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 NOS.
1:23-CV-94
1:23-CV-106

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ORDER GRANTING MOTIONS FOR PRELIMINARY INJUNCTION

Pending before the Court are Plaintiff Regeneron's Motions for Preliminary Injunction [ECF No. 118 in 1:23-CV-94, ECF No. 99 in 1:23-CV-106]. The motions are fully briefed and ripe for decision. For the reasons set forth herein, the motions are **GRANTED**. Additionally, for good cause, the motions for leave to file corrected exhibits filed by Defendant Samsung are **GRANTED**, and the exhibits are considered herein [ECF No. 172-2 in 1:23-CV-94, ECF No. 153-2 in 1:23-CV-106].

I. BACKGROUND INFORMATION

A. Regeneron's Eylea Product

Regeneron invented and developed 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. 3d ----, 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 invented by Regeneron scientists that has been used to treat millions of patients suffering from diseases that can cause vision loss or even blindness." Id. at *13. The active ingredient in Eylea is the fusion protein now referred to as aflibercept. 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 intravitreal injections (injection into the vitreous of the eye). Id. at *13-14.

After more than a decade of development and multiple clinical trials, Regeneron achieved an Eylea formulation that improved on the leading treatment for one angiogenic disease — wet Age-Related Macular Degeneration ("AMD"). Id. at 13 (quoting Trial Tr. 172:16-24 (Yancopoulos)). 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. Id. Following its initial FDA approval, Regeneron tested Eylea's effectiveness in patients with other angiogenic eye disorders, ultimately obtaining approval for Eylea's use to treat those conditions as well. Id. Soon,

Eylea "became the new gold standard of care" for treating such eye disorders. Mylan Trial Tr. at 172:19-20 (ECF No. 118-32, Sheridan Ex. 51).

Following the success of Regeneron's Eylea vial formulation, Regeneron developed and obtained approval in November 2011 for Eylea in a pre-filled syringe ("PFS"). See Sheridan Decl. ¶ 48 (ECF No. 118-26). Then in August 2023, Regeneron received approval to sell Eylea HD, an 8 mg formulation that requires less frequent injections and provides improved anatomical outcomes in the form of drier retinas. Id.; Clark Decl. ¶ 3 (ECF No. 118-39). Eylea HD is currently approved to treat wet AMD, Diabetic Macular Edema ("DME"), and Diabetic Retinopathy ("DR"). Clark Decl. ¶ 3.

B. Other Anti-VEGF Treatments

For the past five years, Eylea has maintained its place as the "category leader" in anti-VEGF treatments, [redacted] The second most popular anti-VEGF agent, Avastin (bevacizumab), [redacted] Avastin is an oncology drug for metastatic colorectal cancer (among other cancers), but ophthalmologists sometimes use it off-label (i.e., for diseases for which it does not have FDA approval) to treat angiogenic eye

disorders. Sheridan Decl. ¶ 55. The third- and fourth-most popular anti-VEGF agents, Vabysmo (faricimab) and Lucentis (ranibizumab) are approved to treat angiogenic eye disorders. Id. ¶¶ 57-59. Genentech manufactures all three drugs. Id. ¶¶ 55, 57-59.

Eylea, Avastin, Vabysmo, and Lucentis make up more than 96% of anti-VEGF ophthalmic sales. Clark Decl. ¶ 6; Clark Ex. 1 at 3-4. Other products on the market—such as Beovu are prescribed less frequently. Regeneron Pharms., Inc. v. Mylan Pharms., Inc., C.A. No. 1:22-cv-61, ECF No. 571 (Trial Tr.) at 861:6-862:4 (Albini). Regeneron contends Eylea has maintained its category leadership due to its safety, efficacy, and dosing advantage. Clark Decl. ¶ 7.

C. Aflibercept Biosimilars

At least [redacted] pharmaceutical companies are developing and seeking FDA approval for aflibercept biosimilars, each of which contains the same active ingredient as Eylea, in a 2 mg vial and in some cases a PFS formulation. Sheridan Decl. ¶ 49. Absent injunctive relief, Regeneron expects [redacted]

D. SB's aBLA and Proposed Biosimilar Product

Samsung Bioepis Co., Ltd. ("SB") is a Korean company headquartered in Incheon, South Korea and is focused on the development of biosimilars to previously licensed reference products like Regeneron's Eylea product. Lee Decl. ¶ 4 (ECF No. 48-2). On February 17, 2023, SB filed aBLA No. 761350 ("SB's aBLA") with FDA seeking approval under the Biologics Price Competition and Innovation Act ("BPCIA"), 42 U.S.C. §§ 262(k)-(l), to market and distribute its biosimilar of Eylea, "SB15," throughout the United States. SB 356h Form (ECF No. 111-4); Trout Ex. B-2 (ECF No. 118-5). [redacted] See SB 356h Form.

SB's aBLA specifies [redacted] Trout Decl. App. B ¶¶ 9-14 (ECF No. 118-4), [redacted] id. ¶ 16 (internal quotations omitted); Trout Ex. B-2. SB's aBLA also specifies the composition of SB15. Trout Decl. App. B ¶ 1; Trout Ex. B-2 at SB15BLA0000598. [redacted]

[redacted] Trout Decl. App. B ¶¶ 2-3.

SB's aBLA also includes a proposed label to be packaged along with the marketed SB15 product. See Trout Decl. App. B ¶¶ 12-13; Trout Ex. B-2. Like the Eylea label, SB's proposed label recommends that doctors use SB15 to treat wet AMD, Macular Edema Following Retinal Vein Occlusion ("RVO"), DME, and DR. Trout Decl. App. B ¶ 12; Trout Ex. B-2.

In connection with SB's aBLA request for FDA approval to market SB15 in the United States, [redacted] SB and a U.S. company called Biogen MA Inc. ("Biogen") entered into a Development and Commercialization Agreement to commercialize SB15 in the United States (among other countries). Id.; [redacted]

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[redacted]

SB does not deny that it will market, sell, and distribute SB15 in West Virginia **through Biogen.** [redacted]

II. PROCEDURAL BACKGROUND

Pursuant to 42 U.S.C. § 262(l)(8)(A), an applicant must provide notice to the reference product sponsor no later than 180 days before the date of the first commercial marketing of the applicant's product. On November 17, 2023, SB transmitted its Notice of Commercial Marketing ("NCM") to Regeneron, stating: [redacted] Id. Subsequently, Regeneron filed the first lawsuit against

SB on November 21, 2023, asserting that SB's proposed SB15 product would infringe at least 37 of its patents. ECF No. 1.

[redacted]

Regeneron filed the second lawsuit against SB on December 27, 2023, as required by 42 U.S.C. § 262(l)(6)(B), asserting that SB's proposed SB15 product would infringe at least 51 of its patents. C.A. No. 1:23-cv-106, ECF No. 1.

On December 28, 2023, Regeneron filed an emergency motion requesting either a schedule for preliminary injunction proceedings or an emergency status conference. ECF No. 40.

On January 4, 2024, SB filed a motion to dismiss for lack of personal jurisdiction. ECF No. 47. Regeneron filed its opposition to that motion on February 19, 2024, ECF No. 111, and SB filed a reply on February 26, 2024, ECF No. 121.

Following the Scheduling Conference in this matter on January 5, 2024, the Court issued an Order Setting the Briefing Schedule on Motions to Dismiss and Setting the Schedule for Preliminary Injunction Proceedings ("Scheduling Order"). ECF No. 69. The Court's Scheduling Order required Regeneron to identify no more than eight patents that may be included in a motion for preliminary injunction. ECF No. 69 at 3. On January 11, 2024 and pursuant to the Scheduling Order, Regeneron provided SB a narrowed list of

patents that may be included in a motion for preliminary injunction, see ECF No. 73, and on February 2, 2024, Regeneron further narrowed that list of patents that may be included in a motion for preliminary injunction, see ECF No. 95.

Pursuant to the Scheduling Order, Regeneron filed a motion for preliminary injunction against SB on February 22, 2024 on the basis of four patents: the Product Patent, and U.S. Patent Nos. 11,104,715, 11,472,861, and 11,535,663 (the "Manufacturing Patents"). ECF No. 118. Regeneron did so given that, pursuant to 42 U.S.C. § 262(k)(7)(A), approval of SB's aBLA may be made effective 180 days after the service of SB's NCM and as soon as Eylea's regulatory exclusivity expires on May 18, 2024. Id. Regeneron's motion asserted claims 4, 7, 9, 11, 14-17 and 55 of the Product Patent (the "Asserted Product Patent Claims") and claims 6 and 12 of the '715 and '861 Patents and claims 3 and 6 of the '663 Patent (the "Asserted Manufacturing Claims"). Id. SB filed its opposition to Regeneron's PI motion on March 21, 2024, Opp. (ECF No. 164-2), and Regeneron filed a reply on April 18, 2024, Reply (ECF No. 194-2). To streamline the issues in dispute in the Preliminary Injunction motions, Regeneron moved to withdraw its Motions for Preliminary Injunction with respect to the Manufacturing Patents on May 21, 2024. ECF No. 231.

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On May 14, 2024, Regeneron filed a motion for a temporary restraining order against SB, ECF No. 219. On May 17, 2024, the Court granted Regeneron's motion for a temporary restraining order, enjoining and restraining SB from manufacturing, using, offering to sell, or selling within the United States, or importing into the United States without a license from Regeneron any product that is the subject of BLA No. 761350, including SB15, until May 31, 2024. ECF No. 224. The Court extended that TRO for fourteen (14) days on May 30, 2024.

On May 20, 2024, the FDA approved SB15 (under the trade name "Opuviz") as an "interchangeable biosimilar" to Eylea. "FDA Approves First Interchangeable Biosimilars to Eylea to Treat Macular Degeneration and Other Eye Conditions," U.S. Food & Drug Administration, https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-first-interchangeable-biosimilars-eylea-treat-macular-degeneration-and-other-eye (May 20, 2024) ("FDA Approval Announcement"). Absent an injunction, SB would be permitted to launch SB15 at the expiration of the temporary restraining order entered by this Court on May 17 and extended on May 30, 2024. ECF No. 206 at 3-4.

[redacted]

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[redacted] Regeneron has sought a preliminary injunction to prevent SB from producing, marketing, or selling their allegedly infringing product until after a decision after a trial on the merits.

The Court has not held an evidentiary hearing on Regeneron's motion for injunctive relief, and one is not necessary here. The Court originally scheduled a hearing on Regeneron's motion for May 2, 2024. On April 23, 2024, the parties filed a joint motion requesting "a status conference to discuss the logistics of the injunction hearings scheduled for May 2, 2024, including the length of the time of the hearings, and the Court's preferences for the presentation of argument." Joint Mot. for Status Conf. (MDL No. 1:24-md-3103, ECF No. No. 9). The parties did not request or otherwise discuss the presentation of testimony or other evidence

during the May 2 hearing in their April 23 submission. Id. On April 24, 2024, the Court continued the May 2 hearing in view of the multi-district litigation consolidation of this and several related proceedings as well as the scheduling of a separate criminal trial. Order Continuing May 2, 2024 Preliminary and Permanent Injunction Hearings (MDL No. 1:24-md-3103, ECF No. No. 13). On May 17, the Court held a status conference in which all parties appeared, and no party objected to the cancellation of the preliminary injunction hearing, sought its reinstatement,[1] or otherwise objected to proceeding on the papers. To the extent any party now argues that a hearing was necessary, the Court finds that the parties waived request to a hearing. See Baxter Healthcare Corp. v. Med. Lab'y Automation, Inc., 1994 WL 695521, at *2 (N.D. Ill. Dec. 9, 1994) ("Baxter did not request an evidentiary hearing or suggest that an evidentiary hearing was needed or would be preferable. . . . A party that rests on affidavits and other written submissions waives an evidentiary hearing."); Sciele Pharma Inc. v. Lupin Ltd., 2012 WL 113004, at *3 (D. Del. Jan. 12, 2012). The Court thus resolves Regeneron's

[1] Even a cursory review of the docket in the MDL and individual member cases will quickly reveal the parties are no stranger to frequent and extensive motions practice. The lack of a motion to reschedule or convene an evidentiary hearing is telling here.

motion for a preliminary injunction based on the parties' written submissions and cited testimony. See Richmond Tenants Org., Inc. v. Kemp, 956 F.2d 1300, 1304 (4th Cir. 1992) (affirming preliminary injunction where "the district court issued a preliminary injunction prohibiting evictions without prior notice and a hearing and enjoining defendants").

III. FACTUAL BACKGROUND

A. Expert Declarants

Regeneron filed declarations from two expert witnesses, Dr. Bernhardt Trout and Dr. Sean Sheridan, and two fact witnesses, Mr. Kevin Clark and Dr. Kenneth Graham, in support of its preliminary injunction based on the Product Patent. SB deposed three of Regeneron's witnesses but declined to take the deposition of Dr. Kenneth Graham, a fact witness. See Regeneron's Opp. to Samsung Bioepis's and Formycon's Mot. to Strike (ECF No. 205) at 5-6, 11. SB presented declarations from three expert witnesses relevant to the Product Patent: Dr. Peter Tessier, Dr. Denis Boyle, and Dr. Ian Cockburn. Regeneron deposed all of SB's witnesses.

1. Regeneron's Declarants

Dr. Bernhardt Trout, Ph.D., addressed the infringement and validity of the Product Patent. Dr. Trout also provided expert testimony regarding infringement and validity of the Product

Patent at the Mylan trial. Dr. Trout is a Professor of Chemical Engineering at the Massachusetts Institute of Technology and holds a Ph.D. in chemical engineering. Trout Decl. ¶¶ 16-17 (ECF No. 118-4). 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. ¶¶ 19-20.

Dr. Sean 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 declaration addressed whether Regeneron would be irreparably harmed by market entry of Eylea biosimilars prior to expiry of the asserted patents. 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.

Kevin 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. Mr. Clark's declaration addressed the effect of biosimilar entry on Regeneron

and its Eylea product.

Dr. Kenneth Graham, Ph.D., is a named inventor on the Product Patent. Dr. Graham has worked at Regeneron for over twenty-two years and is currently the Executive Director of Formulation Development at Regeneron. Graham Decl. ¶ 1. He joined Regeneron's Formulation Development group in 2005, when the group was engaged in aflibercept formulation stability studies. Id. ¶ 2. Dr. Graham's declaration addresses several internal stability studies Regeneron's scientists conducted on aflibercept.

2. SB's Declarants

SB filed an expert declaration from Peter M. Tessier, Ph.D. addressing the validity of the Product Patent. Dr. Tessier is a Professor in the Departments of Pharmaceutical Sciences and Chemical Engineering and Biomedical Engineering at the University of Michigan and holds a Ph.D. in chemical engineering. Tessier Decl. (ECF No. 164-33) ¶¶ 10-11. At the University of Michigan, Dr. Tessier performs research on the formulation of biologics, including research on formulations of protein-based biologics. Tessier Decl. ¶ 10.

SB also filed an expert declaration from Denis M. Boyle, Ph.D., addressing whether SB's SB15 product infringes the Asserted Product Patent Claims. Dr. Boyle is the President and CEO of CMC

BioPharma Consulting, LLC, a company that provides consulting services related to chemistry, manufacturing, and controls for biologics products. Boyle Decl. ¶ 7 (ECF No. 164-11). Dr. Boyle holds a Ph.D. in chemical pathology (medical biochemistry). Id. ¶ 8. Dr. Boyle's previous experience includes work in human biopharmaceuticals development and manufacturing of monoclonal antibodies. Id. ¶¶ 14, 18.

SB filed an expert declaration from Dr. Iain Cockburn, Ph.D., in response to Dr. Sheridan's declaration regarding irreparable harm upon the launch of infringing biosimilars. Cockburn Decl. ¶ 8. Dr. Cockburn is a Professor and the Chair of the Strategy and Innovation Department at Boston University's Questrom School of Business. Id. ¶ 1. Dr. Cockburn holds a Ph.D. in Economics and much of his research has focused on the pharmaceutical and biotechnology industry. Id. ¶¶ 2, 5.

B. Product Patent

The United States Patent and Trademark Office ("USPTO") issued the Product Patent, titled "VEGF Antagonist Formulations Suitable for Intravitreal Administration," on August 10, 2021, to Regeneron Pharmaceuticals, Inc. upon assignment from inventors Eric Furfine, Daniel Dix, Kenneth Graham, and Kelly Frye. Product Patent, Cover Page (ECF No. 118-10, Trout Ex. 65). The Product

Patent claims priority through continuation and divisional applications to Provisional Patent Application No. 60/814,484, filed June 16, 2006. Id.

This Court has previously addressed Regeneron's Eylea product and the Product Patent which Regeneron asserts in this preliminary injunction proceeding. In Regeneron v. Mylan, this Court previously held that the Product Patent was not invalid and that Mylan's Eylea biosimilar, "M710," infringed claims 4, 7, 9, 11, and 14-17 of the Product Patent. Mylan, 2024 WL 382495, at *25-33, 46-70.

The following table lists the claims Regeneron contends that SB infringes, as well as the claims from which they depend. Regeneron PI Br. at 5-8.

Claims of the Product 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, wherein said VEGF antagonist fusion protein is glycosylated and comprises amino acids 27-457 of SEQ ID NO:4; and 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.

Claim 2 (*unasserted*)	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 4	4. The vial of claim 2, wherein said organic co-solvent comprises about 0.03% to about 0.1% polysorbate 20.
Claim 5 (*unasserted*)	5. The vial of claim 2, wherein said organic co-solvent comprises 0.01% to 3% polysorbate 20.
Claim 7	7. The vial of claim 5, wherein said buffer comprises 5-25 mM buffer.
Claim 9	9. The vial of claim 5, wherein said buffer comprises a pH about 6.2-6.3.
Claim 10 (*unasserted*)	10. The vial of claim 5, wherein said stabilizing agent comprises a sugar.
Claim 11	11. The vial of claim 10, wherein said sugar is selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol.
Claim 14	14. The vial of claim 5, wherein said VEGF antagonist fusion protein is glycosylated at asparagine residues corresponding to asparagine residues 62, 94, 149, 222 and 308 of SEQ ID NO: 4.
Claim 15	15. The vial of claim 5, wherein said formulation is capable of providing a turbidity of 0.01 or lower at OD405 after 2 month storage at 5° C.
Claim 16	16. The vial of claim 5, wherein at least 99% of said VEGF antagonist fusion protein is present in native conformation after 2 month storage at 5° C. as measured by size exclusion chromatography.
Claim 17	17. The vial of claim 5, wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5° C. for 24 months as measured by size exclusion chromatography.
Claim 51	51. An ophthalmic formulation comprising:

(*unasserted*)	(a) 40 mg/ml of glycosylated VEGF antagonist fusion protein comprising amino acids 27-457 of SEQ ID NO:4; (b) 0.03% to 0.1% polysorbate; (c) 5-40 mM of sodium phosphate buffer, pH between 5.8-7.0; and (d) sucrose; wherein the ophthalmic formulation is suitable for intravitreal administration; and wherein at least 98% of the VEGF antagonist is present in native conformation following storage at 5° C. for 2 months as measured by size exclusion chromatography.
Claim 55	55. A vial suitable for intravitreal administration comprising the formulation of claim 51.

The meaning and validity of a patent are evaluated from the perspective of a Person of Ordinary Skill in the Art ("POSA"). Neither party has advanced a definition of the POSA at this stage of litigation and the definition does not seem to be an issue of dispute at this time. As such, the Court adopts the definition of the POSA in this case that it adopted in Mylan:

> [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 *22-23.

1. Prior Claim Constructions

This Court already construed two claim terms in the earlier Mylan litigation. In Mylan, "[t]he Court construed 'organic co-solvent' 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 that does not exhibit chemical or physical instability.'" Mylan, 2024 WL 382495, at *17 (quoting Mylan, C.A. No. 1:22-cv-61, ECF No. 427 at 20, 25-26). The parties have applied those constructions in these preliminary injunction proceedings, and the Court applies those constructions here.

2. Infringement

As detailed below, the Court finds that SB's SB15 product meets each and every limitation of the Asserted Product Patent Claims; thus, Regeneron is likely to succeed on infringement of the Asserted Product Patent Claims.

Both sides submitted expert declarations on the topic of infringement of the Asserted Product Patent Claims. Regeneron submitted an expert declaration from Dr. Trout, who explained that SB's SB15 product infringes all of the Asserted Product Patent Claims. Trout Decl. App. B. SB submitted an expert declaration

from Dr. Boyle, who contended that the Asserted Product Patent Claims are not infringed because the aflibercept in SB's SB15 product is not present in at least 98% native conformation as measured by size exclusion chromatography ("SEC"), as construed by the Court. Boyle Decl. ¶¶ 60-82. As explained below, the Court credits the opinions of Dr. Trout over the opinions of Dr. Boyle on issues involving infringement of the Asserted Product Patent Claims.

3. Validity

SB raises two grounds of invalidity with respect to the Product Patent: obviousness-type double patenting and written description. Opp. 3-13. Both parties submitted expert declarations addressing validity. Dr. Trout submitted an expert declaration for Regeneron, and Dr. Tessier submitted an expert declaration for SB.

4. SB15's Launch Will Irreparably Harm Regeneron

As detailed below, the Court finds that SB's launch of SB15 will irreparably harm Regeneron. Regeneron's expert, Dr. Sheridan, submitted a declaration setting forth the anticipated harms that Regeneron would face if a biosimilar such as SB15 were to launch, including harm to market share, pricing, payor relationships, reputation, and research and development funding.

The Vice President of Regeneron's Ophthalmology Commercial Business, Mr. Clark, also submitted a declaration detailing these anticipated harms. As explained below, the Court credits the opinions of Dr. Sheridan and the testimony of Mr. Clark on issues involving irreparable harm with the exception of claimed R&D funding.

Regeneron has demonstrated that it will suffer irreparable harm that a damages award could not fully remedy. A future damages award cannot compensate Regeneron adequately for the harm to its sales, price, relationships with payors and reputation. These harms, while nearly certain to occur, are all but impossible to fully quantify. They are also generally impossible to reverse. The Court will analyze each type of harm in detail below.

IV. ANALYSIS

A. Personal Jurisdiction

1. Regeneron's burden to establish a reasonable probability of success on the question of personal jurisdiction in the context of the direct-file Defendants' jurisdictional challenges[2]

Generally speaking, a plaintiff need only make a prima facie showing of personal jurisdiction to survive a motion to dismiss

[2] "Direct-File Defendants" refers to those defendants against whom Regeneron filed suit in this Court — i.e., SB; Celltrion, Inc.;

for lack of personal jurisdiction pursuant to Federal Rule of Civil Procedure 12(b)(2). Combs v. Bakker, 886 F.2d 673, 676 (4th Cir. 1989); United Coals, Inc. v. Attijariwafa Bank, No. 1:19-cv-95, 2022 WL 4715695, at *3 (N.D.W. Va. Sept. 30, 2022) (Kleeh, C.J.). However, "a party cannot obtain injunctive relief against another without first obtaining in personam jurisdiction over that person." R.M.S. Titanic, Inc. v. Haver, 171 F.3d 943, 958 (4th Cir. 1999). Accordingly, when a challenge to jurisdiction is interposed upon an application for a preliminary injunction, the plaintiff must establish that there is "a reasonable probability of ultimate success upon the question of jurisdiction when the action is tried on the merits." Catalog Mktg. Servs., Ltd. v. Savitch, 1989 WL 42488, at *2 (4th Cir. Apr. 24, 1989) (quoting Visual Scis., Inc. v. Integrated Commc'ns, Inc., 660 F.2d 56, 58 (2d Cir. 1981)). "Reasonable probability" is something "less than a preponderance of the evidence." Buckner v. Polk, 453 F.3d 195, 203 (4th Cir. 2006).

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and Formycon AG — and who have challenged the Court's exercise of personal jurisdiction by means of motions to dismiss for lack of personal jurisdiction.

2. Legal framework for determining whether the Court may exercise personal jurisdiction over the direct-file Defendants

Under Rule 4(k)(1)(A), a district court has personal jurisdiction over a defendant if the defendant "would be subject to the jurisdiction of a court of general jurisdiction in the state where the district court is located" — here, West Virginia. See Acorda Therapeutics Inc. v. Mylan Pharma. Inc., 817 F.3d 755, 759 (Fed. Cir. 2016). Because the West Virginia long-arm statute, W. Va. Code § 56-3-33, is coextensive with the full reach of due process, it is unnecessary to go through the traditional two-step process for determining the existence of personal jurisdiction. See Mey v. All Access Telecom, Inc., 2021 WL 8892199, at *2 (N.D. W. Va. Apr. 23, 2021) (citing In re Celotex Corp., 124 F.3d 619, 627-28 (4th Cir. 1997)). Instead, the statutory inquiry merges with the Constitutional inquiry, and the district court must determine whether exercising personal jurisdiction is consistent with the Due Process Clause. Id. at *2.

