patent") (Ex. 1001), assigned to Patent Owner, Regeneron Pharmaceuticals, Inc. ("Regeneron" or "Patent Owner").

The Challenged Claims are generally directed to a known drug (aflibercept) for a known application (treating wet-AMD or age-related macular degeneration) with a known formulation (a common co-solvent system for ophthalmic use). The claims also recite as a limitation the associated stability property for that claimed formulation (reported in terms of percent "native conformation" of the protein) but those are inherent properties of the claimed formulation.

The Challenged Claims are anticipated by Dix '226. While Patent Owner is likely to point out that this anticipation argument was resolved in Patent Owner's favor by a district court, later developments confirm Petitioner's position: when appealed, the Federal Circuit called into question that same district court decision during oral argument, which resulted in a prompt settlement between the litigating parties before any opinion could issue. Specifically, the Mylan/Biocon Federal Circuit panel hammered home one narrow question as the distinction between

validity and invalidity: whether Dix '226's disclosure of 10-50 mg/ml aflibercept anticipated the claimed 40 mg/ml aflibercept—when no criticality had been shown. The panel began on the very point of "102" anticipation and the issue of "criticality." (Ex. 1008 at 27:3-5.) Indeed, the panel judges used the words "critical" or "criticality" 30 times throughout the oral argument hearing itself. (*Id*.) Petitioner thus raises Ground 1 in the interest of efficiency, because otherwise Petitioner would have to wait until after litigation and a Federal Circuit appeal to permit the Federal Circuit to revisit the anticipation issue in view of Dix '226.

Challenged Claim 1 refers to a formulation for any "VEGF antagonist" that is "glycosylated and comprises 27-457 of SEQ ID NO:4," and there is no dispute that aflibercept was known as a VEGF antagonist that meets this criteria. The focus of claim 1 was thus on three formulation components: "an organic co-solvent, a buffer, and a stabilizing agent." Dix '226 disclosed formulations for aflibercept in particular, and specifically formulations with an organic co-solvent (polysorbate 20), a buffer (a phosphate buffer), and a stabilizing agent (sucrose). These formulation components are shown below, including these exact same excipients recited in dependent Challenged Claims:

Dix '226 Formulation	Challenged Claims Active Ingredients and Excipients
aflibercept	aflibercept
polysorbate 20	an organic co-solvent, with polysorbate 20 in dependent claims
phosphate buffer	a buffer, with phosphate in dependent claims
sucrose	a stabilizing agent, with sucrose in dependent claims

(Ex. 1005). While Challenged Claim 1 does not identify any particular amounts for these ingredients, some dependent claims do. But Dix '226 also disclosed using these ingredients in amounts that include the claimed amounts in those dependent claims. For example, Dix '226 disclosed 10-50 mg/mL aflibercept concentrations (some of the Challenged Claims use 40 mg/mL), Dix '226 disclosed 0.1% polysorbate 20 (some of the Challenged Claims use 0.01-3% polysorbate 20), and Dix '226 disclosed 5-30% sucrose (some of the Challenged Claims use 1-10% sucrose). The Challenged Claims therefore cover no new ground: Dix disclosed useful ranges, and Patent Owner cannot show any criticality for any particular amount within Dix '226's specific ranges. The Mylan/Biocon Federal Circuit panel emphasized that the burden to show criticality falls on the Patent Owner: "[i]f the range overlaps with the prior art range then it's incumbent upon the patent owner to show criticality for its claimed [range]. Is that a correct understanding [of] our case

law?" (Ex. 1008 at 33:23-34:4.)

The Challenged Claims also contain the preamble phrase "suitable for intravitreal administration," but even if that phrase were deemed limiting, it refers to a set of excipients that would be understood as capable of intravitreal administration. The '865 patent itself similarly disclosed nothing more than the excipients themselves, with no actual administration of any kind—intravitreal or otherwise.

The Challenged Claims also require that the formulation is described as "wherein at least 98%" of the aflibercept "is present in native conformation" after storage at 5°C for two months. A stability property is a property associated hand-in-hand with the claimed formulation itself, making percent native conformation an inherent property that adds no patentable weight to the claim. The '865 mentions no other means of obtaining the claimed stability property other than using the claimed formulation components. "It is well-settled that the inclusion of an inherent, but undisclosed, property of a composition does not render a claim to the composition nonobvious." *Hospira, Inc. v. Fresenius Kabi USA, LLC*, 946 F.3d 1322, 1332 (Fed. Cir. 2020). The '865 patent provides the test data to show that the claimed formulation, without more, is attributed to the associated claimed stability property; that proves inherency. *Id*. at 1329-30 ("the work of the inventor or the patentee can

be used as the evidence of inherency").

The Board should institute an *inter partes* review of the Challenged Claims and find those claims unpatentable on the grounds presented herein.

II. MANDATORY NOTICES PURSUANT TO 37 C.F.R. § 42.8(A)(1)

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

The real parties-in-interest for Petitioner are Fresenius Kabi USA, LLC, Fresenius Kabi SwissBioSim GmbH, and Fresenius Kabi AG. Another party-in-interest is Sam Chun Dang Pharm Co., Ltd.

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

The '865 patent was challenged in *Samsung Bioepis Co. Ltd. v. Regeneron Pharmaceuticals, Inc.*, IPR2025-00176 (P.T.A.B.) and *Formycon Inc. v. Regeneron Pharmaceuticals, Inc.*, IPR2025-00233 (P.T.A.B.) and was also challenged in *Celltrion, Inc. v. Regeneron Pharmaceuticals, Inc.*, IPR2025-0456 (P.T.A.B), which were filed on November 20, 2024 and November 29, 2024 and January 15, 2025, respectively. The Board denied institution for all three of these Petitions, but on discretionary grounds. Unlike those Petitions, this Petition relies on Dix '226 for anticipation—which was not raised by any prior petition.

