UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.,
Petitioner

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner

Case IPR2021-00881
Patent No. 9,254,338 B2

PRELIMINARY RESPONSE OF PATENT OWNER REGENERON PHARMACEUTICALS, INC.

TABLE OF CONTENTS

Page No.

I. INTRODUCTION 1

II. THE PETITION SHOULD BE REJECTED FOR CIRCUMVENTING THE WORD LIMIT AND OBFUSCATING ITS GROUNDS 4

A. The Petition Violates the Word Limit 4

B. The Petition Fails the Particularity Requirement 5

C. Janssen Pharmaceuticals, Inc. Is a Real Party-in-Interest 8

III. THE BOARD SHOULD DENY INSTITUTION UNDER 35 U.S.C. § 325(d) 9

A. Petitioner Mischaracterizes the Prosecution History of the '338 Patent and its Foreign Counterpart 9

B. Because the Examiner Considered Substantially the Same Art and Petitioner Does Not Allege Any Error, Institution Should Be Denied 11

1. The Examiner Considered Substantially the Same Art (*Becton*, *Dickinson* Factors (a), (b), and (d)) 11

a. Grounds 1-5 12

b. Ground 6 14

2. Petitioner Fails to Argue that the Examiner Erred in a Manner Material to Patentability (*Becton*, *Dickinson* Factors (c), (e), and (f)) 16

IV. THE BOARD SHOULD DENY INSTITUTION BECAUSE PETITIONER FAILS TO MAKE ITS THRESHOLD SHOWING THAT AT LEAST ONE CHALLENGED CLAIM IS UNPATENTABLE 17

A. Grounds 1, 3-5: Petitioner Fails to Demonstrate that "VEGF Trap-Eye" Was Known in the Art to Correspond to SEQ ID NO: 2 or SEQ ID NO:1 18

1. Petitioner Fails to Establish that "VEGF Trap-Eye" Was Known in the Art to Comprise SEQ ID NO: 2 (Claims 1, 3-11, and 13) 18

a. Petitioner and Its Expert Repeatedly Equate "Aflibercept" with All Variations of "VEGF Trap" 21

b. Petitioner Fails to Address Uncertainty in the Art as to the Amino Acid Sequence of "VEGF Trap-Eye" 24

2. Petitioner Fails to Establish that "VEGF Trap-Eye" Was Known in the Art to Be Encoded by SEQ ID NO:1 26

B. Ground 2: Petitioner Fails to Demonstrate that There Is a Reasonable Likelihood that at Least One of the Challenged Clams Is Anticipated by Adis 28

C. Grounds 1-5: Petitioner Fails to Establish Any of Its References Disclose a "Method of Treating" and "Tertiary Dose" 30

1. Claim Construction 31

a. The Preamble of the Independent Claims Is a Limitation of the Claim 32

b. The Preamble Reflects the Efficacy Required by the Body of the Claim 36

c. The "Tertiary Dose" Must Maintain the Efficacy Gain Achieved After the Initial and Secondary Doses 38

2. Petitioner's References Fail To Disclose A "Method Of Treating" Or A "Tertiary Dose" 46

D. Ground 6: Petitioner Fails to Make a Threshold Showing that Any Challenged Claim Is Obvious Based on Dixon 49

1. Petitioner Fails to Show that the POSA Would Have Had a Reasonable Expectation of Success 50

2. Petitioner's Argument Against Objective Evidence Should Be Rejected 57

V. CONCLUSION 62

TABLE OF AUTHORITIES

Page(s)

Cases

Abraxis Bioscience, Inc. v. Mayne Pharma (USA) Inc.,
467 F.3d 1370 (Fed. Cir. 2006) 39

ABS Global, Inc. v. Cytonome/ST, LLC,
IPR2021-00306, Paper 13 (Jun. 7, 2021) 16

Adaptics Ltd. v. Perfect Co.,
IPR2018-01596, Paper 20 (Mar. 6, 2019) 5, 6

Advanced Bionics, LLC v. MED-EL Elektromedizinische Gerate GmbH,
IPR2019-01469, 2020 WL 740292 (Feb. 13, 2020) 11, 16

Amgen, Inc. v. Alexion Pharms., Inc.,
IPR2019-00739, Paper 15 (Aug. 30, 2019) 28

Apple, Inc. v. ITC,
725 F.3d 1356 (Fed. Cir. 2013) 57

Arthrex, Inc. v. Smith & Nephew, Inc.,
935 F.3d 1319 (Fed. Cir. 2019), cert. denied, 141 S. Ct. 236 (2020) 47

Baldwin Graphic Sys., Inc. v. Siebert, Inc.,
512 F.3d 1338 (Fed. Cir. 2008) 35

Baxalta Inc. v. Genentech, Inc.,
972 F.3d 1341 (Fed. Cir. 2020) 42

Becton, Dickinson & Co. v. B. Braun Melsungen AG,
IPR2017-01586, Paper 8 (Dec. 15, 2017) 11

Bettcher Indus., Inc. v. Bunzl USA, Inc.,
661 F.3d 629 (Fed. Cir. 2011) 47

Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.,
320 F.3d 1339 (Fed. Cir. 2003) 34

Boragen, Inc. v. Syngenta Participations AG,
IPR2020-00124, 2020 WL 2206972 (May 5, 2020) 15

Bristol-Myers Squibb Co. v. Ben Venue Lab'ys, Inc.,
246 F.3d 1368 (Fed. Cir. 2001) 43, 44

C.R. Bard, Inc. v. U.S. Surgical Corp.,
388 F.3d 858 (Fed. Cir. 2004) 33

Continental Can Co. USA v. Monsanto Co.,
948 F.2d 1264 (Fed. Cir. 1991) 21

Dynatemp Int'l, Inc. v. R 421A LLC d/b/a Choice Refrigerants,
IPR2020-01660, Paper 15 (Apr. 20, 2021) 17

E.I. Du Pont de Nemours & Co. v. Monsanto Tech. LLC,
IPR2014-00333, 2014 WL 3507803 (July 11, 2014) 34

Eon-Net LP v. Flagstar Bancorp,
653 F.3d 1314 (Fed. Cir. 2011) 33

Forest Lab'ys, LLC v. Sigmapharm Lab'ys, LLC,
918 F.3d 928 (Fed. Cir. 2019) 33

Gardner Denver, Inc. v. Utex Indus., Inc.,
IPR2020-00333, 2020 WL 4529832 (Aug. 5, 2020) 13

Gilead Scis, Inc. v. United States,
IPR2019-01455, Paper 16 (Feb. 5, 2020) 35, 37, 44, 48

Griffin v. Bertina,
285 F.3d 1029 (Fed. Cir. 2002) 32

Hill-Rom Co. v. Kinetic Concepts, Inc.,
209 F.3d 1337 (Fed. Cir. 2000) 34

In Re: Copaxone Consol. Cases,
906 F.3d 1013 (Fed. Cir. 2018) 44

Insite Vision Inc. v. Sandoz, Inc.,
783 F.3d 853 (Fed. Cir. 2015) 51

Irdeto Access, Inc. v. Echostar Satellite Corp.,
383 F.3d 1295 (Fed. Cir. 2004) 38

Janssen Pharms., Inc. v. Watson Lab'ys, Inc.,
C.A. No. 08-5103(SRC), 2012 WL 3990221 (D.N.J. Sept. 11, 2012) 29

King Pharms. Inc. v. Eon Labs, Inc.,
616 F.3d 1267 (Fed. Cir. 2010) 18

Medicines Company v. Mylan, Inc.,
853 F.3d 1296 (Fed. Cir. 2017) 41, 42

Mylan Lab'ys Ltd. v. Aventis Pharma S.A.,
No. IPR2016-00712, Paper 112 (P.T.A.B. Sept. 22, 2016) 44

MyMail, Ltd. v. Am. Online, Inc.,
476 F.3d 1372 (Fed. Cir. 2007) 38

Net MoneyIN, Inc. v. VeriSign, Inc.,
545 F.3d 1359 (Fed. Cir. 2008) 28

Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.,
868 F.3d 1013 (Fed. Cir. 2017) 32

NXP USA, Inc. v. Impinj, Inc.,
IPR2020-00519, 2020 WL 4805424 (Aug. 17, 2020)..... 13, 14, 15

OSI Pharms. LLC v. Apotex Inc.,
939 F.3d 1375 (Fed. Cir. 2019) 52

Otsuka Pharm. Co. v. Sandoz, Inc.,
678 F.3d 1280 (Fed. Cir. 2012) 51

Phillips v. AWH Corp.,
415 F.3d 1303 (Fed. Cir. 2005) 38

Pi-Net Int'l, Inc. v. JPMorgan Chase & Co.,
600 F. App'x 774 (Fed. Cir. 2015) 5

Pitney Bowes, Inc. v. Hewlett-Packard Co.,
182 F.3d 1298 (Fed. Cir. 1999) 37

Rapoport v. Dement,
254 F.3d 1053 (Fed. Cir. 2001) 35

Regents of Univ. of Minn. v. AGA Med. Corp.,
717 F. 3d 929 (Fed. Cir. 2013) 33

Sanofi Mature IP v. Mylan Lab'ys Ltd.,
757 F. App'x 988 (Fed. Cir. 2019) 35

Schering Corp. v. Amgen Inc.,
222 F.3d 1347 (Fed. Cir. 2000) 24

Sensonics, Inc. v. Aerosonic Corp.,
81 F.3d 1566 (Fed. Cir. 1996) 51

Sony Interactive Ent. LLC v. Terminal Reality, Inc.,
IPR2020-00711, 2020 WL 6065188 (Oct. 13, 2020).....17

Transclean Corp. v. Bridgewood Servs., Inc.,
290 F.3d 1364 (Fed.Cir.2002) 48

UltimatePointer, L.L.C. v. Nintendo Co.,
816 F.3d 816 (Fed. Cir. 2016) 34

Statutes

35 U.S.C. § 312(A)(3)..... 2, 5, 6

35 U.S.C. § 314(a) 3, 8, 17

35 U.S.C. §§ 325(d) 3, 9, 11, 17

Other Authorities

77 Fed. Reg. 48756 (August 14, 2012).....6

77 Fed. Reg. 48763 (August 14, 2012).....6, 7

MPEP § 2173.05(e).....39

Regulations

37 C.F.R. § 42.24(a)(1)(i)).....4

TABLE OF EXHIBITS

Ex. No.	Description
2001	Expert Declaration of Dr. Diana V. Do, M.D.
2002	Curriculum Vitae of Dr. Diana Do
2003	Lucentis (ranibzumab injection) label, revised June 2010
2004	Ex. (a)(1)(a) to Tender Offer Statement to Momenta, filed with SEC on September 2, 2020
2005	Press Release, Johnson & Johnson, *Johnson & Johnson to Acquire Momenta Pharmaceuticals, Inc., Expanding Janssen's Leadership in Novel Treatments for Autoimmune Diseases*, dated August 19, 2020
2006	Press Release, Johnson & Johnson, *Johnson & Johnson Completes Acquisition of Momenta Pharmaceuticals, Inc*, dated October 1, 2020
2007	Press Release, THOMAS REUTERS INTEGRITY "VEGF Trap-Eye final phase II results in age-related macular degeneration presented at 2008 Retina Society Meeting" (September 2008)
2008	Information from ClinicalTrials.gov archive on the VIEW 2 study (NCT00637377) "VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW 2)" versions available and updated on 17 March 2008.
2009	U.S. Patent App. No. 2006/0058234
2010	Excerpts from J.M. Berg *et al*., Biochemistry (5th Ed. 2002)
2011	M.W. Stewart & P.J. Rosenfeld, *Predicted Biological Activity of Intravitreal VEGF Trap*¸ Br. J. Opthamol 92:667-68 (2008)
2012	P. Iacono *et al*., *Antivascular Endothelial Growth Factor in Diabetic Retinopathy*, Dev. Opthamol. 46:39-53 (2010)
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2017	M. Piques et al., *Ribosome and transcript copy numbers, polysome occupancy and enzyme dynamics in Arabidoposis*, Molecular Systems Biology 5: Article number 314 (2009)
2018	Jaffe et al., *Differential Response to Anti-VEGF Regimens in Age-Related Macular Degeneration Patients with Early Persistent Retinal Fluid*, Ophthalmology 2016;123:1856-1864 (2016)
2019	Eylea (aflibercept) Injection label, revised May 2016
2020	A Study Investigating the Safety and Efficacy of Lampalizumab Intravitreal Injections in Participants With Geographic Atrophy Secondary to Age-Related Macular Degeneration (SPECTRI), NCT02247531, ClinicalTrials.gov (August 2, 2021), https://clinicaltrials.gov/ct2/show/NCT02247531?term=lampalizumab&phase=2&draw=2&rank=2
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2022	Efficacy and Safety Trial of Conbercept Intravitreal Injection for Neovascular AMD(PANDA-2), NCT03630952, ClinicalTrials.gov (August 2, 2021), https://clinicaltrials.gov/ct2/show/NCT03630952?term=NCT03630952&draw=2&rank=1
2023	Efficacy and Safety Trial of Conbercept Intravitreal Injection for Neovascular AMD(PANDA-1), NCT03577899, ClinicalTrials.gov (August 2, 2021), https://clinicaltrials.gov/ct2/show/NCT03577899?term=NCT03577899&draw=2&rank=1
2024	A Phase 3 Safety and Efficacy Study of Fovista® (E10030) Intravitreous Administration in Combination With Lucentis® Compared to Lucentis® Monotherapy, NCT01944839, ClinicalTrials.gov (August 2, 2021), https://clinicaltrials.gov/ct2/show/NCT01944839?term=fovista&phase=2&draw=2&rank=1