A court may exercise specific personal jurisdiction without violating the Due Process Clause where the defendant "ha[s] certain minimum contacts with [the forum] such that the maintenance of the suit does not offend traditional notions of fair play and substantial justice." Acorda, 817 F.3d at 759 (quoting Int'l Shoe

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Co. v. Washington, 326 U.S. 310, 316 (1945)). The Supreme Court has held that the minimum-contacts requirement is satisfied where the defendant "purposefully directed" activities at the forum "and the litigation results from alleged injuries that 'arise out of or relate to' those activities." Acorda, 817 F.3d at 759 (quoting Burger King v. Rudzewicz, 471 U.S. 462, 472-73 (1985)).

The Federal Circuit has held that "the minimum-contacts standard is satisfied" where a non-resident defendant files an abbreviated new drug application ("ANDA") "for the purpose of engaging in . . . allegedly wrongful marketing conduct in" the forum state. Id. at 760, 762-63; see also Valeant Pharms. N. Am. LLC v. Mylan Pharms. Inc., 978 F.3d 1374, 1384 (Fed. Cir. 2020) ("We held [in Acorda] that submission with an intent to distribute the generic product in a given state was sufficient for personal jurisdiction purposes."). The Federal Circuit further held that the minimum-contacts requirement is satisfied even where the defendant "does not sell its drugs directly into" the forum state but rather contracts with a wholesaler or distributor to market the drugs in the state. Acorda, 817 F.3d at 763. The court reasoned that the defendant had "taken the costly, significant step" of applying to FDA for approval to market its generic drug in the forum state and elsewhere and that this intent to market

was evidenced by distribution channels the defendant had established — i.e., a "network of independent wholesalers and distributors with which it [had] contract[ed] to market the drugs in" the forum state and elsewhere. Id. at 759-60, 763.

District courts have applied Acorda in the context of both Hatch-Waxman and BPCIA cases. See, e.g., AbbVie Inc. v. Alvotech Hf., 2021 WL 3737733, at *12-13 (N.D. Ill. Aug. 23, 2021) (denying defendant/aBLA-filer's motion to dismiss for lack of personal jurisdiction and rejecting defendant's argument that Acorda did not govern because defendant itself did not "sign" the aBLA); Apicore US LLC v. Beloteca, Inc., 2019 WL 1746079, at *3-4 (E.D. Tex. Apr. 18, 2019) (denying motion to dismiss for lack of personal jurisdiction where defendant filed ANDA to market generic drug throughout the United States, even though defendant was "not licensed to do business in Texas, [did] not have a registered agent in Texas, [did] not have a Texas Taxpayer Number, [was] not licensed as a distributor of prescription drugs sold in Texas," and had entered into an agreement with a Delaware company headquartered in Florida to market, sell, and distribute the generic drug throughout the United States, on the grounds that defendant's "ANDA filing and approval—in combination with its intent to market, distribute, and sell the [accused product]

through [the distributor's] established distribution network, which includes Texas—constitute sufficient minimum contacts with Texas"); Helsinn Healthcare S.A. v. Hospira, Inc., 2016 WL 1338601, at *6-7 (D.N.J. Apr. 5, 2016) (denying motion to dismiss for lack of personal jurisdiction where defendant filed an ANDA to market generic drug throughout the United States, stating that "[t]he facts in Acorda bear a strong similarity to this action," including the fact that defendant would utilize a distributor to market, sell, and distribute the generic in the United States).

3. Regeneron Has Established That It Has At Least a Reasonable Probability of Success on the Question of Jurisdiction When the SB Action Is Tried on the Merits

This Court has already concluded, in connection with Regeneron's Motion for Temporary Restraining Order (ECF No. 219), and based upon the facts set forth above, that Regeneron has demonstrated that there is a reasonable probability of ultimate success upon the question of personal jurisdiction when the action against SB is tried on the merits. See ECF No. 224.

B. Preliminary Injunction

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.

Indeed, patent owners have "a constitutional and statutory grant to exclude others from one's property. U.S. Const. art. I, § 8, cl. 8 ("by securing for limited times to . . . inventors the *exclusive* right to their respective . . . discoveries") (emphasis added); 35 U.S.C. § 154(a)(1) ("Every patent shall contain . . . a grant to the patentee . . . of the *right to exclude others* from making, using, offering for sale, or selling the invention . . . ") (emphasis added). And "the axiomatic remedy for trespass on property rights is removal of the trespasser." Presidio Components, Inc. v. Am. Tech. Ceramics Corp., 702 F.3d 1351, 1362 (Fed. Cir. 2012). A preliminary injunction thus "serve[s] to prevent ongoing trespasses during the pendency of an infringement case." See BlephEx, LLC v. Myco Indus., Inc., 24 F.4th 1391, 1404 (Fed. Cir. 2022).

Issuance of a preliminary injunction depends on four factors: whether (1) the plaintiff likely will succeed on the merits at trial; (2) the plaintiff will be 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 v. NRDC, 555 U.S. 7, 20 (2008). Here, each Winter factor favors entry of a preliminary injunction.

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1. Patent Law Framework

a. Infringement

Under 35 U.S.C. § 271(e)(2), the filing of an aBLA with the FDA "constitutes a technical" act of infringement. Sunovion Pharm., Inc. v. Teva Pharm. USA, Inc., 731 F.3d 1271, 1278 (Fed. Cir. 2013); Amgen Inc. v. Apotex Inc., 712 F. App'x 985, 991-992 (Fed. Cir. 2017) (applying Sunovion to aBLA filing). "[I]f a product that an . . . applicant is asking the FDA to approve . . . falls within the scope of an issued patent, a judgment of infringement must necessarily ensue." Sunovion Pharm., Inc., 731 F.3d at 1278.

Regeneron, as the "patentee seeking relief under § 271(e)(2)[,] bears the burden of proving infringement by a preponderance of the evidence" at trial. Eli Lilly & Co. v. Teva Parenteral Medicines, Inc., 845 F.3d 1357, 1364 (Fed. Cir. 2017).

b. Validity

1. Presumption of Validity

"A patent shall be presumed valid. Each claim of a patent (whether in independent, dependent, or multiple dependent form) shall be presumed valid independently of the validity of other claims." 35 U.S.C. § 282(a). This presumption of validity "exists at every stage of the litigation," Canon Comput. Sys., Inc. v. Nu-

Kote Int'l, Inc., 134 F.3d 1085, 1088 (Fed. Cir. 1998), including the preliminary injunction stage. Titan Tire Corp. v. Case New Holland, Inc., 566 F.3d 1372, 1377 (Fed. Cir. 2009). Thus, if "the challenger fails to identify any persuasive evidence of invalidity, the very existence of the patent satisfies the patentee's burden on the validity issue." Canon Comput. Sys., 134 F.3d at 1088.

A patentee is never required to prove validity. See, e.g., Prometheus Labs., Inc. v. Roxane Labs., Inc., 805 F.3d 1092, 1101-02 (Fed. Cir. 2015) ("[A] patentee never must submit evidence to support . . . that a patent remains valid . . . ." (quoting Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1360 (Fed. Cir. 2007)); Ajinomoto Co. v. Archer-Daniels-Midland Co., 1996 WL 621830, at *5 (D. Del. Oct. 21, 1996) ("It is not necessary that the court hold a patent valid; it is only necessary that it hold that the patent challenger has failed to carry its burden.") (citing Jones v. Hardy, 727 F.2d 1524, 1529 n.3 (Fed. Cir. 1984)), aff'd, 228 F.3d 1338 (Fed. Cir. 2000).

Pursuant to the statutory presumption of 35 U.S.C. § 282(a), Defendants must prove invalidity at trial by clear and convincing evidence. Microsoft Corp. v. i4i Ltd., 564 U.S. 91, 95 (2011). Under the clear and convincing standard, a party alleging

invalidity must create "in the mind of the trier of fact 'an abiding conviction that the truth of [the] factual contention are highly probable.'" Buildex Inc. v. Kason Indus, Inc., 849 F.2d 1461, 1463 (Fed. Cir. 1988) (quoting Colorado v. New Mexico, 467 U.S. 310, 316 (1984)).

"[T]he evidentiary burdens at the preliminary injunction stage track the burdens at trial." Titan Tire, 566 F.3d at 1377; Gonzalez v. O Centro Espirita Beneficente Uniao do Vegetal, 546 U.S. 418, 429-430 (2006) (rejecting argument that plaintiff "should have borne the burden of disproving [affirmative defense] at the hearing on the preliminary injunction"). However, the patentee has the burden to "persuade the court that, despite the challenge presented to validity, the patentee nevertheless is likely to succeed at trial on the validity issue." Titan Tire, 566 F.3d at 1377. The Court "must determine whether it is more likely than not that [Defendants] will be able to prove at trial, by clear and convincing evidence, that the patent is invalid." Id. at 1379. In other words, after weighing the evidence for and against validity available at the preliminary injunction stage, the Court must determine whether Defendants have raised a "'substantial question' concerning the validity of the patent." Id.

"Substantial weight may be given to a patent's litigation history in connection with a motion for relief pendente lite." H.H. Robertson, Co. v. United Steel Deck, Inc., 820 F.2d 384, 388 (Fed. Cir. 1987), abrogated on other grounds, Markman v. Westview Instruments, Inc., 52 F.3d 967 (Fed. Cir. 1995) (en banc); Leeds & Catlin Co. v. Victor Talking Mach. Co., 213 U.S. 301, 311 (1909) ("prior adjudications fortified the presumption of the validity of the patent in suit, and established its scope" and affirming preliminary injunction); see also, e.g., Fireball Gas Tank & Illuminating Co. v. Com. Acetylene Co., 198 F. 650, 653 (8th Cir. 1912) ("It is an incontrovertible rule of equity jurisprudence that where there has been a prior adjudication sustaining a patent . . . where the validity of the patent has been contested on full proofs, the Circuit Court should, upon a motion for a preliminary injunction, sustain the patent and leave the question of its validity to be determined upon the final hearing."), aff'd, 239 U.S. 156 (1915); Hybritech Inc. v. Abbott Labs., 849 F.2d 1446, 1452-53 (Fed. Cir. 1988) ("[T]he patent holder may use a prior adjudication of patent validity involving a different defendant as evidence supporting its burden of proving likelihood of success on the merits."); Atlas Powder Co. v. Ireco Chem., 773 F.2d 1230, 1232 (Fed. Cir. 1985) (similar).

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2. Obviousness-Type Double Patenting

Obviousness-type double patenting ("ODP") "is a judicially created doctrine" "that prevents the extension of the term of a patent . . . by prohibiting the issuance of the claims in a second patent not patentably distinct from the claims of the first patent." Otsuka Pharm. Co. v. Sandoz, Inc., 678 F.3d 1280, 1297 (Fed. Cir. 2012) (internal quotation omitted). There are two steps to the ODP analysis. "First, the court construes the claims in the earlier patent and the claims in the later patent and determines the differences. Second, the court determines whether those differences render the claims patentably distinct." AbbVie Inc. v. Mathilda & Terence Kennedy Inst. of Rheumatology Trust, 764 F.3d 1366, 1374 (Fed. Cir. 2014) (cleaned up). In order for a claim in the later patent to be invalid for ODP, it must either be anticipated by or obvious over the claims in the earlier patent. Id. ODP "turn[s] on a comparison between a patentee's earlier and later claims, with the earlier patent's written description considered only to the extent necessary to construe its claims." Eli Lilly & Co. v. Teva Parenteral Meds. Inc., 689 F.3d 1368, 1378-79 (Fed. Cir. 2012) (emphasis added). In other words, the challenger cannot rely on the teachings of the reference patent's specification to show that a particular limitation was known in

the art. Id.

For an earlier claim to anticipate a later claim, it must disclose "each and every limitation" of the later claim. See Ericsson, Inc. v. D-Link Sys., Inc., 773 F.3d 1201, 1224 (Fed. Cir. 2014). For an earlier claim to render a later claim obvious, "one of ordinary skill in the art would have had reason or motivation to modify the earlier claim[] to . . . the asserted claim with a reasonable expectation of success." Otsuka Pharm. Co., Ltd., 678 F.3d at 1298-99. Further, with regards to obviousness, the party asserting ODP bears the burden to prove that the POSA as of the patent's priority date would have been motivated to modify the "reference claims" of the earlier patent to obtain the asserted claims with a reasonable expectation of success. Otsuka Pharm., 678 F.3d at 1298-99; Eli Lilly, 689 F.3d at 1378.

As in the obviousness context, objective evidence of nonobviousness must be considered. Eli Lilly, 689 F.3d at 1381. Evidence of an invention's unexpected properties and that others have copied the invention (among other evidence) can serve as such objective indicia in support of non-obviousness. See, e.g., WBIP LLC v. Kohler Co., 829 F.3d 1317, 1332-37 (Fed. Cir. 2016); Mintz, 679 F.3d at 1379-80. Likewise, "[e]vidence of industry skepticism

weighs in favor of non-obviousness." WBIP, 829 F.3d at 1335 ("Doubt or disbelief by skilled artisans regarding the likely success of a combination or solution weighs against the notion that one would combine elements in references to achieve the claimed invention."). Objective indicia of nonobviousness also may consist of evidence that a prior art reference taught away from the claimed invention, i.e., that "person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." Millennium Pharm., Inc. v. Sandoz Inc., 862 F.3d 1356, 1366 (Fed. Cir. 2017) (quoting In re Urbanski, 809 F.3d 1237, 1244 (Fed. Cir. 2016)).

Such evidence can help to "guard against slipping into use of hindsight" and "the temptation to read into the prior art the teachings of the invention at issue." Apple Inc. v. Samsung Elecs. Co., 839 F.3d 1034, 1052 (Fed. Cir. 2016) (en banc) (quoting Graham v. John Deere Co., 383 U.S. 1, 36 (1966)); see also WBIP, 829 F.3d at 1328 ("[O]bjective indicia of non-obviousness play an important role as a guard against the statutorily proscribed hindsight reasoning in the obviousness analysis.").

3. Inherency

An earlier claim that does not expressly disclose every limitation of a later claim may still anticipate the later claim if the missing limitation is inherent in the earlier claim. See Allergan, Inc. v. Apotex Inc., 754 F.3d 952, 960 (Fed. Cir. 2014). An inherent limitation must be "necessarily present" in the prior art, id., and "may not be established by probabilities or possibilities," PAR Pharm., Inc. v. TWI Pharm., Inc., 773 F.3d 1186, 1195 (Fed. Cir. 2012); Cont'l Can Co. USA, Inc. v. Monsanto Co., 948 F.2d 1264, 1269 (Fed. Cir. 1991). It is of no matter if the missing limitation often or usually would result from practice of the earlier claim — there is no inherent anticipation unless the missing limitation is present each and every time the earlier claim is practiced. See Glaxo Inc. v. Novopharm Ltd., 52 F.3d 1043, 1047 (Fed. Cir. 1995) (finding no inherent anticipation when the missing limitation was present in thirteen out of fifteen examples of the earlier claim being practiced).

In the obviousness context, the role of inherency is limited because inherent properties may not have been understood by the POSA and thus cannot support the POSA's motivation. As the Federal Circuit has explained, "the use of inherency in the context of obviousness must be carefully circumscribed because '[t]hat which

may be inherent is not necessarily known' and that which is unknown cannot be obvious." Honeywell Int'l Inc. v. Mexichem Amanco Holding, 865 F.3d 1348, 1354 (Fed. Cir. 2017) (quoting In re Rijckaert, 9 F.3d 1531, 1534 (Fed. Cir. 1993)).

4. Written Description

The written description requirement under 35 U.S.C. § 112 provides that a patent specification must "contain a written description of the invention, and of the manner and process of making and using it." 35 U.S.C. § 112 ¶ 1 (pre-AIA). This requirement is met when "the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." Forest Labs., LLC v. Sigmapharm Labs., LLC, 918 F.3d 928, 937 (Fed. Cir. 2019) (quoting Ariad Pharms., Inc. v. Eli Lilly & Co., 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc)).

The patent's specification is not required to have "'either examples or an actual reduction to practice'; rather, the critical inquiry is whether the patentee has provided a description that 'in a definite way identifies the claimed invention' in sufficient detail that a person of ordinary skill would understand that the inventor was in possession of it at the time of filing." Alcon

Rsch. Ltd. v. Barr Labs., Inc., 745 F.3d 1180, 1190-91 (Fed. Cir. 2014) (quoting Ariad, 598 F.3d at 1350).

"A patent satisfies the written description requirement if the specification 'allows [the POSA] to visualize or recognize the identity of the subject matter purportedly described'; the patent need not contain 'either examples or an actual reduction to practice.'" Mylan, 2024 WL 382495, at *63 (quoting Allergan, Inc. v. Sandoz, Inc., 796 F.3d 1293, 1308 (Fed. Cir. 2015)). "[T]he test for sufficiency [of written description] is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." Nalpropion Pharms. v. Actavis, 934 F.3d 1344, 1350 (Fed. Cir. 2019) (internal quotation omitted). There is no requirement, in the context of claim limitations that recite ranges, that the specification provide any examples at all, much less examples for all embodiments throughout the range. Id.; Alcon Rsch, 745 F.3d at 1190-91 (explaining that the specification is not required to have "either examples or an actual reduction to practice"). The specification need not describe "every conceivable and possible future embodiment of [the] invention" for the patent to satisfy the written description requirement. Cordis Corp. v. Medtronic AVE,

Inc., 339 F.3d 1352, 1365 (Fed. Cir. 2003). Further, "a patent claim is not necessarily invalid for lack of written description just because it is broader than the specific examples disclosed." Martek Biosciences Corps. v. Nutrinova, Inc., 579 F.3d 1363, 1371 (Fed. Cir. 2009).

B. Regeneron Is Likely to Succeed on Infringement of the Product Patent

Regeneron is likely to succeed on infringement of the Product Patent. SB disputes infringement of only the at least 98% and 99% native conformation by SEC limitations of the Product Patent, and offers a declaration from Dr. Boyle in support. Regeneron rebuts these points with evidence from Dr. Trout.

As explained below, the Court credits the declaration of Dr. Trout over the declaration of Dr. Boyle for the disputed limitations and credits the unrebutted declaration of Dr. Trout for the undisputed limitations.

1. Undisputed Infringement Issues: SB15 meets the limitations of the Asserted Product Patent Claims other than the limitations involving the at least 98% and 99% native conformation by SEC limitation

SB and Dr. Boyle do not dispute that SB15 meets every limitation of the Asserted Product Patent Claims other than the at least 98% and 99% native conformation by SEC limitations. Dr. Trout's declaration explaining that SB15 meets all limitations of

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the Asserted Product Patent Claims is therefore unrebutted as to all limitations other than the at least 98% and 99% native conformation by SEC limitations. Thus, Regeneron has carried its burden on these issues.

Claim 1. The Court credits Dr. Trout's opinion that SB15 meets each limitation of claim 1 of the Product Patent. As Dr. Trout explained, SB's aBLA states that [redacted] which meets the requirement of claim 1 of "[a] vial comprising an ophthalmic formulation suitable for intravitreal administration." Trout Decl. App. B ¶¶ 9-14.

Dr. Trout also explained that the requirement of "a vascular endothelial growth factor (VEGF) antagonist . . . wherein said VEGF antagonist fusion protein is glycosylated and comprises amino acids 27-457 of SEQ ID NO:4" refers to glycosylated aflibercept, which is described as "SB15" in SB's aBLA. Id. ¶¶ 15-27. First, Dr. Trout explained that the aflibercept in SB15 is a VEGF antagonist. Id. ¶¶ 15-16. Second, Dr. Trout explained that [redacted] amino acids 27-457 of SEQ ID NO:4. Id. ¶¶ 17-24. Third, Dr. Trout explained that [redacted]

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Dr. Trout explained that SB's SB15 product meets the requirement of "an organic co-solvent" in claim 1. Id. ¶¶ 30-42. He explained that which is an organic co-solvent under the Court's claim construction.

Dr. Trout further explained that SB's SB15 product meets the requirement of "a buffer" in claim 1. Id. ¶ 46. He explained that

[redacted]

Dr. Trout further explained that SB's SB15 product meets the requirement of "a stabilizing agent" in claim 1. Id. ¶ 47. [redacted]

SB and its non-infringement expert, Dr. Boyle, offered no argument or evidence that their accused SB15 product does not meet the foregoing limitations of claim 1. The Court thus credits Regeneron's unrebutted evidence, including the declaration of Dr. Trout, that SB's SB15 product meets each of the foregoing claim limitations.

Regarding the dependent claims, aside from the at least 98% native conformation by SEC limitations addressed below, SB did not dispute any limitations of any of the dependent claims of the Asserted Product Patent Claims. Regeneron, through its expert Dr. Trout, explained that SB's SB15 product meets each of these claim limitations, as summarized below. The Court credits Dr. Trout's unrebutted opinions.

Claim 2. The Court credits Dr. Trout's opinion that SB's SB15 product meets the requirement of claim 2 that "wherein the concentration of said VEGF antagonist fusion protein is 40 mg/mL."

Id. ¶¶ 28-29. Dr. Trout explained [redacted]

Claims 2, 4, and 5. In addition to the "organic co-solvent" limitation of claim 1, the Court credits Dr. Trout's opinion that SB's SB15 product meets the requirements of claim 2, 4, and 5: claim 2 specifies that "said organic co-solvent comprises polysorbate"; claim 4 specifies that "said organic co-solvent comprises about 0.03% to about 0.1% polysorbate 20"; and claim 5 specifies that "said organic co-solvent comprises 0.01% to 3% polysorbate 20." Id. ¶¶ 30-45, 69. Dr. Trout explained [redacted]

Claim 7. Regarding claim 7, which recites "wherein said buffer comprises 5-25 mM buffer," the Court credits Dr. Trout's opinion that SB's SB15 product contains a buffer as required by the Asserted Product Patent Claims. Id. ¶ 46. Dr. Trout explained [redacted]

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Claim 9. Regarding claim 9, the Court credits Dr. Trout's opinion that SB's SB15 product meets the requirement that "wherein said buffer comprises a pH about 6.2-6.3." Id. ¶¶ 71-74.

Claims 10 and 11. Regarding claims 10 and 11, the Court credits Dr. Trout's opinion that SB's SB15 product meets the limitations of these claims. Id. ¶¶ 75-76. He explained that SB15 meets the requirement of claim 10 that "said stabilizing agent comprises a sugar. SB15 meets the requirement of claim 11 that "wherein said sugar is selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol." Id.

Claim 14. Regarding claim 14, the Court credits Dr. Trout's opinion Id. ¶¶

77-78. Thus, SB15 meets the requirement of claim 14 that "wherein said VEGF antagonist fusion protein is glycosylated at asparagine residues corresponding to asparagine residues 62, 94, 149, 222 and 308 of SEQ ID NO:4."

Claim 15. Regarding claim 15, the Court credits Dr. Trout's opinion that SB's SB15 product meets the additional limitation of this claim. Id. ¶¶ 79-92. Dr. Trout explained that [redacted] SB15 meets the requirement of claim 15 that "said formulation is capable of providing a turbidity of 0.01 or lower at OD405 after 2 month storage at 5° C." [redacted] thus demonstrating infringement of this limitation. [redacted]

Claim 51. The Court credits Dr. Trout's opinion that SB15 meets each limitation of claim 51 of the Product Patent. Dr. Trout relied on his analysis of claim 1 for the analysis of claim 51. Id. ¶¶ 101-106. [redacted]

[redacted] which meets the requirement of claim 51 of "[a]n ophthalmic formulation" "wherein the ophthalmic formulation is suitable for intravitreal administration." Id. ¶¶ 9-14; 101.

Dr. Trout also explained that the requirement of "40 mg/ml of a glycosylated VEGF antagonist fusion protein comprising amino acids 27-47 of SEQ ID NO:4" refers to 40 mg/ml of glycosylated aflibercept, [redacted] Id. ¶¶ 15-27; 102. First, Dr. Trout explained that the aflibercept in SB15 is a VEGF antagonist. Id. ¶¶ 15-16. Second, Dr. Trout explained that [redacted] Third, Dr. Trout explained that [redacted] Finally, Dr. Trout explained that [redacted]

Dr. Trout explained that SB's SB15 product meets the requirement of "0.03% to 0.1% polysorbate" in claim 51. Id. ¶¶ 30-45; 103. [redacted] and thus SB15 meets the requirements of claim 51. [redacted]

Dr. Trout explained that SB15 meets the requirement of "5-40 mM of sodium phosphate buffer, pH between 5.8-7.0." Id. ¶¶ 69-74; 104. [redacted]

Finally, Dr. Trout explained that SB's SB15 product meets the limitation that recites "sucrose." Id. ¶¶ 75-76; 105. He explained that [redacted] as recited in the claim. Id.

Claim 55. The Court credits Dr. Trout's opinion that SB's SB15 product meets the requirement of "[a] vial suitable for intravitreal administration." Id. ¶ 107. Dr. Trout relied on his analysis of claim 1 for the analysis of claim 55. Id. ¶¶ 107. Specifically, [redacted]

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[redacted] which meets the requirement of claim 1 of "[a] vial comprising an ophthalmic formulation suitable for intravitreal administration." [redacted] Thus, Dr. Trout concluded that SB15 met the requirement of claim 55 of "[a] vial suitable for intravitreal administration." Id. ¶ 107.