The '865 patent was included in litigation filed by Patent Owner against Mylan and Biocon, with a finding after trial in favor of Patent Owner, but then appealed to the Federal Circuit in the matter *Regeneron Pharmaceuticals, Inc. v.*

Mylan Pharmaceuticals Inc., Nos. 24-1965, 24-1966, 24-2002, 24-2009, 24-2019, 24-2058, 24-2082, 24-2083, 24-2147, 24-2156, 24-2351 (Fed. Cir.) The parties to that appeal completed briefing and the Federal Circuit held oral argument. The Court called into question several of the district court's findings in favor of the Patent Owner, with a persistent focus on the Dix '226 reference that is the subject of this Petition.

The panel in the Mylan/Biocon appeal repeatedly placed a particular emphasis on the invalidity analysis based on the '856 patent purporting to cover an individual drug concentration point (40 mg/ml) within a range that Dix '226 already disclosed (10-50 mg/ml). The Court pressed the point that Patent Owner—not the patent challenger—had the burden to show criticality, and that no such evidence had been shown. *E.g.* Ex. 1008 at 32:19-33:2 ("would you agree that putting this one factor to the side that when we have something like this 40 mg per milliliter inside the range in the prior art of 10 to 50, then it's incumbent upon the patent owner to show or demonstrate some kind of criticality?"). This theme was repeated throughout the oral argument. (Ex. 1008 at 9:9-11, 14:9-16:2, 27:5-28:6, 32:19-36:15, 37:21-38:20, 41:9-44:4 discussing lack of criticality.) The Federal Circuit did not have the opportunity to issue a ruling on invalidity in view of Dix '226, however, as the oral argument was held on February 7, 2025, and the parties reported they settled the

matter by April 15, 2025. The settlement was significant, because it came on the heels of the Mylan/Biocon Federal Circuit oral argument—the same oral argument where the Federal Circuit panel expressed severe skepticism about the district court's findings regarding Dix '226—even though Regeneron had won at trial and secured a permanent injunction. To the best of our understanding, no other appeals to the Federal Circuit involving the '865 patent and no other Petitions involving the '865 patent argued invalidity based on Dix '226. And no other cases resulted in settlement, either.

The related '992 patent was challenged in *Chengdu Kanghong Biotechnology Co., Ltd. v. Regeneron Pharmaceuticals, Inc.*, IPR2021-00402 (P.T.A.B.), which the parties voluntarily terminated on June 25, 2021. The '992 patent was also challenged in *Celltrion, Inc. v. Regeneron Pharmaceuticals, Inc.*, IPR2023-00462 (P.T.A.B.), which was instituted on July 20, 2023. Regeneron subsequently disclaimed all challenged claims in response to institution.

The '865 patent is currently being asserted in several ongoing patent litigations as listed below.

Petitioner is not presently involved in any of the ongoing district court litigations or PTAB proceedings. To the best of Petitioner's knowledge, the following are additional judicial or administrative matters that potentially could

affect, or be affected by, a decision in this proceeding:

- *In re: Aflibercept Patent Litigation*, No. 1:24-md-3103 (N.D.W.Va.)
- *Regeneron Pharmaceuticals, Inc. v. Amgen, Inc.*, No. 2:24-cv-264 (C.D. Cal.)
- *Regeneron Pharmaceuticals, Inc. v. Amgen, Inc.*, No. 1:24-cv-39 (N.D.W.Va.)
- *Regeneron Pharmaceuticals, Inc. v. Samsung Bioepis Co., Ltd.*, No. 1:23-cv-106 (N.D.W.Va.)
- *Regeneron Pharmaceuticals, Inc. v. Samsung Bioepis Co., Ltd.*, No. 1:23-cv-94 (N.D.W. Va.)
- *Regeneron Pharmaceuticals, Inc. v. Celltrion, Inc.*, No. 1:23-cv-89 (N.D.W.Va.)
- *Regeneron Pharmaceuticals, Inc. v. Celltrion, Inc.*, No. 1:24-cv-53 (N.D.W.Va.)
- *Regeneron Pharmaceuticals, Inc. v. Formycon*, No. 1:23-cv-00097 (N.D. W.Va.)
- *Regeneron Pharmaceuticals, Inc. v. Sandoz, Inc.*, No. 1:24-cv-85 (N.D.W.Va.)

C. Lead and Backup Counsel (37 C.F.R. § 42.8(b)(3)-(4)

Petitioner hereby identifies its lead and backup counsel as follows:

Lead Counsel	Backup Counsel
Imron T. Aly (Reg. No. 48,706) ArentFox Schiff LLP 233 S. Wacker Dr., Suite 7100 Chicago, IL 60606 Tel: 312.258.5500 Fax: 312.258.5600 Imron.Aly@afslaw.com Petitioner consents to email services at: AFS-Fresenius-aflibercept865IPR@afslaw.com	Sailesh Patel (Reg. No. 46,982) ArentFox Schiff LLP 233 S. Wacker Dr., Suite 7100 Chicago, IL 60606 Tel: 312.258.5500 Fax: 312.258.5600 Sailesh.Patel@afslaw.com

Pursuant to 37 C.F.R. § 42.10(b), a Power of Attorney has been filed herewith.

