

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF WEST VIRGINIA

IN RE: AFLIBERCEPT PATENT
LITIGATION

MDL NO. 1:24-MD-3103-TSK

THIS DOCUMENT RELATES TO
CASE NO.
1:23-CV-39

REDACTED PUBLIC VERSION

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ORDER DENYING REGENERON'S MOTION FOR PRELIMINARY INJUNCTION

Pending before the Court is Plaintiff Regeneron's Motion for Preliminary Injunction. ECF No. 180.¹ The Court has considered the parties' briefing and evidence. ECF Nos. 180, 206, 224, 231-1. The Court convened for oral argument on August 13, 2024. ECF Nos. 241, 243. The motion is fully briefed and ripe for decision. For the reasons set forth herein, the motion is **DENIED**.

I. PRELIMINARY STATEMENT

Plaintiff Regeneron Pharmaceuticals, Inc. ("Regeneron") filed this patent infringement action against Defendant Amgen Inc. ("Amgen"). Amgen disputes the infringement and validity of the patents asserted by Regeneron. At issue in Regeneron's motion for preliminary injunction is one of those patents: U.S. Patent No. 11,084,865 (the "'865 patent" or the "Product Patent"). ECF No.

¹ All docket references are to member case 1:24-cv-39 unless otherwise indicated.

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180-10, Trout Ex. 65.² Regeneron's motion asserts infringement of claims 2, 3, 27, and 28 (the "Asserted Claims"). The Asserted Claims are associated with Regeneron's product Eylea® ("Eylea") and Amgen's filing of an abbreviated Biologics License Application ("BLA") seeking authorization to commercialize "ABP 938," a biosimilar version of Eylea. For the reasons set forth herein, the Court **DENIES** Regeneron's motion. Regeneron has not shown a reasonable likelihood of success on the merits because Amgen has raised a substantial question of noninfringement based on the specific formulation of Amgen's proposed biosimilar product.

This Court has resolved preliminary injunction motions in related cases involving the '865 patent against other defendants in this multidistrict litigation ("MDL"). Those cases are presently on appeal. See In re: Aflibercept Patent Litig., 1:24-md-3103, ECF Nos. 276, 277, 302, 307 (N.D.W. Va.). The Court's ruling on Regeneron's motion against Amgen is resolved on grounds not addressed in the other cases and based on Amgen's formulation.

The Court, having considered the record as a whole, concludes Regeneron has failed to satisfy its burden here. Specifically,

² Citations to "Trout Decl." refer to the June 7, 2024 Opening Expert Declaration of Bernhardt L. Trout, Ph.D. ECF No. 180-3. Citations to "Trout Ex." refer to the exhibits attached to the Trout Decl. ECF Nos. 180-4 to 180-16.

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the Court finds Regeneron has not demonstrated it is likely to prevail on the merits of its claim – that being, infringement. See Henderson for Nat'l Labor Rels. Bd. v. Bluefield Hosp. Co., LLC, 902 F.3d 432, 438-39 (4th Cir. 2018) (finding district courts not required to evaluate all Winter factors “if one is clearly absent”). For that reason, the Court **DENIES** the pending motion.

II. BACKGROUND INFORMATION**A. Regeneron's Eylea Product**

Regeneron developed, markets, and sells Eylea, which the U.S. Food and Drug Administration (“FDA”) approved on November 18, 2011. The Court has previously addressed the pertinent background and development of Eylea. See Regeneron Pharm., Inc. v. Mylan Pharm. Inc., --- F. Supp. ---, 2024 WL 382495, at *13-14 (N.D.W. Va. Jan. 31, 2024) (“Mylan”) (discussing relevant background of Eylea). Eylea is an ophthalmic drug product that has been used to treat patients suffering from diseases that can cause vision loss or even blindness. Id. at *13.

The active ingredient in Eylea is the fusion protein aflibercept. Id. Aflibercept was initially developed as a cancer therapeutic, and Regeneron later discovered that aflibercept could be used to treat angiogenic eye diseases – eye diseases caused by uncontrolled blood vessel growth in the retina – through

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intravitreal injections (injection into the vitreous of the eye).

Id. at *13-14.

Regeneron developed an aflibercept formulation for treating wet Age-Related Macular Degeneration ("AMD") known as Eylea. Id. at *14 (citing Mylan Trial Tr. at 466:22-467:9, 495:15-496:17 (Furfine) (ECF No. 206-6, Chamow Ex. C-4)).³ Regeneron tested Eylea's effectiveness in patients with various other angiogenic eye disorders, obtaining approval for Eylea's use to treat those conditions as well. Id. at *13. Following the FDA's approval of Eylea for administration in a vial presentation, in November 2011, Regeneron subsequently obtained FDA approval to market Eylea in a pre-filled syringe ("PFS") presentation. See Sheridan Decl. ¶ 33.⁴

The Eylea formulation contains 40 mg/ml aflibercept, 10 mM sodium phosphate, 40 mM sodium chloride, 0.03% polysorbate 20, and 5% sucrose, pH 6.2. Mylan, 2024 WL 382495, at *14. The Eylea formulation is the same as Examples 3 and 4 of the '865 patent.

³ Citations to "Chamow Decl." refer to the July 3, 2024 Expert Declaration of Steven M. Chamow, Ph.D. ECF No. 206-2. Citations to "Chamow Ex. C-" refer to the exhibits attached to the Chamow Decl. ECF Nos. 206-3 to 206-25.

⁴ Citations to "Sheridan Decl." refer to the June 7, 2024 Declaration of Sean D. Sheridan, Ph.D. ECF No. 180-17. Citations to "Sheridan Ex." refer to the exhibits attached to the Sheridan Decl. ECF Nos. 180-18 to 180-23.

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See '865 patent at 9:19-10:11; see also Trout Decl. ¶ 428 ("Examples 3 and 4 contain the same components as EYLEA and are embodiments of the claims."). As shown below, Eylea contains a sodium phosphate buffer.

Component	Function	Concentration
Active Ingredient		
Aflibercept	active ingredient	40 mg/ml
Excipients		
sodium phosphate	buffering agent	10 mM
sodium chloride	tonicity agent	40 mM
Sucrose	stabilizing agent	5% (w/v)
polysorbate 20	organic co-solvent	0.03% (w/v)

See Eylea PI 2011 at 9 (ECF No. 180-7, Trout Ex. 16); Trout Decl. ¶ 428; Chamow Decl. ¶ 119.

In August 2023, Regeneron received FDA approval to market Eylea® HD ("Eylea HD"), a formulation containing 114.3 mg/mL aflibercept with a histidine buffer and other excipients. Clark Decl. ¶ 3;⁵ Chamow Decl. ¶ 92; Eylea HD PI 2023 at 5 (ECF No. 206-

⁵ Citations to "Clark Decl." refer to the June 7, 2024 Declaration of Kevin Clark. ECF No. 180-24. Citations to "Clark Ex." refer to the exhibits attached to the Clark Decl. ECF Nos. 180-24, 180-25.

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6, Chamow Ex. C-11). Eylea HD is currently approved to treat wet AMD, Diabetic Macular Edema ("DME"), and Diabetic Retinopathy ("DR"). Clark Decl. ¶ 3. While Eylea contains a phosphate buffer, Eylea HD contains a histidine buffer. Chamow Decl. ¶ 92.

B. Amgen's BLA and Proposed Biosimilar Product

Amgen is a research-based biotechnology company headquartered in Thousand Oaks, California and is the developer of ABP 938, a proposed biosimilar version of Eylea. Heath Decl. ¶¶ 1, 8.⁶ Amgen filed BLA No. 761298 ("Amgen's BLA") with FDA on August 23, 2023, seeking approval under the Biologics Price Competition and Innovation Act ("BPCIA"), 42 U.S.C. §§ 262 (k)-(l), to market and distribute its proposed biosimilar, "ABP 938," in the United States. Heath Decl. ¶ 20; October 17, 2023 Letter to FDA at AMG-AFL-US_00145633⁷ (ECF No. 180-2, Argall Ex. 2).

Amgen's BLA seeks approval to market ABP 938 for the treatment of wet AMD, macular edema following retinal vein occlusion ("RVO"),

⁶ Citations to "Heath Decl." refer to the July 3, 2024 Declaration of Brian Heath in Support of Defendant Amgen Inc.'s Opposition to Plaintiff Regeneron Pharms., Inc.'s Motion for Preliminary Injunction. ECF No. 206-37. Citations to "Heath Ex. H-" refer to the exhibits attached to the Heath Decl. ECF Nos. 206-38 to 206-41.

⁷ Citations to "Argall Ex." refer to the exhibits attached to the June 7, 2024 and July 24, 2024 Declarations of Arthur J. Argall III [sic] Support of Regeneron Pharmaceuticals, Inc.'s Motion for Preliminary Injunction. ECF Nos. 180-2, 224-1.

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DME, and DR. Heath Decl. ¶ 20. Amgen's BLA seeks approval for two presentations of ABP 938: (1) a single-dose vial containing 2 mg aflibercept, sucrose, α,α -Trehalose dihydrate, polysorbate 80, and water for injection; and (2) a single-dose PFS containing 2 mg aflibercept, sucrose, α,α -trehalose dihydrate, polysorbate 80, and water for injection, as shown the chart below reproduced from Amgen's BLA. Id.

Component	Function	Concentration
Active Ingredient		
ABP 938	active ingredient	40 mg/ml
Excipients		
sucrose	stabilizing agent and tonicity modifier	[REDACTED]
α,α -trehalose dihydrate	stabilizing agent and tonicity modifier	[REDACTED]
polysorbate 80	surfactant	[REDACTED]
Water for injection	aqueous solvent	qs to target volume

ABP 938 QOS [Vial] at AMG-AFL-US_00000640 (ECF No. 206-38, Heath Ex. H-4); ABP 938 QOS [PFS] at AMG-AFL-US_00000529-530 (ECF No. 206-38, Heath Ex. H-3).

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The parties do not dispute the contents of Amgen's formulation. See Chamow Decl. ¶ 125 (Table 6); ABP 938 QOS [Vial] at AMG-AFL-US_00000640 (Table 1) (ECF No. 180-4, Trout Ex. A-4); ABP 938 QOS [PFS] at AMG-AFL-US_00000530 (Table 1) (ECF No. 180-4, Trout Ex. A-5). Amgen's BLA states that "ABP 938 has a different formulation than Eylea." ABP 938 Nonclinical Overview at AMG-AFL-US_00000911 (ECF No. 206-20, Chamow Ex. C-112). As is relevant here, ABP 938 does not contain a separate buffer component. Chamow Decl. ¶¶ 223-233; Trout Decl. ¶ 232. As stated in Amgen's BLA,

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C. Other Aflibercept Biosimilars

To date, Regeneron has initiated patent infringement lawsuits against five defendant groups that are seeking FDA approval to market aflibercept biosimilars: Mylan and Biocon Biologics Inc. ("Biocon"), Samsung Bioepis Co., Ltd. ("Samsung"), Celltrion, Inc. ("Celltrion"), Formycon AG ("Formycon"), and Amgen. Although the various defendants' proposed products contain the same active ingredient as Eylea (aflibercept), in the same 2 mg dosage strength, the defendants' formulations differ in their inactive

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ingredients. Opp. at 1;⁸ Chamow Decl. ¶¶ 126-127. The formulation components for the defendant groups, as well as Regeneron, are summarized below:

'865 patent Components	Regeneron's EYLEA Formulation	Mylan's M710 Formula tion	Samsung's SB15 Fo rmulation	Celltrion's CT-P42 Formula tion	Formycon's FYB203 Fo rmulation	Amgen's ABP 938 Formula tion
Active Ingredient						
VEGF Antagonist	40 mg/ml aflibercept	40 mg/ml aflibercept	40 mg/ml aflibercept	40 mg/ml aflibercept	40 mg/ml aflibercept	40 mg/ml aflibercept
Excipients						

⁸ Citations to "Opp." refer to Amgen Inc.'s Brief in Opposition to Regeneron's Motion for Preliminary Injunction, filed July 3, 2024. ECF No. 206.

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Organic Co-Solvent	Polysorbate 20	Polysorbate 20	Polysorbate 20	Polysorbate 20	Polysorbate 20	Polysorbate 80
Buffer	phosphate	histidine	phosphate	histidine	histidine	
Stabilizing Agent	Sucrose	Trehalose	Sucrose	Trehalose	Sucrose	Sucrose / Trehalose
(Optional) Tonicity Agent	Sodium chloride		Sodium chloride	Sodium chloride	Sodium chloride	

See Chamow Decl. ¶ 126 (Table 7); Opp. at 1.

Following a bench trial conducted in June 2023, the Court granted Regeneron's Motion for a Permanent Injunction against Biocon related to Biocon's aflibercept biosimilar ("M710"). See Regeneron Pharms., Inc. v. Mylan Pharms. Inc., 1:22-cv-61, 2024 WL 3177913 (N.D.W. Va. June 21, 2024). The Court also granted Regeneron's Motions for Preliminary Injunction against Samsung (Regeneron Pharms., Inc. v. Samsung Bioepis, Co., Ltd., 1:23-cv-

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94, ECF No. 250 (N.D.W. Va. June 24, 2024); see also 1:23-cv-106, ECF No. 232 (N.D.W. Va. June 24, 2024) ("Samsung"), Formycon (Regeneron Pharms., Inc. v. Formycon AG, 1:23-cv-97, ECF No. 252 (N.D.W. Va. July 9, 2024)) ("Formycon"), and Celltrion (Regeneron Pharms., Inc. v. Celltrion, Inc., 1:23-cv-89, ECF No. 201 (N.D.W. Va. July 9, 2024)) ("Celltrion"). In Samsung, Formycon, and Celltrion, the Court found that Regeneron was likely to succeed in proving that the '865 patent is infringed by Samsung's aflibercept biosimilar product ("SB15"), Formycon's aflibercept biosimilar product ("FYB203"), and Celltrion's aflibercept biosimilar product ("CT-P42"), that those defendants did not raise a substantial question of invalidity or noninfringement with respect to the claims asserted in their respective proceedings, and that Regeneron would suffer irreparable harm if those defendants were permitted to commercialize their respective proposed biosimilar products in the United States.

