UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.,
Petitioner

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner

Inter Partes Review No.: IPR2023-00099

U.S. Patent No. 10,857,205 B2
Filed: August 6, 2018
Issued: December 8, 2020
Inventor: George D. Yancopoulos

Title: USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 10,857,205 B2

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Mylan Pharmaceuticals Inc. ("Petitioner") petitions for *inter partes* review ("IPR") under 35 U.S.C. §§311–319 and 37 C.F.R. §§42 *et seq*., seeking cancellation of Claims 1-3 (the "Challenged Claims") of U.S. Patent No. 10,857,205 ("'205 patent") (Ex.1001), assigned to Regeneron Pharmaceuticals, Inc. ("Regeneron" or "Patent Owner").

I. INTRODUCTION.

The Challenged Claims never should have issued. They are drawn to monthly dosing to treat an angiogenic eye disorder, a regimen that Regeneron has conceded was the prior art "standard of care," well-known and widely used by persons of ordinary skill in the art (hereafter, "POSA") before the priority dates of the claims. Moreover, well before the '205 patent's earliest priority date Regeneron and Bayer incorporated this prior art "standard of care" monthly regimen into their phase 3 clinical trials (COPERNICUS and GALILEO) for the treatment of patients with macular edema following central retinal vein occlusion[1] with EYLEA® (a/k/a VEGF Trap-Eye or aflibercept). These clinical trials and their dosing regimens were

[1] Central retinal vein occlusion is a type of retinal vein occlusion. (Ex.1037, 809; Ex.1032, 627; Ex.1002, ¶¶56-57). Herein, "macular edema following central retinal vein occlusion" is referred to as "CRVO" and "macular edema following retinal vein occlusion" is referred to as "RVO."

disclosed to POSAs as early as 2009 through Regeneron's own press releases, SEC filings, and public clinical trial database submissions. Regeneron then obfuscated these disclosures during prosecution, allowing the '205 patent claims to issue. For at least these reasons, the Challenged Claims are unpatentable.

Petitioner thus files this Petition, supported by expert declarations from Dr. Jay Stewart—a renowned ophthalmologist (Ex.1002), and Dr. Mary Gerritsen—a pharmacologist with over thirty years' experience (Ex.1003).

Anticipation. The Challenged Claims are anticipated. VEGF Trap-Eye was a known blocker of vascular endothelial growth factor ("VEGF") and extensively disclosed in the prior art, including in each of Petitioner's asserted references. The identity of VEGF Trap-Eye as a formulation of aflibercept was independently disclosed well before the earliest alleged priority date of January 2011.[2]

The COPERNICUS and GALILEO clinical trials—including the VEGF Trap-Eye monthly dosing regimens used therein—were widely published in numerous, fully-enabled prior art references, by Regeneron and others, years before the applicable priority dates. These publications disclosed all elements of the dosing

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[2] As discussed below in Section VIII, Petitioner contends Challenged Claims 2-3 are not entitled to a January 2011 priority date. The earliest possible priority date of Claims 2-3 is July 12, 2013.

regimen in Claim 1—most notably, treatment of RVO with 2 mg VEGF Trap-Eye (i.e., aflibercept) administered by intravitreal injection once every 4 weeks (i.e., monthly dosing). Monthly dosing with intravitreal injections is also a regimen which Regeneron has told both the Patent Office and the Board, on numerous occasions, was the standard of care in the prior art.

Moreover, by July 12, 2013 (the earliest priority date for Claims 2 and 3), VEGF Trap-Eye/aflibercept was commercially available as Eylea®, formulated with well-known pharmaceutically acceptable carriers at a concentration of 2 mg per 0.05 ml. Prior art publications disclosing the monthly dosing regimen of the COPERNICUS and GALILEO clinical trials using VEGF Trap-Eye/aflibercept therefore also expressly and inherently disclose the additional limitations of Claims 2 and 3.

Obviousness. All of the Challenged Claims are invalid as obvious.

Prior to 2011, POSAs were strongly motivated to pursue a method of treating the VEGF-mediated RVO by administering an anti-VEGF therapeutic formulated with a pharmaceutically acceptable carrier in a volume of 0.05 ml via intravitreal injection once every 4 weeks. By then, monthly intravitreal dosing of other VEGF antagonists, such as ranibizumab (LUCENTIS®) and bevacizumab (AVASTIN®), was known to be effective at treating RVO. In particular, the prior art discloses what Regeneron refers to as the standard of care prior to 2011: successfully treating RVO

with monthly intravitreal injections of 0.05 ml of ranibizumab. (*See, e.g.*, IPR2021-00881, Paper 41, 10-12; Ex.1086, 17:6-25, 150:2–151:18; Ex.1036; Ex.1066; Ex.1034; Ex.1037; Ex.1011). The prior art also discloses that VEGF Trap-Eye/aflibercept (EYLEA®) was formulated in a pharmaceutically acceptable carrier in a volume of 0.05 ml. (*See, e.g.*, Ex.1014). Combined with the abundance of positive, prior art data from Regeneron's clinical trials, and given ranibizumab's demonstrated success at treating both AMD[3] and RVO, and aflibercept's demonstrated success at treating AMD, a POSA would have reasonably expected success at treating RVO with VEGF Trap-Eye/aflibercept under the claimed method.

II. MANDATORY NOTICES (37 C.F.R. §42.8).

A. REAL PARTIES-IN-INTEREST (37 C.F.R. §42.8(B)(1)).

Viatris Inc. and Mylan Inc. are parent companies of Petitioner Mylan Pharmaceuticals Inc. Accordingly, Viatris Inc., Mylan Inc., and Mylan Pharmaceuticals Inc. are identified as real parties-in-interest ("RPIs") to the current Petition. Momenta Pharmaceuticals, Inc. and Janssen Research & Development

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[3] "AMD" stands for age-related macular degeneration, and is, like RVO, an angiogenic eye disorder. (*See* IPR2021-00881, Paper 73, 10 (Regeneron representing to the Board that "the angiogenic eye disorders identified in the patent are not vastly different from one another.")).

LLC are wholly-owned subsidiaries of Johnson & Johnson, a publicly held company. Momenta Pharmaceuticals, Inc., Janssen Research & Development LLC, and Johnson & Johnson are also RPIs to the current Petition. No other parties exercised or could have exercised control over this Petition; no other parties funded, directed, and controlled this Petition. *See* Trial Practice Guide, 77 Fed. Reg. 48759-60 (Aug. 14, 2012).

B. RELATED MATTERS (37 C.F.R. §42.8(B)(2)).

To the best of Petitioner's knowledge, the following are judicial or administrative matters that would affect, or be affected by, a decision in this proceeding: *Mylan Pharms. Inc. v. Regeneron Pharms., Inc.*, No. IPR2021-00880 (P.T.A.B.), *Mylan Pharms. Inc. v. Regeneron Pharms., Inc.*, No. IPR2021-00881 (P.T.A.B.), *Mylan Pharms. Inc. v. Regeneron Pharms., Inc.*, No. IPR2022-01225 (P.T.A.B.), *Mylan Pharms. Inc. v. Regeneron Pharms., Inc.*, No. IPR2022-01226 (P.T.A.B.), *Apotex Inc. v. Regeneron Pharms., Inc.*, No. IPR2022-01524 (P.T.A.B.), *Regeneron Pharms., Inc. v. Mylan Pharms. Inc.*, 1:22-cv-00061-TSK (N.D.W. Va.), *United States v. Regeneron Pharms., Inc.*, No. 1:20-cv-11217-FDS (D. Mass.), and *Horizon Healthcare Servs., Inc. v. Regeneron Pharms., Inc.*, No. 1:22-cv-10493-FDS (D. Mass.).

In May 2021, Petitioner filed petitions requesting IPR of two patents in the same family as the '205 patent. U.S. Patent No. 9,669,069 and U.S. Patent No.

9,254,338 are the subject of IPR2021-00880 and IPR2021-00881, respectively. The Patent Trial and Appeal Board ("Board") granted those petitions. (IPR2021-00880, Paper 21 (Nov. 10, 2021); IPR2021-00881, Paper 21 (Nov. 10, 2021)). Both of those proceedings are currently pending before the Board, with a final written decision expected in the November 2022 timeframe.

Petitioner also filed two IPRs in July 2022 requesting IPR of two additional patents in the same family as the '205 patent. U.S. Patent No. 10,888,601 and U.S. Patent No. 10,130,681 are the subject of IPR2022-01226 and IPR2022-01225, respectively. Both of those proceedings are currently pending before the Board, with an institution decision expected in the January 2023 timeframe.

U.S. Patent Nos. 9,254,338 B2; 9,669,069 B2; 10,828,345 B2; 10,130,681 B2; 10,888,601 B2; and 11,253,572 B2; and U.S. Patent Application Nos. 17/072,417; 17/112,063; 17/112,404; 17/350,958; and 17/740,744 each claim the benefit of the '205 patent's purported priority date(s).

C. LEAD AND BACK-UP COUNSEL AND SERVICE INFORMATION (37 C.F.R. §42.8(B)(3)-(4)).

Petitioner identifies its lead and backup counsel below. A Power of Attorney is filed concurrently herewith under 37 C.F.R. §42.10(b).

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Please direct all correspondence to lead and back-up counsel at the contact information above. Petitioner also consents to service by email at: MYL_REG_IPR@rmmslegal.com. Petitioner intends to file a motion seeking the admission of William A. Rakoczy, Heinz J. Salmen, Eric R. Hunt, and Lauren M. Lesko to appear *pro hac vice* when authorized to do so.

III. PAYMENT UNDER 37 C.F.R. §42.15(a) AND §42.103.

The required fees are submitted herewith. The undersigned representative of Petitioner hereby authorizes the Patent Office to charge any additional fees or credit any overpayment to Deposit Account 503626.

IV. GROUNDS FOR STANDING (37 C.F.R.§42.104(a)).

Petitioner certifies that the '205 patent—which issued on December 8, 2020—is available for IPR and that Petitioner is not barred or estopped from requesting IPR of the Challenged Claims on the grounds identified herein. Petitioner was served with a district court complaint in *Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals Inc.*, No. 1:22-CV-00061-TSK (N.D.W. Va.) alleging infringement of, *inter alia*, the '205 patent on August 2, 2022, which is less than one year prior to the filing of this Petition. *See Motorola Mobility LLC v. Arnouse*, No. IPR2013-00010, 2013 WL 12349001, *2-3 (P.T.A.B. Jan. 30, 2013).

V. THRESHOLD REQUIREMENT FOR *INTER PARTES* REVIEW.

This Petition meets and exceeds the threshold required under 35 U.S.C. §314(a). As explained below, for each ground, there is a reasonable likelihood that Petitioner will prevail with respect to at least one of the Challenged Claims.

VI. OVERVIEW OF THE '205 PATENT.

A. THE '205 PATENT.[4]

The '205 patent confirms angiogenic eye disorders, such as RVO,[5] were known to be effectively treated through VEGF inhibition. (Ex.1001, 1:31-56).

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[4] The '205 patent is subject to the AIA given the inclusion of new matter in the Continuation-In-Part Application No. 13/940,370, filed July 12, 2013. (*See infra* §VI.B.).

[5] The '205 patent states:

> Nonlimiting examples of angiogenic eye disorders that are treatable using the methods of the present invention include age-related macular degeneration (e.g., wet AMD, exudative AMD, etc.), ***retinal vein occlusion*** (RVO), ***central retinal vein occlusion*** (CRVO; e.g., ***macular edema following CRVO***), branch retinal vein occlusion (BRVO), diabetic macular edema (DME), choroidal neovascularization (CNV; e.g., myopic CNV), iris neovascularization, neovascular glaucoma,

Indeed, prior to January 2011, ranibizumab (LUCENTIS®), an anti-VEGF agent, was FDA-approved, and marketed by Genentech, for monthly administration via intravitreal injection to treat RVO. (*Id.*, 1:57-60; Ex.1011, §2.3; Ex.1034, 15). Bevacizumab (AVASTIN®), another prior art anti-VEGF agent, has been used off-label to treat RVO since long before January 2011. (Ex.1037, 814). Regeneron has argued that the standard of care for RVO prior to 2011 was ranibizumab (LUCENTIS®) or off-label bevacizumab (AVASTIN®), administered monthly via intravitreal injection. (IPR2021-00881, Paper 41, 10-12; Ex.1086, 17:6-25, 150:2–151:18). The specification of the '205 patent confirms that "***prior administration regimens for angiogenic eye disorders...require monthly administrations throughout the entire course of treatment***."[6] (Ex.1001, 2:24-30 (emphasis added); *see also, e.g.*, 1:57-60).

