

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FORMYCON AG,
Petitioner,

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner.

Case: IPR2025-00233
U.S. Patent No. 11,084,865

PATENT OWNER'S PRELIMINARY RESPONSE

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2004	Celltrion Redacted PI Decision, 24-md-3103, Dkt. 248 (N.D.W. Va.)
2005	SB Appeal Decision, 24-1965, Dkt. 76 (Fed. Cir.)
2006	Formycon Appeal Decision, 24-2009, Dkt. 67 (Fed. Cir.)
2007	Celltrion Appeal Decision, 24-2058, Dkt. 62 (Fed. Cir.)
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2026	U.S. Patent Application Publication No. 2003/0113316 (“Kaisheva”)
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I. Preliminary Statement

Regeneron's U.S. Patent 11,084,865 ('865 patent) discloses and claims the formulation of Regeneron's groundbreaking ophthalmic product, Eylea®. The Petition filed by Formycon AG ("Formycon") raises obviousness challenges to the '865 patent that multiple courts repeatedly have considered and rejected, including in connection with a two-week trial, four preliminary-injunction proceedings (including against Formycon), and four co-pending appeals (including one filed by Formycon) to the Federal Circuit. In each case, the defendants—all entities seeking to market biosimilar versions of Eylea®—raised obviousness or obviousness-type double patenting ("ODP") challenges to the '865 patent. Across these proceedings, the district court and the Federal Circuit have considered hundreds of pages of briefing and thousands of pages of expert testimony addressing the '865 patent. And in each case decided to date that addressed those issues—one bench-trial decision, three preliminary-injunction decisions, and three appeal decisions—the district court and the Federal Circuit have upheld the '865 patent against obviousness and ODP challenges raising substantially similar arguments as those in the Petition. Remarkably, Formycon never acknowledges that its Petition seeks reversal of at least seven judicial decisions, including three by the very Court that would review this Board's adjudication of its Petition (if instituted). But ignoring entirely the numerous, well-founded court decisions confirming the novelty and non-

obviousness of the '865 patent claims is no basis for showing a reasonable likelihood of success on unpatentability.

Formycon's Petition should be denied for two fundamental reasons: (1) it raises precisely the kind of inefficient and duplicative validity challenge that *Fintiv* forecloses; and (2) Formycon's arguments on the merits fare no better here than in the prior litigation, and the Petition thus fails to show a likelihood of success.

First, the Petition is contrary to the AIA's basic objective: "to provide an effective and efficient alternative to the district court litigation." *NHK Spring Co. v. Intrix-Plex Tech., Inc.*, IPR2018-00752, 2018 WL 4373643, at *7 (P.T.A.B. Sept. 12, 2018) (precedential). It is difficult to imagine a less efficient use of the Board's resources than to adjudicate, for the eighth time, the same disputes the district court and Federal Circuit already have resolved in Regeneron's favor seven times, across hundreds of pages of decisions. As explained below, the *Fintiv* factors all favor non-institution or at most are neutral.

Second, the district court's and Federal Circuit's analysis of virtually all of Formycon's cited prior art and arguments also forecloses any reasonable likelihood of success. First, as these decisions have held repeatedly, the person of ordinary skill in the art ("POSA") understood that glycosylation of aflibercept—required by each challenged claim—was disfavored for an ophthalmic formulation; and none of Formycon's art is to the contrary. Second, the POSA understood the prior art to

teach away from using the 40 mg/mL aflibercept concentration upon which Formycon's obviousness challenge is premised. Third, the POSA lacked a reasonable expectation of achieving the claimed stability criterion—98% native conformation after two months' storage as measured by size exclusion chromatography ("SEC")—and Formycon has no evidence this criterion was inherent. Each of these three reasons is supported by findings affirmed by the Federal Circuit, and each independently precludes any reasonable likelihood of success.

II. Background

Regeneron has been litigating the '865 patent covering its Eylea[®] product against putative biosimilars, including Formycon, for two-and-a-half years. That litigation has resulted in four decisions of the district court and three decisions of the Federal Circuit addressing the validity of the '865 patent (with another pending). In each of these decisions, the district court and the Federal Circuit concluded, *inter alia*, that the '865 patent is not invalid for obviousness or obviousness-type double patenting ("ODP").

A. Parallel Proceedings

Regeneron has sued Mylan, SB, Formycon, Celltrion, and Amgen for infringement of the '865 patent. These suits have been consolidated for pre-trial purposes as a multidistrict litigation in the Northern District of West Virginia. *In re*

Aflibercept Pat. Litig., 730 F. Supp. 3d 1374, 1377 (J.P.M.L. 2024). That court has issued one bench-trial decision (*Mylan*) and four preliminary-injunction decisions (*SB*, *Formycon*, *Celltrion*, and *Amgen*), and in each other than *Amgen* (which did not address invalidity), the district court rejected obviousness or ODP challenges to the ‘865 patent.

On appeal, the Federal Circuit affirmed three of those decisions, and one (*Mylan*) remains pending.

These decisions repeatedly have confirmed that:

(1) the POSA would have been motivated against using a glycosylated form of aflibercept, *Regeneron Pharm., Inc. v. Mylan Pharm. Inc.*, 714 F. Supp. 3d 652, 740-41 (N.D.W. Va. 2024) (“*Mylan*”); *In re Aflibercept Pat. Litig.*, 2024 WL 3422971, at *25-28 (N.D.W. Va. June 24, 2024) (“*SB PI Decision*”); *In re Aflibercept Pat. Litig.*, 2024 WL 3423047, at *29-32 (N.D.W. Va. July 9, 2024) (“*Formycon PI Decision*”); Ex.2004 (*Celltrion PI Decision*) at 86-97;¹ *Regeneron Pharm., Inc. v. Mylan Pharm. Inc.*, 127 F.4th

¹ The district court’s validity analyses in the *SB PI Decision*, *Formycon PI Decision*, and *Celltrion PI Decision* are substantially similar because the three defendants raised substantially similar ODP defenses. For brevity, Regeneron generally cites the *SB PI Decision*.

896, 913-14 (Fed. Cir. 2025) (“SB”); *Regeneron Pharm., Inc. v. Mylan Pharm. Inc.*, 2025 WL 324288, at *6-7 (Fed. Cir. Jan. 29, 2025) (“Formycon”);

(2) the prior art taught away from using 40 mg/mL aflibercept, *Mylan*, 714 F. Supp. 3d at 737-40;

(3) the POSA would not have been motivated to achieve 98% native conformation after two months’ storage and would not have had a reasonable expectation of success in doing so, and that native-conformation level was not inherent in the prior art, *Mylan*, 714 F. Supp. 3d at 741-42, 744-45; *SB PI Decision*, 2024 WL 3422971, at *28-32; *SB*, 127 F.4th at 912-13; *Formycon*, 2025 WL 324288, at *5-6; *Regeneron Pharm., Inc. v. Mylan Pharm. Inc.*, 2025 WL 706079, at *2-3 (Fed. Cir. Mar. 5, 2025) (“Celltrion”); and

(4) objective evidence has a nexus to, and supports, nonobviousness, *Mylan*, 714 F. Supp. 3d at 745-48; *SB PI Decision*, 2024 WL 3422971, at *33.

B. Formycon’s Petition

Formycon’s Petition repeats the obviousness arguments already considered and rejected by the district court and the Federal Circuit decisions it wholly ignores. For instance, Formycon principally asserts—like Mylan did before—that the POSA would have used Fraser’s formulation as “a natural starting point” and then relied on various secondary references to “optimiz[e]” the concentrations of aflibercept, buffer, organic co-solvent, stabilizing agent, and tonicity agent, as well as the pH, to

make a formulation falling within the scope of the '865 patent claims. Pet. 30, 33-37; *Mylan*, 714 F. Supp. 3d at 723, 743. Like Mylan, Formycon maintains that the POSA would have had a reasonable expectation of success in making a formulation with 98% native conformation. Pet. 46-48; *Mylan*, 714 F. Supp. 3d at 742. Formycon further argues, like Formycon and Mylan before, that aflibercept is necessarily glycosylated, and that 98% native conformation is inherent. Pet. 38-45; *Mylan*, 714 F. Supp. 3d at 741-42; *Formycon PI Decision*, 2024 WL 3423047, at *28-29, *32-35. Finally, Formycon also argues, like it and Mylan before, that objective evidence lacks nexus and does not support nonobviousness. Pet. 62-63; *Mylan*, 714 F. Supp. 3d at 745-48; *Formycon PI Decision*, 2024 WL 3423047, at *37-38.

III. The Board Should Deny Institution Under *Fintiv*

The Board should exercise its discretion under 35 U.S.C. § 314(a) to deny institution of Formycon's Petition. Formycon's Petition, filed 365 days after it was sued, implicates the same or substantially similar claims, prior-art references, and issues that have been decided repeatedly by the district court and the Federal Circuit. Given the considerable investment of the parties and the courts in these proceedings, institution would be highly inefficient. In addition, Formycon's Petition, as explained below, is fatally deficient on the merits. Accordingly, the Board should decline institution.

A. Investments in Overlapping Parallel Litigation (*Fintiv* Factors 3 and 4)

The parties, the district court, and the Federal Circuit all have substantially invested in the *SB*, *Mylan*, *Formycon*, and *Celltrion* litigations—each of which implicates the same patent and similar issues to Formycon’s Petition. The seven court decisions—totaling nearly 1000 pages, *see* Ex.2001-2007, with hundreds of pages on obviousness and ODP—are the culmination of years of litigation between Regeneron and biosimilar manufacturers, including a two-week trial, a lengthy *Markman* hearing in the *Mylan* litigation, four injunction proceedings involving voluminous expert declarations and numerous expert depositions, and four arguments concerning validity before two distinct Federal Circuit panels. The third and fourth *Fintiv* factors thus decisively favor discretionary denial.

1. There Has Been Significant Investments in the Related District Court Litigations and Appeals

a. Investment in the *SB*, *Mylan*, *Formycon*, and *Celltrion* Litigations (*Fintiv* Factor 3)

The district court’s preliminary injunction against Formycon—in which the court directly addressed validity—alone constitutes a substantial investment. *See Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, 2020 WL 2126495, at *4 & n.16 (P.T.A.B. Mar. 20, 2020) (precedential) (identifying a “preliminary injunction order after finding petitioner’s invalidity contentions unlikely to succeed on the merits” as a “substantive order[] related to the patent at issue in the petition” that “favors

denial” (citing *E-One, Inc. v. Oskhosh Corp.*, IPR2019-00162, 2019 WL 2396798 (P.T.A.B. June 5, 2019)); *Int’l Bus. Machs. Corp. v. Trusted Knight Corp.*, IPR2020-00323, 2020 WL 3892131, at *5 (P.T.A.B. July 10, 2020) (same). As the Federal Circuit has explained, the IPR institution “procedure is directly analogous to a district court determining whether there is ‘a likelihood of success on the merits’ and then later deciding the merits of a case.” *Ethicon Endo-Surgery, Inc. v. Covidien LP*, 812 F.3d 1023, 1030 (Fed. Cir. 2016); *Monosol Rx, LLC v. Arius Two, Inc.*, IPR2014-00376, 2016 WL 7985428, at *2 (P.T.A.B. Dec. 19, 2016). Accordingly, the district court’s grant of a preliminary injunction—especially since its decision addressed patent validity—weighs heavily in favor of discretionary denial of institution. *See, e.g., E-One*, IPR2019-00162, 2019 WL 2396798, at *4-9 (denying institution under § 314(a) in light of preliminary injunction); *Edwards Lifesciences Corp. v. Evalve, Inc.*, IPR2019-01479, 2020 WL 927867, at *4-5 (P.T.A.B. Feb. 26, 2020) (similar).