III. PROCEDURAL BACKGROUND

On January 10, 2024, Regeneron filed this lawsuit against Amgen in the United States District Court for the Central District of California asserting 32 of its patents. ECF No. 1.

Pursuant to 42 U.S.C. § 262(1)(8)(A), a biosimilar applicant must provide notice to the reference product sponsor no later than

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180 days before the date of the first commercial marketing of the applicant's product. On February 23, 2024, Amgen transmitted its "Notice of Commercial Marketing" to Regeneron. Under the BPCIA, Amgen may therefore begin commercial marketing of ABP 938 on or after August 21, 2024, if Amgen has received FDA approval.

On April 11, 2024, the United States Judicial Panel on Multidistrict Litigation ordered Regeneron's case against Amgen to be consolidated for pretrial proceedings before this Court with Regeneron's cases against other aflibercept biosimilar applicants. In re: Aflibercept Patent Litig., 1:24-md-3103, ECF No. 1 (N.D.W. Va. Apr. 11, 2024).

On May 24, 2024, the Court issued an Order Setting Briefing Schedule with Respect to Any Motion for Preliminary Injunction Against Amgen. ECF No. 172. The same day, Amgen filed a motion to clarify whether Regeneron's preliminary injunction motion would be limited to the '865 patent. ECF No. 174. On May 28, 2024, the Court issued an Order granting Amgen's motion for clarification limiting any preliminary injunction motion filed against Amgen to the '865 patent, while also amending the preliminary injunction briefing schedule with respect to Amgen. ECF No. 175 ("Scheduling Order"). On June 7, 2024, Regeneron filed a motion for a preliminary injunction against Amgen, based on the '865 patent.

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ECF No. 180-1 ("Motion").⁹ Regeneron's motion asserted claims 2-3 and 27-28 of the '865 patent (the "Asserted Claims"). Id. at 5-6. On July 3, 2024, Amgen filed its opposition. ECF No. 206 ("Opp."). On the same day, Amgen filed a request for oral argument. ECF No. 207. On July 15, 2024, Regeneron filed a response, indicating that Regeneron did not oppose Amgen's request for oral argument. ECF No. 215. On July 22, 2024, Amgen filed a reply in further support of oral argument. ECF No. 217. On July 24, 2024, Regeneron filed its reply brief in support of its preliminary injunction motion. ECF No. 224 ("Reply").¹⁰ On July 29, 2024, Amgen filed a motion for leave to file a surreply (ECF No. 231), with an attached surreply to address issues in Regeneron's Reply. ECF No. 231-1 ("Surreply").¹¹ On July 31, 2024, Regeneron filed an opposition to Amgen's motion for leave to file a surreply. ECF No. 234.

On July 25, 2024, the Court ordered oral argument on Regeneron's motion for preliminary injunction to be held on August

⁹ Citations to "Motion" refer to Regeneron's Opening Brief in Support of Motion for Preliminary Injunction, filed June 7, 2024. ECF No. 180-1.

¹⁰ Citations to "Reply" refer to Regeneron's Reply Brief in Support of Motion for Preliminary Injunction, filed July 24, 2024. ECF No. 224.

¹¹ Citations to "Surreply" refer to Amgen Inc.'s Surreply in Opposition to Regeneron's Motion for Preliminary Injunction, filed July 29, 2024. ECF No. 231-1.

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6, 2024. ECF No. 228. On July 26, 2024, the Court continued the oral argument until August 13, 2024, to accommodate a conflict identified by Regeneron's counsel. ECF No. 229. Oral argument was held before this Court on August 13, 2024. ECF No. 241; ECF No. 243 ("Hearing Tr.").¹²

IV. FACTUAL BACKGROUND

A. Expert Declarants

In support of its preliminary injunction motion, Regeneron filed declarations from two expert witnesses, Dr. Bernhardt Trout and Dr. Sean Sheridan, and one fact witness, Mr. Kevin Clark. Amgen deposed Dr. Sheridan and Mr. Clark. Amgen did not depose Dr. Trout. Amgen presented declarations from two expert witnesses, Dr. Steven Chamow and Dr. David Blackburn, and one fact witness, Mr. Brian Heath. Regeneron deposed all of Amgen's witnesses.

1. Regeneron's Declarants

In support of its motion for a preliminary injunction, Regeneron filed an expert declaration from Dr. Trout addressing infringement and validity with respect to the '865 patent. Dr. Trout had provided testimony on infringement and validity of the '865 patent at the Mylan trial and this Court previously found his

¹² Citations to "Hearing Tr." refer to the transcript of the oral argument held before the Court on August 13, 2024. ECF No. 243.

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testimony to be credible and reliable. Dr. Trout is a professor of Chemical Engineering at the Massachusetts Institute of Technology ("MIT") and holds a Ph.D. in chemical engineering. Trout Decl. ¶¶ 9-10. At MIT, Dr. Trout performs pharmaceutical development and manufacturing research on biopharmaceutical (e.g., protein-based) therapeutics and has worked on approximately fifty biologic therapeutics. Id. ¶¶ 12-13.

Regeneron filed an expert declaration from Dr. Sheridan regarding whether Regeneron would be irreparably harmed. Dr. Sheridan is a Vice President at Charles River Associates, an international business consulting firm, and has a Ph.D. in genetics as well as an MBA with concentrations in finance and economics from the University of Chicago. Sheridan Decl. ¶¶ 1-2. Dr. Sheridan's previous experience has included the quantification of economic damages, and he has experience in modeling and valuation in a variety of intellectual property matters. Id. ¶¶ 3-5.

Regeneron filed a fact witness declaration from Mr. Clark regarding the effect of biosimilar market entry on Regeneron and Eylea and Eylea HD. Mr. Clark is Vice President of Regeneron's Ophthalmology Commercial Business Unit, a role he has held since 2020. Clark Decl. ¶ 1. Mr. Clark's focus at Regeneron has been on the commercialization of Eylea and Eylea HD. Id. ¶ 3.

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2. Amgen's Declarants

Amgen filed an expert declaration from Dr. Chamow regarding infringement and validity of the '865 patent. Dr. Chamow holds a Ph.D. in Biochemistry and is the founder of Chamow and Associates, Inc., a consulting firm that provides product development and guidance and advice to pharmaceutical and biotechnology companies. Chamow Decl. ¶¶ 14, 20. Chamow and Associates, Inc. was acquired by Alira Health, and in 2024, Dr. Chamow transitioned to Principal Consultant. Id. ¶ 20. Dr. Chamow's work includes the characterization of and formulation development for recombinant proteins (including fusion proteins). Id. Dr. Chamow has more than 35 years of biopharmaceutical experience. Id. ¶ 14. Dr. Chamow was employed as a research scientist at Genentech from 1987 to 1998, where he designed and developed recombinant Fc-fusion proteins and monoclonal antibodies, including for manufacturing and testing at clinical scale. Id.

Amgen filed an expert declaration from Dr. David Blackburn addressing irreparable harm, balance of the hardships, and public interest. Dr. Blackburn holds a Ph.D. in Economics from Harvard University and is an applied microeconomist. Blackburn Decl.

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¶ 1.¹³ Dr. Blackburn is the managing director and head of the life science practice for NERA, an economic consulting firm, where he focuses on intellectual property, antitrust, and damages issues, with a substantial portion of this work focused on the pharmaceutical industry. Id. ¶¶ 1-2. Dr. Blackburn has analyzed damages in numerous patent-infringement cases and has taught courses on economics. Id. ¶ 2.

Amgen filed a declaration from a fact witness, Mr. Brian Heath, regarding the harms that Amgen would suffer if the Court were to enjoin Amgen and prevent it from launching ABP 938 until after a trial on the merits. Mr. Heath serves as Vice President & General Manager of the U.S. Oncology Business Unit at Amgen. Heath Decl. ¶ 1. Mr. Heath's responsibilities involve leading marketing, coverage, pricing, strategy, and contract operations at Amgen for ABP 938. Id. ¶¶ 1-3.

B. Regeneron's '865 Patent

The United States Patent and Trademark Office ("USPTO") issued the '865 patent, titled "VEGF Antagonist Formulations Suitable for Intravitreal Administration," on August 10, 2021, to

¹³ Citations to "Blackburn Decl." refer to the July 3, 2024 Expert Declaration of David Blackburn, Ph.D. ECF No. 206-26. Citations to "Blackburn Ex. B-" refer to the exhibits attached to the Blackburn Decl. ECF Nos. 206-27 to 206-36.

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Regeneron Pharmaceuticals, Inc. as assignee from named inventors Eric Furfine, Daniel Dix, Kenneth Graham, and Kelly Frye. '865 patent at Cover Page. The '865 patent claims priority through continuation and divisional applications to Provisional Patent Application No. 60/814,484 ("'484 provisional") (ECF No. 180-12, Trout Ex. 96), which is identified as having been filed on June 16, 2006. Id.

C. Asserted Claims

The following table lists the Asserted Claims Regeneron alleges that Amgen infringes on this motion and the claims from which they depend. See Motion at 5-6.

Claims of the '865 patent	
Claim 1 (unasserted)	1. A vial comprising an ophthalmic formulation suitable for intravitreal administration that comprises: a vascular endothelial growth factor (VEGF) antagonist, an organic co-solvent, a buffer, a stabilizing agent,

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	<p>wherein said VEGF antagonist fusion protein is glycosylated and comprises amino acids 27-457 of SEQ ID NO:4; and</p> <p>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.</p>
Claim 2	2. The vial of claim 1, wherein the concentration of said VEGF antagonist fusion protein is 40 mg/ml, and wherein said organic co-solvent comprises polysorbate.
Claim 3	3. The vial of claim 2, wherein said organic co-solvent comprises 0.01% to 3% polysorbate.
Claim 26 (unasserted)	26. A pre-filled syringe comprising an ophthalmic formulation suitable for intravitreal administration comprising: a vascular endothelial growth factor (VEGF) antagonist fusion protein, an organic co-solvent, a buffer, and a stabilizing agent;

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	<p>wherein said VEGF antagonist fusion protein is glycosylated and comprises amino acids 27-457 of SEQ ID NO:4; and</p> <p>wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5° C. for two months as measured by size exclusion chromatography.</p>
Claim 27	<p>27. The pre-filled syringe of claim 26, wherein the concentration of said VEGF antagonist fusion protein is 40 mg/ml, and wherein said organic co-solvent comprises polysorbate.</p>
Claim 28	<p>28. The pre-filled syringe of claim 27, wherein said organic co-solvent comprises 0.01% to 3% polysorbate.</p>

D. Definition of a POSA

The parties have advanced slightly differing definitions of a Person of Ordinary Skill in the Art ("POSA"). The definition does not appear to be an issue of material dispute at this time, as neither party contends the differences between these

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definitions affect assessment of the issues raised. The findings detailed below would be no different were the Court to perform the required analysis under the definition of the POSA adopted in the Mylan case or under Amgen's proposed definition. The Court adopts the definition applied in the Mylan case, for the reasons given in the Mylan case:

[T]he POSA 'would be a professional with a master's degree at least in a relevant field, so a technical field directly relevant to formulations here.' Tr. 2092:6-17 (Trout); PDX-9.002 (explaining that the POSA 'would have held an advanced degree, such as a Master's in a biopharmaceutical science, or a related discipline, such as chemical engineering, and several years of experience in the development of biologics products. Alternatively, the POSA could have a Ph.D. in such discipline and less experience. The POSA may collaborate with others, including a medical doctor with experience treating ophthalmic diseases.').

Mylan, 2024 WL 382495, at *22.

E. Prior Claim Constructions

In the earlier Mylan case, the Court was asked to expressly construe two claim terms:

The Court construed "organic cosolvent" to mean "an organic substance added to the primary solvent to increase the solubility of the solute, here a VEGF antagonist" . . . [and] construed "native conformation" to mean "the original intact form of the VEGF antagonist, which is a form

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that does not exhibit chemical or physical instability."

Mylan, 2024 WL 382495, at *17 (quoting Mylan, 1:22-cv-61, ECF No. 427 at 20, 25-26). The parties have applied those constructions in these preliminary injunction proceedings.

In Mylan, the Court also addressed Mylan's challenge to the validity of the claims of the '865 patent under 35 U.S.C. § 112 for lack of written description and lack of enablement. Id. at *63-70. In Mylan, the defendants "criticize[d] the claims for reciting the structural categories of 'buffer' and 'stabilizing agent' instead of specific chemical structures." Id. at *64. Regeneron responded to this challenge by adducing testimony at trial that "buffers were 'a known set of structures,'" represented by the "handful of buffers that the POSA would consider in a formulation" Id. (citing Mylan Trial Tr. at 1509:13-1510:9, 1494:6-25 (ECF No. 206-6, Chamow Ex. C-5)). Dr. Trout offered trial testimony in support of Regeneron's position. Following trial, after considering the trial testimony and admitted evidence, the Court issued a decision upholding the validity of the asserted claims of the '865 patent. In doing so, the Court made rulings on the scope of the claims and whether the properly construed claims are commensurate with the scope of the specification. See Revolution Eyewear Inc. v. Aspex Eyewear Inc.,

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563 F.3d 1358, 1367 (Fed. Cir. 2009) ("[A] claim construction and a written description analysis are two separate processes. However, they serve related functions in determining whether a claim is commensurate with the scope of the specification – a court looks to the specification for guidance to ascertain the scope of the claim in claim construction; it also looks to the specification to decide whether the disclosure provides adequate support for the claims in written description analysis."); McRO, Inc. v. Bandai Namco Games Am., Inc., 959 F.3d 1091, 1100 (Fed. Cir. 2020) ("[T]he 'enablement inquiry necessarily depends on an interpretation of the claims.'") (quoting Liquid Dynamics Corp. v. Vaughan Co., 449 F.3d 1209, 1224 n. 2 (Fed. Cir. 2006)).

