

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FRESENIUS KABI SWISSBIOSIM GMBH,
Petitioner,

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner.

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

PATENT OWNER'S PRELIMINARY RESPONSE

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2003	Formycon Redacted PI Decision, 24-md-3103, Dkt. 247 (N.D.W. Va.)
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.)
2008	Fresenius, Fresenius to Expand Biopharma Portfolio with a New Licensing Agreement to Commercialize a Proposed Aflibercept Biosimilar (Dec. 20, 2024), https://www.fresenius.com/node/6982
2009	Email from D. Berl to S. Gibson re Scheduling Conference (Sept. 12, 2025)
2010	Zaltrap® Label
2011	Regeneron v. Mylan, 22-cv-61, Trial Transcript (Public Excerpts) (N.D.W. Va.)
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2013	Regeneron v. Mylan, 22-cv-61, Trial Ex. DTX-3619A, Fusion Proteins Disclosed in Papadopoulos
2014	International Publication No. WO 00/75319 (“WO 00/75319”)
2015	U.S. Patent Application Pub. No. 2006/0058234 A1 (“Daly”)
2016	W. Wang, Protein Aggregation and Its Inhibition in Biopharmaceutics, 289 INT. J. PHARM. 1 (2005) (“Wang 2005”)
2017	J. Gaudreault et al., Preclinical pharmacokinetics of Ranibizumab (rhuFabV2) after a single intravitreal administration, 46(2) INVEST OPHTHALMOL VIS SCI. 726 (2005) (“Gaudreault”)

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2019	International Publication No. WO 2005/102303 A2 (“Peyman”)
2020	M.R. Marmour, Retinal detachment from hyperosmotic intravitreal injection, 18(12) INVEST OPHTHALMOL VIS SCI. 1237 (1979) (“Marmour ”)
2021	Declaration of Kenneth S. Graham, dated April 18, 2024
2022	Excerpts of File History of U.S. Patent No. 11,084,865

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®.

Over the past three years, the '865 patent has been the subject of fiercely disputed litigation in a consolidated multidistrict litigation ("MDL") proceeding. Challenger after challenger raised virtually every invalidity argument known to Patent Law—including anticipation, obviousness, written description, enablement, and double-patenting. The '865 patent survived them all. Four District Court decisions and three Federal Circuit decisions all reached the same conclusion: The '865 patent is valid. Still other validity challenges were raised in three IPR petitions—all of which the Board denied given the parallel MDL litigation, the interests of efficiency and integrity of the adjudicative system, and the weakness of the petitions retreading validity arguments already considered and rejected across years of litigation and hundreds of pages of decisions.

Throughout these proceedings, Fresenius has sat idly by. Only now, years into extensive litigation on the '865 patent, has Fresenius decided to advance its challenge, which like the prior petitioners, repeats a defense already considered and rejected in a detailed decision following a two-week trial. But Fresenius cannot turn back the clock. The invalidity ground it asserts—anticipation over Dix '226 (Ex.1005)—is the exact same one previously advanced in the MDL litigation; they

both involve the same statutory basis, the same asserted art, and the same arguments. At a two-week bench trial before Chief Judge Kleeh of the U.S. District Court for the Northern District of West Virginia, MDL defendants Mylan and Biocon argued that the '865 patent is invalid as anticipated by Dix '226. The District Court resoundingly rejected that argument on numerous bases in a thoroughly reasoned post-trial decision. The District Court's detailed post-trial findings were correct, and they foreclose Fresenius's challenge here. As the District Court found, Dix '226 fails to disclose the 40 mg/ml concentration requirement of the challenged claims; Dix '226 discloses cancer formulations, not ophthalmic formulations suitable for intravitreal administration; and Dix '226 fails to disclose the limitations of the challenged claims "arranged as in the claim." Fresenius's petition offers no basis to disturb the District Court's well-reasoned findings, reached after observing live witness testimony from numerous experts and inventors. It is difficult to conjure a more wasteful and inefficient use of this Board's resources than to repeat the District Court's effort and evaluate the same argument rejected following trial. Accordingly, the Board should deny institution.

II. Background

Regeneron has been litigating the '865 patent covering its Eylea[®] product against putative biosimilars for three 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. In each of those decisions, the '865 patent's validity was upheld. Moreover, the District Court made—and the Federal Circuit affirmed—numerous findings that fatally undermine Fresenius's Petition, including the District Court's rejection of the same validity ground that Fresenius advances here. These prior court decisions foreclose Fresenius from showing any likelihood that the challenged claims are invalid.

A. Parallel Proceedings

Regeneron sued Mylan, Samsung Bioepis ("SB"), Formycon, Celltrion, Amgen, and Sandoz for infringement of the '865 patent. The suits were consolidated for pre-trial purposes as a multidistrict litigation ("MDL") in the Northern District of West Virginia. *In re Aflibercept Pat. Litig.*, 730 F. Supp. 3d 1374, 1377 (J.P.M.L. 2024). If Fresenius elects to pursue commercialization in the United States of its "proposed Aflibercept biosimilar," Ex.2008 (Fresenius Press Release), it too will become a defendant in the same MDL. The District Court overseeing the MDL has issued one bench-trial decision (*Mylan*) and three preliminary-injunction decisions (*SB*, *Formycon*, and *Celltrion*) in which it rejected every one of those defendants' invalidity challenges to the '865 patent. *See Regeneron Pharm., Inc. v. Mylan Pharm. Inc.*, 714 F. Supp. 3d 652 (N.D.W. Va. 2024) ("*Mylan*"); *In re Aflibercept Pat. Litig.*, 2024 WL 3422971 (N.D.W. Va. June 24, 2024) ("*SB PI Decision*"); *In re Aflibercept Pat. Litig.*, 2024 WL 3423047 (N.D.W. Va. July 9, 2024) ("*Formycon*

PI Decision”); Ex.2004 (“*Celltrion PI Decision*”). On appeal, the Federal Circuit affirmed all three preliminary-injunction decisions. *See Regeneron Pharm., Inc. v. Mylan Pharm. Inc.*, 127 F.4th 896 (Fed. Cir. 2025) (“*SB*”); *Regeneron Pharm., Inc. v. Mylan Pharm. Inc.*, 2025 WL 324288 (Fed. Cir. Jan. 29, 2025) (“*Formycon*”); *Regeneron Pharm., Inc. v. Mylan Pharm. Inc.*, 2025 WL 706079 (Fed. Cir. Mar. 5, 2025) (“*Celltrion*”).

The District Court’s decisions, as relevant here, determined that:

(1) the disclosures in U.S. Patent 10,406,226 (Ex.1005, “Dix ’226” or “Dix”) of formulations containing 10-50 mg/ml of “a generic ‘VEGF-specific fusion protein antagonist’” and of a “40 mg/ml pre-lyophilized solution” are not anticipatory, because separate and apart from any deficiencies in those prior-art disclosures, Dix ’226 does not teach all the elements as arranged in the ’865 claims, *i.e.*, an ophthalmic formulation comprising 40 mg/ml aflibercept with at least 98% native conformation after two months’ storage, *Mylan*, 714 F. Supp. 3d at 730-34;

(2) Dix ’226 disclosed a range that is too broad to invoke a presumption of anticipation, rendering criticality irrelevant, *id.*;

(3) even if criticality were relevant, the 40 mg/ml concentration recited by all but two challenged claims is critical, *id.* at 731, 734; and

(4) ophthalmic formulations with 40 mg/ml aflibercept do not necessarily achieve at least 98% native conformation after two months' storage, *SB PI Decision*, 2024 WL 3422971, at *28-31; *Formycon PI Decision*, 2024 WL 3423047, at *32-35 (N.D.W. Va. July 9, 2024); Ex.2004 (*Celltrion PI Decision*) at 97-109, meaning that, even if the prior art taught ophthalmic formulations with 40 mg/ml aflibercept, those formulations would not necessarily have the claimed stability.