But the district court did far more. It conducted a two-week trial in the *Mylan* case and three other preliminary-injunction proceedings focused on validity of the ’865 patent. As described below (*infra* III.A.2), Formycon’s Petition substantially overlaps with the *SB*, *Mylan*, *Formycon*, and *Celltrion* litigations, so all four parallel proceedings are relevant to the Board’s *Fintiv* analysis. *See generally Edwards Lifesciences Corp. v. Colibri Heart Valve LLC*, IPR2020-01649, 2021 WL 1158197,

at *5-6 (P.T.A.B. Mar. 26, 2021); *Dolby Labs., Inc. v. Intertrust Techs. Corp.*, IPR2020-00661, 2020 WL 6084148, at *5-7 (P.T.A.B. Oct. 15, 2020); *TCO AS v. NCS Multistage Inc.*, PGR2020-00077, 2021 WL 662165, at *6-7 (P.T.A.B. Feb. 18, 2021). In these four litigations, the district court has conducted the *Mylan* bench trial and *Markman* hearing; considered testimony from seven experts addressing the '865 patent; resolved three preliminary-injunction motions, one permanent-injunction motion, two motions for temporary restraining orders, and three motions to strike validity-related fact declarations, among others; and issued hundreds of pages of analysis on obviousness and ODP alone. It is hard to overstate the district court's investment in these cases generally and in the '865 patent in particular.

And that MDL litigation, of course, is ongoing. Formycon's MDL co-defendant has proposed a schedule with trial occurring in March 2026. Ex.2008. If that schedule is adopted, the district court and parties in the *Formycon* litigation will further invest in claim construction, fact discovery, expert discovery, summary judgment, *Daubert*, motions-in-limine, and a bench trial—all before the Board would issue its Final Written Decision here. *Id.* And the coordinated cases against the other biosimilars likewise will resume, further compounding these parallel proceedings.

b. Investment in the *SB*, *Mylan*, *Celltrion*, and *Formycon* Appeals

The substantial investment in the appeals from those decisions likewise supports discretionary denial. The Federal Circuit has held argument on five appeals from the *Mylan* trial and injunction decisions relating to the '865 patent, in December (*SB* and *Formycon*), January (*Amgen*), and February (*Mylan* and *Celltrion*). The Federal Circuit has issued decisions in the *SB*, *Formycon*, and *Celltrion* appeals that address (and reject) many of the assertions in *Formycon*'s Petition. *See infra* IV.D.1, IV.D.3. Given the Federal Circuit's median time of 85 days between oral argument and decision, *see* Days from Argument to Decision, <https://federalcircuitry.mofo.com/statistics>, the decision in *Mylan*'s expedited appeal regarding the novelty and non-obviousness of the '865 patent, including over the Fraser prior art in *Formycon*'s Petition, likely will issue in or soon after May 2025. *See infra* III.A.2.b-c. Institution of *inter partes* review after such investments by the parties, district court, and Federal Circuit would be manifestly inefficient. *Cf. Snap Inc. v. Blackberry Ltd.*, IPR2020-00392, Paper 8 at 12-16 (P.T.A.B. July 13, 2020) (finding *Fintiv* factors favored discretionary denial where appeal of final district-court determination of patent invalidity was pending before Federal Circuit).

c. *Formycon*'s Unexplained Delay

Formycon's undue delay in filing its Petition further favors discretionary denial. *Formycon* did not file its Petition until late November 2024, exactly 365

days after Regeneron filed suit, nine months after Regeneron filed its preliminary-injunction motion, and five months after the district court granted Regeneron's motion. Formycon's delay in challenging the '865 patent was, in short, a tactical choice.

Formycon has offered no excuse for its delay, which substantially increased the costs incurred by the parties and the courts. Pet. 69-70. Formycon's unexplained delay thus weighs in favor of discretionary denial. *Fintiv*, 2020 WL 2126495, at *5; *Ericsson Inc. v. Godo Kaisha IP Bridge 1*, IPR2022-00725, 2022 WL 16704704, at *4 (P.T.A.B. Nov. 2, 2022).

2. The Related Litigation Overlaps with Formycon's Petition (*Fintiv* Factor 4)

The fourth *Fintiv* factor weighs heavily in favor of discretionary denial. The claims Formycon challenges in its Petition substantially overlap with the claims challenged at the district court; its arguments to the contrary are unavailing. The prior-art references and factual issues implicated by Formycon's Petition also substantially overlap with those before the district court. Accordingly, this factor strongly favors discretionary denial.

a. The Challenged Claims Substantially Overlap

Formycon's Petition challenges claims 1-12, 14-17, 19-20, 22-36, 39-42, 44-45, and 47-55. Pet. 1. Claims 4, 7, 9, 11, and 14-17 are at issue in the *Mylan* litigation and were asserted in preliminary-injunction proceedings against

Formycon. *Mylan*, 714 F. Supp. 3d at 677; *Formycon PI Decision*, 2024 WL 3423047, at *3. Formycon’s Petition thus challenges all the claims asserted in the *Mylan* and *Formycon* proceedings.

Formycon cannot foreclose discretionary denial merely by challenging additional claims that have not been asserted or otherwise disputed in the parallel proceedings. Pet. 69-70. The Board has repeatedly affirmed that “the mere existence of non-overlapping claims does not ... favor[] institution”; rather, the Board considers “the similarity of the claims challenged in the petition to those at issue in the district court” as well as the other claims’ significance. *E.g.*, *Samsung Elecs. Co. v. Clear Imaging Rsch., LLC*, IPR2020-01551, 2021 WL 628829, at *8-9 (P.T.A.B. Feb. 17, 2021); *Amazon.com, Inc. v. Vocalife LLC*, IPR2020-00864, 2020 WL 6323540, at *5 (P.T.A.B. Oct. 28, 2020).

Formycon does not argue that the additional claims implicate limitations that materially differ from those in the parallel proceedings. Rather, Formycon repeatedly asserts the opposite. *E.g.*, Pet. 49-61 (dependent claims are “obvious for the same reasons as” claims from which they depend); Pet. 1 (“Both sets of claims,” *i.e.*, the vial and pre-filled syringe claims, “are rendered obvious by two publications”); Pet. 63 (“[T]he Ground II claims are obvious for the same reasons as described above regarding the Ground I claims.”); Pet. 63-66 (PFS claims are

“obvious for the same reasons as set forth in Section VII with respect the Vial Claims”).

Furthermore, Formycon has not explained how it would be prejudiced by non-institution. Formycon merely complains that, absent institution, the nonoverlapping claims’ validity might not be adjudicated. Pet. 69-70. But Formycon would suffer no prejudice from non-adjudication of similar claims that were not asserted in the preliminary-injunction proceedings and are unlikely to be relevant to the parties’ dispute. *Amazon.com*, 2020 WL 6323540, at *5.

b. The Prior-Art References Substantially Overlap

The Petition relies on prior art that substantially overlaps with the art asserted by Mylan. Fraser, Wulff, the 2006 Presentations, FDA Guidance, Nayar, the ’319 publication, and the ’309 publication are Formycon’s “key prior art.” Pet. 24-29. Fraser and Wulff are Formycon’s primary references, with Formycon characterizing the latter as “disclos[ing] the same aflibercept formulation used in *Fraser*,” but “to inhibit thecal angiogenesis” instead of “ovarian angiogenesis.” Pet. 24-26. Formycon also cites to Holash, Dix, and Liu. Pet. 18 n.1, 23, 42-44, 57-59. Before the district court, Mylan also advanced two Fraser-based obviousness combinations, *Mylan*, 714 F. Supp. 3d at 736, 743, and also relied on Wulff, the ’319 publication, Dix, Holash, and Liu, *id.* at 681-82, 697-98, 736-48.

Formycon's prior-art references also substantially overlap with the references it relied on in the preliminary-injunction proceedings. Formycon cites Daly, for instance, as teaching that aflibercept was known to be glycosylated at specific asparagine residues (Pet. 39). Formycon identically relied on Daly before the district court, which found that Daly teaches that aflibercept is not necessarily glycosylated and cited Daly in support of its finding that the POSA would not have been motivated to use glycosylated aflibercept. *Formycon PI Decision*, 2024 WL 3423047, at *29-31. Holash and Nayar were also at issue before the district court. *Id.* at *31, *37; *see* Pet. 18 n.1, 27, 63.

c. The Issues Substantially Overlap

There is a substantial overlap in issues between Formycon's Petition and the four parallel litigations. Specifically, Mylan—like Formycon here—asserted that the POSA had motivation to use 40 mg/mL aflibercept in an ophthalmic formulation, that aflibercept is necessarily glycosylated, that the POSA was motivated with a reasonable expectation of success to make formulations with 98% native conformation, and that no objective evidence supported nonobviousness. *Compare Mylan*, 714 F. Supp. 3d at 736-48, *with* Pet. 30, 33-48, 62-63. Furthermore, SB, Formycon, and Celltrion—again, like Formycon here—asserted before the district court that aflibercept is necessarily glycosylated; that 98% native conformation is inherent in formulations with the ingredients, concentrations, and pH recited by the

claims; that the POSA was motivated with a reasonable expectation of success to make formulations with 98% native conformation; and that no objective evidence supported nonobviousness. *Compare Formycon PI Decision*, 2024 WL 3423047, at *28-38, *with* Pet. 30, 33-48, 62-63. In rejecting those arguments, the district court made numerous factual findings, foreclosing Formycon's obviousness challenge here: (1) the prior art taught against formulations with 40 mg/mL of aflibercept; (2) aflibercept is not necessarily glycosylated; (3) the POSA was motivated against using glycosylated aflibercept; (4) 98% native conformation is not inherent in aflibercept formulations; (5) the POSA was not motivated with a reasonable expectation of success to make aflibercept formulations with 98% native conformation, and (6) secondary considerations support nonobviousness. *See Mylan*, 714 F. Supp. 3d at 736-48; *SB PI Decision*, 2024 WL 3422971, at *21-33. Based on the same or substantially overlapping prior art relied on here by SB, the Federal Circuit has already affirmed findings (2)-(5). *See SB*, 127 F.4th at 912-14; *Formycon*, 2025 WL 324288, at *5-7; *Celltrion*, 2025 WL 706079, at *3. Formycon would have to revisit and reverse all of those court findings—and others detailed below—in order to prevail. *Infra* IV.D.1-4.

B. There Is No Possibility of a Stay (*Fintiv* Factor 1)

Formycon has not sought to stay the district-court litigation, and Formycon's MDL co-defendant SB has sought an accelerated schedule in which trial would be

held in March 2026. Ex.2008. Regeneron does not intend to seek a stay either. Accordingly, the first *Fintiv* factor favors discretionary denial.