The Court's trial decision, upholding validity over Mylan's written description challenge, credited Dr. Trout's analysis and conclusion. Mylan, 2024 WL 382495, at *64 ("The Court credits Dr. Trout's analysis and conclusion."). The Court also credited Regeneron's expert testimony "that each of the claim limitations in the Product Patent have 'common structural features,' including the 'very specific' VEGF antagonist and the categories of organic co-solvent, buffer, and stabilizing agent." Id. at *64 (citing Mylan Trial Tr. at 2109:17–2110:3 (ECF No. 206-6, Chamow Ex. C-6)); see also id. at *65 ("[H]ere the claims are limited to a

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specific protein molecule at a specific concentration along with other known structures (a buffer, stabilizing agent, and polysorbate 20)”) (emphasis added).

In Mylan, the Court found that buffers were “a known set of structures” represented by the “handful of buffers” that the POSA would consider for the claimed formulation, and the POSA therefore could “visualize or recognize” the claimed buffer structures. Id. at *64 (citing Mylan Trial Tr. at 1494:6-25 (ECF No. 206-6, Chamow Ex. C-5)). The Court thus found that, for such known classes of structures, the patent did not need to provide an exhaustive description to the POSA. Id. The Court concluded that “[s]ince the specification here identifies the common structural features of the claimed compositions – 40 mg/ml aflibercept, polysorbate 20, a buffer, and a stabilizing agent – and provides multiple examples thereof,” the written description requirement was satisfied. Id.; see also id. (“Following this analysis, Dr. Trout testified that the Product Patent provided ‘species or examples representative of the genus,’ claimed structures rather than function, and thus provided adequate written description for the asserted claims.”) (citing Mylan Trial Tr. at 2111:1-21 (ECF No. 206-6, Chamow Ex. C-6)).

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The Court similarly credited testimony from Dr. Trout in the context of rejecting Mylan's enablement challenges. The Court credited Dr. Trout's testimony that "the asserted claims are 'narrow' rather than broad, because they claim 'one specific biologic molecule . . . with a specific sequence ID' at just one concentration (40 mg/ml), in a vial for intravitreal administration, and further claim specific structural components including a buffer, stabilizing agent, and the organic co-solvent of polysorbate 20 within a 'narrow range.'" Id. at *66 (emphasis added) (citing Mylan Trial Tr. at 2089:10-2090:4 (ECF No. 206-6, Chamow Ex. C-6)). The Court found that the defendants had not proven that identifying formulations having the claimed structure "40 mg/ml of glycosylated aflibercept and polysorbate 20 within the specified concentration range, plus a buffer and a stabilizing agent" would require undue experimentation. Id. at *70 (emphasis added).

With respect to the claimed component of "a buffer," the Court found that the "excipients recited in the claims are also structures: categories for the buffer and stabilizing agent, and a specific substance (polysorbate 20) for the organic co-solvent." Id. (emphasis added).

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The Court granted Regeneron's preliminary injunction motion in Formycon. In that case, Formycon proposed that the "buffer" term be construed to refer "to a phosphate buffer, and not any other type of buffer." Formycon, 1:23-cv-97, ECF No. 252 at 47. Regeneron proposed the term be construed as "a substance that resists changes to pH upon addition of an acid or base within an optimal pH range through a proton-donating component and/or a proton-accepting component, including, for example, histidine, phosphate, and proteins like aflibercept." Id. The Court adopted Regeneron's construction for the purpose of resolving the disputes at issue in Formycon. Id. Like Mylan's product (which the Court had earlier found to be infringing), Formycon's product contains a separate histidine buffer. Id. at 62-63. Formycon argued that the claim term "a buffer" should be construed as limited to a phosphate buffer. Based on this proposed limiting construction, Formycon argued that it does not infringe. Id. at 61-62. As discussed in the Formycon decision, "a buffer" is not so limited. Id. Because the term "buffer" in the '865 patent is not limited to a phosphate buffer, and Formycon's product contains a separate histidine buffer, the Court found that Regeneron had established a likelihood that Formycon's product would infringe the claims.

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As noted above, in Formycon, the Court did not address the claim construction issue that Amgen raises in this case. Id. at 62-63.

V. DECISION SUMMARY

For readability, the Court provides this brief summary of its findings here.

As reflected during the arguments presented during the hearing conducted on this motion, the parties' central dispute is whether the Asserted Claims require that the "VEGF antagonist" and the "buffer" be separate and distinct components of the claimed formulation. During the hearing, the Court inquired whether it had previously addressed this claim construction dispute in any of its prior rulings in the MDL. Hearing Tr. at 52:10-11. Counsel for Amgen confirmed that the Court has not been asked to consider whether the claimed aflibercept can also satisfy the separately claimed buffer of the Asserted Claims. Id. at 52:1-17. Counsel for Regeneron did not disagree. Id. at 20:9-16. Accordingly, this Court resolves this dispute, as it has arisen for the first time in the context of this case.

Amgen proposes that the Asserted Claims require that the claimed "VEGF antagonist" and the claimed "buffer" be separate components. Opp. at 1-2, 6-12. Regeneron argues that the VEGF antagonist can also satisfy the limitation of the claimed buffer.

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Reply at 1-12. This dispute requires the Court to construe for the first time the claim term "an ophthalmic formulation . . . that comprises: a vascular endothelial growth factor (VEGF) antagonist[,] an organic co-solvent, a buffer, and a stabilizing agent." '865 patent at claims 1 and 26. The Court addresses the parties' various arguments in detail below and briefly summarizes its ruling on this claim construction issue, and the implications of the Court's construction, here.

The Federal Circuit addressed the claim construction issue of separate versus overlapping claim elements in Becton, Dickinson & Co. v. Tyco Healthcare Grp., LP, 616 F.3d 1249 (Fed. Cir. 2010), stating: "Where a claim lists elements separately, the clear implication of the claim language is that those elements are distinct components of the patented invention." Id. at 1254 (cleaned up). Both parties cite and discuss Becton, as well as later cases applying Becton, in their briefs. Becton and its progeny were likewise a focus of the hearing. Hearing Tr. at 26:17-32:10, 56:18-59:7, 62:23-66:16.

Having considered the parties' arguments, legal precedent, and evidence, and for the reasons set forth in detail below, the Court construes the Asserted Claims to require that the claimed "VEGF antagonist" be a separate component from the claimed

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"buffer." There is no dispute that ABP 938 lacks a separate buffer.¹⁴ Amgen has therefore raised a substantial question of noninfringement, and Regeneron has not demonstrated a likelihood of success on merits. Winter v. Nat. Res. Def. Council, Inc., 555 U.S. 7, 20 (2008) (identifying factors as: (1) likelihood of success on the merits, (2) irreparable harm, (3) balancing of the hardships, (4) public interest).

On this record, where there is no dispute as to infringement under the Court's construction, the first Winter factor outweighs any other basis for preliminary injunctive relief, even if the other three factors are assumed to weigh in Regeneron's favor. "A preliminary injunction should not issue if the accused infringer raises a substantial question concerning either infringement or validity." Metalcraft of Mayville, Inc. v. The Toro Co., 848 F.3d 1358, 1364 (Fed. Cir. 2017) (internal quotations and citation omitted); see also Mylan Institutional LLC v. Aurobindo Pharma Ltd., 857 F.3d 858, 866 (Fed. Cir. 2017) ("A preliminary injunction should not issue if the accused infringer raises a substantial question [of] infringement"); see also Genentech, Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1364 (Fed. Cir. 1997) ("[I]f [Defendant] raises a 'substantial question' concerning validity,

¹⁴ Trout Decl. ¶ 232; Chamow Decl. ¶ 125.

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enforceability, or infringement (i.e., asserts a defense that [Plaintiff] cannot show 'lacks substantial merit') the preliminary injunction should not issue."); Sofamor Danek Grp., Inc. v. DePuy-Motech, Inc., 74 F.3d 1216, 1219 (Fed. Cir. 1996) (holding that likelihood of success on the merits is "central to the movant's burden."). The Court finds that the substantial question raised is central and weighs heavily against granting a preliminary injunction.

A preliminary injunction cannot issue absent a "clear showing" that all four requirements are satisfied. Leaders of a Beautiful Struggle v. Baltimore Police Dep't, 979 F.3d 219, 226 (4th Cir. 2020). Plus, the "[p]laintiff bears the burden of establishing that each of these factors supports granting the injunction." Direx Israel Ltd. v. Breakthrough Med. Corp., 952 F.2d 802, 812 (4th Cir. 1991) (internal quotations and citation omitted); see Winter, 555 U.S. at 22 (recognizing that because a preliminary injunction is "an extraordinary remedy," it "may only be awarded upon a clear showing that plaintiff is entitled to such relief"). Accordingly, a court need not address all four Winter factors if one or more factors is not satisfied. See Henderson, 902 F.3d at 439.

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The Court, therefore, does not address the other Winter factors. See Jack Guttman, Inc. v. Kopykake Enterprises, Inc., 302 F.3d 1352, 1356 (Fed. Cir. 2002) ("While granting a preliminary injunction requires analysis of all four factors . . . a trial court may . . . deny a motion based on a patentee's failure to show any one of the four factors – especially either of the first two – without analyzing the others.") (citing Polymer Techs., Inc. v. Bridwell, 103 F.3d 970, 973-974 (Fed. Cir. 1996)); Henderson, 902 F.3d at 439 (holding "nothing . . . suggests that a district court must mechanically consider all four Winter factors if one is clearly absent").

VI. ANALYSIS

A. Preliminary Injunction Standards

The Patent Act provides that in patent infringement cases, courts "may grant injunctions in accordance with the principles of equity to prevent the violation of any right secured by patent, on such terms as the court deems reasonable." 35 U.S.C. § 283. "A preliminary injunction is an extraordinary remedy never awarded as of right." Takeda Pharms. U.S.A., Inc. v. Mylan Pharms. Inc., 967 F.3d 1339, 1345 (Fed. Cir. 2020) (quoting Winter, 555 U.S. at 24). The movant must establish that: (1) the plaintiff likely will succeed on the merits at trial; (2) the plaintiff will be

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irreparably injured if an injunction is not granted; (3) the balance of hardships favors the plaintiff; and (4) the public interest will be furthered by an injunction. See Winter, 555 U.S. at 20.

The likelihood of success factor is "central to the movant's burden" and "requires proof on both validity and infringement." Sofamor, 74 F.3d at 1219. Accordingly, if an alleged infringer "raises a 'substantial question' concerning validity, enforceability, or infringement (i.e., asserts a defense that [the patentee] cannot show 'lacks substantial merit') the preliminary injunction should not issue." Genentech, 108 F.3d at 1364. When the patentee fails to show a likelihood of success on infringement, preliminary injunctive relief may be denied. See, e.g., id.; Mylan, 857 F.3d at 866; Sofamor, 74 F.3d at 1219; Takeda Pharms. U.S.A., Inc. v. West-Ward Pharm. Corp., 785 F.3d 625, 634 (Fed. Cir. 2015) (affirming denial of preliminary injunction for lack of likelihood of success on infringement); Abbott Labs. v. Sandoz, Inc., 566 F.3d 1282, 1299 (Fed. Cir. 2009).

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B. Regeneron is not likely to succeed on the merits.

1. The Court construes the disputed claim term "an ophthalmic formulation that comprises" to require a "buffer" that is separate and distinct from the "VEGF antagonist."

"Only when a claim is properly understood can a determination be made whether the claim 'reads on' an accused device or method." Amazon.com, Inc. v. Barnesandnoble.com, Inc., 239 F.3d 1343, 1351 (Fed. Cir. 2001). Thus, "[b]efore deciding whether an accused device infringes asserted claims, a court must first construe the claim language to determine the meaning and scope of the claims." Rambus Inc. v. Infinion Techs, AG, 318 F.3d 1081, 1087 (Fed. Cir. 2003).

The Supreme Court has explained: "[A] district court's construction of a patent claim, like a district court's interpretation of a written instrument, often requires the judge only to examine and to construe the document's words without requiring the judge to resolve any underlying factual disputes. As all parties agree, when the district court reviews only evidence intrinsic to the patent (the patent claims and specifications, along with the patent's prosecution history), the judge's determination will amount solely to a determination of law" Teva Pharms. USA, Inc. v. Sandoz, Inc., 574 U.S. 318, 331 (2015). Likewise, "the ultimate question of the proper

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construction of the patent [is] a question of law in the way that we treat document construction as a question of law” Id. at 325 (citing Markman v. Westview Instruments, Inc., 517 U.S. 388-391).

“[T]he claims of a patent define the invention to which the patentee is entitled the right to exclude.” Phillips v. AWH Corp., 415 F.3d 1303, 1312 (Fed. Cir. 2005) (en banc) (cleaned up). “[T]he ordinary and customary meaning of a claim term is the meaning that the term would have to a [POSA] in question at the time of the invention.” Id. at 1313. Claim construction “begin[s] with the intrinsic evidence, which includes the claims, written description, and prosecution history.” Seabed Geosolutions (US) Inc. v. Magseis FF LLC, 8 F.4th 1285, 1287 (Fed. Cir. 2021). “The construction that stays true to the claim language and most naturally aligns with the patent’s description of the invention will be, in the end, the correct construction.” Phillips, 415 F.3d at 1316 (quoting Renishaw PLC v. Marposs Societa’ per Azioni, 158 F.3d 1243, 1250 (Fed. Cir. 1998)).