Multiple panels at the Federal Circuit, in turn, affirmed the *SB*, *Formycon*, and *Celltrion* preliminary-injunction decisions, including the District Court's non-inherency finding. *SB*, 127 F.4th at 913; *Formycon*, 2025 WL 324288, at *5-6; *Celltrion*, 2025 WL 706079, at *3.

Certain MDL member cases have since settled, including the *Mylan* case, which settled during pendency of the appeal, and the *Formycon* and *Celltrion* cases, which settled following remand from appeal. No. 24-2002, ECF No. 58 (Fed. Cir. Apr. 14, 2025); No. 24-md-3103, ECF Nos. 661 (N.D.W. Va. Sept. 29, 2025), 673 (N.D.W. Va. Oct. 21, 2025).

B. Fresenius's Petition

Fresenius's Petition repeats the anticipation and inherency arguments already considered and rejected by the District Court and Federal Circuit decisions discussed above. Its sole ground (Pet. 11) is the same one raised by *Mylan* and considered and

rejected by the District Court. Like Mylan, Fresenius asserts that Dix '226's disclosure of 10-50 mg/ml of a VEGF antagonist anticipates the 40 mg/ml aflibercept formulations claimed by the '865 patent because the ranges overlap and the 40 mg/ml concentration is not critical. Pet. 2-3, 18, 31-32. Like Mylan, Fresenius asserts that Dix '226's disclosure of a "pre-lyophilized solution" with 40 mg/ml of a VEGF antagonist fusion protein anticipates the 40 mg/ml aflibercept formulations claimed by the '865 patent. Pet. 18-19.

Fresenius also advances inherency arguments that likewise have been rejected. Like SB, Formycon, and Celltrion, Fresenius argues that formulations with 40 mg/ml of aflibercept necessarily have at least 98% native conformation after two months' storage. Pet. 1. ("the associated stability property . . . are inherent properties of the claimed formulation"); Pet. 4 ("percent native conformation [is] an inherent property that adds no patentable weight to the claim"); Pet. 29 ("The stability is therefore an inherent property . . ."); Pet. 33 ("[F]ormulations with 40 mg/ml and polysorbate 20 in the claimed amounts would inherently meet the stability limitations of claim 1 . . ."); Pet. 39 ("A 40 mg/ml aflibercept formulation with the claimed amounts of polysorbate 20 and sucrose would necessarily meet the 99% native conformation stability requirement at 2 months."); Pet. 40 ("A 40 mg/ml formulation would inherently also meet the stability as Dix demonstrates that there is less aggregation when the aflibercept concentration is lower.").

Fresenius's Petition is fatally undermined by the fact that each of those arguments has already been considered and rejected—often repeatedly so—in the above-discussed decisions. Fresenius, however, ignores almost all of them and instead focuses solely on *Mylan* and the singular issue of criticality. But Fresenius does not cite any new evidence or argument as to criticality; rather, it relies exclusively on questions regarding criticality raised by a subset of judges on the Federal Circuit panel during the *Mylan* oral argument. Pet. 32 (arguing that panel's questions "call into question and render irrelevant the district court's finding that Dix '226 did not anticipate the Challenged Claims"); Pet. 1-4, 6, 30-31 (similar). Notably, however, Fresenius's one-sided characterization of the oral argument ignores all the panel's questions recognizing the deficiencies in Mylan's position, *e.g.*, regarding the non-inherency of the 98% native conformation limitation and the breadth of Dix '226's disclosed range as compared to the specifically recited 40 mg/ml concentration. Ex.1008 at 7:11-13, 11:20-24, 17:6-13, 35:4-9, 45:22-46:4. And Fresenius neglects to mention, let alone demonstrate error in, the District Court's non-criticality findings that independently foreclose anticipation.

III. Fresenius Fails To Show a Reasonable Likelihood That the '865 Patent Claims Are Anticipated

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.

However, aflibercept originally was developed to treat cancer by systemic administration into the bloodstream, leveraging the prolonged serum half-life aflibercept possessed. *Mylan*, 714 F. Supp. 3d at 691-92; *Formycon PI Decision*, 2024 WL 3423047, at *31. Aflibercept was approved to treat certain cancers under the trade name Zaltrap[®]. Ex.2010 (Zaltrap[®] label).

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.2011, 448:1-12 (Furfine). At the time of the invention, the leading ophthalmic VEGF antagonist in development was Genentech’s ranibizumab. Ex.2011, 448:18-449:6, 450:14-19 (Furfine). Whereas aflibercept is a synthetic fusion protein, ranibizumab is an antibody fragment. Ex.2011, 1035:4-9 (Rabinow), 451:5-14, 456:6-12 (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.2011, 2013:14-17, 2014:21-2015:16 (Trout), 448:1-6, 456:6-9 (Furfine)); Ex.2012 (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.

As of the priority date of the '865 patent, Regeneron had disclosed multiple VEGF Trap fusion proteins. At least 8 distinct VEGF receptor fusion proteins were disclosed in WO 00/75319, a publication describing Regeneron's invention of several VEGF antagonist fusion proteins. *Mylan*, 714 F. Supp. 3d at 698; Ex.2011, 2020:7-2022:16 (Trout); Ex.2013 (Trial Ex. DTX-3619A); *see also* Ex.2014 (WO 00/75319), Figs. 10A-10D, 13A-13D, 14-14C, 15A-15C, 16A-16D, 22A-22C (identifying other fusion proteins). The amino acid sequence from Fig. 24A-24C in WO 00/75319 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.2011, 2022:4-16 (Trout). A fusion protein called “mini-Trap” was another VEGF Trap protein developed in parallel by Regeneron “as a backup candidate in case the full-length aflibercept proved incapable of sufficiently penetrating into the retina,” *Mylan*, 714 F. Supp. 3d at 692, and disclosed in the Daly reference, U.S. Patent Application Pub.

No. 2006/0058234. Ex.2015 (Daly), ¶ 9; *Formycon PI Decision*, 2024 WL 3423047, at *30.

2. 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, 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

3. Asserted Prior Art

a. Dix '226 (Ex.1005)

Dix '226 “is directed to formulations of VEGF antagonists for cancer” and “does not include any teaching of an ‘ophthalmic formulation[s]’ or intravitreal administration.” *Mylan*, 714 F. Supp. 3d at 730.¹ Specifically, Dix '226 teaches that VEGF “is nearly ubiquitous in human cancer, consistent with its role as a key mediator of tumor neoangiogenesis,” and that “[b]lockade of VEGF function, by binding to the molecule or its VEGFR-2 receptor, inhibits growth of implanted tumor cells.” Ex.1005, 1:43-47. Dix thus disclosed formulations of VEGF Trap antagonists which “can either be delivered subcutaneously or diluted and delivered by intravenous infusion.” Ex.1005, 10:8-10. However, Dix nowhere teaches that its formulations could be used ophthalmically or that they were suitable for intravitreal injection.

¹ At trial, the parties disputed whether Dix '226 is prior art to the '865 patent, *Mylan*, 714 F. Supp. 3d at 745, but the Court rejected anticipation without deciding the prior art issue, *id.* at 730-34. The Board should reject institution here for the same reasons. While Regeneron assumes that Dix is prior art for purposes of this Preliminary Response, Regeneron reserves the right to swear behind Dix in the event institution is granted.