D. Service Information (37 C.F.R. § 42.8(b)(4))

This Petition is being served by Federal Express Next Business Day Delivery to the correspondence address of record for the '345 patent:

191459 - A&P - Regeneron (Prosecution)
601 Massachusetts Ave., NW
Washington, DC 20001-3743

The Petition is further being served on Litigation Counsel for Regeneron Pharmaceuticals, Inc. by electronic mail at: dberl@wc.com.

Please direct all correspondence to lead and back-up counsel at the contact information above. Petitioner also consents to service by email at: AFS-Fresenius-aflibercept865IPR@afslaw.com.

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

The requisite filing fee of $73,000 (request fee of $29,500, post-institution fee of $43,500) for a Petition for *Inter Partes* Review is submitted herewith. Claims 1-5, 7-30, 32-50 are requested for review as part of this Petition. If any additional fees are due during this proceeding, the Office is authorized to charge such fees to Deposit Account No. 506990. Any overpayment or refund of fees may also be deposited in this Deposit Account.

III. GROUNDS FOR STANDING (37 C.F.R. § 42.104(A); 37 C.F.R. §§ 42.101(A)-(C))

Petitioner certifies that the '865 patent is available for IPR and that Petitioner is not barred or estopped from requesting this review.

IV. THRESHOLD REQUIREMENT FOR *INTER PARTES* REVIEW.

This Petition meets and exceeds the threshold required under 35 U.S.C. § 314(a). As explained herein, there is a reasonable likelihood that Petitioner will prevail with respect to at least one of the Challenged Claims, because the prior art anticipates the Challenged Claims and the Federal Circuit court hearing cited herein suggested the panel was strongly considering invalidity issues, although the appeal was settled and dismissed before an opinion issued.

V. IDENTIFICATION OF CHALLENGE AND RELIEF REQUESTED

A. Identification of Challenge (37 C.F.R. § 42.104(b))

Petitioner requests IPR of '865 patent claims 1-5, 7-30, 32-50 and that the Board cancel those claims as unpatentable.

B. Grounds of Challenge (37 C.F.R. § 42.204(b)(2))

Petitioner respectfully requests that the Board grant institution of IPR on the Challenged Claims based on the following grounds:

Statutory Grounds of Challenge		
Ground I	Claims **1-5, 7-30, 32-50**	Anticipated by Dix '226

VI. THE '865 PATENT

A. Overview

The '865 patent is entitled "VEGF Antagonist Formulations Suitable for Intravitreal Administration." The '865 patent describes the invention as "[s]table formulations of a VEGF- specific protein antagonist" comprising a "VEGF 'trap' antagonist with a pharmaceutically acceptable carrier." Ex. 1001 at 2:14-19; Ex. 1002, ¶ 32. VEGF is a known protein that helps 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, 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." Ex. 1001 at 6:40-42; Ex. 1002, ¶ 33

The '865 patent states 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." Ex. 1001 at 6:32-38; Ex. 1002, ¶ 34. Confirming the well-established state of the art for the known glycosylation and aflibercept composition, the patent says nothing more about glycosylation. *Id*.

The '865 patent includes eight examples, which describe combinations of protein, buffer, stabilizer and one of two "organic co-solvents." The Examples generally include 20 to 50 mg/ml of "VEGF Trap (SEQ ID NO:4)" protein (aflibercept) in combination with phosphate buffer, sodium chloride, and polysorbate 20 in varying combinations at a pH of 6.25 or 6.3. *Id*., Examples 1, 3-8; Ex. 1002, ¶ 35. Some also include sucrose. *Id*., Examples 1-4, 7. The Examples also provide the pH of the formulation over time.

The '865 patent examples report the formulation's stability after storage at 5 °C. The patent reports "% VEGF Trap Native Configuration" (as measured by size-exclusion chromatography ("SEC")) after storage periods that run from zero to 24 months, and also reports on turbidity after these periods. *See, e.g.*, *Id*., Tables 1-8; Ex. 1002, ¶ 36. Other than making the claimed formulations and testing them for their resulting native configuration and turbidity properties, the '865 patent does not teach additional steps to achieve the claimed properties. Ex. 1002, ¶ 37.

The '865 patent also does not disclose any actual administration, much less

intravitreal administration, in any test subject. The '865 patent merely lists formulation examples, and labels those formulation as "***suitable*** for intravitreal administration," based only on the components of the formulations themselves. *Id.* (emphasis added).

B. Priority Date

The '865 patent claims priority to ten prior patent applications and one provisional application No. 60/814,484, filed on June 16, 2006. Ex. 1001 at Related U.S. Application Data. That is the appropriate priority date.

C. The Challenged Claims

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

D. Prosecution History

During prosecution of the '865 patent, the claims were rejected on procedural grounds for obviousness-type double patenting. Ex. 1004, Mar. 19, 2021 Office Action at p. 127-128; Ex. 1002, ¶ 39. To overcome the rejection, Regeneron relied

on the stability limitations recited in the claims. *Id.,* May 5, 2021 Response at p. 110-112. Notably, Regeneron did not argue that the recited stability values were unexpected, or that anything other than the formulation itself was responsible for the associated claimed stability limitations.

E. Level of Ordinary Skill in the Art

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. Ex. 1002, ¶¶ 40-41. The POSA may also have had less education but more practical relevant work experience. *Id.* 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 apply prior art ranges to develop a resulting formulation. *Id.* This individual also would have been able to use state-of-the-art analytical methods, such as SEC, to assess stability and compatibility. *Id.*

The POSA may collaborate with others, including a medical doctor with experience treating ophthalmic diseases. Ex. 1002, ¶ 42. 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. *Id.* These individuals would have worked together as needed during development. *Id.*

VII. SCOPE AND CONTENT OF THE PRIOR ART

Petitioner summarizes the scope and content of the prior art, including the disclosures of its primary prior art references, below.