C. Trial May Be Scheduled as Early as March 2026 (*Fintiv* Factor 2)

The second *Fintiv* factor also favors discretionary denial, or is at least neutral. The Board’s statutory deadline for a final written decision would be approximately June 17, 2026. Formycon’s MDL co-defendant SB has proposed a trial date three months earlier, in March 2026. Ex.2008. Regeneron proposed that the district court convene a status conference upon resolution of the remaining pending appeals and then determine an appropriate schedule for the various parties in the MDL. Ex.2009.

In light of the significant investments in the various parallel proceedings that have already occurred and Formycon’s delay in filing its Petition, *see supra* III.A.1.c, the second *Fintiv* factor favors discretionary denial, or at least is neutral. *See Glob. Tel*link Corp. v. HLFIP Holding, Inc.*, IPR2021-00444, 2021 WL 3117130, at *7-14 (P.T.A.B. July 22, 2021) (denying institution, notwithstanding district court having not yet set trial date, based on substantial investments in and significant overlap between petition and parallel proceedings); *Mylan Labs. Ltd. v. Janssen Pharmaceutica NV*, IPR2020-00440, 2020 WL 5580472, at *6-11 (P.T.A.B. Sept. 16, 2020) (denying institution despite “[a] trial date ha[ving] not been set for the *Mylan* litigation”).

D. The Parties Are the Same as the Parallel Litigation (*Fintiv* Factor 5)

The fifth *Fintiv* factor also favors denial. Formycon is the “same party” as the parallel *Formycon* litigation. *Fintiv*, 2020 WL 2126495, at *2. The *Formycon* case is part of an MDL also including the *Mylan*, *SB*, and *Celltrion* cases. Given the overlap between these proceedings discussed above, the fifth *Fintiv* factor heavily favors denial. *See, e.g., id.* at *6 (“An unrelated petitioner should, therefore, address any other district court or Federal Circuit proceedings involving the challenged patent to discuss why addressing the same or substantially the same issues would not be duplicative of the prior case even if the petition is brought by a different party.”); *Mylan*, 2020 WL 5580472, at *7, *10 (“[B]ecause the Petitioner is the same as the defendant in the *Mylan* litigation, and because the issues in both the *Teva* and *Mylan* litigations are substantially the same as those raised in the Petition, *Fintiv* factor #5 favors denial.” (citations omitted)).

E. Formycon Is Not Likely To Succeed (*Fintiv* Factor 6)

Finally, the sixth *Fintiv* factor strongly favors discretionary denial. As discussed below, Formycon cannot demonstrate a reasonable likelihood that the claims are unpatentable, especially in light of its failure to show error in or even address the numerous district court and Federal Circuit outcome-determinative findings.

IV. Formycon Fails To Show a Reasonable Likelihood That the '865 Patent Claims Would Have Been Obvious

The numerous prior district court and Federal Circuit adjudications of the '865 patent's validity foreclose Formycon's likelihood of success. Remarkably, Formycon proceeds as if these decisions do not exist. But those decisions repeatedly have made numerous findings independently foreclosing Formycon's obviousness theories here.

A. Technical Overview

The '865 patent discloses and claims ophthalmic formulations of the fusion protein aflibercept, including Eylea[®]. Eylea[®] contains 40 mg/mL of a glycosylated form of aflibercept along with other ingredients. "Aflibercept is known as a 'VEGF antagonist' or 'VEGF trap' due to its ability to bind, or 'trap,' a protein called vascular endothelial growth factor (VEGF) before VEGF can bind to receptors in the human body and stimulate blood-vessel growth. Aflibercept formulations have been approved by the FDA for the treatment of several angiogenic eye diseases (*i.e.*, diseases related to blood-vessel growth in the eye) via intravitreal administration." *SB*, 127 F.4th at 903.

1. Fusion Proteins

Eylea[®] was the first fusion-protein ophthalmic drug product. Fusion proteins are formed by fusing together different domains of multiple proteins. Ex.2010, 448:1-12 (Furfine). At the time of the invention, the leading ophthalmic VEGF

antagonist in development was Genentech's ranibizumab. Ex.2010, 448:18-449:6, 450:14-19 (Furfine). Whereas aflibercept is a synthetic fusion protein, ranibizumab is an antibody fragment. Ex.2010, 1035:4-9 (Rabinow), 451:5-14, 456:6-9 (Furfine).

“[F]usion proteins are fundamentally different from antibodies in that fusion proteins are synthetic molecules made by humans, while antibodies have evolved over time to be stable.” *Mylan*, 714 F. Supp. 3d at 737 (citing Ex.2010, 2013:14-17, 2014:21-2015:16 (Trout), 448:1-6, 456:6-9 (Furfine)); Ex.2011 (Fast), 15 (“In comparison with native IgG proteins, wherein interdomain interactions presumably have evolved to provide mutual stabilization, fusion proteins may lack such stabilizing interdomain stabilization.”); *SB PI Decision*, 2024 WL 3422971, at *31.

2. Glycosylation

In a “glycosylated” protein, certain amino acids have attached carbohydrates called glycans. *Mylan*, 714 F. Supp. 3d at 695-96; Ex.1007 ¶28. Glycans increase the size of the protein, *Mylan*, 714 F. Supp. 3d at 741, and glycosylation was understood to affect multiple properties, including the protein's pharmacokinetics, activation of effector functions, and others, as described below. *SB PI Decision*, 2024 WL 3422971, at *26-28. “VEGF Trap proteins could be made in CHO cells and glycosylated ... or made in E. coli or mutant CHO cells and not glycosylated.” *SB PI Decision*, 2024 WL 3422971, at *26; Ex.1039 (Daly) ¶¶38, 43; *Formycon*, 2025 WL 3242888, at *7.

Both the district court and the Federal Circuit repeatedly held that the POSA was *not* motivated to use a glycosylated form of aflibercept in an ophthalmic formulation, as required in each challenged claim. *SB PI Decision*, 2024 WL 3422971, at *28, *aff'd*, 127 F.4th at 913; *Mylan*, 714 F. Supp. 3d at 741; *Formycon*, 2025 WL 324288, at *6-7.

3. The '865 Patent

Claim 4 of the '865 patent is illustrative and requires the following limitations (emphases added):

4. 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, and

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[;]

wherein the concentration of said VEGF antagonist fusion protein is 40 mg/ml[;]

[and] wherein said organic co-solvent comprises about 0.03% to about 0.1% polysorbate 20.

The patent discloses eight working examples of aflibercept formulations, with certain stability measurements reported after storage. One of these stability measurements is the protein’s “native conformation,” which refers to “the original intact form of the VEGF antagonist, which is a form that does not exhibit chemical or physical instability.” *Mylan*, 714 F. Supp. 3d at 696. Proteins not in their native conformation can aggregate, reducing therapeutic activity and potentially leading to severe problems such as inflammation or an adverse immune response. *Id.* at 707; *SB PI Decision*, 2024 WL 3422971, at *33.

The patent’s working examples vary in their ingredients and/or container systems. In each example, the formulations were evaluated based on several characteristics, including “Native Configuration.” *E.g.*, ’865 patent, 8:45-57, Tables 1-8. As relevant here, the reported “native configuration” (synonymous with “native conformation”) in each example over 2-3 months is summarized below:

Example	Native Conformation	Time (months)
1	98.7	3
2	98.5	3
3	99.2	2
4	99.1	2

5	99.2	2
6	99.1	3
7	99.3	2
8	98.9	2

4. Prior Art

a. Fraser (Ex.1009)

“Fraser disclosed a composition having 24.3 mg/ml of a VEGF Trap that was used to investigate ovarian functions in monkeys.” *Mylan*, 714 F. Supp. 3d at 740; Ex.1009, 1115. Fraser does not teach any specific amino acid sequence. *Mylan*, 714 F. Supp. 3d at 741. Nor does Fraser teach anything regarding intravitreal injections; Fraser instead disclosed intravenous use of a VEGF Trap to study ovarian function. *Id.* at 740. The composition in Fraser included “5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20 [a brand name for polysorbate 20], with either 20% glycerol or 20% sucrose.” Ex.1009, 1115. Fraser also describes a “control” formulation containing Human Fc “at a concentration of 19.7 mg/ml in buffer composed of 40 mM phosphate and 20 mM NaCl (pH 7.4).” *Id.*

Fraser does not describe any stability data regarding its VEGF Trap. It teaches that “[t]he compounds were stored at -20 C until required, at which time they were thawed. Any compound remaining was stored at 4 C and used within 2 wk.” *Id.*

b. Wulff (Ex.1016)

Like Fraser, Wulff is a preclinical study of “Ovulation in the Primate” that involved treatment with a VEGF Trap. *Mylan*, 714 F. Supp. 3d at 697-98; Ex.1016, 2797. Wulff does not identify any amino acid sequence; it teaches intravenous use of “VEGF Trap R1R2” which was expressed in CHO cells. Ex.1016, 2798. Wulff does not disclose any formulation of its VEGF Trap but does describe a “vehicle containing 5 mM phosphate, 5 mM citrate, 100 mM sodium chloride, 0.1% (wt/vol) Tween 20, and 20% (wt/vol) sucrose.” *Id.*

Also like Fraser, Wulff does not describe any stability data regarding its VEGF Trap and does not teach anything regarding intravitreal use.

c. 2006 Presentations (Ex.1011-13)²

The 2006 Presentations describe results reported by Regeneron from the initial Phase 1 trials for an unspecified “VEGF Trap” as the studies were ongoing. *E.g.*, Ex.1011, 8; *see Mylan*, 714 F. Supp. 3d at 685 (describing certain of Regeneron’s clinical trials). The 2006 Presentations evaluated both systemic administration of a VEGF Trap, Ex.1011, 10, as in Fraser and Wulff, as well as intravitreal administration, *id.*, 15. For intravitreal administration, the 2006 Presentations described evaluating six different dose levels: 0.05, 0.15, 0.5, 1.0, 2.0,

² Regeneron assumes here that the 2006 Presentations are prior art.

and 4.0 mg. Ex.1012, 20. However, the 2006 Presentations only show actual data from the 0.5 and 1.0 mg doses. Ex.1011, 16-21; Ex.1012, 21; Ex.1013, 23. The 2006 Presentations report that the “maximum tolerated dose [was] not reached” but do not teach which dose was preferable. Ex.1013, 22.

The 2006 Presentations do not teach the amino acid sequence of the VEGF Trap protein used in the studies, whether or to what extent it was glycosylated, its stability or lack thereof, what volume(s) were used for the injections, or any aspect of the formulation(s) used.

d. '319 Publication (Ex.1029)

The '319 Publication (Ex.1029), called “Papadopoulos” in district court proceedings, described Regeneron’s invention of several VEGF antagonist fusion proteins. *Mylan*, 714 F. Supp. 3d at 698; *SB PI Decision*, 2024 WL 3422971, at *26; Ex.2010, 2020:7-2022:16 (Trout); Ex.2012 (Trial Ex. DTX-3619A). Papadopoulos discloses at least 8 distinct VEGF receptor fusion proteins. Ex.2010, 2020:25-2021:24 (Trout); Ex.2012 (Trial Ex. DTX-3619A); *see also* Ex.1029, Fig.10A-10D, 13A-13D, 14-14C, 15A-15C, 16A-16D, 22A-22C (identifying other fusion proteins). The amino acid sequence from Fig. 24A-24C is the same as SEQ ID NO:4 in the '865 patent; however, the amino acid sequence from Fig. 21A-21C, for example, is different. Ex.2010, 2022:4-16 (Trout).