2. Disputed Limitations: The aflibercept in SB15 satisfies the % native conformation by SEC limitations

Each Asserted Product Patent Claim requires the VEGF antagonist fusion protein be present in levels of at least 98% native conformation, as measured by SEC—either expressly or by virtue of its dependency on another patent claim. Claim 1 recites "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"; claim 16 recites "wherein at least 99% of said VEGF antagonist fusion protein is present in native conformation after 2 month storage at 5° C, as measured by size exclusion chromatography"; claim 17 recites "wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5° C for 24 months as measured by size exclusion chromatography"; and claim 51 recites "wherein at least 98% of the VEGF antagonist is present in native

conformation following storage at 5° C for 2 months as measured by size exclusion chromatography."

The parties dispute whether the aflibercept in the SB15 product is present at levels of at least 98% or 99% native conformation as measured by SEC. This dispute centers on which analytical tests are required to measure the percentage of aflibercept present in native conformation as measured by SEC under the Court's construction of "native conformation." As mentioned above, the Court previously construed the term "native conformation" to mean "the original intact form of the VEGF antagonist, which is a form that does not exhibit chemical or physical instability." Mylan, 2024 WL 382495, at *17 (quoting Mylan, C.A. No. 1:22-cv-61, ECF No. 427 at 20, 25-26). SB contends that SEC is not a required analytical method to determine the percentage of VEGF antagonist present in native conformation under the Court's construction, and that other analytical tests such as LC-ESI-MS, non-reduced CE-SDS, and icIEF are more appropriate to determine whether the product meets the claimed percentage. Regeneron contends that measuring the percentage of aflibercept present in native conformation under the Court's construction requires analysis by SEC. For the reasons explained below, the Court agrees with Regeneron.

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This Court in Mylan construed the claim term "native conformation." Mylan, C.A. No. 1:22-cv-61, ECF No. 427 at 25 ("the claim language, 'native conformation' is construed"); id. (discussing "the term 'native conformation' itself"). The Court expressly declined to construe "other claim elements (e.g., . . . as measured by size exclusion chromatography)," which are "properly considered during the infringement and invalidity part of the case." Id. at 26. Thus, "as measured by size-exclusion chromatography" remains a requirement of the claims, and the Court's construction of "native conformation" did not eliminate the required "as measured by size-exclusion chromatography" limitation from the claims of the Product Patent.

SB's interpretation of the Court's construction omits the "as measured by [SEC]" claim term required by each Asserted Product Patent Claim. Digital-Vending v. Univ. of Phoenix, 672 F.3d 1270, 1275 (Fed. Cir. 2012) (underscoring "the importance of construing claim terms in light of the surrounding language" so "words in a claim are not rendered superfluous"). Indeed, [redacted]

[redacted] There is only one analytical test recited in the Asserted Product Patent Claims for measuring percent native conformation: size-exclusion chromatography. SB's attempt to read additional analytical test requirements into the claims is improper. Phillips, 415 F.3d at 1320.

Dr. Trout and Dr. Boyle do not dispute that the claims recite only SEC as an analytical method, nor do they dispute that LC-ESI-MS, non-reduced CE-SDS, and icIEF are not recited in the claims. Boyle Tr. 131:8-132:4, 163:2-11, 277:18-278:6. Moreover, neither Dr. Trout nor Dr. Boyle dispute that SEC measures aggregation, which is a form of chemical and physical instability. Id. 125:4-21, 126:18-127:16. Consistent with the view that SEC alone can measure chemical and physical instability, this Court in the Mylan case found that the Product Patent's examples, which provide SEC data, meet the "native conformation" limitation as construed by the Court. Mylan, 2024 WL 382495, at *67-68.

Further, the Court finds Dr. Trout's testimony to be more credible than Dr. Boyle's. Dr. Trout's opinions were consistent with the Product Patent's claims, the Court's claim construction, [redacted] By contrast, Dr. Boyle's opinions [redacted] he improperly based his analysis on three analytical

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tests that are neither recited in nor required by the Asserted Product Patent Claims. He insisted on reading the Court's construction in a vacuum, and, as a result, his opinion directly conflicts with the Court's finding in Mylan—that the patent's examples (which provide SEC data) meet the "native conformation" limitations. Boyle Tr. 263:3-8, 231:1-9, 170:4-179:1, 220:7-225:8; Mylan, 2024 WL 382495, at *64. The Court observes that SB's position on infringement of this limitation is inconsistent with its position that the "stable" limitation of the '594 patent is patentably indistinct from the native conformation limitation in the Product Patent. SB attempts to have it both ways by having its experts apply opposing interpretations of the Court's claim construction depending on whether they are arguing non-infringement or invalidity, which is improper. TVIIM, LLC v. McAfee, Inc., 851 F.3d 1356, 1362 (Fed. Cir. 2017) ("Claim terms must be construed the same way for the purpose of determining invalidity and infringement."). For purposes of infringement, Dr. Boyle interprets the Court's construction to require analytical tests that are not recited in the claim in concluding that FYB203 contains less than 98% native conformation, whereas for purposes of invalidity, Dr. Tessier assumes the limitation requires less — i.e., only SEC data — and that the patent's and Regeneron's

internal data tables reporting only SEC data suffice to meet 98% native conformation.

Thus, the Court agrees with Regeneron that measuring the percentage of aflibercept present in native conformation under the Court's construction of the Asserted Claims requires analysis by SEC.

The proper question for infringement is whether at least 98% (or, for purposes of asserted claim 16, 99%) of SB15's aflibercept is present in "native conformation," as that term was construed by the Court, as measured by SEC. This Court credits the opinions of Dr. Trout, and finds that at least 98% and 99% of the aflibercept in SB15 is present in native conformation, as measured by SEC and at the claimed storage conditions. As Dr. Trout explained, [redacted]

[redacted]

** SEALED **

ORDER GRANTING MOTIONS FOR PRELIMINARY INJUNCTION

[redacted]

In sum, having considered the evidence regarding whether at least 98% and 99% of the aflibercept in SB15 "is present in native conformation," the Court credits Dr. Trout's opinion [redacted] demonstrate that SB's SB15 product meets the requirements of the Asserted Product Patent Claims.

3. Regeneron Is Likely to Succeed on Validity of the Product Patent

SB advances two invalidity defenses to the Product Patent: obviousness-type double patenting, and lack of written description. Opp. 3-13. For the following reasons, SB's arguments do not raise a "substantial question" of validity of the Product Patent, and Regeneron has established a likelihood of success on the merits regarding the Product Patent's validity. See Titan Tire, 566 F.3d at 1380.

¶¶ 58-68, 95, 98, 106.

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a. Obviousness-Type Double Patenting

SB argues that the Product Patent is invalid for nonstatutory obviousness-type double patenting over claim 5 of U.S. Patent No. 9,340,594 (the "'594 patent"). Regeneron responds that the '594 patent is not a proper reference patent for ODP against the Product Patent. And even if the '594 patent were an ODP reference patent, Regeneron contends that the asserted claims of the Product Patent are patentably distinct over claim 5 of the '594 patent ("'594 claim 5") for multiple reasons.

There is no dispute that the asserted claims of the Product Patent and '594 claim 5 differ in several respects. First, all asserted claims of the Product Patent require that the VEGF antagonist "is glycosylated," while '594 claim 5 is silent as to glycosylation. Second, the asserted claims of the Product Patent recite that "at least 98% of the VEGF antagonist is present in native conformation following storage at 5° C. for two months as measured by size exclusion chromatography," while '594 claim 5 does not recite such level of native conformation. Third, asserted claims 4, 7, 9, 11, and 14-17 of the Product Patent recite a "vial" while '594 claim 5 requires a "pre-filled syringe."

Regeneron argues that each of these differences independently constitutes a patentable distinction over '594 claim 5 that

forecloses ODP. Regeneron further argues that objective evidence of nonobviousness further rebuts ODP.

The Court agrees with Regeneron that SB has not met its burden of showing a substantial question of ODP. As discussed further below, the Court concludes that the ’594 patent is not a proper ODP reference patent to the Product Patent. Furthermore, the Court concludes that each of the differences between the asserted claims of the Product Patent and ’594 claim 5 constitutes a patentable distinction that precludes ODP.

1. The ’594 patent is not a proper ODP reference

The ’594 Patent is a Regeneron patent directed to “[o]phthalmic formulations of a vascular endothelial growth factor (VEGF)-specific fusion protein antagonist . . . suitable for intravitreal administration to the eye.” ’594 Patent at Abstract. The ’594 Patent was filed on June 14, 2014 and granted on May 17, 2016. Like the Product Patent, the ’594 Patent is a continuation of U.S. Pat. Appl. No. 11/818,463, which was filed on June 14, 2007. Both the ’594 Patent and the Product Patent share the same specification, priority date, and statutory term.

During the ’594 patent prosecution, the Examiner rejected the claims on the ground of nonstatutory obviousness-type double patenting. July 14, 2014 Final Office Action, U.S. Pat. Appl. No.

14/330,096, at 6 (ECF No. 164-85, Tessier Ex. 51). In the rejection letter, the PTO informed Regeneron that "[a] timely filed terminal disclaimer in compliance with 37 CPR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground." Id. at 5. Regeneron then filed a terminal disclaimer to another patent that expired in 2021 (via yet another terminal disclaimer) "[s]olely in the interest of promoting prosecution and reserving the right to pursue the subject matter in another application." Response to Final Office Action, Appl. No. 14/330,096 (Filed July 14, 2014) (ECF No. 164-85, Tessier Ex. 51). The application that became the '594 patent was then granted.

As explained in detail below, because the Product Patent and the '594 Patent share the same parent patent and have the same statutory term, the '594 Patent cannot be an ODP reference for the Product Patent simply because the '594 patent expired after a terminal disclaimer.

"Nonstatutory double patenting is a judicially created doctrine grounded in public policy that prevents the extension of the term of a patent . . . ." Otsuka Pharm., 678 F.3d at 1297 (cleaned up). "Since the inception of our patent laws," it has been recognized that an individual cannot "obtain[] more than one

patent on the same invention." AbbVie, 764 F.3d at 1372. As Justice Story explained in 1819, "if [a patentee] can successively take out at different times new patents for the same invention . . . it would completely destroy the whole consideration derived by the public for the grant of the patent, the right to use the invention at the expiration of the term specified in the original grant." Id. (citing Odiorne v. Amesbury Nail Factory, 18 F. Cas. 578, 579 (C.C.D. Mass. 1819)). In other words, "[t]he ban on double patenting ensures that the public gets the benefit of the invention after the original period of monopoly expires." Id.

If there is no extension of the original monopoly period, i.e., the statutory term of the patent grant, there cannot be ODP. Because both the '594 patent and the Product Patent are continuations of application No. 11/818,463, filed on June 14, 2007, both patents share the same specification, priority date, and statutory term — i.e., "20 years" from the date "such application was filed," June 14, 2027. 35 U.S.C. § 154(a)(2). The original monopoly period of the entire patent family runs from June 14, 2007 to June 14, 2027. Therefore, the '594 patent cannot be an ODP reference for the Product Patent because the Product Patent does not and cannot extend the original monopoly period of

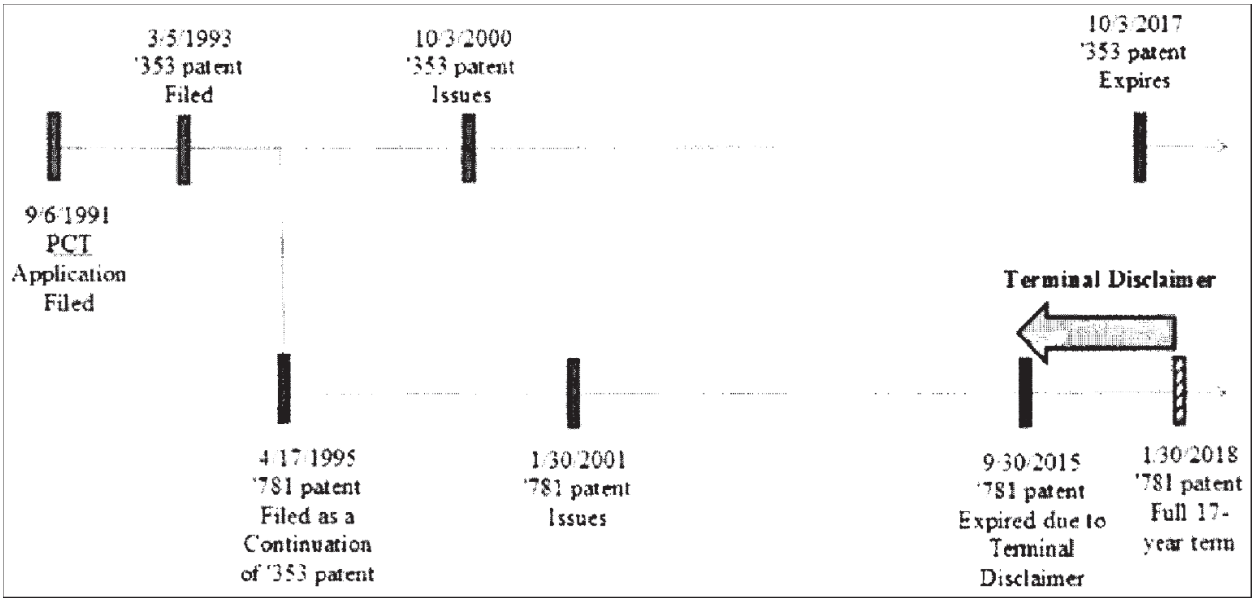
any patent in its family.[4]

The fact that, during the '594 patent prosecution, Regeneron filed a "terminal disclaimer" to another patent that expired in 2021 does not change this conclusion. The '594 patent was rendered unenforceable before the end of its statutory 20-year term, and before the statutory term of the Product Patent, solely due to this terminal disclaimer. Regeneron filed the terminal disclaimer "[s]olely in the interest of promoting prosecution and reserving the right to pursue the subject matter in another application." Response to Final Office Action, Appl. No. 14/330,096 (Filed July 14, 2014). As the Federal Circuit has held, "the filing of a terminal disclaimer simply serves the statutory function of removing the rejection of double patenting, and raises neither presumption nor estoppel on the merits of the rejection." Quad Env't. Techs. Corp. v. Union Sanitary Dist., 946 F.2d 870, 874 (Fed. Cir. 1991); see Motionless Keyboard Co. v. Microsoft Corp., 486 F.3d 1376, 1385 (Fed. Cir. 2007) ("A terminal disclaimer simply is not an admission that a later-filed invention is

[4] As noted in In re Cellect, LLC, the original monopoly period does not include any extension granted pursuant to Patent Term Adjustment under 35 U.S.C. § 154(b). 81 F.4th 1216 (Fed. Cir. 2023). No such extension is present in connection with the Product Patent, which expires after its statutory 20-year term on June 14, 2027.

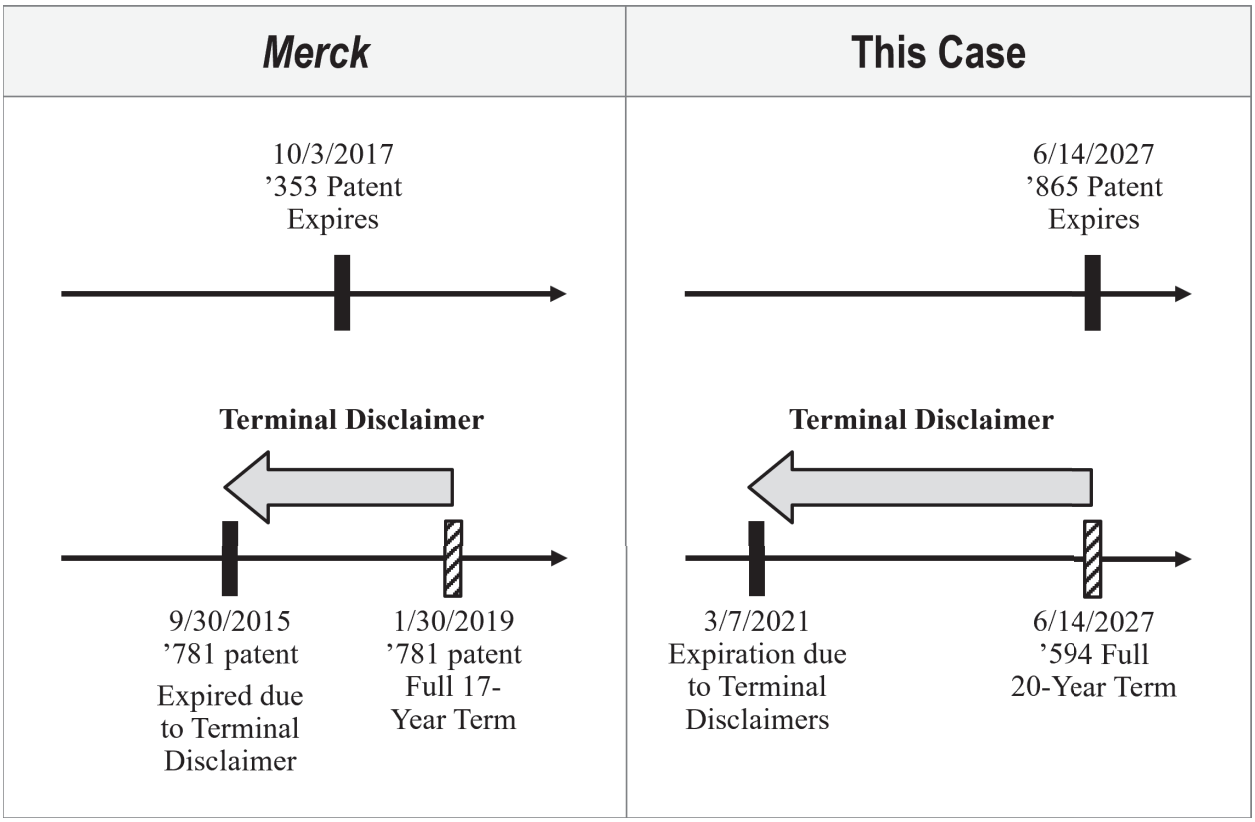
obvious."); Ortho Pharm. Corp. v. Smith, 959 F.2d 936, 941 (Fed. Cir. 1992) (rejecting argument that patent applicant admitted to obviousness-type double patenting by filing terminal disclaimer). Instead, a terminal disclaimer is a voluntary filing by a patentee that "dedicate[s] to the public" part of the patent's term. 35 U.S.C. § 253(b).

SB has cited no authority for the proposition that the filing of a terminal disclaimer in one patent can invalidate a related patent for ODP. In contrast, the only case cited by the parties that addressed whether one patent's terminal disclaimer can invalidate a related patent for ODP held that it could not. See Merck Sharp & Dohme Corp. v. Teva Pharms. USA, Inc., 217 F. Supp. 3d 782, 787-88 (D. Del. 2016). Specifically, in Merck the defendant alleged that a terminal disclaimer caused a patent to expire earlier than the asserted patent and thus rendered it invalid for ODP. Id. at 787. The court's illustration of the various expiration dates in Merck is shown below:



Id. As the depiction shows, the alleged '781 reference patent expired before the asserted ('353) patent solely due to a terminal disclaimer. And Merck held that the '781 patent "from the same family" could not serve as an ODP reference patent: "[u]nder the particular circumstances, the oddity of using the '781 patent as a reference patent to cut short the '353 patent's (the first issued parent patent) term of exclusivity is rejected. This is not an instance of a patentee seeking to extend the patent term with 'sequential' applications." Id. The Court agrees with the analysis in Merck; just as in that case, Regeneron does not seek any "extension of the term of a patent" contrary to the equitable principles underlying ODP. Otsuka Pharm., 678 F.3d at 1297. It seeks only the 20-year statutory term afforded under the statute.

35 U.S.C. § 154(a)(2). As illustrated below, the facts here are not meaningfully distinguishable from Merck:



The Court has considered In re Yamazaki, where the Federal Circuit held that "[w]hen a patent issues subject to a terminal disclaimer, the patentee . . . reduced the [patent] term itself by effectively eliminating the disclaimed portion from the original patent." In re Yamazaki, 702 F.3d 1327, 1333 (Fed. Cir. 2012). Yamazaki, however, did not address the ODP doctrine, and no court has extended it to that context to hold that the filing of a terminal disclaimer in one patent can invalidate a related patent

for ODP. In contrast, the mere fact that two patents have different expiry dates does not automatically give rise to ODP. For example, in Hoffmann-La Roche Inc. v. Orchid Chems. & Pharms. Ltd., 2011 WL 4433575, at *3 (D.N.J. Mar. 17, 2011), the court held there was no ODP where an alleged reference patent expired before its statutory term due to nonpayment of maintenance fees, "since it does nothing to effectuate the prohibition against double patenting." Id.; see also Novartis AG v. Ezra Ventures LLC, 909 F.3d 1367, 1374-75 (Fed. Cir. 2018) (rejecting ODP challenge even though related patents expired on different dates as a result of patent term extension under 35 U.S.C. § 156). Here too, the Court finds that "it does nothing to effectuate the prohibition against double patenting" to essentially propagate a terminal disclaimer from one patent in the family to another. Roche, 2011 WL 4433575, at *3. Indeed, the Federal Circuit has rejected ODP challenges premised on extending terminal disclaimers throughout a family. See Ortho Pharm Corp., 959 F.2d at 941.

The Court has also considered Federal Circuit precedent explicitly speaking to the issue of when a patent can serve as an ODP reference and have found them to be distinguishable from this matter. In Gilead Sciences, Inc. v. Natco Pharma Ltd., "[d]espite the[] similarities in content" between two patents (the '375 patent

and '483 patent), the patentee filed the '375 patent and then "crafted a separate 'chain' of applications having a later priority date than the '375 patent family" that "resulted in the issuance of the '483 patent." 753 F.3d 1208, 1210 (Fed. Cir. 2014). Thus, the asserted patent and the reference patent had different statutory terms. The specific question at issue in Gilead was "whether a later-issued patent can serve as a double patenting reference for an earlier-issued patent if the later one expires first." Id. at 1214. The Federal Circuit held that it could. Id. at 1217. But that is irrelevant to the question of the effect of terminal disclaimer on the ODP analysis here; regardless of the respective issuance dates of the Product Patent and the '594 patents, the patents undisputedly share the same priority date and 20-year term, but for the '594 patent's terminal disclaimers.

Gilead is further distinguishable from this case because, as the Federal Circuit later explained in Novartis, the Gilead decision was driven by the court's concern about the potential "gamesmanship issue" that could arise if ODP were based solely on a patent's issue date. Novartis, 909 F.3d at 1374. Gilead prevented "a situation where 'inventors could routinely orchestrate' longer patent-exclusivity periods by (1) filing serial patent applications on obvious modifications of an

invention, (2) claiming different priority dates in each, and then (3) strategically responding to prosecution deadlines such that the application claiming the latest filing date issues first, without triggering a terminal disclaimer for the earlier filed applications." Id. at 1375 (quoting Gilead, F.3d at 1215). This potential for gamesmanship is not at issue in a case, like the one here, where the two patents claim the same priority date and thus share the same 20-year term. Merck similarly found Gilead to be inapplicable when the putative reference patent only expired before the asserted patent because of a terminal disclaimer because it "is not an instance of a patentee seeking to extend the patent term with 'sequential' applications." Merck, 217 F. Supp. at 787-88.

Similar gamesmanship was at play in AbbVie, 764 F.3d 1366. There, the patentee "claimed a priority date of October 8, 1992 (the filing date of an earlier application), for the '766 patent" and "claimed a later priority date [for the '442 patent], August 1, 1996 (the filing date of the application that issued as the '766 patent), so that the '442 patent would expire after the '766 patent." Id. at 1373 n.2. The Court held that the patentee "is not entitled to an extra six years of monopoly solely because it filed a separate application unless the two inventions are

patentably distinct." Id. at 1374. As in Gilead, AbbVie did not and could not address the effect of terminal disclaimer of the putative reference patent on the ODP analysis. Unlike the patentees in Gilead and AbbVie, Regeneron did not attempt to circumvent the expiration of the '594 patent by creating a different priority chain for the Product Patent to extend its term.

As discussed above, In re Cellect stands for the proposition that "for a patent that has received PTA, regardless whether or not a terminal disclaimer is required or has been filed, [ODP] must be based on the expiration date of the patent after [Patent Term Adjustment ("PTA")][5] has been added." 81 F.4th 1216, 1229 (Fed. Cir. 2023) (footnote added). In other words, a patent that expired after an asserted patent's original expiration date but before the asserted patent's expiration date with PTA could serve as a proper ODP reference. But here, the Product Patent was not extended by PTA or otherwise; Regeneron seeks only the Product Patent's ordinary 20-year statutory term, and so Cellect does not apply here.