A. Background

1. VEGF

VEGF is a naturally-occurring protein that is involved in the process by which new blood vessels are formed, known as "angiogenesis." Ex. 1002, ¶ 45. VEGF binds to VEGF receptors on the surfaces of cells that facilitate angiogenesis. *Id.* (citing Ex. 1005 at 1:43-60).

By 2005, it was known that VEGF had a role in tumor angiogenesis, and a number of VEGF inhibitors had been developed as potential cancer therapies. Ex. 1002, ¶ 46 .

2. Aflibercept

During this time, Regeneron developed aflibercept, another VEGF inhibitor. The aflibercept compound itself was prior art by the priority date for the '865 patent. Aflibercept was known as "VEGF-Trap$_{R1R2}$", "VEGFR1R2-FcΔC1(a)," and "VEGF Trap-Eye" at the time. Ex. 1002, ¶ 48. Aflibercept is a fusion protein of domain 2 of

the human VEGFR1 receptor and domain 3 of the human VEGFR2 receptor, linked via the Fc domain of a human IgG antibody. *Id.*

3. Protein Stability

As of the priority date, it was well known that proteins like aflibercept had the potential to degrade via known mechanisms.

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

B. Key Prior Art

1. Dix '226 (Ex. 1005)

U.S. Patent No. 10,406,226 ("Dix '226") is titled "Method of manufacturing VEGF antagonist fusion proteins." It was issued to Regeneron and is prior art under at least 102(e)(2). 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.

a. Inventive Entity

Dix '226 shares two named inventors (Daniel Dix and Kelly Frye) with the

'865 patent, but is considered "by another" because there are several differences in inventorship between the '865 patent and the earlier filed Dix '226 patent. Eric Furfine and Kenneth Graham are inventors on the '865 patent, but are not listed inventors of the Dix '226 patent. Moreover, Susan Kautz is listed as an inventor on Dix '226, but is not an inventor on the '865 patent. The inventive entity is different if not all inventors are the same. The fact that the '865 patent and the Dix '226 reference have one or more inventors in common is immaterial. *In re Kaplan,* 368 F.2d 866 (C.C.P.A. 1966); *Riverwood Int'l Corp. v. RA Jones & Co.,* 324 F.3d 1346, 1348 (Fed. Cir. 2003); *Ex parte DesOrmeaux,* 25 USPQ2d 2040 (Bd. Pat. App. & Inter. 1992). Dix '226 is prior art to the '965 patent under pre-AIA 35 U.S.C. 102(e)(2). Dix '226 anticipates the Challenged Claims.

b. Dix '226 Taught Aflibercept Formulations

Dix '226 already disclosed all of the claimed features, and those are discussed in detail below as part of the anticipation claim analysis. As a preview of the formulation disclosures, Dix '226 disclosed aflibercept formulations in particular, using polysorbate 20 as the preferred organic cosolvent, phosphate and/or citrate buffers (Ex. 1005 at 1:58-64; 2:3-6), and sucrose as a preferred stabilizing agent or lyoprotectant (*Id.* 2:35-37). Ex. 1002, ¶ 53. The below table summarizes the pertinent disclosures from Dix '226:

	VEGF Trap (aflib)	Buffer	Tonicity agent	Co-solvent	Stabilizing agent	pH
Dix '226 Specification (2:20-34)	10-50 mg/mL	1-10 mM phosphate, 1-10 mM citrate	25-150 mM NaCl	0.05-0.15% polysorbate 20	5-30% sucrose	6.0-6.5
Dix '226 Specification (Tables 1-6)	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
Narrowest '865 claims	40 mg/ml	5-25 mM buffer	tonicity agent	0.03-0.1% polysorbate 20	1 to 7.5% sucrose	6.2-6.3

Ex. 1002, ¶ 57. Dix '226 disclosed using 10-50 mg/ml aflibercept, and showed that these formulations would work for their intended purpose. Dix '226 even identified specifically a 40 mg/ml pre-lyophilized formulation that was lyophilized and reconstituted to an 80 mg/ml solution. Ex. 1002, ¶ 94. Dix thus demonstrated that 40 mg/ml would have been an easily achievable concentration. While Dix also disclosed formulations with higher aflibercept concentrations, and associated those formulations with higher sucrose levels to stabilize those higher concentrations, Dix '226 disclosed relatively narrow formulation ranges within which a POSA would have routinely worked. 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. Ex. 1001 at 2:63-66; Ex. 1002, ¶ 54.

In another embodiment, "the pre-lyophilized formulation consists of about10 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) [aflibercept], 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." Ex. 1001 at 3:27-34; Ex. 1002, ¶ 55.

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. Ex. 1001 at 7:62-65; Ex. 1002, ¶ 56.

c. Dix '226 Reported Validating Stability Results

Dix '226 did not just disclose formulations, but also tested them, including for meeting 98% native conformation as measured by SEC after storage at 5 ˚C. 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. Ex. 1002, ¶ 58. A POSA would have understood based on general knowledge that SE-HPLC disclosed in Dix '226 is a type of SEC. The core principle of both is to separate molecules based on their size, using a porous gel or bead-packed column. Ex. 1002, ¶ 59.