The parties dispute how to construe the claim term “an ophthalmic formulation . . . that comprises: a vascular endothelial growth factor (VEGF) antagonist[,], an organic co-solvent, a buffer, and a stabilizing agent.” Amgen proposes that

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this term should be construed to mean "a formulation that comprises four separate components: (1) a VEGF antagonist; (2) an organic co-solvent; (3) a buffer; and (4) a stabilizing agent." Regeneron argues that the Asserted Claims permit one formulation component category, namely, the "VEGF antagonist," to satisfy multiple of the claim elements, namely, both the "VEGF antagonist" element and the "buffer" element.

Accordingly, the central dispute between the parties on the construction of this term is whether the claimed "buffer" must be a separate and distinct component from the claimed "VEGF antagonist." As explained infra, the Court construes the claims to require a buffer that is separate and distinct from the VEGF antagonist. In particular, the Court construes the term "an ophthalmic formulation . . . that comprises: a vascular endothelial growth factor (VEGF) antagonist[,], an organic co-solvent, a buffer, and a stabilizing agent" to mean "a formulation that comprises four separate components: (1) a VEGF antagonist; (2) an organic co-solvent; (3) a buffer; and (4) a stabilizing agent."

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2. The claims separately list "a VEGF antagonist" and "a buffer," giving rise to a presumption that they are separate and distinct components of the claimed formulation.

Both parties cite and discuss a line of cases addressing the issue of whether separately listed elements should be construed to require separate components. The Federal Circuit has consistently held that separately listing elements in a claim creates a presumption that each element is a separate and distinct component of the invention. In Becton, the Federal Circuit held:

Where a claim lists elements separately, the clear implication of the claim language is that those elements are distinct components of the patented invention." 616 F.3d at 1254 (cleaned up). The Federal Circuit has further explained that by listing elements separately, there is "a presumption that those components are distinct."

Kyocera Senco Indus. Tools Inc. v. Int'l Trade Comm'n, 22 F.4th 1369, 1382 (Fed. Cir. 2022) ("The asserted claims list those elements separately There is, therefore, a presumption that those components are distinct."); Google v. Ecofactor, 92 F.4th 1049, 1058 (Fed. Cir. 2024) ("[T]here is a 'presumption' that separately listed claim limitations may indicate separate and distinct physical structure. . . ."); HTC Corp. v. Cellular Commc'ns Equip., LLC, 701 F. App'x 978, 982 (Fed. Cir. 2017) ("The separate naming of two structures in the claim strongly implies

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that the named entities are not one and the same structure.") (citing Becton, 616 F.3d at 1254). The Court considers this line of cases in construing the claims.

Initially, the parties do not dispute the Asserted Claims separately list the claimed "VEGF antagonist" and the "buffer." '865 patent at claims 1 and 26; Hearing Tr. at 20:2-3. Under Becton, therefore, the separate listing of these elements establishes a presumption the claimed "VEGF antagonist" and "buffer" are distinct components. Id.; see also Kyocera, 22 F.4th at 1382; Google, 92 F.4th at 1058. The parties' dispute is not whether the claims list these four elements separately, or whether the presumption applies, but whether this presumption is rebutted by the evidence of record.

a. The claim language does not overcome the presumption of separateness and further supports that the claimed "VEGF antagonist" and the claimed "buffer" are separate components.

To determine whether the presumption of separateness is rebutted, the Court must look to the intrinsic evidence, that is, the patent itself, including the claims and the specification. The cases the parties cite consistently hold that to overcome the presumption of separateness, the intrinsic record must indicate that the inventors disclosed and intended to claim a composition where one component can satisfy multiple claim limitations.

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Becton, 616 F.3d at 1254-55 ("A long line of cases indicates that evidence intrinsic to the patent—particularly the patent's specification . . . is the primary source for determining claim meaning," finding "[t]here is nothing in the asserted claims to suggest that the hinged arm and the spring means can be the same structure" and "[t]he specification, moreover confirms that the spring means is a separate element from the hinged arm") (quoting in part Astrazeneca AB v. Mut. Pharm. Co., 384 F.3d 1333, 1336 (Fed. Cir. 2004)); Kyocera, 22 F.4th at 1382 ("No party has identified claim language overcoming the presumption Nor is there any language in the written description that overcomes that presumption"); Google, 92 F.4th at 1058 ("Here, the claim language and specification rebut any presumption"); Merck Sharp & Dohme, LLC v. Mylan Pharms. Inc., 1:19-cv-00101, 2022 U.S. Dist. LEXIS 195204, at *61 (N.D.W. Va. Sept. 21, 2022) ("Nothing in the '921 patent prevents a single ingredient, such as [REDACTED] from satisfying multiple claim limitations").

In the context of pharmaceutical formulation claims presenting a similar listing of elements, courts have looked to whether the intrinsic evidence shows that the patentee intended, as expressed through the patent's disclosures, that separately listed elements could be satisfied by a single component. See Sun

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Pharm. Indus. Ltd. v. Saptalis Pharms., LLC, 18-cv-648, 2019 WL 2549267, at *7 (D. Del. June 19, 2019) (Bryson, J.) ("[T]he Court must look beyond the functionality of the claim terms to determine whether the patentee intended a single ingredient to satisfy both the sweetener and the polyhydroxy alcohol limitations."); Otsuka Pharm. Co., Ltd. v. Mylan Lab'ys Ltd., 22-cv-464, 2023 WL 5928313, at *3 (D. Del. Sept. 12, 2023) ("Nothing else in claim 9 or any of the rest of the claims suggests that a single excipient can satisfy more than one of the agent terms. Neither does the specification.").

Courts may also consider other factors arising from the intrinsic evidence. In Becton, referring to the intrinsic record only, the Court considered whether having two claim elements satisfied by the same structure would have "render[ed] the asserted claims nonsensical." Becton, 616 F.3d at 1255; see also Bot M8 LLC v. Sony Interactive Entm't. LLC, 2022-cv-1569, 2023 WL 5606978, at *4 (Fed. Cir. Aug. 30, 2023). The Federal Circuit has held that claims should not be construed in a manner that renders a term "superfluous." Digital-Vending Servs. Int'l, LLC v. Univ. of Phoenix, Inc., 672 F.3d 1270, 1275 (Fed. Cir. 2012) (noting "the importance of construing claim terms in light of the surrounding claim language, such that words in a claim are not rendered

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superfluous"); SSI Techs., LLC v. Dongguan Zhengyang Elec. Mech. LTD., 59 F.4th 1328, 1335 (Fed. Cir. 2023) (rejecting construction rendering a claim element "superfluous"); Exxon Chem. Patents, Inc. v. Lubrizol Corp., 64 F.3d 1553, 1557 (Fed. Cir. 1995) (holding that the court "must give meaning to all the words in [the] claims."). These principles guide the Court's analysis.

The Court first addresses the claim language. All the claims of the '865 patent obviously list the "VEGF antagonist" and "buffer" separately. See '865 patent at claims. Regarding the dependent claims, claim 2 recites a VEGF antagonist concentration of "40 mg/ml." Claim 7 recites a different concentration range of the buffer, of "5-25 mM." '865 patent at claims 2 and 7.¹⁵ The components are listed with different concentrations and different units of measurement. The VEGF antagonist is measured in "mg/mL" (a unit of measurement), whereas the buffer is measured in the "mM" (a different unit of measurement). The clear implication of the claims' use of different units of measurement for these two components is that the components are separate and distinct.¹⁶

¹⁵ Claim 7 depends from claim 2 (claim 7 refers back to claim 5, which refers back to claim 2, which refers back to claim 1). Thus, claim 7 includes all the limitations of claims 1, 2, and 5.

¹⁶ Dr. Chamow explains, and Dr. Trout does not dispute, the different units of measurement in the dependent claims are consistent with how the POSA would measure distinct components.

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The parties do not dispute that a POSA would have been able to convert the claimed 40 mg/ml of aflibercept in claim 2 to its corresponding amount measured in mM, which equals 0.347 mM of aflibercept.¹⁷ Chamow Decl. ¶ 171; Reply at 11 n.3 ("[T]he POSA would perform an 'easy calculation' to convert between the two, Chamow Tr. 52:13-54:4."). This amount (0.347 mM of aflibercept) is substantially outside of the claimed concentration range of 5-25 mM recited for the "buffer" in claim 7. This claim language is rendered nonsensical unless the "VEGF antagonist" and the "buffer" are interpreted as separate and distinct components. Accordingly, the dependent claims are consistent with the clear implication that the claimed "buffer" must be separate from the "VEGF antagonist," and further support that this is the proper construction.

In addition, it is undisputed that aflibercept is always present in the claimed formulation, as indicated by the claim language specifying the amino acid sequence for aflibercept

Chamow Decl. ¶¶ 39-40 (explaining "mg/ml" is the standard way to refer to concentration of an active ingredient in a pharmaceutical formulation whereas "mM" designates a concentration of a buffer, by denoting the number of ionizable molecules available to provide buffering capacity).

¹⁷ As discussed later herein, similar calculations in the context of the '865 patent specification were also discussed at the hearing. Hearing Tr. at 61:8-62:7.

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("wherein said VEGF antagonist fusion protein . . . comprises amino acids 27-457 of SEQ ID NO:4 . . ."). In view of this claim language, which requires aflibercept be present in the formulation, permitting the "VEGF antagonist" to also be the recited "buffer" would render the term "buffer" superfluous and nonsensical in this context.

Regeneron argues that the recited "buffer" is not necessarily superfluous because the POSA would have understood that the aflibercept does not always function as a buffer. Motion at 12-13. Amgen responds that Regeneron has not cited any disclosure in the specification of the '865 patent that references this concept, or that would lead a POSA to understanding such a concept. Opp. at 14. Regeneron further argues that while the Asserted Claims are not limited with respect to pH, the POSA would have understood that aflibercept is a buffer within a narrow pH range, and that, in situations outside of that pH range, the formulation might also require a separate buffer. Motion at 12-13; Reply at 4. Amgen responds that the '865 patent includes dependent claims that recite the requirements of both aflibercept and a "buffer" even though the recited pH ranges are within the narrow range in which Regeneron asserts aflibercept has buffering capacity, thus rendering "buffer" superfluous and nonsensical. '865 patent at

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claims 9 and 34 (requiring a formulation with 40 mg/ml of aflibercept and "a buffer," wherein "said buffer comprises a pH about 6.2-6.3"); Opp. at 14-15; Chamow Decl. ¶¶ 203-214.¹⁸ See In re Varma, 816 F.3d 1352, 1363 (Fed. Cir. 2016) (rejecting a claim construction that was inconsistent with all of the claims of a patent, noting "the principle that the same phrase in different claims of the same patent should have the same meaning is a strong one, overcome only if it is clear that the same phrase has different meanings in different claims") (cleaned up); see also Boss Indus., Inc. v. Yamaha Motor Corp. U.S.A., Inc., 333 F. App'x 531, 541 (Fed. Cir. 2009) (rejecting construction that is "contradicted by the unasserted claims"). In view of these dependent claims, the Court finds that the intrinsic evidence supports construing the Asserted Claims to require a separate buffer. A contrary construction renders the term "buffer" superfluous and nonsensical.

Additionally, Amgen notes that Regeneron's argument is inconsistent with its arguments in the Mylan case where it admitted

¹⁸ The '865 patent discloses that the VEGF antagonist (aflibercept) is only stable within a pH range of 5.8-7.0, and not at just any pH. '865 patent at 2:38; Chamow Decl. ¶¶ 209-210. Consistent with the specification's teaching, the Court held in Mylan that the claims were directed to "a buffer such as phosphate and other known buffers that would achieve the disclosed pH range" (i.e., a pH of 5.8-7.0). Mylan, 2024 WL 382495, at *67 (emphasis added).

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with respect to the "buffer" that "whether it works or not, it's structurally limited." Mylan Trial Tr. at 33:1-7 (ECF No. 206-6, Chamow Ex. C-3). If aflibercept has a structure that satisfies the "buffer" element, "whether it works or not," then the term "a buffer" would be rendered superfluous because aflibercept, which is undisputedly a required element of the asserted claims, would likewise always satisfy the "buffer" limitation.

Having considered the claims through the prism of the above principles, the Court finds the claim language does not rebut the presumption of separateness and, in fact, further supports that the "VEGF antagonist" and "buffer" must be separate components.

b. The specification does not provide any evidence to overcome the presumption of separateness and further supports that the "VEGF antagonist" and "buffer" are separate components.

"[T]he specification 'is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term.'" Phillips, 415 F.3d at 1315 (quoting Vitronics Corp. v. Conceptor, Inc., 90 F.3d 1576, 1582 (Fed. Cir. 1996)).

As instructed by Becton and its progeny, the Court looks to the specification to determine whether there is evidence sufficient to rebut the presumption that the claims require separate and distinct components. 616 F.3d at 1254. Like the

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claims, the specification of the '865 patent uniformly describes the "VEGF antagonist" and the "buffer" as separate and distinct components of the formulation. The specification describes a VEGF antagonist as "a compound capable of blocking or inhibiting the biological action of vascular endothelial growth factor (VEGF), and includes fusion proteins capable of trapping VEGF." '865 patent at 6:27-30. In a separate description, the specification describes that "the buffering agent, may be, for example, phosphate buffer." Id. at 2:45-48. The specification does not suggest that the VEGF antagonist can be a buffer or vice versa. Regeneron has not identified any such disclosure in the specification of the '865 patent. See Reply at 10.