2025	A Phase 3 Safety and Efficacy Study of Fovista® (E10030) Intravitreous Administration in Combination With Lucentis® Compared to Lucentis® Monotherapy, ClinicalTrials.gov (August 2, 2021), https://clinicaltrials.gov/ct2/show/NCT01940900?term=fovista&phase=2&draw=2&rank=2
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2029	Bhisitkul, Robert B. and Stewart, Jay M., *Alternative anti-VEGF treatment regimens in exudative age-related macular degeneration*, Expert Rev. Ophthalmol., Vol. 5, No. 6 (2010).
2030	Park, Young Gun et al., *New Approach to Anti-VEGF Agents for Age-Related Macular Degeneration*, Journal of Ophthalmology (2012).
2031	Spaide, Richard, *Ranibizumab According to Need: A Treatment for Age-related Macular Degeneration*, American Journal of Ophthalmology (April 2007)
2032	Boyer, David S., *A Phase IIIb Study to Evaluate the Safety of Ranibizumab in Subjects with Neovascular Age-related Macular Degeneration*, Ophthalmology, Vol. 116, No. 9 (Sept. 2009)
2033	Lucentis (ranibzumab injection) label, revised March 2018
2034	U.S. Patent No. 7,303,746
2035	U.S. Patent No. 7,521,049
2036	U.S. Patent No. 7,303,747
2037	U.S. Patent No. 7,306,799
2038	Macugen (pegaptanib sodium injection) label submitted with NDA 21-756
2039	Press Release, *Regeneron*, *Regeneron Reports Fourth Quarter and Full Year 2012 Financial and Operating Results*, dated February 14, 2013
2040	Press Release, *Regeneron*, *Regeneron Reports Fourth Quarter and Full Year 2019 Financial and Operating Results*, dated February 6, 2030

2041	Press Release, Regeneron, *Regeneron and Bayer Report Positive Results for VEGF Trap-Eye in Phase 3 Study in Central Retinal Vein Occlusion (CRVO) and in Phase 2 Study in Diabetic Macular Edema (DME)*, dated December 20, 2010
2042	J.P. Levine *et al.*, *Macular Hemorrhage in Neovascular Age-related Macular Degeneration After Stabilization With Antiangiogenic Therapy*, Retina 29(8):1074-79 (2009)

Regeneron Pharmaceuticals, Inc. ("Patent Owner" or "Regeneron") submits this preliminary response pursuant to 35 U.S.C. § 313 and 37 C.F.R. § 42.107 to Mylan Pharmaceuticals Inc.'s ("Petitioner's" or "MPI's") request for *inter partes* review ("IPR") of claims 1, 3-11, 13-14, 16-24 and 26 ("the Challenged Claims") of U.S. Patent No. 9,254,338 ("the '338 Patent," Ex. 1001).

I. INTRODUCTION

Petitioner is developing a biosimilar of EYLEA® and files this challenge to invalidate Regeneron's '338 Patent, which covers the FDA-recommended dosing regimen for EYLEA®. Petitioner's challenge relies entirely on references disclosing the design of Regeneron's Phase 3 trials. But Petitioner fundamentally ignores that there existed great uncertainty as to whether an extended, fixed dosing regimen (Q8) would work until Regeneron's Phase 3 clinical trial results showed that it could. Petitioner also ignores that this same prospective dosing regimen was before the Examiner during prosecution of the '338 Patent.

Before EYLEA®, the standard of care for treating angiogenic eye disorders was monthly intravitreal injections of ranibizumab (Lucentis®), an antibody fragment that binds Vascular Endothelial Growth Factor ("VEGF"), or monthly off-label use of bevacizumab (Avastin®), an anti-VEGF antibody. The great burden of monthly intravitreal injections led to several attempts to decrease the frequency of injections and physician monitoring. Ex. 1018, 1, and 9-10. However, existing VEGF inhibitors were ineffective at maintaining vision when

dosed on a fixed quarterly basis or on an "as-needed" (*pro re nata*) basis without monthly monitoring visits. Ex. 1018, 10; Ex. 1001, 1:55-59; Ex. 2003, 5. Indeed, before the results of Regeneron's pivotal Phase 3 trials, no one had demonstrated that a longer-than-monthly fixed dosing regimen (*e.g.*, eight weeks or longer) could maintain, let alone improve, vision.

Regeneron's Phase 3 clinical trial results surprisingly demonstrated that "remarkably similar improvement in vision and anatomic measures can be achieved" with less frequent EYLEA® dosing as compared to monthly ranibizumab injections. Ex. 1018, 10. Having secured the data necessary to support the eight-week extended dosing regimen of the instant claims, Regeneron obtained FDA approval for EYLEA® and was awarded the '338 Patent covering its recommended dosing regimen. EYLEA®'s duration and ability to extend the time between injections has made it a life-changing drug and revolutionized the treatment of angiogenic eye disorders. Given the long-felt need and repeated failures of others to reduce treatment burden and injection frequency, EYLEA® has enjoyed great commercial success.

The Petition should be denied for at least the following reasons:

First, Petitioner flouts the Board's rules by circumventing word count limits and also by disregarding the particularity requirement of 35 U.S.C. § 312(A)(3), presenting "catch-all" obviousness arguments that do not differentiate between seven references and fifteen obviousness theories.

Second, Petitioner's challenges rely on substantially the same art that was previously before the U.S. Patent & Trademark Office ("Office") and considered by the Examiner, yet Petitioner does not allege that the Examiner erred in a manner material to the patentability of the Challenged Claims, warranting discretionary denial under 35 U.S.C. §§ 325(d) and 314(a).

Third, Petitioner fails to demonstrate that its cited references expressly or inherently disclose the amino acid or nucleic acid sequence limitations of the Challenged Claims. Petitioner argues that its cited art inherently discloses aflibercept and its amino acid and nucleic acid sequences through reference to "VEGF Trap-Eye." But Petitioner relies on inference to connect "VEGF Trap-Eye" and "aflibercept" that the prior art does not support, and the Federal Circuit has repeatedly held that probabilities are insufficient for anticipation.

Fourth, Petitioner's anticipation challenges also rely on an erroneous claim construction that seeks to eliminate the efficacy requirements of the Challenged Claims and Petitioner never shows that the "method of treating" and "tertiary dose" limitations, which require efficacy, are disclosed either expressly or inherently in its cited references.

Fifth, Petitioner relies on Regeneron's Phase 2 clinical trial results for its obviousness challenge. But that trial tested a different dosing regimen from that claimed in the '338 Patent and failed to provide the skilled artisan with ***any*** expectation of success — let alone a reasonable one — in practicing the claimed

inventions. In fact, those clinical trial results showed just the opposite —that it was not expected that VEGF Trap-Eye would be effective if dosed at eight-week intervals. Petitioner also ignores that before the priority date, no one, including Regeneron, had ever shown that a fixed eight-week (or longer) dosing regimen could maintain, let alone improve, vision.

II. THE PETITION SHOULD BE REJECTED FOR CIRCUMVENTING THE WORD LIMIT AND OBFUSCATING ITS GROUNDS

A. The Petition Violates the Word Limit

The Petition exceeds the 14,000-word limit (37 C.F.R. § 42.24(a)(1)(i)). Despite certifying that the word count for its petition is 13,904 words (Pet., Cert. of Compliance), the Petition's word count includes only the typed words of the Petition. The word count ignores words in images of text from the '338 Patent specification, including a lengthy passage of text on which Petitioner substantively relies for its arguments. *See e.g.*, Pet., 12; *see also* Pet., 9, 29. In total, Petitioner fails to account for 224 words in text images in the Petition which, when included, results in a word count of 14,128 words. Petitioner, thus, disregards the Board's rules, as evidenced by Petitioner's use of the same tactic in its Petition filed in IPR2021-00880. Paper 1. This is a reason to deny institution. Trial Practice Guide (November 2019) at 40 ("Excessive words in figures, drawings, or images, deleting spacing between words, or using excessive acronyms or abbreviations for word phrases, in order to circumvent the rules on

word count, may lead to a party's brief not being considered."); *see Pi-Net Int'l, Inc. v. JPMorgan Chase & Co.*, 600 F. App'x 774 (Fed. Cir. 2015) (denying request to file a corrected brief and dismissing appeal because appellant violated word count).

The proper remedy here is to deny institution, thereby allowing Petitioner to refile a petition that properly conforms with the Board's word count rules. No time bar precludes Petitioner from refiling a petition challenging the '338 Patent.

B. The Petition Fails the Particularity Requirement

Despite exceeding the allowed word count, Petitioner still has not managed to state, with particularity, the grounds on which the challenge to each claim is based. Accordingly, the Petition presents an inefficient use of the Board's time and resources, as well as procedural unfairness to Regeneron.

A petition "may be considered only if . . . the petition identifies, in writing and with particularity, each claim challenged, the grounds on which the challenge to each claim is based, and the evidence that supports the grounds for the challenge to each claim." 35 U.S.C. § 312(a)(3); *see also Adaptics Ltd. v. Perfect Co.*, IPR2018-01596, Paper 20 at 15-24 (Mar. 6, 2019) (informative). "[T]he Board may consider whether a lack of particularity as to one or more of the asserted grounds justifies denial of an entire petition." *Id.* at 17. Furthermore, the Office Patent Trial Practice Guide advises practitioners to "focus on concise, well-organized, easy-to-follow arguments supported by readily identifiable evidence of

record." 77 Fed. Reg. 48756, 48763 (August 14, 2012).

Here, Petitioner does not satisfy the particularity requirements under § 312(a)(3) for at least Ground 6 because the Petition suffers from the same deficiencies identified by the Board in *Adaptics*. Specifically, Ground 6 is a "catch-all" ground that alleges that the Challenged Claims are obvious over seven references under fifteen different theories:

1. Dixon;
2. Dixon + the '758 Patent;
3. Dixon + Dix;
4. Adis;
5. Adis + the '758 Patent;
6. Adis + Dix;
7. Regeneron (8-May-2008);
8. Regeneron (8-May-2008) + the '758 Patent;
9. Regeneron (8-May-2008) + Dix;
10. NCT-795;
11. NCT-795 + the '758 Patent;
12. NCT-795 + Dix;
13. NCT-377;
14. NCT-377 + the '758 Patent;

15.NCT-377 + Dix.

See Pet., 62.

Petitioner asserts that five references (Dixon, Adis, Regeneron (8-May-2008), NCT-795, and NCT-377) are interchangeable. Id. at 62 n.12. Petitioner does not explain why all five are necessary for this obviousness ground, nor how each combination differs from the others. Rather, these five references are cited for the disclosure of the same alleged feature. This is at odds with the Office's direction to "avoid submitting a repository of all the information that a judge could possibly consider," and inundates the Board with excessive references for its consideration. 77 Fed. Reg. at 48763.

Furthermore, Petitioner only addresses Dixon in Ground 6 and relegates the other four primary references and fifteen different obviousness theories to a footnote. Pet., 62 n.12. This leaves the Board and Regeneron to fill in the gaps of the Petition. Regeneron is at an unfair disadvantage of having to guess which theories Petitioner will pursue, what evidence allegedly supports those theories, and what purported motivations and reasonable expectation of success Petitioner might advance were trial instituted.

As each theory constitutes a distinct ground, Petitioner impermissibly shifts the burden to the Board and Regeneron to understand the multiplicity of obviousness grounds presented. For at least the reasons above, Regeneron respectfully requests denial of the petition under 35 U.S.C. § 314(a).

C. Janssen Pharmaceuticals, Inc. Is a Real Party-in-Interest

Petitioner also fails to identify the correct RPIs in its Petition. Petitioner identifies Viatris Inc., Mylan Inc., Mylan Pharmaceuticals Inc., Momenta Pharmaceuticals, Inc., and Johnson & Johnson as real parties-in-interest to the instant Petition. Pet., 4. Petitioner states "[n]o other parties exercised or could have exercised control over this Petition; no other parties funded, directed and controlled this Petition." *Id.* However, Regeneron understands from publicly available documents that Janssen Pharmaceuticals, Inc. ("Janssen") is a real party-in-interest for the same reasons Mylan disclosed these other entities. Multiple Johnson & Johnson press releases and Securities Exchange Commission filings indicate that Janssen, a pharmaceutical company headquartered in Beerse, Belgium, and owned by Johnson & Johnson, is managing the business and operations of Momenta, generally, and the acquired Momenta pipeline of clinical and pre-clinical assets, including a biosimilar to EYLEA®. Ex. 2004, 46 ("the business and operations of Momenta will be managed as one of the Janssen Pharmaceuticals Companies of Johnson & Johnson."); *see also* Ex. 2005; Ex. 2006.