The SEC results are shown in Tables 1 and 2, respectively. Both show that well over 98% of the VEGF trap was in native conformation after 2 months at 5 ˚C. *Id.*

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

Example 5 tests the stability of a formulation of aflibercept with 5 mM phosphate and 5mM citrate as buffers, .1% polysorbate 20, 100 mM NaCl, 20% sucrose and 25 mg/ml VEGF trap protein. Ex. 1002, ¶ 60.

Table 9 demonstrates that this formulation had greater than 99% remaining in native conformation after 24 months of storage at 5 ˚s C at Ex. 1002, ¶ 61:

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

d. Dix '226 Demonstrated Stable High-Concentration Formulations

Dix '226 did not just test low concentration formulations, but also high concentration formulations that would be useful for intravitreal administration because a higher concentration permits a lower administration volume. The 25 mg/ml example is a high-concentration formulation, for which Dix '226 disclosed detailed formulation and express stability data. A POSA reviewing Dix '226 would have thus recognized that high concentrations were not a problem for aflibercept. Ex. 1002, ¶¶ 62, 63.

Dix '226 disclosed a 100 mg/ml example. After lyophilization, the reconstituted 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. Ex.

1002, ¶ 64.

Dix '226 disclosed 50 mg/ml examples, too. One example used 10 mM histidine, 1.5% PEG 3350, 0.75% glycine, 2.5% sucrose, 50mg/ml VEGF protein, pH 6.3, and is reconstituted to a formulation containing 20 mM histidine, 3% PEG 3350, 1.5% glycine, and 5% sucrose. Ex. 1002, ¶ 65.

Dix '226 reported validating stability results for these higher-concentration 50-100 mg/ml aflibercept formulations. The results were summarized in Table 7:

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

As shown in Table 7, percent degradation was very low even after extended tested time periods. Ex. 1002, ¶ 66-67. 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. GROUND 1: DIX '226 ANTICIPATES THE CHALLENGED CLAIMS

Dix '226 anticipates the Challenged Claims. Dix '226 is presumptively a prior art reference under Section 102(e)(2) and may be used to demonstrate anticipation.

A. Claim 1 and Claim 26

1. A vial (claim 1) or PFS (claim 26) comprising an ophthalmic formulation suitable for intravitreal administration that comprises:

Independent claims 1 and 26 are identical except that claim 1 is directed to a vial while claim 26 is directed to a 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.

As for the container, a POSA would have known that injectable formulations were stored in either vials or PFS. There was nothing novel about the container choice for aflibercept formulations. Dix '226 expressly disclosed both. Dix '226 disclosed vials as a suitable storage container. (Ex. 1005, 3:51-55). Ex. 1002, ¶ 69. The Dix '226 patent also disclosed an embodiment using a PFS. (Ex. 1005, 9:27-41; Ex. 1002, ¶ 70. Dix '226 disclosed that injecting the drug directly to the eye, whether drawn from a vial or directly using PFS, would allow administration "at a concentration higher than that delivered by IV infusion." Ex. 1005 at 10:30-32; Ex. 1002, ¶ 70.

As for the term "suitable for intravitreal administration," the term appears in the preamble for the Challenged Claims. The term need not be deemed a limitation, because it is in the preamble and provides a statement of intended use; all Challenged Claims are composition claims that remain defined by the formulation components and associated stability property. "[P]reambles describing the use of an invention generally do not limit the claims because the patentability of apparatus or composition claims depends on the claimed structure." *Catalina Mktg. Int'l v. Coolsavings.com*, 289 F.3d 801, 809 (Fed. Cir. 2002). Preambles are not limitations where they were not used "to distinguish the prior art." *Id*. at 810. For the '865 patent in particular, counsel for Patent Owner represented at the Federal Circuit oral argument in *Regeneron v. Mylan* that "[t]he preamble was never a basis to distinguish the prior art." Ex. 1008 at 44:5-11.

Even if the term were deemed to be a limitation, the phrase "suitable for intravitreal administration" merely refers to a set of ingredients that a POSA would recognize as capable of being injected into the eye. The district court in the *Regeneron v. Mylan* case appeared to deem this term satisfied so long as a POSA would recognize that excipients used in a formulation were capable of being injected into the eye. Ex. 1007 at 205; Ex. 1002, ¶ 71. 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." Ex. 1007 at 209; Ex. 1002, ¶ 71 Dix '226 meets this standard. Dix '226 disclosed formulations with excipients used in marketed products—and indeed with the same excipients used in the '865 patent without requiring any additional testing—so therefore known to be "suitable for intravitreal administration." Ex. 1002 at ¶ 72.

2. a vascular endothelial growth factor (VEGF) antagonist

Dix '226 disclosed formulations with a VEGF antagonist (aflibercept). Ex. 1002, ¶ 52 66. It disclosed "more preferably, SEQ ID NO:4," which is aflibercept. Ex. 1005 at 5:37-42; Ex. 1002, ¶ 75-77.

3. an organic co-solvent

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. Ex. 1005 Examples 1, 3-5; Ex. 1002, ¶ 78.

4. a buffer

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; *id.* at 10:15-25; Ex. 1002, ¶ 79.

5. a stabilizing agent

Dix '226 formulation 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, 11:15, 27:98; Ex. 1002, ¶ 80.

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

Aflibercept is a VEGF antagonist fusion protein that comprises amino acids 27-457 of SEQ ID NO:4. Dix '226 disclosed "more preferably, SEQ ID NO:4," which is aflibercept. (5:37-42). Dix then described the claimed glycosylation and residue descriptions. 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. Ex. 1002, ¶ 81

The sequence and glycosylation of aflibercept were known in the art at the time of the priority date. 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. Ex. 1005 at col. 5:37-42; Ex. 1002, ¶ 76-77.