> post-surgical fibrosis in glaucoma, proliferative vitreoretinopathy (PVR), optic disc neovascularization, corneal neovascularization, retinal neovascularization, vitreal neovascularization, pannus, pterygium, vascular retinopathy, and diabetic retinopathies.

(Ex.1001, 5:26-39 (emphasis added)).

[6] During prosecution of each of the related '338 and '069 patents, Regeneron

The ’205 patent claims a dosing regimen for treating macular edema following RVO via administering 2 mg VEGF Trap-Eye/aflibercept by intravitreal injection once every 4 weeks. (Ex.1001, 21:56-59 (Claim 1)). Claims 2 and 3 specify that the VEGF Trap-Eye/aflibercept is administered in a volume of 0.05 ml and is formulated with a pharmaceutically acceptable carrier. (*Id.*, 21:60–22:57 (Claims 2-3)). This is the prior art COPERNICUS/GALILEO regimen, which eventually became FDA-approved for EYLEA®: treatment of “Patients with Macular Edema Secondary to CRVO” with “monthly injections of... 2 mg intravitreal VEGFT.” (*Id.*, 14:56-63).

B. PROSECUTION HISTORY OF THE ’205 PATENT.

The ’205 patent derives via a series of continuations from U.S. Patent Application Serial No. 13/940,370, filed July 12, 2013 (the “’370 Application”), which in turn is a continuation-in-part of International Patent Application No. PCT/US2012/020855 (the “’855 PCT Application”). (Ex.1001, 1:7-15). On its face, the ’205 patent purports to claim priority to three U.S. Provisional Applications: No.

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overcame the Examiner’s double patenting rejections by contrasting extended dosing regimens in the pending claims against the prior art practice of monthly dosing. (Ex.1017, 338-39 (9/11/2015 Amendment); Ex.1016, 109-10 (1/30/2017 Amendment)).

61/432,245, filed on January 13, 2011 (the "'245 Provisional Application"); No. 61/434,836, filed on January 21, 2011 (the "'836 Provisional Application"); and No. 61/561,957, filed on November 21, 2011 (the "'957 Provisional Application"). (Ex.1001, 1:7-20).

1. Preliminary Amendment.

a. Support for Claim 1.

In a Preliminary Amendment, Regeneron added what would issue as Claim 1, citing as support "paragraph [0010] and throughout the specification." (Ex.1019, 6 (8-6-2018 Preliminary Amendment)). Paragraph [0010], disclosing FDA approval of Eylea® in November 2011 for the treatment of wet AMD, appears in none of the provisional applications. (*Compare* Ex.1017, 13-14 ('370 Application) *with* Ex.1023, 5 ('957 Provisional Application)). Example 6, the only Example purportedly disclosing a method of treating RVO, only appears in the '957 Provisional Application. (*Compare* Ex.1023, 20-21 *with* Ex.1024, 16-17; Ex.1025, 19-20). Petitioner assumes a January 13, 2011 earliest priority date for Claim 1 for purposes of this IPR only, and reserves the right to challenge a Regeneron claim to that date, or to any other date to which it is not entitled.

b. Support for Claims 2 and 3.

In the same Preliminary Amendment, Regeneron added what would issue as Claim 2, citing as alleged support "paragraph [0070] and throughout the specification." (Ex.1019, 6). Paragraph [0070], disclosing a dosing regimen of

"VEGFT 2 mg (0.05 ml) administered by intravitreal injection once every 4 weeks (monthly)," appears for the first time in the '370 Application. (*Compare* Ex.1017, 29 *with* Ex.1044, 21). The 0.05 ml element of Claims 2 and 3 does not appear anywhere else in the specification. Claims 2 and 3 therefore have an earliest possible priority date of July 12, 2013, the filing date of the '370 Application.[7] (Ex.1001, 22:55-57; Ex.1002, ¶¶36-46).

2. Third-Party Submission and Non-Final Rejection.

On April 27, 2009, a Third-Party Submission Under 37 C.F.R. §1.290 was filed. (Ex.1019, 104). Among the art submitted was a record of the phase 3 GALILEO trial, NCT-973 (Ex.1029). (Ex.1019, 107). On December 10, 2019, the Examiner rejected the pending claims as anticipated by, or obvious over, NCT-973. (Ex.1019, 912-15).

On January 27, 2020, Regeneron filed an Information Disclosure Statement (IDS) including, *inter alia*, the clinicaltrials.gov archive of NCT-973. (*Id.*, 958-59). Regeneron followed up with another IDS on February 21, 2020, listing 23 different versions of NCT-973 from the clinicaltrials.gov archive. (*Id.*, 986-89). In an Amendment, Regeneron argued that earlier versions of NCT-973 "did not disclose

[7] Petitioner assumes this date for Claims 2 and 3 for purposes of this IPR only, and reserves the right to challenge a Regeneron claim to that date, or to any other priority.

administering 2 mg of aflibercept each month." (*Id.*, 954). Specifically, Regeneron "confirm[ed] that none of the clinicaltrials.gov updates identified as having dates on or before January 11, 2012 disclosed the recited 2 mg dosing regimen." (*Id.*, 1388).

Notably, Regeneron did not inform the Examiner that the clinicaltrials.gov site for Regeneron's identical COPERNICUS phase 3 trial, NCT-072 (Ex.1059), did, in fact, disclose "the recited 2 mg dosing regimen... on or before January 11, 2012." (Ex.1009).

3. *Post*-Allowance IDS Filings.

On April 1, 2020, the Examiner filed a Notice of Allowance. (Ex.1019, 1617). The Examiner wrote that "[n]one of the published clinicaltrials.gov updates having dates on before [sic] January 11, 2012 disclose the dosing regimen recited in the instant claims." (*Id.*, 1622-23). Again, NCT-072 *did* disclose the claimed dosing regimen, but it was not before the Examiner.

Three months ***after*** the Notice of Allowance, on June 30, 2020, Regeneron filed an IDS with 24 Regeneron press releases, including Regeneron (30-April-2009). (*Id.*, 1648-49). On July 16, 2020, Regeneron filed an additional IDS with 76 previously undisclosed references comprising a total of 4,652 pages. (*Id.*, 1732-36, 1737-6389). Buried in those thousands of pages was NCT-072, as well as several Regeneron SEC filings similar to 2009 10-Q. (*Id.*, 1734).

On July 22, 2020, the Examiner filed another Notice of Allowance. (*Id.*,

6395). Under "Reasons for Allowance," the Examiner wrote that "[t]he information disclosure statements (IDS) filed 30 June 2020 and 16 July 2020 have been considered," and that "[a]fter careful consideration, the Examiner has determined that none of the information contained therein raises new issues of patentability." (*Id.*, 6400). However, Regeneron never informed the Examiner that the post-allowance IDSs *included* prior art references that expressly contradicted the Examiner's Notice of Allowance finding that "[n]one of the published clinicaltrials.gov updates having dates on before January 11, 2012 disclose the dosing regimen recited in the instant claims."

VII. DISCRETIONARY DENIAL IS UNWARRANTED.

A. DISCRETIONARY DENIAL UNDER *FINTIV* IS UNWARRANTED.

Regeneron argues in related proceedings that *Fintiv* compels denial. But Regeneron misapplies the *Fintiv* factors and disregards the Director's guidance. First, Regeneron ignores the Director's recent rule that the Board "*will not* rely on the *Fintiv* factors to discretionarily deny institution in view of parallel district court litigation where a petition presents compelling evidence of unpatentability." Vidal 6-21-22 Memorandum, 2-3; *id.* at 5 ("The patent system and the public good benefit from instituting compelling unpatentability challenges."). Petitioner has articulated several compelling grounds of unpatentability herein, particularly given that in the '205 patent, Regeneron has merely patented what it concedes are prior art

administration regimens. (*See, e.g.*, Ex.1001, 2:24-31 ("[8-week dosing] allows for less frequent dosing…compared to *prior administration regimens for angiogenic eye disorders which require monthly administrations* throughout the entire course of treatment.") (emphasis added)). Thus, in view of Director Vidal's Memorandum, and the Board's prior decisions, the Board need not look beyond *Fintiv* factor six. *STMicroelectronics, Inc. v. Trs. of Purdue Univ.*, IPR2022-00309, Paper 14, 7-10 (P.T.A.B. Jul. 6, 2022); *see also Illumina, Inc. v. Trs. of Columbia Univ.*, IPR2020-00988, Paper 20, 15 (P.T.A.B. Dec. 8, 2020) (declining to deny under *Fintiv* in light of strong merits evidence despite four factors weighing in favor of denial); *Synthego Corp. v. Agilent Techs., Inc.*, IPR2022-00402, Paper 11, 18-19 (P.T.A.B. May 31, 2022) (granting institution as efficiency and integrity of the system would not be served by denying institution with particularly strong evidence on the merits); *Samsung Elecs. Co. v. Scramoge Tech., Ltd.*, IPR2022-00241, Paper 10, 14 (P.T.A.B. June 13, 2022) ("very strong" evidence on the merits outweigh concurrent litigation involving earlier scheduled trial date and significant overlap in proceedings).

Second, even if the Board does consider the other *Fintiv* factors, none compel denial. Regeneron filed suit indiscriminately on 24 patents in the Northern District of West Virginia. In the Regeneron-proposed schedule adopted by the Court, trial is in June 2023, but limited to *only 3 of the 24 patents-in-suit*. (Dkt. No. 87,

Regeneron Pharm., Inc. v. Mylan Pharm. Inc., 1:22-cv-00061-TSK (N.D.W. Va.)). Importantly, no clarity was provided regarding the disposition of the remaining 21 patents, leaving open the possibility of serial follow-on litigations years into the future. As of the filing of this petition, Regeneron has not indicated whether it will choose the '205 patent as one of the 3 patents for the June 2023 trial, or whether Regeneron will save one or more claims of the '205 patent, for assertion sometime between now and its estimated expiration in the early 2030's.

In short, Regeneron has not committed to the '205 patent being tried in June 2023. Consequently, at this time, there is *no* overlap between the district court and IPR issues—*Fintiv* factor four does not warrant denial.

B. *GENERAL PLASTIC* DISCRETIONARY DENIAL IS UNWARRANTED.

Regeneron argues in related proceedings that *General Plastic* compels denial. However, Regeneron concedes that *General Plastic* is limited to multiple petitions challenging the *same patent*. The present petition is the first petition challenging the '205 patent, and the first to challenge claims in the patent family directed to monthly dosing to treat RVO.

Under Regeneron's view, a patent owner should be permitted to serially patent the same invention over and over, but with all patents except the first being shielded from IPR challenges because any such challenges would rely on similar grounds as the first. This is absurd, and illustrates precisely the type of patent system abuse that

the IPR regime was designed to correct.

None of Regeneron's cited cases support the extreme view Regeneron is taking with respect to *General Plastic*. (*See, e.g.*, IPR2022-01225, Paper 14, 4-11). For example, *Microsoft* involved challenges to the *same patent*; *Abiomed* takes pains to note that the petition in question was the twentieth petition filed challenging the same 6 patents—*all previous nineteen petitions had been denied*. *Samsung* involved a third petition against the *same patent claims* as two prior petitions—*both of which had been denied*.

Indeed, should Regeneron make the same extreme, and frivolous *General Plastic* argument here, it should be rejected.

C. 35 U.S.C. §325(d) Discretionary Denial Is Unwarranted.

Any argument that Petitioner's grounds or asserted prior art are cumulative of the '205 patent's prosecution should be rejected. As set forth below, the record confirms that the Examiner either (1) was not presented with the same or substantially the same art or arguments as Petitioner's, especially given Regeneron's obscuration of relevant art, and/or (2) materially erred in allowing the Challenged Claims. *Advanced Bionics, LLC v. Med-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, 2020 WL 740292, at *3-4 (P.T.A.B. Feb. 13, 2020) (precedential) (citing *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 (P.T.A.B. Dec. 15, 2017)).

***Becton, Dickinson* Factors (a) and (b).** Neither "the same [nor] substantially the same" art or arguments were previously presented to the Office during prosecution of the Challenged Claims. PO will likely argue that NCT-072 (Ex.1009), Regeneron (30-April-2009) (Ex.1012), and SEC forms similar to 2009 10-Q (Ex.1021), were submitted to the Office and marked "considered" by the Examiner.

But these asserted references were only included on a series of *post*-allowance IDS forms, buried among thousands of pages of art. (Ex.1017, 1648-49; *id.*, 1734). Indeed, none were cited or relied upon by the Examiner and Regeneron never alerted the Examiner of their specific relevance to the Examiner's prior reasons for allowance. Accordingly, the intrinsic record does not reflect that the Examiner evaluated any of Petitioner's asserted art, nor that the Examiner appreciated or understood their disclosures' relevance to the claims.