The specification states: "Preferably, the liquid formulation comprises a pharmaceutically effective amount of the VEGF antagonist. The formulation can also comprise one or more pharmaceutically acceptable carriers, buffers, tonicity agents, stabilizers, and/or excipients." '865 patent at 6:65-7:2 (emphasis added). The phrase "can also comprise" indicates the "buffer" is separate from the "pharmaceutically effective" VEGF antagonist. Id.; Chamow Decl. ¶ 175.

There is no dispute that, in every example and every embodiment in the '865 patent, the formulation is described as

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containing both a VEGF antagonist and a separate buffer. The specification includes eight example formulations and twenty-two (22) embodiments, each of which describes the VEGF antagonist (aflibercept) plus a buffer. '865 patent at Examples (8:32-58, 8:60-9:17, 9:19-44, 9:45-10:10, 10:13-38, 10:40-67, 11:1-26, 12:1-26); id. at Embodiments (2:33-38, 2:53-57, 2:58-62, 2:63-67, 3:1-5, 3:6-10, 3:11-16, 3:36-40, 3:40-43, 3:48-52, 3:53-57, 3:66-4:2, 4:2-6, 4:11-19, 4:22-26, 4:31-35, 4:36-40, 4:40-44, 4:45-48, 4:48-53, 4:54-58, 4:58-62). Regeneron has not cited any contrary examples or embodiments in the specification indicating that the VEGF antagonist could serve as the buffer. See Reply at 10.

Amgen identifies evidence in the specification indicating the VEGF antagonist and the buffer cannot be the same component. Amgen notes that, in all but two embodiments of the '865 patent, the buffer is described as a phosphate buffer. Hearing Tr. at 61:8-14. Thus, in all those embodiments it is clear the VEGF antagonist is not the buffer, because the buffer is a phosphate buffer. In the two embodiments that do not expressly identify the buffer as a phosphate buffer, the specification discloses that the VEGF antagonist is present in an amount of "1-100 mg/ml." '865 patent at 2:34, 3:12. These two disclosures further specify the amount of the "buffering agent" as "5-40 mM." Id. at 2:37, 3:14. Amgen

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argues that, even at the highest amount disclosed in the '865 patent (100 mg/ml of aflibercept) a conversion of 100 mg/ml of aflibercept to its corresponding mM concentration equals, at most, 0.87 mM of aflibercept. Chamow Decl. ¶ 171; Reply at 11 n.3. This is significant because the highest amount of aflibercept disclosed in the '865 patent (0.87 mM aflibercept) is well below the lowest concentration of "buffer" described in the '865 patent (5 mM of buffer). Chamow Decl. ¶ 171. Based on this calculation, which is not disputed, the VEGF antagonist and the buffer could not possibly be the same. It is also the case throughout the entire specification that the highest concentration of VEGF antagonist described is 100 mg/ml (or 0.87 mM aflibercept), and the lowest concentration of buffer described is 5 mM. Accordingly, a construction permitting the "buffer" and the "VEGF antagonist" to be the same, as Regeneron proposes, would be nonsensical because these concentration ranges do not overlap.

In terms of intrinsic evidence, Regeneron identifies two passages from the specification in support of its argument that the VEGF antagonist and buffer are not separate and distinct. One passage is from the background section of the '865 patent and

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refers to U.S. Patent No. 6,777,429 ("the '429 patent").¹⁹ '865 patent at 2:1-4; Motion at 12; Trout Decl. ¶ 81; Reply at 9-10. Regeneron argues that the '429 patent teaches certain components (other than the VEGF antagonist and the buffer) disclosed by the '865 patent can have different functions than those specified in the '865 patent, such that all components can be presumed to have more than one function within the formulation. Motion at 12; Reply at 10. Amgen responds that a citation to something outside the '865 patent, that does not disclose that aflibercept can be a buffer, does not overcome what is in the specification, including the fact that every example and embodiment in the specification describes the VEGF antagonist and buffer as separate components. Opp. at 11.

Regardless of whether the '429 patent was properly incorporated by reference into the '865 patent, the Court finds that it is insufficient to overcome what is repeatedly and consistently described in the specification of the '865 patent. Trustees of Columbia Univ. v. Symantec Corp., 811 F.3d 1359, 1368 (Fed. Cir. 2016) ("[F]leeting references cannot overcome the

¹⁹ The '429 patent is cited in the background section of the '865 patent for the proposition that: "Ophthalmic formulations are known, see for example, U.S. Pat. Nos. 7,033,604 and 6,777,429. An ophthalmic formulation of a VEGF antibody is described in U.S. Pat. No. 6,676,941." '865 patent at 2:1-4.

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overwhelming evidence in the specification[.]"). Regeneron does not contend that the '429 patent addresses whether aflibercept can serve as a buffer, and there is no dispute that the '429 patent does not relate to either aflibercept or protein formulations where the protein serves as a buffer. See Reply at 10.

Second, Regeneron points to a passage in the specification, which states: "Unless stated otherwise, all technical and scientific terms and phrases used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention belongs." '865 patent at 5:39-42. This passage is not specific to the subject matter of the claims and describes and does not suggest that aflibercept can serve as a buffer in an ophthalmic formulation and does not otherwise support that proposition. The passage falls into the category of generic boilerplate language. D Three Enters., LLC v. SunModo Corp., 890 F.3d 1042, 1051 (Fed. Cir. 2018) ("[B]oilerplate language at the end of the . . . specification is not sufficient to show adequate disclosure of the actual combinations and attachments used in the . . . [c]laims.").

Having assessed the intrinsic evidence of record, the Court finds that neither of the passages Regeneron cited to the Court overcome the presumption that the "VEGF antagonist" and "buffer"

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are separate components of the claimed formulation. The parties direct the Court to various decisions applying the Becton principles discussed above. Having considered these cases, the Court finds this case most similar to Sun Pharm. Indus. Ltd. v. Saptalis Pharms., LLC, No. 18-cv-648-WCB, 2019 WL 2549267 (D. Del. June 19, 2019) and Otsuka Pharm. Co. v. Mylan Lab'ys Ltd., No. 22-cv-464-CFC-JLH, 2023 WL 5928313 (D. Del. Sept. 12, 2023). In Sun, the court concluded that a single ingredient recited in the claims could not satisfy both the "sweetener" and "polyhydroxy alcohol" elements, because the description of the invention in the patent-in-suit "does not contemplate that a single ingredient can satisfy both the 'sweetener' and the 'polyhydroxy alcohol' limitations." 2019 WL 2549267, at *6. The court observed that "every exemplary formulation in the specification" lists the components as separate components. Id. Here, the '865 patent does not exemplify or suggest that the aflibercept can satisfy both the "VEGF antagonist" and "buffer" limitations, and every example and embodiment includes a buffer that is separate from, and present in addition to, the aflibercept. '865 patent at 8:32-12:26.

In Sun, the court considered that "it would be difficult for a single ingredient to fall within the concentration ranges for both the sweetener and the polyhydroxy alcohol limitations in claim

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4." 2019 WL 2549267, at *6 n.3. The Sun court noted that a dependent claim required a sweetener to be in a range of about 55% to 65%, which incorporated the requirement of the independent claim that polyhydroxy alcohol be present in an amount of about 15% to 55%. Id. The court noted that those two amounts "overlap only at 'the about 55%' point, so the only way the ingredient could satisfy both requirements would be for the amount of the ingredient to be 'about 55%.'" Id. The court found that even if "it may be true that certain components" satisfy multiple components, the claims still required "separate ingredients" given the difficulty of that result. Id. at *7. Amgen argues that the situation in the '865 patent even more clearly dictates separateness, because the '865 patent discloses only ranges that do not overlap at all, even at a single point. Amgen notes the non-overlapping ranges make it a "physical impossibility" for the "VEGF antagonist" to also be the "buffer." Becton, 616 F.3d at 1255. A finding that the claimed VEGF antagonist and the claimed buffer could be met by a single component would thus lead to a nonsensical result.²⁰

²⁰ Regeneron has not explained how to avoid these nonsensical results, which weighs in favor of concluding that the '865 patent "prevents" the possibility of the VEGF antagonist and buffer being one and the same component. Merck v. Mylan, 2022 U.S. Dist. LEXIS 195204, at *61 (N.D.W. Va. Sept. 26, 2022).

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In Otsuka v. Mylan, another case cited and discussed by the parties as relevant to this issue, the court construed the claims to require four separate components (or agents) because the examples of each component provided in the specification "do not overlap," and because the specification "discusses each agent separately." 2023 WL 5928313, at *3. The court noted that in every example, the specification "discusses each agent separately." Id. Giving weight to that fact, the court concluded: "[T]he claims suggest that the elements have to be distinct components, and nothing else in the claims or the specification or any other evidence changes my mind about that." Id. Here, there is no dispute that the specification of the '865 patent identifies the VEGF antagonist and the buffer as separate and distinct components in every example and embodiment, and there is no dispute that the '865 patent lacks any disclosure stating that the functions are overlapping. Reply at 10; '865 patent at Examples (8:32-58, 8:60-9:17, 9:19-44, 9:45-10:10, 10:13-38, 10:40-67, 11:1-26, 12:1-26).

Regeneron argues that a POSA would have generally understood that one ingredient could satisfy multiple functions, relying on extrinsic evidence to do so. Motion at 12; Reply at 11. Amgen relies on Sun and Otsuka, where the courts considered the same

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type of argument and found that a POSA's understanding that an ingredient may have multiple functions does not overcome the presumption of separateness absent support in the intrinsic record. Opp. at 9-10; Surreply at 5; Hearing Tr. at 63:25-65:7. In Sun, the court found that a POSA's understanding that formulation components may "share overlapping functionality" could not overcome the clear implication of the claim language and specification, which consistently identified those components separately. 2019 WL 2549267, at *6 ("[T]he Court must look beyond the functionality of the claim terms to determine whether the patentee intended a single ingredient to satisfy both the sweetener and the [] alcohol limitations."). Similarly, in Otsuka, the court agreed that "a person of ordinary skill in the art would generally understand that a given excipient can serve multiple pharmaceutical functions." 2023 WL 5928313, at *3. But the court explained: "[T]hat doesn't change the fact that the appropriate claim construction requires the claimed injection vehicle to have four components." Id. Thus, even if the Court were to credit Regeneron's contention that formulation components, generally, can have more than one function (Reply at 10), the Court must still give primacy to the intrinsic evidence of the '865 patent in this

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analysis.²¹ For the reasons set forth above, the Court finds that the intrinsic evidence is clear and uniform that the "VEGF antagonist" and the "buffer" are separate components, and that claims and embodiments would be rendered nonsensical were this Court to adopt a construction wherein the two could be one and the same.

Regeneron argues that Powell v. Home Depot U.S.A., Inc., 663 F.3d 1221 (Fed. Cir. 2011) supports a contrary interpretation. Reply at 11. In Powell, the Federal Circuit held that the recited "cutting box" could also serve as the recited "dust collection structure." 663 F.3d at 1231-32. In Powell, however, the specification provided express written description that "[the] [c]utting box . . . functions to contain the sawdust[.]" Id. at 1231. Powell is thus a case where the intrinsic evidence (i.e., the specification) disclosed that the separately listed elements could overlap in function, which overcame the presumption of separateness. Id. at 1231-32. Likewise, in Retractable Techs.,

²¹ During oral argument, Regeneron argued that "in every case where there's evidence that one ingredient can reasonably meet two claim limitations . . . then one ingredient was held to meet two limitations." Hearing Tr. at 27:8-12. However, as discussed herein, the courts in the Sun and Otsuka cases both considered and credited evidence that one excipient could satisfy multiple functions. Sun, 2019 WL 2549267, at *6; Otsuka, 2023 WL 5928313, at *3. Yet, the courts found that the intrinsic record in both cases did not overcome the presumption of separateness. See id.

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Inc. v. Becton, Dickinson & Co., the court held that the claimed "needle holder" and the claimed "retainer member" were not necessarily separate and distinct components of the invention because the claim language specified that the "needle holder" "further comprises" a "retainer member." 653 F.3d 1296, 1303-04 (Fed. Cir. 2011). The patent specification in Retractable also repeatedly explained how the two components could be "welded together" into a single structure. Id. at 1303, 1306. Likewise, in Bot M8 LLC, the court found the presumption of separateness was overcome by disclosures in the specification that did not teach "that each limitation must be contained in a distinct program." 2023 WL 5606978, at *4 (also rejecting patentee's reliance on the prosecution history to show separateness). Here, neither the claims nor the specification of the '865 patent explain or suggest that the VEGF antagonist can serve as the buffer, or vice versa, or that these components can overlap in function. Rather, the claims and the specification further support and confirm that they cannot be one and the same. Powell, Retractable, and Bot M8 are distinguishable on that basis.

Accordingly, the Court finds nothing in the intrinsic evidence to overcome the presumption of separateness, and the intrinsic evidence clearly supports a construction requiring

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separateness. Regeneron has not overcome the presumption of separateness arising from the claim language. Becton, 616 F.3d at 1254-55.

Finally, the parties dispute the relevance of certain evidence, namely, the testimony given during a deposition by Amgen's expert, Dr. Chamow. Reply at 10; Surreply at 1-6. Regeneron cites the deposition testimony of Dr. Chamow to argue that the components can overlap in terms of their function. Reply at 1, 10. Amgen responds that Dr. Chamow's deposition testimony was not discussing the claims of the '865 patent, but rather extrinsic evidence.²² Surreply at 4-5 (citing Chamow Tr. 240:9-248:17 (discussing Gokarn); id. 316:10-12 (Amgen's formulation); id. 145:4-146:14 (scientific article); id. 138:19-139:18 (DHHS publication); id. 142:11-144:8 (scientific article); id. 99:22-100:5 (Gokarn); id. 132:11-135:13, 137:13-22 (scientific article)). While the parties dispute the context and relevance of this testimony, even considering the deposition testimony of Dr. Chamow as Regeneron presents it, the Court still finds insufficient

²² The parties dispute whether Dr. Chamow's deposition testimony is extrinsic evidence (as Amgen argues) or expert opinion regarding what a POSA would have understood about the intrinsic evidence (as Regeneron argues). As discussed in the next section, Dr. Chamow's deposition testimony is extrinsic evidence. However, ultimately the Court finds the cited testimony not sufficiently focused on the '865 patent to weigh significantly in the Court's analysis.