Papadopoulos identifies several different “suitable host cell[s]” “for the production of a fusion polypeptide,” including “a bacterial cell, yeast cell, insect cell, or mammalian cell,” and more specifically including “E. Coli,” “a COS cell,” and “a CHO cell.” Ex.1029, 12:19-26.

B. Person of Ordinary Skill

The district court applied the following POSA definition in its decisions:

[T]he 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, 714 F. Supp. 3d at 702; *Formycon PI Decision*, 2024 WL 3423047, at *7. Formycon now advances a higher level of ordinary skill than what it previously advanced in the district court, where the parties applied the same POSA definition as in *Mylan*. Pet. 13-14 (citing Ex.1002 ¶¶58-60).

Regeneron proposes that the Board adopt the same POSA definition that has consistently governed these cases. Regardless, applying either POSA definition, Formycon fails to show a reasonable likelihood of success.

C. Claim Construction

In the *Mylan* litigation, “the parties stipulated that the term ‘glycosylated’ in claim 1 of the Product Patent is construed as ‘containing at least one amino acid residue with an attached carbohydrate.’” *Mylan*, 714 F. Supp. 3d at 695-96.

The district court also 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.” *Id.* at 696.

D. Ground 1: Formycon Fails To Demonstrate Obviousness over Fraser, Wulff, the Three 2006 Presentations, the '319 Publication, and FDA Container Closure Guidance

Formycon contends that the POSA would have started with the intravenous formulation disclosed in Fraser for a nonclinical study about ovarian function in macaques, and then modified virtually every aspect of this formulation in view of the six other references in Ground 1 along with multiple others. Pet. 10; *see also* Pet. 39 (relying on additional art, including Daly (Ex.1039)); Pet. 42 (relying on Dix (Ex.1021)). Formycon’s proposed modifications are shown below in red:

	Fraser	Formycon's "Modified Fraser/Wulff Formulation" (Pet. 43)
VEGF antagonist amino acid sequence	Not disclosed	Amino acids 27-457 of SEQ ID NO:4
Glycosylation	Not disclosed	Glycosylated
VEGF Antagonist concentration	24.3 mg/mL	40 mg/mL
Stability	Not disclosed	Unknown
Buffer	5 mM phosphate, 5 mM citrate	5 mM phosphate, 5 mM citrate
Organic Co-Solvent	0.1% polysorbate 20	0.1% polysorbate 20
Stabilizing Agent	20% sucrose or 20% glycerol	10% or 5% sucrose
Tonicity agent	100 mM NaCl	Unspecified reduction in NaCl
pH	6.0	6.0-6.3

Formycon's "modified" formulation contrived from a half-dozen references is the epitome of hindsight and fails for numerous reasons. At least four independent reasons foreclose a reasonable likelihood of success.

First, the prior art motivated against using a glycosylated form of aflibercept for an intravitreal drug product, as the district court and the Federal Circuit have held repeatedly. Formycon fails to address the courts' analyses and the prior art teachings supporting them, which compel the same outcome here.

Second, the district court found that the prior art taught away from using 40 mg/mL aflibercept. Formycon again ignores this finding, which likewise refutes its modified formulation, and points to no prior art teaching or suggesting a 40 mg/mL ophthalmic formulation of aflibercept.

Third, no evidence teaches or suggests that Formycon’s modified formulation inherently would achieve the 98% native conformation limitation. Formycon has *no evidence* regarding the stability of any such formulation, let alone evidence that the alleged modified formulation necessarily would achieve 98% native conformation, as inherency requires. Nor would the POSA reasonably have expected Formycon’s modified formulation to achieve that stability level. To the contrary, Fraser did not report any stability data, and Formycon’s modifications of nearly doubling the protein concentration while halving the stabilizing agent (*i.e.*, sucrose) concentration would have been expected to *reduce* stability.

Fourth, as the district court has found in *Mylan* and in the *Formycon PI Decision*, objective evidence of nonobviousness strongly support nonobviousness.

1. The POSA Would Have Been Motivated Against Using Glycosylated Aflibercept

Every challenged claim requires that the recited VEGF antagonist “is glycosylated.” *E.g.*, ’865 patent, claim 1. Neither Fraser nor Wulff teaches the aflibercept amino acid sequence or whether it was glycosylated. Although Formycon cites to prior art teachings that VEGF antagonists like aflibercept *could* be glycosylated, it points to no evidence that the POSA *was motivated* to use glycosylated aflibercept in an ophthalmic formulation. Pet. 38-40.

Across six decisions to date—one district court trial decision, three preliminary injunctions, and two appeal decisions—the district court and the Federal

Circuit consistently have ruled that, while it was known that VEGF Traps like aflibercept could be glycosylated, the POSA would have been motivated *against* using glycosylated aflibercept. *E.g.*, *SB PI Decision*, 2024 WL 3422971, at *28 (“Taken together, the evidence decisively points against a motivation to glycosylate the VEGF trap claimed in ’594 claim 5.”), *aff’d*, 127 F.4th at 913 (affirming finding that “a relevant artisan lacked the motivation to use glycosylated aflibercept”); *Mylan*, 714 F. Supp. 3d at 741 (“the POSA would have sought to use nonglycosylated aflibercept, because glycosylation increases size and thus decreases retinal penetration”); *Formycon*, 2025 WL 324288, at *6-7 (affirming finding that evidence cumulatively “points against a motivation to glycosylate”). *Formycon* does not address, much less refute, these decisions or the evidence underlying them. They are fatal to *Formycon*’s Petition.

a. Retinal Penetration

First, the district court and Federal Circuit explained that “a relevant artisan would deem glycosylation undesirable because it increases the size of the protein and thus reduces its ability to penetrate into the retina, which is important for the desired therapeutic effect.” *Formycon*, 2025 WL 324288, at *6; *SB PI Decision*, 2024 WL 3422971, at *26; *Mylan*, 714 F. Supp. 3d at 740-41. Numerous prior art references taught that increasing molecular size would reduce a molecule’s penetration into the retina, the site of action for the VEGF antagonist. Ex.1068

(Gaudreault), 726, 731 (“[P]enetration of ranibizumab into the retina is critical for its clinical use,” and its “ability [to penetrate the retina] has been attributed to [its] small molecule size” of 48 kDa); Ex.2013 (Ghate), 281 (the retina’s “internal limiting membrane” was “impermeable to ... globular molecules > 70 kDa”); Ex.2014 (Jackson), 2141 (“The [retinal exclusion limit] in human tissue was 76.5 ± 1.5 kDa.”); Ex.1039 (Daly) ¶43 (the smaller 46 kDa “mini-trap” had “optimized characteristics for local/intra-vitreous delivery” and “has the ability to penetrate through the inner-limiting membrane (ILM) in the eye, and diffuse through the vitreous to the retina/retinal pigment epithelial (RPE) layer which will help to treat retinal disease”); *see also* Ex.1049 (Jaffe), 74 (“The ability of ranibizumab to penetrate the retina is likely related to the internal limiting lamina pores that only allow” smaller molecules to penetrate).

Aflibercept has a molecular weight of approximately 115 kDa when glycosylated, with approximately 18 kDa contributed by the glycans, *see* Ex.1039 (Daly) ¶¶74, 79 (reporting 18 kDa difference between glycosylated and nonglycosylated miniTrap); Ex.1099 ¶36 (18 kDa contributed by glycans for full-length VEGF antagonist protein); *Mylan*, 714 F. Supp. 3d at 740; *see also* Ex.2010, 2028:10-22 (Trout). Because aflibercept was over twice the size of ranibizumab, even after the patent’s priority date the prior art expressed skepticism regarding the penetration of full-length VEGF antagonists. Ex.2015 (Ferrara 2006), 862

(discussing “limited efficacy” of intravitreal administration of VEGF Trap molecule in published preclinical study and suggesting that “it may be due, at least in part, to the existence of a barrier to the transretinal penetration of large molecules such as the VEGF-trap.”); *see also* Ex.1068 (Gaudreault), 726. Thus, the Federal Circuit affirmed that “to minimize protein size in pursuit of greater retinal penetration,” the POSA would have been motivated against using a glycosylated form of aflibercept. *Formycon*, 2025 WL 324288, at *6.

Formycon acknowledges neither the courts’ multiple holdings regarding glycosylation and retinal penetration nor the prior art’s teachings—even though Formycon relies on the same prior art the courts interpreted to have motivated the POSA against glycosylation. *Compare* Pet. 39 (relying Daly for glycosylation), *with Formycon*, 2025 WL 324288, at *6-7 (Daly motivated the POSA against using glycosylation); *SB PI Decision*, 2024 WL 3422971, at *26 (same). This alone forecloses a reasonable likelihood of demonstrating any motivation to use the claimed glycosylated aflibercept.

b. Systemic Half-Life

Second, the Federal Circuit has affirmed that the POSA “would have been motivated to pursue non-glycosylated aflibercept, which has a shorter half-life and thus diminishes undesirable effects of extended trapping of VEGF outside the eye (systemic exposure).” *Formycon*, 2025 WL 324288, at *7; *see SB PI Decision*, 2024

WL 3422971, at *27 (same). Glycosylation was understood to increase serum half-life. *SB PI Decision*, 2024 WL 3422971, at *27 (citing testimony from Regeneron’s and Formycon’s experts); Ex.2016 (Sinclair), 1626, 1632; Ex.2017 (Marinero), 512. And the prior art also taught that “for ophthalmic use, ‘shorter serum half life’ was desirable.” *SB PI Decision*, 2024 WL 3422971, at *27 (quoting Ex.1039 (Daly) ¶43); Ex.1039 (Daly) ¶43 (describing VEGF antagonists, including a “smaller, non-glycosylated mini-trap expressed in *E. coli* ... [with] optimized characteristics for local/intravitreal delivery, i.e. *a shorter serum half life for faster clearance and minimizing unwanted systemic exposure*” (emphasis added)); Ex.1068 (Gaudreault), 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.”).

As with retinal penetration, Formycon does not address the courts’ holdings about the POSA’s motivation regarding systemic half-life, or the teachings of the prior art, which separately refute motivation to use glycosylated aflibercept in an ophthalmic formulation.

c. Inflammation

Third, the Federal Circuit affirmed that “a relevant artisan would have been deterred from pursuing glycosylation due to evidence that it might lead to inflammation.” *Formycon*, 2025 WL 324288, at *7. Citing the testimony of

Formycon’s own expert, the district court found “that glycosylation of aflibercept’s ‘Fc’ portion activates ‘effector functions,’ including immune-mediated toxicities.” *Formycon PI Decision*, 2024 WL 3423047, at *31; *see* Ex.1029 (Papadopoulos), fig.24B-C (annotating Fc portion of same amino acid sequence as aflibercept, including asparagine residue 308); *e.g.*, ’865 patent, claim 14 (identifying asparagine residue 308 as N-linked glycosylation site). The prior art taught that effector functions could be eliminated by using a nonglycosylated Fc region. Ex.1039 (Daly) ¶38; Ex.2018 (Shields), 6594 (removing glycosylation of Fc region “abolished binding” to Fc-gamma receptors and thus eliminated Fc-gamma-receptor-dependent effector function). And because inflammation was “an extremely concerning phenomenon for any intravitreal drug product to exhibit,” the Federal Circuit affirmed the district court’s finding based on the prior art and expert testimony “that a relevant artisan would avoid glycosylation to minimize the risk of inflammation.” *Formycon*, 2025 WL 324288, at *7.