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

a. The stability limitations were expressly disclosed

The Dix '226 formulations also meet the claimed stability characteristics (percent "native conformation" of the protein and turbidity). The claimed stability is anticipated based on the data reported within Dix '226. In Table 9, Dix '226 reports that the "native conformation" was above 99% after 24 months and still above 98% after 36 months at 5 ºC as measured by SE-HPLC, which is a type of size exclusion chromatography (SEC). (Ex. 1005 at Table 9; Ex. 1002, ¶ 83. The formulation tested in Table 9 contained "about 5mM phosphate, 5 mM citrate, 100 mM NaCl, 0.1% polysorbate 20, 20% sucrose and 25 mg/ml VEGF trap protein." Exh. 1005 at col. 12:1-10.

b. The stability limitations represent an inherent property

The stability of a formulation is a property of that formulation, and reflects a standard test result for a formulation. An anticipatory formulation does not become valid for reporting the results of an inherent property. "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342,

1347 (Fed. Cir. 1999) (citation omitted).

The ’865 patent itself reported testing using the claimed formulation, and attributed the claimed stability properties to nothing other 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. “Extrinsic evidence can be used to demonstrate what is ‘necessarily present’ in a prior art embodiment even if the extrinsic evidence is not itself prior art.” *Hospira*, 946 F.3d at 1329. The claimed 98 or 99% “native conformation” at 2 months would have been inherent to the formulation in Dix ’226.

B. 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”

Dependent claims 2 and 27 depend from claim 1 and 26 respectively. Claims 2 and 27 both add the requirement for a 40 mg/mL aflibercept concentration and specify the organic co-solvent comprises polysorbate. Polysorbate as the claimed organic co-solvent is satisfied, as Dix ‘226 expressly disclosed using either polysorbate 20 or PEG 3350 and provides several examples using polysorbate 20 as the organic co-solvent. Ex. 1002 ¶ 91 .

As to the 40 mg/ml concentration, Dix ’226 disclosed a focused range encompassing 40 mg/ml, and Patent Owner failed to show any criticality.

Specifically, Dix '226 disclosed a range of 10 to 50 mg/ml aflibercept, and a POSA would have understood this range to be narrow in scope because it gave limited options, and because a POSA would have preferred concentrations at the higher end of the range to accommodate intravitreal injection volumes. Moreover, neither the '856 patent nor the Patent Owner reported any special or critical characteristic associated with 40 mg/ml, as opposed to any other value within the range 10-50 mg/ml. Ex. 1002, ¶ 86, 90.

In *ClearValue, Inc. v. Pearl River Polymers, Inc.*, the Federal Circuit addressed the question of claim anticipation in view of prior art ranges. 668 F.3d 1340, 1344-45 (Fed. Cir. 2012). That case confirmed that claims are anticipated if they fall within prior art ranges, unless ***the patentee*** can show criticality. *Id*. The *ClearValue* court distinguished *Atofina*, an earlier case where the patentee claimed temperature values that fell within prior art ranges, because "Atofina described this [claimed] temperature range as 'critical'" and that different subsets of the prior art ranges were inoperable. *Id*. (discussing *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991 (Fed. Cir. 2006)). But in *ClearValue*, the patentee made no such criticality showing, so the Court held the claims invalid as anticipated, noting that because the patentee showed no criticality, "[t]his case is not *Atofina*." *Id*. at 1345.

The Federal Circuit replayed this exact discussion in the oral argument for the

Regeneron v. Mylan appeal that settled shortly after the oral argument. In particular, the panel noted that "it seems like the thrust of the thinking of -- for criticality is comparing what you've claimed against other embodiments that come within the prior art range." (Ex. 1008 at 36:7-15). Importantly, the panel explained during questioning that "the claimed invention is critical only if it can be shown that the claimed invention only works for 40 mg and not for others." *Id*. at 38:2-20. Several other questions echoed this same important point about criticality, that Patent Owner needed to show criticality for the claimed 40 mg/ml concentration over the prior art 10-50 mg/ml range:

> - "Would you agree that putting this one factor to the side [whether aflibercept was included in the 10-50 mg/ml disclosure] that when we have something like this 40 mg per milliliter inside the range in the prior art of 10 to 50, then it's incumbent on the patent owner to show or demonstrate some kind of criticality?" (*Id.* at 32:19-33:2)
>
> - "If the range overlaps with the prior art range then it's incumbent upon the patent owner to show criticality for its claimed [range]. Is that a correct understanding [of] our case law?" (*Id*. at 33:23-34:4)
>
> - "The inquiry doesn't seem to me, is whether the 40 mg concentration is desirable but whether it's critical to the operability of the claimed invention. In other words, the claimed invention is critical only if it can be shown that the claimed invention only works for 40 mg and not for others." (*Id*. at 38:2-20)
>
> - "I don't see anything in the record that indicates

> here is why 40 did something different and therefore, critical to the operability of our [claimed] drug – drug product compared to other things that are not prior art knowledge. And I thought that is the nature of the criticality analysis." (*Id*. at 41:9-21)

While we recognize the Federal Circuit did not get the chance to issue an opinion, these statements remain compelling to explain why Patent Owner settled with Mylan. At a minimum, they call into question and render irrelevant the district court's finding that Dix '226 did not anticipate the Challenged Claims, because the district court failed properly to apply *ClearValue* and Patent Owner failed to provide evidence of criticality.