None of the VEGF formulations disclosed in Dix '226 contain 40 mg/ml of aflibercept, nor are there any stability results for any liquid formulations containing less than 20% sucrose. For example, Example 1 discloses testing of a liquid formulation containing, *inter alia*, 50 mg/ml of a VEGF antagonist and 20% sucrose. Ex.1005, 7:60-8:20. Dix teaches another formulation with 50 mg/ml of a VEGF antagonist and 20% sucrose and teaches that “[d]ue to the high osmolality of this formulation, it is diluted 3-fold to achieve an iso-osmolar solution for intravenous administration.” Ex.1005, 10:4-14. Dix nowhere suggests that such a formulation could be used ophthalmically or adapted for intravitreal injection. To the contrary, the testimony at trial was clear that the inventors did not even consider adapting the aflibercept cancer formulation containing “20 percent sucrose” to ophthalmic use, because “it had a really high osmolality” of approximately “1100, 1160 milliosmoles” and “was designed to be a concentrate that you would put into an [intravenous] bag, dilute out, and give to a patient through an IV.” Ex.2011, 1679:13-21.

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; *SB PI Decision*, 2024 WL 3422971, at *7.

Fresenius appears to offer a definition with a higher level of ordinary skill. Pet. 14-15. Regeneron proposes that the Board adopt the same POSA definition that has consistently governed these cases. Regardless, applying either POSA definition, Fresenius fails to show a reasonable likelihood of success.

C. Ground 1: Fresenius Fails To Demonstrate Anticipation over Dix '226

To anticipate, (1) “the four corners of a single, prior art document [must] describe every element of the claimed invention,” and (2) the prior art document “must also disclose those elements arranged as in the claim.” *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008) (cleaned up). But as the District Court already found, Dix '226 does not teach any formulation with an aflibercept concentration of 40 mg/ml, which is required by all but two challenged claims. *Mylan*, 714 F. Supp. 3d at 732-34. Furthermore, as the District Court also found, Dix '226 does not disclose the claim limitations “arranged as in the claim,” which separately defeats anticipation for every claim. *Mylan*, 714 F. Supp. 3d at 733 (discussing *Net MoneyIN*, 545 F.3d at 1370-71). Specifically, Dix does not disclose

an ophthalmic formulation suitable for intravitreal administration 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, as required by every challenged claim. Because Dix fails to anticipate for multiple reasons, institution should be denied.

1. Dix '226 Does Not Teach 40 mg/ml Aflibercept

All but two of the challenged claims (claims 1 and 26) recite 40 mg/ml of aflibercept. Dix '226 nowhere teaches any formulation with this concentration. As the District Court found, Dix's disclosure of 10-50 mg/ml of a generic VEGF antagonist fusion protein is insufficient to make out a *prima facie* case of anticipation. Even if it were, the District Court correctly found that concentration is critical to the durability, safety, and efficacy of the claimed formulations. Finally, Dix's disclosure of pre-lyophilized formulations does not disclose ophthalmic formulations comprising 40 mg/ml aflibercept.

a. Fresenius Has Not Made Out a *Prima Facie* Case of Anticipation

“[T]he disclosure of a range is not a disclosure of the endpoints of the range or other discrete points within the range.” *UCB, Inc. v. Actavis Labs. UT, Inc.*, 65 F.4th 679, 688 (Fed. Cir. 2023). Specifically, only “a very small genus” may anticipate specific values within a range. *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006). The District Court found that the 10-50 mg/ml range

disclosed in Dix of an unspecified fusion protein was not a “very small” range and thus could not anticipate the specific 40 mg/ml concentration in the claims. *Mylan*, 714 F. Supp. 3d at 732. Fresenius shows no error in that finding, which forecloses anticipation regardless of criticality.

As relevant here, all but two of the challenged claims require an ophthalmic formulation of aflibercept—a glycosylated “VEGF antagonist fusion protein [which] comprises amino acids 27-457 of SEQ ID NO:4,” Ex.1001, claim 1—at the concentration of 40 mg/ml. Dix ’226 teaches no formulation with a 40 mg/ml concentration; it teaches a range of “10-50 mg/ml of the fusion protein.” *Mylan*, 714 F. Supp. 3d at 730 (quoting Ex.1005 at 2:23); *see also* Ex.1005 at 7:8-9 (“about 10 mg/ml to about 50 mg/ml fusion protein”); *id.* at 7:12-13 (“about 10[-]50 mg/ml fusion protein”). The District Court found that “the range of 10-50 mg/ml is not a small range,” because “this range encompasses hundreds of discrete concentrations between 10 and 50 (like ‘28’ mg/ml, ‘37.2’ mg/ml, and ‘49.35’ mg/ml).” *Mylan*, 714 F. Supp. 3d at 730, 732. The Court further found that Dix ’226’s disclosure “is not linked to aflibercept specifically, but instead refers to a generic ‘VEGF-specific fusion protein antagonist.’” *Id.* at 730 (quoting Ex.1005, 2:20-23). “[M]ultiple fusion proteins would fall within that genus,” and “Dix ’226 identifies at least two such fusion proteins by sequence,” *id.* at 730-31, specifically SEQ ID NO:2 and SEQ ID NO:4, Ex.1005, 2:12-14, 5:35-36, claim 1. “[A]nd more would fall within the

class.” *Mylan*, 714 F. Supp. 3d at 731; *see also id.* at 732 (noting that Dix ’226’s disclosure of a genus of concentrations is “further enlarged by the fact that Dix’s range is not limited to aflibercept, but rather covers a broader generic set of ‘VEGF-specific fusion protein antagonist’ molecules”). Regeneron had disclosed numerous VEGF antagonist fusion proteins, including the mini-Trap designed specifically for ophthalmic use and others that are not within the scope of challenged claims. *Supra* III.A.1; Ex.2015 (Daly), ¶ 43.

Accordingly, Fresenius’s characterization of Dix ’226 as “disclos[ing] . . . 10-50 mg/ml aflibercept” (Pet. 2) is erroneous and commits the same error the District Court rejected in *Mylan*. 714 F. Supp. 3d at 731 (“Thus, the Defendants’ argument based on ‘Dix ’226’s disclosed aflibercept protein range of 10 to 50 mg/ml’ incorrectly describes Dix’s disclosed genus.” (citation omitted)). Instead, “[t]he disclosure in Dix ’226 of ‘10-50 mg/ml of the fusion protein’ refers to a large range of numerical concentrations and also encompasses multiple different fusion proteins.” *Id.* Because “only ‘a very small genus’ may anticipate specific intervening values,” Dix’s disclosure is simply too broad to make out a *prima facie* case of anticipation. *Mylan*, 714 F. Supp. 3d at 732 (quoting *Atofina*, 441 F.3d at 999). Fresenius offers no basis to relitigate this outcome-determinative finding here.

That there are no “overlapping ranges” here further precludes Fresenius from making out “a ‘prima facie case of anticipation.’” *Id.* at 731. Each challenged claim

(except claims 1 and 26) “recites the specific concentration of 40 mg/ml aflibercept, not a range of concentrations.” *Id.* But “the Federal Circuit has held that criticality is a factor only where a disclosed range ‘overlaps’ with a ‘claimed range,’ not a specific point.” *Id.* at 733 (quoting *Genentech, Inc. v. Hospira, Inc.*, 946 F.3d 1333, 1338 (Fed. Cir. 2020) (emphasis omitted)). Fresenius has “cite[d] no case where a court considered criticality in an anticipation inquiry under these circumstances,” *i.e.*, where the claims recite “a specific concentration—40 mg/ml—not a ‘claimed range.’” *Id.* In contrast, the district court in *Janssen Pharmaceuticals, Inc. v. Watson Laboratories, Inc.*, rejected an anticipation theory indistinguishable from Fresenius’s here, concluding that a dosage range of “.02-.05 mg” did not anticipate a specific dose of “.025 mg.” 2012 WL 3990221, at *6-10 (D.N.J. Sept. 11, 2012). The Board should hold the same here: as *Mylan* explained, the “holding in *Janssen* is consistent with Federal Circuit precedent explaining that where ‘[t]he disclosure is only that of a range, not a specific [point] in that range, . . . the disclosure of a range is no more a disclosure of the end points of the range than it is of each of the intermediate points.’” 714 F. Supp. 3d at 733 (quoting *Atofina*, 441 F.3d at 1000; citing *UCB*, 65 F.4th at 688 (alterations in original)). Fresenius fails to even address this precedent.