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support in the intrinsic evidence to adopt Regeneron's interpretation of the claims. The Court finds that such evidence, as explained in Sun and Otsuka, does not override the clear intrinsic evidence supporting separateness. Even accepting that components other than those two claim elements may, in some instances, have overlapping functionality, this would also be insufficient to alter the assessment as it relates to the dispute concerning separateness between the "VEGF antagonist" and the "buffer."

c. The extrinsic evidence does not overcome the presumption of separateness and does not show that the "VEGF antagonist" and the "buffer" should be construed as overlapping elements.

As discussed above, there is no dispute as to what the '865 patent says and does not say. Regeneron does not contend that the '865 patent discloses, including in any examples or embodiments, that the VEGF antagonist can be the "buffer" in this patent. Rather, Regeneron has embraced the lack of disclosure, arguing instead that "[a] patent need not teach, and preferably omits, what is well known in the art." Reply at 10. Regeneron argues that using aflibercept as a buffer was so "well known in the art" such that no description in the specification was necessary for a POSA to understand that the claimed VEGF antagonist can serve as the separately claimed "buffer." Id. For this proposition,

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Regeneron directs the Court to references and expert testimony (id.), which is extrinsic evidence. Phillips, 415 F.3d at 1317. For its part, Amgen disagrees and presents contrary evidence that it was not well known in the art that aflibercept could serve as a buffer in a pharmaceutical formulation.

Extrinsic evidence “‘consists of all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises.’” Phillips, 415 F.3d at 1317 (quoting Markman v. Westview Instruments, Inc., 52 F.3d 967, 980 (Fed. Cir. 1995), aff'd, 517 U.S. 370 (1996)). “[E]xtrinsic evidence in the form of expert testimony can be useful to . . . provide background on the technology at issue, to explain how an invention works, to ensure that the court’s understanding of the technical aspects of the patent is consistent with that of a person of skill in the art, or to establish that a particular term in the patent or the prior art has a particular meaning in the pertinent field.” Id. at 1318. The Federal Circuit has cautioned that “while extrinsic evidence can shed useful light on the relevant art,” it is “less significant than the intrinsic record in determining the legally operative meaning of claim language.” Id. at 1317 (quotations omitted).

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"[E]xtrinsic evidence in general [i]s less reliable than the patent and its prosecution history in determining how to read claim terms, for several reasons." Id. at 1318. "[E]xtrinsic evidence by definition is not part of the patent and does not have the specification's virtue of being created at the time of patent prosecution for the purpose of explaining the patent's scope and meaning." Id. "[W]hile claims are construed as they would be understood by a hypothetical person of skill in the art, extrinsic publications may not be written by or for skilled artisans and therefore may not reflect the understanding of a skilled artisan in the field of the patent." Id. "[U]ndue reliance on extrinsic evidence poses the risk that it will be used to change the meaning of claims in derogation of the 'indisputable public records consisting of the claims, the specification and the prosecution history,' thereby undermining the public notice function of patents." Id. at 1319 (internal citation omitted). Further, "extrinsic evidence consisting of expert reports and testimony is generated at the time of and for the purpose of litigation and thus can suffer from bias that is not present in intrinsic evidence." Id. at 1318. "[T]here is a virtually unbounded universe of potential extrinsic evidence of some marginal relevance that could be brought to bear on any claim construction

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question." Id. "In the course of litigation, each party will naturally choose the pieces of extrinsic evidence most favorable to its cause, leaving the court with the considerable task of filtering the useful extrinsic evidence from the fluff." Id. (citing Daubert v. Merrell Dow Pharms., Inc., 509 U.S. 579, 595 (1993)). "In sum, extrinsic evidence may be useful to the court, but it is unlikely to result in a reliable interpretation of patent claim scope unless considered in the context of the intrinsic evidence." Id. at 1319. The Court considers these principles in evaluating the extrinsic evidence.

Regeneron argues it is appropriate to consider extrinsic evidence to determine whether the presumption of separateness is overcome. Hearing Tr. at 27:8-12. Regeneron relies on Powell and Merck v. Mylan to argue the court can consider extrinsic evidence to overcome the presumption of separateness. Id. The Court notes, however, that the expert testimony cited in those cases was considered in the context of the infringement analysis in both cases, not claim construction. Powell v. Home Depot U.S.A., Inc., 663 F.3d at 1231-32 ("Turning back to the true infringement issue . . . [t]he experts agreed. . ."); Merck v. Mylan, 2022 U.S. Dist. LEXIS 195204, at *60 (discussing the testimony of Dr. Little under the heading of "Mylan's Janumet® ANDA Product literally

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Infringes Limitation (f)"). Additionally, as noted above, the case law as a whole makes clear that the intrinsic (not extrinsic) record must be consulted and should be given primacy in determining whether the presumption of separateness is overcome. See, e.g., Becton, 616 F.3d at 1254-55; Kyocera, 22 F.4th at 1382; Google, 92 F.4th at 1058.

Regeneron has proffered evidence in the form of reference documents and expert testimony that is "external to the patent and prosecution history." Phillips, 415 F.3d at 1317. The Court initially notes that it need not consider this extrinsic evidence for claim construction where, as here, the intrinsic evidence is clear and unambiguous. Seabed, 8 F.4th at 1287 ("If the meaning of a claim term is clear from the intrinsic evidence, there is no reason to resort to extrinsic evidence."); see also Profectus Tech. LLC v. Huawei Techs. Co., 823 F.3d 1375, 1380 (Fed. Cir. 2016) ("Extrinsic evidence may not be used 'to contradict claim meaning that is unambiguous in light of the intrinsic evidence.'" (quoting Phillips, 415 F.3d at 1324)); Helmsderfer v. Bobrick Washroom Equip., Inc., 527 F.3d 1379, 1382 (Fed. Cir. 2008) (holding extrinsic evidence cannot "contradict the meaning otherwise apparent from the intrinsic record").

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For the reasons above, the claims and specification are clear and uniform in supporting that the Asserted Claims require separate components such that the buffer must be separate and distinct from the VEGF antagonist. Becton emphasizes the importance of intrinsic evidence in this analysis: "A long line of cases indicates that evidence intrinsic to the patent – particularly the patent's specification, including the inventors' statutorily-required written description of the invention – is the primary source for determining claim meaning." Id. at 1255 (quoting AstraZeneca AB v. Mut. Pharm. Co., 384 F.3d 1333, 1336 (Fed. Cir. 2004)). Cases cited by both parties that have applied Becton to resolve similar types of issues have followed this rubric and reached a claim construction based on intrinsic evidence. Opp. at 6, 10; Reply at 10-11 (citing Becton, Kyocera, Google, Powell, Sun, Otsuka v. Mylan, and Merck v. Mylan).

But, for completeness, the Court has considered the extrinsic evidence that Regeneron cites and finds that the evidence supports the construction that the claims require the VEGF antagonist and buffer to be separate and distinct components. Having considered the extrinsic evidence Regeneron cites in support of its position that the VEGF antagonist can also be the claimed buffer, the Court concludes that none of the extrinsic evidence discloses that

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aflibercept can function as a buffer in a pharmaceutical formulation, let alone in a manner that indicates this was so well known such that disclosure in the patent was not needed, as Regeneron argues. Phillips, 415 F.3d at 1317; Profectus, 823 F.3d at 1380; Helmsderfer, 527 F.3d at 1382.

Regeneron and Dr. Trout cite to certain references, which are extrinsic evidence, including: Christensen-1966 (ECF No. 180-15, Trout Ex. 123), Abe-2000 (ECF No. 180-15, Trout Ex. 121), Wyman-1939 (ECF No. 180-16, Trout Ex. 138), Nozaki-1967 (ECF No. 180-15, Trout Ex. 124), and WO 2006/138181 ("Gokarn") (ECF No. 180-15, Trout Ex. 125). Motion at 10; Reply at 3-4; Trout Decl. ¶¶ 76-78. Regeneron points to this evidence as support for the proposition that proteins have been known for decades to be buffers or have buffering capacity. Reply at 3-4.

Amgen disputes the contention that the extrinsic evidence cited by Regeneron supports the proposition that aflibercept was "well known" by the POSA to be capable of serving as a buffer in a stable ophthalmic formulation suitable for intravitreal injection during the relevant timeframe. Opp. at 4, 19. Amgen responds that none of these references show that aflibercept was understood to be capable of serving as a buffer in a pharmaceutical composition, especially when considered as of the effective filing

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date of the '865 patent (June 16, 2006). See Chamow Tr. 297:21-298:2 (ECF No. 224-1, Argall Ex. 14) ("What was not known was: How do you actually do that? What are the conditions that are necessary to actually reduce that to practice?"). Further, Amgen argued that only one of these references (Gokarn) relates to pharmaceutical compositions. Chamow Decl. ¶ 199; see also Christensen-1966 at 38, 40 (Trout Ex. 123) (discussing "hemoglobin" and "serum albumin"); Abe-2000 at Title (Trout Ex. 121) (discussing "vertebrate muscles"); Wyman-1939 at Title (Trout Ex. 138) (discussing "horse oxyhemoglobin"); Nozaki-1967 at 715 (Trout Ex. 124) (discussing "enzymes"). Amgen observes that aflibercept was not discovered until after many of the cited references, and none of the references relates to aflibercept, including Gokarn. Opp. at 19 (citing Chamow Decl. ¶¶ 198-200).

The parties dispute the relevance of Gokarn, which is an Amgen patent publication filed on June 8, 2006, eight days before the priority date of the '865 patent – June 16, 2006. Amgen notes Gokarn provides no example of a buffer-free aflibercept formulation, no data for a buffer-free aflibercept formulation, no data on the buffering capacity of aflibercept, no pH range within which aflibercept could provide buffering capacity, and no teaching about how to formulate aflibercept in a stable ophthalmic

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formulation suitable for intravitreal injection without a separate buffer. Opp. at 19-20. Amgen argues this was discovered, years later, by Amgen scientists, as reflected in Amgen's later patent filings. Opp. at 4, 19; Chamow Decl. ¶¶ 110-111 (citing Amgen 2020-Publication (ECF No. 206-10, Chamow Ex. C-39) and WO ' 476 Publication (ECF No. 206-6, Chamow Ex. C-10)).

Amgen's position is supported by Coherus Bioscis., Inc. v. AbbVie Biotech. Ltd., No. IPR2017-00822, 2017 WL 3974063, at *10 (P.T.A.B. Sept. 7, 2017), where the Patent Trial and Appeal Board ("PTAB") addressed the novelty and nonobviousness of buffer-free protein formulations. See also Opp. at 19. As noted by the PTAB, "[e]ven as late as 2015, all commercially available aqueous monoclonal antibody formulations were provided with a buffering system." Coherus Bioscis., Inc., 2017 WL 3974063, at *10 (emphasis in original); Chamow Decl. ¶ 219. There appears to be no factual dispute that, as of June 2006, there were no formulations of any fusion protein (or aflibercept specifically) or any intravitreal protein formulation that lacked a separate buffer. Chamow Decl. ¶¶ 91-93, 126, 238. This extrinsic evidence supports Amgen's contention that the POSA at the relevant time (i.e., June 2006) would not consider a therapeutic fusion protein like aflibercept to be a "buffer" in the context of the '865 patent. Amgen notes,

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and Regeneron does not dispute that, if approved, ABP 938 will be the first FDA-approved buffer-free fusion protein formulation. Opp. at 1, 19-20; Chamow Decl. ¶¶ 91-93, 126, 238.

Accordingly, even considering this extrinsic evidence, the Court finds that the evidence does not show that aflibercept was known as (or understood to be) a buffer in a pharmaceutical composition during the relevant timeframe. This combined with the clarity of the intrinsic record counsels that the claimed "VEGF antagonist" and claimed "buffer" must be separate components.

Moreover, the Court finds that the Gokarn application is not available, as a matter of law, as extrinsic evidence of how a POSA would have interpreted the '865 patent at the time the '865 patent was filed.

When interpreting the claims of a patent, material that became available to the POSA only after the "effective filing date" of the patent generally cannot be relied upon to show how a claim term would have been understood by a POSA "at the time of the invention." Phillips, 415 F.3d at 1313 ("[T]he ordinary and customary meaning of a claim term is the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application.") (citations omitted) (emphasis added);

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Kopykake Enters., Inc. v. Lucks Co., 264 F.3d 1377, 1383 (Fed. Cir. 2001) ("[W]hen a claim term understood to have a narrow meaning when the application is filed later acquires a broader definition, the literal scope of the term is limited to what it was understood to mean at the time of filing.") (emphasis added); Schering Corp. v. Amgen Inc., 222 F.3d 1347, 1353-54 (Fed. Cir. 2000) (holding claims must be construed "at the time of filing" based on what is "supported" by the specification and one cannot "enlarge the scope of the patent to embrace technology arising after"); PC Connector Sols. LLC v. SmartDisk Corp., 406 F.3d 1359, 1363 (Fed. Cir. 2005) ("A claim cannot have different meanings at different times; its meaning must be interpreted as of its effective filing date.") (emphasis added).