In addition, and as an independent basis to show that Dix '226 disclosed 40 mg/ml, the POSA would look to the examples to identify specifically workable ranges that were enabled by Dix '226 and therefore remain anticipated. Indeed, 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. 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. (Ex. 7 and 8).

It should be noted that the ’865 patent itself does not disclose a 40 mg/mL formulation with the particular combination of components as claimed in claim 2 or claim 27.

C. Claims 3-5 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”

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. Dix ’226 expressly disclosed polysorbate 20 and did so at 0.1% wt/vol. Ex. 1002, ¶ 91.

Moreover, 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. 1002, ¶ 91-92.

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

Dependent claim 7 depends from claim 5. Dependent claim 32 depends from claim 30. Claims 7 and 30 specify that the buffer comprises 5-25 mM buffer. Dix ’226 satisfies this limitation. Dix ’226 taught embodiments with about 10 mM

phosphate or histidine buffer and thus these claims are anticipated. Ex. 1005 at Example 1; Ex. 1002, ¶ 93.

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"

Dependent claims 8-9 depend from claim 5. Dependent claims 33-34 depend from claim 30. Claim 8 and claim 33 require that the buffer comprises a pH between "about 5.8-7" while claim 9 and 34 require a pH of "about 6.2-6.3." Dix '226 disclosed that the preferred pH of the examples falls within these ranges. Ex. 1002, ¶ 93.

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"

Claims 10-11 and 19 depend from claim 5. Claims 35-36 and 44 depend from claim 30. These dependent claims add the requirement that the claimed stabilizing agent is a sugar, including sucrose and not containing trehalose. Ex. 1002, ¶ 95.

Dix '226 disclosed formulations using sucrose only as stabilizer without any trehalose. Thus, these claims are anticipated by Dix '226. Ex. 1002, ¶ 95.

G. Claims 12, 20, 37 and 45 – "stabilizing agent comprises 1.0-7.5% of sucrose", "stabilizing agent comprises 1.0-10% of sucrose"

Claims 12 and 20 depend from claim 5. Claims 37 and 45 depend from claim 30. Dependent claims 12 and 37 specify that the stabilizing agent comprises 1-7.5%

as the amount of sucrose. Dependent claims 20 and 45 specify that the stabilizing agent comprises 1-10% sucrose. Ex. 1002, ¶ 96.

Dix '226 anticipates these ranges by disclosing overlapping values. Dix '226 disclosed a sucrose range from 5 to 30% including specifically for formulations with 0.01% to 3% of polysorbate 20. *Id.*

Example 4 in Dix '226 disclosed liquid formulations of high-concentration aflibercept, and tested sucrose across the range of 5-20%. Ex. 1005 at 10:27-30. Table 7 reported confirmatory stability results for 50-100 mg/ml aflibercept formulations:

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

The text in Table 7 did not identify sucrose levels, but the text above Table 7 and describing the results reported that the liquid "formulation comprises 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." Ex. 1005 at 10:27-30 (emphasis added). The

specification thus confirmed that the disclosed range resulted in stable formulations.

The Dix '226 formulation, the suitable sucrose range expressly referenced 5% to to 30% sucrose, which includes the 5% sucrose value in the Challenged Claims. (Ex. 1002, ¶¶ 96-97). Moreover, Petitioner has not asserted any criticality for the 5% in the '865 patent, and to the contrary the claims cover different ranges thereby confirming the absence of criticality. Because Dix '226 disclosed 5% sucrose, that value anticipates the 1-7.5% and 1-10% ranges found in claims 12, 20, 37, and 45.

1. Claims 14, 22, 39, and 47 – "glycosylated at asparagine residues corresponding to asparagine residues 62, 94, 149, 222 and 308 of SEQ ID NO: 4"

Claims 14 and 22 depend from claim 5. Claims 39 and 47 depend from claim 30. These claims further add that the VEGF antagonist fusion protein is glycosylated at asparagine residues corresponding to asparagine residues 62, 94, 149, 222 and 308 of SEQ ID NO: 4 (aflibercept). Ex. 1002, ¶ 99. That disclosure is met as a descriptor for aflibercept.

Dix '226 disclosed and discussed aflibercept. The VEGF fusion protein antagonist disclosed in Dix '226 is glycosylated at those residues. Dix disclosed a specific embodiment of the preferred amino acids 27-457 of SEQ. ID NO. 4 and is glycosylated at Asn [asparagine] residues 62, 94, 149, 222 and 308. Ex. 1002, ¶ 99.

H. Claims 15, 23, 40, and 48 – "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"

Claims 15, 23, 40 and 48 require a turbidity of 0.01 or lower at OD_{405} after 2 months storage at 5 °C. Turbidity is an inherent property of a formulation, just like the percent native conformation. Proving inherency for this limitation requires only showing a formulation that is "capable of" providing the claimed turbidity level—which was already established in the prior art. Ex. 1002, ¶ 100

Based on the teachings of Dix '226 and the '865 patent, an anticipatory formulation with the claimed components will necessarily meet the claimed stability criteria. *Id.* As shown in the table below, the '865 patent and Dix '226 examples both tested a range of concentrations for the VEGF Trap active and excipients that achieved the recited turbidity values, and the 40 mg/ml formulation in dependent claims 15, 23, 40 and 48 would necessarily satisfy the turbidity level below 0.01 under the claimed temperature and time conditions. Ex. 1002, ¶ 101