In sum, Fresenius has failed to show a *prima facie* case of anticipation. Dix ’226 discloses a broad, “five-fold range of 10-50 mg/ml” that encompasses multiple

VEGF antagonists, *id.* at 732, *i.e.*, a “very wide prior-art range.” *Janssen Pharm., Inc. v. Teva Pharm. USA, Inc.*, 141 F.4th 1367, 1376 (Fed. Cir. 2025); *see also Atofina*, 441 F.3d at 999 (discussing need for “a very small genus” for a genus to be considered a disclosure of each species within it). The claims, in contrast, recite a specific concentration—40 mg/ml—of a specific glycosylated fusion protein with a specific sequence.

Fresenius asserts that any value that “fall[s] within prior art ranges” suffices for *prima facie* anticipation, Pet. 30, but no precedent supports that reading, which would eviscerate *Atofina*. Rather, the Federal Circuit has explained that “[h]ow [the POSA] would understand the relative size of a genus or species in a particular technology is of critical importance” in assessing whether a prior-art range anticipates, and that the Federal Circuit’s “decision in *ClearValue*,” relied on by Fresenius (Pet. 30), “does nothing to alter” *Atofina*. *OSRAM Sylvania v. Am. Induction Techs., Inc.*, 701 F.3d 698, 705-06 (Fed. Cir. 2012). Regardless, *ClearValue, Inc. v. Pearl River Polymers, Inc.*, 668 F.3d 1340, 1344-45 (Fed. Cir. 2012), is inapposite. Unlike the specific 40 mg/ml concentration claimed here, *ClearValue* addressed an asserted claim that recited a range (not a specific value)—water with “alkalinity less than or equal to 50 ppm,” compared to “water with alkalinity of 150 ppm or less” taught in the prior art. *Id.* at 1344. Furthermore, there was no dispute that the range applied to the same thing in both the prior art and the

claims: “water,” *id.*, but here, the claims recite a specific glycosylated fusion protein having a particular amino acid sequence, whereas Dix’s range is generically associated with a generic “VEGF-specific fusion protein.” *See, e.g.*, Ex.1005, 2:20-24. Accordingly, *ClearValue* does not address the circumstances here and cannot relieve Fresenius of its burden to make out a *prima facie* case of anticipation.

Fresenius does not even mention the District Court’s findings on *prima facie* anticipation, let alone demonstrate error in them. While Fresenius observes that some Federal Circuit panel members posed questions regarding the District Court’s analysis, Pet. 30-32, it offers no support for its outlandish, citation-free assertion that those questions somehow “render irrelevant the district court’s” decision, Pet. 32; to the contrary, “[e]xperience teaches that questions asked by a Judge at oral argument are a rather poor predictor of a decision yet to be made.” *Cerini v. Warrior Energy Servs., Inc.*, 2014 WL 7015992, at *3 n.3 (W.D. Pa. Dec. 11, 2014). And to the extent those questions are relevant, Fresenius ignores that the panel repeatedly acknowledged that the *Mylan* decision may be affirmed on multiple bases, including “roadblocks” that preclude a finding of anticipation that the panel members never questioned. *E.g.*, Ex.1008 at 35:4-9 (“[A]s I understand your argument, you’ve got roadblocks that’s setting up before we have to worry about criticality. One is we’re dealing with, as you would call it, a class of VEGF antagonists and two, the size of the prior art . . . range is just too big.”); *id.* 7:11-13 (“I haven’t found a case, which

is our case, which is the prior art has the range [of values] and the patent has just one [value].”); *id.* at 11:20-24 (“And here we have not a claimed range but a claimed point. And then the question is well, when we look at INEOS or ClearVa- -- Value or anything else I can get my hands on, I don’t see that specific fact pattern.”). For example, the panel observed that “even if Dix discloses the 40 mg . . . there is nothing in Dix that that necessarily leads to that particular formulation that would get you this . . . particularized stability” required. Ex.1008, 17:6-13; *see also id.*, 45:22-46:7 (similar). Fresenius therefore cannot make out a *prima facie* case of anticipation, and there is no burden on Regeneron to show the criticality of the 40 mg/ml concentration. Fresenius’s complete failure to engage with the District Court’s findings regarding whether Dix ’226 makes out a *prima facie* case of anticipation fatally undermines its ability to show a reasonable likelihood of unpatentability. *Cf. Samsung Bioepis Co., Ltd. v. Regeneron Pharm., Inc.*, IPR2025-00176, Paper 12, at 22-23 (P.T.A.B. June 2, 2025) (“The fact that Petitioner elected not to mention, much less attempt to address the substance of the district court’s findings . . . , suggests a weakness in this aspect of its asserted grounds.”).

b. The 40 mg/ml Concentration Is Critical

Even if Dix ’226’s disclosure were sufficient to make out a *prima facie* case of anticipation (it cannot, as the District Court found), the challenged claims still would not be anticipated. That is because the 40 mg/ml concentration is critical, as

the District Court also correctly found. *See Mylan*, 714 F. Supp. 3d at 731, 734, 746-47. Criticality may be shown through evidence that a structure “would operate differently at various points within the [prior-art] range,” *OSRAM*, 701 F.3d at 706, and may be supported by the same evidence supporting unexpected properties, *In re Applied Materials, Inc.*, 692 F.3d 1289, 1297 (Fed. Cir. 2012). That showing is easily made here: protein concentration affects numerous formulation properties causing a formulation to “operate differently” at different concentrations, and the District Court found that only at the 40 mg/ml concentration did Regeneron achieve the unexpected combination of safety, efficacy, and durability that made Eylea[®] such a “revolutionary” treatment. *Mylan*, 714 F. Supp. 3d at 746. Dix ’226 therefore cannot anticipate the 40 mg/ml concentration.

There can be no dispute that the concentration of the active protein in an ophthalmic formulation is critical to numerous formulation characteristics. On one hand, higher protein concentration causes a “greater risk of aggregation.” *Mylan*, 714 F. Supp. 3d at 737 (citing Ex.2016 (Wang 2005) at 9); Ex.2016 (Wang 2005) at 9 (“Protein concentration is another important factor in protein aggregation. . . . Increasing protein concentration generally increases protein aggregation . . . because proteins may need a critical concentration to form the initial nucleus for initiation of the aggregation process.”)). And “protein aggregation is arguably the most common and troubling manifestation of protein instability, almost in all phases of protein drug

development,” with the “[p]resence of any insoluble aggregates in a protein pharmaceutical . . . generally unacceptable for product release.” Ex.2016 (Wang 2005) at 3; *see also Mylan*, 714 F. Supp. 3d at 707 (“A protein coming out of solution can lead to several potential problems, including protein inactivation, inflammation, and even adverse immune responses.”); *SB PI Decision*, 2024 WL 3422971, at *33, *48 (similar). Dix itself reflects the influence of protein concentration on aggregation in its formulations, showing that as protein concentration increases, the percent native conformation decreases upon storage:

Example	Concentration	Time Point	% Native Conformation
9 (Table 9)	25 mg/ml	12 months	99.5
1 (Table 1)	50 mg/ml	12 months	98.6
2 (Table 3)	75 mg/ml	12 months	94.5
3 (Table 5)	100 mg/ml	12 months	93.9

Finally, in the relevant ophthalmic context, increased concentration can result in vision-threatening side effects such as inflammation. For instance, in studies with ranibizumab, “[a]fter IVT administration, transient ocular inflammation, primarily vitreous cloudiness, ranged from *absent to moderate* (500 µg/eye) and *moderate to severe* (2000 µg/eye).” Ex.2017 (Gaudreault 2005) at 727-28 (emphases added). In other words, as the dose increased from 500-2000 µg/eye (corresponding to an increase from 10-40 mg/ml, as shown in the table below), inflammation worsened:

TABLE 1. Treatment Groups Assignment

Group	Number per Group (M/F)	Route	Day Administered	Dose	Dose Concentrations (mg/mL)	Dose Volume
1	3/3	ITV	1	500 µg/eye	10	50 µL/eye
2	3/3	ITV	1	2000 µg/eye	40	50 µL/eye
3	2/2	IV	1	1000 µg/animal	1	1 mL
4	2/2	IV	1	4000 µg/animal	4	1 mL

Id. at 727.