Finally, in Eli Lilly & Co. v. Barr Labs., Inc., the reference

[5] PTA grants a patent term extension beyond the normal 20-year statutory term if the issuance of a patent is delayed due to bureaucratic delays of the USPTO. In re Cellect, 81 F.4th at 1223-24.

patent was unrelated to and expired earlier than the asserted patent. 251 F.3d 955, 959 (Fed. Cir. 2001). The patentee attempted to circumvent this typical ODP scenario by disclaiming the reference patent during the course of the litigation. Id. The Court explained that "[a] patent owner cannot avoid double patenting by disclaiming the earlier patent" and that "double patenting precludes [the asserted patent] from extending beyond the termination date of the [reference patent], whether that termination date is at the end of its normal term or, as in this case, is the date it is terminated via disclaimer." Id. at 967 n.5. Thus, in Barr the Court held that a statutory disclaimer of a proper reference patent could not be used to "avoid" ODP, id., but here the question is whether a terminal disclaimer in the '594 patent (filed years before this lawsuit) *creates* ODP between related patents that otherwise share the same statutory term. Barr (unlike Merck, discussed above) did not address that question and thus fails to support SB's ODP theory.

The terminal disclaimer of the '594 patent does not change the fact that both patents have the same priority date, and the Product Patent's term never has been extended. Accordingly, the '594 patent cannot be an ODP reference for the Product Patent. Therefore, because SB's ODP theory of invalidity relies on an

improper ODP reference patent, Regeneron has established a likelihood that it will succeed on SB's ODP defense.

2. The Product Patent claims are patentably distinct from SB's asserted reference claim

The Court further concludes that even if the '594 patent were a proper reference patent, SB has not raised a substantial question that the Product Patent is invalid for ODP.

Unlike SB's asserted ODP reference claim, '594 claim 5, the asserted claims of the Product Patent recite a "glycosylated" protein and 98% native conformation. As explained in more detail below, because '594 claim 5 does not disclose each and every limitation in the asserted claims, either expressly or inherently, '594 claim 5 does not anticipate the asserted claims. With regards to obviousness, this Court finds that (1) the POSA lacked motivation to use glycosylated aflibercept, a requirement of the Product Patent but not '594 claim 5;[6] (2) the Product Patent's "98% native conformation" claim limitation is not inherent in claim 5 of the '594 patent; (3) the POSA lacked motivation to change '594 claim 5's PFS to the Product Patent's vial; and (4) objective evidence strongly supports nonobviousness of the Product Patent's

[6] This finding is consistent with this Court's identical finding in Regeneron v. Mylan, 2024 WL 382495, at *55.

asserted claims.[7] The only ODP reference claim asserted by SB is '594 claim 5, and as explained below, SB has not met its burden to show a substantial question that the Product Patent's asserted claims are anticipated or obvious over '594 claim 5; accordingly, the Court holds that Regeneron is likely to succeed on ODP.

a. Claim Construction

The first step in the ODP analysis requires construing the disputed terms of the relevant claims. AbbVie, 764 F.3d at 1374. SB's ODP reference claim, claim 5 of the '594 patent, is set forth below along with the pertinent claims from which claim 5 depends:

> 3. The pre-filled syringe according to claim 2, wherein the VEGF trap is stable for at least 4 months.
> 4. The pre-filled syringe according to claim 3, wherein the VEGF trap consists of amino acids 27-457 of SEQ ID NO:4.
>
> 5. The pre-filled syringe according to claim 4, wherein the stable ophthalmic formulation comprises 40 mg/mL of the VEGF trap, 10 mM phosphate, 40 mM NaCI, 0.03% polysorbate 20, 5% sucrose, at pH 6.2-6.4.

The parties dispute the construction of "VEGF trap consists of amino acids 27-457 of SEQ ID NO:4." While SB does not appear to argue that "stable" is synonymous with 98% native conformation as

[7] This finding is also consistent with the Court's Mylan decision. Mylan, 2024 WL 382495, at *59.

measured by SEC after 2 month storage at 5 degrees C, the Court must make a finding on this issue in order to perform the next steps of the ODP analysis.

i. "Stable"

For the following reasons, the Court holds that "stable" is not limited to 98% native conformation as measured by SEC after 2 month storage at 5 degrees C.

"[T]he words of a claim are generally given their ordinary and customary meaning . . . [which] 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." Phillips v. AWH Corp., 415 F.3d 1303, 1312-13 (Fed. Cir. 2005) (en banc) (cleaned up). The POSA "is deemed to read the claim term . . . in the context of the entire patent, including the specification." Id. at 1313.

The specification of the '594 patent makes clear that a POSA would not understand "stable" as limited to "98% native conformation as measured by SEC." The specification of the '594 patent has numerous descriptions of stability beyond simply 98% native conformation as measured by SEC. First, the '594 patent specification teaches that "at least 90%" non-aggregated protein is preferred, thereby confirming that levels of non-aggregation below 98% in the patent's formulations are not only permissible,

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but desirable. '594 patent 6:15-25. Second, the patent describes multiple aspects of stability, including aggregation, deamination, and precipitation. Id., 5:27-34 ("Proteins possess unique chemical and physical properties that present stability problems: a variety of degradation pathways exist for proteins, implicating both chemical and physical instability. Chemical instability includes deamination, aggregation, clipping of the peptide backbone, and oxidation of methionine residues. Physical instability encompasses many phenomena, including, for example, aggregation and/or precipitation."). Third, the patent describes multiple ways to determine stability, including visual inspection of color and appearance, SDS-PAGE, isoelectric focusing, and SEC. Id., 6:42-48 ("Stability is determined in a number of ways at specified time points, including determination of pH, visual inspection of color and appearance, determination of total protein con tent by methods known in the art, e.g., UV spectroscopy, and purity is determined by, for example, SDS-PAGE, size-exclusion HPLC, bioassay determination of activity, isoelectric focusing, and isoaspartate quantification."). These disclosures confirm that "stable" has a broader meaning than any one particular SEC measurement of aggregation.

Experts from both sides agree that the term "stable" in claim

5 of the '594 patent is not limited to 98% native conformation as measured by SEC. As Regeneron's expert, Dr. Trout, explained in his declaration, a POSA would not understand the meaning of "stable" as being limited to percent native conformation as measured by SEC. Trout Decl. ¶ 385. He further explained that if stability is measured by percent native conformation by SEC, then the POSA would understand that the fusion protein can be stable despite having less than 98% native conformation by SEC. Trout Decl. ¶¶ 386-387. Dr. Trout explained that both the specification and the ordinary meaning of the term to practitioners in the field supported this broader understanding of "stable" as encompassing less than 98% and types of stability other than those measured by SEC. Trout Decl. ¶¶ 385-87. SB's expert, Dr. Tessier, agreed. In his declaration, he did not dispute Dr. Trout's evidence or conclusions that the ordinary understanding of "stable" to the POSA includes percentages below 98%. Tessier Decl. ¶¶ 154-55, 160. Dr. Tessier testified at his deposition that "It's my understanding that the term stable in claim 5 would include the stability, for example, in example 4, but **it's not necessarily limited to it.**" Tessier Tr. 15:1-9 (emphasis added) (ECF No. 194-3, Patel Ex. 5). The undisputed ordinary meaning of "stable" as including stability below 98% controls. Thorner v. Sony Comput.

Entmt. Am. LLC, 669 F.3d 1362, 1365 (Fed. Cir. 2012) ("The words of a claim are generally given their ordinary and customary meaning as understood by a person of ordinary skill in the art when read in the context of the specification and prosecution history," unless either of the "only two exceptions" apply, lexicography or disavowal).

The Court's conclusion is bolstered by the fact that another patent in the same family as the Product Patent and the '594 patent claims a "stable ophthalmic formulation" "wherein 90% or more of the weight of the fusion protein is not present as an aggregate" — thus indicating that the meaning of "stable" does not implicitly require 98% native conformation by SEC. Specifically, claims 1 and 2 of U.S. Patent 9,914,763 (the "'763 patent"), which shares the same specification as the '594 patent, read as follows:

> 1. A prefilled glass syringe suitable for intravitreal administration ***containing a stable ophthalmic formulation***, comprising:
> a vascular endothelial growth factor (VEGF) antagonist,
> an organic co-solvent,
> a buffer, and
> a stabilizing agent,
> wherein the VEGF antagonist is a fusion protein produced in a Chinese Hamster Ovary (CHO) cell, the fusion protein comprising an immunoglobin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component.
> 2. The prefilled glass syringe of claim 1, ***wherein 90% or more of the weight of the fusion protein is***

not present as an aggregate.

'763 patent (Trout Ex. 76, ECF No. 118-10) (emphases added). Thus, because claim 2 depends from claim 1, it must "specify a further limitation of the subject matter claimed" in the independent claim from which it depends, 35 U.S.C. § 112(d), and "stable" in claim 1 must be broader than the "90% or more" limitation in claim 2. Consistent with the statute, the Federal Circuit has held that it is improper for courts to construe claims such that a dependent claim would "have no scope and thus be meaningless." Littelfuse, Inc. v. Mersen USA EP Corp., 29 F.4th 1376, 1380 (Fed. Cir. 2022). So, under a construction limiting "stable" to 98% native conformation, claim 2 of the '763 patent is meaningless because "stable" would already require a lower level of aggregates (98% native conformation) than specified in dependent claim 2. Such a construction not only reads in an unwritten numerical aggregate limitation into "stable," it also reads in a stricter threshold than what claim 2 recites expressly. Such a construction would render claim 2 of the '763 patent a nullity, inconsistent with the Federal Circuit's clear precedent. That court likewise has dictated that claim terms appearing in multiple patents in a family, such as "stable" in the '763 and '594 patents here, must be construed consistently between those patents. See SightSound

Techs., LLC v. Apple Inc., 809 F.3d 1307, 1316 (Fed. Cir. 2015) ("[W]here multiple patents derive from the same parent application and share many common terms, we must interpret the claims consistently across all asserted patents." (internal quotation omitted)); Omega Eng'g, Inc. v. Raytek Corp., 334 F.3d 1314, 1334 (Fed. Cir. 2003) (noting that claim terms in related patents should be construed consistently). Applying the 98% native conformation construction to the '763 patent, claim 2 would improperly "have no scope and thus be meaningless," as "stable" in claim 1 would require a more stringent stability limitation than the one set forth in dependent claim 2.

The prosecution history further reinforces that "stable" does not imply 98% native conformation. The Examiner reviewing the Product Patent concluded that the 98% native conformation limitation in the Product Patent was patentably distinct over — i.e. not inherent in, and different from — the '594 patent's claims to a "stable" formulation. During Prosecution of the Product Patent, the Examiner initially entered an ODP rejection based on the '594 patent. Product Patent File History at RGN-EYLEA-BIOSIM-00016064 (ECF No. 118-10, Trout Ex. 66). Regeneron explained that the Product Patent claims were patentably distinct, explaining that the claims that ultimately issued in the Product

Patent recited "the stability of the protein conformation in storage over a period of time" — i.e., the 98% native conformation limitation, whereas the '594 claims did not. Id. at -085-086. The Examiner then allowed the claims. Id. at -109-110. This further supports that the 98% native conformation by SEC limitation is distinct from "stable" as recited in the claims of the '594 patent.

Thus, properly understood, "stable" as required in '594 claim 5 is broader than, and not limited to, "at least 98% . . . native conformation . . . as measured by size exclusion chromatography." Having concluded that "stable for at least 4 months" is not limited to 98% native conformation as measured by SEC, the Court need not further construe that term in the '594 patent to resolve the parties' ODP dispute. See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co., 868 F.3d 1013, 1017 (Fed. Cir. 2017) ("[Courts] need only construe terms . . . to the extent necessary to resolve the [parties'] controversy.") (internal quotation omitted).

ii. "VEGF Trap"

SB argues that the term "VEGF trap consists of amino acids 27-457 of SEQ ID NO:4"[8] in claim 5 of the '594 patent should be

[8] For readability, this term will be referred to as "VEGF trap."

construed to require glycosylation at five specific residues in the protein's amino acid sequence. Opp. 6-7. Regeneron responds that the term "VEGF trap" should not be construed as including SB's proposed glycosylation requirement, given that this term (like the rest of claim 5 of the '594 patent) does not recite any glycosylation requirement. Reply 4.

The Court agrees with Regeneron. Neither '594 claim 5 nor any claim from which it depends recites any limitation with respect to glycosylation. It is black letter law that courts cannot "read limitations from the specification into the claims." Thorner, 669 F.3d at 1366; see also Markman v. Westview Instruments, Inc., 52 F.3d 967, 980 (Fed. Cir. 1995) (en banc) ("The written description part of the specification itself does not delimit the right to exclude. That is the function and purpose of claims."); Phillips, 415 F.3d at 1319-20 (explaining that it is "one of the cardinal sins of patent law" to "read[] a limitation from the written description into the claims" (internal quotation omitted)). SB provides no basis in either the claim language or the specification for such a glycosylation limitation in '594 claim 5.

SB's construction, moreover, would render meaningless the express glycosylation limitations in the Product Patent claims. As the Federal Circuit has explained, "[i]t is highly disfavored

to construe [claim] terms in a way that renders them void, meaningless, or superfluous," but that is what SB's proposed construction does. Intel Corp. v. Qualcomm Inc., 21 F.4th 801, 810 (Fed. Cir. 2021) (quoting Wasica Fin. GmbH v. Cont'l Auto. Sys., Inc., 853 F.3d 1272, 1288 n.10 (Fed. Cir. 2017)); see Littelfuse, 29 F.4th at 1380. The "VEGF trap" recited in claim 5 of the '594 patent possesses the identical amino acid sequence as that recited in claim 1 of the Product Patent. Compare '594 patent, claim 4 (claiming a "VEGF trap consists of amino acids 27-457 of SEQ ID NO:4," upon which claim 5 depends); with Product Patent, claim 1 ("wherein said VEGF antagonist fusion protein is glycosylated and comprises amino acids 27-457 of SEQ ID NO:4"). Regeneron drafted claim 5 of the '594 patent not to include any glycosylation requirement. By contrast, Regeneron drafted claim 1 of the Product Patent expressly to require glycosylation. See Product Patent, claim 1 ("wherein said VEGF antagonist fusion protein is glycosylated") & claim 14 ("wherein said VEGF antagonist fusion protein is glycosylated at asparagine residues corresponding to asparagine residues 62, 94, 149, 222 and 308 of SEQ ID NO: 4").

The differences in the claims of these related patents indicate that claim 5 of the '594 patent should not be construed

to require glycosylation. Claim terms in related patents must be interpreted consistently. SightSound, 809 F.3d at 1316 ("[W]here multiple patents derive from the same parent application and share many common terms, we must interpret the claims consistently across all asserted patents." (internal quotation omitted)). Doing so here, under SB's construction, would render both the "is glycosylated" limitation of claim 1 (required by all asserted Product Patent claims) and the entirety of claim 14 (which requires glycosylation at specified sites) nullities—a "highly disfavored" result. Intel, 21 F.4th at 810.

Further, SB's proposed construction, which requires that the claimed aflibercept is necessarily glycosylated, contradicts undisputed evidence that aflibercept is not necessarily glycosylated. Neither '594 claim 5 nor the Asserted Product Patent Claims limit the type of cell that may be used to produce the claimed protein. As explained by experts on both sides, aflibercept (having the amino acid sequence 27-457 of SEQ ID NO:4 set forth in the Product Patent) can be produced from different cells, only some of which result in glycosylation of aflibercept. See Trout Decl. ¶¶ 107, 380 (explaining if *E. Coli* cells are used to produce aflibercept, then the resulting aflibercept would not be glycosylated); id. ¶ 381 (stating that producing aflibercept in

a CHO cell "would not inevitably result in glycosylated aflibercept"); Tessier Tr. 138:15-21 (agreeing that Daly, a prior art reference, disclosed that glycosylation can be eliminated by producing a protein in mutant CHO cell lines). Thus, contrary to the implication of SB's construction, both side's experts agree that aflibercept is not necessarily glycosylated. That conclusion is consistent with the prior art reference Daly (U.S. Patent Application Publication 2006/0058234), which explains that mutant CHO cell lines can eliminate glycosylation in a VEGF antagonist fusion protein. Daly ¶ 38 (ECF No. 118-10, Trout Ex. 61). It is also consistent with this Court's identical finding in the Mylan post-trial decision. Mylan, 2024 WL 382495, at *55 ("[E]ven if a protein contains amino acid sequences that may be glycosylated, a given protein may not be glycosylated." (citing Dr. Trout's testimony)).

In sum, the Court agrees with Regeneron that "VEGF trap" should not be construed to mean "glycosylated VEGF trap."

b. No motivation to use glycosylated aflibercept.

The second step of an ODP analysis requires comparing the construed reference patent claims with the asserted claims. AbbVie, 764 F.3d at 1374, 1378. As explained above, the parties agree that asserted reference claim 5 of the '594 patent differs

in multiple respects from the asserted claims of the Product Patent. If any of those differences are not obvious or anticipated, SB cannot prove ODP. The Court analyzes each of those differences in turn and concludes that SB is not likely to succeed in proving that the Asserted Product Patent Claims are anticipated or rendered obvious by claim 5 of the '594 patent, thereby foreclosing a finding of ODP. Otsuka Pharm., 678 F.3d at 1298.

The Product Patent's asserted claims, unlike '594 claim 5, recite a "glycosylated" VEGF antagonist. SB argues that it would have been obvious to a POSA to use glycosylated aflibercept and therefore '594 claim 5 renders the asserted claims obvious. The Court disagrees with both of SB's assertions and, based on the present record, finds that this difference between the reference claims and the Asserted Product Patent Claims is not indistinct.

SB argues that '594 claim 5 anticipates the asserted claims of the Product Patent because '594 claim 5 covers a genus that includes only two species, glycosylated and unglycosylated aflibercept. Opp. 6. "It is well established that the disclosure of a genus in the prior art is not necessarily a disclosure of every species that is a member of that genus." Atofina v. Great Lakes Chem. Corp., 441 F.3d 991, 999 (Fed. Cir. 2006). However, "a very small genus can be a disclosure of each species within the

genus." Id. Contrary to SB's assertions, even considering only glycosylation, the genus claimed in '594 claim 5 encompasses more than just two species. Because aflibercept has five distinct glycosylation sites, SB's expert, Dr. Tessier, agreed that there are at least thirty possible glycosylated forms of aflibercept, Tessier Tr. 130:21-131:8, in addition to the nonglycosylated form. This is not a "very small genus" for purposes of a finding of anticipation. Atofina, 441 F.3d at 999.

Moreover, for anticipation, a single reference must not only "disclose all elements of the claim within [its] four corners," but "all elements of a claimed invention **arranged as in the claim**." Net MoneyIN, Inc. v. Verisign, Inc., 545 F.3d 1359, 1369 (Fed. Cir. 2008) (emphasis added) (internal quotation omitted). But in addition to encompassing every glycosylation profile, '594 claim 5 recites a range of pH values from 6.2-6.4, and does not recite the 98% native conformation limitation recited in claim 1. Thus, the POSA would need to select not only a particular glycosylation profile, but also a specific pH value that results in 98% native conformation as recited in the Product Patent claims. But SB has cited no evidence that any other glycosylation profile than the one described in the patent (which may not be considered as prior art, see Eli Lilly, 689 F.3d at 1379-80), or a formulation at a pH

of 6.4, would achieve 98% native conformation. Dr. Tessier clarified that he did not "have an opinion about that sequence without glycosylation at the five sites" and that there was no native conformation data (even in the non-prior-art patent) at pH 6.4. Tessier Tr. 117:12-20, 132:15-20, 133:18-19. Accordingly, SB has not made a showing that the genus recited in '594 claim 5 is "very small" or that it recites every element of claim 1 of the Product Patent "as arranged in the claim," and thus has not shown a substantial question of anticipation. Atofina, 441 F.3d at 999; Net MoneyIN, 545 F.3d at 1369; Mylan, 2024 WL 382495, at *47-48 (rejecting similar anticipation argument).

SB argues that glycosylation would have been obvious because the POSA would have been motivated to use a glycosylated form of aflibercept as recited in the claimed ophthalmic formulations. However, the evidence shows that the POSA would not have been motivated to use glycosylated aflibercept for an ophthalmic formulation.

Obviousness addresses what is, "on balance, desirable," not what is "feasible." Winner Intern. Royalty Corp. v. Wang, 202 F.3d 1340, 1349 (Fed. Cir. 2000); see Orexo AB v. Actavis, 903 F.3d 1265, 1272-73 (Fed. Cir. 2018). The prior art taught that VEGF Trap proteins could be made in CHO cells and glycosylated

(Papadopoulos at 26:5-10 (ECF No. 118-11, Trout Ex. 84)); Tessier Decl. ¶¶ 99-102) or made in *E. coli* or mutant CHO cells and not glycosylated (Trout Decl. ¶ 107; Tessier Tr. 138:15-21; Daly ¶¶ 38, 43). And for an ophthalmic formulation like that claimed in Product Patent, the prior art's teachings would have motivated the POSA against using glycosylated aflibercept. More specifically, the art showed that a POSA would avoid glycosylation because it would increase the size of aflibercept, thereby reducing retinal penetration, and also because it would undesirably increase systemic exposure and the risk of inflammation. Trout Decl. ¶¶ 376-82. First, Daly taught that mini-Traps—substantially smaller VEGF Trap molecules than aflibercept—including a "*smaller*, non-glycosylated mini-trap expressed in *E. coli* . . . has optimized characteristics for local, intravitreal delivery, i.e. a shorter serum half life for faster clearance and minimizing unwanted systemic exposure." Daly ¶¶ 38, 43. As this Court previously found, because aflibercept is larger when glycosylated, the POSA expected reduced retinal penetration and would thus "have sought to use nonglycosylated aflibercept because glycosylation increases size and thus decreases retinal penetration." Mylan, 2024 WL 382495, at *55 (citing Dr. Trout). As the Court has previously recognized, numerous prior art references taught that

larger molecules would have inferior retinal penetration. Id. at *14, 54 (citing Gaudreault, Jackson, Ghate); Ghate at 281 (ECF No. 118-8, Trout Ex. 26) (the retina's "internal limiting membrane" was "impermeable to . . . globular molecules > 70 kDa"); Jackson at 2141 (ECF No. 118-8, Trout Ex. 28) ("The [retinal exclusion limit] in human tissue was 76.5 ± 1.5 kDa."); Gaudreault at 726, 731 (ECF No. 118-8, Trout Ex. 24) ("[P]enetration of ranibizumab into the retina is critical for its clinical use" and ranibizumab's "ability [to penetrate the retina] has been attributed to [its] small molecule size."). Regeneron cites the same prior-art evidence here. Trout Decl. ¶¶ 308, 364, 377. Consistent with its prior decision in the Mylan case, the Court finds here that the POSA would have been motivated to avoid increasing the molecular size of aflibercept by using its glycosylated form.

The Court has considered the Rosenfeld reference (ECF No. 164-62, Tessier Ex. 18), where researchers investigated in early clinical studies the use of intravitreal bevacizumab, a molecule with a larger molecular weight than aflibercept. However, a reference introduced by Regeneron, Ferrara 2006 (ECF No. 118-8, Trout Ex. 21), comprehensively reviewed the ranibizumab, bevacizumab, and VEGF Trap literature, including Rosenfeld's research, and reported "skepticism specifically directed at

intravitreal compositions comprising high molecular weight proteins such as VEGF Trap fusion proteins." Mylan, 2024 WL 382495, at *60; Trout Decl. ¶¶ 308, 364, 377; Ferrara 2006 at 862-63. Ferrara 2006 specifically cautioned against overreliance on the early findings reported in Rosenfeld, explaining that "[a]lthough intriguing, these early findings are difficult to compare with data from rigorous, double-masked, controlled phase 3 trials of verteporfin photodynamic therapy, pegaptanib, and, more recently, ranibizumab." Ferrara 2006 at 866. Ferrara 2006 observed that "it is noteworthy that initial, uncontrolled phase 1 or 2 studies with pegaptanib or verteporfin photodynamic therapy suggested a considerably greater benefit in AMD patients than that eventually demonstrated in randomized phase 3 studies, further emphasizing the difficulty of interpreting early clinical results." Id. Thus, Rosenfeld does not overcome the repeated teachings in the prior art motivating the POSA against using a larger molecule for an ophthalmic formulation, which would have dissuaded the POSA from using glycosylated aflibercept. See Henny Penny Corp. v. Frymaster LLC, 938 F.3d 1324, 1331-32 (Fed. Cir. 2019) (the cited prior art "must be considered for all its teachings, not selectively").

Second, SB argues that the pharmacokinetics of glycosylated

aflibercept would motivate a POSA to use glycosylated aflibercept. Opp. 8-9. That argument also runs contrary to the prior art's teachings. The pharmacokinetics of glycosylated aflibercept that provide a longer half-life were only disclosed as favorable to treat *cancer*, by "extend[ing] *in vivo* half life" in the bloodstream. Holash at 11393-94 (ECF No. 118-8, Trout Ex. 27); Trout Decl. ¶ 379. By contrast, the prior art relating both to VEGF Traps and ranibizumab taught that, for *ophthalmic* use, "*shorter* serum half life" was desirable. Daly ¶ 43 (emphasis added); see also Mylan, 2024 WL 382495, at *6; Gaudreault at 731 ("The low circulating concentrations of ranibizumab after [intravitreal] administration may be important in the clinical setting, because VEGF is necessary for normal physiological functions such as tissue repair and reproduction."). Both Regeneron's and SB's expert witnesses agree that glycosylation lengthens serum half-life in the bloodstream. Trout Decl. ¶ 379, Tessier Tr. 198:7-14. Thus, the Court finds that the prior art would motivate a POSA against using glycosylated aflibercept in formulations for ophthalmic use.