	VEGF Trap (aflib)	**Buffer**	**Tonicity agent**	**Co-solvent**	**Stabilizing agent**	**pH**	**Turbidity**
'865 patent Examples	20-50 mg/mL	5-10 mM phosphate	20-135 mM NaCl	0.015-0.1% polysorbate 20 or 3% PEG 3350	0-5% sucrose	6.25-6.3	0.0 to 0.01 at 2-3 months
Dix '226 Specification (Tables 1-6)	50 to 100 mg/mL	5-10 mM phosphate; 5 mM	50 mM NaCl	0.1% polysorbate 20	20% sucrose	6.0-6.3	0.0 to 0.01 for up to 15-24 months

		phos - phat e and 5 mM citrat e					
Narrowest **'865 claims**	40 mg/ml	5-25 mM buffer	tonicity agent	0.03-0.1% polysorbat e 20	1 to 7.5% sucrose	6.2-6.3	0.01 or lower at 2 months

Ex. 1002, ¶ 101.

Furthermore, Dix '226 provided turbidity data for even more formulations with different excipients and concentrations. Ex. 1002, ¶ 102. All of the Dix '226 formulations met the recited turbidity limitations—and for longer periods of time—showing to a POSA that the claimed turbidity requirement was not a particularly unique or demanding threshold. *Id.* The '865 patent's formulations with sucrose even at the lower end of the disclosed range in Dix achieved the claimed turbidity values.

As with the native conformation stability limitation, the '865 patent does not separately teach obtaining the claimed turbidity other than by making the formulation by assembling the components. And a 40 mg/ml aflibercept formulation with polysorbate disclosed in Dix '226 already fell in the range of Example '865 formulations that achieved the claimed turbidity. Ex. 1002, ¶ 104 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 meets the turbidity limitation both expressly and inherently. *Id.*

I. 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"

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 .1% polysorbate 20, and 1 to 10% sucrose have 99% native conformation at 2 months. Ex. 1002, ¶ 103.

These claims would be inherently anticipated for the same reasons explained with respect to claim 12, 20, 37, and 45. 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. Ex. 1002, ¶ 103.

J. 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"

The stability limitations of these claims— 98% stability at 24 months—are anticipated for the same reasons set out in the prior section. .

Furthermore, the 24 month stability data in the '865 patent examples and Dix

'226 confirm that the Dix '226 lower-end sucrose formulation will have the requisite stability. Specifically, aflibercept formulations with the same ingredients as the lower-end sucrose Dix '226 formulation, and specifically those that include polysorbate 20 like the lower-end sucrose Dix '226 formulation, achieved greater than 98% stability after 24 months. *See, e.g.,* Ex. 1005, Tables 1 and 9 (disclosing 98.3 and 99.3% native conformation at 24 months); Ex. 1001, Table 1 (disclosing 98.1% native conformation at 24 months); Ex. 1002, ¶ 104.

Dix's Example 4 showed a 50 mg/ml aflibercept formulation that retains 99.3% native conformation at 24 months. (Table 7). A 40 mg/ml formulation would inherently also meet the stability as Dix demonstrates that there is less aggregation when the aflibercept concentration is lower. *Id.*

As shown in the table below, the lower-end sucrose 40 mg/ml aflibercept Dix '226 formulation (Modified Dix '226) would necessarily have the claimed stability because that modified Dix '226 formulation falls within the described ranges of aflibercept and excipients tested in the '865 patent and Dix '226 for stability.

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

		and 5 mM citrate					
Dix '226 Included Values	40 mg/mL	5 mM phosphate 5 mM citrate	100 mM NaCl	0.1% polysorbate	5% sucrose	6.0-6.3	

Ex. 1002, ¶105.

Furthermore, Patent Owner cannot show the formulation lacks the claimed stability. *See In re Best*, 562 F.2d 1252, 1255 (C.C.P.A. 1977).

IX. DISCRETION UNDER § 325(D) AND § 314

Consistent with the guidance provided by "FAQs for Interim Processes for PTAB Workload Management," Petitioner does not present affirmative arguments in anticipation of what Patent Owner may argue by way of briefing seeking discretionary denial. Petitioner will present arguments in an Opposition Brief, should Patent Owner elect to file a Discretionary Denial Brief.

X. CONCLUSION

For the foregoing reasons, Petitioner has established a reasonable likelihood that claims 1-5, 7-30 and 32-50 are unpatentable. Petitioner therefore respectfully requests that *inter partes* review of the '865 patent be granted.

Dated: July 14, 2025

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(a) and (d), the undersigned hereby certify that the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 11,084,865 complies with the type-volume limitation of 37 C.F.R. § 42.24(a)(1)(i) and (b)(1)(i) permitting a petition of up to 14,000 words because, exclusive of the exempted portions, it contains 7,183 words as counted by the word processing program used to prepare the paper.

Date: July 14, 2025

Respectfully submitted,

By: */Imron T. Aly/*

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CERTIFICATE OF SERVICE

Pursuant to 37 CFR §§ 42.6(e)(4)(i) *et seq.* and 42.105(b), the undersigned certifies that on July 14, 2025, a complete and entire copy of this Petition for *Inter Partes* Review of U.S. Patent No. 11,084,865, Power of Attorney, and all supporting exhibits were provided via Federal Express to the Patent Owner at the correspondence address of record as follows:

By electronic mail to: dberl@wc.com

By Federal Express Next Business Day Delivery to :
191459 - A&P - Regeneron (Prosecution)
601 Massachusetts Ave., NW
Washington, DC 20001-3743

/s/ Nicole S. Lynch
Nicole S. Lynch