While denial of institution is warranted here, if the Board grants institution, it should require Petitioner to file updated mandatory disclosures identifying Janssen as a real party-in-interest.

III. THE BOARD SHOULD DENY INSTITUTION UNDER 35 U.S.C. § 325(D)

The Board should exercise its discretion and deny institution under 35 U.S.C. § 325(d) because Petitioner relies on substantially the same art that was already considered by the Examiner during prosecution of the '338 Patent, and fails to argue that the Examiner made any error material to the patentability of the Challenged Claims in considering that art.

A. Petitioner Mischaracterizes the Prosecution History of the '338 Patent and its Foreign Counterpart

Petitioner repeatedly and baselessly attempts to cast doubt on Regeneron's candor with the Office. Specifically, Petitioner incorrectly asserts that "***none*** of the numerous pre-2011 publications disclosing the VIEW1/VIEW2 dosing regimens . . . were submitted to or cited by the Examiner during prosecution." Pet., 27. This is incorrect. To the contrary, Regeneron's VIEW1/2 dosing regimens were before the Examiner and considered during prosecution of the '338 Patent. On October 18, 2013, Regeneron presented a September 28, 2008, Regeneron Press Release ("9/28/2008 Press Release") to the Office in an IDS, which was marked considered by the Examiner. Ex. 1017, 60 and 277. The 9/28/2008 Press Release discloses the same VIEW1/2 prospective dosing regimen that Petitioner relies on in Grounds 1-5 of its Petition. Ex. 2007, 1; *see* Section III.B, *infra*.

In addition, Petitioner asserts that Regeneron never cited art from EP-325 (the European counterpart to the '338 Patent) to the Examiner of the '338 Patent

and suggests that this was the reason the ’338 Patent issued, where its European counterpart did not. Pet., 11. This is also false.

With only one exception[1], all of the art cited in EP-325 was submitted to the Office and considered by the Examiner in the prosecution of the ’338 Patent or applications that continued therefrom. Petitioner insinuates that Regeneron hid art cited in third-party observations in EP-325 from the Office, but omits that the third-party observations were not filed with the EPO until seven months ***after*** the ’338 Patent issued. Ex. 1063, 214-371; 372-391. Even so, Regeneron submitted the art cited in these third-party observations with the Office in continuing prosecution in multiple applications of the same family, all of which were examined and allowed over such art. Moreover, Petitioner also ignores that the EPO relied on ***disclosure of the clinical trial results*** from Regeneron’s Phase 3 VIEW 1/2 trials, less than a year before patent filing, to challenge novelty in EP-325. Ex. 1063, 606-607. However, under U.S. Patent Law, such disclosure is not

[1] Annex 4, a November 30, 2010, ClinicalTrials.gov archive of the VIEW 2 Study, is the only third party-cited reference that does not appear on an IDS submitted during prosecution of Patent No. 9,669,069. Ex. 1063, 665-668. Annex 4 is § 102(a) art and is cumulative of a March 2008 VIEW 2 archive that was submitted during prosecution of the ’069 Patent, which issued from a continuation from the ’338 Patent. Ex. 2008.

a bar to novelty, and all such disclosures were before the Office in continuing prosecution. Thus, not only were references related to VIEW1/VIEW2 dosing regimen provided to the Office, but the Examiner fully considered those disclosures in allowing the '338 Patent.

B. Because the Examiner Considered Substantially the Same Art and Petitioner Does Not Allege Any Error, Institution Should Be Denied

The Board applies a two-part framework to analyze discretionary denial under § 325(d): "(1) whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office; and (2) if either condition of [the] first part of the framework is satisfied, whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims." *Advanced Bionics, LLC v. MED-EL Elektromedizinische Gerate GmbH*, IPR2019-01469, 2020 WL 740292, at *3-4 (Feb. 13, 2020) (citing *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 (Dec. 15, 2017)).

1. The Examiner Considered Substantially the Same Art (*Becton, Dickinson* Factors (a), (b), and (d))

The art relied upon in Petitioner's Grounds is substantially the same as the art presented to, and considered by, the Examiner during '338 Patent prosecution, thus satisfying step one of the *Advanced Bionics* framework.

a. Grounds 1-5

Central to Petitioner's Grounds 1-5 is that Dixon, Adis, the 5/8/08 Press Release, NCT-795, and NCT-377 each purportedly discloses the prospective VIEW1/2 dosing regimen. Pet., 27-36.

As discussed above, Regeneron presented a 9/28/2008 Press Release to the Office in an IDS during prosecution of the '338 Patent, which was marked considered by the Examiner. Ex. 1017, 60 and 277; Ex. 2007. As shown below, the 9/28/08 Press Release discloses the same VIEW1/2 prospective dosing regimen that Petitioner relies on in its Grounds 1-5. Ex. 2007, 1. Dixon, Adis,[2] the 5/8/08 Press Release, NCT-795, and NCT-377 are essentially identical to the disclosure of the 9/28/08 Press Release:

[2] While Adis discloses the administration of aflibercept, not VEGF Trap-Eye, (Ex. 1007, 263), Petitioner's anticipation arguments purport that the POSA would have understood "aflibercept" and "VEGF Trap-Eye" to be synonymous. Pet., 23. Therefore, according to Petitioner's characterization of aflibercept and "VEGF Trap-Eye," Adis contains essentially the same disclosure as the 9/28/08 Press Release.

9/28/08 Press Release (Ex. 2007, 1)	**Dixon (Ex. 1006, 1576)**	**Adis (Ex. 1007, 263)**	**5/8/08 Press Release (Ex. 1013)**	**NCT-795 & NCT-377 (Ex. 1014, 8; Ex. 1015, 6)**
"In [VIEW1/2], …VEGF Trap-Eye [will be] dosed 0.5 mg every 4 weeks, 2 mg every 4 weeks, **or 2 mg every 8 weeks (following three monthly doses)**…."	"[Phase 3] will evaluate the safety and efficacy of VEGF Trap-Eye at doses of. . . **2.0 mg at an 8 week dosing interval (following three monthly doses)**."	"The non-inferiority, [VIEW1] . . . study will evaluate the safety and efficacy of intravitreal aflibercept at . . . **2.0 mg at an 8-week dosing interval** . . . ."	VIEW2 "will evaluate the safety and efficacy of VEGF Trap-Eye at . . . **2.0 mg at an 8-week dosing interval, including one additional 2.0 mg dose at week four.**"	"**2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at week 4)** during the first year."

The Board has found that substantially the same prior art was previously presented to the Office when the asserted references are cumulative of references provided to the Examiner in an IDS. *NXP USA, Inc. v. Impinj, Inc.*, IPR2020-00519, 2020 WL 4805424, at *3-5 (Aug. 17, 2020); *Gardner Denver, Inc. v. Utex Indus., Inc.*, IPR2020-00333, 2020 WL 4529832, at *5 (Aug. 5, 2020). Thus, the Office was presented with art that was "substantially the same as" Dixon, Adis, the 5/8/08 Press Release, NCT-795, and NCT-377 because Petitioner's use of each is cumulative of the 9/28/08 Press Release.

Petitioner has not identified any material differences between the asserted art and the 9/28/08 Press Release. When a petitioner fails to identify any specific

differences between the asserted art and previously considered art, the Board has properly concluded that the asserted art is cumulative of art that was previously submitted to the Office. *See NXP USA*, 2020 WL 4805424, at *4-5.

b. Ground 6

In Ground 6, Petitioner argues that Dixon's disclosure of "positive Phase II trial data," *i.e.*, the results of Regeneron's CLEAR-IT 2 trial, would have provided the POSA with a reasonable expectation of success. Pet., 64. However, as shown below, the 9/28/08 Press Release that Regeneron disclosed to the Office in an IDS discloses the same CLEAR-IT 2 clinical trial results as Dixon:

9/28/08 Press Release (Ex. 2007, 1)	**Dixon (Ex. 1006, 1576)**
"Two groups initially received monthly doses of 0.5 or 2.0 milligrams (mg) of VEGF Trap-Eye (at weeks 0, 4, 8, and 12) and three groups received quarterly doses of 0.5, 2.0, or 4.0 mg of VEGF Trap-Eye (at baseline and week 12)."	"Two groups initially received monthly doses of 0.5 or 2.0 milligrams (mg) of VEGF Trap-Eye (at weeks 0, 4, 8, and 12) and three groups received quarterly doses of 0.5, 2.0, or 4.0 mg of VEGF Trap-Eye (at baseline and week 12)."

In addition, Petitioner argues that the '758 Patent (Ex. 1010) and Dix (Ex. 1033) each purportedly "disclose[] the VEGF Trap-Eye sequence and domain architecture." Pet., 63. But substantially the same disclosures as set forth in both of those references were presented to the Examiner during prosecution of the '338 Patent.

When a continuation-in-part of an asserted reference (1) includes the same disclosure as the disclosure in the asserted reference upon which the Petitioner

relies, and (2) was provided to the Examiner in an IDS, the Board has determined that substantially the same reference was presented to the Office. *Boragen, Inc. v. Syngenta Participations AG*, IPR2020-00124, 2020 WL 2206972, at *8 (May 5, 2020). Here, Regeneron provided a continuation-in-part of the '758 Patent, U.S. Patent App. No. 2006/0058234 (Ex. 2009) ("the '234 Application"), to the Office in an IDS, and the Examiner marked it considered during prosecution. Ex. 1017, 66 and 112. The '234 Application contains the same amino acid sequence that Petitioner identifies as the VEGF Trap-Eye sequence in the '758 Patent. *Compare* Ex. 2009, SEQ ID No. 7 *with* Ex. 1010, Figs. 24A-C. Accordingly, the '758 Patent is substantially the same as the '234 Application, which was considered by the Examiner during original prosecution.

Likewise, the Dix reference is also cumulative of the '234 Application. Petitioner asserts that Dix discloses the amino acid sequence of "VEGF Trap-Eye." Pet., 63. As noted above, the '234 Application discloses the identical sequence. *Compare* Ex. 2009, SEQ ID NO. 7 *with* Ex. 1033, SEQ ID NO. 3. Thus, although Dix was not previously presented to the Office, it is cumulative of the '234 Application that the Examiner considered during prosecution of the '338 Patent.

Thus, the Office was previously presented with "substantially the same" art as the '758 Patent and Dix. *See e.g.*, *NXP USA*, 2020 WL 4805424, at *4-5.

2. Petitioner Fails to Argue that the Examiner Erred in a Manner Material to Patentability (*Becton, Dickinson* Factors (c), (e), and (f))

Because substantially the same art was previously presented to the Office, Petitioner must show that the Office erred in a manner material to the patentability of the Challenged Claims. "An example of a material error may include misapprehending or overlooking specific teachings of the relevant prior art where those teachings impact patentability of the challenged claims." *Advanced Bionics*, 2020 WL 740292, at *3 n.9. "If reasonable minds can disagree regarding the purported treatment of the art or arguments, it cannot be said that the Office erred in a manner material to patentability." *Id.* at *3.

Petitioner never once alleges that the Examiner committed any error; indeed, the word "error" does not appear anywhere in the Petition. Nor does Petitioner allege that the Examiner overlooked or misapprehended something during prosecution. The Board has repeatedly determined that failure to allege material error is a sufficient basis to determine that a petitioner did not carry its burden as to step two. *E.g.*, *ABS Global, Inc. v. Cytonome/ST, LLC,* IPR2021-00306, Paper 13 at 13-14 (Jun. 7, 2021) ("[W]here Petitioner has made no allegation of material error beyond the allegation that the Examiner did not apply the [asserted] reference and has not pointed out any specific disclosure from [the asserted reference] that was overlooked by the Office, we agree with Patent Owner that Petitioner fails to demonstrate material error."); *Sony Interactive Ent.*

LLC v. Terminal Reality, Inc., IPR2020-00711, 2020 WL 6065188, at *5 (Oct. 13, 2020) ("Sony [Petitioner] was provided the opportunity to provide explanation [of material error], but Sony was silent in this regard…. Accordingly, *Becton, Dickinson* Factor (e) favors exercising our discretion to deny institution.").

Because substantially the same art was previously presented to the Office and was considered by the Examiner, and Petitioner fails to demonstrate that the Examiner committed an error material to the patentability of the Challenged Claims, the Board should exercise its discretion and deny institution under § 325(d). *See Dynatemp Int'l, Inc. v. R 421A LLC d/b/a Choice Refrigerants*, IPR2020-01660, Paper 15, 20-26 (Apr. 20, 2021) (institution denied where seven of eight asserted references were cumulative of previously presented reference and petitioner did not identify or sufficiently explain material error).

IV. THE BOARD SHOULD DENY INSTITUTION BECAUSE PETITIONER FAILS TO MAKE ITS THRESHOLD SHOWING THAT AT LEAST ONE CHALLENGED CLAIM IS UNPATENTABLE

For the reasons discussed below, Petitioner fails to "demonstrate that there is a reasonable likelihood that at least 1 of the" '338 Patent claims is unpatentable for Grounds 1 through 6, and thus, denial of the petition is warranted. 35 U.S.C. § 314(a).