With aflibercept, by contrast, the 40 mg/ml concentration unexpectedly proved crucial to Eylea®’s groundbreaking success. Specifically, “a key insight of the inventors [of the ’865 patent] was that ‘every time you double the concentration [of aflibercept] that you inject, you get an extra half-life.’” *Mylan*, 714 F. Supp. 3d at 747 (citation omitted). By increasing the concentration of aflibercept to a “higher 40 mg/ml concentration, resulting in a 2 mg dose,” Regeneron discovered that it was possible to use “a bimonthly dosing regimen.” *Id.* At that concentration, Eylea® had “the durability to be dosed half as frequently as ranibizumab (after three loading doses for wet AMD).” *Id.* at 746. Such “[e]xtended 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.2018 (Thomas) at 498)); *see also id.* (“The ‘captivating aspect’ of aflibercept that made ‘bimonthly dosing’ possible and ‘altered current regimens of monthly dosing’ was its ‘extended half-life.’” (citations omitted)); *id.* (“[T]hese

‘captivating’ properties . . . enabled a major change in the treatment of ophthalmic disease . . .”). “Only with the higher 40 mg/ml concentration . . . did Regeneron even attempt a bimonthly dosing regimen,” as at lower concentrations, there is no evidence that aflibercept would have a sufficiently high half-life to permit such reduced injection frequency. *Mylan*, 714 F. Supp. 3d at 747; *see also id.* (“[T]he aflibercept protein does contribute to the longer half-life of Eylea, but aflibercept’s concentration is also critical to its half-life.” (citation omitted)). There is no evidence that any other concentration within the range of 10-50 mg/ml can achieve the “captivating properties” that facilitated extended dosing and adoption of the product.

Furthermore, despite using this higher, 40 mg/ml concentration, the inventors unexpectedly achieved both safety and efficacy, unlike with ranibizumab. As the Court found, this too was tied to the claimed concentration and formulation achieving the required 98% native conformation: “the stability of the claimed compositions, including the required 98% native conformation, indicated to the POSA that the ‘there’s a relatively lower risk of inflammation.’” *Mylan*, 714 F. Supp. 3d at 747 (quoting Ex.2011, Tr. 2170:5-21). In contrast, Gaudreault 2005 explained how increasing ranibizumab concentration from 10 to 40 mg/ml did not offer improved VEGF inhibition but did result in increased inflammation. Ex.2017 (Gaudreault 2005) at 726-28, 732; *Mylan*, 714 F. Supp. 3d at 737. In contrast, with 40 mg/ml aflibercept, Eylea[®] achieved “comparable (1) safety and (2) efficacy to

ranibizumab.” *Mylan*, 714 F. Supp. 3d at 746; *see also* Ex.2018 (Thomas) at 498-99 (discussing clinical studies “show[ing] that aflibercept was noninferior to ranibizumab in preventing vision loss with comparable vision gains[] [and] safety,” that “aflibercept dosed intravitreally each month or every 2 months after three initial monthly doses resulted in comparable efficacy and safety to monthly ranibizumab,” and that “[c]ompared to current treatments, aflibercept has shown equal efficacy and safety”). Moreover, notwithstanding prior-art teachings that increased protein concentration may increase aggregation, *e.g.*, Ex.2016 (Wang 2005) at 3, 9, the inventors of the ’865 patent achieved highly stable formulations even at the 40 mg/ml concentration, thus contributing to the formulation’s safety. *See Mylan*, 714 F. Supp. 3d at 747. There is no evidence that any aflibercept concentration within the range of 10-50 mg/ml, other than the claimed 40 mg/ml, achieves these properties either.

In sum, in defiance of the prior art teaching lower protein concentration, Regeneron unexpectedly attempted and achieved bimonthly dosing “[o]nly with the higher 40 mg/ml concentration.” *Id.* At that concentration, the inventors also achieved highly stable formulations with comparable safety and efficacy to ranibizumab notwithstanding prior-art teachings that higher concentrations increase aggregation, decrease safety, and do not improve efficacy. *Id.* at 746-47. Because “the inventors specifically chose the 40 mg/ml concentration to maximize the half-

life of aflibercept in the eye while minimizing toxicity and stability concerns, and their selection of 40 mg/ml contributed to the beneficial properties of Eylea,” that concentration is critical, rebutting any possible case of anticipation based on Dix ’226’s 10-50 mg/ml disclosure. *Id.* at 731 (citations omitted).

Fresenius neither acknowledges any of the above-discussed evidence that the 40 mg/ml concentration was critical to Eylea®’s groundbreaking combination of safety, efficacy, and durability nor demonstrates that those same benefits could be achieved at other concentrations in Dix ’226’s 10-50 mg/ml range. Rather than engage with this evidence, Fresenius simply ignores it. Fresenius cites no new evidence and advances no new arguments. Fresenius instead cites questions from certain judges on the *Mylan* panel. *E.g.*, Pet. 2 (asserting, without evidence, that “no criticality had been shown” and that “the panel judges used the words ‘critical’ or ‘criticality’ 30 times throughout the oral argument hearing itself”); Pet. 3 (“[P]atent Owner cannot show any criticality for any particular amount within Dix ’226’s specific ranges. The Mylan/Biocon Federal Circuit panel emphasized that the burden to show criticality falls on the Patent Owner.”); Pet. 6, 31-32. As discussed above, Fresenius’s characterization of the Federal Circuit panel’s questions is selective and wholly misleading, including in its failure to address statements acknowledging the multiple hurdles and roadblocks—in addition to the district court’s criticality finding—that Mylan had to overcome in order to prove that Dix

anticipated. But more fundamentally, judges' questions at oral argument are not evidence, and they do not reflect a court's holdings, *see Cerini*, 2014 WL 7015992, at *3 n.3: only decisions and orders do that, and Fresenius—remarkably—ignores actual district and appellate court findings in favor of judicial musings and inquiries during oral argument. Simply put, Fresenius's handpicked questions from an oral argument are no basis to disregard the District Court's thorough decision reached after a two-week trial. Because Fresenius never meaningfully engages with the District Court's analysis or findings, it cannot make out a reasonable likelihood that the challenged claims are anticipated. *Cf. Samsung*, IPR2025-00176, Paper 12, at 22-23.

c. Dix '226's Pre-lyophilized Disclosures Are Not Anticipatory

Finally, like Mylan, Fresenius asserts that Dix '226's purported disclosure of "a 40 mg/ml pre-lyophilized formulation that was lyophilized and reconstituted to an 80 mg/ml solution" is anticipatory. Pet. 18. Specifically, Fresenius asserts that "Dix '226 disclosed a pre-lyophilized aflibercept formulation with 40 mg/ml aflibercept" and that "[t]he fact that it was pre-lyophilized does not put the formulation outside the scope of [the challenged claims]." Pet. 32.

The District Court, however, conducted a trial and already found this disclosure non-anticipatory and rejected Fresenius's exact arguments. Fresenius offers no reason for a different outcome.

