UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.,
Petitioner

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner

Case IPR2021-00880
Patent No. 9,669,069 B2

PRELIMINARY RESPONSE OF PATENT OWNER REGENERON PHARMACEUTICALS, INC.

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2001	Exhibit Number Unused
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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)
2013	D.V. Do *et al*., *An Exploratory Study of the Safety, Tolerability and Bioactivity of a Single Intravitreal Injection of Vascular Endothelial Growth Factor Trap-Eye in Patients With Diabetic Macular Oedema*, Br. J. Opthamol 93:144-49 (2009)
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2016	T. Hachiya et al., *Increase in respiratory cost at high growth temperature is attributed to high protein turnover cost in Petunia x hybrida petals*, Plant, Cell, and Environment, 30:1269-1283 (2007)

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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
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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

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2028	Regeneron Pharmaceuticals Inc., "VEGF Trap-Eye CLEAR-IT 2 Final Primary Endpoint Results" presented at the 2007 Retina Society Conference in Boston, Massachusetts (September 30, 2007)
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 and 8-12 ("Challenged Claims") of U.S. Patent No. 9,669,069 ("the '069 Patent," Ex. 1001).

I. INTRODUCTION

Petitioner, who is developing a biosimilar of EYLEA® for the treatment of angiogenic eye disorders, files this challenge to try to invalidate Regeneron's '069 Patent, which covers an alternate approved dosing regimen for EYLEA®.

Before the development of EYLEA®, the standard of care for treatment of 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 injections led to several attempts to increase intervals between injections. Ex. 1018, 1 and 9. However, existing VEGF inhibitors were not effective at maintaining vision through fixed quarterly or "as needed" (*pro re nata*) dosing regimens. Ex. 1001, 1:55-59; Ex. 2003, 5.

Regeneron sought to develop a therapy that would finally improve ***and*** maintain visual acuity with extended time between injections. The '069 Patent discloses and claims the administration of a specific VEGF antagonist using a dosing regimen that includes a single initial dose of the VEGF antagonist,

followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist, where the tertiary doses are "administered on an as-needed/*pro re nata* (PRN) basis, based on visual and/or anatomical outcomes as assessed by a physician or other qualified medical professional."

As set forth herein and in the accompanying exhibits, the Petition should be denied for at least the following independent reasons:

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

Second, Petitioner bases its challenges on the same or substantially the same prior art that was previously before the U.S. Patent & Trademark Office ("Office") and was 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 makes no effort to show that the art relied upon in any of its Grounds discloses, expressly or inherently, that the PRN dosing of the claimed VEGF Trap fusion protein be administered "based on visual and/or anatomical outcomes as assessed by a physician or other qualified medical professional." Instead, Petitioner argues — unconvincingly — that this limitation is a "mental

step" that should be afforded no patentable weight. Because Petitioner's claim construction position lacks merit and it has utterly failed to show this limitation in its cited art, it has not met its threshold burden under 35 U.S.C. §§ 314(a) and 312(a)(3), and the Board should deny institution for this reason alone.

Fourth, Petitioner's anticipation challenges also fail because Petitioner does not demonstrate that the claims' required nucleic acid or amino acid sequence was expressly or inherently disclosed in its cited references. Petitioner's anticipation position depends on its unsupported theory that the alleged prior art inherently discloses aflibercept and its amino acid and nucleic acid sequences through reference to "VEGF Trap-Eye." But Petitioner relies on inference to make a connection between "VEGF Trap-Eye" and "aflibercept" that the prior art does not support, and the Federal Circuit has repeatedly held that such mere possibilities or probabilities are insufficient for anticipation.

Fifth, Petitioner's Ground 4 anticipation and obviousness challenges additionally fail because its cited art fails to disclose a "tertiary dose" that "is administered on an as-needed/*pro re nata* PRN basis" and, further, Petitioner fails to show that the person of ordinary skill in the art ("POSA") would have been motivated to modify a fixed 8-week tertiary dosing regimen to become a PRN tertiary dosing regimen, as required by each of the Challenged Claims.