A. Grounds 1, 3-5: Petitioner Fails to Demonstrate that "VEGF Trap-Eye" Was Known in the Art to Correspond to SEQ ID NO: 2 or SEQ ID NO:1

Petitioner asserts that Dixon (Ground 1), Regeneron (8-May-2008) (Ground 3), NCT-795 (Ground 4) and NCT-377 (Ground 5) anticipate the Challenged Claims. Anticipation requires "each and every claim limitation [to be] found either expressly or inherently in a single prior art reference." *King Pharms. Inc. v. Eon Labs, Inc.*, 616 F.3d 1267, 1274 (Fed. Cir. 2010) (quotations omitted).

Petitioner's anticipation argument relies on its unproven assumption that "VEGF Trap-Eye" was known in the art to possess the same amino acid sequence as aflibercept. However, none of Petitioner's cited references discloses the amino acid sequence of "VEGF Trap-Eye." To show inherent anticipation of the amino acid and nucleic acid limitations of claims 1 and 14, respectively, Petitioner must establish that the amino acid sequence of "VEGF Trap-Eye" was known to be the same as the amino acid sequence of aflibercept. Petitioner's anticipation argument should be rejected because Petitioner fails to establish that "VEGF Trap-Eye" was known in the art to have the amino acid sequence of SEQ ID NO:2 or be encoded by the nucleic acid sequence of SEQ ID NO:1.

1. Petitioner Fails to Establish that "VEGF Trap-Eye" Was Known in the Art to Comprise SEQ ID NO: 2 (Claims 1, 3-11, and 13)

Claim 1 and its dependent claims require the administration of a VEGF antagonist comprising amino acids 27-457 of SEQ ID NO:2. Ex. 1001, 23:12-17.

Since none of the cited references disclose any sequence information for "VEGF Trap-Eye," Petitioner argues that the "express disclosure of VEGF Trap-Eye thus anticipates," because "amino acid and structural information for VEGF Trap-Eye … was well-known and widely published to skilled artisans." Pet., 40-41.

But Petitioner has not identified ***any*** prior art that disclosed the amino acid sequence or nucleic acid sequence for "VEGF Trap-Eye." Specifically, Grounds 1 and 3-5 rely on Dixon, Regeneron (8-May-2008), NCT-795 and NCT-377, respectively. The full extent of Dixon's disclosure regarding "VEGF Trap-Eye" is that "VEGF Trap-Eye" is "a fusion protein of binding domains of VEGF receptors-1 and -2 attached the Fc fragment of human IgG." Ex. 1006, 1576. Nothing more is provided that would allow the POSA to differentiate Dixon's "VEGF Trap-Eye" from any other proteins comprising an hVEGF-R1 domain 2, hVEGF-R2 domain 3, and a human Fc region. Notably, Dixon does not specify which amino acids of the VEGF receptor-1 or receptor-2 domains comprise "VEGF Trap-Eye." Dixon also does not say that "VEGF Trap-Eye" and aflibercept have the same amino acid sequence, but only that "VEGF Trap-Eye" and aflibercept (the oncology product) share a "molecular structure." Ex. 1006, 1575. As explained below, this is not a disclosure of VEGF Trap-Eye's amino acid sequence.

Regeneron (8-May-2008) reports on the initiation of VIEW1/2 clinical trials for "evaluating VEGF Trap-Eye for the treatment of the neovascular from of Age-

related Macular Degeneration (wet AMD)." Ex. 1013, 1. Regeneron (8-May-2008) refers exclusively to administration of "VEGF Trap-Eye" and provides only that "VEGF Trap-Eye" "is a fully human, soluble VEGF receptor fusion protein that binds all forms of VEGF-A along with the related placental growth factor (PIGF) and VEGF-B." *Id.* at 2. This reference thus does not disclose an amino acid sequence for VEGF Trap-Eye.

NCT-795 and NCT-377 reflect historical changes for VIEW1/2 clinical trials as posted on clinicaltrials.gov. Ex. 1014, 3; Ex. 1015, 3. Both NCT-795 and NCT-377 state that "2.0 mg ***VEGF Trap-Eye*** [was] administered every 8 weeks (including one additional 2.0 mg dose at Week 4) during the first year." Ex. 1014, 8; Ex. 1015, 6 (emphasis added). Neither NCT-795 nor NCT-377 provides any information regarding the amino acid sequence of "VEGF Trap" or "VEGF Trap-Eye."

Based largely on Dixon's disclosure that "VEGF Trap-Eye and aflibercept (the oncology product) have the same molecular structure," Petitioner argues that "VEGF Trap-Eye" would be understood to refer to aflibercept — and to only aflibercept — and that aflibercept's amino acid sequence was well-known. Pet., 40-41 (quoting Ex. 1006, 1576-1575). However, Petitioner ignores evidence that the POSA would ***not*** have understood that VEGF Trap-Eye and aflibercept ***necessarily*** have the same amino acid sequence, such as the evidence discussed below showing different reported molecular weights for VEGF Trap-Eye and

aflibercept, and inconsistent descriptions of "VEGF Trap," "VEGF Trap-Eye" and "aflibercept" in the art. Consequently, Petitioner fails to satisfy its burden to show that, as of January 2011, the POSA would have known that the amino acid sequence of "VEGF Trap-Eye" was necessarily the same as the amino acid sequence of aflibercept and, as a result, that SEQ ID NO:2 was inherently disclosed by Dixon.

Petitioner's burden to show inherent anticipation is exacting, and Petitioner does not come close to meeting it here. The prior art's use of the term "VEGF Trap-Eye" was inconsistent, and Petitioner fails to show a clear or uniform understanding that "VEGF Trap-Eye" was just another name for "aflibercept" in the art. *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991) (To establish inherency, the extrinsic evidence "must make clear that the missing descriptive matter is ***necessarily present*** … and that it would be so recognized by persons of ordinary skill.") (emphasis added).

a. Petitioner and Its Expert Repeatedly Equate "Aflibercept" with All Variations of "VEGF Trap"

Petitioner relies on the disclosure of "VEGF Trap-Eye" as anticipating the claimed sequence information, but as shown above, identifies no amino acid sequence information for "VEGF Trap-Eye."

Petitioner relies heavily on a statement in Dixon that "VEGF Trap-Eye" and aflibercept (the oncology product) share a "molecular structure." Ex. 1006, 1575. But Dixon does not state that "VEGF Trap-Eye" and aflibercept have an identical

amino acid sequence. And Petitioner provides no evidence that the POSA would understand a shared "molecular structure" to indicate an identical amino acid sequence.[3] Indeed, in the immediately preceding paragraph, Dixon discloses that: "Structurally, VEGF Trap-Eye is a fusion protein of key binding domains of human VEGFR-1 and -2 combined with a human IgG Fc fragment (Fig. 1)." Ex. 1006, 1575. Dixon's Figure 1 shows a stylized version of VEGF receptors 1 and 2 and the binding domains that lead to the creation of a VEGF Trap molecule. *Id.* at 1576. Thus, Dixon itself suggests that the "molecular structure" of VEGF Trap-Eye may refer to a more general selection and arrangement of receptor binding domains and an Fc region, not a precise amino acid, or nucleic acid sequence.

Given the absence of any sequence disclosure in Dixon, Petitioner tries to connect the dots by arguing that "VEGF Trap-Eye" and aflibercept were different names for the very same protein: "Aflibercept, VEGF Trap, VEGF Trap-Eye, VEGF-Trap$_{R1R2}$, and AVE0005 are simply different names for the ***same molecule***." Pet., 23 (emphasis added); Ex. 1002, ¶18. However, by equating

[3] A protein molecule has multiple levels of "structure": primary (the amino acid sequence), secondary (spatial arrangement of adjacent amino acid residues), tertiary (overall three-dimensional structure), and quaternary (arrangement of several protein chains or subunits). Ex. 2010, 15-16.

"VEGF Trap Eye" with all variations of "VEGF Trap" nomenclature, including VEGF Trap names that were known in the art to refer to a genus of proteins, Petitioner and Dr. Albini only underscore the uncertainty confronting the POSA regarding the identity and sequence of "VEGF Trap-Eye."

Not only does Petitioner fail to meet its burden, but it also fails to consider evidence that would signal to the POSA that "VEGF Trap-Eye" was used to describe many different fusion proteins. For example, "VEGF Trap" was known in the art to encompass a genus of engineered fusion proteins, each having a different amino acid sequence. Holash 2002 *et al.* describes several different Regeneron-developed VEGF-Traps (*e.g.*, VEGF $Trap_{parental}$, VEGF-$Trap_{\Delta B1}$, VEGF-$Trap_{\Delta B2}$, VEGF $Trap_{R1R2}$). Ex. 1004, 11394. Notably, Holash never uses the term "VEGF Trap-Eye" (or aflibercept) for any of the VEGF Trap fusion proteins it describes. And none of VEGF $Trap_{parental}$, VEGF-$Trap_{\Delta B1}$, VEGF-$Trap_{\Delta B2}$ satisfies the sequence limitation of the Challenged Claims. Thus, the POSA would have known of numerous Regeneron "VEGF-Trap" molecules, including many that do not comprise SEQ ID NO:2.

To succeed on its inherency theory, Petitioner must establish that "VEGF Trap-Eye" as disclosed by Dixon and understood by the POSA as of the priority date ***necessarily*** referred to a ***single*** protein (aflibercept) having the amino acid

sequence of SEQ ID NO:2.[4] Yet Petitioner equates "VEGF Trap-Eye" with various names that connoted an entire class of molecules. Petitioner has not and cannot establish that the POSA understood that "VEGF Trap-Eye" ***necessarily*** possessed the same amino acid sequence as aflibercept.

b. Petitioner Fails to Address Uncertainty in the Art as to the Amino Acid Sequence of "VEGF Trap-Eye"

As of the priority date, the POSA would have been aware of inconsistent reports in the literature regarding the molecular weight of "VEGF Trap-Eye." For example, a 2009 publication reports that "***VEGF Trap-Eye[24] is a 110-kDa*** recombinant protein," while a 2010 publication reports that "***VEGF Trap-Eye (Regeneron Inc.) is a 115-kDa*** recombinant fusion protein." Ex. 1075, 403; *see*

[4] Petitioner also relies on Regeneron's PTE Application (Ex. 1024), filed nearly a year after the priority date, to try to connect "VEGF Trap-Eye" to "aflibercept" (Pet., 24), but the meaning of "VEGF Trap-Eye" must be understood as the POSA would view the term as of the priority date without reference to how the term may have later changed. *See Schering Corp. v. Amgen Inc.*, 222 F.3d 1347, 1354 (Fed. Cir. 2000) (holding a term is to be understood based on knowledge in the art as of the priority date, even if it later acquires a different meaning). Accordingly, the meaning of the term "VEGF Trap-Eye" must encompass all possible molecules to which that term referred as of the priority date.

also Ex. 2011, 667 ("VEGF Trap, ***a 110 kDa soluble protein***…."); *cf.* Ex. 2012, 49 and Ex. 2013, 144 ("***VEGF Trap is a 115 kDa*** recombinant fusion protein….") (emphases added).

Conversely, the molecular weight of aflibercept was routinely reported as 115 kDa. *See e.g.*, Ex. 2014, 596 ("…***aflibercept*** is a soluble fusion protein …. Its molecular weight is ***115 kDa***…"); Ex. 2015, [0003] and [0010] (explaining that "VEGF Trap" is a chimeric protein with several embodiments and "has a molecular weight which is substantially less than that of Avastin (***115 kDa for aflibercept*** versus 160 kDa for Avastin)….") (emphases added).

The POSA would have understood that differences in protein molecular weights can reflect differences in the amino acid sequences of the proteins. Specifically, 5,000 Da could equate to a sequence difference of ~42 amino acids (the average molecular weight of an amino acid is ~110-118 Da). Ex. 2016, 1272; Ex. 2017, 11. Thus, in light of a difference of 5,000 Da in the reported molecular weights of "VEGF Trap-Eye," the POSA may have understood the term to refer to a family of fusion proteins with different amino acid sequences having molecular weights in the range of 110-115 kDa. Or the POSA may have understood "VEGF Trap-Eye" to refer to two "VEGF Trap" fusion proteins with different amino acid sequences, one weighing 110 kDa and the other weighing 115 kDa. Or, alternatively, the POSA may have understood "VEGF Trap-Eye" to refer to a single protein amino acid sequence, such as the sequence of aflibercept or that of

another protein the class of VEGF Traps. The Petition, however, is devoid of evidence indicating how the POSA would have understood these varying prior art disclosures regarding the identity of the term "VEGF Trap-Eye."

In view of this conflicting prior art, Petitioner fails to establish that the term "VEGF Trap-Eye" was known to necessarily refer to aflibercept, and to comprise the amino acid sequence of SEQ ID NO:2. Consequently, Petitioner fails to show that its cited art anticipates claims 1, 3-11, and 13.