Dix's pertinent disclosure teaches that "a 40 mg/ml pre-lyophilized solution is lyophilized and reconstituted to a 80 mg/ml solution." Ex.1005, 3:60-62. That is it: Dix nowhere mentions what specific protein is in that solution, what components it has, or anything regarding its stability. Directly contrary to Fresenius's bare assertion that the pre-lyophilized solution "has the same excipients used in the '865 patent," Pet. 32, the District Court found that "Dix '226 does not indicate whether the pre-lyophilized solution contains aflibercept or any other limitation of the claims," nor would a POSA "expect this manufacturing intermediate to meet the 98% native conformation limitation over two months, as a formulator would not 'store it for nearly that long.'" *Mylan*, 714 F. Supp. 3d at 731, 733 (citation omitted). "Dix's '40 mg/ml pre-lyophilized solution' does not refer to any kind of formulation to be administered, much less an ophthalmic formulation or, as the claim requires, an ophthalmic formulation of aflibercept." *Id.* at 731-32. And as discussed below, *infra* III.C.2, this "isolated disclosure of 40 mg/ml pre-lyophilized solution, unconnected to any of the other claim elements, is not a disclosure of each element 'arranged as in the claim.'" *Id.* at 733 (quoting *Net MoneyIN*, 545 F.3d at 1370). Fresenius's failure to engage with these findings by the District Court regarding Dix '226's pre-lyophilized disclosure further underscores its inability to show a reasonable likelihood of success of unpatentability for any of the challenged claims. *Samsung*, IPR2025-00176, Paper 12, at 22-23.

Separately, while Fresenius asserts, without any support, that the pre-lyophilized solution is “ready to be injected,” Pet. 32, the District Court found precisely the opposite: crediting the testimony of Regeneron’s expert, the Court found that “a pre-lyophilized solution is only ‘a manufacturing intermediate’ *not intended for any kind of injection.*” *Mylan*, 714 F. Supp. 3d at 731 (emphasis added) (citation omitted). This finding “is consistent with the disclosure of Dix, which states that the pre-lyophilized solution ‘is lyophilized and reconstituted’ to a different concentration,” and which “does not disclose the pre-lyophilized solution as being stored *or injected.*” *Id.* (emphasis added) (quoting Ex.1005 at 3:60-61). In other words, *contra* Fresenius (at 18, 32), there is no evidence that “pre-lyophilized solutions” are suitable for anything other lyophilization, much less suitable for intravitreal injection.

2. Dix ’226 Does Not Teach the Limitations Arranged as in the Claims

A prior-art reference can be anticipatory only if it discloses “all elements of a claimed invention *arranged as in the claim.*” *Net MoneyIN*, 545 F.3d at 1370-71 (emphasis in original) (citation omitted). Because Dix ’226 has no disclosure of (1) 40 mg/ml aflibercept, in (2) an ophthalmic formulation suitable for intravitreal administration, (3) 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, it fails to anticipate all challenged claims (all challenged claims

require (2) and (3), while every challenged claim except claims 1 and 26 require (1), (2), and (3)). That deficiency in Fresenius’s argument is independent of the criticality issue on which it myopically focuses. Furthermore, as the District Court and Federal Circuit have held a half-dozen times, the 98% native conformation limitation is not inherent to the claimed formulation.

a. Dix ’226 Does Not Disclose the 40 mg/ml Concentration Arranged as in the Claim

Because Dix nowhere teaches 40 mg/ml aflibercept, *supra* III.C.1, Dix also does not teach 40 mg/ml as arranged in the claim. All but two challenged claims require a 40 mg/ml concentration of aflibercept along with, *inter alia*, 98% native conformation after two months’ storage. As *Mylan* found, Dix ’226 discloses neither a 40 mg/ml ophthalmic formulation nor such a formulation that meets the 98% native conformation limitation. *Mylan*, 714 F. Supp. 3d at 732. This separately forecloses anticipation of each challenged claim except claims 1 and 26.

Fresenius makes no effort (at 29-33) to show that Dix ’226 discloses the 40 mg/ml limitation as arranged in the claim. *Id.* Fresenius instead repeats what the district court held was Mylan’s error in its “‘mechanistic dissection and recombination’ of disclosures from Dix ’226 [which] involve[] just the kind of impermissible ‘hindsight anticipation[]’ relying on ‘the guidance of a[] [patentee’s] disclosures’ that precedent has long forbid.” *Id.* at 733 (quoting *In re Ruschig*, 343 F.2d 965, 974 (C.C.P.A. 1965)). Because anticipation requires that the prior-art

reference “disclose each element ‘arranged as in the claim,’” *id.* (quoting *Net MoneyIN, Inc.*, 545 F.3d at 1370-71), Fresenius’s discussion of the 40 mg/ml limitation in a vacuum without reference to the 98% native conformation limitation is fatal to Fresenius’s argument.

The lack of any disclosure in Dix ’226 of a 40 mg/ml formulation with 98% native conformation is apparent from the face of the document. Dix ’226 discloses the stability of formulations with 25, 50, 75, and 100 mg/ml aflibercept. Ex.1005, Examples 1-5. Plainly, none of these formulations contain 40 mg/ml aflibercept. And because the 98% native conformation limitation is not inherent in the formulation claimed in the ’865 patent, as set forth below, *infra* III.C.2.b.3, Fresenius cannot demonstrate a reasonable likelihood that Dix ’226 teaches a 40 mg/ml formulation that meets the 98% native conformation limitation.

b. Dix Does Not Disclose Any Ophthalmic Formulation Achieving 98% Native Conformation

1) The Preamble Is Limiting.

Claims 1 and 26 recite a vial or PFS “comprising an ophthalmic formulation suitable for intravitreal administration,” but Dix ’226 provides no disclosures of any ophthalmic formulations suitable for intravitreal administration and thus does not teach any such formulation with the requisite 98% native conformation. Dix therefore cannot anticipate the challenged claims of the ’865 patent.

As a threshold matter, Fresenius asserts that the preamble is not limiting and can be ignored, Pet. 25, but in doing so Fresenius fails to address the District Court’s analysis of the preamble phrase “ophthalmic formulation suitable for intravitreal administration” with regard to both indefiniteness and anticipation that necessarily depended on the phrase being limiting. *Mylan*, 714 F. Supp. 3d at 732, 748-51. Fresenius offers no basis to depart from the District Court, and its construction should thus be rejected.

With respect to indefiniteness, the District Court concluded that “suitable for intravitreal administration” was not indefinite and, therefore, that a POSA could understand with “reasonable certainty” what this term means in the claims. *Mylan*, 714 F. Supp. 3d at 748-51. In particular, the District Court credited the testimony of Regeneron’s expert, Dr. Trout, that the skilled person would understand what was “suitable for intravitreal administration” not by simply erasing the term, but rather by reference to, for example, “structures that had been used in intravitreal administration.” *Id.* at 751; *see* Ex.2019 (Peyman). On anticipation, the District Court explicitly determined that an “ophthalmic formulation” is “required by each claim,” *Mylan*, 714 F. Supp. 3d at 732, but that “Dix ’226 does not include any teaching of an ‘ophthalmic formulation[s]’ or intravitreal administration, to which the [’865] Patent claims are directed.” *Id.* at 730. The absence of “any ophthalmic formulation” was “separately . . . fatal to” anticipation, as it precluded any showing

that Dix disclosed each claim element “arranged as in the claim.” *Id.* at 732-33. Fresenius offers no way to square any of these determinations with the preamble being nonlimiting, because there is none; the absence of a claim limitation could not somehow both be “fatal to” anticipation if that limitation were not in fact limiting. Fresenius’ failure to engage with the District Court’s findings and analysis alone warrants rejection of its argument.