As with retinal penetration and systemic half-life, Formycon and its expert do not address the courts’ analyses or the supportive evidence that the POSA was motivated to avoid glycosylation to reduce the risk of inflammation—a conclusion substantiated by the link between glycosylation and effector function established by Formycon’s own expert.

d. Formycon Advances No Motivation to Glycosylate

Formycon cites no evidence of any motivation to use a glycosylated form of aflibercept for intravitreal administration. Pet. 38-40. “Obviousness addresses what is, ‘on balance, desirable,’ not what is ‘feasible.’” *SB PI Decision*, 2024 WL 3422971, at *26 (quoting *Winner Int’l Royalty Corp. v. Wang*, 202 F.3d 1340, 1349 (Fed. Cir. 2000)); *Orexo AB v. Actavis*, 903 F.3d 1265, 1272-73 (Fed. Cir. 2018)). That VEGF antagonists like aflibercept *could be* glycosylated is not evidence that the POSA had motivation to pursue glycosylation for an ophthalmic formulation, as specifically claimed. Formycon’s absence of any evidence regarding motivation is fatal to its Petition. Fraser and Wulff are silent on glycosylation, and none of Formycon’s cited art teach to use a glycosylated form of aflibercept for ophthalmic use; thus, Formycon argues that the POSA would look to Papadopoulos and Daly, which disclose CHO cells, and conclude that “when aflibercept is expressed in a CHO cell it will be glycosylated ... at five asparagine residues: 62, 94, 149, 222 and 308.” Pet. 39. Formycon’s argument suffers from numerous flaws.

First, the prior art does not teach that VEGF antagonists like aflibercept could *only* be made using CHO cells, *contra* Pet. 38-39. Although Papadopoulos does describe using CHO cells to make glycosylated fusion proteins, Pet. 38, it also describes other “suitable host cell[s]” such as “a bacterial cell, yeast cell, [or] insect cell,” and specifically discloses *E. Coli*, a specific and well-known bacterial cell

system that produces nonglycosylated proteins, including ranibizumab. Ex.1029, 12:19-26; Ex.2019 (Shams), 31:21-25. Likewise, Daly describes 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,” and which had comparable binding affinity to a glycosylated version. Ex.1039 (Daly) ¶¶38, 43, 63; *SB PI Decision*, 2024 WL 3422971, at *26-27. Thus, contrary to Formycon’s premise, the POSA was not limited to using CHO cells; the prior art disclosed other methods of producing VEGF antagonist proteins, like *E. Coli*, which indisputably would result in nonglycosylated proteins, consistent with the POSA’s “pursuit of greater retinal penetration and lower systemic exposure and inflammation risk.” *Formycon*, 2025 WL 324288, at *6; *supra* IV.D.1. Formycon and Dr. Zhou simply ignore these teachings. *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, even if the POSA used CHO cells, Formycon ignores Daly’s express disclosure of modified CHO cells “which either *eliminate glycosylation* or modify the extent of glycosylation,” which both the district court and Federal Circuit recognized. Ex.1039 ¶38 (emphasis added); *Formycon*, 2025 WL 324288, at *7; *SB PI Decision*, 2024 WL 3422971, at *27. Here, the POSA would have been motivated

to use modified CHO cells that eliminate glycosylation for the reasons provided above. *Supra* IV.D.1.a-c. The disclosures in Daly cited by Formycon are not to the contrary. Although Daly provides “*specific embodiments* ... [where] a mammalian cell line such as a CHO cell” may be used to generate glycosylated aflibercept, Ex.1039 ¶13 (emphasis added), including Example 8, *id.* ¶¶64, 80-84, such disclosure hardly negates Daly’s teaching of other CHO cells that do not glycosylate, *id.* ¶38; *Henny Penny*, 938 F.3d at 1331-32. Indeed, even Formycon’s cited disclosure (¶13) describes *E. coli* and other cells that would generate nonglycosylated aflibercept.³

Third, whether the POSA would “expect” aflibercept to be glycosylated if expressed in glycosylating CHO cells is irrelevant, Pet. 40, because here the POSA would be *motivated against* glycosylation. *Supra* IV.D.1.a-c. Both motivation and reasonable expectation of success are necessary for obviousness, *e.g.*, *In re Cyclobenzaprine Pat. Litig.*, 676 F.3d 1063, 1069 (Fed. Cir. 2012).

³ It is unclear whether Formycon argues that glycosylation would be inherent when producing VEGF antagonists like aflibercept in CHO cells. Pet. 38-40. Regardless, consistent with Daly’s disclosure of CHO cells and other systems that do not glycosylate, the district court rejected inherency. *Mylan*, 714 F. Supp. 3d at 741 (crediting testimony that “even if a protein contains amino acid sequences that may be glycosylated, a given protein may not be glycosylated”); Ex.2016 (Sinclair), 1627-28, 1632 (same).

2. The Prior Art Taught Away from Using 40 mg/mL of Aflibercept

Formycon's "Modified Fraser/Wulff formulation" requires (among other modifications) increasing the concentration of the VEGF Trap in Fraser and Wulff from 24.3 mg/mL to 40 mg/mL. Pet. 49-51. The district court found that the prior art *taught away* from precisely this modification. *Mylan*, 714 F. Supp. 3d at 737-740. Formycon's principal basis for increasing the concentration to 40 mg/mL is to mimic one concentration purportedly used for the off-label small-molecule compound triamcinolone (trade name Kenalog[®]), a glucocorticoid that is not a protein, much less a fusion protein, and which is approximately *265 times smaller* than aflibercept and has nothing whatsoever to do with inhibiting VEGF. Pet. 49-50. Formycon's modification is transparent hindsight and should be rejected. Formycon also cites interim results from Regeneron's clinical trials, but the presentations on which Formycon relies do not teach or suggest a 40 mg/mL formulation of aflibercept.

a. The District Court Found Teaching Away From 40 mg/mL Aflibercept

Like Formycon, Mylan advanced an obviousness theory based on Fraser. *Mylan*, 714 F. Supp. 3d at 736. Mylan, however, relied on the disclosure of a 40 mg/mL formulation of ranibizumab, which at the priority date was the leading VEGF antagonist molecule designed for intravitreal administration. *Id.* at 684, 692, 737.

The disclosure in Gaudreault of a 40 mg/mL formulation of ranibizumab is the sole teaching of a 40 mg/mL VEGF antagonist (together with a buffer, a stabilizing agent, and 0.05% polysorbate 20 for intravitreal injection) in the prior art. Ex.1068 (Gaudreault), 727. The district court thus determined that Gaudreault was the closest prior art. *Mylan*, 714 F. Supp. 3d at 746. Although Formycon recognizes that ranibizumab (unlike triamcinolone) shares the same basic mechanism of action as aflibercept, Pet. 16 (observing that both molecules bind and inhibit VEGF), it otherwise ignores the prior art directed to ranibizumab.

The reason for that omission is simple: as the district court found, Gaudreault's 40 mg/mL formulation resulted in "moderate to severe" inflammation and "taught against 'following the path set out in the reference,' (using a 40 mg/ml formulation of a VEGF antagonist in an ophthalmic formulation) and 'led [the POSA] in a direction divergent from the path that was taken in the claim' (40 mg/ml of aflibercept)." *Mylan*, 714 F. Supp. 3d at 737 (quoting *AstraZeneca AB v. Mylan Pharm. Inc.*, 19 F.4th 1325, 1337 (Fed. Cir. 2021)); Ex.1068, 727-28. The district court found that the inflammation resulting from the 40 mg/mL formulation "persisted for seven days and was 'problematic from an immune response standpoint' and thus 'would teach the [POSA] away from the 40 mg/ml.'" *Mylan*, 714 F. Supp. 3d at 737 (quoting Ex.2010, 2041:1-10 (Trout)). In contrast, "the 10 mg/ml ranibizumab formulation did not exhibit such levels of inflammation, and the

authors found that this lower ‘dose provides maximum inhibition of VEGF.’” *Id.* (quoting Ex.2010, 2041:22-2042:9 (Trout) (citing Ex.1068 (Gaudreault), 732)); *see* Ex.1068 (Gaudreault), 727 (10 mg/mL concentration resulted in “absent to moderate” inflammation).

The district court considered the differences between aflibercept and ranibizumab and found that they would have only further discouraged use of 40 mg/mL aflibercept. “[A]flibercept was much more potent than ranibizumab,” and accordingly “less aflibercept is needed to inhibit the same amount of VEGF as compared to ranibizumab.” *Mylan*, 714 F. Supp. 3d at 737. Furthermore, the court found that “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 (or antibody fragments like ranibizumab).” *Id.* at 742. Importantly for present purposes, fusion proteins’ greater propensity for aggregation would be exacerbated by increasing concentration to 40 mg/mL and would further risk inflammation. *Id.* at 737 (noting the “greater risk of aggregation caused by a higher concentration” (citing Ex.2020 (Wang 2005), 9)); *see* Ex.2020 (Wang 2005), 9 (explaining that “[i]ncreasing protein concentration generally increases protein aggregation” and that “protein aggregates often have stronger immunogenicity or toxicity.”); Ex.2021 (Wang 1999), 137 (“Protein aggregates may have ... altered immunogenicity.”);

Accordingly, in view of undisputed evidence that Gaudreault's inflammation resulting from a 40 mg/mL VEGF antagonist formulation "was an extremely concerning phenomenon for any intravitreal drug product to exhibit, as it could result in vision loss and thus defeat the purpose of using an ophthalmic drug product in the first place," the court found that the prior art taught away from using 40 mg/mL of aflibercept. *Mylan*, 714 F. Supp. 3d at 738. This evidence is equally applicable here, particularly as it is the only evidence of any 40 mg/mL intravitreal formulation of a VEGF antagonist. *See Monarch Knitting Machinery Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 885 (Fed. Cir. 1998) (finding teaching away based on reference that was not part of obviousness combination); *Gillette Co. v. S.C. Johnson & Son, Inc.*, 919 F.2d 720, 724 (Fed. Cir. 1990) (finding teaching away where closest prior art discouraged claimed invention).

b. Formycon's Arguments Fail To Establish a Motivation To Use 40 mg/mL Aflibercept

Formycon's theory is that the POSA would have been motivated to select (1) a 0.1 mL volume and (2) a 4 mg dose of aflibercept to arrive at (3) a 40 mg/mL concentration, which "[a] number of approved intravitreal drugs and drugs in clinical trials as of March 2006 used." Pet. 49-50. Each of Formycon's selections is driven by hindsight rather than the prior art's teachings.

1) The prior art does not teach or suggest using 40 mg/mL of aflibercept or any VEGF antagonist.