The Court notes that its finding in Mylan that a longer half-life was advantageous since it allowed for smaller doses and less-frequent dosing, Mylan, 2024 WL 382495, at *59, was based on

Regeneron's discovery that Eylea's long half-life unexpectedly facilitated extended dosing, *not* on any document that could properly be considered prior art in the obviousness analysis, see 35 U.S.C. § 103(a) ("Patentability shall not be negatived by the manner in which the invention was made."); Otsuka Pharm., 678 F.3d at 1296 ("The inventor's own path itself never leads to a conclusion of obviousness; that is hindsight."). Indeed, this Court previously explained that "the law does not require the inventors to have appreciated that the Eylea composition they invented would become the success it is; 'understanding of the full range of an invention is not always achieved at the time of filing the patent application,' and unexpected properties need not be appreciated at the time of the invention." Mylan, 2024 WL 382495, at *60 (quoting Knoll Pharm. Co. v. Teva Pharm. USA, Inc., 367 F.3d 1381, 1384-85 (Fed. Cir. 2004)).

Third, SB argues that glycosylation may contribute to binding affinity, see Opp. 8 (citing Tessier Decl. ¶¶ 235-245), but it cites no art to directly support this assumption. Daly taught that "[a]ffinity measurements showed that the non-glycosylated fusion polypeptides expressed in E. coli or the glycosylated polypeptides expressed in CHO cells had comparable binding affinity for VEGF as the full-sized parent trap." Daly ¶ 63. Dr.

Trout examined this data, which was the only data comparing glycosylated and nonglycosylated VEGF traps, and came to the unrebutted conclusion that glycosylated and nonglycosylated aflibercept have comparable affinity. Trout Decl. ¶ 377. Dr. Tessier offered no contrary testimony and did not address these data. So, a POSA would not have been motivated to use glycosylated aflibercept on the basis of its comparative binding affinity.

Fourth, Dr. Tessier explained that glycosylation of aflibercept's "Fc" portion activates "effector functions," including immune-mediated toxicities. Tessier Decl. ¶ 101 ("[G]lycosylation of the Fc region is important for IgG and Fc-fusion protein binding to FcgRs, which results in various effector functions, such as antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC)."); Tessier Tr. 148:17-22; *cf.* Trout Decl. ¶¶ 362-63. In the context of ophthalmic use, Daly taught that the "Fc" portion "may be modified to reduce effector functions," by "eliminat[ing] glycosylation." Daly ¶ 38. Dr. Tessier did not dispute that, for ophthalmic use, an immune response via glycosylation is undesirable, but did "not believe" this concern "would outweigh the benefits of using a glycosylated molecule." Tessier Tr. 155:18-156:10, 169:22-170:12. Dr. Tessier is not a physician, and he did not consult a physician to arrive

at his conclusion. Id. 170:7-12, 171:4-6 (agreeing that "it would be logical to discuss with a medical professional" risks of effector functions). As such, the Court does not credit Dr. Tessier's testimony on this point. It is also inconsistent with this Court's prior finding in its obviousness analysis that "'moderate to severe' inflammation was an extremely concerning phenomenon for any intravitreal drug product to exhibit." Mylan, 2024 WL 382495, at *52. These immunological concerns would further motivate the POSA against using glycosylated aflibercept.

Finally, SB cites argument from Dr. Tessier that that the POSA would have used glycosylated aflibercept for stability reasons. Opp. 8 (citing Tessier Decl. ¶¶ 235-245). However, Dr. Tessier identified no prior art that compared the stability of glycosylated and nonglycosylated aflibercept. Tessier Tr. 205:3-19. Moreover, SB has not produced any prior art that teaches that glycosylation improves aflibercept's stability in the presence of a stabilizing agent and organic co-solvent, as required by '594 claim 5. *Id.* 202:10-205:19. Further, '594 claim 5 depends from claim 3, which recites that "the VEGF trap is stable for at least 4 months" irrespective of glycosylation. SB fails to provide a persuasive reason why stability concerns would motivate the POSA, beginning with a stable formulation from claim 5 of the '594

patent, to glycosylate aflibercept.

Taken together, the evidence decisively points against a motivation to glycosylate the VEGF trap claimed in ’594 claim 5. Thus, it would not have been obvious to the POSA to modify ’594 claim 5 to arrive at the asserted claims of the Product Patent.

c. The Product Patent’s “98% native conformation” claim limitation is not inherent in claim 5 of the ’594 patent

Another difference between the asserted claims of the Product Patent and ’594 claim 5 is that the former requires “at least 98% [or 99%, in claim 16] of the VEGF antagonist is present in native conformation following storage at 5° C. for two months as measured by size exclusion chromatography” whereas the latter recites that “the VEGF trap is stable for at least 4 months.” As explained below, the Court concludes that the 98% native conformation claim limitation is not inherent in the subject matter claimed in ’594 claim 5.

A missing claim limitation can be met for purposes of anticipation or obviousness by showing that the limitation is inherent in the reference claim. See PAR Pharm., 773 F.3d at 1194-95. An inherent limitation, however, must be “necessarily present,” Apotex, 754 F.3d at 960, and “may not be established by probabilities or possibilities,” Mylan, 2024 WL 382495, at *55

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(quoting PAR Pharm., 773 F.3d at 1194). And in the context of obviousness in particular, the Federal Circuit has explained that the role of inherency is limited: "the use of inherency in the context of obviousness must be carefully circumscribed because '[t]hat which may be inherent is not necessarily known' and that which is unknown cannot be obvious." Honeywell, 865 F.3d at 1354 (quoting Rijckaert, 9 F.3d at 1534). Thus, in order for the 98% native conformation claim limitation to be inherent in '594 claim 5, '594 claim 5 must necessarily and always meet the Product Patent's 98% native conformation claim limitation. Apotex, 754 F.3d at 960; Glaxo Inc., 52 F.3d at 1047.

Neither '594 claim 5 nor the shared specification of the '594 patent and the Product Patent discloses that a "stable" ophthalmic formulation within '594 claim 5 necessarily has 98% native conformation. As described above, the patent describes that the "fusion protein is preferably substantially free of aggregates . . . [which] means that **at least 90%** of the weight of fusion protein **is not present in an aggregate** at the time the fusion protein is used to prepare the pharmaceutically effective formulation." Product Patent, 6:50-55 (emphasis added). As Dr. Tessier agreed, the patent thus teaches preparing a preferred formulation that has at least 90% protein in non-aggregated form.

Tessier Tr. 35:20-36:14. And because there is no dispute that the level of aggregation would not decrease after "the time the fusion protein is used to prepare the . . . formulation" (as described further below), a "stable" ophthalmic formulation does not necessarily possess 98% native conformation as measured by size exclusion chromatography after two months storage. See Apotex, 754 F.3d at 960-61 (finding no inherency when the claimed property is sometimes, but not always, present in the anticipating reference); PAR Pharm., 773 F.3d at 1195-96 (noting the same rule applies to an obviousness reference). This disclosure from the patents' common specification, together with the admission from SB's expert, is sufficient for the Court to find that the 98% native conformation limitation is not inherent in the subject matter of '594 claim 5.

In its opposition to Regeneron's preliminary injunction motion, SB relied on internal Regeneron data as evidence of inherency.[9] In response, Regeneron pointed to other internal data showing that a specific aflibercept formulation did not have 98% native conformation even at time zero and before storage, and

[9] The parties do not dispute that such data may be considered in evaluating inherency. See Hospira, Inc. v. Fresenius Kabi USA, LLC, 946 F.3d 1322, 1329-30 (Fed. Cir. 2020).

therefore would not meet the Product Patent claim limitation requiring at least 98% native conformation as measured by SEC after 2 months. Although not necessary to the Court's finding, this "SS195" data confirms that the 98% native conformation limitation is not inherent in '594 claim 5. See Reply 7; Graham Decl. ¶ 11; SS-195 Stability Data (ECF No. 113-3, Trout Ex. 106 (corrected)). The SS195 data corresponds to an internal stability study performed by Regeneron on a formulation that falls within the scope of '594 claim 5 (40 mg/mL of aflibercept, 10 mM phosphate, 0.03% polysorbate 20, 5% sucrose, and 40 mM NaCl at pH 6.25), a fact that SB does not dispute. See Tessier Tr. 84:4-6 (agreeing that '594 claim 5 is not limited to any particular lot of aflibercept); Graham Decl. ¶ 10. The formulation tested in the SS195 study possessed less than 98% native conformation by SEC even at time zero, before any storage. Graham Decl. ¶ 11 (showing percent native conformation at time zero of 97.3, 97.7, and values in between); SS-195 Stability Data. This data comports with the common disclosure in the Product Patent and the '594 patent stating that "preferably . . . at least 90% of the weight of fusion protein is not present in an aggregate at the time the fusion protein is used to prepare the pharmaceutically effective formulation." Product Patent, 6:50-55. And it also demonstrates that not every

formulation falling within the scope of '594 claim 5 "necessarily" achieves 98% native conformation, as required for a finding of inherency. See Glaxo, 52 F.3d at 1047-48; PAR Pharm., 773 F.3d at 1195-96.

In SB's reply in support of its motion to strike Dr. Graham's testimony, SB argues that the SS195 composition is not within '594 claim 5 because the study does not report 4-month storage data and thus has not been proven to meet the "stable" limitation. Reply re Mot. to Strike at 1-2 (No. 24-md-3103, ECF No. 41). That is inconsistent with SB's prior argument that the 98% native conformation limitation is inherent based on the specification's disclosure, which also does not contain 4-month data for Examples 3 and 4 on which SB relies. Opp. 9-10. Regardless, as the Court described above, "stable" as required in '594 claim 5 is a lower requirement than the 98% native conformation limitation in the Product Patent, and SB bears the burden on invalidity and inherency. BlephEx, 24 F.4th at 1399. The data in SS195 demonstrates that formulations containing the structures recited in '594 claim 5 do not necessarily contain 98% native conformation, even before any storage, and nor does "stable" as required in '594 claim 5 require 98% native conformation. The data thus supports that "stable" formulations need not possess 98% native

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conformation, consistent with the patent's teachings.

SB does not dispute that a formulation starting with less than 98% native conformation could not possess 98% native conformation after 2 months' storage. The evidence demonstrates that the process of protein aggregation is irreversible, so that the percent native conformation will be the same or lower after two months' storage, as compared to time zero. SB's expert, Dr. Tessier, did not dispute this proposition, Tessier Tr. 31:16-32:9; and in fact he relied upon it in his declaration, Tessier Decl. ¶ 52 n.2 ("[D]ata for 1 and 3 months of 99.2 and 99.1 % monomer, respectively, would imply that at 2 months, the % monomer would be between these values."). Regeneron's expert, Dr. Trout, likewise explained that aggregation is irreversible. Trout Decl. App. A ¶ 61 ("[I]f the percentage native conformation is greater than 98% at 3 months, then it must necessarily have been greater than 98% after 2 months."). This finding is consistent with the Court's prior finding that the process of aggregation is irreversible. Mylan, 2024 WL 382495, at *32. Thus, because the SS195 data, consistent with the '594 and Product Patent specification, demonstrates that a formulation falling within the scope of '594 claim 5 can have less than 98% native conformation by SEC at time zero, it also demonstrates that a formulation falling within the

scope of '594 claim 5 can have less than 98% native conformation by SEC following storage for 2 months at 5°C. These data confirm the Court's finding that the 98% native conformation limitation of the Product Patent claims is not inherent in '594 claim 5, because formulations falling within the scope of '594 claim 5 do not necessarily meet the at least 98% native conformation claim limitation. Glaxo, 52 F.3d at 1047-48; PAR Pharm., 773 F.3d at 1195-96.

SB points to other data, from Examples 3 and 4 of the '594 patent, in which a composition falling within the scope of '594 claim 5 exhibited at least 98% native conformation. Opp. 9-10. As an initial matter, SB incorrectly equates Examples 3 and 4 with '594 claim 5. Opp. 10. Examples 3 and 4, as well as Eylea itself, are specific compositions that are not prior art. See Eli Lilly, 689 F.3d at 1380 (explaining that the "double patenting analysis . . . turns on an evaluation of what [the patentee] has claimed, not what it has disclosed" and requires "[p]utting aside the teachings in the [] patent's specification"). There is no dispute that Eylea was not sold until well after the 2006 priority date of the Product Patent and is not prior art. And while these Examples (and Eylea) are embodiments of '594 claim 5, that claim is not limited to those embodiments. To the contrary, "although

the specification often describes very specific embodiments of the invention, [the Federal Circuit] ha[s] repeatedly warned against confining the claims to those embodiments." Phillips, 415 F.3d at 1319-20. Notably, '594 claim 5 is not limited to any lot of aflibercept, or any particular glycosylation pattern of aflibercept, and recites a range of pH values, and SB has failed to present persuasive evidence how or why the POSA would be motivated to obtain the specific examples in the patent specification or Eylea, which are not prior art.

For example, '594 claim 5 recites a pH range of "pH 6.2-6.4," whereas Examples 3 and 4 are limited to "pH 6.3." Compare '594 Patent at claim 5 with id. at 8:55-63, 9:15-24. SB's own expert could not identify a reason that the POSA would select the pH of 6.3 recited in Examples 3 and 4 from the broader genus of pH 6.2-6.4 that is recited in '594 claim 5. Tessier Tr. 116:5-11. Thus, although Examples 3 and 4 both meet the 98% native conformation limitation, both examples are limited to formulations having a pH of 6.3; these examples do not correspond to formulations with "pH 6.2-6.4" as recited in '594 claim 5. SB cites no percent native conformation data for formulations at pH 6.4 and provides no evidence that a '594 claim 5 formulation at pH 6.4 necessarily has 98% native conformation. Nor does SB identify a reason why the

POSA practicing '594 claim 5 would select any particular pH within the claimed range or exclude formulations at pH 6.4, which is expressly recited in '594 claim 5. Dr. Tessier admitted that he did not "consider the pH sensitivity of aflibercept as part of this matter." Id., 117:21-118:7. Dr. Tessier also refused repeatedly to testify that practice of '594 claim 5 at pH 6.4 necessarily would have 98% native conformation, asserting instead that he had no reason to doubt that it would. Id., 118:8-124:21. This probabilistic evidence cannot prove inherency. Apotex, 754 F.3d at 960-61.

Because the pH of 6.3 in the patent's examples is not prior art, it cannot be relied upon for obviousness — both because "[o]bviousness cannot be predicated on what is unknown," In re Rijckaert, 9 F.3d at 1534, and because the '594 patent's specification "does not qualify as prior art" in ODP, Eli Lilly, 689 F.3d at 1379. Without any **prior art** basis to select the pH in the examples to meet the Product Patent claims, SB's ODP defense fails. In re Kaplan, 789 F.2d 1574, 1580 (Fed. Cir. 1986).

In any event, SB's reliance on the native conformation data in Examples 3 and 4 is legally inadequate to prove inherency. That the practice of '594 claim 5 **sometimes** results in 98% native conformation is insufficient; inherency requires that the 98%

native conformation limitation be present **necessarily**, not just possibly or probably. The Federal Circuit's Glaxo v. Novopharm precedent is instructive. Glaxo, 52 F.3d at 1043. There, the patent challenger argued that a claimed crystal was inherent from a prior art process because "experts performed the process disclosed in [the prior art] thirteen times and each time they made" the claimed crystal ("Form 2"). Id. at 1047. But the Court held that was not sufficient to show inherency because two other times the prior art process was performed, and the claimed crystal did not form. Id. at 1047-48 ("Glaxo's David Collin originally made Form 1 by practicing [the prior art process], and . . . Glaxo's expert, Nicholas Crouch, did too."); see also Apotex, 754 F.3d at 960-61 (finding no inherent anticipation when "it was at least **possible**" to perform the prior art process in a way that does not result in the asserted claim) (emphasis in original); PersonalWeb Techs., LLC v. Apple, Inc., 917 F.3d 1376, 1382 (Fed. Cir. 2019) ("[M]ere possibility is not enough" for inherency). The facts of Glaxo are materially indistinguishable from the ones here, as the evidence demonstrates that '594 claim 5 compositions may well achieve the 98% native conformation limitation (as in Example 4 of the patent) but they also may not (as in SS195) and the formulations referenced in the specification

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having 90% or less than 90% protein in non-aggregate form at the time of preparation), and in other instances there is simply no evidence one way or the other whether compositions would necessarily achieve 98% native conformation (as with a pH of 6.4). The same result as Glaxo thus applies here as well: 98% native conformation as claimed in the Product Patent is not inherent.

The Court has also considered the Federal Circuit's decision in Hospira, Inc. v. Fresenius Kabi USA, LLC, 946 F.3d 1322 (Fed. Cir. 2020), and concludes that it does not support a finding of inherency. There, the Federal Circuit upheld an enablement finding where it "relied on fact and expert testimony regarding the stability data for more than 20 tested samples . . . , all of which met the [claim limitation]." Id. at 1327, 1330-31. Here, in contrast, all of the formulations within the scope of the reference claim do not meet the 98% native conformation limitation, as demonstrated by both the specification itself and the internal Regeneron data. SB therefore has failed to establish evidence that compositions within claim 5 necessarily possess the 98% native conformation limitation.

Finally, the Court notes that a patent challenger like SB who argues invalidity on a basis already addressed during prosecution bears "the added burden of overcoming the deference that is due to

a qualified government agency presumed to have properly done its job." PowerOasis, Inc. v. T-Mobile USA, Inc., 522 F.3d 1299, 1304 (Fed. Cir. 2008) (internal quotation omitted). The Court's conclusion that the 98% native conformation claim limitation is not inherent in the subject matter claimed in '594 claim 5 is consistent with the Examiner's prior determination of this issue, and SB has not met its burden of demonstrating a substantial question of invalidity.

The Court further notes that patent office issued interim decisions as to a related patent, U.S. Patent 10,464,992 (ECF No. 108-11, Trout Ex. 64), to institute reexamination and inter partes review. See Celltrion, Inc. v. Regeneron Pharm., Inc., 2023 WL 5166828 (P.T.A.B. July 20, 2023). It is undisputed that Regeneron later disclaimed the '992 patent. However, Regeneron does not assert the '992 patent here and the Court does not find that the interim patent office decisions as to the '992 patent undermine the Product Patent asserted here. Notably, the '992 patent claims do not require 40 mg/mL of aflibercept and are silent as to whether aflibercept is glycosylated. The significant differences in the scope of the '992 patent and Product Patent claims and the preliminary nature of the decisions render them at most tangentially relevant and insufficient to support inherency or

undermine the Examiner's conclusions regarding the Product Patent.

For all of these reasons, the Court finds that the 98% native conformation limitation of the Product Patent claims is not inherent in '594 claim 5.

SB also argues that even if not inherent, the 98% native conformation limitation would have been obvious. Opp. 10. But regardless, Dr. Trout has provided testimony that the POSA beginning with claim 5 of the '594 patent would not have been motivated to achieve the 98% native conformation limitation and would not have had a reasonable expectation of achieving that level of native conformation after two-months' storage. Trout Decl. ¶¶ 339-40, 385-87, 390. SB did not rebut that evidence. Dr. Trout further explained that no prior art relied on by SB teaches native conformation levels of aflibercept (Trout Decl. ¶¶ 339-40), that the POSA would not have been motivated to obtain such a high level of native conformation as lower levels would have been considered acceptable (Trout Decl. ¶¶ 385-87), and that even if the POSA did possess such motivation, the POSA would not have reasonably expected to obtain 98% native conformation after two-months' storage given the absence of any relevant prior art teachings as to aflibercept's stability, Trout Decl. ¶¶ 339-40, 390; see Mylan, 2024 WL 382495, at *56 ("Dr. Trout explained that because fusion

proteins are synthetic 'Frankenstein' molecules that, unlike antibodies, did not evolve to possess inherent stability, the POSA would expect fusion proteins like aflibercept to have lower stability than antibodies . . . ."). There does not appear to be any dispute that "[j]ust because one protein has a given native conformation at a specific condition, the [POSA] wouldn't expect that a different protein will have the same native conformation at that condition," consistent with the Court's prior finding. Mylan, 2024 WL 382495, at *56 (alternations in original) (emphasis removed). The Court thus credits Dr. Trout's testimony that the 98% native conformation limitation would not have been obvious. SB's generic argument that the POSA would have sought to purify aflibercept fails to present a substantial question of invalidity.

d. SB's motion to strike portions of Regeneron's reply brief and the Graham declarations

By separate Order, the Court denied SB's Motion to Strike with respect to portions of Regeneron's reply brief and the Graham declaration. The Court incorporates the findings of that Order here.

Even if SB's motion to strike were granted, however, the Court would reach the same conclusion that the 98% limitation in not inherent in '594 claim 5. SB had the burden to present a

substantial question of ODP based on its assertion that the 98% limitation is inherent in '594 claim 5, BlephEx, 24 F.4th at 1399, contrary to the Examiner's finding. Trout Decl. ¶ 235. The SS195 formulation and data were in the record independent of Regeneron's reply brief or the Graham declaration. Trout Decl. ¶ 235. While SB focuses exclusively on the internal data where a '594 claim 5 formulation met the 98% limitation, the Court may not cherrypick that data while ignoring the same type of data in SS195 for a formulation that did not achieve 98% native conformation. See Glaxo, 52 F.3d at 1047-48.

Even were the data from SS195 not considered, SB still does not present a substantial question that '594 claim 5 necessarily meets the 98% native conformation limitation. As discussed above, SB's reliance on limited examples from the patent specification that meet the 98% native conformation limitation is not sufficient to show that practicing '594 claim 5 results in the 98% native conformation limitation being met each and every time, as inherency requires. The patent specification makes clear that less than 98% native conformation is acceptable, and in fact preferable, for the "stable" formulation of '594 claim 5. See Product Patent, 6:50-55 ("[The] fusion protein is preferably substantially free of aggregates . . . [which] means that at least 90% of the weight of

fusion protein is not present in an aggregate at the time the fusion protein is used to prepare the pharmaceutically effective formulation."). And as discussed above, SB provides no evidence that a '594 claim 5 formulation at pH 6.4 and irrespective of glycosylation necessarily has 98% native conformation. Thus, SB's inherency argument does not raise a substantial question of validity as to any asserted claim of the Product Patent.

e. No motivation to change a PFS to a vial.

SB argues that a POSA would be motivated to replace the pre-filled syringe (PFS) of '594 claim 5 with the vial recited in asserted claims 4, 7, 9, 11, and 14-17 of the Product Patent. Opp. 10. Here too, SB does not meet its burden to show a substantial question of validity.

As stated previously, obviousness addresses what is, "on balance, desirable," not what is "feasible," Winner, 202 F.3d at 1349; Orexo AB, 903 F.3d at 1272-73. The evidence need not rise to the level of teaching away to defeat the showing of motivation to modify the claim. Arctic Cat Inc. v. Bombardier Recreational Prods. Inc., 876 F.3d 1350, 1363 (Fed. Cir. 2017). SB cites evidence that the prior art disclosed that biologic products were available in vials. Opp. 10 (citing Tessier Decl. ¶¶ 226). However, merely showing that a modification is possible does not

show that such a modification is desirable and is thus insufficient to prove obviousness. SB also argues that the FDA's 1999 Container Closure Guidance "recommends that injectable formulations be packing in vials" and that "[v]ials are less complicated to develop and more likely to provide a stable formulation because a PFS has more surfaces that can interact with solution and cause problems such as aggregation." Opp. 10-11. However, as Dr. Trout notes, '594 claim 5 already specifies that the formulation is stable, so stability concerns would not have motivated a POSA to replace the PFS with a vial. Trout Decl. ¶ 395. Dr. Trout further cited the prior art's teaching that the "most preferred" dosage form for a therapeutic protein product was "a solution formulation that is typically stored in the refrigerator and preferably in a pre-filled syringe." Trout Decl. ¶ 393 (citing Trout Ex. 40 (Nayar 2002) at 183-184). Dr. Tessier did not dispute this or address the teaching in Nayar 2002. Thus, SB has not presented sufficient evidence to raise a substantial question of ODP based on the POSA's motivation to modify the PFS of '594 claim 5 to the vial claimed in the Product Patent, and thus has not raised a substantial question that the vial recited in asserted claims 4, 7, 9, 11, and 14-17 of the Product Patent is obvious over the PFS of '594 claim 5.

f. Objective evidence supports nonobviousness

Objective evidence must be considered before concluding that a claim is obvious. In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Pat. Litig., 676 F.3d 1063, 1079 (Fed. Cir. 2012). Objective evidence supports the Court's holding that SB has failed to raise a substantial question that the asserted claims of the Product Patent are obvious over '594 claim 5. Dr. Trout explained in his declaration that "[t]here was significant industry skepticism both towards VEGF Trap molecules and using VEGF Trap molecules in the eye," "[t]he efficacy of EYLEA as an intravitreal injection demonstrated unexpected properties," and that "evidence of copying supports the nonobviousness of the [Product Patent's] Asserted claims." Trout Decl. ¶ 361-69, 416. The Court credits Dr. Trout's opinion, relying on the same evidence addressed at Mylan, and concludes, as in Mylan, that objective evidence strongly supports nonobviousness here as well. See Mylan, 2024 WL 382495, at *59-60.