Fresenius’s position also fails on the merits. A claim preamble is limiting when it is “‘necessary to give life, meaning, and vitality’ to the claim,” including when it “discloses a fundamental characteristic of the claimed invention that is properly construed as a limitation” or is described as an “important aspect of the invention.” *Poly-Am., L.P. v. GSE Lining Tech., Inc.*, 383 F.3d 1303, 1309-10 (Fed. Cir. 2004); *Sanofi Mature IP v. Mylan Labs. Ltd.*, 757 F. App’x 988, 993 (Fed. Cir. 2019). Fresenius cites no case where a term analogous to “ophthalmic formulation suitable for direct administration” was held to be nonlimiting. Precedent is to the contrary; in addition to *Mylan*, the court in *Impax Labs., Inc. v. Lannett Holdings, Inc.*, 2015 WL 7737309, at *3 (D. Del. Dec. 1, 2015), held the analogous term “pharmaceutical formulation suitable for intranasal administration” to be limiting because it “does more than state an intended use for the formulations” by instructing that the formulations “must possess features making them appropriate for intranasal use.” *See also Integra Lifesciences Corp. v. HyperBranch Med. Tech., Inc.*, 2018

WL 430177, at *5 (D. Del. Jan. 16, 2018) (similar for “suitable to coat a tissue of a patient”); *Cytec Corp. v. Tripath Imaging, Inc.*, 2005 WL 3177877, at *14-16 (D. Mass. Nov. 28, 2005) (same for “suitably” or “suitable”); *Litepanels, LTD v. Switronix, Inc.*, 2014 WL 11788567, at *3-4 (E.D. Tex. July 16, 2014) (similar for “suitable to provide proper illumination for lighting of a subject in film or video”); *Biacore v. Thermo Bioanalysis Corp.*, 79 F. Supp. 2d 422, 456-57 (D. Del. 1999) (similar for “suitable for use in a biosensor”).

The same is true here. Similar to *Impax*, 2015 WL 7737309, at *3, the terms “ophthalmic formulation” and “suitable for intravitreal administration” are used repeatedly throughout the specification, and indeed, the patent is *entitled* “VEGF antagonist formulations suitable for intravitreal administration.” *See* Ex.1001, Title Page; 1:45-52; 2:10-38; 2:53-67; 3:1-16; 3:36-57; 3:66-4:62; 5:23-25; 6:60-7:25; 7:26-8:3; 8:32-59. This easily meets the level of “importan[ce]” to support the preamble as limiting the claim. *Sanofi Mature IP*, 757 F. App’x at 993. And of course, the testimony at trial is consistent; as *Mylan* explained, the POSA would not skip past suitability for intravitreal administration but rather “assess suitability by looking ‘to the teachings of the patent,’ which describe exemplary excipients . . . and then, if needed, looking at ‘the literature’ for suitable excipients with ‘structures that had been used in intravitreal administration’ and consulting an ophthalmologist.” 714 F. Supp. 3d at 749 (quoting Ex.2011, 2112:20-2113:7 (Trout)).

The prosecution history is in accord. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1317 (Fed. Cir. 2005) (“[T]he prosecution history can often inform the meaning of the claim language by demonstrating how the inventor understood the invention.”). During prosecution of the ’865 patent, the Examiner issued a non-final rejection on the basis of obviousness-type double patenting. Ex.2022 (Excerpts of File History of U.S. Patent No. 11,084,86) at 3. At an Examiner interview, “it was pointed out that all the pending claims are interconnected by being directed to the invention which comprises: (a) an ophthalmic formulation” *Id.* at 10. Regeneron did not dispute this characterization, demonstrating that both the Examiner and Regeneron understood Regeneron’s invention to be limited to ophthalmic formulations.

Fresenius’s suggestion that Regeneron’s counsel described the preamble as nonlimiting badly mischaracterizes the *Mylan* oral argument transcript. Pet. 25. In fact, Regeneron’s counsel did the exact opposite, expressly describing the preamble as a “*limitation*.” Ex.1008, 44:22-45:1 (“what that *limitation* means is contains components that can be used intravitreally”). Thus, Regeneron’s counsel’s statements are fully consistent with the District Court’s *Mylan* decision, which as

described above reflects the limiting nature of the “suitable for intravitreal administration” term in the preamble.²

Fresenius asserts that even if limiting, the meaning of the “suitable for intravitreal administration” term from *Mylan* encompassed any “excipients used in a formulation . . . capable of being injected into the eye.” Pet. 25. But that is not what the District Court held; rather, it held that the POSA “would assess suitability by looking ‘to the teachings of the patent,’ which describe exemplary excipients . . . and then, if needed, looking at ‘the literature’ for suitable excipients with ‘structures that had been used in intravitreal administration’ and consulting an

² Contrary to Fresenius’s mischaracterization, the oral argument exchange was focused on the separate question of whether the District Court was “relying upon . . . the preambles” in its anticipation decision. Ex.1008 at 44:12-13. One of the Federal Circuit judges commented that the “district court in part relied on” the preamble to distinguish the prior art, *id.* 44:4-5; *see also Mylan*, 714 F. Supp. 3d at 732. As Regeneron’s counsel then explained, he “d[id]n’t read the district court’s decision as *relying upon* the preambles,” which were “never a basis to distinguish the prior art,” Ex.1008 at 43:22-44:13 (emphasis added) (cleaned up). That statement was correct: the District Court’s rejection of anticipation in *Mylan* was not reliant upon the preamble, as other distinctions—including Dix’s failure to teach any 40 mg/ml concentration, much less such a formulation meeting the 98% native conformation limitation—fully foreclosed anticipation of all claims at issue. 714 F. Supp. 3d at 731; *see also id.* at 732-33.

ophthalmologist.” 714 F. Supp. 3d at 749. Fresenius’s view that any substance, in any amount, “capable of being injected into the eye” could satisfy an “ophthalmic formulation suitable for intravitreal administration” is thus devoid of any support, Pet. 25, and is again contradicted by the trial evidence, which established that whether an excipient is “suitable” depends on the characteristics of the specific ingredient, including its concentration.

For example, the Peyman reference (Ex.2019), relied on by the court in its analysis of this term, makes clear (in the exact line the District Court cites) that what is “suitable for treating ocular neovascularization” encompasses both the pertinent ingredient’s “concentration and dose.” Ex.2019, 3:26; *Mylan*, 714 F. Supp. 3d at 749. Fresenius offers no reason to excise those aspects of the district court’s reasoned opinion from the determination of whether an excipient is “suitable.” And as detailed further below, the trial testimony was consistent with the literature relied on by the District Court. Mylan’s expert, for example, explained that different formulations of aflibercept differed in their osmolarity based on the amount of ingredients, and that that it was known since the 1970s that with “higher osmolarity, there was a risk, a very high risk, for retinal detachment.” Ex.2011, 825:4-12; *infra* III.C.2.b.2. Consistent with that knowledge, Regeneron did not even consider using its cancer formulation with a “really high osmolality” for its intravitreal product. Ex.2011, 1679:16-21.

**2) The District Court Found That Dix '226
Teaches No Ophthalmic Formulation Meeting
the 98% Native Conformation Limitation**

Fresenius cannot show that Dix discloses all claim elements arranged as in the claim because Dix teaches no ophthalmic formulation suitable for intravitreal administration that achieves 98% native conformation, as *Mylan* held. 714 F. Supp. 3d at 732. This forecloses anticipation for every challenged claim.

“The requirement that the prior art elements themselves be arranged as in the claim means that claims cannot be treated as mere catalogs of separate parts, in disregard of the part-to-part relationships set forth in the claims and that give the claims their meaning.” *Therasense, Inc. v. Becton, Dickinson & Co.*, 593 F.3d 1325, 1332 (Fed. Cir. 2010) (cleaned up). Claim 1 requires an “ophthalmic formulation suitable for intravitreal administration” “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.” Because Dix “does not include any teaching of an ‘ophthalmic formulation[s]’ or intravitreal administration,” *Mylan*, 714 F. Supp. 3d at 730, it cannot teach such a formulation that achieves 98% native conformation as claim 1 requires.