2. Petitioner Fails to Establish that "VEGF Trap-Eye" Was Known in the Art to Be Encoded by SEQ ID NO:1

Claim 14 and its dependent claims require that the VEGF antagonist is a receptor-based chimeric molecule encoded by the nucleic acid sequence of SEQ ID NO:1. Ex. 1001, 24:13-15. Petitioner argues that "[l]ike the amino acid sequence, the nucleotide sequence for VEGF Trap-Eye was disclosed in the prior art and well known to skilled artisans." Pet., 41 (citing Ex. 1002, ¶¶147-150). Yet, neither the amino acid sequence nor nucleic acid sequence of "VEGF Trap-Eye" is expressly disclosed in Petitioner's cited art. Moreover, because Petitioner fails to establish that "VEGF Trap-Eye" necessarily has the amino acid sequence of aflibercept, it also fails to show that "VEGF Trap-Eye" is necessarily encoded by the nucleic acid sequence of SEQ ID. NO:1.

Petitioner and its expert Dr. Albini argue that "the sequence aspect of clam 14 was widely published in the prior art" based on Dixon (Ex. 1006), the '758

patent (Ex. 1010), Dix (Ex. 1033), and the ’095 patent (Ex. 1039).[5] Ex. 1002, ¶149. However, none of these references discloses the nucleic acid sequence of “VEGF Trap-Eye.”

Dixon does not disclose any nucleic acid sequence information, let alone the nucleic acid sequence for “VEGF Trap-Eye.” Dixon’s generic disclosures of “VEGF Trap-Eye” or aflibercept, without correlating those terms to SEQ ID NO:1, is insufficient.

Likewise, Petitioner fails to show that the nucleic acid sequences disclosed in the ’758 Patent, Dix, and the ’095 Patent were known by the POSA to correspond to either “VEGF Trap-Eye” or “aflibercept.” The ’758 Patent discloses VEGF-binding construct sequences. Ex. 1010, 10:15-17 (“FIG. 24A-24C. Nucleotide (SEQ ID NO:15) and deduced amino acid sequence (SEQ ID NO:16) of the modified Flt1 receptor termed VEGFR1R2-FcAC1(a).”). But the ’758 Patent does not correlate these disclosed nucleic acid sequences to the terms “VEGF Trap-Eye” or “aflibercept.” Dix also discloses nucleic acid sequences of “VEGF trap proteins” or “VEGF antagonist” fusion proteins but never identifies these proteins as “VEGF Trap-Eye” or “aflibercept.” Ex. 1033, [0013]-[0014], [0030]. Likewise, the ’095 Patent never equates any of its

[5] Dr. Albini also cites to Exs. 1007 and 1021 that do not include any sequence information. Ex. 1002, ¶149.

disclosed nucleic acid sequences with "VEGF Trap-Eye" or "aflibercept."

The mere possibility that "VEGF Trap-Eye" or "aflibercept" could comprise a nucleic acid sequence meeting the limitation of claim 14 is insufficient to demonstrate inherency for anticipation. *See Amgen, Inc. v. Alexion Pharms., Inc.*, IPR2019-00739, Paper 15, at 24-25 (Aug. 30, 2019) (rejecting inherent anticipation where "eculizumab" referred to at least two different proteins in the prior art, including the unclaimed "Thomas IgG4 isotype eculizumab").

B. Ground 2: Petitioner Fails to Demonstrate that There Is a Reasonable Likelihood that at Least One of the Challenged Clams Is Anticipated by Adis

Petitioner fails to show that there is a reasonable likelihood that at least one Challenged Claim is unpatentable for anticipation based on Adis. To anticipate, a reference "must not only disclose all elements of the claims within the four corners of the document, but must also disclose those elements arranged as in the claim." *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008) (internal quotations omitted).

Petitioner relies on two passages in Adis, regarding the prospective VIEW1/2 trials, as disclosing the claimed dosing regimen. Pet., 45-46. For VIEW 1, Petitioner relies on the following passage:

> [S]tudy will evaluate the safety and efficacy of intravitreal aflibercept at doses of 0.5 mg and 2.0 mg administered at 4-week dosing intervals, and 2.0 mg at an 8-week dosing interval, compared with 0.5 mg ranibizumab administered every 4 weeks.

Ex. 1007, 263.

This passage does ***not*** disclose the claimed regimen of an initial dose followed by one or more secondary doses 2 to 4 weeks after the preceding dose, followed by tertiary doses every 8 weeks. To be clear, Adis's description of VIEW 1 makes no mention of an initial dose or secondary doses preceding an 8-week dosing interval.

For VIEW 2, Petitioner relies on the following passage:

> This study will evaluate the safety and efficacy of aflibercept at 0.5 mg and 2.0 mg administered at 4-week intervals and 2.0 mg at an 8-week dosing interval, ***including one additional 2.0 mg dose at week 4***.

Ex. 1007, 263 (emphasis added).

But Adis's description of VIEW 2 does not specify which of these three study arms receives the "one additional 2.0 mg dose at week 4." Petitioner and its expert use hindsight to interpret this passage to arrive at the claimed regimen. *Janssen Pharms., Inc. v. Watson Lab'ys, Inc.*, C.A. No. 08-5103(SRC), 2012 WL 3990221, at *6-10 (D.N.J. Sept. 11, 2012) ("There is no legal basis for rewriting the prior art to create a hindsight anticipation."). But the language of Adis is unclear, and this passage could be interpreted by the POSA to mean several different possible regimens, including (1) 0.5 mg administered at 4-week dosing intervals with an additional 2.0 mg dose at week 4; (2) 2.0 mg administered at 4-week dosing intervals, with an additional 2.0 mg dose at week 4; or (3) 2.0 mg at

an 8-week dosing interval with an additional 2.0 mg dose at week 4. It is also possible that the POSA would have concluded that Adis's description of VIEW 2, which is inconsistent with Adis's description of the VIEW 1 dosing regimen, was simply incorrect. Consequently, Petitioner fails to show that the disclosures in Adis are arranged as in the Challenged Claims of the '338 Patent.

C. Grounds 1-5: Petitioner Fails to Establish Any of Its References Disclose a "Method of Treating" and "Tertiary Dose"

None of Petitioner's cited references expressly discloses the required efficacy limitations. Nor could they, as each reference discloses a prospective study that had not yet occurred.[6] *See e.g.*, Ex. 1006, 1576 (The Phase 3 study "***will evaluate*** the safety and efficacy of intravitreal VEGF Trap-Eye at doses of 0.5 and 2.0 mg administered at 4-week dosing intervals and 2.0 mg at an 8 week dosing interval (following three monthly doses)…") (emphasis added).

Unable to show these limitations in the art, Petitioner argues alternatively that: (1) the Challenged Claims require no efficacy; or (2) the required efficacy is inherent to the disclosed prospective dosing regimen. Neither argument succeeds.

[6] At the time of publication of each reference relied on by Petitioner for anticipation, testing in the VIEW trials was incomplete and the results were unknown. *See, e.g.*, Ex. 1006, 1577.

1. Claim Construction

Petitioner's proposed claim construction is so divorced from the '338 Patent's claims, specification, and prosecution history, that it renders the treatment of the "method of treating" claims meaningless. Without the requirement of an efficacious method of treating, as Petitioner proposes, the Challenged Claims would cover administering a VEGF antagonist fusion protein to individuals with any disease, or even no disease at all. It would also cover administering such minute quantities of the fusion protein — in sub-nanogram quantities, for example — that no POSA would understand to constitute a "method of treating."

The claim language and intrinsic record make two things abundantly clear: (1) the claimed methods of treatment are for people suffering from an angiogenic eye disorder; and (2) the claimed dosing regimens were a significant advance over existing therapies because they enabled less frequent dosing while maintaining a high degree of therapeutic efficacy. Petitioner does not dispute either point. Instead, it offers various (erroneous) reasons to ignore this unambiguous intrinsic evidence. For the reasons explained below, Regeneron's constructions should be adopted.[7]

[7] Petitioner proposes constructions for (1) "4 weeks" and "Pro re Nata (PRN)"; and (2) "VEGFR1 Component," "VEGFR2 Component" and the "Multimerization Component." Pet., 16-17. Regeneron does not advance claim construction positions for these terms because construction of these terms is not necessary to

a. The Preamble of the Independent Claims Is a Limitation of the Claim

The preamble of claims 1 and 14 — "A method for treating an angiogenic eye disorder in a patient" — is limiting because it (1) imparts meaning to the claims and (2) provides the antecedent basis for the term "patient" in the body of the independent claims and the types of angiogenic eye disorders specified in the body of the dependent claims.

The preamble is not merely a statement of intended results but, as evidenced by the specification, gives life and meaning to the claims. *See, e.g.*, *Griffin v. Bertina*, 285 F.3d 1029, 1033 (Fed. Cir. 2002). The preamble sets forth the essence of the claimed invention — "treat[ment] [of] an angiogenic eye disorder in a patient." Ex. 1001, claims 1, 14; *see also* Ex. 1001, Abstract ("The present invention provides methods for treating angiogenic eye disorders …."); *id.* at 2:3-22 (same); *Griffin*, 285 F.3d at 1033 (construing preamble that recites a "method

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resolve the arguments presented in this preliminary response. *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (providing claim construction only "to the extent necessary to resolve the controversy."). Likewise, Petitioner argues that Regeneron "ignores construing 'initial' and 'secondary'" doses. *See* Pet., 15. Because the terms "initial" and "secondary" need not be construed to resolve Petitioner's grounds, it is unnecessary to construe them here. *Nidec*, 868 F.3d at 1017.

for diagnosing" as limiting because "[d]iagnosis is … the essence of th[e] invention; its appearance in the count gives 'life and meaning' to the manipulative steps"). Without limiting the claim to treating patients, the remaining steps of the claim become a meaningless exercise in administering a drug to a person who may have no need whatsoever for the treatment.

The specification confirms what the explicit language of the preamble dictates — that treatment of an angiogenic eye disorder is the entire purpose of the claimed invention: "the invention relates to the administration of VEGF antagonists to ***treat*** eye disorder caused by or associated with angiogenesis. Ex. 1001, 1:18-21 (emphasis added); *see also id.*, 1:63-66 ("The present invention provides methods for ***treating*** angiogenic eye disorders.") (emphasis added), *id.*, 3:19-20 (same), *id.*, 7:15-19 (same). Thus, Petitioner is wrong to assert that "[n]othing in the intrinsic record here suggests" that the preamble is limiting. Pet. 18. To the contrary, the Federal Circuit has routinely held that descriptions of "the present invention" such as these are limiting. *See, e.g.*, *Regents of Univ. of Minn. v. AGA Med. Corp.*, 717 F. 3d 929, 936 (Fed. Cir. 2013); *see also Eon-Net LP v. Flagstar Bancorp*, 653 F.3d 1314, 1322 (Fed. Cir. 2011); *C.R. Bard, Inc. v. U.S. Surgical Corp.*, 388 F.3d 858, 864 (Fed. Cir. 2004). The Federal Circuit also looks to a patent's title and abstract to inform claim construction. *See, e.g.*, *Forest Lab'ys, LLC v. Sigmapharm Lab'ys, LLC*, 918 F.3d 928, 933 (Fed. Cir. 2019) (title); *UltimatePointer, L.L.C. v. Nintendo Co.*, 816 F.3d 816, 823 (Fed. Cir.

2016) (title); *Hill-Rom Co. v. Kinetic Concepts, Inc.*, 209 F.3d 1337, 1341 & n.* (Fed. Cir. 2000) (abstract, collecting cases). Both the '338 Patent's title and abstract explicitly reference treatment, confirming Regeneron's interpretation of the claims. Ex. 1001 at 1 (Title, "Use of a VEGF Antagonist to Treat Angiogenic Disorders"); *id.* (Abstract, "The present invention provides methods for treating angiogenic eye disorders . . . . The methods of the present invention are useful for the treatment of angiogenic eye disorders . . . .").

Enforcing the preamble limitation grounds the claims in this clear utility — treating subjects suffering from angiogenic eye disorders. *See, e.g., Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp*., 320 F.3d 1339, 1345 (Fed. Cir. 2003) (construing the preamble as limiting because without the preamble, "the claimed method reduces to nothing more than a process … whose absence of fathomable utility" is "nothing but an academic exercise."); *E.I. Du Pont de Nemours & Co. v. Monsanto Tech. LLC*, IPR2014-00333, 2014 WL 3507803, at *4-5 (July 11, 2014) (construing the preamble as limiting because the POSA "would not understand the utility of the process" "without construing the preamble language of the claim as limiting"). Thus, the preamble makes clear that the recited dosing regimen must ***treat*** a patient with an angiogenic eye disorder.

Also, the preamble of claims 1 and 14 (which recites "a patient" and "an angiogenic eye disorder") provides an antecedent basis for "the patient" who is treated and for the "angiogenic eye disorders" that are specified in dependent

claims 6, 7, 18, and 20. The method comprises "sequentially administering ***to the patient***" doses of VEGF antagonist in order to treat an angiogenic eye disorder. Ex. 1001, claims 1, 14 (emphasis added). This "sequentially administering" step depends upon the preamble. Without the preamble, it would be unclear ***who*** is receiving sequentially administered doses, *i.e.*, being treated for an angiogenic eye disorder. The MPEP and case law confirm that the use of the indefinite article "a" in the preamble is a signal that it serves as the antecedent basis for the reference to the same object in the body when preceded by the definite article "the." MPEP § 2173.05(e); *Baldwin Graphic Sys., Inc. v. Siebert, Inc.*, 512 F.3d 1338, 1342 (Fed. Cir. 2008).