The Federal Circuit has held that objective evidence may be "probative of nonobviousness even if it was not precisely limited to the point of novelty of the claimed combination." Henny Penny, 938 F.3d at 1334. While "the identified objective indicia must be directed to what was not known in the prior art, . . . 'what was

not known in the prior art ... may well be the novel combination or arrangement of known individual elements.'" Id. at 1333 (quoting Novartis AG v. Torrent Pharm. Ltd., 853 F.3d 1316, 1331 (Fed. Cir. 2017)). Dr. Trout explained, and the parties do not appear to dispute, that Eylea is an embodiment of the asserted claims. Accordingly, "there is a presumption of nexus for objective considerations when the patentee shows that the asserted objective evidence is tied to a specific product and that product is the invention disclosed and claimed in the patent." WBIP, 829 F.3d at 1329 (internal quotation omitted); see also Immunex Corp. v. Sandoz Inc., 964 F.3d 1049, 1067 (Fed. Cir. 2020) ("Nexus is appropriately presumed in this case where the court concluded that the claims are directed to the active ingredient in [the patentee's biologic product] and its method of manufacture."). Nexus can be presumed in this case because Regeneron has shown that the objective evidence is tied to Eylea and Eylea is an embodiment of the asserted claims in the Product Patent.

Moreover, even if the specific differences between the claims of the Product Patent and '594 claim 5 were relevant, the Court still finds that the objective evidence would weigh in favor of nonobviousness. Unlike the claims of the '594 patent, the Product Patent claims require that aflibercept is glycosylated (as in

Eylea) and that the composition meets the 98% native conformation limitation. As this Court found in Mylan, and as the current record reflects, "the stability of the claimed compositions, including the required 98% native conformation, indicated to the POSA that the 'there's a relatively lower risk of inflammation'" as compared to a formulation with lower native conformation (and thus more protein aggregates). Mylan, 2024 WL 382495, at *60; Trout Decl. ¶ 369.

Even without objective evidence of nonobviousness, the Court would find that SB has not raised a substantial question that the Product Patent is invalid for ODP. See AstraZeneca AB v. Aurobindo Pharma Ltd., 232 F. Supp. 3d 636, 649 n.8 (D. Del. 2017) ("Because Aurobindo has failed to establish a prima facie case of obviousness, the court does not address AstraZeneca's secondary considerations."); Takeda Pharm. Co. v. Handa Pharm., 2013 WL 9853725, at *66 (N.D. Cal. Oct. 17, 2013) ("[T]he absence of secondary considerations does not prove obviousness."). Nevertheless, as explained, the available objective evidence, taken together with the other evidence of record, supports the Court's conclusion that SB has failed to raise a substantial question that the asserted claims of the Product Patent are obvious over '594 claim 5.

g. Written Description

SB argues that the Product Patent's asserted claims are invalid for lack of written description because the claim language "at least 98% . . . native conformation following storage at 5° C. for two months" denotes a range of 98%-100%, but the specification discloses two relevant percent native conformations: 99.1% and 99.2%. Opp. 11. The Court disagrees and concludes that SB fails to demonstrate a substantial question of invalidity based on lack of written description. This holding is consistent with the Court's holding in Mylan. See Mylan, 2024 WL 382495, at *64, 66 (crediting Dr. Trout's analysis and conclusion that "all of the Product Patent's examples have 'at least 98 percent native conformation as measured by SEC after two months'" and that the Product Patent provided "adequate written description for the asserted claims").

The specification need not describe "every conceivable and possible future embodiment of [the] invention." Cordis Corp., 339 F.3d at 1365. Open-ended claims, such as the "at least" claim here, "may be supported if there is an inherent, albeit not precisely known, upper limit and the specification enables one of skill in the art to approach that limit." Andersen Corp. v. Fiber Composites, LLC, 474 F.3d 1361, 1376-77 (Fed. Cir. 2007) (quoting

Scripps Clinic & Research Found. v. Genentech, Inc., 927 F.2d 1565, 1572 (Fed. Cir. 1991)). "At least" claims are ubiquitous in pharmaceutical patents.[10] SB's expert Dr. Tessier stated that the absolute upper limit of the "at least" limitation at issue here is, at most, 100%. See Tessier ¶ 339 ("[I]n my opinion, the language 'at least' denotes a range starting at the recited value and going as high as 100%"). Dr. Tessier also testified that practically, "most proteins are not purified to [100%]." Tessier Tr. 210:21-22. Thus, the maximum percent native conformation "would be limited by what a person skilled in the art would understand to be workable," which here would be somewhat less than

[10] Patents with "at least" claims related to purity have frequently been litigated without a finding that the patent is invalid or requiring examples that reach 100% purity. See Glaxo Grp. Ltd. v. Apotex, Inc., 376 F.3d 1339, 1343 (Fed. Cir. 2004) ("Cefuroxime axetil in amorphous form essentially free from crystalline material, and having a purity of at least 95% aside from residual solvents."); Cipla Ltd. v. Sunovion Pharms. Inc., 174 F. Supp. 3d 869, 871 (D. Del. 2016) ("[p]ure and isolated Levalbuterol L-tartrate having an enantiomeric excess of at least 95%"); United Cannabis Corp. v. Pure Hemp Collective Inc., 2019 WL 1651846, at *2 (D. Colo. Apr. 17, 2019) ("[E]very independent claim describes '[a] liquid cannabinoid formulation, wherein at least 95% of the total cannabinoids is' a specified cannabinoid or combination of them."); Mylan Institutional LLC v. Aurobindo Pharma Ltd., 2016 WL 7587325, at *7 (E.D. Tex. 2016) ("A compound N-[4-[[4-(diethyl amino) phenyl] (2,5-disulfophenyl) methylene]-2,5-cyclohexadien-1-ylidene]-N-ethylethanaminium, sodium salt having a purity of at least 99.0% by HPLC.").

100% (the theoretical maximum). Ralston Purina Co. v. Far-Mar-Co., 772 F.2d 1570, 1576 (Fed. Cir. 1985); see also FS.com Inc. v. Int'l Trade Comm., 65 F.4th 1373, 1376 (Fed. Cir. 2023) (finding the inherent upper limit to be the limit of what was technologically feasible). As stated in Andersen, the inherent upper limit need not be precisely known provided it can be shown that an inherent upper limit exists. 474 F.3d at 1376-77.

Open-ended claims, such as the "at least" claim here, need not by supported by an embodiment at that upper limit; the patent need only "enable[] [the POSA] to approach that limit." Anderson, 474 F.3d at 1377. For example, in Anderson, the patent recited an open-ended claim — "a Youngs modulus rating of greater than 500,000." Id. at 1376. At trial, the evidence showed that "the inventors did not obtain results with a modulus value of greater than 1.2 million." Id. However, the Court held that there was adequate written description because "a person of skill in the art would recognize that the upper limit of the Young's modulus of the structural member would lie somewhere between the Young's modulus of the wood fiber and that of the polymer used in the composition." Id. Thus, although the results did not reach the upper limit (which was not numerically defined), the Court held that written description was satisfied because the disclosure allowed the POSA

"to approach that limit." Id. The Federal Circuit's other relevant precedent is consistent. For example, in Nalpropion Pharms. v. Actavis Labs. FL, Inc., the claims recited "at least 99%" dissolution within a certain time, and the Federal Circuit upheld written description despite citing no results between 99-100%. 934 F.3d at 1349, 1351; see also Ralston Purina, 772 F.2d at 1576 (Fed. Cir. 1985) (finding written description support for claims of "at least 25% by weight" despite no disclosure of 100% by weight); FS.com, 65 F.4th at 1375-77 ("at least [98] fiber optic connections per U space" enabled despite no disclosures between 98 and upper limit of 144 connections per U space).

Under the Federal Circuit's standard, the Court finds that the Product Patent's specification amply supports the claim reciting "at least 98%" native conformation. In his declaration, Dr. Trout explained that the Product Patent includes eight examples representative of the genus, each of which "achieved 98% or greater native conformation over two months storage as measured by size exclusion chromatography." Trout Decl. ¶¶ 450-51. More specifically, the results in the patent show between 98.5 and 99.2% native conformation for the liquid formulations tested after storage for 2-3 months. Id.; Product Patent, Tables 1-6. This led Dr. Trout to the conclusion that "the specification teaches

the POSA representative formulations with the claimed elements and possession of the claimed genus." Trout Decl. ¶ 451. The Court credits Dr. Trout's analysis and conclusion, as it did in Mylan. Mylan, 2024 WL 382495, at *64. The Product Patent's multiple disclosures of native conformations less than 1% shy of 100% (the absolute upper limit for the claim term, which "in general" is not met for proteins, Tessier Tr. 210:4-211:2) meets the Federal Circuit's standard. See Product Patent Table 3 (99.2% native conformation at two months), Table 4 (99.1% native conformation at two months); Andersen, 474 F.3d at 1377.

Indivior UK Ltd. v. Dr. Reddy's Labs. S.A., 18 F.4th 1323 (Fed. Cir. 2021), the case SB relies on, is inapposite. In Indivior UK Ltd., the patent claimed a range of "about 40 wt % to about 60 wt %," but the specification disclosed neither endpoint. 18 F.4th at 1328. The only disclosures in the specification that explicitly fell within the claimed range were a disclosure of "at least 25%", which the Court notes is "quite out of the [claimed] range," and a disclosure of "at least 50%," which the Court found to be "hardly clear support in light of other inconsistent language." Id. at 1329. The Court also rejected the post hoc attempt to "select several components [in the example tables], add up the individual values, determine the aggregate percentages, and

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then couple those aggregate percentages with other examples" to arrive at the claimed range. Id. at 1329. But no such post-hoc rationalization is necessary here: the Product Patent claims "at least 98%" native conformation, and 98% is simply the highest whole number achieved in each example (all of which met the claim limitation).

The Court has also considered the Federal Circuit's nonprecedential decision in Columbia Ins. Co. v. Simpson Strong-Tie Inc., 2023 WL 2733427 (Fed. Cir. Mar. 31, 2023), where the patent at issue had the opposite problem as the patent in Indivior. The patent in Columbia claimed a range, but the specification only disclosed the lower bound of the range. 2023 WL 2733427 at *4-5. There was no disclosure of any other number within the range and there was nothing in the specification to suggest to a POSA that the inventors possessed anything other than the exact lower bound of their invention. Id. As previously noted, the Product Patent contained multiple disclosures of native conformations throughout the range of 98% to 100%. Unlike in Columbia, it is clear to a POSA reading the Product Patent that inventors possessed the entirety of the claimed subject matter as required under Andersen.

In sum, the Court holds that SB has not raised a substantial question of invalidity due to a lack of written description with

respect to any asserted claim of the Product Patent. Because SB does not raise any arguments addressed to any limitation other than the 98% native conformation limitation recited in claims 1 and 26, there is no substantial question as to the Asserted Product Patent Claims (which all depend from claims 1 or 26 and are thus narrower than those claims).

C. Irreparable Harm

Regeneron "must make a clear showing that [they are] at risk of irreparable harm, which entails showing a likelihood of substantial and immediate irreparable injury." See Apple, Inc. v. Samsung Elecs. Co., 678 F.3d 1314, 1325 (Fed. Cir. 2012) ("Apple I") (internal quotation marks omitted). The patentee must also establish that the harm is related to the infringement, a requirement referred to as the "causal nexus" requirement. Id. at 1324.

"Irreparable injury encompasses different types of losses that are often difficult to quantify." Douglas Dynamics, LLC v. Buyers Prods. Co., 717 F.3d 1336, 1344 (Fed. Cir. 2013). Accordingly, courts recognize multiple types of irreparable harm. See, e.g., Celsis In Vitro, Inc. v. CellzDirect, Inc., 664 F.3d 922, 930-31 (Fed. Cir. 2012) ("Price erosion, loss of goodwill, damage to reputation, and loss of business opportunities are all

valid grounds for finding irreparable harm.").

The evidence shows that Regeneron would experience irreparable injury if SB launches SB15. Harm from the infringing product's competition for the same customers "is not speculative." Trebro Mfg., Inc. v. Firefly Equip. LLC, 748 F.3d 1159, 1170 (Fed. Cir. 2014).

1. Loss of Sales and Market Share

A showing of lost market share and sales can support a finding of irreparable harm. See Robert Bosch LLC v. Pylon Mfg. Corp., 659 F.3d 1142, 1154 (Fed. Cir. 2011).

In particular, the prospect of direct competition from an infringing competitor "strongly shows a probability for irreparable harm." See Trebro Mfg., 748 F.3d at 1170-71 (recognizing a strong "probability for irreparable harm" where an alleged infringer "is a direct competitor" and explaining that "[t]he district court's blanket dismissal of evidence showing likely loss of market share and loss of access to customers was an error of law") (internal quotation marks omitted). "Loss of market share constitutes irreparable injury because market share is so difficult to recover. . . . Moreover, [t]he right to exclude direct competition in a limited sphere, a right inherent in the grant of a patent, is irreparably harmed by the loss of sales and the

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competitive foothold that the infringer will gain." Indivior Inc. v. Dr. Reddy's Lab'ys S.A., 2018 WL 3496643, at *12 (D.N.J. July 20, 2018) (internal citations and quotation marks omitted), vacated on other grounds, 752 F. App'x 1024 (Fed. Cir. 2018); see also Abbott Lab'ys v. Sandoz, Inc., 544 F.3d 1341, 1361-62 (Fed. Cir. 2008) (holding that "precedent supports" recognizing "market share and revenue loss" as irreparable harms if the infringer enters the market "while the litigation proceeds"). This Court has recently recognized the same. See In re: Aflibercept Patent Litigation, 1:24-MD-3103, ECF No. 794, at 25-26 (N.D.W. Va. June 11, 2024).

"Where two companies are in competition against one another, the patentee suffers the harm — often irreparable — of being forced to compete against products that incorporate and infringe its own patented inventions." Douglas Dynamics, 717 F.3d at 1345 (reversing denial of permanent injunction); see also Presidio Components, 702 F.3d at 1363 (''Direct competition in the same market is certainly one factor suggesting strongly the potential for irreparable harm without enforcement of the right to exclude.").

The likelihood of irreparable harm increases in cases involving markets with few competitors. See Lonza Walkersville,

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Inc. v. Adva Biotech., Ltd., 581 F. Supp. 3d 736, 750 (D. Md. 2022) ("Given the size and nature of the relevant market . . . a sale of [the infringing product] would quite likely be a lost sale for [the patentee]."), appeal dismissed, 2022 WL 1634221 (Fed. Cir. May 24, 2022). But irreparable harm from direct competition often exists even when there are multiple competing products. See, e.g., ePlus, Inc. v. Lawson Software, Inc., 2011 WL 2119410, at *9 (E.D. Va. May 23, 2011) (finding irreparable harm when there are at least eight "companies that compete in the market"), modified, 946 F. Supp. 2d 459 (E.D. Va. 2013), vacated on other grounds, 760 F.3d 1350 (Fed. Cir. 2014); SynQor, Inc. v. Artesyn Techs., Inc., 2011 WL 238645, at *1, *3 (E.D. Tex. Jan. 24, 2011) (finding irreparable harm when there were 11 competitors); Callaway Golf Co. v. Acushnet Co., 585 F. Supp. 2d 600, 619-21 & n.22 (D. Del. 2008) (finding irreparable harm when there were 17 competitors), aff'd in part, vacated in part on other grounds, 576 F.3d 1331 (Fed. Cir. 2009).

Harm from competition is not limited to harm to products that practice the patent. It exists whenever products are "competing for the same customers in the same markets," Presidio Components, 702 F.3d at 1363, or when products "meet the same needs," Broadcom Corp. v. Emulex Corp., 2012 WL 13036855, at *3 (C.D. Cal. Mar. 16, 2012), aff'd, 732 F.3d 1325 (Fed. Cir. 2013). Indeed, a patentee

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can establish irreparable harm even if "it does not currently practice the claimed inventions" at all. Broadcom Corp. v. Qualcomm, Inc., 543 F.3d 683, 703 (Fed. Cir. 2008); see also Presidio Components, 702 F.3d at 1363 ("Even without practicing the claimed invention, the patentee can suffer irreparable injury.").

There are only a handful of anti-VEGF medications currently on the market to treat angiogenic eye disorders, Clark Decl. ¶ 6, and SB does not dispute that Regeneron's Eylea products are the only anti-VEGF medications with aflibercept. Cockburn Decl. ¶ 57 (testifying Eylea and Eylea HD are the only FDA approved aflibercept medications in the U.S.). While other medications exist that treat the same conditions as Eylea, Regeneron has presented testimony that those medications are clinically inferior to Eylea in certain respects. Clark Decl. ¶ 7; Mylan Trial Tr. 172:16-21 (Yancopoulos), Regeneron Pharms., Inc. v. Mylan Pharms., Inc., No. 22-cv-61-TSK (N.D.W. Va. June 12, 2023), ECF No. 558; *id.* at 309:13-20 (Csaky) ("[Ophthalmologists] all kind of believe that Eylea still is the best anti-VEGF agent out there."); id. at 861:24-862:4 (Albini) (discussing the safety issues with Beovu).

For example, Lucentis, the leading treatment for angiogenic eye disorders before Eylea's launch, must be dosed monthly,

compared to Eylea's extended dosing interval of every eight weeks. Mylan Trial Tr. 123:15-124:5 (Yancopoulos). Other medications come with safety concerns or result in patients gaining less visual acuity than similarly situated patients taking Eylea. Clark Decl. ¶ 7. Eylea is thus the preferred treatment of many ophthalmologists. Id.; Mylan Trial Tr. 1917:12-1918:2 (Csaky), Regeneron Pharms., Inc. v. Mylan Pharms., Inc., No. 22-cv-61-TSK (N.D.W. Va. June 22, 2023), ECF No. 568; see also id. at 172:169-210 (Yancopoulos) (Eylea viewed as the "gold standard"). Indeed, SB's own economic expert acknowledges that the other available medications are inferior to Eylea. Cockburn Decl. ¶ 66 ("I understand that Eylea's superior clinical characteristics compared to most anti-VEGF drugs may have contributed to its resilience thus far in the face of competition.").

The evidence shows that if an aflibercept biosimilar launches, healthcare providers are likely to view it as interchangeable with Eylea. Sheridan Decl. ¶¶ 32-33 ("[B]iosimilars are known as interchangeable products."); Cockburn Decl. ¶ 58 ("[A] manufacturer can demonstrate interchangeability by showing that its drug would be 'expected to produce the same clinical result as the reference product in any given patient' and proving that it would be 'safe for a patient to switch between the

reference product and [its biosimilar version].") (alteration in original). This view will be bolstered by FDA's decision to designate SB15 as an "interchangeable biosimilar[] to Eylea (aflibercept)." FDA Approval Announcement.

Thus, while other anti-VEGF medications such as Lucentis and Avastin have not been viewed by clinicians as comparable to Eylea, SB15 [redacted] FDA Approval Announcement. The Court finds that providers are likely to treat it as such and could choose to use SB15 instead of Eylea.

Given the FDA's recent grant of that interchangeability status, health care providers are likely "to be comfortable with switching Eylea patients to SB15." Sheridan Ex. B-4 (ECF No. 118-27) at -286. Starting with Regeneron's original product, the parties agree that SB15 will take market share from Eylea 2 mg sold in a vial. [redacted]

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ORDER GRANTING MOTIONS FOR PRELIMINARY INJUNCTION

One matter requires clarification – what defines the universe of potential irreparable harm to Regeneron. Regeneron urges the Court to consider SB15's alleged potential impact on Regeneron's entire suite of Eylea product offerings – vial, PFS and Eylea HD. This Court declined that invitation in Mylan and does so here for the same reasons. As noted in noted in Mylan, the claims resolved in the Court's Trial Decision were not directed to the aflibercept molecule generally, but to a vial deli very mechanism specifically. See In re: Aflibercept Patent Litigation, ECF No. 794, at 16-24.

The Second Circuit explained the difference in the market between anti-VEGF medications presented in the form of a vial and those presented in the form of a PFS:

> For several years after they were first introduced, anti-VEGF medications [like aflibercept] were packaged into vials and administered in a two-step process. A doctor would first fill a syringe with medicine from an anti-VEGF vial and then inject the drug into a patient's eye. The newer versions of the medications are sold in prefilled syringes ("PFSs") and administered in one step. PFSs contain the same medication as vials but are injected directly into the patient's eye. This simpler process carries a significantly

> lower risk of complications and infections and is now the preferred way of administering anti-VEGF medications.

Regeneron Pharms., Inc. v. Novartis Pharma AG, 96 F.4th 327, 332 (2d Cir. 2024). [redacted]

Given the above and other record evidence considered, the 2 mg aflibercept vials, 2 mg aflibercept PFS, and the 8 mg Eylea HD products represent distinct products and markets for purposes of assessing irreparable harm.

The Court concludes, however, that Regeneron will likely be irreparably harmed by the entry of the biosimilar SB15 because Regeneron will be "forced to compete against products that

incorporate and infringe its own patented inventions." Douglas Dynamics, 717 F.3d at 1345; see also Abbott Lab'ys, 544 F.3d at 1361-62.

The Court further concludes that the harm from competition with an infringing product is all the more acute here because the infringing product will be marketed as a biosimilar. By its nature, a biosimilar is a near-exact clinical substitute for its reference product. If SB15 enters the market it will appear, not merely as a direct competitor, but as a purported replacement for Eylea. See FDA Approval Announcement. And physicians are likely to directly substitute it for Eylea. [redacted] Indeed, Regeneron's forecasts predict significant lost sales and a decrease in market share for its Eylea product if a biosimilar such as SB15 launches. Sheridan Ex. 99 at -480-81.

"Given the size and nature of the anti-VEGF patient population. . . a sale of [SB15] would quite likely be a lost sale for [Regeneron]." Lonza Walkersville, 581 F. Supp. 3d at 750. "Loss of market share constitutes irreparable injury because

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market share is so difficult to recover. Moreover, the right to exclude direct competition in a limited sphere, a right inherent in the grant of a patent, is irreparably harmed by the loss of sales and the competitive foothold that the infringer will gain." Indivior, 2018 WL 3496643, at *12 (internal citations and quotation marks omitted). SB's own expert, Dr. Cockburn acknowledged that [redacted] sales following the launch of SB15 would change the treatment landscape: "those sales will provide ophthalmologists with critical post-launch demonstration of safety and efficacy." Cockburn Decl. ¶ 156. During his deposition, he further acknowledged that anything "more than a trace level of sales . . . represents real world evidence [redacted] Cockburn Tr. 85:5-9. In light of this evidence, the Court concludes that Regeneron has demonstrated irreparable harm from SB15 competition with its Eylea vial product.

Finally, SB argues (Opp. 23) that Regeneron's lost market share is quantifiable and that legal remedies are adequate to compensate Regeneron. This Court disagrees. Courts regularly recognize that being forced to "compete against products that incorporate and infringe [one's] own patented inventions" creates irreparable harm. Douglas Dynamics, 717 F.3d at 1345. SB's

attempt to distinguish Janssen Prods., L.P. v. Lupin Ltd., 109 F. Supp. 3d 650, 696-97 (D.N.J. 2014), modified, 2016 WL 1029269 (D.N.J. Mar. 15, 2016) (Opp. 23) does not support its position. Although Janssen presented evidence that it would lose "virtually all" of its sales, nowhere did the Janssen court demand such a high bar for injunctive relief. See Janssen, 109 F. Supp. 3d at 696-97.

SB also relies on Metalcraft of Mayville, Inc. v. The Toro Company, 848 F.3d 1358, 1368 (Fed. Cir. 2017), but that case confirms that an infringer may cause irreparable harm even if there are a dozen other infringers in the marketplace. In Metalcraft, the court upheld the trial court's finding of irreparable harm where the Federal Circuit understood that "losses of customers may have far-reaching, long-term impact on [the patentee's] revenues and the sales lost . . . are difficult to quantify due to 'ecosystem effects, where one company's customers will continue to buy that company's products.'" Id. (quoting Apple Inc. v. Samsung Elecs. Co. ("Apple VI"), 809 F.3d 633, 641, 645 (Fed. Cir. 2015)). Similarly here, there is no way to know how many patients Regeneron will lose because of payor policies, and those losses are likely to be permanent. Sheridan Decl. ¶¶ 75-76. Thus, this Court

concludes that Regeneron has shown its likely harm due to lost market share and sales is not addressable through legal remedies.

2. Price Erosion

When a competing product launches, the patented product often has to drop its price to remain competitive. This drop in price is consistently recognized as a source of irreparable harm. See, e.g., Celsis In Vitro, 664 F.3d at 930 (affirming price erosion as source of irreparable harm); Sanofi-Synthelabo v. Apotex, Inc., 470 F.3d 1368, 1383 n.9 (Fed. Cir. 2006) (same); Abbott Lab'ys, 544 F.3d at 1362 (same).