Formycon asserts that the POSA would select the claimed 40 mg/mL concentration because it was a “commonly used concentration” for intravitreal drugs. Pet. 50. The only disclosed 40 mg/mL concentrations that Formycon points to involve ranibizumab and Kenalog. Pet. 50; Ex.1005 ¶25. The ranibizumab 40 mg/mL formulation, as explained above, *taught away* from that concentration because the resulting inflammation was “extremely concerning.” *Mylan*, 714 F. Supp. 3d at 738. Genentech itself abandoned its 40 mg/mL formulation. *Id.*

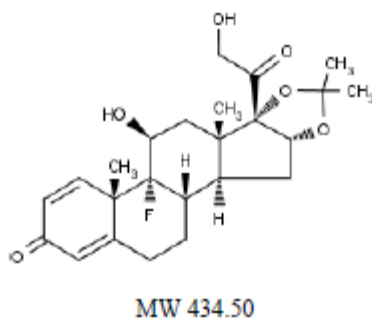
Formycon’s Petition identifies no error in this teach-away finding and instead largely ignores ranibizumab. Pet. 50. Formycon’s expert Dr. Lefkowitz cites clinical studies of ranibizumab, Ex.1005 ¶25, but they further teach away from using a 40 mg/mL formulation. In Genentech’s principal clinical trial on safety, patients experienced dose-dependent increases in inflammation and “dose-limiting toxicity”—including, in one patient, transient vision loss—at a 1000 µg dose, which corresponds to a 20 mg/mL concentration using ranibizumab’s disclosed 50 µL volume. Ex.2022 (Rosenfeld 2005), 1049, 1050. Thus, the investigators did not even attempt the 2 mg dose corresponding to a 40 mg/mL concentration at that volume, *id.*, and Genentech never sought approval for a 40 mg/mL formulation.

Dr. Lefkowitz cites another ranibizumab clinical study involving a more complex dosing regimen where patients received escalating doses over time, with one group that escalated to 1 mg (Group 1) and two other groups concluding with

doses up to 2 mg (Groups 2 and 3). Ex.1005 ¶25 n.4 (citing Ex.1050; Ex.1051); Ex.1051, 99-100. Ex.1050 is a research article that was published after the invention date (in April 2006) and thus is not prior art. However, in the earlier abstract (Ex.1051) the authors found no clinical benefit to using a higher dose—to the contrary, Group 1, which involved no 2 mg doses, achieved *greater* increases in visual acuity than the *higher-dose* Groups 2 and 3. Ex.1051, 100. Formycon does not argue either reference would have led the POSA to either use the more complicated escalation strategy in this study or to increase concentration to 40 mg/mL. Pet. 50. Moreover, Ex.1051 does not disclose the injection volume and thus Formycon provides no basis to conclude that any of the formulations used 40 mg/mL of ranibizumab.

The other 40 mg/mL concentration Formycon cites is Kenalog, containing the active ingredient triamcinolone. Ex.1062, 2. Triamcinolone has nothing to do with VEGF; it is a glucocorticoid that acts as an “adrenocortical steroid[]” for its “anti-inflammatory effects.” *Id.* Formycon advances no evidence that the POSA would simply apply a concentration for one molecule to another, when the two molecules have entirely different properties and mechanisms of action.

Moreover, triamcinolone and aflibercept are nothing alike structurally. Triamcinolone is a small molecule having a molecular weight of 434.5 Daltons:



Ex.1062, 1. The claimed fully glycosylated aflibercept, in contrast, is a fusion protein, comprised of hundreds of amino acids, with a molecular weight of 115,000 Daltons. Formycon cites no contemporaneous evidence in support of its theory that the POSA was motivated to use a 40 mg/mL concentration of aflibercept for an ophthalmic formulation merely because triamcinolone was used at that concentration. There is none.

More fundamentally, even if the POSA were to put aside these differences between the two molecules, the label for Kenalog, cited by Dr. Lefkowitz as indicative of the “standard formulation” at the time (Ex.1005 ¶31), states (in all caps) that its “FORMULATION IS SUITABLE FOR INTRAMUSCULAR AND INTRA-ARTICULAR USE ONLY,” and is “*NOT FOR ... INTRAOCULAR USE.*” Ex.1062, 1 (italicized emphasis added). It explains that “[s]everal instances of blindness have been reported following injection of corticosteroid suspensions into the nasal turbinates and intralesional injection about the head,” and “[a]dequate studies to demonstrate the safety of Kenalog by ... intraocular (intravitreal)

injections have not been performed.” Ex.1062, 8. The POSA—viewing the prior art as a whole as required, *Henny Penny*, 938 F.3d at 1331-32—would not have chosen an aflibercept concentration by following, of all things, a molecule whose label explicitly states that it is not for use in the eye.⁴

2) Formycon’s dose and volume selections are supported only by hindsight

Without any basis in the prior art to select a 40 mg/mL concentration, Formycon attempts to derive that concentration by cobbling together a 4 mg dose from the 2006 Presentations with a 100 µL volume from Kenalog. Pet. 49-50. This hindsight argument fails to show obviousness.

First, Formycon selects a 100 µL volume arbitrarily, based on Kenalog. Pet. 49. But just as Kenalog would not have indicated what concentration of aflibercept to use, it would not have taught what injection volume to use. *See supra* IV.D.2.b.1. As Formycon’s expert acknowledges, the POSA would have viewed a range of

⁴ Formycon cites two publications involving investigators’ experimentation with intravitreal Kenalog, despite its lack of approval. Ex.1063, Ex.1064; Ex.1005 ¶31. Formycon arbitrarily excludes the preferred Kenalog dosage of 20 mg (with an unspecified volume) described in Jonas 2005, which further undermines Formycon’s motivation argument. Ex.1063, 587, 605. Under Formycon’s theory that injection volume would not exceed 100 µL, 20 mg of Kenalog would necessarily correspond to a minimum concentration of 200 mg/mL, far higher than 40 mg/mL.

volumes—approximately 50-100 μL —as possibilities. Ex.1005 ¶23. Notably, intravitreal ranibizumab—which, as a VEGF antagonist, was far more relevant than Kenalog—used a 50 μL injection volume. Ex.2022 (Rosenfeld 2005), 1051-52; Ex.1068 (Gaudreault), 727; Ex.2019 (Shams), 34:5. Macugen[®]—a VEGF antagonist albeit not a protein—used a volume of 90 μl . Ex.1045 (Macugen Label), 1-2. Formycon offers no reason why a POSA would have selected a 100 μl volume instead of a 50 μl or 90 μl volume.

Second, and also fatally for Formycon, the prior art contains no support for Formycon’s selection of the “maximum dose” of 4 mg referenced in the 2006 Presentations from Regeneron’s then-ongoing clinical trials for an unspecified VEGF Trap. Pet. 50. The 2006 Presentations do not disclose what concentration of the VEGF Trap was used, what the injection volume was, or any other aspect of the formulation. And nothing in the 2006 Presentations teaches to simply choose the highest dose. Rather, the 2006 Presentations disclose clinical data only for *lower* doses of 0.5 and 1.0 mg. Ex.1011, 16-21; Ex.1012, 21; Ex.1013, 23. Even at a 50 μL volume, those doses would result in concentrations of 10 and 20 mg/mL, respectively, in line with the VEGF Trap concentrations used in Fraser and Wulff. *Mylan*, 714 F. Supp. 3d at 740; Ex.1016, 2798. Formycon offers no reason for ignoring these dosages emphasized in the 2006 Presentations and instead selecting the highest dose.

While the 2006 Presentations indicate that the “maximum *tolerated* dose [was] not reached,” Ex.1013, 22, that is hardly an indication that the highest dose tested was desirable. The “maximum tolerated dose” is not a preferred dose; it is the “dose that produces grade 3 (severe) or grade 4 (life-threatening) toxicity in 30% or fewer of the patients tested.” Ex.2023 (Stedmans Med. Dictionary), 265360. Formycon points to no evidence that the POSA would have sought to approach that limit by choosing the highest dose tested in an ongoing clinical trial. To the contrary, the POSA would have understood that “[b]ecause of its higher potency, *less* aflibercept is needed to inhibit the same amount of VEGF as compared to ranibizumab,” *Mylan*, 714 F. Supp. 3d at 737 (emphasis added), which achieved maximum VEGF inhibition at only 10 mg/mL with a 0.5 mg dose, *i.e.*, one of the two doses for which Regeneron reported data in the 2006 Presentations, Ex.1068 (Gaudreault), 727, 732. Accordingly, the 2006 Presentations reinforce the court’s finding that “nothing in the prior art that would have pointed a POSA to the 40 mg/ml concentration absent hindsight in working backwards from the claimed invention.” *Mylan*, 714 F. Supp. 3d at 738.

Finally, Formycon argues that the POSA “would have been motivated to use as [] high [a] concentration as possible” to minimize the number of injections. Pet. 50-51. First, as the district court found, the prior art concerning ranibizumab taught precisely the opposite. *Supra* IV.D.2.a-b.1. Second, as the district court also held,

increasing concentration causes a “greater risk of aggregation” and associated inflammation and toxicity. *Mylan*, 714 F. Supp. 3d at 737 (citing Ex.2020 (Wang 2005), 9)); *see* Ex.2020 (Wang 2005), 9; Ex.2021 (Wang 1999), 137. Formycon simply ignores this concern; the POSA cannot. *Monarch*, 139 F.3d at 885; *Henny Penny*, 938 F.3d at 1331-32. Neither Fraser nor Wulff nor Formycon’s secondary references (including the 2006 Presentations, Pet. 29) report *anything* regarding the stability of aflibercept, much less at increased concentrations. If anything, Fraser indicates that its 24.3 mg/mL VEGF Trap formulation was not stable at 5°C, as it was stored frozen and discarded after two weeks following thawing. Ex.1009, 1115. Thus, Formycon fails to demonstrate that the POSA would have been motivated to use a 40 mg/mL concentration of aflibercept with a reasonable expectation of success.

Taken together, Formycon cannot show a reasonable likelihood of success with respect to either its proposed dose or volume modifications of Fraser and Wulff; each failure independently forecloses obviousness.

3. The 98% Native Conformation Limitation Is Not Inherent or Obvious

Every challenged claim requires that the VEGF antagonist achieve a particular stability criterion—98% native conformation after (at least) two months’ storage. Formycon fails to show a reasonable likelihood of success that this limitation was inherent or obvious.

a. The District Court and Federal Circuit Found That 98% Native Conformation Is Not Inherent or Obvious

SB, Formycon, Celltrion, and Mylan advanced arguments at the district court and Federal Circuit that the 98% native conformation limitation of claim 1 of the '865 patent ("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") is inherent and/or obvious. The courts rejected these arguments repeatedly, and the Board should do the same here.