Likewise, claims 6, 7, 18, and 20 that recite the particular "angiogenic eye disorder[s]" to be treated rely on the preamble for their antecedent basis. *See id.* at claims 6, 7, 18, and 20. Because the preamble provides an antecedent basis on which other claim limitations rely, it is a positive limitation of the claims. *See, e.g.*, *Sanofi Mature IP v. Mylan Lab'ys Ltd.*, 757 F. App'x 988, 993 (Fed. Cir. 2019) (finding the preamble — "a method of increasing survival" — to be limiting because it provides an antecedent basis for which a later limitation — "a patient in need thereof" — relied); *Rapoport v. Dement*, 254 F.3d 1053, 1059 (Fed. Cir. 2001) (finding preamble limiting because otherwise "the phrase 'to a patient in need of such treatment' would not have a proper antecedent basis"); *Gilead Scis, Inc. v. United States*, IPR2019-01455, Paper 16 at 24 (Feb. 5, 2020) (finding

preamble provides information about the body of the claim because "an immunodeficiency retrovirus" provides an antecedent basis for language in the claim body — "the immunodeficiency retrovirus"). Thus, contrary to Petitioner's bald assertion (Pet., 20), the terms "patient" and "angiogenic eye disorder" find antecedent basis in the preamble.

b. The Preamble Reflects the Efficacy Required by the Body of the Claim

The preamble requires that the recited method steps produce an effective method of treatment. As discussed above, this construction is supported by the intrinsic record. It is also supported by the body of the claim itself. Claims 1 and 14 require the sequential administration of an initial dose, secondary doses, and one or more tertiary doses. As discussed below, "tertiary dose(s)" require maintaining the efficacy gain of the initial and secondary doses. Thus, the method steps of the body of the claim that require administering an initial dose and one or more secondary doses must result in efficacy, which is maintained with the "tertiary dose(s)." As of January 2011, the POSA would have understood the recited "method of treating" to require efficacy based on the plain language of the claim read as a whole and based on the intrinsic record of the '338 Patent.

Petitioner argues that "the patent does not provide a definition or any metric for what constitutes 'treating' an angiogenic eye disorder" and thus "a [POSA] would apply the term's plain and ordinary meaning: administering a therapeutic to a patient, without a specific degree of efficacy required." Pet., 21. But the

preamble must be construed consistently with the efficacy demanded of the claim as a whole.[8] *See Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1306 (Fed. Cir. 1999) ("[I]t is essential that the court" "construe the preamble and the remainder of the claim … as one unified and internally consistent recitation of the claimed invention" where the preamble uses language that is repeated in the body of the claim, and is therefore "intimately meshed with the ensuing language in the claim"); *see also Gilead Scis.*, IPR2019-01455, Paper 16 at 24 (finding that the preamble provides "sufficient context" for terms in the body of the claim). As discussed below, the term "tertiary dose(s)" in the body of the claims connotes a specific level of efficacy, and the "method of treating" limitation conforms to this required efficacy and identifies the purpose thereof — for the treatment of an angiogenic eye disorder in a patient.

Finally, Petitioner argues that the preamble is non-limiting (Pet., 17-20) but relies on cases that are factually distinguishable where the claim as a whole, not just the preamble, was found to have no efficacy limitation.

[8] Contrary to Petitioner's suggestion, (Pet., 20), there is no general rule that efficacy language in a claim is non-limiting. *See, e.g., Gilead Scis,*, IPR2019-01455, Paper 16 at 26 ("Whether such language should be given patentable weight turns on facts unique to each patent.").

c. The "Tertiary Dose" Must Maintain the Efficacy Gain Achieved After the Initial and Secondary Doses

The claim term "tertiary dose(s)" means "dose(s), administered after the initial and secondary doses, that maintain(s) the efficacy gain achieved after the initial and secondary doses." This follows from the intrinsic record and a straightforward application of Federal Circuit precedent.

Under *Phillips*, claim terms are afforded "their ordinary and customary meaning," which is "the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-13 (Fed. Cir. 2005). But where a term has "no previous meaning to those of ordinary skill in the prior art," one looks "[elsewhere] in the patent." *Irdeto Access, Inc. v. Echostar Satellite Corp.*, 383 F.3d 1295, 1300 (Fed. Cir. 2004).

Both parties' experts agree that "tertiary dose" does not have a "previous meaning to those of ordinary skill in the art," (Ex. 2001, ¶43; Ex. 1002, ¶41), "apart from the patent." *Irdeto Access, Inc.*, 383 F.3d at 1300; *MyMail, Ltd. v. Am. Online, Inc.*, 476 F.3d 1372, 1376 (Fed. Cir. 2007). The parties also agree that "tertiary dose(s)" occur after secondary doses. Ex. 1001, 3:31-38. Stating that the "tertiary dose" comes after the secondary dose, however, does not provide a complete definition of "tertiary dose." Accordingly, the Board must look to the specification as a whole to construe "tertiary dose." *Id.*; *see, e.g., Abraxis*

Bioscience, Inc. v. Mayne Pharma (USA) Inc., 467 F.3d 1370, 1376-77 (Fed. Cir. 2006) (construing claim term in light of "the entire specification" not just on a passage purporting to define the term).

The '338 Patent's "entire specification" and prosecution history confirm Regeneron's construction. At the time of filing, therapies for the treatment of angiogenic eye disorders using VEGF antagonists existed in the art. Ex. 1001, 1:49-52. Nonetheless, the '338 Patent recognized that there remained a need for less frequent dosing regimens that could maintain a high degree of efficacy. *Id.* at 1: 55-59. The '338 Patent successfully addressed this long-felt need:

> The present inventors have ***surprisingly*** discovered that ***beneficial therapeutic effects*** can be achieved in patients suffering from angiogenic eye disorders by administering a VEGF antagonist to a patient at a frequency of once every 8 or more weeks, especially when such doses are preceded by about three doses administered to the patient at a frequency of about 2 to 4 weeks.

Id. at 2:3-10 (emphases added).[9]

[9] Petitioner argues that Regeneron is "reading-in limitations" from the '338 specification, particularly the passage at column 2 that describes "bi-monthly dosing." Pet., 14. Not so. This is not a case where a party has proposed a construction that is consistent only with a single embodiment described in the specification. Rather, the entire specification, and indeed the essence of the

The ’338 Patent discloses that a key benefit of the claimed dosing regimens is that for “most of the course of treatment (*i.e.*, the ***tertiary doses***),” *id.* at 2:15-22 (emphasis added), pFFatients may be treated less frequently as compared to therapies that existed in the art. The disclosed dosing regimens were a significant advance over existing therapies because they enabled less frequent dosing while maintaining a high degree of therapeutic efficacy.

During prosecution, Regeneron relied on the unexpected results of the claimed invention to overcome a double patenting rejection because the claimed invention resulted in surprising efficacy despite less frequent dosing than the standard of care (*i.e.*, monthly dosing). Ex. 1017, 288-291, 315. Regeneron’s argument during prosecution that less frequent, tertiary dosing “once every 8 weeks” was surprisingly efficacious ultimately resulted in the issuance of the Challenged Claims. Accordingly, the prosecution history confirms that “tertiary dose” connotes a specific level of efficacy.[10]

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invention, teaches that less frequent maintenance doses can be highly effective for the treatment of angiogenic eye disorders.

[10] Petitioner relies on *Purdue* and *Mylan* to argue that Regeneron “is foreclosed … from arguing that its reliance on alleged ‘unexpected results’ during prosecution demonstrates that efficacy is a necessary feature of the claimed method.” Pet., 18. But *Purdue* relates to prosecution history estoppel, which is not at issue here.

Petitioner argues that the specification provides an explicit definition for "tertiary dose" that preempts further construction. Pet., 13-14. This is wrong for many reasons.

First, the specification does not formally define "tertiary doses," it merely states that "tertiary doses" occur after secondary doses. Ex. 1001, 3:31-38. When a patent owner uses an unmistakable format to define certain terms but not others, a court will not presume those other terms have been formally defined by the inventor. For example, in *Medicines Company v. Mylan, Inc.*, 853 F.3d 1296, 1306 (Fed. Cir. 2017), the Patent Owner had used an unmistakable format to define certain terms, such as "batches," "pharmaceutical batches" and "drug product." *See id* at 1300. ("'Batches' or **'**pharmaceutical batches**'** as defined herein may include . . . ."). Accordingly, the Federal Circuit held that a different statement, taken directly from the specification, was not definitional, because "it does not accord with the linguistic formula used by the patentee to signal the

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Moreover, *Mylan* is distinguishable because the Board's conclusion that prosecution history statements did not support construing the preamble as limiting was based on the fact that the disputed preamble term was not discussed during prosecution. But here, "tertiary dose" is in the body of the claim, not the preamble, and regardless, Regeneron's discussion of unexpected results during prosecution was unequivocally related to the "tertiary dose" limitation.

designation of other defined terms – including 'batches.'" *Id.* at 1306.

Here, Regeneron has used a specific "linguistic format" to define terms. *See, e.g.*, Ex. 1001, 3:18-21 ("***As used herein***, the term 'about,' when used in reference to a particular recited numerical value, ***means*** . . . ."); *id.* at 3:32-36 ("***As used herein***, 'sequentially administering' ***means*** that each dose of VEGF antagonist is administered to the patient at a different point in time . . . ."); *id.* at 4:50-52 ("***As used herein***, the expression 'VEGF antagonist' ***means*** . . . ."); *id.* at 5:23-26 ("The expression 'angiogenic eye disorder,' ***as used herein, means*** any disease of the eye . . . ."); (emphases added).

Regeneron did not use this linguistic format to describe a "tertiary dose" as occurring after the secondary dose. *See, e.g.*, Ex. 1001, 3:42-44 ("The terms 'initial dose,' 'secondary doses,' and 'tertiary doses,' refer to the temporal sequence of administration of the VEGF antagonist."). Accordingly, the specification does not provide an express definition of "tertiary dose."

Second, Petitioner reads this particular passage from the '338 Patent in a vacuum. While Regeneron agrees that the "tertiary dose" is third in sequence, knowing the temporal sequence of administration does not say anything else about the dose. Claim construction, however, requires "consider[ation] [of] the specification as a whole." *Baxalta Inc. v. Genentech, Inc.*, 972 F.3d 1341, 1347 (Fed. Cir. 2020) (reversing claim construction based solely on one statement in the

specification). Considering the entire specification as a whole, it is clear that the term "tertiary dose(s)" means "dose(s), administered after the initial and secondary doses, that maintain(s) the efficacy gain achieved after the initial and secondary doses."

Third, Petitioner's argument that Regeneron's proposed construction of "tertiary dose" is "in conflict with the plain language of the '338 claims" (Pet., 14 n.4.) is tautological and presupposes that the claim has been construed to eliminate the efficacy limitations of the claim.

Fourth, Petitioner also argues that there is no efficacy requirement recited by the Challenged Claims and cites several distinguishable cases in support. For example, Petitioner relies heavily on *Bristol*, but ignores a critical difference between the Challenged Claims and the claims therein. *See Bristol-Myers Squibb Co. v. Ben Venue Lab'ys, Inc.*, 246 F.3d 1368, 1375 (Fed. Cir. 2001). The claimed method steps in *Bristol*, unlike here, "are performed in the same way regardless of whether or not the patient experiences a reduction in the hematologic toxicity" because the *Bristol* claims expressly specify each of the manipulative steps, including the timing and amount of administration, so any functional limitation was found to be superfluous. *Id.* at 1375.[11]

[11] Bristol attempted to capitalize on this arguing "that the claims of each patent would be infringed without a showing of an objective response in every patient."

In contrast, here, the Challenged Claims do not expressly specify both the dosage amount and the exact frequency of the dosing. Therefore, unlike the claims in *Bristol*, the efficacy limitations of the claim serve to limit and specify the manipulative steps of the claim. *See Gilead Scis.*, IPR2019-01455, Paper 16 at 25 (construing claims to require an efficacy limitation and distinguishing *Bristol* because the claims in *Bristol* "expressly included specific dosage information as material claim elements" whereas the claims-at-issue did not).

Petitioner's other method of treatment cases are likewise distinguishable because they too involve claims that specify the exact dose and frequency, and efficacy would not change the manipulative steps. *See In Re: Copaxone Consol. Cases*, 906 F.3d 1013, 1022-23 (Fed. Cir. 2018) (efficacy not required because it "does not change the express dosing amount or method already disclosed in the claims"); *Mylan Lab'ys Ltd. v. Aventis Pharma S.A.*, No. IPR2016-00712, Paper 112 (P.T.A.B. Sept. 22, 2016) (specifying a single dose with a precise frequency).