Indeed, the only fact Patent Owner can point to is that the references (or similar references) were "disclosed" on an IDS; however, "[t]he Board has consistently declined exercising its discretion under Section 325(d) when the only fact a Patent Owner can point to is that a reference was disclosed to the Examiner during the prosecution." *Amgen Inc. v. Alexion Pharms., Inc.*, IPR2019-00739, Paper 15, 62 (P.T.A.B. Aug. 30, 2019) (citing *Amneal Pharms. LLC v. Alkermes Pharma Ireland Ltd.*, IPR2018-00943, Paper 8, 40 (P.T.A.B. Nov. 7, 2018));

Amazon.com, Inc. v. M2M Solutions LLC, IPR2019-01205, Paper 14, 15-16 (P.T.A.B. Jan. 27, 2020) (instituting IPR where "the prosecution history record shows that the various IDSs include at least about a few hundred references" and "[n]othing in the record indicate[d] that the Examiner substantively considered…the prior art"); *id.* at 16 ("[A] reference that 'was neither applied against the claims nor discussed by the Examiner' does not weigh in favor of exercising the Board's discretion under §325(d) to deny a petition." (citations omitted)); *Shenzhen Zhiyi Tech. Co. v. iRobot Corp.*, IPR2017-02137, Paper 9, 9-10 (P.T.A.B. Apr. 2, 2018) (declining to deny institution under §325(d) when reference merely cited in an IDS; reference not relied upon by the Examiner, but rather, was merely "included in the approximately fifteen pages of cited references"); *Nitto Denko Corp. v. Hutchinson Tech. Inc.*, IPR2018-00955, Paper 7, 15-17 (P.T.A.B. Dec. 4, 2018) (instituting IPR review despite asserted reference being submitted in an IDS which the examiner initialed). Indeed, PO's *post*-allowance IDS submissions of Petitioner's asserted art buried in over a hundred other references does not rise to the level of candor and good faith required before the Patent Office.

In sum, Petitioner's asserted art was neither "involved" nor "evaluated" during prosecution, and therefore, the prior art herein is not substantially the same as that previously considered by the Office. *Becton, Dickinson*, IPR2017-01586, Paper 8, 17; 35 U.S.C. §325(d).

Becton, Dickinson* Factor (d).** Additionally, none of Petitioner's grounds or art, including NCT-072, Regeneron (30-April-2009), or 2009 10-Q, were actually applied against the claims or discussed by the Examiner. *Amazon.com*, IPR2019-01205, Paper 14, 16. The Examiner initially rejected the pending claims under §102 and §103 as anticipated by, or obvious over, a different clinical trial, NCT-973. (Ex.1019, 912-15 (12-10-2019 Non-Final Rejection)). Regeneron overcame the Examiner's rejections by arguing that 2 mg was not disclosed in the NCT-973 site until after the alleged priority date. (*Id.*, 953-55 (1-23-2020 Amendment)). As discussed above, Regeneron withheld from the Examiner until after allowance that NCT-072, Regeneron (30-April-2009), and 2009 10-Q ***did disclose the claimed 2 mg of aflibercept well ***before*** the alleged priority date. As a result, the Examiner withdrew the §102 and §103 rejections under the incorrect assumption that "[n]one of the published clinicaltrials.gov updates having dates on before [sic] January 11, 2012 disclose the dosing regimen recited in the instant claims." (*Id.*, 1622 (4-1-2020 Notice of Allowance)).

***Becton, Dickinson* Factors (c), (e), and (f): The Examiner Erred.** As explained above, the answer to *Advanced Bionics*' first inquiry is a definitive "no." Accordingly, a showing of Examiner error is unnecessary. Nonetheless, to the extent the Board disagrees, discretionary denial still is not warranted because Regeneron obscured, and the Examiner overlooked, each reference's anticipatory disclosures,

constituting material error. *Advanced Bionics*, IPR2019-01469, Paper 6, 10 (listing silence as evidence of error). As stated above and in more detail below, NCT-072, Regeneron (30-April-2009), and 2009 10-Q disclose, *before* January 11, 2012, every element of the Challenged Claims, including the 2 mg disclosure that Regeneron argued to the Examiner was not present in the prior art. Such disclosures directly contradicted the Examiner's original reasons for allowance (*see* Ex.1019, 1622-23) and therefore should have raised new issues of patentability. Consequently, the Examiner erred and the Examiner's stated "careful consideration" of "[t]he information disclosure statements (IDS) filed 30 June 2020 and 16 July 2020," cannot equate to consideration of Petitioner's asserted art in the manner contemplated by *Advanced Bionics* or *Becton, Dickinson*.

Moreover, the Examiner erred by failing to consider the varying priority dates for the challenged claims, e.g., the fact that RVO clinical trial results were not included in the specification until the November 2011 application, and that the 0.05 ml disclosure was not included until the July 2013 application. The Examiner also erred in failing to consider the additional prior art that was available in view of these later dates. Consequently, the Examiner should have (at least) rejected the pending claims using the references disclosing the 2 mg disclosure, including with the art combinations presented herein. The Examiner's failure to consider these references

and PO's late additions to the specification constitutes material error relevant to the patentability of the '205 patent claims.

Petitioner's Additional Evidence and Arguments. Finally, the Examiner did not have the benefit of the additional evidence and facts Petitioner presents to the Board here, further weighing against §325(d) denial. For example, Petitioner provides an analysis of the earliest priority dates to which each claim is entitled, and expert declarations (Ex.1002; Ex.1003) that set forth the POSA's understanding of the prior art disclosures, and their public availability, thus warranting reconsideration of the prior art and arguments. *Guardian Indus. Corp. v. Pilkington Deutschland AG*, IPR2016-01635, Paper 9, 9-10 (P.T.A.B. Feb. 15, 2017); *Taro Pharms. U.S.A., Inc. v. Apotex Techs., Inc.*, IPR2017-01446, 2017 WL 6206129, at *8-9 (P.T.A.B. Nov. 28, 2017) (declining to deny petition under §325(d) where petitioner presented new declaration evidence); *Tandus Flooring, Inc. v. Interface, Inc.*, IPR2013–00333, 2013 WL 8595289, at *2 (P.T.A.B. Dec. 9, 2013) (same).

Moreover, as stated above, Petitioner's anticipation and obviousness arguments were not considered or applied by the Examiner during prosecution of the '205 patent claims, and the Examiner's failure to reject claims over the art and grounds herein, and failure to properly analyze the timing of PO's additions to the specification, constitutes material error. In sum, the '205 patent claims would not

have been allowed had the Office considered the evidence and arguments presented herein.

VIII. OVERVIEW OF PETITIONER'S CHALLENGES AND REQUESTED RELIEF.

A. STATUTORY GROUNDS OF CHALLENGE.

The following prior art references anticipate the Challenged Claims:

Ground	Proposed Rejections (35 U.S.C. §102)
1	NCT-072
2	Regeneron (30-April-2009)
3	2009 10-Q

In addition, the following render the Challenged Claims obvious:

Ground	Proposed Rejections (35 U.S.C. §103)
4	NCT-072 alone or in view of Sophie and/or NCT-795
5	Regeneron (30-April-2009) alone or in view of Sophie and/or NCT-795
6	2009 10-Q alone or in view of Sophie and/or NCT-795
7	Dixon in combination with Kreatsoulas, either alone or in view of Sophie and/or NCT-795

Petitioner's full statement of reasons for the relief requested is set forth below, and in the supporting expert declarations of Drs. Stewart and Gerritsen.

IX. CLAIM CONSTRUCTION (37 C.F.R. §42.104(b)(3)).

In accordance with 37 C.F.R. §42.100(b), Challenged Claims are "construed using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. § 282(b)," *i.e.*, the *Phillips* standard. 83 Fed. Reg. 197, 51340-51359 (Oct. 11, 2018); *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005). Petitioner and Dr. Stewart, have applied this standard.

A. THE "METHOD FOR TREATING" PREAMBLE IS NOT A LIMITATION AND PO'S ANTICIPATED ARGUMENT THAT THE PREAMBLE IS A POSITIVE LIMITATION SHOULD BE REJECTED.

The "method for treating" preamble of the Challenged Claims is "merely a statement of purpose or intended use" for the claimed dosing regimen(s) and is non-limiting. *Vizio, Inc. v. Int'l Trade Comm'n*, 605 F.3d 1330, 1340-41 (Fed. Cir. 2010) ; *Bristol-Myers Squibb Co. v. Ben Venue Lab'ys, Inc.*, 246 F.3d 1368, 1375 (Fed. Cir. 2001); *Arctic Cat Inc. v. GEP Power Prods., Inc.*, 919 F.3d 1320, 1327 (Fed. Cir. 2019) ("as a general rule preamble language is not treated as limiting")). Indeed, "method for treating"—like the "method" preamble in *Bio-Rad*—neither provides antecedent basis for any other claim element[8] nor gives life, meaning or vitality to the claimed dosing regimen, and thus, it is not a limitation. *Bio-Rad Lab'ys, Inc. v. 10X Genomics Inc.*, 967 F.3d 1353, 1371 (Fed. Cir. 2020) (citing *TomTom, Inc. v.*

[8] "Treating" (or any form of "treat") appears nowhere else in any of the claims.

Adolph, 790 F.3d 1315, 1322-24 (Fed. Cir. 2015) ("In *TomTom*... [t]he two-part preamble of the asserted claim recited: '[1] [a] method for generating and updating data [2] for use in a destination tracking system of at least one mobile unit comprising….We held that the first part of the preamble, 'method for generating and updating data,' was not limiting and did not provide an antecedent basis for any claim terms. We also found that the term did not recite essential structure or steps, or give necessary life, meaning, and vitality to the claim; rather, it stated 'a purpose or intended use.'" (citations omitted)); *In Re: Copaxone Consol. Cases*, 906 F.3d 1013, 1022-23 (Fed. Cir. 2018) (preamble non-limiting where it "does not change the express dosing amount or method already disclosed in the claims, or otherwise result in a manipulative difference in the steps of the claims"). Nothing in the intrinsic record here suggests otherwise. Any argument that "a human subject" and "macular edema following retinal vein occlusion" claim terms find their respective meaning in the preamble is meritless. Like in *Copaxone*, the preamble does not "change the express dosing amount or method already disclosed in the claims, or otherwise result in a manipulative difference in the steps of the claims." *Copaxone*, 906 F.3d at 1023. Instead, the claimed dosing regimen stays the same, and "the steps…are performed in the same way regardless whether or not the patient experiences" treatment of their RVO. *Bristol-Myers*, 246 F.3d at 1375. Consequently, the "method for treating" element in the preamble does not constitute

a positive limitation, but is merely a statement of *intended* purpose, and therefore, not a limitation. *Id.* at 1374-75; *Copaxone*, 906 F.3d at 1022-23; *Bio-Rad*, 967 F.3d 1371 (citing *TomTom*, 790 F.3d 1322-24).

Further, there is no evidence PO asserted the preamble to traverse any Examiner rejections. (*See, e.g.*, Ex.1019, 205FH, 1622-23 (4-1-2020 Notice of Allowability)).

For these reasons, Petitioner submits that the preamble is non-limiting and no construction is necessary.

B. IF A LIMITATION, THE PREAMBLE'S PLAIN AND ORDINARY MEANING, WHICH DOES NOT PROVIDE ANY SPECIFIC EFFICACY REQUIREMENT, MUST GOVERN.

If the Board finds it a limitation, the "method for treating" preamble should be construed to have its plain and ordinary meaning—"administering a therapeutic to a patient, without a specific degree of efficacy required." (*See, e.g.*, IPR2021-00881, Paper 21, 21 ("the preambles of the independent claims do not require the recited method steps to provide an *effective* treatment.")). In its previous finding, the Board rejected Regeneron's arguments to the contrary, noting that "Patent Owner does not direct us to any other portion of the claims or written description in the '338 patent that supports finding that the claimed method for treating an angiogenic eye disorder requires such treatment method to have any particular level of effectiveness." (*Id.*, 20). The '205 patent shares the same specification as the '338

patent, and the claims of both are directed to a "method for treating" an angiogenic eye disorder. Consequently, Regeneron's arguments similarly fail here. *See Samsung Elecs. Co. v. Elm 3DS Innovations, LLC*, 925 F.3d 1373, 1378 (Fed. Cir. 2019) ("Where multiple patents derive from the same parent application and share many common terms, we must interpret the claims consistently across all asserted patents."). If limiting, the preamble is "a statement of the intentional purpose for which the method must be performed." *GlaxoSmithKline LLC v. Glenmark Pharms., Inc.*, No. 14-877-LPS-CJB, 2016 WL 3186657, at *7 (D. Del. June 3, 2016). In other words, performing the claimed method on a given patient or patient population with an "intent to treat" is the same as performing the claimed method, regardless of clinical outcome. Regeneron has offered a smorgasbord of shifting constructions for the term in prior IPRs/PGRs, none —including its "a high level of efficacy that is not inferior to the existing standard-of-care" option (IPR2021-00881, Paper 41, 12)—find support in the intrinsic record and thus should be rejected.