Gokarn is a patent publication filed on June 8, 2006, and first published on December 28, 2006. Motion at 8, 10, 13; Reply at 4, 6-7. Therefore, it was not publicly available on June 16, 2006, when Regeneron filed the application for the '865 patent. Accordingly, as of the filing date of the application for the '865 patent, Gokarn "does not show what [was] known generally to 'any person skilled in the art,' to quote from § 112." In re Glass, 492 F.2d 1228, 1232 (C.C.P.A. 1974); Eli Lilly & Co. v. Sicor Pharms., Inc., 705 F. Supp. 2d 971, 996 n.30 (S.D. Ind. 2010)

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(explaining that while secret prior art under pre-AIA 35 U.S.C. § 102(e) "is available for assessing obviousness under 35 U.S.C. § 103 . . . [,] it is not evidence of what was generally known in the art"), aff'd, 426 F. App'x 892 (Fed. Cir. 2011). As explained in In re Glass, "as a matter of common sense, it is clear that the contents of a patent application which may be available as 'prior art' under § 102(e) to show that another was the first inventor may not have been known to anyone other than the inventor, his attorney, and the Patent Office examiner, and perhaps the assignee." 492 F.2d at 1231-32.²³

As noted above, the Court concludes that Gokarn, regardless of its content and availability, is insufficient to rebut the presumption of separateness based on the intrinsic record. On the legal question of whether Gokarn is available, while the Court observes the footnote cited by Regeneron, the Court defers to the Federal Circuit's more recent en banc decision in Phillips, that

²³ Regeneron contends that under footnote 6 of In re Glass, prior art under § 102(e) can be relied on for claim construction. That footnote, however, does not specifically address secret prior art but rather discusses indefiniteness (35 U.S.C. § 112, second paragraph), which is not at issue here. Cases decided after In re Glass makes clear that references available to the POSA only after the date of invention (or effective filing date) should not be relied upon for establishing what was generally known to a POSA. Phillips, 415 F.3d at 1313 (noting claims are to be construed based on the understanding of a person of ordinary skill in the art "at the time of the invention").

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claim construction must be based on what was generally known by the POSA "at the time of the invention." Phillips, 415 F.3d at 1313. The Court does not read In re Glass as dictating the opposite, particularly given the footnote's reference to a different legal inquiry (indefiniteness under 35 U.S.C. § 112, second paragraph) and the holding in In re Glass that secret prior art cannot show what was generally known. In re Glass, 492 F.2d at 1231-32 (holding that secret prior art cannot show "what is known generally to any person skilled in the art," because that art, while technically prior art, was not "known to anyone other than the inventor, his attorney, and the Patent Office examiner[.]"). The Court therefore finds that Gokarn cannot be used as Regeneron suggests, that is, as evidence of the POSA's understanding of what was generally known in the art as of the filing date of the '865 patent.

Regardless, Gokarn supports Amgen's contention that at the time of the '865 patent, "the utility of proteins, particularly biopharmaceutical proteins, to be formulated in self-buffering compositions, particularly pharmaceutically acceptable compositions, has not been recognized" by those skilled in the art. Gokarn at 27:10-13 (Trout Ex. 125). In other words, Gokarn

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is evidence that buffer-free formulations of protein therapeutics were not "well known" as of the '865 patent filing date.

Regeneron also cites U.S. Patent 11,607,451 ("the '451 patent"), which is related to Gokarn, as extrinsic evidence in support of its construction. Reply at 6. The '451 patent post-dates the '865 patent. ECF No. 224-1, Argall Ex. 17. Regardless of whether the '451 patent properly informs this claim construction analysis, Regeneron does not contend that the '451 patent teaches or suggests that aflibercept can serve as a buffer, or that it relates to aflibercept. Consequently, the '451 patent does not inform whether aflibercept can serve as a buffer in a context akin to the '865 patent and it carries little if any weight in this analysis. To the extent the '451 patent was unavailable to a POSA as of June 16, 2006, it is not probative of what the POSA would have understood as of that date. Phillips, 415 F.3d at 1313; Kopykake, 264 F.3d at 1383; Schering, 222 F.3d at 1353-54; PC Connector Sols, 406 F.3d at 1363.

Regeneron also points to the deposition testimony of Amgen's expert, Dr. Chamow. Reply at 1-3, 5-12. The expert testimony is extrinsic evidence. Phillips, 415 F.3d at 1317. Amgen disputes Regeneron's characterization of Dr. Chamow's deposition testimony. Dr. Chamow testified that the Asserted Claims require four separate

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components. See Chamow Tr. 26:13-27:4 ("A POSA would understand, in reading this claim, that . . . by listing the four components separately, the interpretation is that these are separate and distinct categories of components and, in fact, that these represent separate and distinct structures."); id. 46:7-47:15 ("[A]s I read what was done and what was written up in '865, there's no evidence to me that these inventors were thinking that these – that anything less than these four categories would work for them."); id. 149:9-14 ("It is an ophthalmic formulation that comprises ingredient one, a vascular endothelial growth factor antagonist, ingredient two, an organic co-solvent, ingredient three, a buffer, ingredient four, a stabilizing agent. That's four ingredients."); id. 151:16-152:1 ("Q: The '865 patent does not expressly state that the formulation ingredients cannot serve multiple roles; right? A: Yeah, Counsel, there's nothing in this patent that tells me that these categories are interchangeable."); id. 167:16-22 ("So the VEGF antagonist is a listed component of Claim 1. It is separate and distinct from the other listed components, one of them being a buffer. There is no indication from Claim 1 or any other part of this patent that the VEGF antagonist would or could serve in that capacity."). Viewed in

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context, this testimony does not undermine the ultimate conclusion that the Asserted Claims require four separate components.

d. Dr. Chamow's deposition testimony does not undermine but rather confirms construing the claims as requiring the "VEGF antagonist" and the "buffer" to be separate components.

In its Reply brief, Regeneron argues that Dr. Chamow's deposition testimony compels a finding that Amgen infringes the asserted claims of the '865 patent. Reply at 1-2, 12. After reviewing Dr. Chamow's testimony in context and in light of the legal principles discussed above, the Court concludes that Dr. Chamow's testimony does not compel such a conclusion. The Court rather views Dr. Chamow's testimony as confirming that the claims must be construed to require that the "VEGF antagonist" and the "buffer" are separate and distinct components of the claimed formulation.

First, Regeneron points to Dr. Chamow's testimony that "at 40 mgs per ml," "aflibercept does serve as a buffer in Amgen's formulation." Chamow Tr. 316:10-12. Regeneron points to this testimony as an admission that Amgen's formulation has a buffer, and as an admission that aflibercept can be both the VEGF antagonist and the buffer in Amgen's formulation. The Court finds that Dr. Chamow's testimony does not support Regeneron's arguments. Dr. Chamow's testimony that "aflibercept does serve as

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a buffer in Amgen's formulation," Chamow Tr. 316:10-12, is consistent with what appears in Amgen's BLA. See Chamow Decl. ¶¶ 125, 226; Trout Ex. A-4 at AMG-AFL-US_00000641. This testimony is not an admission that Amgen infringes the asserted claims because it does not contemplate the correct construction of the asserted claims, based on the '865 patent. When asked about whether the claims require separate components, Dr. Chamow testified: "That says to me there are four separate components here. There is nothing in this claim and there's nothing, in fact, anywhere in this patent that suggests that these are not separate and distinct components." Chamow Tr. 27:8-28:3. This testimony is consistent with the claim construction issue presented, which concerns whether the claims of the '865 patent (as distinct from Amgen's formulation for ABP 938) require separate and distinct components in order to satisfy the "VEGF antagonist" and "buffer" claim limitations.

Dr. Chamow further testified: "And in the time frame of 2006, which is the relevant time frame here, there was—the plain and ordinary meaning of a 'buffer' was clearly an excipient (i.e., an inactive ingredient). There was no evidence or any information that a POSA might have used to consider that a buffer should be anything else." Chamow Tr. 193:8-14. This testimony confirms the

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'865 patent does not provide support for aflibercept serving as a buffer in a pharmaceutical formulation. For the reasons explained above, it is not proper to rely on testimony about a recently developed product, in this case Amgen's, to demonstrate the understanding of a POSA as of June 16, 2006. The cited testimony is about Amgen's development of a formulation for ABP 938, not about what the inventors of the '865 patent invented, disclosed, or claimed in the '865 patent.

Finally, to the extent that Regeneron cites additional passages from Dr. Chamow's testimony, the Court finds that none of that testimony compels a finding in support of Regeneron.

e. Regeneron's claim construction arguments conflict with the trial record developed during the Mylan case and this Court's rulings in the Mylan case that credited Regeneron's expert Dr. Trout.

The Court's construction here is consistent with the record and its findings in the Mylan case. In the Mylan case, Mylan challenged the claims of the '865 patent as invalid under 35 U.S.C. § 112 for lack of written description and lack of enablement. In responding to Mylan's invalidity challenges, Regeneron advanced testimony, given at trial by Dr. Trout, that the claims were limited to a "'very specific' VEGF antagonist and the categories of organic co-solvent, buffer, and stabilizing agent." Mylan, 2024 WL 382495, at *64. Dr. Trout testified that the claims of

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the '865 patent were "'narrow' rather than broad, because they claim 'one specific biologic molecule . . . with a specific sequence ID' at just one concentration (40 mg/ml), in a vial for intravitreal administration, and **further claim** specific structural components, including a buffer, stabilizing agent, and the organic co-solvent of polysorbate 20 within a 'narrow range.'" Id. at *66 (emphasis added). The Court credited Dr. Trout's trial testimony and found that the claims required "a specific protein molecule at a specific concentration **along with other** known structures (a buffer, stabilizing agent, and polysorbate 20)." Id. at *65 (emphasis added); see also id. at *60 ("The claimed composition - 40 mg/ml of aflibercept, with polysorbate 20, a buffer, and a stabilizing agent. . .") (emphasis added); see also id. at *70 ("the claimed structure (40 mg/ml of glycosylated aflibercept and polysorbate 20 within the specified concentration range, **plus a buffer** and a stabilizing agent") (emphasis added). Regeneron argues that its arguments in Mylan were not inconsistent based on a passage in Dr. Trout's expert report. Reply at 6-7. The statement in Dr. Trout's expert report upon which Regeneron relies states "Dr. MacMichael cites to Gokarn, but the cited disclosure only teaches that proteins themselves have some buffering capacity." Mylan Trout Responsive Report at ¶ 381 (ECF

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No. 206-7, Chamow Ex. C-22)). That sentence from Dr. Trout's expert report does not explain Dr. Trout's testimony at trial that the claims require a buffer in addition to the required aflibercept.

During the Mylan trial Regeneron and its expert referred to the "buffer" of the '865 patent claims as an "excipient," which also supports that it is a separate and distinct component from the claimed "VEGF antagonist" active ingredient. Regeneron's Proposed Findings of Fact and Conclusions of Law at ¶ 452 (ECF No. 206-5, Chamow Ex. C-2 Part 2) ("The **excipients** recited in the claims are also structures: categories for the buffer and stabilizing agent") (emphasis added); id. at ¶ 80 (ECF No. 206-4, Chamow Ex. C-2 Part 1) ("[T]he Product Patent—which lists examples and amounts of stabilizing agent and **buffer excipients** for use in the claimed formulations—is also present in the Furfine Provisional.") (emphasis added); id. at ¶ 147 ("[T]he prior art taught 'how to substitute one **excipient** in a category, such as a stabilizing agent or **buffer**, for another'") (emphasis added). Dr. Trout repeatedly used the term "excipient" to refer to the "buffer" recited in the claims of the '865 patent. Mylan Trial Tr. at 2125:21-25 (ECF No. 206-6, Chamow Ex. C-6) ("Q: Buffers were known **excipients** and have been used for decades to stabilize the pH of solutions, including in formulations, correct? A: Yes.

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With other molecules, yes.") (emphasis added); id. at 2106:2-6 ("Q: [D]id the prior art teach how to substitute one **excipient** in a category, such as a stabilizing agent or **buffer**, for another? A: Yes.") (emphasis added); Mylan Trout Responsive Report ¶ 364 (ECF No. 206-7, Chamow Ex. C-22) ("Buffers were known **excipients** and have been used for decades to stabilize the pH of solutions, including in formulations.") (emphasis added); id. ¶ 369 ("The '865 Claims set forth a specific agent that inhibits VEGF . . . along with several recited **excipients** (an organic co-solvent, a buffer, and a stabilizing agent) . . .") (emphasis added). The VEGF antagonist was never referred to as an "excipient" during the Mylan trial, consistent with it being referred to as the active ingredient in the formulation. See, e.g., Mylan, 2024 WL 382495, at *62, *67, *68.

Consistent with the testimony credited in the Court's decision, the Court upheld the validity of the claims in Mylan, finding: "The **excipients** recited in the claims are also structures: categories for the **buffer** and stabilizing agent" Id. at *70 (emphasis added). Viewed in this context, Regeneron's statements and positions taken by Regeneron in the Mylan case, which the Court credited, undermine Regeneron's arguments that the VEGF antagonist and buffer can be one and the same.

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f. Having determined that the asserted claims require a "buffer" that is separate from the "VEGF antagonist," the Court need not address the proper construction of the term "buffer" and declines to do so.

In its Motion, Regeneron proposed that the term "a buffer" be construed to mean "a **substance** that resists changes to pH upon addition of an acid or base within an optimal pH range through a proton donating component and/or a proton-accepting component," and in its Reply added "**and thereby includes phosphate, histidine, and proteins like aflibercept.**" Motion at 7; Reply at 3 (emphases added). Amgen disputed Regeneron's proposed construction, arguing that the term should be construed to mean "an **excipient** that resists changes to pH upon addition of an acid or base within an optimal pH range through a proton-donating component and a proton-accepting component." Opp. at 12 (emphasis added). The dispute between the parties thus centers on whether the "buffer" must be an "excipient" (meaning separate from the aflibercept), as Amgen proposes, or whether it can be any "substance," including the active ingredient (aflibercept) as Regeneron proposes.