Fifth, Petitioner argues that under Regeneron's construction, the '338 Patent, and related U.S. Patent No. 10,828,345 ("the '345 Patent"), whose tertiary doses are administered at least 12 weeks after the preceding dose, would "require a different construction." Pet., 14 n.4. Not so. While the frequency of the

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Id. at 1375. The court explained "Bristol cannot have an expression be limiting in this context and non-limiting in another." *Id.*

"tertiary dose" differs between the '338 claims (≥ 8 weeks apart) and the '345 claims (≥ 12 weeks apart) based on the plain language of the respective claims, this difference is not relevant to Regeneron's proposed construction of "tertiary dose." Regeneron's proposed construction of "tertiary dose" does not require a particular dosing frequency; rather, it requires that the tertiary dose must maintain a certain therapeutic effect.

Sixth, Petitioner argues that Regeneron's expected construction "injects ambiguity and indefiniteness where there is none" because the terms "maintain," "therapeutic effect," and "throughout the course of treatment" lack both definition and plain and ordinary meaning. Pet., 15. As an initial matter, Regeneron is not proposing a construction containing the phrase "throughout the course of treatment."[12] And, in any event, Regeneron's construction is clear: the patient continues to maintain the improvement he or she achieved following the initial and secondary doses. Ex. 2001, ¶48. Petitioner fails to explain what about Regeneron's construction is ambiguous.

Finally, Petitioner argues that the '338 specification only requires that

[12] Regeneron proposes slightly different language in its proffered construction of "tertiary dose" than it did in PGR2021-00035 to clarify that the therapeutic effect to which the invention is directed is "maintain[ing] the efficacy gain achieved after the initial and secondary doses."

"efficacy" be a "loss of fifteen or fewer letters in the Early Treatment Diabetic Retinopathy Study ("ETDRS") visual acuity chart within 104 weeks of treatment initiation" based on the specification. Pet. 21; Ex. 1002, ¶43. But the POSA reading the claims in view of the specification and prosecution history would understand that this minimal level of efficacy is not sufficient for the methods of treating claimed in the '338 Patent. For example, if a patient achieved a gain in letters after the initial and secondary doses, then declined after the tertiary dose(s) began, but still exhibited a loss of fewer than 15 letters during the tertiary dosing, the POSA would not consider that to be an effective method of treatment in the context of the '338 Patent. Ex. 2001, ¶48.

Thus, the preamble of claims 1 and 14 is a positive limitation that requires treatment of an angiogenic eye disorder and provides context for the efficacy limitation required by the term "tertiary dose." And the term "tertiary dose" should be construed to mean "dose(s), administered after the initial and secondary doses, that maintain(s) the efficacy gain achieved after the initial and secondary doses."

2. Petitioner's References Fail To Disclose A "Method Of Treating" Or A "Tertiary Dose"

As noted above, none of Petitioner's cited references expressly discloses an effective method of treatment or a "tertiary dose" that maintains the efficacy gain achieved after the initial and secondary doses. Moreover, Petitioner does not even attempt to show that the administration of "VEGF Trap-Eye," at the disclosed

dosage and dosing intervals as described by the allegedly anticipatory references[13] necessarily results in an effective method of treatment or a "tertiary dose." Because Petitioner fails to show the efficacy limitations were necessarily present in its cited references, institution of the Petition should be denied. *Bettcher Indus., Inc. v. Bunzl USA, Inc.*, 661 F.3d 629, 639 (Fed. Cir. 2011) (inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient" to establish inherency.). Moreover, insofar as the Board may not craft new grounds of unpatentability not advanced by the petitioner, it would be inappropriate even to consider such a hypothetical inherency argument. *Arthrex, Inc. v. Smith & Nephew, Inc.*, 935 F.3d 1319, 1326 (Fed. Cir. 2019), cert. denied, 141 S. Ct. 236 (2020).

Indeed, it is known that administration of aflibercept using the claimed dosing regimen will not result in an effective method for treating/tertiary dose for some patients. A retrospective analysis of VIEW (hereinafter "Jaffe") showed 8-week dosing was significantly less effective than monthly dosing in approximately 20% of patients from the VIEW trials. Ex. 2018, 1861 ("[W]hen early persistent fluid was present after the initial 3 injections (a finding present in approximately 20% of eyes initially treated with IAI and in 30% of eyes with Rq4), there may be

[13] Dixon, Adis, Regeneron (8-May-2008), NCT-795 and NCT-377.

a benefit to monthly IAI compared with the other regimens[.]"). Consequently, in 2016, EYLEA®'s label was amended to specify that "***[s]ome*** patients may need every 4 week (monthly) dosing after the first 12 weeks (3 months)." Ex. 2019, 1; s*ee also id*. ("[A]dditional efficacy was not demonstrated in ***most*** patients when EYLEA was dosed every 4 weeks compared to every 8 weeks.") (emphases added).

Thus, the claimed dosing regimen may not be efficacious in some patients, and consequently, the required efficacy is not inherent in the dosing regimen. *See Gilead Scis.*, IPR2019-01455, Paper 16, 41 ("We are, however, unpersuaded that inherency has been shown on this record. … [B]ased on the evidence here, it is possible (even if 'unlikely') for an individual to receive combination therapy of FTC and DTF (or Truvada) and not be protected from infection.").

Additionally, even if Petitioner had established that "VEGF Trap-Eye" necessarily had the required amino acid and nucleic acid sequence (for the reasons in Section IV.A, it has not), Petitioner's inherency argument also fails to account for other variables that could impact the required efficacy of the claimed dosing regimen. "[A]nticipation by inherent disclosure is appropriate only when the reference discloses prior art that must ***necessarily*** include the unstated limitation, [or the reference] cannot inherently anticipate the claims." *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed.Cir.2002) (emphasis in original). Neither Petitioner nor its expert account for potential variables in, *inter*

alia, the preparation of the VEGF antagonist, its final formulation for administration, or the underlying exclusion criteria for patients to be treated, none of which are specified in Petitioner's cited art. Indeed, the cited references emphasize that special purification and formulation of EYLEA® was necessary for intravitreal administration. *See, e.g.*, Ex. 1006, 1575; Ex. 1005, 2142. What is needed to achieve the required efficacy is absent from any of Petitioner's allegedly anticipating references, and Petitioner makes no effort to show that the disclosed prospective dosing regimen of "VEGF Trap-Eye" necessarily results in a "method of treating" or a "tertiary dose," which require efficacy.

Consequently, Petitioner has not satisfied its burden to show anticipation of a "method of treating" or a "tertiary dose."

D. Ground 6: Petitioner Fails to Make a Threshold Showing that Any Challenged Claim Is Obvious Based on Dixon

Petitioner fails to show that there is a reasonable likelihood that at least one of the Challenged Claims is unpatentable as obvious based on Dixon (either alone or in combination with the '758 Patent or Dix) (Ground 6).[14] Petitioner argues that the Challenged Claims would have been obvious in view of Dixon's disclosure of Regeneron's Phase 2, CLEAR-IT 2 clinical trial data — a trial that

[14] Because Petitioner has not sufficiently disclosed its alternative obviousness theories (*see* Section II.B, *supra*), Regeneron addresses Petitioner's failures in Ground 6 as it relates to Dixon only.

tested a different dosing regimen than that claimed in the '338 Patent. Petitioner's Ground 6 argument should be rejected because (1) Petitioner fails to show a reasonable expectation of success of the claimed dosing regimen based on the CLEAR-IT 2 clinical trial results; (2) Petitioner's argument for no objective considerations is premised on a faulty claim construction and is factually flawed; and (3) objective indicia of non-obviousness further support the patentability of the Challenged Claims.

1. Petitioner Fails to Show that the POSA Would Have Had a Reasonable Expectation of Success

Petitioner argues that the POSA would have had a reasonable expectation of success for Regeneron's claimed Q8 dosing regimen in view of the positive Phase 2 [CLEAR-IT 2] data for VEGF Trap-Eye disclosed in Dixon. Pet., 64-65. But Petitioner fails to address significant differences between Regeneron's Phase 2 dosing regimen and the prospective Phase 3 dosing regimen. Petitioner also cherry-picks Regeneron's Phase 2 clinical trial results to suggest incorrectly that success for Regeneron's Phase 3 pivotal trial was expected. Not only is Petitioner's assertion unsupported by the factual record, but the published results of CLEAR-IT 2, the prior failures for extended dosing regimens, and the clinical trial design for VIEW1/2 demonstrate that there was great uncertainty as to whether Regeneron's extended fixed dosing regimen (with ≥ 8 weeks maintenance dosing) would work until Regeneron proved that it could.

First, Petitioner suggests that the very fact that Regeneron chose to run

Phase 3 trials means that the POSA would have expected the 8-week dosing regimen to be successful.[15] Pet., 64. Likewise, Petitioner's expert, Dr. Albini, states "Regeneron would not have settled on [3 monthly loading dose/every-8-week in the VIEW studies] without having a reasonable expectation that it would be successful." Ex. 1002, ¶368. Thus, Petitioner and its expert impermissibly work backwards from Regeneron's own inventive path, using improper hindsight. *See Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1296 (Fed. Cir. 2012) ("The inventor's own path itself never leads to obviousness; that is hindsight."). The Board should not follow Petitioner's lead and assess the validity of the Challenged Claims using this "illogical and inappropriate process." *Sensonics, Inc. v. Aerosonic Corp.*, 81 F.3d 1566, 1570 (Fed. Cir. 1996); *see also Insite Vision Inc. v. Sandoz, Inc.*, 783 F.3d 853, 859 (Fed. Cir. 2015) ("Defining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness.").

Large-scale Phase 3 clinical trials routinely fail, even when a Phase 2

[15] Petitioner misleadingly suggests that "Dixon reports, the Phase 2 CLEAR-IT 2 AMD trials were so promising that Phase 3 trials involving > 2000 patients were launched." Pet., 64. Dixon says no such thing. To the contrary, as discussed *infra*, Dixon notes that the Phase 3 VIEW results are required to know whether VEGF Trap-Eye will offer longer duration therapy.

clinical trial shows promise. Indeed, the art is littered with Phase 3 clinical trial failures of VEGF inhibitors for angiogenic eye disorders. Ex. 2020, 1-2; Ex. 2021, 1-2 (lampalizumab Phase 3 clinical trials, enrolling 975 and 906 patients, failed to meet primary endpoints); Ex. 2022, 1-2; Ex. 2023, 1-2 (Conbercept Phase 3 clinical trials, enrolling 1,157 and 1,157 patients, failed to meet primary endpoints); Ex. 2024, 1-2; Ex. 2025, 1-2 (Fovista Phase 2 clinical trials, enrolling 619 and 627 patients, failed to meet primary endpoints).

Thus, the fact that Regeneron initiated a Phase 3 clinical trial is not *prima facie* evidence of a reasonable expectation of success. *See OSI Pharms. LLC v. Apotex Inc.*, 939 F.3d 1375, 1378-79 (Fed. Cir. 2019) (finding that initiation of phase 2 trials does not show reasonable expectation of success). Indeed, both Fovista and Conbercept failed to meet their primary endpoints in Phase 3 studies, despite promising Phase 2 results. Ex. 2024; Ex. 2025; Ex. 2026, 1; Ex. 2022; Ex. 2023; Ex. 2027, 1.

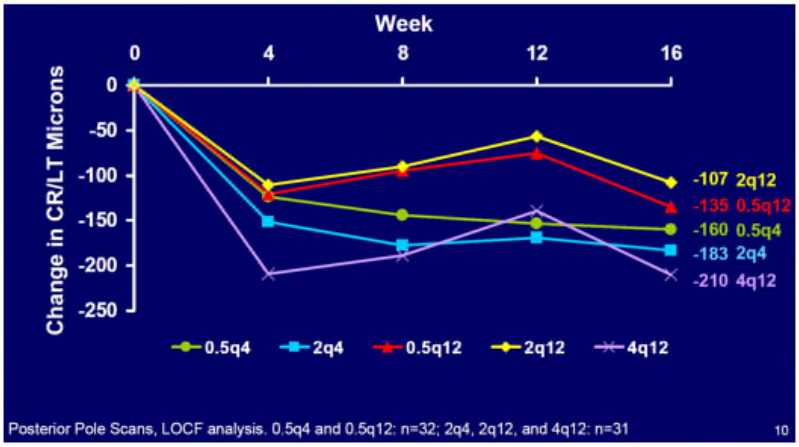
Perhaps most tellingly, the design of the VIEW1/2 trials demonstrates that Regeneron itself was hedging its bets on an extended 8-week dosing regimen. VIEW1/2 tested three treatment arms against a ranibizumab non-inferiority comparator — a 0.5 mg monthly dosing arm, and both a 4-week and 8-week 2 mg dosing arm (following three monthly loading doses). *See* Ex. 1006, 1576. If Regeneron had been reasonably certain that 8-week maintenance dosing would work, it had every incentive to eliminate the 4-week VEGF Trap-Eye treatment

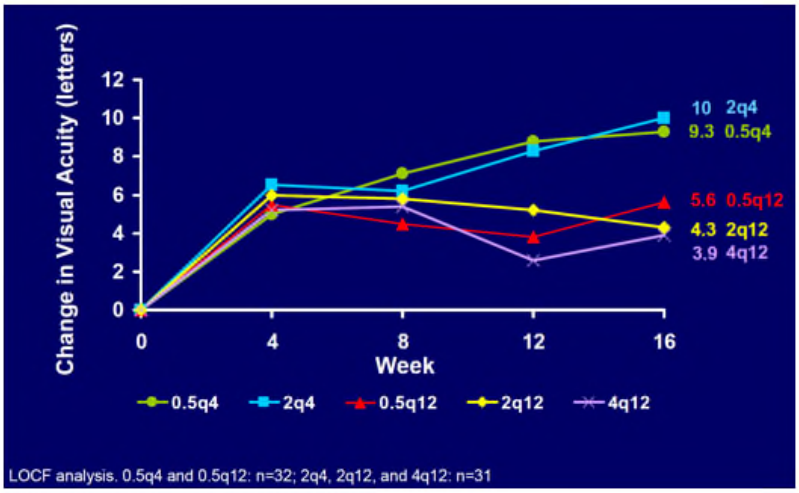
arms. An additional treatment arm significantly increases the time and expense (by millions of dollars) required to conduct a clinical trial. The added expense and effort would make no sense if Regeneron had a reasonable expectation that its prospective 8-week maintenance dosing arm would be successful.