First, there are no data in the '205 patent showing non-inferiority to any so-called "standard of care" for RVO. (Ex.1001, 5:21-39). Example 6 of the '205 patent, disclosing Regeneron's COPERNICUS trial, includes sham (i.e., placebo) injections as the only comparator—i.e., ***not*** a comparison against the so-called "standard of care" at the time. (*Id.*, 14:56–15:34 (Example 6); IPR2021-00881, Paper 41, 10-12; Ex.1086, 17:6-25, 150:2-151:18).

Second, reading-in a "high level of efficacy" here would be committing "one of the cardinal sins of patent law." *SciMed Life Sys., Inc. v. Advanced Cardiovascular Sys., Inc.*, 242 F.3d 1337, 1340 (Fed. Cir. 2001); *Copaxone*, 906 F.3d at 1023. Indeed, the intrinsic record states that "beneficial therapeutic effects ***can be*** achieved in patients suffering from angiogenic eye disorders [*e.g.*, RVO] by administering a VEGF antagonist"—not "must be" achieved. (Ex.1001, 2:11-15 (emphasis added); IPR2021-00881, Paper 21, 21). Indeed, the '205 patent (Example 6) demonstrates that only about half of the COPERNICUS patients met the primary endpoint of the clinical study—namely, a gain of 15 or more letters on the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity chart (56.1% at Week 24 and 55.3% at Week 52). (Ex.1001, 15:5-14).

Third, under Regeneron's anticipated construction (which relies entirely on extrinsic evidence), a POSA is only able to determine infringement (or not) *retroactively*. Such an extrinsic construction undermines the patent's notice function. *Phillips*, 415 F.3d at 1319.

Finally, Regeneron's anticipated "high level of efficacy" construction generates §112 enablement, written description, and indefiniteness problems as well, because the specification provides no means or parameters for ascertaining, *inter alia*, what constitutes a "***high*** level of efficacy" for RVO, when to make the efficacy assessment, how long the high level of efficacy must be maintained, and what to

compare it to. (Ex.1002, ¶¶50-54); *Rhine v. Casio, Inc.*, 183 F.3d 1342, 1345 (Fed. Cir. 1999) (constructions rendering claims invalid or meaningless should be avoided). The same is true of Regeneron's "not inferior to the existing standard-of-care."[9] Accordingly, Regeneron's anticipated construction opens the claims to a near-infinite level of variability and subjectivity, and therefore, cannot be correct.

X. PERSON OF ORDINARY SKILL IN THE ART (POSA).

A POSA is presumed to be aware of all pertinent art, think along the lines of conventional wisdom, and possess common sense and ordinary creativity in the pertinent field. A POSA here would have: (1) knowledge regarding the diagnosis and treatment of angiogenic eye disorders, including the administration of therapies to treat said disorders; and (2) the ability to understand results and findings presented or published by others in the field, including the publications discussed herein. Typically, such a person would have an advanced degree, such as an M.D. or Ph.D. (or equivalent, or less education but considerable professional experience in the

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[9] Non-inferiority is a *population*-based clinical trial statistical determination. (Ex.1018, 2537 ("All aflibercept *groups* were noninferior…")). There is no support in the specification describing how to assess whether the treatment of the claimed *single human subject* is "not inferior to the existing standard-of-care."

medical, biotechnological, or pharmaceutical field), with practical academic or medical experience in (i) developing treatments for angiogenic eye disorders (such as CRVO), including through the use of VEGF antagonists, or (ii) treating of same, including through the use of VEGF antagonists. (Ex.1002, ¶¶26-28; Ex.1003, ¶¶21-25; *see* IPR2021-00881, Paper 21, 16 ("Petitioner's definition of one of [a POSA] is reasonable and consistent with the '338 patent and the prior art of record")).

XI. TECHNOLOGICAL BACKGROUND AND PRIOR ART SCOPE.

Publications below reflect anticipatory disclosures of the subject matter in the Challenged Claims, together with knowledge that POSAs would bring to bear in reading the prior art at the time of the inventions, *i.e.*, no earlier than January 13, 2011 for Claim 1[10] or July 12, 2013 for Claims 2 and 3. *Ariosa Diagnostics v. Verinata Health, Inc.*, 805 F.3d 1359, 1367-68 (Fed. Cir. 2015). As established in *KSR*, the knowledge of a POSA is part of the store of public knowledge that must be consulted when considering whether a claimed invention would have been obvious. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 415-22 (2007).

A. MACULAR EDEMA FOLLOWING RETINAL VEIN OCCLUSION.

The Challenged Claims are directed to "[a] method for treating macular edema following retinal vein occlusion." (Ex.1001, 2156-57). EYLEA was first approved

[10] *See supra* §VI.B.1.a.

for treating RVO by monthly injection in 2012. The '205 patent claims were first filed in August 2018. RVO refers generally to occlusion of the retinal fundus by hemorrhaging from the retinal capillaries. (Ex.1037, 809; Ex.1032, 627; Ex.1002, ¶¶55-58). RVO is classified according to which area or areas of the retinal fundus are affected: central RVO affects the entire retinal fundus, and branch RVO affects part of the retinal fundus corresponding to the hemorrhaging retinal capillary. (Ex.1037, 809; Ex.1002, ¶¶55-56). Central RVO is therefore a type of retinal vein occlusion.

B. VEGF TRAP-EYE/AFLIBERCEPT.

VEGF Trap-Eye/aflibercept is an engineered prior art fusion protein consisting of domain 2 of the human VEGF receptor 1 (VEGFR1) and domain 3 of the human VEGF receptor 2 (VEGFR2), fused to the Fc portion of human IgG_1. (*See* Ex.1007, 261; Ex.1002, ¶66). The terms "VEGF Trap-Eye" and aflibercept are widely known to refer to the same molecule. (Ex.1006, Abstract ("[o]ne promising new drug is aflibercept (VEGF Trap-Eye)"); Ex.1022, 16 ("VEGF Trap-Eye (aflibercept ophthalmic solution)...is being developed"); Ex.1021, 18, 19 ("VEGF Trap-Eye is a specially purified and formulated form of VEGF Trap [defined as aflibercept on p. 18 in the same document] for use in intraocular applications.")).

VEGF Trap-Eye/aflibercept was developed to target angiogenic eye disorders, such as AMD, diabetic macular edema (DME), and RVO. (Ex.1002, ¶¶68-71). As

of the relevant timeframe, other anti-VEGF agents were already approved by the FDA and being used (in some cases off-label) in the treatment of these angiogenic eye disorders, including two monoclonal antibodies, ranibizumab (LUCENTIS) and bevacizumab (AVASTIN). Like VEGF Trap-Eye/aflibercept, these earlier generation therapeutics targeted VEGF by binding to, and thus inhibiting, the activity of VEGF-A. (Ex.1002, ¶¶60-65).

Regeneron's clinical trials for VEGF Trap-Eye/aflibercept date back to the mid-2000's, when Regeneron first placed the molecule into trials for the treatment of AMD. (Ex.1005, 2147). Upon receiving promising results, Regeneron and Bayer proceeded to explore additional eye disease indications as part of its VEGF Trap-Eye program and, in April 2009, Regeneron publicly announced its phase 3 RVO clinical trials. (Ex.1028, 1; *see also* Ex.1009, 3-5; Ex.1029, 3-5; Ex.1021, 19-20; Ex.1002, ¶¶84-86, 88-91). The phase 3 program in RVO included the COPERNICUS and GALILEO studies, involved six monthly intravitreal injections of VEGF Trap-Eye (aflibercept) at a dose of 2 mg compared against sham control injections in the first phase, followed by as-needed (or PRN) dosing in the second phase. (*See* Ex.1021, 20; *see also* Ex.1063, 1). The COPERNICUS/GALILEO monthly dosing regimen is the same regimen Regeneron claimed years later in the '205 patent.

C. PETITIONER'S PRIOR ART REFERENCES.[11]

1. NCT-072 (Ex.1009).

NCT-072 is an on-line record disclosing the COPERNICUS regimen Regeneron submitted to the ClinicalTrials.gov database maintained by the National Library of Medicine at the National Institutes of Health ("NIH"). ClinicalTrials.gov is a website "***intended for a wide audience***, including individuals with serious or life-threatening diseases or conditions, ***members of the public***, ***health care providers, and researchers***." (*See* Ex.1085, 2 (emphasis added)). After Congress passed the Food and Drug Administration Modernization Act of 1997, which required "a public information resource on certain clinical trials," NIH created ClinicalTrials.gov in 2000. (*Id.*). In 2007, Congress expanded the requirements for submitting clinical trial information with laws penalizing non-compliance, including "withholding of NIH grant funding and civil monetary penalties of up to $10,000 a day." (*Id.* at 3; *see also* Ex.1003, ¶¶53-57).

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[11] The asserted prior art references all qualify as publications that were available to interested POSAs before the priority dates of the Challenged Claims. (*See* Ex.1003, ¶¶31-80; Ex.1002, ¶¶83, 87, 88 & n.8; *see also* Ex.1072, 79, 95; Ex.1059).

As shown in the following, NCT-072 is a §102 printed publication. *See Hulu, LLC v. Sound View Innovations*, No. IPR2018-01039, 2019 WL 7000067, *5 (P.T.A.B. Dec. 20, 2019).

NCT-072 (an electronic publication) "was accessible to persons concerned with the art to which the document relates." MPEP §2128. In fact, the Board has found a ClinicalTrials.gov printout analogous to NCT-072 qualifies as a prior art printed publication. *Grünenthal GMBH v. Antecip Bioventures II LLC*, No. PGR2019-00026, 2020 WL 4341822, *8 (P.T.A.B. May 5, 2020). Here, the evidence confirms that NCT-072—including the COPERNICUS dosing regimen and other clinical study details provided therein—was publicly available on the ClinicalTrials.gov website prior to January 13, 2011.

First, the History of Changes archive that ClinicalTrials.gov maintains for each study demonstrates the COPERNICUS regimen was disclosed to the public before January 13, 2011, the earliest possible priority date of Challenged Claim 1.[12] (Ex.1009, 1-2).

Second, Regeneron has not contested the public accessibility of Regeneron's submissions to the ClinicalTrials.gov database in related proceeding IPR2021-00881

[12] As explained above, the earliest possible priority date to which Challenged Claims 2 and 3 are entitled is even later—July 12, 2013. (*Supra* §VI.B.1.).

or during prosecution. In fact, during prosecution, Regeneron specifically relied on archived versions of the GALILEO phase 3 clinical trial for VEGF Trap-Eye in the treatment of RVO in overcoming the Examiner's rejection of the pending claims under 35 U.S.C. §§102 and 103. (Ex.1019, 953-54; *id.*, 1388; *id.*, 1622-23).

Third, NCT-072 was expressly cited in the prior art itself, demonstrating its actual publication and availability to interested POSAs. (Ex.1072, 95 ("In the COPERNICUS study (NCT00943072)"); *id.*, 79 (Table 7) ("Data current as of September 2010."); Ex.1003, ¶¶53-70).

Finally, in support of this Petition, Drs. Gerritsen and Stewart each declare in their experience and expert opinion that clinical study details were publicly accessible from ClinicalTrials.gov to skilled artisans—who were both interested in and familiar with such reports—as of their posted dates. (Ex.1003, ¶¶53-70; Ex.1002, ¶¶77-83). As such, NCT-072 is a printed publication that was accessible to the relevant public more than one year before January 13, 2011, and thus constitutes prior art under both pre-AIA 35 U.S.C. §102(b) and post-AIA 35 U.S.C. §102(a)(1), (2).

NCT-072 discloses Regeneron's COPERNICUS trial: "a phase 3 study to determine the efficacy of VEGF Trap-Eye injected into the eye on vision function in subjects with macular edema as a consequence of central retinal vein occlusion." (Ex.1009, 3). NCT-072 discloses the treatment arms for COPERNICUS: "Monthly

IVT [intravitreal] injection of VEGF Trap-Eye 2.0 mg" compared against "Monthly Sham IVT injection." (*Id.*, 4; Ex.1002, ¶¶84-86).