Finally, Petitioner's Ground 5 obviousness challenge additionally should be rejected because Petitioner fails to show that the POSA would have been

motivated to reduce the four monthly loading doses[1] in Regeneron's Phase 2 clinical trials to three monthly loading doses, and further fails to address that the clinical trial results and the art as a whole would caution against such a modification.

For these reasons, as explained further below, Regeneron respectfully requests that the Board deny institution of the Petition.

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 13,951 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 '069 Patent specification, including a lengthy passage of text on which Petitioner substantively relies for its arguments. *See e.g.*, Pet., 14-15. In total, Petitioner fails to account for 186 words in text images in the Petition which, when included, results in a word count of 14,137 words. Thus, Petitioner disregards the Board's rules, as further evidenced by Petitioner's use of the same tactic in its Petition filed in IPR2021-00881. Paper 1. This is a reason to deny institution. Trial

[1] The recited initial and secondary doses are also referred to as "loading doses" and the recited tertiary doses are also referred to as "maintenance doses" herein.

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 '069 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 has not satisfied the particularity requirements under § 312(a)(3) for at least Ground 5 because the Petition suffers from the same deficiencies identified by the Board in *Adaptics*. Specifically, Ground 5 is a "catch-all" ground that alleges that the Challenged Claims are obvious over six references under at least seven and as many as nine different theories:

1. Heier-2009 + Mitchell;
2. Heier-2009 + Mitchell + the '758 Patent;
3. Heier-2009 + Mitchell + Dix;
4. Heier-2009 + Dixon;
5. Heier-2009 + Dixon + the '758 Patent;
6. Heier-2009 + Dixon + Dix;
7. Heier-2009 + Lalwani;
8. Heier-2009 + Lalwani + the '758 Patent; and
9. Heier-2009 + Lalwani + Dix.

See Pet., 60-61 n.22.

Importantly, Petitioner fails to explain why each of these combinations is necessary. *Id.* at 60-67. Rather, as in *Adaptics*, Petitioner impermissibly assumes

that Heier-2009 does not disclose one or more claim limitations and leaves it to the Board and Regeneron to fill in the gaps of its Petition. Petitioner also does not explain the differences between at least independent claim 1 and the alleged primary reference, Heier-2009, much less the other secondary or tertiary references, or the differences between each of the various secondary references (Mitchell, Dixon, Lalwani) or between each of the various tertiary references (the '758 Patent and Dixon). *Id*. at 63-66. Consequently, as in *Adaptics*, Petitioner turns the Petition into an empty invitation to the Board and Regeneron to ascertain what evidence purportedly supports the full breadth of Petitioner's contentions.

Beyond its failure to identify how each combination maps to the claim limitations or the differences between each combination, Petitioner does not articulate any specific motivation to combine or modify at least: (1) Heier-2009 with Lalwani, (2) the Heier-2009 and Mitchell combination with either of the two tertiary references, or (3) the Heier-2009 and Dixon combination with either of the two tertiary references. Again, this lack of particularization leaves Regeneron and the Board to search the record for the evidence that would support Petitioner's theories.

Compounding Petitioner's lack of specificity as to the distinct combinations comprising Ground 5, Petitioner uses its cited references inconsistently. Three of the seven obviousness theories Petitioner sets out in Ground 5 involve combining

Heier-2009 (Ex. 1020) with Dixon (Ex. 1006), even though these two references are characterized elsewhere in the Petition as alternative references. *Compare* Pet., 60-67 (Ground 5) (arguing Heier-2009 and Dixon must be combined) *with* Pet., 45-50 (Grounds 1 & 2) (arguing Heier-2009 and Dixon both independently anticipate). Specifically, Petitioner argues that each of Heier-2009 and Dixon represent ***alternative*** disclosures anticipating claim 1. *Id.* at 46 ("[E]ach of Heier-2009 and Dixon disclose every element of independent claim 1."); *see also, id.* at 61-62 n.23 ("[B]oth Heier-2009 and Dixon are directed toward and expressly disclose VEGF Trap-Eye."). Yet, in Ground 5, Petitioner asserts Heier-2009 and Dixon ***in combination*** disclose all the elements of claim 1. *Id.* at 62-66 ("A skilled artisan naturally would have been motivated to combine the successful PRN regimen of CLEAR-IT-2 from Heier-2009 with the widely used loading regimen of three monthly doses disclosed in Mitchell and Dixon—to arrive at a regimen falling squarely within Challenged Claim 1."); *see also, id.* at 68-69 ("Heier-2009 plus Dixon").