"The phenomenon of price erosion in the pharmaceutical industry is well known." Hoffmann-La Roche Inc. v. Cobalt Pharms. Inc., 2010 WL 4687839, at *12 (D.N.J. Nov. 10, 2010), modified, 2012 WL 458435 (D.N.J. Feb. 9, 2012). And "[p]rice erosion is most likely to occur in cases . . . in which no generic competitors have yet entered the marketplace, placing the patentee in an exclusive position." Id.

Price erosion is typically irreversible even if the infringing product exits the market because returning prices to pre-infringement levels risks loss of goodwill and reputation with payors and customers. Sanofi-Synthelabo v. Apotex Inc., 488 F. Supp. 2d 317, 343 (S.D.N.Y. 2006) (patentee would be "harmed by

loss of consumer good will by customers who will have grown accustomed to lower prices" if it restored pre-infringement pricing), aff'd, 470 F.3d 1368 (Fed. Cir. 2006); Celsis In Vitro, 664 F.3d at 930 (same).

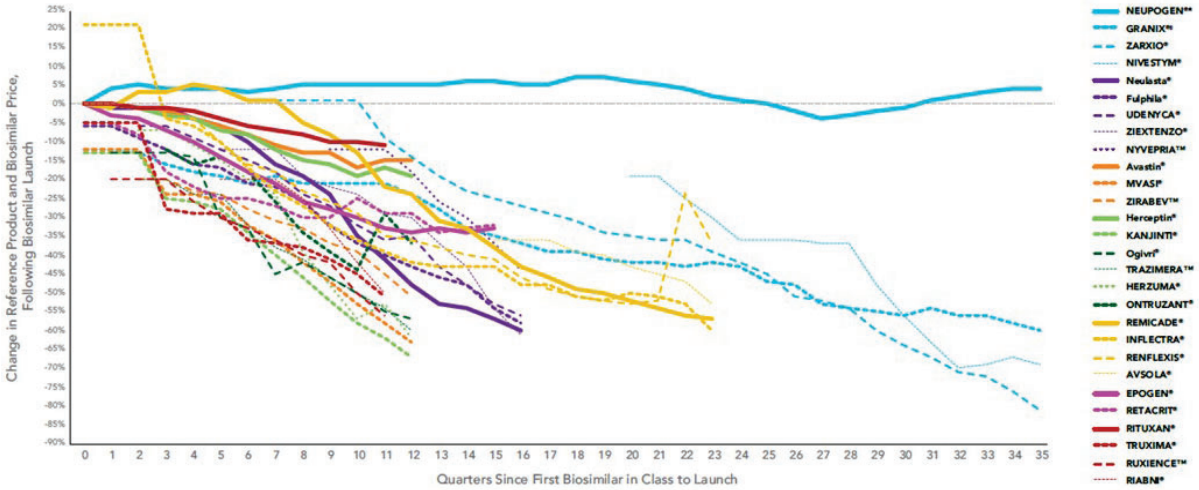
Regeneron has also shown that SB15's launch will force Regeneron to reduce the prices of its Eylea products. Clark Decl. ¶¶ 8-10; Sheridan Decl. ¶ 62. [redacted]

a. The launch of a biosimilar typically causes price erosion

[redacted] The WAC is the price a drug manufacturer lists, not including any discounts, rebates, or negotiated price reductions. Id. ¶ 35. And biosimilars launch at an average ASP — the average price that manufacturers charge purchasers after discounts and rebates—that is half that of the branded drug. Id. ¶¶ 35, 38. [redacted]

SB's Biosimilar Market Report for Q1 2024 states that "[b]iosimilar launches have led to significant price decreases over time," and "[o]n average, ASP declined by 41% three years . . . post first biosimilar launch with more mature markets demonstrating increasing price concessions." Sheridan Ex. 33 at 12 (ECF No. 118-30).

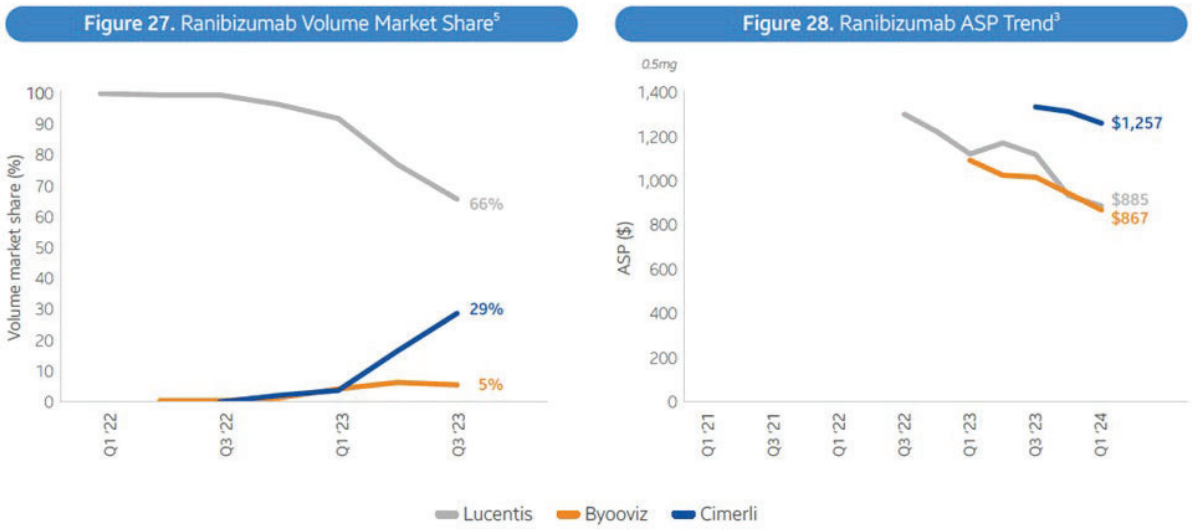
Amgen has observed the same trend, stating in its 2022 Biosimilars Trend Report that the ASP "for both reference products and biosimilars" "is declining, due to competition." Sheridan Ex. 52 at 6 (ECF No. 118-32); see Sheridan Decl. ¶ 39. This same report shows that biosimilar prices "have decreased at a negative compound annual growth rate . . . of -9% to -24%," and "[t]he prices of most reference products have decreased at a negative [compound annual growth rate] of -4% to -21%." Sheridan Ex. 52 at 6. Amgen's 2022 Report contains a graph illustrating the trend in reference products' declining ASP following the launch of biosimilars:



Id. 13 (Fig. 5); Sheridan Decl. ¶ 39.

Ophthalmic drugs are not immune from this trend, as the launch of ranibizumab biosimilars has shown. Sheridan Decl. ¶ 41; Sheridan Ex. 33 at 9 ("Recent ranibizumab biosimilar launches have already led to lower reference product ASP costs."). When these biosimilars entered the market, Genentech, the maker of the branded biologic Lucentis, was forced to reduce its ASP to or below the ASPs of the competing biosimilars. Sheridan Decl. ¶ 41. As of Q1 2024, the ASP of all ranibizumab products has declined 23% since the biosimilars' launch. Sheridan Ex. 33 at 22. Despite these price reductions, Lucentis continued to lose significant market share to ranibizumab biosimilars; as of Q3 2023 the two ranibizumab biosimilars hold a combined market share of 34%. Id.

The figures below, featured in SB's 2024 Market Report, illustrate the decline in Lucentis's ASP and market share that ranibizumab biosimilars caused:



Id. at 22 (Figs. 27 and 28).

However, although biosimilars often launch at a discount to the reference products price — on average at an ASP that is half the cost of the reference product — price erosion from a biosimilar launch can occur regardless of the launch price. Sheridan Decl. ¶ 38.

b. Regeneron will likely experience price erosion if SB15 launches

The downward pricing pressure Eylea will face after SB15's launch is different in kind from ordinary, non-biosimilar competition with other anti-VEGF medications. Almost across the

board, biosimilars lead to permanent price erosion of the reference drug. That is because their launch causes the reference drug to compete for the first time with its own formulation. The same will happen with Eylea if SB15 is allowed to launch.

[redacted]

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Indeed, SB's own evidence confirms that Eylea will likely experience price erosion from SB15 launching. SB publicly acknowledges that biosimilars erode price for ophthalmological biologics. See Sheridan Ex. 33 at 22; Sheridan Ex. 82 (ECF No. 118-35) at 1 (identifying erosion of Lucentis pricing). But

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[redacted]

[redacted]

SB argues Eylea "would fall into the category of price-stable reference drugs" because "Regeneron already has implemented a biosimilar defense strategy: not to compete on price but rather to transition patients to Regeneron's second generation version, Eylea HD." Opp. 22. This is unlikely to be true. [redacted]

Further, if Regeneron is forced to lower prices on Eylea because of biosimilar entry, such price erosion will likely be

permanent. [redacted]

Dr. Cockburn suggests in his report that Regeneron could later reverse rebates and discounts. Cockburn ¶¶ 81-82. As Dr. Cockburn admitted in his deposition, however, because doctors are reimbursed based on lagging prices, "if the direction of the [sales

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price] changes, then there will be a period during which the providers will be somewhat squeezed." Cockburn Tr. at 54:19-55:4. [redacted] Should Regeneron nonetheless attempt to revert prices on Eylea to their original values despite the foregoing, it would suffer further harm in the form of reputational damage and loss of goodwill.

[redacted] "[p]rice

erosion is most likely to occur in cases . . . in which no generic competitors have yet entered the marketplace, placing the patentee in an exclusive position." Hoffmann-La Roche, 2010 WL 4687839, at *12. Currently, Regeneron is the only company with an aflibercept product on the market, [redacted] The Court does not credit SB's assertion that "Regeneron already has implemented a biosimilar defense strategy: not to compete on price but rather to transition patients to Regeneron's second generation version, Eylea HD." [redacted]

Moreover, Regeneron's irreparable harm from price erosion would be irreversible even if SB eventually loses at trial and SB15 exits the market. For one, contractual price concessions

would be locked in for at least the terms of the contracts. And, because Medicare reimbursement rates lag market pricing, future price increases would leave physicians paying a higher rate to purchase Eylea than they were being reimbursed. [redacted] In short, Regeneron could only raise its prices by risking the "loss of consumer good will by customers who will have grown accustomed to lower prices." Sanofi-Synthelabo, 488 F. Supp. 2d at 343.

3. Disruption of Patentee-Payor Relationships

When "third-party payors control a substantial portion of . . . sales," the entry of a competing drug product has the "potential to irreversibly alter the reimbursement relationship" and create irreparable harm to patentees. Hoffmann-La Roche, 2010 WL 4687839, at *12. These harms are distinct from price erosion and arise from irreversible formulary position losses. And courts have recognized this economic reality in the pharmaceutical market when an infringing drug launches. See King Pharm., Inc. v. Corepharma, *LLC*, 2010 WL 1850200, at *3 (D.N.J. May 7, 2010) (crediting economist's testimony that "payors . . . will move [the patentee]'s patented product off of their formularies in the presence of generic competitors").

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Harm to payor relationships and status are well-recognized as irreparable. See Indivior Inc., 2018 WL 3496643, at *12 ("Courts have found that a reduction of market share due to the loss of formulary status and a change in tier pricing, constitutes irreparable harm."); Abbott Lab'ys, 544 F.3d at 1361-62 (similar).

The Court finds that the entry of SB15 will "irreversibly alter the reimbursement relationship" and impose long term damage to Regeneron. Hoffmann-La Roche, 2010 WL 4687839, at *12. SB15's launch is likely to disrupt Regeneron's relationships with payors permanently. Sheridan Decl. ¶¶ 85-87. When a lower-cost treatment (e.g., a biosimilar) comes on the market, [redacted] This requirement is known as a "step edit," referring to patients having to "step through" the cheaper alternative before trying the more expensive drug. Clark Decl. ¶ 14. Once insurers and other payors implement a step edit, the more expensive medication becomes a second-line treatment, [redacted] Sheridan Decl. ¶¶ 64, 76, 84; Clark Decl. ¶ 11. Harms from step edits are incalculable because there "is no effective way to . . . ascertain the people who do not knock

on the door . . . because of the existence of the infringer." Celsis In Vitro, 664 F.3d at 930 (citation omitted).

Regeneron's evidence showed that Eylea is now a first-line treatment for [redacted] patients with angiogenic eye disorders. Clark Decl. ¶ 14; Sheridan Decl. ¶ 64. In other words, those patients receive insurance coverage for Eylea without first trying another treatment option or experiencing a "single step edit." And only [redacted] are currently subject to a "double step edit" under which they must try two other medications before receiving coverage for Eylea. Sheridan Decl. ¶ 64; Clark Decl. ¶ 14.

[redacted] It is thus reasonable to expect that an aflibercept biosimilar launching likely will encourage more payers to implement an Eylea step edit. This effect will be more pronounced if the biosimilar launches at

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a substantial discount relative to Eylea. [redacted]

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Harm to Regeneron from step edits is likely irreversible.

This Court concludes that the likely harm to Regeneron from a "loss of formulary status and a change in tier pricing,

constitutes irreparable harm." Indivior Inc., 2018 WL 3496643, at *12.

4. Reputational Harm

As this Court recently recognized in granting a permanent injunction against Mylan, see In re: Aflibercept Patent Litigation, ECF No. 794, at 39-42, reputational injury is a well-recognized form of irreparable harm. Douglas Dynamics, 717 F.3d at 1344-45. This can occur when a doctors or patients know that a patentee is responsible for removing an available drug. See AstraZeneca LP v. Apotex, Inc., 623 F. Supp. 2d 579, 613 (D.N.J. 2009) ("AstraZeneca claims that an unauthorized launch by Apotex (followed by a subsequent exit) would result in intangible and unquantifiable damage to AstraZeneca's reputation and goodwill. For example, they assert that doctors who would have prescribed Apotex's BIS may blame AstraZeneca for the sudden unavailability of Apotex's generic BIS once Apotex is forced to leave the market. . . . The Court agrees that an unauthorized launch by Apotex would have some intangible effects on AstraZeneca's goodwill."), supplemented, 623 F. Supp. 2d 615 (D.N.J. 2009), aff'd, 633 F.3d 1042 (Fed. Cir. 2010); Baxalta Incorp. v. Genentech, Inc., 2018 WL 3742610, at *11 (D. Del. Aug. 7, 2018) (where defendant already launched its product prior to the

preliminary injunction hearing, patentee would suffer reputational harm when doctors would know that patentee was responsible for removing an available drug).

Regeneron has established that it will suffer reputational harms in the pharmaceutical community and among healthcare professionals if SB15 is permitted to launch but later is removed from the market. If SB15 launches and then is taken off the market as a result of litigation, providers and, most importantly, patients will blame Regeneron for the loss of their chosen treatment. Sheridan Decl. ¶¶ 85-87. Unlike a course of antibiotics or a temporary pain-relief medication, patients must take aflibercept regularly for a long time. Cockburn Decl. ¶ 53; Mylan Trial Tr. 137:3-14 (Yancopoulos). SB15's removal from the market after a trial, once it has been administered to perhaps thousands of patients, will disrupt these patients' course of treatment. Not only may patients feel uncomfortable switching medication mid-course; they will also have to seek approval from private insurers and Medicare and Medicaid for a different product, a process likely to interrupt their treatment. Sheridan Decl. ¶ 87. [redacted]

[redacted] The Court finds that this harm to Regeneron's relationships with its customers and their treatment regimen would be likely were SB15 permitted to launch.

SB argues that Baxalta, the case cited by Regeneron to establish that such reputational harms are legally cognizable, "found the opposite." Opp. 24. This is incorrect. In Baxalta, the accused drug was already on the market and would remain available for a subset of patients irrespective of any injunction, and doctors would blame the patentee for removing that drug as a treatment choice for the remainder of patients. 2018 WL 3742610, at *11. SB also does not account for the holding of Douglas Dynamics, which confirms that irreparable harm can be found in an analogous circumstance. 717 F.3d at 1344. Because Regeneron has established that it likely would be blamed for the removal of SB15 should SB15 launch and then be removed from the market post-judgment for Regeneron, Regeneron has demonstrated irreparable reputational harm.

5. Marketing and Training Costs

Courts often consider the effect of infringing activity on the patented product's salesforce and marketing activity. See Sanofi-Synthelabo, 488 F. Supp. 2d 317 at 342 ("Sanofi has shown

for the purposes of this motion that it will be irreparably harmed . . . by layoffs of employees involved in marketing Plavix," a patented product, upon the launch of a lower cost generic); Bio-Rad Lab'ys, Inc v. 10X Genomics, Inc., 967 F.3d 1353, 1378 (Fed. Cir. 2020) (crediting the trial court's finding that the patentee would have to "increase its marketing costs" in considering irreparable harm).

Regeneron presented evidence that it would have to invest in new marketing and training efforts upon the launch of one or more infringing biosimilars. Clark Decl. ¶ 18. SB's briefing does not address this source of irreparable harm, [redacted]

Further, Dr. Cockburn lacks expertise in the ophthalmologic pharmaceutical industry, while Mr. Clark is responsible for actually implementing these marketing and training programs for Regeneron and is aware of their costs. As such, the Court credits Regeneron's representations that it will have to develop new training programs in response to SB15 launching.

6. Research and Development

Regeneron also suggests, as a separate form of irreparable harm, that its research and development (R&D) funding and spending will be negatively affected if SB15 launches. The Court rejects this as a basis of irreparable harm here.

As it did in Mylan, the Court finds Regeneron did not meet its burden with this element of claimed irreparable harm. See In re: Aflibercept Patent Litigation, ECF No. 794, at 42-46. The Federal Circuit cautioned against allowing generalized assertions that loss of revenue would lead to a loss of research and development opportunities because

> that claim of injury is not materially different from any claim of injury by a business that is deprived of funds that it could usefully reinvest. If a claim of lost opportunity to conduct research were sufficient to compel a finding of irreparable harm, it is hard to imagine any manufacturer with a research and development program that could not make the same claim and thus be equally entitled to preliminary injunctive

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> relief. Such a rule would convert the "extraordinary" relief of a preliminary injunction into a standard remedy, available whenever the plaintiff has shown a likelihood of success on the merits.

Eli Lilly & Co. v. Am. Cyanamid Co., 82 F.3d 1568, 1578 (Fed. Cir. 1996) (affirming denial of injunction against generic drug competitor). This principle also differentiates a case upon which Regeneron relies, Amgen v. F. Hoffman-LaRoche, 581 F. Supp. 2d 160, 212 (D. Mass. 2008). In Amgen, the district court noted that Amgen's infringed patents were directed to "the source" of "what enables mass production and commercial viability" of the drug at issue. 581 F. Supp.2d at 195. The patents also were "admittedly 'the foundation of Amgen's business,'" and any question into their value or ability to keep other competitors off the market would cause Amgen to lose access to research and development funds. Id. at 212. Regeneron's cited cases also do not support a finding of irreparable harm. In Mylan Institutional, for example, there was evidence of record that the harm to R&D would result from the loss of "half or more of [patentee's] revenue," [redacted] See Mylan Institutional LLC v. Aurobindo Pharma Ltd, 2016 WL 7587325, at *23 (E.D. Tex. Nov. 21, 2016). The same is true of Regeneron's Janssen case. See Janssen Prods., L.P. v.

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Lupin Ltd., 109 F. Supp. 3d 650, 697 (D.N.J. 2014) (irreparable harm where evidence indicates "Janssen would lose 70 to 80 percent of its sales upon a generic launch"). Therefore, consistent with this Court's findings in Mylan, Regeneron's claimed impact on R&D prospects finds no basis in either fact or law, and the Court does not rely upon it in issuing the preliminary injunction.

7. Near-Term Harms to Regeneron

The evidence indicates that SB15's launch will harm Regeneron's Eylea vial product on a timeline that requires injunctive relief. [redacted] SB argues that because the uptake of biosimilars in ophthalmology will be slow, any possible irreparable harm is unlikely to materialize on a timeline sufficient to warrant injunctive relief. Opp. 24; Cockburn Decl. ¶¶ 89-92. The record does not support that argument.

a. Regeneron is likely to experience immediate share loss

As an initial matter, Anti-VEGF drugs with biosimilars have seen significant market share erosion over a short time period. For example, despite launching in mid-2019, as of 2020, bevacizumab biosimilars achieved a higher share of the market than branded Avastin. Sheridan Ex. 33 at 14. By Q3 2023, biosimilars made up 87% of all bevacizumab sales. Id.

This experience is consistent with industry expectations for biosimilars generally. The SB Biosimilar Market Report for Q1 2024 states: "On average, biosimilars gain 53% market share within three years (12 quarters) post initial launch." Sheridan Ex. 33 at 11. Those averages, however, reflect data for biosimilars with variable uptake speeds, which can be categorized as fast or slow. Id. Ophthalmology biosimilars are classified as exhibiting a "fast uptake speed." Id.

SB's argument that ophthalmologists will be slow to adopt an aflibercept biosimilar is thus outdated. SB's expert relies heavily on "a survey conducted in 2022" in which "most ophthalmologists reported that they either 'have very limited knowledge of clinical trial design for biosimilars' or that '[c]linical trials conducted on biosimilars are not large enough in size in order to adequately investigate efficacy and safety.'"

See Cockburn Decl. ¶ 41 (alteration in original); Cockburn Ex. 137 (Dkts. 165-187, 165-188) at -65. However, ophthalmology biosimilars have experienced additional uptake since then, and ophthalmologists are likely aware that others are in the pipeline. Sheridan Ex. 33 at 11 (SB Biosimilar Market Report showing rapid uptake of Ranibizumab (Lucentis) biosimilars in the first four quarters post-launch). While ophthalmologists may have hesitated to embrace an ophthalmology biosimilar before any were available, these attitudes have likely changed now that doctors have been using such products for years. [redacted]

In fact, the most recent survey data from the same group that conducted the earlier study shows that ophthalmologists are more comfortable prescribing biosimilars today. See Cockburn Ex. 137 at -968 (identifying year-on-year increases in the number of physicians who would be willing to switch new and existing patients having success on a reference biologic for treatment of neovascular age-related macular degeneration to a biosimilar). During his deposition, Dr. Cockburn conceded he did not include the report

text demonstrating increasing physician familiarity with biosimilars in his report. Cockburn Tr. 60:19-61:4 ("Q. And your declaration does not acknowledge the report's conclusion that ophthalmologists believe their knowledge was increasing, Right? A. I don't think it's a question of not acknowledging it. I haven't copied that language."). Indeed, SB's own most recent study on biosimilars noted "Fast Uptake Speed" as a feature of "[o]ncology, pegfilgrastim, and ophthalmology biosimilars." Sheridan Ex. 33 at 11. There is no reason to credit the idea that physicians will be hesitant to prescribe biosimilars when the data shows the opposite and continues to trend in that direction.

b. Regeneron is likely to experience immediate price erosion

Regeneron is also likely to experience immediate price erosion, as demonstrated by the example of ranibizumab biosimilars. [redacted]

[redacted] Lucentis's experience thus presents applicable evidence that ophthalmology biosimilar entry will cause price erosion of the reference product, and it also suggests that Eylea's price erosion may be particularly steep.

SB asserts that Regeneron will not suffer immediate price erosion because "the evidence shows that reference drugs can and do maintain price stability 12-18 months after biosimilar launch, even when the biosimilars are substantially discounted." Opp. 21. [redacted]

The Court finds that price erosion is likely to occur as soon as aflibercept biosimilars launch, [redacted].

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c. Regeneron will likely experience immediate harm to payor relationships

Regeneron also faces substantial risk that its Eylea vial product — the subject of the Asserted Product Patent — will become subject to step edits shortly after a biosimilar's launch. [redacted]

d. SB15's launch will immediately cause Regeneron's other harms

Regeneron's marketing and training efforts would occur immediately following any SB15 launch, and its most significant reputational harms would likely be incurred whenever SB15 is removed from the market, such as after a final judgment of infringement is issued.

Accordingly, the Court finds it likely that Regeneron would suffer immediate harm from SB15 launching.

e. Complexities in the Competitive Landscape

Accepted methods of calculating lost profits would likely not account for the harm to Regeneron from SB15's launch.

First, a damages expert quantifies lost profits in a patent infringement matter based on the but-for competitive landscape; that is, an analysis of what the competitive market would have been at a particular moment in time absent an infringing product's entry. Sheridan Decl. ¶ 88. Where the marketplace at issue is dynamic or in flux, limiting the analysis to a particular moment in time requires simplifying assumptions and tends to understate damages. Id.

The market for anti-VEGF ophthalmic treatments is in flux, given the entry and exit of several competing products, approvals of new indications for existing products, and changing patient populations. Id. ¶¶ 89, 99-100. Eylea currently faces competition from non-infringing products — other anti-VEGF biologics like Avastin and Lucentis — which in turn have their own biosimilars and may generate yet more biosimilar entrants. Id. ¶ 90. In addition, up to [redacted] other aflibercept biosimilars could seek to launch in 2024 unless enjoined, with more to follow. Id. Isolating and fully capturing the impact of one biosimilar would be difficult, if not impossible. Id. ¶ 93. Regeneron will have

to adjust its marketing strategies in response to each entry and exit, which will affect the market in turn. Id. ¶¶ 91, 95.