In *SB*, *Formycon*, and *Celltrion*, the ODP reference claim required that the VEGF Trap be "stable for at least 4 months," while claim 4 of the '865 patent required the 98% native conformation limitation. *E.g.*, *SB*, 127 F.4th at 912. In all three cases, the district court held that the 98% limitation was not inherent. *E.g.*, *SB PI Decision*, 2024 WL 3422971, at *28-31. In those proceedings, Regeneron introduced data for a specific aflibercept formulation sample ("SS195" data) that did not meet the 98% native confirmation limitation but otherwise fell within the scope of claim 1 of the '865 patent. *E.g.*, *SB PI Decision*, 2024 WL 3422971, at *29. The court held that this data "confirms that the 98% native conformation limitation is not

inherent in” the reference claim at issue. *Id.* In its *Celltrion* decision, the Federal Circuit affirmed the district court’s non-inherency finding. 2025 WL 706079, at *3.⁵

In *SB*, *Formycon*, and *Celltrion*, the district court also found that the Defendants’ obviousness arguments regarding the 98% native conformation limitation failed to present a substantial question of invalidity, *e.g.*, *SB PI Decision*, 2024 WL 3422971, at *31, and the Federal Circuit thrice affirmed that conclusion, *SB*, 127 F.4th at 912-13; *Formycon*, 2025 WL 324288, at *5-6; *Celltrion*, 2025 WL 706079, at *3. In particular, the Federal Circuit in *Celltrion* affirmed the findings that the POSA “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.” *Celltrion*, 2025 WL 706079, at *3 (quotation marks omitted).

The district court rejected a similar obviousness argument in *Mylan*, finding that the POSA would not have had a reasonable expectation of success in modifying a combination of Fraser to achieve the 98% native conformation limitation. *Mylan*, 714 F. Supp. 3d at 741.

⁵ *SB* did not challenge non-inherency on appeal, *SB*, 127 F.4th at 913, and *Formycon*’s inherency argument was forfeited, *Formycon*, 2025 WL 324288, at *5.

b. Formycon Fails To Show a Reasonable Likelihood of Inherent Obviousness

Formycon contrived the Modified Fraser/Wulff formulation as a hypothetical formulation pieced together from disparate teachings of multiple references. *See supra* 27. Formycon presents no evidence that such a formulation ever existed or evidence regarding the actual native conformation of any such formulation after two months' storage. Pet. 40-45. Notwithstanding the absence of any stability data for this formulation, Formycon argues that the Modified Fraser/Wulff formulation inherently meets the 98% native confirmation limitation of claim 1. Pet. 40-45. Formycon's arguments fail to show inherent obviousness with respect to the 98% limitation.

To establish inherency, a patent challenger must show that a missing limitation is "necessarily present" in the prior art. *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 960 (Fed. Cir. 2014). Inherency "may not be established by probabilities or possibilities." *Par Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1195 (Fed. Cir. 2014).

Formycon cannot show a reasonable likelihood that *every* Modified Fraser/Wulff formulation possesses 98% native conformation as claimed because Formycon has no evidence that *any* such formulation possesses 98% native conformation. Formycon conjured the non-existent Modified Fraser/Wulff formulation, and Formycon has no direct evidence of its stability. Formycon thus

relies on stability data from samples of other formulations (none of which are identical to the Modified Fraser/Wulff formulation), analogizes those formulations to the Modified Fraser/Wulff formulation, and asks the Board to hazard that, if some samples of different formulations met the 98% stability limitation, so too would the Modified Fraser/Wulff formulation. The Federal Circuit squarely has held that such guesswork cannot meet the high standard for inherency. *See Par*, 773 F.3d at 1195 (“The mere fact that a certain thing may result from a given set of circumstances is not sufficient [for inherency].”).

Formycon analogizes the Modified Fraser/Wulff formulation to those disclosed in U.S. Patent No. 8,110,546 (Ex.1021, “Dix”),⁶ including Example 5. Both the Dix formulations with 50 mg/mL or less aflibercept and the original Fraser/Wulff formulation had 20% sucrose, a stabilizing agent. Pet. 31, 44. But to create the Modified Fraser/Wulff formulation that Formycon contends is suitable for intravitreal use, Formycon reduced the stabilizing agent from 20% to 5-10% sucrose,

⁶ Formycon does not argue that Dix is prior art. The earliest nonprovisional filing for Dix is March 22, 2006, after the invention date; thus, Dix could only be prior art under 35 U.S.C. § 102(e) through its provisional application filing, but Formycon has does not assert or advance the requisite evidence that Dix is “entitled to the filing date of its provisional application.” *Dynamic Drinkware, LLC v. National Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015). Thus, Dix can be used, if at all, only for inherency. *See Par*, 773 F.3d at 1194-95.

Pet. 33, a decrease of 50-75%. Formycon offers not even a scintilla of evidence that the stability data of the Dix formulations would *necessarily* be unchanged in view of Formycon's proposed dramatic decrease in stabilizing agent to create the Modified Fraser/Wulff formulation. The stability of the Dix formulation, with its relatively high concentration of stabilizing agent (among other differences), is simply irrelevant to whether the Modified Dix/Fraser formulation inherently possesses 98% native conformation. *See Par*, 773 F.3d at 1196.

Formycon also analogizes the Modified Fraser/Wulff formulation to formulations in the '865 patent's examples. But those formulations are not the same as the Modified Fraser/Wulff formulation either. *Compare* Pet. 43 with '865 Patent, Examples 1-8. Attempting to sidestep this deficiency, Formycon amalgamates different amounts of different ingredients and the various pHs of all the '865 example formulations into ranges and argues that because the "Modified Fraser/Wulff formulation falls well within the ranges of formulations tested in the '865 patent and Dix that achieve better than 98% stability at two months, ... the Modified Fraser/Wulff formulation will have the claimed stability." Pet. 43-44. But again, that is simply Formycon's guesswork, not evidence of inherency. *Par*, 773 F.3d at 1195; *Apotex*, 754 F.3d at 960.

Formycon cites its expert's generic testimony that "[i]t is common in the industry to perform stability testing on formulations with varying excipients in

varying concentrations over a range of pH values” and that “[i]t is commonly accepted that a formulation falling within these ranges will have the established stability of the tested formulation.” Pet. 45. However, even assuming that the Modified Fraser/Wulff formulation falls within the range of the ’865 patent’s exemplified formulations (it does not, as discussed below), Formycon’s argument fails for two reasons. First, even assuming *arguendo* it is “commonly” or “widely” accepted that, in general, formulations within the ranges of tested formulations share the stability of the tested formulations, Pet. 45; Ex.1002 ¶148, this probabilistic evidence cannot prove inherency. *Apotex*, 754 F.3d at 960-61; *PersonalWeb Techs., LLC v. Apple, Inc.*, 917 F.3d 1376, 1382 (Fed. Cir. 2019) (“mere possibility is not enough” for inherency); *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1294 n.1 (Fed. Cir. 2013) (inherent obviousness did not apply because the record did not establish whether “the mere administration of 0.2% brimonidine and 0.5% timolol twice daily in any fixed combination formulation inherently produces the claimed result” or if “only certain fixed-combination formulations produce this result”).

Second, the district court expressly found an *actual* formulation falling within the ranges of the ’865 patent’s exemplified formulations (having the same ingredients and amounts as the ’865 patent’s Example 3) did *not* meet the 98% stability limitation: Regeneron’s “SS195” data. *SB PI Decision*, 2024 WL 3422971, at *29. The SS195 formulation falls within what Formycon has termed the ’865

example ranges (40 mg/mL of aflibercept, 10 mM phosphate, 0.03% polysorbate 20, 5% sucrose, and 40 mM NaCl at pH 6.25). *See* Ex.2024 (Graham Decl.) ¶10. The SS195 formulation had less than 98% native conformation by SEC at time zero, before any storage. Ex.2024 (Graham Decl.) ¶11, Ex.6 (showing percent native conformation at time zero of 97.3, 97.7, and values in between). Because the process of protein aggregation is irreversible, *Mylan*, 714 F. Supp. 3d at 714; *SB PI Decision*, 2024 WL 3422971, at *29, a formulation starting with less than 98% native conformation could not have 98% native conformation after 2 months' storage. Thus, the SS195 formulation, falling within what Formycon has deemed the '865 example ranges, does not have the claimed 98% native conformation. Accordingly, the record is clear, and multiple courts have held, that formulations falling within those ranges do not necessarily achieve 98% native conformation, as a finding of inherency would require. *Celltrion*, 2025 WL 706079, at *3; *SB PI Decision*, 2024 WL 3422971, at *29; *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 prior art being practiced).

Furthermore, contrary to Formycon's assertion, the Modified Fraser/Wulff formulation does *not* "fall[] squarely within the[] ranges" of the '865 examples. Pet. 43. Rather, the buffer composition, stabilizing agent concentration, and pH of the Modified Fraser/Wulff formulation all fall at least partially *outside* the '865 example

ranges:

Attribute	'865 Example Range	Modified Fraser/Wulff Formulation (Pet. 43)
pH	6.25-6.3	6.0-6.3
Stabilizing Agent	0-5% sucrose	Around 5% sucrose or around 10% sucrose (Pet. 43 n.7)
Buffer Composition	5-10 mM phosphate	5 mM phosphate 5 mM citrate

Formycon cites no native conformation data for intravitreal formulations at pH 6.0-6.24, with 10% sucrose, or with a citrate buffering agent, and provides no evidence that such formulation necessarily has 98% native conformation. Formycon attempts to brush aside these differences with an unsubstantiated assertion that “based on standard industry principles, the Modified Fraser/Wulff formulation would have the recited stability even with these differences.” Pet. 45 (citing Ex.1002 ¶¶148-156). Not only does the SS195 data refute this understanding, Formycon fails even to cite expert testimony supporting this assertion. *See* Ex.1002 ¶¶148-156 (providing no opinion on the stability of formulations falling outside those ranges). By failing to provide any evidence of the stability of any formulation falling within the ranges encompassed by Formycon’s Modified Fraser/Wulff formulation, let alone all such formulations, Formycon fails to meet its burden to show a reasonable likelihood that the 98% native conformation limitation is present *necessarily*, not just possibly or probably, in the Modified Fraser/Wulff formulation. *Glaxo*, 52 F.3d

at 1047-48; *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).

Formycon bears the burden to show a reasonable likelihood that the Modified Fraser/Wulff formulation necessarily achieves the 98% limitation. 35 U.S.C. § 316(e). Formycon’s attempt to shift the burden to Regeneron, Pet. 41, flouts binding Federal Circuit precedent and the presumption of validity. “[T]he burden of persuasion is on the petitioner to prove ‘unpatentability by a preponderance of the evidence,’ 35 U.S.C. § 316(e), and that burden never shifts to the patentee.” *In re Magnum Oil Tools Int’l*, 829 F.3d 1364, 1375 (Fed. Cir. 2016) (quoting *Dynamic Drinkware*, 800 F.3d at 1378). There is no exception for inherency. *See Knauf Insulation, Inc. v. Rockwool Int’l A/S*, 788 F. App’x 728, 734 (Fed. Cir. 2019) (“[I]t was Petitioner’s burden to prove that every limitation in the claim was found in the prior art, either inherently or explicitly.”); *Crown Ops. Int’l, Ltd. v. Solutia Inc.*, 289 F.3d 1367, 1377 (Fed. Cir. 2002).