Having determined that the claims require a "buffer" that is separate from the "VEGF antagonist," which is sufficient to raise a substantial question of noninfringement as discussed below, the Court need not address the proposed constructions of the term "buffer." O2 Micro Int'l Ltd. v. Beyond Innovation Tech. Co.,

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Ltd., 521 F.3d 1351, 1362 (Fed. Cir. 2008) ("We, however, recognize that district courts are not (and should not be) required to construe every limitation present in a patent's asserted claims."); U.S. Surgical Corp. v. Ethicon, Inc., 103 F.3d 1554, 1568 (Fed. Cir. 1997) (holding that claim construction "is not an obligatory exercise in redundancy."). Accordingly, the Court declines to construe the term "buffer" at this stage.

g. Regeneron has not demonstrated a likelihood that Amgen infringes.

Under the Court's construction that the claims require four separate components, there is at least a substantial question concerning infringement. Genentech, 108 F.3d at 1364 (holding that if an alleged infringer "raises a substantial question concerning validity, enforceability, or infringement (i.e., asserts a defense that [the patentee] cannot show lacks substantial merit) the preliminary injunction should not issue") (cleaned up). There is no dispute about what components are present in the formulation for ABP 938. Trout Decl. ¶ 232; Chamow Decl. ¶ 125. Likewise, there is no dispute that ABP 938 does not contain a separate buffer.

On this record, the Court finds that Regeneron has not established a likelihood of success on the merits of its infringement allegations. The Court here addresses the parties'

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arguments with respect to literal infringement and infringement based on the doctrine of equivalents ("DOE").

1. Regeneron has not demonstrated a likelihood that Amgen literally infringes the Asserted Claims.

"To establish literal infringement, every limitation set forth in a claim must be found in an accused product, exactly." Duncan Parking Techs., Inc. v. IPS Grp., Inc., 914 F.3d 1347, 1360 (Fed. Cir. 2019) (quoting Southwall Techs., Inc. v. Cardinal IG Co., 54 F.3d 1570, 1575 (Fed. Cir. 1995)); see also Forest Lab'ys, Inc. v. Abbott Lab'ys, 239 F.3d 1305, 1310 (Fed. Cir. 2001) ("A patentee claiming infringement must present proof that the accused product meets each and every claim limitation.") (citing J.T. Eaton & Co. v. Atlantic Paste & Glue Co., 106 F.3d 1563, 1570-71 (Fed. Cir. 1997)). Dependent claims are construed to encompass all the limitations of the claims from which they depend. 35 U.S.C. § 112(d). Accordingly, "[o]ne who does not infringe an independent claim cannot infringe a claim dependent on (and thus containing all the limitations of) that [independent] claim." Monsanto Co. v. Syngenta Seeds, Inc., 503 F.3d 1352, 1359 (Fed. Cir. 2007) (citing Wahpeton Canvas Co. v. Frontier, Inc., 870 F.2d 1546, 1552 (Fed. Cir. 1989)).

Under the claim construction adopted above, Amgen has raised a substantial question of infringement with respect to the Asserted

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Claims. There is no dispute that ABP 938 does not contain "a buffer" that is separate from the other components listed in the claims, namely, the VEGF antagonist. See generally, Motion; see generally Reply. Under the Court's construction, the aflibercept in the formulation for ABP 938 cannot satisfy both the "[VEGF] antagonist" and "buffer" limitations of the Asserted Claims, rendering the "buffer" a missing element for purposes of literal infringement. This missing element raises a substantial question of noninfringement, and the Court finds that Regeneron has not established a likelihood of success on the merits with respect to literal infringement on this motion. The Court accords significant weight to this determination in the analysis, in part, due to the undisputed nature of the facts concerning infringement based on Amgen's formulation.

2. Regeneron has not demonstrated a likelihood that Amgen infringes the Asserted Claims under the Doctrine of Equivalents.

Preliminary injunctions based on infringement under the DOE are rare. Aurobindo, 857 F.3d at 866 ("This appeal is unusual . . . in that it arises from the grant of a preliminary injunction based on [DOE]. There are few such reported decisions"); see also Ranbaxy Pharms. Inc. v. Apotex, Inc., 350 F.3d 1235, 1241 (Fed. Cir. 2003) (affirming denial of

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preliminary injunction where the patentee failed to demonstrate a likelihood of success in proving infringement under the DOE). Infringement based on the DOE is regarded as a "highly factual inquiry [that] rarely comes clear on a premature record." Jeneric/Pentron, Inc. v. Dillon Co., 205 F.3d 1377, 1384 (Fed. Cir. 2000). On the posture of resolving a preliminary injunction motion, it is not ideal for the Court to engage with highly factual inquiries, such as DOE. Regeneron does not address its arguments related to DOE in its Reply, making Amgen's arguments in opposition substantively unrebutted on this record. Compare Opp. at 16-18, with Reply at 12 (responding only that: "In view of this record, there is no need for the Court to address the doctrine of equivalents.").

"Each element contained in a patent claim is deemed material to defining the scope of the patented invention, and thus the doctrine of equivalents must be applied to individual elements of the claim, not to the invention as a whole." Warner-Jenkinson Co. v. Hilton Davis Chem. Co., 520 U.S. 17, 29 (1997). "[T]he application of [DOE], even as to an individual element, is not allowed such broad play as to effectively eliminate [an] element in its entirety." Id. This principle is known as vitiation, which

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counsels against applying the DOE in a manner that reads out entire limitations.

The Supreme Court has set forth two frameworks for evaluating DOE: (1) the "function-way-result test" and (2) the "insubstantial differences" test. See Aurobindo, 857 F.3d at 866 (citing Graver Tank & Mfg. Co. v. Linde Air Prod. Co., 339 U.S. 605, 608-609 (1950)). The first test asks whether the accused product performs "substantially the same function in substantially the same way to obtain the same result." Id. The second test asks "whether the accused product or process is substantially different from what is patented." Id. The Federal Circuit has explained that "non-mechanical cases may not be well-suited to consideration under the [function-way-result] test." Id. at 867. This is "particularly true in the chemical arts," where the insubstantial differences test is regarded as "more suitable . . . for determining equivalence" because chemicals having significantly different structures may seem equivalent, even when they are not. Id. at 867-69.

Regeneron argues that "even were the Court to construe 'buffer' not to include proteins like aflibercept, ABP 938 would still infringe under the DOE," citing the function-way-result test. Motion at 13-14. Regeneron argues that the 40 mg/mL of

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aflibercept in ABP 938: performs the same function as the claimed "buffer" (in terms of maintaining the pH); does so in substantially the same way ("the 28 histidine residues in each aflibercept dimer absorb and release protons, just like free histidine in solution"); and achieves substantially the same result as the "buffer" (a stabilized pH during storage). Id. at 14. Regeneron does not argue infringement under the DOE based on the insubstantial differences test. For its part, Amgen disputes (i) Regeneron's reliance on DOE to eliminate the "buffer" limitation altogether, (ii) Regeneron's use of the function-way-result test for DOE (rather than the insubstantial differences test), and (iii) Regeneron's application of the function-way-result test. Opp. at 16-17. As noted, Regeneron offered no reply arguments in response to Amgen's opposition. The issue of DOE was not raised by either party at the hearing. Consequently, Amgen's disputes regarding this highly factual inquiry go substantively un rebutted.

The Court is mindful that DOE is a highly factual inquiry that rarely becomes clear without a full record. See Jeneric, 205 F.3d at 1384. That is true here, and Regeneron's arguments and Amgen's responses illustrate why, regardless of whether Regeneron or Amgen is correct, Regeneron's arguments based on the DOE do not favor granting a preliminary injunction, even accepting all of

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Regeneron's assertions. For completeness, however, the Court concludes that Regeneron has not demonstrated a likelihood of success on the merits of its DOE claim, at least because its DOE theory vitiates the term "buffer" by eliminating it entirely, which is prohibited. Warner-Jenkinson, 520 U.S. at 29 ("[T]he application of [DOE], even as to an individual element, is not allowed such broad play as to effectively eliminate [an] element in its entirety."). Because its Reply is silent on this topic, Regeneron has not attempted to rebut Amgen's arguments regarding claim vitiation. See Opp. at 17. The Court finds vitiation to foreclose Regeneron's DOE theory.

* * *

While unnecessary for the Court to address Amgen's additional arguments regarding why there is no infringement under DOE, the Court agrees with Amgen's un rebutted argument that in a chemical case like this one, it is more appropriate to consider DOE by applying the insubstantial differences test. Aurobindo, 857 F.3d at 867-69. Regeneron does not address the insubstantial differences test and not doing so weighs against finding that there is likelihood of success on the merits of infringement under DOE. With respect to that test, Amgen notes that there are significant differences between the claimed "VEGF antagonist" (aflibercept)

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and the "buffer" in terms of structure, formulation approach, functionality, and operation. Opp. at 17; Chamow Decl. ¶¶ 235-247. It is undisputed that the aflibercept in ABP 938 is a large complex macromolecule, orders of magnitude bigger than the small-molecule phosphate buffer exemplified throughout the '865 patent. Chamow Decl. ¶ 229 (Figure 13). Amgen argues that a formulation lacking a buffer offers advantages over a formulation that has a buffer, in terms of using fewer ingredients, which reduces the complexity of the formulation as well as the risk of introducing impurities. Id. ¶ 241. While advantageous, a buffer-free formulation is not straight-forward or easy to develop. Id. ¶¶ 93, 100-101, 104-107, 136. Amgen notes that, if approved, ABP 938 would be the first buffer-free fusion protein formulation approved by FDA. Id. ¶ 238. These arguments and Amgen's expert testimony in support thereof were unrebutted, and for this additional reason, the Court agrees with Amgen that there are substantial differences between the aflibercept in ABP 938 and the claimed buffer.

Even applying the function-way-result test, the Court does not find a likelihood of success on the merits of proving infringement under the DOE. With respect to "function," the '865 patent describes that the function of the buffer is to establish a desired pH. '865 patent at 6:56-58, 3:44-47; Mylan, 2024 WL

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382495, at *67 ("Dr. Trout highlighted the patent's disclosure of 'known structures' as the claimed components, including . . . a buffer such as phosphate and other known buffers that would achieve the disclosed pH range"). [REDACTED]

[REDACTED] Dr. Trout did not address or rebut Amgen's argument and expert testimony that a buffer is an inactive ingredient, while the function of aflibercept is to create a therapeutic effect. Thus, the POSA would have understood that the claimed buffer is a non-therapeutic agent and serves a different function than aflibercept as the active ingredient. Id.

With respect to "way," the aflibercept in ABP 938 incidentally protects itself against pH-induced degradation. Id. ¶ 261. By contrast, a "buffer" predictably establishes a pH based on being free in solution and available to contribute buffering capacity depending on its concentration, and thus, appropriate amounts of a buffer can be added to achieve a desired pH in a formulation. Id. ¶¶ 228-232, 261. Amgen explains that this is not the case with ABP 938. [REDACTED]

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Amgen explains that Dr. Trout testified in his declaration that aflibercept acts the same as a buffer simply because "histidine residues in a protein structure can absorb and release protons as a consequence of the structure of histidine's imidazole ring," which is the "same mechanism or way by which sodium phosphate . . . resists changes to pH." Trout Decl. ¶ 293. This testimony, even if assumed to be true, does not address the several differences discussed above in the "way" aflibercept achieves its function compared to the claimed buffer, which presently stands un rebutted. Thus, the Court credits Amgen's arguments that the buffer of the '865 patent achieves its function in a substantially different way than how aflibercept achieves its function in ABP 938.

With respect to "result," Regeneron argues that both a conventional buffer and aflibercept achieve "a stabilized pH" during storage. Motion at 14; Trout Decl. ¶ 294. Amgen responds that ABP 938 offers more and different results, namely: one fewer excipient; lower ionic strength; and improved long-term stability relative to the buffered formulations shown in the '865 patent. Opp. at 17; Chamow Decl. ¶¶ 275-281. Regeneron and its expert did not attempt to rebut any of these differences. Accordingly, the Court credits the differences presented by Amgen and its expert.

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Ultimately, in view of the highly factual disputes between the parties, the Court cannot find a likelihood of success on Regeneron's DOE theory, which is deficient on the basis that it vitiates the "buffer" limitation, fails to apply the insubstantial differences test, and does not contest many differences alleged by Amgen to exist with respect to each factor in the function-way-result test.

VII. CONCLUSION

For the foregoing reasons, Plaintiff's Motion for Preliminary Injunction is **DENIED**.

Defendant Amgen's Motion for Leave to File Surreply [ECF No. 299] is **DENIED AS MOOT**.

The Court is filing this Order under seal, as the Court understands that there is information herein that the parties have designated Confidential or Outside Counsel Eyes Only under the Protective Order. The Court expects the parties to confer on preparing and submitting a public version containing appropriate redactions to protect each party's confidential information. The parties shall meet and confer to discuss which portions of this Order can be unsealed. **They shall submit a joint proposed redacted version for the Court's review within seven (7) days of the entry of this Order.**

IN RE: AFLIBERCEPT PATENT LITIGATION

1:24-MD-3103

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The Clerk is **DIRECTED** to transmit copies of this Order **only** to counsel for Regeneron and Amgen in case 1:24-CV-39.

DATED: September 23, 2024



THOMAS S. KLEE, CHIEF JUDGE
NORTHERN DISTRICT OF WEST VIRGINIA