Fresenius argues that the example disclosed in Table 9 in Dix '226 achieved 98% native conformation, Pet. 28, but Fresenius provides no evidence that the formulation in Table 9 is an ophthalmic formulation suitable for intravitreal

administration. Nor could it. The Table 9 example contains 20% sucrose and 100 mM NaCl, Pet. 28 (quoting Dix '226 at 12:1-10), and fatally, the Petition does not cite a shred of evidence that the combination of 20% sucrose and 100 mM NaCl would be “excipients suitable for intravitreal injection” to constitute an “ophthalmic formulation suitable for intravitreal administration,” where Dix *not once* even mentions ophthalmic or intravitreal administration. *Mylan*, 714 F. Supp. 3d at 750. Rather, Dix, directed to Regeneron’s aflibercept cancer formulation, Ex.1005, 1:43-45, teaches that the same formulation described in example 4 and Table 9 had a “high osmolality” that required “3-fold” dilution to be administered *intravenously*. Ex.1005, 10:1-12, 12:1-4.

The evidence from the District Court trial uniformly establishes that such high-osmolality formulations are not ophthalmic formulations suitable for intravitreal injection. First, the District Court’s analysis of “suitable for intravitreal administration” contemplated that the POSA could “consult an ophthalmologist,” *Mylan*, 714 F. Supp. 3d at 750, and Mylan’s ophthalmologist expert (Dr. Albini) testified that high-osmolality formulations would present significant clinical risks. Ex.2011, 824:22-826:2 (Albini). Specifically, Dr. Albini referenced the prior art “Marmor” study (Ex.2020) and explained that it was known that with “higher osmolality, there was a risk, a very high risk, for retinal detachment.” Ex.2011, 825:4-12. Consistent with Dr. Albini’s testimony, Marmor reported that injection

of a hyperosmotic “1000 mOsm solution caused rapid whitening of the posterior retina *followed by the development of a large detachment and permanent retinal degeneration*” in an animal model. Ex.2020, Abstract. In view of that understanding, Dr. Albin expressed “concern that the higher osmolarity of ziv-aflibercept [the generic name for Regeneron’s aflibercept cancer product] relative to aflibercept . . . may cause a clinical problem.” Ex.2011, 824:22-825:3.³ Mylan’s formulation expert, Dr. Rabinow, likewise agreed at trial that “something over 850 milliosmoles would not be a good idea to inject intravitreally.” Ex.2011, 1172:4-12.

Second, again consistent with Dr. Albin’s testimony, Dr. Graham, a named inventor on the ’865 patent, explained that “the cancer formulation” was never even considered for intravitreal use, because it “was designed to be a concentrate that you would put into an IV bag, dilute out, and give to a patient through an IV. So it had a really high osmolality, like 1100, 1160 milliosmoles. It had a lot of sucrose in it, 20 percent sucrose.” Ex.2011, 1679:13-20 (Graham); *see also* Ex.2011, 1741:24-1742:3 (Graham). Dix’s own express teaching is consistent, Ex.1005, 10:1-12, 12:1-4, and as Dr. Albin and Dr. Rabinow explained (and Fresenius’s Petition does not

³ Dr. Albin referenced a post-priority paper but did not comment on specific aspects of that paper in his testimony.

refute), formulations with that level of osmolality were not considered suitable for intravitreal administration. Ex.2011, 824:22-825:3 (Albini), 1172:4-12 (Rabinow).

In contrast to this weight of evidence, Fresenius presents nothing to indicate that a formulation with such a “high osmolality,” posing “a very high risk[] for retinal detachment” and/or requiring “3-fold dilution,” would somehow be suitable for intravitreal administration, and thus cannot show an express disclosure in Dix of an ophthalmic formulation suitable for intravitreal administration as required for anticipation.

At bottom, Fresenius has presented no evidence of a formulation disclosed in Dix ’226 that meets the 98% limitation while being an ophthalmic formulation suitable for intravitreal injection. This forecloses anticipation.

3) 98% Native Conformation Is Not Inherent.

Finally, Fresenius tries to resurrect an argument that the 98% limitation is an inherent property of the claimed formulation. To date, six decisions—three from the district court, and three from the Federal Circuit—have confirmed that the 98% native conformation limitation is not an inherent property. *SB PI Decision*, 2024 WL 3422971, at *28-32; *Formycon PI Decision*, 2024 WL 3423047, at *32-37; Ex.2004 (*Celltrion PI Decision*) at 97-113; *SB*, 127 F.4th at 913; *Formycon*, 2025 WL 324288, at *5-6; *Celltrion*, 2025 WL 706079, at *3. Fresenius’s argument is even weaker than those prior failed arguments, as it does not even reference any

particular prior-art formulation, but rather focuses only on the “’865 patent itself.” Pet. 29. The formulations described in the ’865 patent, however, are undisputedly different from those in Dix and thus cannot support that the Fresenius’s unspecified “formulation in Dix” would necessarily possess 98% native conformation. *Id.*

An inherent limitation must be “necessarily present” in the prior art, *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 960 (Fed. Cir. 2014), and “may not be established by probabilities or possibilities.” *Mylan*, 714 F. Supp. 3d at 741 (quoting *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1194 (Fed. Cir. 2014)). Fresenius, as the petitioner, bears the “burden of persuasion . . . 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) (quotation omitted).⁴ That burden applies to inherency as well. *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) (patent challenger “bears an evidentiary burden to establish that the limitation was necessarily present”).

⁴ The Federal Circuit in *Magnum Oil* explained that although “a burden-shifting framework makes sense in the prosecution context,” it “does not apply in the adjudicatory context of an IPR.” *Magnum Oil*, 829 F.3d at 1375.

But here, the examples of the '865 patent are undisputedly not the same “prior art embodiment[s]” (Pet. 29) in Dix—no example in the '865 patent is the same as any embodiment in Dix, *compare* Ex.1001, Examples 1-8, *with* Ex.1005, Examples 1-9; *see Formycon PI Decision*, 2024 WL 3423047, at *34 (rejecting inherency where reference claim encompassed range of pH values (“6.2-6.4”) distinct from embodiment relied upon for inherency (“6.3”)). While Fresenius asserts that the claimed 98% native conformation “would have been inherent to” an unspecified “formulation in Dix,” Pet. 29, it offers no evidence meeting the high bar for inherency. That a formulation could “*sometimes* result[] in 98% native conformation is insufficient; inherency requires that the 98% native conformation limitation be present necessarily, not just possibly or probably.” *SB PI Decision*, 2024 WL 3422971, at *30 (emphasis added); *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). Fresenius offers no such evidence.

As Fresenius notes, “[e]xtrinsic evidence can be used to demonstrate what is ‘necessarily present’ in a prior art embodiment even if the extrinsic evidence is not itself prior art.” Pet. 29 (quoting *Hospira*, 946 F.3d at 1329). The district court expressly found that 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" formulation. *SB PI Decision*, 2024 WL 3422971, at *29; *Formycon PI Decision*, 2024 WL 3423047, at *33; *Celltron PI Decision*, Ex.2004 at 100-01. The SS195 formulation had less than 98% native conformation by SEC at time zero, before any storage. Ex.2021 (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 does not have the claimed 98% native conformation. Accordingly, the record is clear, and multiple courts have held, that formulations falling within the parameters claimed in every '865 patent claim at issue do not necessarily achieve 98% native conformation, as a finding of inherency would require. *Formycon*, 2025 WL 324288, at *5; *Celltrion*, 2025 WL 706079, at *3; *SB PI Decision*, 2024 WL 3422971, at *29; *see Glaxo*, 52 F.3d at 1047. As the district court held, and Federal Circuit repeatedly affirmed, *e.g.*, *Formycon*, 2025 WL 324288, at *5, this is fatal to Fresenius's inherency argument.

Date: October 23, 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 10,220 words as counted by the word processing program used for its preparation (Microsoft Word 2019).

Date: October 23, 2025

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

The undersigned hereby certifies that on October 23, 2025, I caused true and correct copies of the following materials:

- Patent Owner's Preliminary Response
- Patent Owner's Exhibit List
- Exhibits 2010-2022

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