Formycon’s reliance on *In re Best*, 562 F.2d 1252 (C.C.P.A. 1977) for its burden-shifting theory, Pet. 41, is misplaced. *In re Best* is an appeal from the Board’s rejection of claims in a pending application. 562 F.2d at 1252. The Federal Circuit has made clear that “a burden-shifting framework makes sense in the prosecution context,” like that of *Best*, but “does not apply in the adjudicatory

context of an IPR.” *Magnum Oil*, 829 F.3d at 1375. It is not Regeneron’s burden to disprove inherency of the 98% stability limitation in Modified Fraser/Wulff. Formycon alone bears that burden to show the Modified Fraser/Wulff formulation would inherently meet the 98% native conformation limitation; it cannot do so.

c. The POSA Was Not Motivated To Achieve 98% Native Conformation With a Reasonable Expectation of Success

If not inherent, Formycon also argues that achieving the 98% native conformation would have been obvious. Pet. 46-48. Obviousness requires both that a POSA be motivated to modify the prior art to achieve the claimed invention and that a POSA would have a reasonable expectation of success in doing so. *Cyclobenzaprine*, 676 F.3d at 1068-69. Formycon does not meet its burden of proving either obviousness factor.

Motivation. The district court and Federal Circuit have both held that the POSA was not motivated to obtain the claimed 98% native conformation limitation. *Celltrion*, 2025 WL 706079, at *3; *SB PI Decision*, 2024 WL 3422971, at *31. A POSA “would not have been motivated to obtain such a high level of native conformation as lower levels would have been considered acceptable,” and thus the “generic argument that the POSA would have sought to purify aflibercept” fails to support a motivation to achieve the specifically recited 98% native conformation. *SB PI Decision*, 2024 WL 3422971, at *31. The courts’ holdings are supported by

the prior art and FDA guidance. *See* Ex.2025 (Andya), ¶49 (“[A] ‘stable’ formulation may be one wherein less than about 10% and preferably less than about 5% of the protein is present as an aggregate in the formulation.”); Ex.2026 (Kaisheva) ¶36 (similar); Ex.2027 (FDA Guidance for Industry), 11 (defining “significant change” as “[a] 5 percent change in assay from its initial value”).

Formycon provides no prior-art evidence undermining the courts’ decisions and indeed relies on no prior art disclosing any stability data for aflibercept or motivation to pursue any stability level. Pet. 46-47. Instead, Formycon alleges only a generic motivation to “maximize stability” (Pet. 46) that the district court and Federal Circuit have already rejected. *Celltrion*, 2025 WL 706079, at *3; Ex.2004 (*Celltrion PI Decision*) at 109-10.

Reasonable Expectation of Success. Formycon also fails to show a reasonable likelihood that the POSA would have reasonably expected to achieve the claimed 98% stability with the Modified Fraser/Wulff formulation. Formycon provides *no evidence* regarding the stability of aflibercept in the prior art, and the district court has held repeatedly that the POSA lacked a reasonable expectation of success in achieving the claimed 98% native conformation. *Mylan*, 714 F. Supp. 3d at 742; *SB PI Decision*, 2024 WL 3422971, at *31. The district court found that “higher protein concentrations increase the risk for instability, and the claimed concentration of aflibercept (40 mg/ml) is four times higher than the 10 mg/ml

concentration of” a prior art formulation, ranibizumab. *Mylan*, 714 F. Supp. 3d at 742. Furthermore, the court found that a POSA would expect aflibercept, an artificial fusion protein, to be less stable than proteins like antibodies that evolved to have stability, because fusion proteins “did not evolve to possess inherent stability.” *Id.*; see also *SB PI Decision*, 2024 WL 3422971, at *31. And here, Formycon’s modifications to Fraser and Wulff—which do not disclose their formulations are stable, and actually suggest otherwise, *supra* IV.A.4.a-b, IV.D.2.b.2—would have been expected to *decrease* stability by simultaneously increasing protein concentration by over 60% while reducing the amount of stabilizing agent by 50-75%. *Mylan*, 714 F. Supp. 3d at 742. With no native conformation data in the prior art and hindsight-driven modifications that would have been expected to reduce stability further, Formycon cannot establish any expectation of success in achieving 98% native conformation as claimed.

Formycon attempts to downplay the reasonable expectation of success by arguing that achieving the 98% stability limitation would require “minor optimizations to the [Modified Fraser/Wulff] formula.” Pet. 47. However, the Modified Fraser/Wulff formulation is in-and-of itself an extensively modified version of the prior art formulations in Fraser and Wulff. Unlike Formycon’s cited *E.I. Dupont de Nemours v. Synvina C.V.*, this is not a case where the “general conditions” of the claimed aflibercept formulation were disclosed in the prior art.

904 F.3d 996, 1006 (Fed. Cir. 2018). “[T]o have a reasonable expectation of success, one must be motivated to do more than merely to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.” *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006). Formycon offers no more than the legally insufficient “vary all parameters” approach, guided by no information regarding the stability of aflibercept.

Finally, Formycon irrelevantly argues that the ’865 patent “broadly claims formulations” and “assumes a POSA can adjust the specific amounts of those ingredients ... to achieve the claimed level of stability.” Pet. 48. The ’865 patent must teach a POSA how to practice the claimed invention, but it is not prior art, and its disclosure is irrelevant to the obviousness inquiry. *See Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1310 (Fed. Cir. 2015) (“The obviousness inquiry turns on what the prior art would have taught a [POSA] and whether the claimed invention would have been obvious in view of the prior art.... In contrast, the enablement inquiry turns on whether the skilled artisan, after reading the specification, would be able to make and use the claimed invention without undue experimentation.”). Regardless, as the Federal Circuit and the district court have held repeatedly, the ’865 patent specification—which unlike the prior art, includes numerous working examples of

formulations meeting the 98% native conformation limitation—provides written description support for the claims. *SB*, 127 F.4th at 914-17; *Mylan*, 714 F. Supp. 3d at 751-54. That has no bearing on whether a POSA would have a reasonable expectation of success in achieving the 98% native conformation limitation based on prior art that provides no stability data for aflibercept whatsoever.

4. Objective Evidence Forecloses Obviousness

The district court credited Regeneron’s objective evidence of nonobviousness presented at trial and in preliminary injunction proceedings. *Mylan*, 714 F. Supp. 3d at 745-748; *e.g.*, *SB PI Decision*, 2024 WL 3422971, at *33. That objective evidence is equally applicable here and independently forecloses obviousness.

a. Teaching Away

The prior art taught away from 40 mg/mL aflibercept, which is relevant both as objective evidence, *Monarch*, 139 F.3d at 885, and to the POSA’s motivation, *supra* IV.D.2. The same evidence described above thus also applies here. *Mylan*, 714 F. Supp. 3d at 745-46.

b. Unexpected Properties

The district court also found that Eylea[®] achieved “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).” *Mylan*, 714 F. Supp. 3d at 746 (citing Ex.2028

(Thomas), 4). “Extended dosing with Eylea was not only unexpected, but revolutionary, providing ‘immediate benefits to patients who have a difficult time with intravitreal dosage administration’ for the first time.” *Id.* (quoting Ex.2028 (Thomas), 4). As the court found, these “captivating” properties were a “difference in kind” as compared to Gaudreault’s 40 mg/mL formulation—the “closest prior art” and only disclosure of an ophthalmic formulation containing 40 mg/mL of a VEGF antagonist along with the other structural components required by the claims—which resulted in inflammation and was ultimately discarded. *Id.* (quoting *Allergan*, 796 F.3d at 1307). Again, this evidence applies equally here, as Formycon does not address the court’s findings and presents no prior art indicating that 40 mg/mL of a VEGF antagonist together with the other structural components would have been expected to exhibit such properties.

Furthermore, the district court found that there was a nexus “between Eylea’s unexpected properties and the claimed invention.” *Mylan*, 714 F. Supp. 3d at 746. Eylea[®] is an embodiment of each claim because it indisputably includes aflibercept and each of the claimed structural components. *Id.* at 746. The court found that the “unexpected properties stemmed from the claimed compositions as a whole, including the 40 mg/ml aflibercept concentration” (which contributed to Eylea[®]’s half-life) required by each claim other than claims 1 and 26 as well as “the required 98% native conformation” (indicating lower risk of inflammation) required by every

claim. *Id.* at 746-47 (citing *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1330 (Fed. Cir. 2016)). Thus, there is a nexus between Eylea[®]'s unexpected properties and the claimed invention.

c. Industry Skepticism

The district court found industry skepticism based on the prior art's teachings that "clinical use of fusion proteins like aflibercept 'remains to be validated' and suggested that the 'junctions between the various structural elements in such multi-component molecules can generate an immune response.'" *Mylan*, 714 F. Supp. 3d at 747 (quoting Ex.2029 (Ferrara 2004), 397). The court credited testimony that this skepticism directed at a possible immune response would have been a concern to the POSA and thus supported nonobviousness of the claims specifically requiring the claimed fusion protein, and it does so here as well. *Id.* at 748. The court likewise found that the suggestion in Ferrara 2006 that VEGF Trap molecules may not penetrate to the retina also constituted skepticism, and that further supports nonobviousness here. *Id.* (citing Ex.2015, 862).

d. Copying

Formycon also copied the claimed formulations. *Formycon PI Decision*, 2024 WL 3423047, at *37-38; *see also Mylan*, 714 F. Supp. 3d at 748. Formycon's proposed biosimilar uses the same exact molecule (glycosylated aflibercept) at the same concentration with the same amount of buffer and the same organic co-solvent

at the same amount (polysorbate 20) as Eylea[®]. Ex.2031 (AHZANTIVE(R) Label), 13-14. Formycon had “access to” the Eylea[®] formulation published in the parents of the ’865 patent (the ’261 patent issued in 2009, ’865 patent, 1:34-35) and the Eylea[®] label (published in 2011, Ex.2032, 9), and its near-identical formulation has “substantial similarity” to Eylea[®]. *Medtronic, Inc. v. Teleflex Innovations S.a.r.l.*, 70 F.4th 1331, 1340 (Fed. Cir. 2023). Thus, copying further supports nonobviousness.

E. Ground 2: Formycon Fails To Demonstrate Obviousness over Fraser, Wulff, the Three 2006 Presentations, the ’319 Publication, and Nayar

Formycon’s arguments regarding Ground 2 are directed to the ’865 patent’s claims reciting a pre-filled syringe, rather than a vial as in Ground 1. Pet. 63. However, Formycon raises the same substantive arguments against these claims based on the Modified Fraser/Wulff formulation, Pet. 63, and these arguments fail for the same reasons as articulated above regarding Ground 1, which are independent of the choice of vial or pre-filled syringe. *Supra* IV.D.

Date: March 17, 2025

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CERTIFICATION UNDER 37 C.F.R. § 42.24(d)

In accordance with 37 C.F.R. § 42.24, as amended, the undersigned certifies that this Patent Owner Preliminary Response complies with the applicable type volume limitations of 37 C.F.R. §§ 42.24(a)(i) and 42.24(b)(1). Exclusive of the portions exempted by 37 C.F.R. § 42.24(a), this Patent Owner Preliminary Response contains 13,907 words as counted by the word processing program used for its preparation (Microsoft Word 2019).

Date: March 17, 2025

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CERTIFICATE OF SERVICE
(37 C.F.R. § 42.6(e))

The undersigned hereby certifies that on March 17, 2025, I caused true and correct copies of the following materials:

- Patent Owner's Preliminary Response
- Patent Owner's Exhibit List
- Exhibits 2001-2029, 2031, 2032

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