Second, the impact of payor policies will be difficult to calculate over the life of the product and is likely to be undervalued in any such calculation. If payors implement step edits, moving patients away from Eylea, many of these customers will never purchase Eylea. There is no way to know how many patients Regeneron will lose because of these step edits, and those losses are likely to be permanent. Sheridan Decl. ¶¶ 75-76. The parties thus could not quantify adequately the patients who would have been treated with an Eylea product had they not first been forced to step through an infringing biosimilar.

Third, Regeneron has shown that it would be difficult to account for the harm it will suffer to its reputation and the efforts it will undertake to develop new training programs in response to SB15 launching. Although it is likely that these harms would result from SB15 launching, the scope of harm is yet unknown and would be difficult to address in a damages model.

These factors pile uncertainty upon uncertainty in any damages model. Thus, the market positions of Eylea but-for one specific infringing biosimilar's launch would be particularly difficult to estimate. And were a damages expert to attempt

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estimating Regeneron's damages due to SB15's launch, he or she would have to employ a slew of simplifying assumptions, resulting in a lower damages amount that would not fully reflect the harm Regeneron would have suffered.

f. Causal Nexus

To obtain injunctive relief, a patentee must show "some causal nexus between [a defendant's infringement] and [the] alleged harm" — i.e., "show that the patentee is irreparably harmed *by the infringement*." Apple Inc. v. Samsung Elecs. Co., 735 F.3d 1352, 1363-64 (Fed. Cir. 2013) ("Apple III").

In cases involving "complex, multi-featured" products, such as "smartphones and tablets," where consumer demand is driven by some features of the finished good and not others, this nexus analysis can be complicated. Id. at 1362; see also Genband US LLC v. Metaswitch Networks, Corp., 861 F.3d 1378, 1384 (Fed. Cir. 2017) (discussing "the causation approach suitable for a multi-feature, multi-purchaser context"). In such cases, a patentee must show "some connection between the patented feature and demand" for the accused product, though it need not "show that a patented feature is the exclusive reason for consumer demand." Apple III, 735 F.3d at 1364.

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The nexus inquiry can be much simpler for products that "ha[ve] a small number of features," like medications. Id. at 1361-62. That is because the nexus inquiry has "little work to do . . . when the infringing product contains no feature relevant to consumers' purchasing decisions other than what the patent claims." Genband, 861 F.3d at 1384 n.2. Accordingly, the multi-feature nexus analysis is straightforward for patents that cover the product itself instead of a "feature" or "attribute[] of the finished consumer good" because "it is not possible to separate" the patent "from the product itself in evaluating consumer demand and nexus." Janssen Prods., 109 F. Supp. 3d at 700. In such cases, nexus is "apparent." Genband, 861 F.3d at 1384 n.2. If the "Patent encompasses nearly the entire Device[, then] . . . [d]emand for the Device can fairly be described as demand for the Patent." Apnea Scis. Corp. v. Koncept Innovators, Inc., 2016 WL 9086937, at *6 (C.D. Cal. Nov. 7, 2016); see also Power Probe Grp., Inc. v. Innova Elecs. Corp., 2023 WL 7043388, at *13 (D. Nev. Oct. 25, 2023) (distinguishing multi-featured nexus inquiry because "Plaintiff's patent encompasses the entire product at issue, not merely a feature, and Plaintiff's evidence that it will likely suffer irreparable harm absent an injunction demonstrates the requisite causal nexus").

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Applying the above principles to the pharmaceutical context, the nexus requirement is satisfied if a manufacturer "would not be able to make the products proposed in its" regulatory filing without infringing the asserted patents. Janssen Prods., 109 F. Supp. 3d at 700; see also Mylan Institutional LLC v. Aurobindo Pharma Ltd., 857 F.3d 858, 873 (Fed. Cir. 2017) (upholding nexus finding because "[w]ithout infringing the . . . patents" defendants "would not be able to make the . . . product described in its ANDA") (internal quotation marks omitted).

If the connection between the infringed patent and the harm is undeniable, courts have found irreparable harm without discussing the nexus factor. See Metalcraft of Mayville, 848 F.3d at 1368-69 (affirming the grant of a preliminary injunction after reciting, but not discussing, the nexus requirement of the irreparable harm factor); see also In re Depomed Patent Litig., 2016 WL 7163647, at *78 (D.N.J. Sept. 30, 2016), aff'd sub nom. Grunenthal GMBH v. Alkem Lab'ys Ltd., 919 F.3d 1333 (Fed. Cir. 2019) (finding irreparable harm after reciting, but not discussing, the nexus requirement).

This Court finds that Regeneron has shown "some causal nexus between [SB15's infringement] and the alleged harm," which is

sufficient to demonstrate that it "is irreparably harmed by the infringement." Apple III, 735 F.3d at 1363.

SB's SB15 product is not a "complex, multi-featured" product like "smartphones and tablets," where consumer demand is driven by some features of the finished product and not others. Id. at 1362. In Apple III, for example, the patentee sought to enjoin the sale of various smartphones and tablets, and the patents at issue were directed to specific features of those devices, like pinch-to-zoom and double-tap-to-zoom functionalities that allow users to navigate the display screens. Id. at 1358. SB15 does not have analogous segregable features that one can mentally divide and then ask: "Is this a feature that drives demand?" There is no "feature" that parallels, for example, a double-tap to zoom gesture on a smart phone. Thus, Regeneron need not show the specific "connection between the patented feature and demand" that is required in cases involving multi-featured products. Id. at 1364.

In other words, the nexus inquiry has "little work to do" because SB15 "contains no feature relevant to consumers' purchasing decisions other than what the patent claims," which is the drug product. Genband, 861 F.3d at 1384, n.2. The multi-feature nexus analysis does not apply to the Product Patent because its claims cover SB15 itself — [redacted]

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[redacted]—not a "feature" or "attribute[] of the finished consumer good." Janssen Prods., 109 F. Supp. 3d at 700. Indeed, in assessing another nexus question, the Court previously noted that there was a connection between the Product Patent's claims and certain unexpected properties because Eylea exhibited those properties and Eylea "is the invention disclosed and claimed in the [product] patent." Mylan, 2024 WL 382495, at *60. So too here. The claims require a vial comprising aflibercept, an organic co-solvent, a buffer, and a stabilizing agent and 98% native conformation as measured by size exclusion chromotography. SB's SB15 product—not a component or feature thereof—is the subject of the infringed claims. As a result, "it is not possible to separate" the Product Patent "from the product itself in evaluating consumer demand and nexus." Janssen Prods, 109 F. Supp. 3d at 700. Thus, nexus is "apparent." Genband, 861 F.3d at 1384, n.2.

In yet another framing of this concept that applies in the pharmaceutical context, the nexus requirement is satisfied here because SB "would not be able to make the products proposed in its" BLA without infringing the Product Patent. Janssen Prods., 109 F. Supp. 3d at 700. This Court has already held that SB's BLA Product likely infringes the asserted claims of the Product Patent.

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** SEALED **

ORDER GRANTING MOTIONS FOR PRELIMINARY INJUNCTION

[redacted]

[redacted] Because "without infringing the . . . patents" SB "would not be able to make the . . . product described in" their BLA, SB's infringement is prerequisite to SB15's sales and Regeneron's harm. Mylan Inst'l, 857 F.3d at 873.

Even were the Court to ignore that SB has sought and received FDA approval only for SB15 and ask instead whether Defendants could have made and obtained approval for some non-infringing alternative biosimilar product, the result of the Court's analysis would be the same. Dr. Trout explained that SB15 could not "simply alter the SB15 formulation to attempt to avoid infringement" and that "any necessary changes would require additional testing and other product changes, with no guarantee that a non-infringing product would work as intended." Trout App'x B ¶ 5.

SB nonetheless asserts that the nexus requirement is not met because Regeneron's expert Dr. Trout "provided testimony confirming lack of nexus." Opp. 18-19. SB claims that Dr. Trout testified that "only 95% stability, not the 98%" specified in the patent, is sufficient for FDA approval. Id. [redacted]

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ORDER GRANTING MOTIONS FOR PRELIMINARY INJUNCTION

[redacted] Rather, any necessary changes would require additional testing and other product changes, with no guarantee that a non-infringing product would work as intended." Id. ¶ 5.

Alternatively, the Court holds that Regeneron has demonstrated nexus even under the multi-feature standard. The Court previously found that "Eylea demonstrated three critical and unexpected properties: comparable (1) safety and (2) efficacy to ranibizumab, along with (3) the durability to be dosed half as frequently as ranibizumab (after three loading doses for wet AMD)" and that Regeneron had "established a sufficient nexus between the claims [of the Product Patent] and the unexpected properties." Mylan, 2024 WL 382495, at *59-60. With respect to efficacy and extended dosing intervals, the Court found: "The record at trial demonstrated that the unexpected properties stemmed from the claimed compositions as a whole, including the 40 mg/ml aflibercept concentration. . . . [T]he aflibercept protein does contribute to the longer half-life of Eylea, . . . but aflibercept's concentration is also critical to its half-

life." Id. at *60. With respect to safety, the Court found: "[T]he stability of the claimed compositions, including the required 98% native conformation, indicated to the POSA that there's a relatively lower risk of inflammation." Id. (quotation marks omitted). These features help drive Eylea's success; SB's infringement of the Product patent will thus likewise drive the success of its product, and cause Regeneron's harm.

The nexus requirement is thus satisfied.

D. The Balance of Equities Favors an Injunction.

This third injunctive relief factor requires the Court to balance the harm an injunction would cause to the party opposing an injunction with the harm the movant would suffer should the requested injunction be denied. Robert Bosch, 659 F.3d at 1156. In performing this balancing of hardships, the Court considers only the harm to the parties, not to the interests of third parties such as customers or patients. Acumed LLC v. Stryker Corp., 551 F.3d 1323, 1330 (Fed. Cir. 2008).

Regeneron contends that, absent injunctive relief, SB will launch SB15 and compete directly with Regeneron, placing a substantial hardship on Regeneron. Regeneron PI Br. at 20-24. Regeneron argues that such sales of SB15 will cause it to suffer irreparable harms, including market share erosion, price erosion,

disruption of payor relationships, harm to the commercial trajectory of Regeneron's Eylea HD product, reputational harm, and loss of research and development funding. Regeneron submits testimony from Mr. Clark and Dr. Sheridan to substantiate those harms. Clark Decl. ¶¶ 6-19; Sheridan Decl. ¶¶ 60-101.

SB argues it too will suffer lost sales if an injunction is entered. SB contends that [redacted] Opp. at 25. While the precise amount of lost sales of SB15 is uncertain, Regeneron does not dispute at least some sales will be lost if an injunction is entered.

SB also argues it will be harmed by any delay in the launch of SB15 because such delay will prevent the accumulation of "post-launch evidence of safety and efficacy" of SB15. Opp. at 25; Cockburn ¶ 156. SB and its economics expert, Dr. Cockburn, claim that real world evidence of efficacy is important because "ophthalmologists are less familiar with biosimilars than doctors in other fields" which causes them to be "reluctant to use biosimilars" absent such evidence. Opp. at 25 [redacted]; Cockburn Decl. ¶¶ 41, 154, 156; Cockburn Tr. at

56:2-61:18, 82:13-85:17. Thus, SB claims that delay in garnering this evidence will "set SB back 12-18 months." Opp. at 25.

Regeneron responds that lost sales of SB15 are not harms that should be given weight in the balance of hardships analysis, as they would be sales of a product that likely will be found to infringe Regeneron's patent rights. Reply at 15. Regeneron further contends that any harms to SB from the lost sales of SB15 will be fully redressed by requiring Regeneron to post a bond pursuant to Rule 65(c) of the Federal Rules of Civil Procedure. Regeneron PI Br. at 25 n.6. With respect to SB's argument that a delay in launching SB15 will prevent it from generating real world evidence that would better position SB15 in the market in the future, Regeneron also points out this is precisely what Regeneron seeks to avoid with an injunction—SB15's pre-trial sales will generate evidence harming Regeneron. Reply at 15.

The Court finds the balance of hardships favors the requested injunctive relief here. As described above, the Court finds that the launch and continued sale of SB15 in the absence of an injunction will result in direct competition between SB and Regeneron and cause harms to Regeneron that cannot be fully calculated, quantified, or compensated by remedies available at law. See Sheridan Decl. ¶¶ 60-101. Forcing a patentee to compete

directly with its patented technology results in substantial hardship on the patentee. Robert Bosch, 659 F.3d at 1156 ("requiring [the patentee] to compete against its own patented invention, with the resultant harms described above, places a substantial hardship on [the patentee]"); Hafco Foundry & Mach. Co. v. GMS Mine Repair & Maint., Inc., 2018 WL 1786588, at *4 (S.D. W. Va. Apr. 12, 2018) (patentee "will be forced to compete against its own patent, in itself, a significant hardship"). Absent an injunction, SB will launch and sell SB15 during the pendency of this litigation, and those sales will cause Regeneron to suffer market share erosion, price erosion and disruption of payor relationships. See Clark Decl. ¶¶ 6-19; Sheridan Decl. ¶¶ 60-101. In the event SB15 were later removed from the market, SB's at-risk launch also would cause Regeneron to suffer loss of reputation and goodwill should Regeneron attempt to recapture the higher prices eroded by SB. See Clark Decl. ¶ 11; Sheridan Decl. ¶¶ 84-87. And, in the event SB15 were later removed from the market by a subsequent injunction, Regeneron also would suffer loss of reputation and goodwill associated with being faulted for the removal of a competing product from the market. Regeneron PI Br. at 23 (citing Baxalta, 2018 WL 3742610, at *11).

While SB will lose some prospective revenue from issuance of

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an injunction, those lost sales of SB15 do not tip the balance in SB's favor. SB's lost sales result from its decision to develop and seek to market SB15, a drug product the Court has determined likely will be found to infringe at least the Asserted Product Patent Claims. Such lost infringing sales typically are not given meaningful weight in a balance of hardships analysis. See Celsis In Vitro, Inc., 664 F.3d at 931 ("[T]he preliminary record suggests that LTC's losses were the result of its own calculated risk in selling a product with knowledge of Celsis' patent."); Acumed v. Stryker, 551 F.3d 1323, 1330 (Fed. Cir. 2008) (finding no abuse of discretion where a district court did not to consider [the accused infringer's] expenses in designing and marketing the [accused product], since those expenses related to an infringing product"); Broadcom v. Qualcomm, 543 F.3d 683, 704 (Fed. Cir. 2008) (agreeing that an accused infringer "should not be permitted to prevail on a theory that successful exploitation of infringing technology shields a party from injunctive relief."); Sanofi-Synthelabo v. Apotex, Inc., 470 F.3d 1368 (Fed. Cir. 2006) (noting that the accused infringer's harms were "almost entirely preventable" and "the result of its own calculated risk"); Windsurfing Int'l v. AMF, 782 F.2d 995, 1003 n.12 (Fed. Cir. 1986) ("One who elects to build a business on a product found to infringe cannot be heard to

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complain if an injunction against continuing infringement destroys the business so elected."). Even were SB's lost sales given full weight here, the Court would find they do not outweigh the above-described irreparable harms that Regeneron would incur in the absence of an injunction.

The Court's conclusion on this factor is further supported by the fact that SB has not yet launched SB15. An injunction therefore will not force SB to withdraw its product from the market and face the potential consequences and harms that may flow from such withdrawal. Instead, an injunction simply will maintain the status quo pending trial, imposing only a relatively minimal hardship on SB. See Impax Labs., Inc. v. Aventis Pharms., Inc., 235 F. Supp. 2d 390, 396 (D. Del. 2002) ("[G]ranting the Motion for Preliminary Injunction will cause Impax only minimal hardship since doing so will leave Impax in the same position as it was in before the injunction was granted, i.e., excluded from the riluzole market."). The harm from a patentee's loss of the value of its patent is more substantial than the harm from an accused infringer's inability to enter the market earlier. See Glaxo Grp. Ltd. v. Apotex, Inc., 64 F. App'x 751, 756 (Fed. Cir. 2003) ("[W]ithout the preliminary injunction, Glaxo would lose the value of its patent while Apotex would only lose the ability to go on to

the market and begin earning profits earlier."). Thus, Regeneron's hardship absent an injunction outweighs SB's hardship if an injunction delays its early entry into the aflibercept market.

The Court's conclusion is also supported by the bond requirement of Rule 65(c) of the Federal Rules of Civil Procedure. Regeneron must "give[] security in an amount that the court considers proper to pay the costs and damages sustained by any party found to have been wrongfully enjoined or restrained." Fed. R. Civ. P. 65(c). Such a bond will ensure SB will be compensated for any lost revenue in the event the Court's injunction is later reversed. Id.; Glaxo Grp., 64 F. App'x at 756.

With respect to SB's contention that an injunction will delay its accumulation of real-world evidence that ultimately will harm SB15's adoption and market position in the future, the Court does not believe such harms are sufficient to tilt the balance of hardships in SB's favor. As with lost sales, this harm is a result of SB's own decision to invest in the development of an aflibercept biosimilar the Court has found likely to infringe. Moreover, Regeneron points out and the Court agrees that, while a delay in generating post-launch evidence of SB15's efficacy and safety would hinder SB's efforts to establish a foothold in the market, the denial of an injunction and SB's generating of such evidence

would cause Regeneron to suffer a parallel injury. That is, the real-world evidence that would benefit SB would equally harm Regeneron, allowing a direct competitor to establish a foothold in a market it would not otherwise have been able to penetrate. See Celsis In Vitro, Inc., 664 F.3d at 931 (finding parallel harm to an alleged infringer upon entry of preliminary injunction would also be incurred by the patentee absent a preliminary injunction). For these reasons, this harm does not shift the balance of hardships in either direction.

E. The Public Interest Favors an Injunction.

The final factor in the injunctive relief analysis requires the Court to consider the impact of an injunction on the public interest. Hybritech v. Abbott Labs., 849 F.2d 1446, 1458 (Fed. Cir. 1988). There is a well-recognized "public interest in protecting rights secured by valid patents." Id.; see also, e.g., Sanofi-Synthelabo v. Apotex, Inc., 470 F.3d 1368, 1383-84 (Fed. Cir. 2006); Patlex Corp. v. Mossinghoff, 758 F.2d 594, 599 (Fed. Cir. 1985). This factor "nearly always weighs in favor of protecting property rights in the absence of countervailing factors, especially when the patentee practices his inventions." Apple IV, 809 F.3d at 647.

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Regeneron contends the public interest factor favors entry of an injunction because the public benefits from innovation in the pharmaceutical industry and that such innovation is fostered by intellectual property rights. Regeneron PI Br. at 25. Regeneron points out that it has invested billions to discover and develop its own medicines and argues that this work is made possible by Regeneron's intellectual property and the sales of its patent-protected products, including Eylea. Id.; Clark Decl. ¶ 19. For its part, SB contends this factor counsels against an injunction because the public has an interest in access to lower-cost aflibercept products. Opp. at 25.

The Court finds the public interest factor favors entry of an injunction. Intellectual property rights promote innovation across a number of fields, including pharmaceuticals. The Court finds there exists a public interest in protecting such rights and encouraging this innovation. Sanofi-Synthelabo, 470 F.3d at 1383-84; Hybritech, 849 F.2d at 1458; Patlex Corp., 758 F.2d at 599. For the reasons discussed above, the Court has found Regeneron is likely to demonstrate SB's sales of SB15 would infringe the Asserted Product Patent Claims and that such claims are likely valid. The public has an interest in safeguarding these patent rights.

SB does not identify any interest the public may have in accessing its aflibercept biosimilar beyond a general interest in access to lower-cost drug products. Opp. at 25. The Court finds such interest is outweighed by the compelling interest in fostering pharmaceutical innovation. In reaching this conclusion, the Court finds itself in company with most of courts that have considered this issue, including the Federal Circuit. See, e.g., Hybritech, 849 F.2d at 1458; Douglas Dynamics,717 F.3d at 1346 ("[T]he public has a greater interest in acquiring new technology through the protections provided by the Patent Act than it has in buying 'cheaper knock-offs.'").

The Court recognizes the apparent tension between traditional patent law concepts and the BPCIA, particularly as it pertains to the public interest factor. Of course, "the public has a well-recognized interest in protecting patent rights and fostering innovation," Apple, 809 F. 3d at 647, Congress also has enacted significant legislation, the BPCIA, that is designed to foster competition and make alternative and lower-cost therapeutics available to patients, and Courts have expressly found in the BPCIA biosimilar context that "[f]or pharmaceutical drugs that prolong and save lives, there is a critical public interest in affordable access to those drugs," Genentech, Inc. v. Immunex Rhode Island

Corp., 395 F. Supp. 3d 357, 366 n.6 (D. Del. 2019), aff'd, 964 F.3d 1109 (Fed. Cir. 2020); see also Janssen Biotech, Inc. v. Celltrion Healthcare Co., 210 F. Supp. 3d 244, 252 (D. Mass. 2016) (recognizing a strong public interest in "[a] less expensive biosimilar alternative to compete fairly with [the reference product]"). Nonetheless, after considering the applicable authority, even if not squarely within BPCIA's umbrella, the Court ultimately concludes that the public interest factor also weighs in favor of preliminary injunctive relief here.

V. CONCLUSION

Upon consideration of Plaintiff's Motion for Preliminary Injunction, accompanying Memorandum in Support, exhibits attached thereto, and all of the evidence presented before this Court, for the reasons set forth below, it is **ORDERED THAT:**

Pursuant to Federal Rule of Civil Procedure 65, Regeneron's Motions for Preliminary Injunctions are **GRANTED** [ECF No. 118 in 1:23-CV-94, ECF No. 99 in 1:23-CV-106]. The Court finds that it need not resolve SB's emergency motion to compel before issuing this ruling, and the emergency motion to compel is **DENIED** without prejudice [ECF No. 200-2 in 1:23-CV-94, ECF No. 182-2 in 1:23-CV-106].

Pursuant to Federal Rule of Civil Procedure 65(d)(1), and for

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the reasons provided herein, the Court makes the following findings and conclusions based upon the preliminary record developed in connection with Regeneron's motions.

1. Defendant SB has sought FDA approval via its Biologics License Application No. 761350 to market a biosimilar version of Regeneron's drug EYLEA®. SB's product that is the subject of this BLA is also known as "SB15."

2. Regeneron has demonstrated that it is likely to succeed in proving that the SB15 formulation described in BLA No. 761350 infringes claims 4, 7, 9, 11, 14-17, and 55 of U.S. Patent No. 11,084,865 (the '865 Patent).

3. SB has not demonstrated that there is a substantial question about the validity of the infringed claims of the '865 Patent.

4. Regeneron has demonstrated that any manufacture, importation, or commercialization of SB15 prior to the expiry of the '865 Patent will cause it irreparable harm.

5. Regeneron has demonstrated that the balance of hardships favors Regeneron, not SB.

6. Regeneron has demonstrated that the public interest favors granting the preliminary injunctions in order to protect intellectual property rights and because the public is already

able to receive aflibercept therapy in the form of EYLEA®.

7. Regeneron has demonstrated that there is a reasonable probability of ultimate success upon the question of personal jurisdiction when the actions against SB are tried on the merits.

A. Scope of Injunction and Meet-and-Confer Requirement

The Court is mindful that there are complexities associated with the multi-jurisdiction manufacture of SB's product for markets outside the United States — markets which are beyond the territorial reach of U.S. patent laws. Microsoft Corp. v. AT&T Corp., 550 U.S. 437, 454-55 (2007) ("The presumption that United States law governs domestically but does not rule the world applies with particular force in patent law."). In order to ensure that the injunction entered by this Court does not ensnare activity that it is not meant to ensnare, and does not disrupt activities directed to non-U.S. markets, **the Court hereby orders the parties to meet and confer regarding the conditions and scope of the injunction and jointly submit to the Court a proposed form of injunction order within five (5) business days of entry of this order.** The Court further finds that because the only harm that Regeneron presented in the record of these injunction proceedings is directed to commercial marketing within the U.S., the proposed form of injunction should likewise be restricted to prohibiting

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the commercial sale to customers in the U.S. of SB products subject to the BLA No. 761350 product that the FDA approved on May 20, 2024.

B. Meet-and-Confer on Public Order

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.**

C. Rule 65(c) Security

Pursuant to Rule 65(c), the Court must require sufficient security from Plaintiff in an amount the Court considers proper to pay the costs and damages sustained by any wrongfully enjoined party. **The parties are hereby ordered to meet and confer regarding an appropriate security amount and form within five (5) days of entry of this Order. They shall thereafter submit a joint proposed order establishing security under Rule 65(c). If no joint proposal**

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is feasible after good faith joint efforts, each party shall submit their own proposal with supporting evidence for the Court's consideration and a proposed order effectuating same within ten (10) days of entry of this order.

It is so **ORDERED.**

The Clerk is **DIRECTED** to transmit copies of this Order **only** to counsel for Regeneron and SB in cases 1:23-CV-94 and 1:23-CV-106.

DATED: June 14, 2024

Tom S Kleeh

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