This inconsistency as to whether Heier-2009 and Dixon are alternative references anticipating the Challenged Claims or are cumulative references that render the Challenged Claims obvious in combination makes Petitioner's arguments impermissibly ambiguous and difficult to understand. The Board has previously deemed similar confusing and inconsistent arguments to lack particularity and has exercised its discretion to deny the entire Petition under these

circumstances. *See, e.g.*, *EIK Eng'g Sdn. Bhd. v. Wilco Marsh Buggies & Draglines, Inc.*, IPR2020-00344, Paper 7 at 2 (June 23, 2020), *reh'g denied*, IPR2020-00344, Paper 12 (Mar. 4, 2021).

For at least the above reasons, Petitioner has not satisfied the requirement to state, with particularity, the grounds on which the challenge to each claim is based. Accordingly, the Petition presents procedural unfairness to Regeneron, as well as an inefficient use of the Board's time and resources. Consequently, 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., 4-5. Petitioner stated "[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 the same or substantially the same art that was considered by the Examiner during prosecution of the '069 Patent and fails to argue the Examiner made any error material to the patentability of the Challenged Claims.

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

The art relied upon in Petitioner's Grounds is the same or substantially the same as the art presented to, and considered by, the Examiner during prosecution of the '069 Patent, thus satisfying step one of the *Advanced Bionics* framework.

1. Dixon

Dixon appears on the face of the '069 Patent. Ex. 1001, 2. Petitioner fails to acknowledge that Dixon was submitted to the Office in an IDS during

prosecution and was marked "considered" by the Examiner. Ex. 1017, 121 (cited in IDS dated 1/27/2017); *id*. at 168 (marked considered by Examiner). The Board has consistently found that citation in an IDS is sufficient to satisfy step one of the *Advanced Bionics* framework. *See, e.g., ABS Global, Inc. v. Cytonome/ST, LLC*, IPR2021-00306, Paper 13 at 10 (Jun. 7, 2021); *see also Philip Morris Prods., S.A. v. Rai Strategic Holdings, Inc.*, IPR2020-00921, 2020 WL 6750120, at *5 (Nov. 16, 2020) ("Applying the *Advanced Bionics* two-part framework to Patent Owner's arguments, we determine that the art presented in the Petition is the same as the art previously presented to the Office during examination because all of Petitioner's references were cited in an IDS and are listed as cited art on the front face of the '268 Patent."). Thus, Dixon was previously presented to and considered by the Office.

2. Heier-2009

Although Heier-2009 was not previously presented to the Office, it is cumulative of at least Dixon, which was presented to the Office in an IDS that was considered by the Examiner. Ex. 1017, 121, and 168.

Petitioner asserts that "Heier-2009 and Dixon each disclose Regeneron's 'CLEAR-IT-2' Phase 2 trial studying VEGF Trap-Eye as a therapy for treating AMD … [and] thus anticipat[e] all limitations of at least Challenged Claims 1 and 9-12." Pet., 45. Petitioner does not allege that Heier-2009 discloses material facts or information that are absent in Dixon. Indeed, Petitioner alleges that both Dixon

and Heier-2009 disclose the same prospective CLEAR-IT 2 dosing regimen. *Id.* at 45. Petitioner groups Grounds 1 (Heier-2009) and 2 (Dixon) together in its Petition, essentially admitting that Heier-2009 and Dixon are equivalent. *Id*. at 45-50. Where, as here, a petitioner fails to identify any 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, Inc. v. Impinj, Inc.*, IPR2020-00519, 2020 WL 4805424, at *4-5 (Aug. 17, 2020) (institution denied where asserted reference found cumulative of previously presented reference because "Petitioner … [did] not identify any specific information in the [asserted references] that [was] 'additional' to or 'different' than the information in the [previously presented reference]"); *see Evergreen Theragnostics, Inc. v. Advanced Accelerator Applications SA*, PGR2021-00003, Paper 10 at 10-13 (Apr. 15, 2021) (finding multiple references cumulative of those cited in IDS during prosecution because previously presented references taught same features as asserted art); *see also Gardner Denver, Inc. v. Utex Indus., Inc.*, IPR2020-00333, 2020 WL 4529832, at *5-6 (Aug. 5, 2020) (same).