2. NCT-795 (Ex.1014).

NCT-795, like NCT-072 (above), is an on-line record from NIH's ClinicalTrials.gov website. As shown, NCT-795 is also a §102 printed publication. *Hulu*, 2019 WL 7000067, at *5; *see also Grünenthal*, 2020 WL 4341822, at *8 (ClinicalTrials.gov print-out qualified as a prior art printed publication).

Each of the following independently confirm that NCT-795 was publicly available and accessible to interested, skilled artisans prior to 2011 (*see* MPEP §2128): (i) the History of Changes archive for NCT-795 (Ex.1014, 1-3); (ii) prior art references expressly citing NCT-795 (Ex.1006, 1579 (Bibliography No. 47) ("Accessed 28 Sep 2008"); *id.* (Bibliography No. 46) ("Accessed 28 Sep 2008"); Ex.1072, 94-95); and (iii) Dr. Gerritsen's declaration, providing her experience and expert opinion (Ex.1003, ¶¶53-57, 59-70; *see also* Ex.1002, ¶87). As such, NCT-795 thus constitutes prior art under both pre-AIA 35 U.S.C. §102(b) and post-AIA 35 U.S.C. §102(a)(1), (2).

NCT-795 discloses Regeneron's Phase 3 VIEW1 trial for the treatment of AMD. (Ex.1014, 3-5). NCT-795 also discloses that a 2 mg dose of VEGF Trap-Eye is formulated at a concentration of 40 mg/ml, and that "[t]he injection vol[ume] will be 50 μL (0.05 mL)." (*Id.*, 5).

3. Kreatsoulas (Ex.1049).

Kreatsoulas published in 2009, and thus constitutes prior art to all of the Challenged Claims under both pre-AIA 35 U.S.C. §102(b) and post-AIA 35 U.S.C. §102(a)(1), (2). Kreatsoulas discloses as follows:

> In July, Genentech, Inc., announced positive 6-month results from the phase 3 BRAVO and CRUISE trials. The BRAVO study showed that injections of ranibizumab (Lucentis, Genentech, Inc.) improved BCVA from baseline in patients with macular edema due to BRVO compared with sham. The CRUISE study showed early and sustained improvement in BCVA through 6 months in patients with macular edema due to CRVO receiving monthly injections of ranibizumab.

(Ex.1049, 20; Ex.1002, ¶94). Kreatsoulas further discloses: "During the first 6-month period, participants received monthly injections of either 0.3 mg or 0.5 mg of ranibizumab (n=265 per study) or monthly sham injections (n=132 per study)." (Ex.1049, 21; Ex.1002, ¶94).

4. Regeneron (30-April-2009) (Ex.1028).

Regeneron (30-April-2009) published on April 30, 2009, and thus constitutes prior art to all of the Challenged Claims under both pre-AIA 35 U.S.C. §102(b) and post-AIA 35 U.S.C. §102(a)(1), (2). Regeneron has not contested Regeneron (30-April-2009)'s status as prior art in related proceeding IPR2021-00881.

Regeneron (30-April-2009) reports the COPERNICUS and GALILEO trials and sets forth the dosing regimen encompassed by the Challenged Claims: "Patients in both studies will receive 6 monthly intravitreal injections of... VEGF Trap-Eye at a dose of 2 milligrams (mg)." (Ex.1028, 1; Ex.1002, ¶¶89-90; Ex.1003, ¶¶36-44). Regeneron (30-April-2009) also reports that "the underlying biology of CRVO is related to edema and the growth of abnormal new blood vessels that are mediated by vascular endothelial growth factor (VEGF)." (Ex.1028, 1; Ex.1002, ¶91).

5. 2009 10-Q (Ex.1021).

2009 10-Q was filed on or about November 3, 2009, and thus constitutes prior art to all of the Challenged Claims under both pre-AIA 35 U.S.C. §102(b) and post-AIA 35 U.S.C. §102(a)(1), (2). (*See* Ex.1021, 55; *see also* Ex.1003, ¶¶71-80). Regeneron has not contested 2009 10-Q as prior art in related proceeding IPR2021-00881.

2009 10-Q reports that "VEGF Trap-Eye is a specially purified and formulated form of VEGF Trap [defined as aflibercept at p. 18 of the same document] for use in intraocular applications." (Ex.1021, 19; *id.*, 18; Ex.1002, ¶93). In addition, 2009 10-Q reports the COPERNICUS/GALILEO clinical trials, including the claimed dosing regimen:

> VEGF Trap-Eye is also in Phase 3 development for the treatment of [CRVO], another cause of blindness. The COPERNICUS…study is

being led by Regeneron and the GALILEO…study is being led by Bayer HealthCare. Patients in both studies will receive six monthly intravitreal injections of either VEGF Trap-Eye at a dose of 2 mg or sham control injections. The primary endpoint of both studies is improvement in visual acuity versus baseline after six months of treatment. At the end of the initial six months, patients will be dosed on a PRN basis for another six months.

(Ex.1021, 20; Ex.1002, ¶93).

6. Sophie (Ex.1010).

Sophie published May 29, 2012, and thus constitutes prior art to at least Claims 2 and 3 under both pre-AIA 35 U.S.C. §102(b) and post-AIA 35 U.S.C. §102(a)(1), (2). Sophie discloses that "[a]flibercept (VEGF Trap-Eye) is available as a preservative-free, sterile, aqueous solution in a single-use, glass vial designed to deliver 0.05 mL VEGF Trap (40 mg/mL in 10 mM sodium phosphate, 40 mM sodium chloride, 0.03% polysorbate 20, and 5% sucrose, pH 6.2)." (Ex.1010, 6; Ex.1002, ¶104). Sophie also discloses the COPERNICUS/GALILEO trials as using the claimed method for treatment:

COPERNICUS…and GALILEO…are two phase 3 trials following 189 and 172 patients with CRVO respectively. Patients are given monthly 2.0 mg VEGF Trap-Eye or sham injections for the first 6 months

followed by PRN treatment for the next 6 months.

(Ex.1010, 14; Ex.1002, ¶104). Sophie further discloses the COPERNICUS/GALILEO 6-month results:

> At month 6, 56.1% and 60.2% of patients treated with VEGF Trap-Eye gained at least 15 letters from baseline compared to 12.3% and 22.1% of patients treated with sham, in the COPERNICUS and GALILEO studies, respectively.

(Ex.1010, 14).

7. Dixon (Ex.1006).

Dixon published in 2009 and thus constitutes prior art under both pre-AIA 35 U.S.C. §102(b) and post-AIA 35 U.S.C. §102(a)(1), (2). Regeneron has confirmed that "Dixon was publicly accessible in print by October 2009, and online by August 20, 2009." (*See Regeneron Pharms., Inc. v. Novartis Pharma AG*, IPR2021-00816, Paper 1, 23 (P.T.A.B. Apr. 16, 2021)). Regeneron also has not contested Dixon's prior art status in related proceedings IPR2021-00880 and -881. Dixon's disclosures are described in detail in Dr. Stewart's expert declaration. (Ex.1002, ¶¶95-103).

Dixon discloses that for AMD treatments, "[o]ne promising new drug is aflibercept (VEGF Trap-Eye), a fusion protein that blocks all isoforms of VEGF-A and placental growth factors-1 and -2." (Ex.1006, 1573). Dixon teaches that VEGF Trap-Eye is an "anti-VEGF therapy, with Phase I and II trial data indicating safety,

tolerability and efficacy for the treatment of neovascular AMD." (*Id.*). Dixon discloses the Phase 3 VIEW1/VIEW2 dosing regimens: an "8 week dosing interval (following three monthly doses)." (*Id.*, 1576).

Dixon also discloses the promising results of the phase 2 CLEAR-IT-2 study of VEGF Trap-Eye in AMD, reporting that patients treated with four monthly loading doses of VEGF Trap-Eye (2.0 mg) followed by PRN dosing exhibited mean improvement in visual acuity of nine (9.0) EDTRS letters and a mean decrease in retinal thickness of 143 μm. (*Id.*).

Additionally, Dixon discloses that "VEGF Trap-Eye [the ophthalmology product] and aflibercept (the oncology product) have the same molecular structure." (*Id.*, 1575; 1573 ("***[o]ne*** promising new drug is aflibercept (VEGF Trap-Eye)") (emphasis added)). Dixon notes that the ophthalmology product is differently purified and formulated than the oncology product (*id.*, 1575), however, the active (VEGF Trap-Eye/aflibercept) is the same in both presentations. In addition, Dixon discusses the half-lives of aflibercept in both systemic and intravitreal contexts, informing a POSA that aflibercept was the active ingredient in both oncology settings (where systemic administration is the norm) and eye disorder settings (where intravitreal administration is the norm). (*Id.*, 1575 ("free aflibercept has a terminal half-life of ~17 days in the circulation. The half-life of human intravitreal doses is unknown")).

Dixon additionally discloses:

> VEGF Trap-Eye is under Phase II investigation in DME and Phase III investigation in central retinal vein occlusion. The FDA approval of VEGF Trap-Eye for these indications would significantly add to the ophthalmologists' armamentarium for treatment of retinal vascular disease.

(*Id.*, 1577-78).

XII. GROUNDS FOR UNPATENTABILITY—DETAILED ANALYSIS.

A. ANTICIPATION.

The Challenged Claims are anticipated by each of NCT-072, Regeneron (30-April-2009), and 2009 10-Q. Each reference discloses all limitations of the Challenged Claims, expressly or inherently.

1. Legal standards.

Anticipation requires a "single prior art reference disclose[], either expressly or inherently, each limitation of the claim." *In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1349 (Fed. Cir. 2002).

A claim is inherently anticipated if "the natural result flowing from the operation as taught would result in the performance of the questioned function." *King Pharms., Inc. v. Eon Labs, Inc.*, 616 F.3d 1267, 1275 (Fed. Cir. 2010). Newly discovered results or new benefits of a known process directed to the same purpose are not patentable because such results are inherent. *Id.*; *In re Omeprazole Patent*

Litig., 483 F.3d 1364, 1373 (Fed. Cir. 2007); *Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1378 (Fed. Cir. 2005) ("method for treating skin sunburn" inherently anticipated where court held that "[i]f [the prior art reference] discloses the very same methods, then the particular benefits must naturally flow from those methods even if not recognized as benefits at the time of [the prior art's] disclosure").

In addition, "anticipation does not require actual performance of suggestions in a disclosure. Rather, anticipation only requires that those suggestions be enabling to one of skill in the art." *Bristol-Myers*, 246 F.3d 1379. Here, the Challenged Claims require only a dosing regimen to treat macular edema following RVO, without any particular efficacy or result (IPR2021-00881, Paper 21, 20-23; Ex.1002, ¶¶48-54), and therefore "proof of efficacy is not required in order for a [prior art] reference to be enabled for purposes of anticipation." *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1326 (Fed. Cir. 2005).

2. Ground 1: NCT-072 Anticipates the Challenged Claims.

Independent Claim 1 is anticipated by NCT-072, as shown in the following table, and confirmed by Dr. Stewart (Ex.1002, ¶¶110-11):

Claim 1:	**NCT-072:**
A method for treating macular edema following retinal vein occlusion in a human subject	"Phase 3 Study…of Repeated Intravitreal Administration of Vascular Endothelial Growth Factor Trap-Eye in Subjects With Macular Edema

Claim 1:	**NCT-072:**
	Secondary to Central Retinal Vein Occlusion."[13] (Ex.1009, 2-3).
comprising administering 2 mg aflibercept to the subject	"Experimental: VEGF Trap-Eye Monthly IVT injection of VEGF Trap-Eye 2.0 mg until Week 24 Primary Endpoint." (*Id.*, 4). "Biological: VEGF Trap-Eye 2.0 mg Monthly intravitreal injection out to the Week 24 Primary endpoint." (*Id.*). A POSA would have understood VEGF Trap-Eye to refer to aflibercept. (*See supra* §§XI.B, XI.C.7; Ex.1002, ¶¶72-76).
by intravitreal injection once every 4 weeks	"Experimental: VEGF Trap-Eye Monthly[14] IVT injection of VEGF Trap-Eye 2.0 mg until Week 24 Primary Endpoint." (Ex.1009, 4). "Biological: VEGF Trap-Eye 2.0 mg Monthly intravitreal injection out to the Week 24 Primary endpoint." (*Id.*).