Second, Petitioner argues that Dixon's disclosure of positive Phase 2 results from CLEAR-IT 2 (testing four monthly loading doses followed by PRN dosing) would have provided the POSA with a reasonable expectation of success. Pet., 64-65. To the contrary, the CLEAR-IT 2 trial results called into question the viability of an 8-week dosing regimen for VEGF Trap-Eye.

The CLEAR-IT 2 12-week primary endpoint data indicated that the therapeutic effect of VEGF Trap-Eye began to decrease between the week-4 and week-8 timepoints in the quarterly dosing arms, and the only treatment arms that were successful in sustaining therapeutic efficacy were the monthly treatment dosing arms (*i.e.*, 0.5Q4 and 2Q4). This is shown in the figure below, which was presented at the September 30, 2007, Retina Society Conference in Boston,

Massachusetts. Ex. 2028.





The top panel reports on central retinal/lesion thickness. A decrease in retinal thickness generally corresponds to a drying of the macula and the fluid that is created by the angiogenic process of wet AMD. The bottom panel reports visual acuity. As shown at the 8-week timepoint, there is re-accumulation of fluid by week 8 in the top figure (curves for arms 0.5Q12, 2Q12 and 4Q12 trend upward) in the treatment arms that received a dose at week 0 and a dose at week 12. This increased retinal thickness trend continues through week 12. The POSA

would have understood that fluid reaccumulation between weeks 4 and 8 on CRT would strongly suggest that VEGF Trap-Eye has less durability than 8 weeks. Likewise, in the bottom figure, visual acuity decreased at week 8 in the 0.5Q12 and 2Q12 arms relative to visual acuity at week-4, suggesting that VEGF Trap-Eye's effect was waning sometime between week-4 and week-8. Thus, rather than providing an expectation of success for a Q8 dosing regimen, the clinical trial results from CLEAR-IT 2 would have provided a basis to doubt that VEGF Trap-Eye would be successful on an 8-week dosing schedule.

Third, there was great uncertainty in the art regarding extended dosing based on prior failures, which Petitioner ignores. For example, Heier 2012 explains: "fixed quarterly[9,10] or 'as needed' (*pro re nata* [PRN]) dosing regimens,[11,12] without requiring monthly monitoring visits, were not effective at maintaining vision." Ex. 1018, 2537. Notably, Heier 2012 cites the same clinical trials on which Petitioner attempts to rely — EXCITE (Ex. 2029, 803; Ex. 2030, 3) (resulting in inferior therapeutic outcomes with quarterly as compared to monthly dosing of ranibizumab); HORIZON (Ex. 2029, 803) (resulting in inferior therapeutic outcomes with PRN dosing as compared to monthly dosing of ranibizumab); PIER (Ex. 2031, 680; Ex. 1027, 1425) (resulting in inferior therapeutic outcomes with quarterly dosing as opposed to monthly dosing of ranibizumab); and SAILOR (Ex. 2032, 1738) (resulting in inferior therapeutic outcomes with PRN dosing as compared to monthly dosing of ranibizumab) —

but reaches the opposite conclusion, *i.e.*, that these dosing regimens were not effective at maintaining vision. Indeed, Dixon notes that the PIER and PrONTO studies "seem to indicate that quarterly dosing is associated with poorer outcomes, but it may be possible to extend the time between injections if the patient is frequently monitored." Dixon at 1574, 1577.

Finally, nothing in Dixon itself taught that a fixed extended dosing regimen was likely to work. To the contrary, Dixon cautioned against over-interpreting Phase 2 results:

> ***The most effective dosing regimen and monitoring program for anti-VEGF therapy has yet to be firmly established*** but new treatments are aimed at extending and improving on the efficacy of ranibizumab.

Ex. 1006, 1576-77 (citations omitted) (emphasis added). In fact, Dixon notes that the durability of VEGF Trap-Eye and its adoption in clinical practice will only be known after Regeneron's Phase 3 clinical trial results are reported:

> Data from the Phase II study with VEGF Trap-Eye were positive ***…. Its adoption into clinical practice will depend on efficacy at 4 and 8 week intervals.*** If effective at 4 week intervals only, VEGF Trap-Eye will be adopted into clinical practice if it offers a competitive price advantage over ranibizumab. ***If effective at 8 week intervals, VEGF Trap-Eye offers the opportunity to significantly reduce treatment burden on patients and physicians, which would probably find wide acceptance.***

Ex. 1006, 1577 (citations omitted) (emphases added).

2. Petitioner's Argument Against Objective Evidence Should Be Rejected

The Federal Circuit has "repeatedly held that . . . objective evidence of secondary considerations . . . must be considered before determining whether the claimed invention would have been obvious." *Apple, Inc. v. ITC*, 725 F.3d 1356, 1365 (Fed. Cir. 2013). Such objective indicia include long-felt but unsolved need, unexpected results, and commercial success. *Id.* at 1375.

First, Petitioner's arguments against objective evidence are premised on a faulty claim construction that ignores the efficacy limitations of the Challenged Claims. Pet., 66. Petitioner argues that, because the claims do not require efficacy, the unexpected efficacy results of the claimed dosing regimen are irrelevant. Petitioner cites *Ormco* and *Kao* for the proposition that "if the [objective indicia] is due to an unclaimed feature of the device, the [objective indicia] is irrelevant." *Id.* But the objective indicia supporting nonobviousness of the Challenged Claims is directly tied to the claimed extended dosing regimens.

Second, Petitioner argues that Regeneron's showing of unexpected results during prosecution was flawed because it allegedly omitted "highly pertinent" information from the Examiner. This is incorrect and Petitioner's argument lacks merit.

Petitioner asserts Regeneron failed to disclose pre-January 2011 disclosures of the prospective VIEW1/2 dosing regimen to the Examiner. Pet., 67. But, as

detailed in Section III.B above, this is not so. For example, the 9/28/08 Press Release, which sets forth an identical disclosure to the disclosures on which Petitioner now relies for its anticipation arguments, was submitted to and considered by the Examiner.

Petitioner also contends that Regeneron mischaracterized "the standard of care at the time as monthly dosing, which ignored the actual practice of ophthalmologists at the time, who had begun using PRN or treat-and-extend dosing after a series of monthly loading doses." *Id.* But there was no satisfactory extended dosing regimen available at the time of the invention.

Before Regeneron's invention, there were two approved anti-VEGF therapies in use in clinical practice — Lucentis® and Avastin®.[16] Avastin, approved only for oncology indications, was used off-label and the FDA-approved, recommended label dosing for Lucentis was monthly intravitreal injections. Ex. 2003 ("recommended to be administered by intravitreal injection once a month (approximately 28 days)."). Petitioner points to various ranibizumab clinical trials to suggest that PRN or "less frequent dosing" was the standard of care, but those trials showed that PRN and quarterly dosing were not as effective and did not change the standard of care. Even today, the

[16] Macugen, an anti-VEGF aptamer, was also approved for the treatment of AMD, but its use was largely minimal once Lucentis was approved.

recommended administration of Lucentis remains monthly injections. Ex. 2033.

Next, Petitioner argues that "there is nothing unexpected about the every-eight-week results in light of the Phase 2 results obtained by Regeneron—results that were omitted from their arguments to the Examiner." Pet., 67. This argument belies the facts. Regeneron's Phase 2 results were submitted to and considered by the Examiner, including in the 9/28/08 Press Release. Ex. 2007. As explained in Section IV.D.1, *supra*, Regeneron's Phase 2 clinical trial data, which tested a completely different dosing regimen, did not prophesy the results of the claimed dosing regimen. It was not until the VIEW1/2 results were published that it was known that an 8-week dosing regimen could be successful, and, surprisingly, that it could be non-inferior to monthly dosing with ranibizumab.

Petitioner also argues "Regeneron's claims of 'an infinite number of different treatment protocols' to choose from ignored the practical realities facing physicians at the time." Pet., 68. While it is unclear how this statement is relevant to Regeneron's showing of unexpected results, Petitioner's statement is unfounded. Regeneron made this statement in response to an obviousness-type

double patenting rejection based on the Weigand Patents,[17, 18] which even the Examiner recognized did not "disclose the dosing schedules set forth in the instant claims." Ex. 1017. at 266.

Additionally, Petitioner's unsupported attorney argument that "[monthly] dosing would have been avoided if possible," "anything more frequent than monthly dosing would not have been considered," and "a new entrant to the anti-VEGF market naturally would have considered bi-monthly or quarterly dosing" (Pet., 68) is contradicted by the FDA-approved label for Lucentis® and the fact

[17] U.S. Patent No. 7,303,746 ("the '746 Patent"), U.S. Patent No. 7,303,747 ("the '747 Patent"), U.S. Patent No. 7,306,799 ("the '799 Patent"), and U.S. Patent No. 7,521,049 ("the '049 Patent") (collectively, "the Wiegand patents").

[18] Petitioner improperly refers to the Wiegand patents as "Monthly-Dosing Patents." Pet., 9 n.3. There is nothing to suggest that the Wiegand patents are directed to "monthly dosing regimens." Neither the '746 Patent nor the '049 Patent claim any particular dosing regimen or dosing interval. Ex. 2034, 69:50-70:60; Ex. 2035, 39:38-42:5. And the '747 Patent and '799 Patent recite a variety of dosing intervals, *e.g.*, "at least two weeks apart," "at least 4 weeks apart," "at least 3 months apart," or "at least 6 months apart." Ex. 2036, 39:66-42:3; Ex. 2037, 39:40-40:44.

that Macugen was approved for 6-week dosing. Ex. 2038.

Petitioner tries to erase the overwhelming evidence of long-felt but unmet need by arguing that Regeneron's testing of its own inventive dosing regimen anticipated itself: "[b]y 2009, the claimed dosing regimen was already publicly disclosed by Regeneron itself, and thus any 'unmet' need had already been fulfilled well before the '338 patent was filed." Pet., 69. Petitioner disregards that it was not until the inventions of the '338 Patent, ***after*** the VIEW1/2 study results were obtained that anyone, including Regeneron, understood the that the remarkable advantage of fixed 8-week dosing could be realized.

Notably, Regeneron was not the first or only FDA-approved anti-VEGF therapy used by clinicians for the treatment of angiogenic eye disorders. Indeed, when EYLEA® launched in late 2011, both Lucentis and off-label Avastin were widely used for the treatment of wAMD and other angiogenic eye disorders. Nonetheless, Regeneron's U.S. sales of EYLEA® have grown significantly since launch. Ex. 2039, 1; Ex. 2040, 4 . Petitioner's assertion that the '338 Patent's claimed dosing regimens were obvious before January 2011 is contradicted by the extraordinary commercial success that EYLEA® has enjoyed since launch.

In the unlikely event it is required, Regeneron can and will present additional compelling evidence of objective indicia, including at least (1) commercial success of EYLEA®; (2) the claimed treatment produced unexpected results; (3) others have tried and failed to develop a treatment capable of extended,

fixed dosing; and (4) long-felt but unmet need for an extended dosing regimen.

V. CONCLUSION

For the foregoing reasons, the Board should deny institution of MPI's petition for IPR of all Challenged Claims of the '338 Patent.

Dated: August 16, 2021

Respectfully Submitted,

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CERTIFICATE OF COMPLIANCE

The undersigned certifies that this preliminary response complies with the type-volume limitations of 37 C.F.R. § 42.24(a)(1)(i). This preliminary response (including figure labels and annotations) contains 13,928 words as calculated by the "Word Count" feature of Microsoft Word 2010, the word processing program used to create it.

The undersigned further certifies that this preliminary response complies with the typeface requirements of 37 C.F.R. § 42.6(a)(2)(ii) and typestyle requirements of 37 C.F.R. § 42.6(a)(2)(iii). This preliminary response has been prepared in a proportionally spaced typeface using Microsoft Word 2010 in Times New Roman 14-point font.

/s/ Deborah E. Fishman

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e)(4)(i) *et seq*. and 42.105(b), the undersigned Certifies that on April 14, 2021, a true and entire copy of this **PRELIMINARY RESPONSE OF PATENT OWNER REGENERON PHARMACEUTICALS, INC.**, and all supporting exhibits, were served via e-mail to the Petitioner at the following email addresses:

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