[13] As discussed above in §XI.A, central RVO is a type of RVO, so prior art directed to central RVO anticipates claims directed to RVO. *See In re Slayter*, 276 F.2d 408, 411 (C.C.P.A. 1960); *In re Gosteli*, 872 F.2d 1008, 1009-12 (Fed. Cir. 1989).

[14] The '205 patent states that "'monthly' dosing is equivalent to dosing once every four weeks." (Ex.1001, 7:67-8:2).

(Ex.1002, ¶111).

Claim 2 further recites "wherein the aflibercept is administered in a volume of 0.05 ml." The priority date of Claim 2 is no earlier than July 12, 2013. (*See supra* §VI.B.). By this date—and, indeed before January 13, 2011—it was widely known that VEGF Trap-Eye/aflibercept was formulated at a concentration of 2 mg per 0.05 ml. (Ex.1014, 5; Ex.1010, 6; Ex.1013, 1-2; Ex.1001, 2:51-52 (disclosing EYLEA FDA approval in November 2011); Ex.1021, 19 ("VEGF Trap-Eye is a specially purified and ***formulated*** form of VEGF Trap") (emphasis added); Ex.1061, 145; Ex.1002, ¶¶112-13, 108-09, 116). Indeed, this was known even well before January 13, 2011. (*See, e.g.*, Ex.1014, 5; Ex.1061, 145; Ex.1002, ¶¶114-16).

NCT-072 (Ex.1009) discloses 2 mg VEGF Trap-Eye, as noted in the table above, and therefore discloses (expressly and inherently) the corresponding volume of VEGF Trap-Eye: 0.05 ml. NCT-072 thus anticipates Claim 2. *In re Baxter Travenol Labs*, 952 F.2d 388, 390 (Fed. Cir. 1991) ("extrinsic evidence may be considered when it is used to explain, but not expand, the meaning of a reference").

Claim 3 recites "wherein the aflibercept is in a pharmaceutical formulation comprising a pharmaceutically acceptable carrier." As shown above, NCT-072 discloses administration of VEGF Trap-Eye via intravitreal injection, and therefore would have been understood by a skilled artisan to expressly and inherently disclose

aflibercept in a pharmaceutical formulation comprising a pharmaceutically acceptable carrier. (Ex.1002, ¶¶118-21).

Regarding the "comprising a pharmaceutically acceptable carrier" element, Regeneron concedes that "a multitude of appropriate formulations can be found in the formulary known to all pharmaceutical chemists," citing to a 1975 version of Remington's Pharmaceutical Sciences. (Ex.1001, 5:41-59). Regeneron continues, explaining that a formulation is suitable "provided that the VEGF antagonist is not inactivated by the formulation and the formulation is physiologically compatible and tolerable with the route of administration." (*Id.*, 5:66-6:3). Regeneron then cites a 1998 reference, Powell et al., from the Journal of Pharmaceutical Science Technology, "and the citations therein for additional information related to excipients and carriers *well-known to pharmaceutical chemists*." (*Id*., 6:3-7 (emphasis added)). Indeed, exemplary pharmaceutical formulations of aflibercept with pharmaceutically acceptable carriers were known in the art—*and patented by Regeneron*—years before the earliest possible priority date of the '205 patent. (*See, e.g.*, Ex.1033, [0003]-[0004], [0007], [0014]; Ex.1008, Claim 1 (claiming VEGFR1R2-FcΔC1(a) (i.e., aflibercept) "in a pharmaceutically acceptable carrier"); Ex.1057, Claim 12 ("VEGF trap"…"and a pharmaceutically acceptable carrier"); Ex.1087, Claim 11 ("A pharmaceutical composition comprising the VEGF trap of claim 10, and a pharmaceutically acceptable carrier."); Ex.1088, Claim 6 (claiming

"[a] pharmaceutical composition comprising" aflibercept "and a pharmaceutically acceptable carrier"); *see also* Ex.1002, ¶105-07). Consequently, the Claim 3 limitation merely recites what was well-known in the art, and therefore, is neither entitled to patentable weight nor sufficient to distinguish Challenged Claim 3 from the prior art. *Ex Parte Turnpaugh*, No. 2008-2558, 2008 WL 4325212, *7 (B.P.A.I. Sept. 19, 2008) ("The arguments furnished are not persuasive of the separate patentability of claim 2 because, as correctly noted by the Examiner, visible laser lights would have been a well known option for the focused light source of [another prior art reference].").

Separately, the priority date of Claim 3 is no earlier than July 12, 2013. (*See supra* §VI.B.). By this date, it was publicly known that FDA approved VEGF Trap-Eye/aflibercept "in a single-use, glass vial designed to deliver 0.05 mL VEGF Trap (40 mg/mL in 10 mM sodium phosphate, 40 mM sodium chloride, 0.03% polysorbate 20, and 5% sucrose, pH 6.2)." (Ex.1010, 6; Ex.1013, 5; Ex.1001, 2:51-52 ("approved by the FDA in November 2011"); Ex.1022, 16 ("VEGF Trap-Eye (aflibercept ophthalmic solution)...is being developed"); Ex.1021, 18-19 ("VEGF Trap-Eye is a specially purified and ***formulated*** form of VEGF Trap [defined as aflibercept on p. 18 in the same document] for use in intraocular applications.") (emphasis added)). NCT-072 discloses VEGF Trap-Eye, as noted in the table above, and therefore, given the widely disclosed formulation and volume of aflibercept,

expressly and inherently discloses that VEGF Trap-Eye is a pharmaceutical formulation comprising aflibercept and pharmaceutically acceptable carriers. NCT-072 thus anticipates Claim 3. *In re Baxter Travenol Labs*, 952 F.2d 390.

* * *

Accordingly, NCT-072 discloses the limitations of each Challenged Claim, and thus anticipates.

3. Grounds 2 and 3: Regeneron (30-April-2009) and 2009 10-Q Anticipate the Challenged Claims.

Independent Claim 1 is anticipated by Regeneron (30-April-2009) and 2009 10-Q, which, as shown below, and confirmed by Dr. Stewart (Ex.1002, ¶¶122-23, 134-35), disclose each and every element:

Claim 1:	**Prior Art:**
A method for treating macular edema following retinal vein occlusion in a human subject	**Regeneron (30-April-2009)**: "[T]he companies are extending their global development program for VEGF Trap-Eye, an investigational agent for the treatment of certain eye diseases, to include Central Retinal Vein Occlusion (CRVO)." (Ex.1028, 1).
	2009 10-Q: "VEGF Trap-Eye is also in Phase 3 development for the treatment of [CRVO], another cause of blindness." (Ex.1021, 20).
comprising administering 2 mg aflibercept to the subject	**Regeneron (30-April-2009)**: "Patients in both studies will receive 6 monthly intravitreal injections of...VEGF Trap-Eye at a dose of 2 milligrams (mg)." (Ex.1028, 1).

Claim 1:	**Prior Art:**
	2009 10-Q: "Patients in both studies will receive six monthly intravitreal injections of...VEGF Trap-Eye at a dose of 2 mg..." (Ex.1021, 20).
by intravitreal injection once every 4 weeks.	**Regeneron (30-April-2009)**: "Patients in both studies will receive 6 monthly[15] intravitreal injections of...VEGF Trap-Eye at a dose of 2 milligrams (mg)." (Ex.1028, 1).
	2009 10-Q: "Patients in both studies will receive six monthly[16] intravitreal injections of...VEGF Trap-Eye at a dose of 2 mg…" (Ex.1021, 20).

(Ex.1002, ¶¶123, 134). A POSA would have understood VEGF Trap-Eye to refer to aflibercept. (*See supra* §§XI.B, XI.C.7; Ex.1002, ¶¶72-76).

Claim 2 further recites "wherein the aflibercept is administered in a volume of 0.05 ml." The priority date of Claim 2 is no earlier than July 12, 2013. (*See supra* §VI.B.). By this date, it was publicly known that VEGF Trap-Eye was formulated at a concentration of 2 mg per 0.05 ml. (*See, e.g.* Ex.1014, 5; Ex.1010, 6; *see also* Ex.1013, 1-2; Ex.1001, 2:51-52 ("Aflibercept (EYLEA™, Regeneron Pharmaceuticals, Inc) was approved by the FDA in November 2011"); Ex.1021, 19 ("VEGF Trap-Eye is a specially purified and ***formulated*** form of VEGF Trap")

[15] *See supra* note 14.

[16] *See supra* note 14.

(emphasis added); Ex.1002, ¶¶108-09, 124-25, 128, 136-37, 140). Indeed, this was known even well before January 13, 2011. (*See, e.g.*, Ex.1014, 5; Ex.1061, 145; Ex.1002, ¶¶126-28, 138-40; *see also* Ex.1002, ¶105-07).

Regeneron (30-April-2009) and 2009 10-Q expressly disclose 2 mg VEGF Trap-Eye, as noted in the table above, and therefore expressly and inherently disclose the corresponding volume of VEGF Trap-Eye: 0.05 ml, thus anticipating Claim 2. *In re Baxter Travenol Labs*, 952 F.2d 390.

Claim 3. Because aflibercept cannot be intravitreally injected without being in a "pharmaceutically acceptable carrier," Regeneron (30-April-2009) and 2009 10-Q's disclosure of monthly intravitreal injections expressly and inherently disclose administration of a pharmaceutical formulation comprising a pharmaceutically acceptable carrier. (Ex.1002, ¶¶ 130-33, 142-45). For the reasons stated above, the language "pharmaceutical formulation comprising a pharmaceutically acceptable carrier" cannot impart patentability to Claim 3 and is not entitled to patentable weight.

As discussed for Ground 1, Regeneron concedes in the specification that pharmaceutically acceptable carriers were, and had been for decades, well-known in the art. (Ex.1001, 5:41-59; 5:66-6:38). Indeed, aflibercept in a "pharmaceutically acceptable carrier" was patented by Regeneron well before the '205 patent filing date. (*See, e.g.*, Ex.1033, [0003]-[0004], [0007], [0014]; Ex.1008, Claim 1;

Ex.1057, Claim 12; Ex.1087, Claim 11; Ex.1088, Claim 6). The Claim 3 limitation thus merely recites what was well-known in the art, a fact conceded by Regeneron in the intrinsic record, rendering it devoid of patentable weight and insufficient to distinguish the claim from the prior art. *Ex Parte Turnpaugh*, 2008 WL 4325212, at *7.

In addition, the priority date of Claim 3 is no earlier than July 12, 2013. (*See supra* §VI.B.). By this date, it was publicly known that VEGF Trap-Eye had been approved, commercially available as Eylea, and formulated in pharmaceutically acceptable carrier(s). (Ex.1010, 6; Ex.1013, 5; Ex.1001, 2:51-52; Ex.1022, 16 ("VEGF Trap-Eye (aflibercept ophthalmic solution)…is being developed"); Ex.1021, 18-19 (VEGF Trap-Eye is "a specially purified and ***formulated*** form of VEGF Trap [defined as aflibercept on p. 18 in the same document] for use in intraocular applications.") (emphasis added)). Regeneron (30-April-2009) and 2009 10-Q expressly disclose VEGF Trap-Eye, as noted in the table above, and therefore expressly and inherently disclose that VEGF Trap-Eye is necessarily a pharmaceutical formulation comprising aflibercept and pharmaceutically acceptable carriers. Regeneron (30-April-2009) and 2009 10-Q thus anticipate Claim 3. *In re Baxter Travenol Labs*, 952 F.2d 390.

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Each anticipatory reference asserted herein (NCT-072, Regeneron (30-April-

2009), and 2009 10-Q) is presumed enabling and it is Regeneron's burden to rebut those presumptions. *In re Antor Media Corp.*, 689 F.3d 1282, 1287-88 (Fed. Cir. 2012); *Cubist Pharms., Inc. v. Hospira, Inc.*, 75 F. Supp. 3d 641, 659-60 (D. Del. 2014) (rejecting patentee's arguments that prior art reference disclosing exact dosage amount and dosing interval was not enabled). Indeed, each reference sets forth a clear method and dosing regimen that POSAs would have no trouble following. Moreover, the preamble—even if it is assumed limiting—does not help Regeneron. The VEGF Trap-Eye/aflibercept Phase 3 data showed "treating" macular edema following CRVO with VEGF Trap-Eye (Ex.1009, 2-3; Ex.1028, 1; Ex.1021, 19-20), and therefore efficacy is expressly and inherently disclosed.

Accordingly, the COPERNICUS/GALILEO Phase 3 dosing regimen disclosures of NCT-072, Regeneron (30-April-2009), and 2009 10-Q expressly and inherently disclose the limitation of each Challenged Claim and thus anticipate.

B. OBVIOUSNESS.

The Challenged Claims are also obvious.

1. Legal standards.

Claims are invalid under 35 U.S.C. §103(a) if the differences between the claims and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the pertinent art. *KSR*, 550 U.S. at 406. Furthermore, "[w]hen there is a design need or

market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense." *Id.* at 421.

When relying on secondary considerations, a patentee must establish a nexus between the secondary considerations and the claimed invention. *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311-12 (Fed. Cir. 2006). There is no nexus unless the offered secondary consideration actually results from something that is both claimed and novel in the claim. *In re Huai-Hung Kao*, 639 F.3d 1057, 1068, 1074 (Fed. Cir. 2011).

2. Grounds 4-6: The Challenged Claims Are Obvious Over Each of the Anticipatory References Alone, or in View of Sophie and/or NCT-795.

As discussed above, each of NCT-072, Regeneron (30-April-2009), and 2009 10-Q (collectively, the "anticipatory references") disclose each and every element of the Challenged Claims and thus anticipates them. (*Supra* §XII.A.). Separately, each of the anticipatory references render the Challenged Claims obvious in light of the (i) disclosure of the claimed method of treating macular edema following RVO (2 mg aflibercept administered via monthly intravitreal injection) in each of the anticipatory references; (ii) motivation of a POSA to adopt those prior art methods

of treating RVO; (iii) disclosure of the claimed 0.05 ml dose volume in each of Sophie and NCT-795; and (iv) a POSA's general knowledge and understanding.

The claimed dosing regimen. As discussed above, each of the anticipatory references disclose the claimed method of treating RVO with 2 mg aflibercept administered via monthly intravitreal injection. (*Supra* §XII.A.; Ex.1009, 2-4; Ex.1028, 1; Ex.1021, 19-20). Further, monthly dosing was already a commonly used, and approved, dosing regimen for anti-VEGF agents in treating angiogenic eye disorders. Indeed, in connection with an IPR proceeding on the related '338 patent, Regeneron's clinician expert, Dr. Do, testified that the standard of care for RVO prior to 2011 was ranibizumab (Lucentis®) or off-label bevacizumab (Avastin®), administered monthly via intravitreal injection. (Ex.1062, ¶¶68, 72-73; Ex.1086, 17:6-25, 150:2-151:18; *see also* IPR2021-00881, Paper 41, 1-2, 4, 12-13). Regeneron made similar arguments to overcome double patenting rejections during prosecution of each of the related '338 and '069 patents. (Ex.1017, 338-39 (9/11/2015 Amendment); Ex.1016, 109-10 (1/30/2017 Amendment)). Furthermore, the '205 patent specification makes clear that the purported invention was *extended* (i.e., 8 weeks or more) dosing regimens, and expressly distinguishes those from *prior art monthly dosing*. (Ex.1001, 1:57-60; *see also id.*, 2:24-30 ("prior administration regimens for angiogenic eye disorders... require monthly administrations throughout the entire course of treatment.")). As a result, it would have been obvious to a POSA

to treat RVO by administering aflibercept according to the once-monthly standard of care. Accordingly, Claim 1 is obvious in view of each of the anticipatory references on their own.

The claimed volume and formulation. By July 12, 2013, a POSA would have been aware that 2 mg of VEGF Trap-Eye, by then commercially available as Eylea®, was formulated with pharmaceutically acceptable carriers into a volume of 0.05 ml. (*Supra* §XII.A.2-3; Ex.1010, 6; *see also* Ex.1013, 1-2; Ex.1001, 2:51-52). This also was well-known prior to 2011. (*Supra* §XII.A.2-3; *see also* Ex.1014, 5; Ex.1061, 145). Accordingly, the limitations of Claims 2 and 3 are expressly and inherently disclosed by the use of the term "VEGF Trap-Eye" in the anticipatory references. In addition, Claims 2 and 3 would have been obvious over the anticipatory references in view of the disclosures of 0.05 ml of aflibercept in a pharmaceutical formulation with a pharmaceutically acceptable carrier in each of Sophie and/or NCT-795, and in light of the knowledge, understandings, and skill of the person of ordinary skill at the relevant time.

Moreover, as discussed above in Section XII.A.2., Patent Owner concedes in the specification that pharmaceutically acceptable carriers were, and had been for decades, well-known in the art. (Ex.1001, 5:41-5:59, 5:66-6:38). The Claim 3 limitation thus merely recites what was well-known in the art, a fact conceded by Regeneron in the intrinsic record, rendering it devoid of patentable weight and

insufficient to distinguish Claim 3 from the prior art. *Ex Parte Turnpaugh*, 2008 WL 4325212, at *7. Even if given patentable weight, the limitation is found in the prior art, including in Sophie and the Eylea label.[17] (Ex.1010, 6; Ex.1013, 1-2).

Motivation. Prior to January 13, 2011, the earliest possible priority date of Claim 1, the prior art provided an abundance of disclosures providing for monthly administration of anti-VEGF agents, including aflibercept, for the treatment of angiogenic eye disorders. (Ex.1028, 1; Ex.1002 ¶¶ 147, 154, 161). Treatment of RVO with VEGF Trap-Eye (i.e., aflibercept) would have been obvious, given the POSA's knowledge that "the underlying biology of CRVO is related to edema and the growth of abnormal new blood vessels that are mediated by vascular endothelial growth factor (VEGF)." (Ex.1028, 1). The anticipatory references generally, and Regeneron (30-April-2009) specifically, thus "go beyond just illuminating a known problem; they also expressly propose the claimed solution." *Bayer Healthcare*

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[17] As noted above, even if Regeneron argues for an earlier priority date in an effort to antedate Sophie, a POSA would already have been aware from Regeneron's earlier clinical trial disclosures in NCT-795 that the 2 mg formulation of VEGF Trap-Eye was formulated in a 0.05 ml dose, and would have necessarily included a pharmaceutically acceptable carrier, rendering the claims obvious over each of the RVO references in view of NCT-795. (*See, e.g.*, Ex.1014, 4-7).

Pharms., Inc. v. Watson Pharms., Inc., 713 F.3d 1369, 1375-76 (Fed. Cir. 2013). A POSA also would have been motivated to employ the monthly dosing disclosed in the anticipatory references, including because monthly dosing was widely known and used by practitioners, and widely published as a dosing regimen for aflibercept. (*See infra* §XII.B.3). Further, a POSA would have been motivated to provide and use an intravitreally injectable formulation of aflibercept in a small enough volume (0.05 ml) to accommodate injection into the vitreal space, which was known to be of finite size and not amenable to receiving large volumes of injected medication, and hence was the volume used in previous clinical trials involving intravitreal injections of aflibercept. (Ex.1040, 79; Ex.1010, 6; Ex.1013, 1-2; Ex.1014, 4-7; Ex.1002 ¶¶150-52, 157-59, 164-66). Likewise, a POSA would have been motivated to provide and use intravitreally injectable aflibercept in a formulation with a pharmaceutically acceptable carrier, as had been used in previous clinical trials involving intravitreal injections of aflibercept so as to be non-toxic to patients' eyes. (Ex.1040, 74; Ex.1013, 5-6; Ex.1014, 4-7; Ex.1002 ¶¶150-52, 157-59, 164-66).

Reasonable expectation of success. Although no particular level of efficacy is required under the Challenged Claims (*supra* §IX.B.; IPR2021-00881, Paper 21, 20-23), a POSA would have had a reasonable expectation of success in treating RVO patients monthly with 2 mg of aflibercept, at least based on the successful use of aflibercept in treating other angiogenic eye disorders. (*See* Ex.1006, 1576-77 ("Data

from the Phase II study with VEGF Trap-Eye were positive."); Ex.1020, 45 (phase 2 study of VEGF Trap-Eye in AMD "demonstrates that patients with neovascular AMD achieved and maintained significant improvement in BCVA"); IPR2022-01225, Paper 14, 59 ("[T]he only [CLEAR-IT 2] treatment arms that were successful in maintaining a dry retina were the monthly dosing arms"); Ex.1002, ¶¶148-49, 155-56, 162-63); *Helsinn Healthcare*, 2018 WL 623642, at *6 ("[P]hase 3 studies are expensive and are not undertaken lightly."). Indeed, as Regeneron argues in related IPR proceedings, "[o]nce VEGF Trap was shown to be highly effective (*i.e.*, non-inferior to Lucentis) in wAMD [wet age-related macular degeneration], the POSA would have expected it to also be highly effective for other angiogenic eye disorders." (IPR2022-01225, Paper 14, 27-28). A POSA also would have had a reasonable expectation of success at providing and using a 0.05 ml formulation, including one containing a pharmaceutically acceptable carrier, for the treatment of RVO given the successful completion of several phase 2 and phase 3 clinical trials with the same formulation of aflibercept, and FDA approval of the aflibercept formulation, all well before the earliest possible priority date of claims 2 and 3. (Ex.1010, 6-10; Ex.1013, 5-7; Ex.1014, 4-7; Ex.1002 ¶¶150-52, 157-59, 164-66).

3. Ground 7: The Challenged Claims Are Obvious Over Dixon in Combination with Kreatsoulas, Either Alone or in View of Sophie and/or NCT-795.

Claim 1 is obvious in light of (i) Kreatsoulas' disclosure that monthly

administration of ranibizumab was effective in treating RVO; (ii) Dixon's disclosure that monthly administration of VEGF Trap-Eye was thought to be at least as effective as monthly administration of ranibizumab in treating AMD; and (iii) Dixon's disclosure that VEGF Trap-Eye was in phase 3 clinical trials for the treatment of RVO. A POSA would have been motivated to use monthly administration of VEGF Trap-Eye in treating RVO, and would have had a reasonable expectation of success with such a dosing regimen because VEGF Trap-Eye, like ranibizumab, also had been shown to be effective in treating AMD, and was known to have pharmacokinetic properties as good as, or even better than, ranibizumab.

Kreatsoulas discloses that ranibizumab was effective in treating RVO. As Dr. Yancopoulos, the named inventor of the '205 patent, wrote in 2010, "[r]anibizumab has since been studied in other eye diseases and recently gained approval for retinal vein occlusion." (Ex.1034, 15). Ranibizumab already had been approved for AMD, and had recently gained approval for the treatment of RVO on the basis of phase 3 BRVO and CRUISE trials, each of which investigated the efficacy and safety of ranibizumab in treating macular edema following RVO. (Ex.1037, 814; Ex.1050, 777). In 2009, Kreatsoulas had reported on "positive 6-month results from the phase 3 BRAVO and CRUISE trials." (Ex.1049, 20; *id.*, 21 ("During the first 6-month period, participants received monthly injections of either

0.3 mg or 0.5 mg of ranibizumab (n=265 per study) or monthly sham injections (n=132 per study)."); *see also* Ex.1002, ¶¶94, 168). The results were "improved BCVA from baseline in patients with macular edema due to BRVO compared with sham," and "early and sustained improvement in BCVA through 6 months in patients with macular edema due to CRVO receiving monthly injections of ranibizumab." (Ex.1049, 21; Ex.1002, ¶¶94, 168).

Relatedly, in connection with an IPR proceeding on the related '338 patent, Regeneron's clinician expert, Dr. Do, testified that the standard of care for RVO prior to 2011 was ranibizumab (Lucentis®) or off-label bevacizumab (Avastin®), administered monthly via intravitreal injection. (IPR2021-00881, Paper 41, 1-2, 4, 10-13; Ex.1086, 17:6-25, 150:2-151:18; Ex.1062 ¶¶68, 72-73, Ex.1002,¶¶65, 169). Regeneron made similar arguments to overcome double patenting rejections during prosecution of each of the related '338 and '069 patents. (Ex.1017, 338-39 (9/11/2015 Amendment); Ex.1016, 109-10 (1/30/2017 Amendment)). The '205 patent specification similarly states that "FDA-approved treatments of angiogenic eye disorders such as AMD and CRVO include the administration of an anti-VEGF antibody called ranibizumab (Lucentis®, Genentech, Inc.) on a monthly basis by intravitreal injection." (Ex.1001, 1:57-60; *see also* 2:24-30 ("prior administration regimens for angiogenic eye disorders... require monthly administrations throughout the entire course of treatment."); Ex.1002, ¶169). Accordingly, ranibizumab was

known to effectively treat both AMD and RVO using monthly administration. (Ex.1002, ¶¶168-70).

Dixon discloses that monthly administration of VEGF Trap-Eye was thought to be at least as effective as monthly administration of ranibizumab in treating AMD. VEGF Trap-Eye is, like ranibizumab, a VEGF antagonist. Dixon teaches that VEGF Trap-Eye is an "anti-VEGF therapy, with Phase I and II trial data indicating safety, tolerability and efficacy for the treatment of neovascular AMD." (Ex.1006, 1573; *see also id.*, 1576 (reporting results of phase 2 clinical studies); Ex.1002, ¶¶98-101). Moreover, Dixon discloses that the VIEW1 and VIEW2 phase 3 clinical trials were comparing 2 mg VEGF Trap-Eye administered via monthly intravitreal injections with 0.5 mg ranibizumab, also administered via monthly intravitreal injections, for the treatment of AMD. (*Id.*, 1576; *see also* Ex.1014, 5; Ex.1002, ¶102). Dixon further discloses that additional dosing regimens were also tested in the VIEW1/VIEW2 phase 3 clinical trials, examining less frequent administration of VEGF Trap-Eye with monthly administration of ranibizumab. (Ex.1006, 1576; Ex.1002, ¶102). The setup of the VIEW1/VIEW2 trials reflects the knowledge in the art at the time, also disclosed in Dixon, that VEGF Trap-Eye was known to bind VEGF with higher affinity than antibody fragments such as ranibizumab, and was also predicted to have "longer duration of effect in the eye." (*Id.*, 1577; *see also* Ex.1061, 148-49; Ex.1002, ¶¶99, 171). A POSA would therefore

have understood from Dixon, including its disclosure of the Phase 2 results, that VEGF Trap-Eye was expected to be at least as effective in treating AMD as ranibizumab, and likely to be more effective. (Ex.1002, ¶171).

A POSA would have been motivated to use VEGF Trap-Eye (aflibercept) in treating RVO, and would have expected the method to be successful. As Dixon states, a POSA would have been motivated to use VEGF Trap-Eye for the treatment of RVO, understanding that it "would significantly add to the ophthalmologists' armamentarium for treatment of retinal vascular disease." (Ex.1006, 1577-78; Ex.1002, ¶¶103, 171). Indeed, as Dixon reports, VEGF Trap-Eye was already in phase 3 clinical trials for RVO. (*Id.*). And as Regeneron argues in a related IPR proceeding, "[o]nce VEGF Trap was shown to be highly effective (i.e., non-inferior to Lucentis) in wAMD [wet age-related macular degeneration], the POSA would have expected it to also be highly effective for other angiogenic eye disorders." (IPR2022-01225, Paper 14, 27-28). Regeneron further argues that a POSA would understand VEGF Trap-Eye to be comparably effective to ranibizumab even in the absence of results from direct head-to-head comparisons in noninferiority trials such as VIEW 1 and VIEW 2. (*Id.*, 28). And indeed, based on its reported potency and longer half-life, a POSA would have expected VEGF Trap-Eye to be at least as effective, if not more so, than ranibizumab in treating angiogenic eye disorders, including RVO. (Ex.1006, 1577; Ex.1061, 148-49; Ex.1002, ¶171). Accordingly, a

POSA would have been motivated to use VEGF Trap-Eye in the treatment of RVO. While the claims do not require any specific degree of efficacy, a POSA would have expected a degree of success in treating RVO given the success demonstrated in both AMD and RVO with ranibizumab, and the success in treating AMD with VEGF Trap-Eye. (Ex.1002, ¶¶167-73). Furthermore, a POSA would have had a reasonable expectation of success at using a 2 mg formulation of aflibercept given that this same dose was the one shown to be safe and effective in treating AMD. (Ex.1006, 1576-77; Ex.1002, ¶172). A POSA would therefore have been motivated to use the 2 mg dose of VEGF Trap-Eye already shown to be safe and effective in AMD clinical trials, and would have expected the 2 mg dose of VEGF Trap-Eye to be similarly successful in treating RVO. (Ex.1002, ¶¶172-73).

A POSA would have been motivated to use monthly intravitreal injections of VEGF Trap-Eye (aflibercept) in treating RVO, and would have expected the monthly dosing regimen to be successful. As Regeneron argues in related IPR proceedings, monthly administration of a VEGF antagonist via intravitreal injection was the prior art standard of care for angiogenic eye disorders, including RVO. (IPR2021-00881, Paper 41, 7, 10-12; *see also* Ex.1062 ¶¶68, 72-73; Ex.1086, 17:6-25, 150:2-151:18; Ex.1002, ¶¶61-65, 169). Regeneron made similar arguments to overcome double patenting rejections during prosecution of each of the related '338 and '069 patents, and concedes as much in the '205 specification. (Ex.1017, 338-39

(9/11/2015 Amendment); Ex.1016, 109-10 (1/30/2017 Amendment); Ex.1001, 1:57-60; *see also* Ex.1001, 2:24-30 ("prior administration regimens for angiogenic eye disorders...require monthly administrations throughout the entire course of treatment"); Ex.1002, ¶169). And indeed Kreatsoulas disclosed that this "standard of care," monthly administration of ranibizumab via intravitreal injection, was effective in treating RVO. (Ex.1049, 20-21; Ex.1002, ¶¶94, 168-70). Dixon also discloses that patients treated with four monthly loading doses of VEGF Trap-Eye (2.0 mg) followed by PRN dosing exhibited mean improvement in visual acuity of nine (9.0) ETDRS letters and a mean decrease in retinal thickness of 143 μm. (Ex.1006, 1576; Ex.1002, ¶¶100-01, 171-73). A POSA therefore would have been motivated to use monthly administration of VEGF Trap-Eye via intravitreal injections (which would have resulted in *more* VEGF Trap-Eye being administered than even under the CLEAR-IT-2 PRN dosing scheme), in accordance with the once-monthly standard of care at the time. (Ex.1002, ¶¶169-73). And given the knowledge in the art that VEGF Trap-Eye binds VEGF with higher affinity than antibody fragments such as ranibizumab, and was also predicted to have "longer duration of effect in the eye," a POSA would have reasonably expected monthly intravitreal injections of VEGF Trap-Eye to be successful in treating RVO. (Ex.1006, 1577; *see also* Ex.1061, 148-49; Ex.1002, ¶¶169-73).

Claim 2: volume of 0.05 ml. The priority date of Claim 2 is no earlier than

July 12, 2013. (*See supra* §VI.B.). By this date, it was publicly known that VEGF Trap-Eye/aflibercept was formulated at a concentration of 2 mg per 0.05 ml. (*See, e.g.*, Ex.1014, 5; Ex.1010, 6; *see also* Ex.1013, 1-2; Ex.1001, 2:51-52 ("Aflibercept (EYLEA™, Regeneron Pharmaceuticals, Inc) was approved by the FDA in November 2011"); Ex.1021, 18-19 ("VEGF Trap-Eye is a specially purified and ***formulated*** form of VEGF Trap") (emphasis added); Ex.1002, ¶176).

However, assuming Regeneron argues for a 2011 priority date, it was known prior to 2011 that the 2 mg dose of VEGF Trap-Eye and the 0.5 mg dose of ranibizumab were both administered in a volume of 0.05 ml when compared against one another in the VIEW1 phase 3 clinical trial (Ex.1006, 1576; Ex.1014, 5, Ex.1002, ¶¶87, 177). It would therefore have been obvious to a POSA to administer the same 0.05 ml formulation of VEGF Trap-Eye for the treatment of RVO. A POSA would have been motivated to use, and would have expected a dose of 2 mg VEGF Trap-Eye in a volume of 0.05 ml to be technically feasible (i.e., successful), based on the disclosure of such a dose in such a volume in NCT-795. (Ex.1002, ¶¶176-79). A POSA would have been motivated not to exceed this amount because it was known in the art that the risk of complications rose with increasing volumes of intravitreal injections. (Ex.1040, 79).

Claim 3: pharmaceutical formulation comprising a pharmaceutically acceptable carrier. The priority date of Claim 3 is no earlier than July 12, 2013.

(*See supra* §VI.B.). By this date, it was publicly known that VEGF Trap-Eye had been approved by the FDA and that "[a]flibercept (VEGF Trap-Eye) is available as a preservative-free, sterile, aqueous solution in a single-use, glass vial designed to deliver 0.05 mL VEGF Trap (40 mg/mL in 10 mM sodium phosphate, 40 mM sodium chloride, 0.03% polysorbate 20, and 5% sucrose, pH 6.2)." (Ex.1010, 6; Ex.1013, 5; Ex.1001, 2:51-52 ("Aflibercept (EYLEA™, Regeneron Pharmaceuticals, Inc) was approved by the FDA in November 2011"); Ex.1021, 19 ("VEGF Trap-Eye is a specially purified and ***formulated*** form of VEGF Trap") (emphasis added)).

In addition, prior to 2011, NCT-795 discloses administration of VEGF Trap-Eye via intravitreal injection, and therefore would have been understood by a skilled artisan to inherently disclose that aflibercept, the active ingredient of VEGF Trap-Eye, is in a pharmaceutical formulation comprising a pharmaceutically acceptable carrier. (Ex.1002 ¶¶176-79; *see also* Ex.1033, [0003], [0007], [0014]).

Furthermore, Regeneron concedes in the specification in its discussion of the term pharmaceutically acceptable carrier that "[a] multitude of appropriate formulations can be found in the formulary known to all pharmaceutical chemists," citing to a 1975 version of Remington's Pharmaceutical Sciences. (Ex.1001, 5:55-59). Regeneron continues, explaining that a formulation is suitable "provided that the VEGF antagonist is not inactivated by the formulation and the formulation is

physiologically compatible and tolerable with the route of administration." (*Id.*, 5:66-6:3). Regeneron then cites a 1998 reference, Powell et al., from the Journal of Pharmaceutical Science Technology, "and the citations therein for additional information related to excipients and carriers *well-known to pharmaceutical chemists*." (*Id*., 6:3-7 (emphasis added)). The limitation of Claim 3 thus merely recites what was well-known in the art long before the '205 patent, a fact that Regeneron concedes to in the intrinsic record. Therefore, this additional limitation is not entitled to patentable weight and is not sufficient to distinguish the claim from the prior art. *Ex Parte Turnpaugh*, 2008 WL 4325212, at *7 ("The arguments furnished are not persuasive of the separate patentability of claim 2 because, as correctly noted by the Examiner, visible laser lights would have been a well known option for the focused light source of [another prior art reference].").

4. No secondary considerations.

Petitioner is not aware of any secondary considerations (or the requisite nexus) that would support a finding of non-obviousness. Even if there were, they would be irrelevant to the anticipation grounds presented in Grounds 1-3, and could not overcome the strong *prima facie* case of obviousness presented in Grounds 4-7. *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010).

No Unexpected Results. The Challenged Claims do not require any particular levels of efficacy. (*See, e.g.*, IPR2021-00881, Paper 21, 21-23, 31-32). Further,

Petitioner is not aware of any claim to unexpected results that would render the claims nonobvious, none having been presented during prosecution, and there was nothing unexpected about the claimed dosing regimen itself, which had already been disclosed in the prior art.

No Long-Felt, Unmet Need. Regeneron cannot establish a "need" or show that any such need was "long-felt." Regeneron disclosed the claimed dosing regimen to the general public in the prior art. (*See, e.g.*, *supra* §XII.A; Ex.1002, ¶¶180-81).

No Nexus. Regeneron cannot establish a nexus of any purported commercial success to the Challenged Claims. (Ex.1002, ¶182). Regeneron already has argued that EYLEA's purported commercial success is attributable to "extended" dosing regimens, like those claimed in the '338 patent. (IPR2021-00881, Paper 41, 61-62). Consequently, Petitioner is not aware of any evidence tying any secondary consideration to the claimed monthly dosing regimen for RVO. Petitioner reserves the right to more specifically respond to any assertions of secondary considerations that Regeneron alleges during this proceeding.

XIII. CONCLUSION.

The Challenged Claims are unpatentable in view of the Grounds asserted herein. Petitioner requests that trial be instituted and the Challenged Claims cancelled.

Dated: October 28, 2022

Respectfully Submitted,

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that a true and correct copy of the foregoing Petitioner Mylan Pharmaceuticals Inc.'s Petition for *Inter Partes* Review of U.S. Patent No. 10,857,205 B2 and Exhibits 1001-1089 were served on October 28, 2022, via FedEx Priority Overnight on the Patent Owner at the correspondence address of record for U.S. Patent No. 10,857,205 B2 as evidenced in Patent Center:

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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that this Petition complies with the type-volume limitation of 37 C.F.R. § 42.24(a). The word count application of the word processing program used to prepare this Petition indicates that the Petition contains 13,939 words. This total does not include the tables of contents and authorities, mandatory notices, the caption page, table of exhibits, certificate of service, or this certificate of word count. 37 C.F.R. § 42.24(a).

Dated: October 28, 2022

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