As discussed, Dixon was submitted to the Office in an IDS that was considered by the Examiner. Ex. 1017, 121, and 168. Therefore, the Office was presented with art that was "substantially the same as" Heier-2009.

3. Regeneron (30-April-2009)

Although Regeneron (30-April-2009) was not previously presented to the Office, it is cumulative of Regeneron (20-December-2010), which was submitted to the Office in an IDS and marked considered by the Examiner. Ex. 1017, 122, 169.

Petitioner alleges that Regeneron (30-April-2009) teaches the dosing regimen of the COPERNICUS trial. Pet., 37, 50. Regeneron (20-December-2010), which was submitted to the Office, also discloses the dosing regimen of COPERNICUS. Ex. 2042, 2. The following table compares the Regeneron (20-December-2010) disclosure of the COPERNICUS dosing regimen to the Regeneron (30-April-2009) disclosure relied upon by Petitioner in its Grounds:

Regeneron (20-December-2010) (Ex. 2042, 2)	**Regeneron (30-April-2009) (Ex. 1028, 1)**
"Patients in the COPERNICUS … stud[y] receive six monthly injections of either VEGF Trap-Eye at a dose of 2mg or sham injections. … At the end of the initial six months, all patients randomized to VEGF Trap-Eye are dosed on a PRN (as needed) basis for another six months."	"Patients … will receive 6 monthly intravitreal injections of either VEGF Trap-Eye at a dose of 2 milligrams (mg) or sham control injections. … At the end of the initial 6 months, all patients will be dosed on a PRN (as needed) basis for another 6 months."

As with Heier-2009 and Dixon, *supra,* Petitioner does not identify any material differences between Regeneron (30-April-2009) and Regeneron (20-December-2010). Thus, because Regeneron (20-December-2010) is cumulative of Regeneron (30-April-2009), substantially the same art was previously presented to the Office.

4. Mitchell

While Mitchell was not previously presented to the Office, Mitchell is cumulative of Dixon, which, as discussed *supra*, was provided to the Office in an IDS and considered by the Examiner during the prosecution of the '069 Patent. Ex. 1017, 121, and 168.

Petitioner asserts that both Mitchell and Dixon "teach anti-VEGF regimens for AMD employing an initial dose (week 0), one or more secondary doses administered four weeks after the immediately preceding dose (weeks 4 and 8) - for a total of three loading doses, and tertiary PRN dosing." Pet., 81. Petitioner identifies no material differences between Mitchell and Dixon. Thus, because Mitchell is cumulative of Dixon, which was provided to the Office in an IDS and considered by the Examiner, substantially the same art as Mitchell was previously presented to the Office. *See NXP USA*, 2020 WL 4805424, at *4-5; *see also Evergreen Theragnostics*, PGR2021-00003, Paper 10 at 10-13; *Gardner Denver*, 2020 WL 4529832 at *5-6.

5. '758 Patent and Dix

Petitioner argues that the '758 Patent and Dix each purportedly "disclose the VEGF Trap-Eye sequences…." Pet., 62 n.23. When a continuation-in-part application 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, United States Patent Application Publication No. 2006/0058234 (Ex. 2009) (“the ’234 Application”) to the Office in an IDS and the Examiner marked it considered during prosecution of the ’069 Patent. 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 and Dix. *Compare* Ex. 2009, SEQ ID No. 7 *with* Ex. 1010, Figs. 24A-C. The ’758 Patent and the ’234 Application both identify this sequence as “VEGFR1R2-FcΔC1.” Ex. 1010, 10:15-17; Ex. 2009, [0023]. Accordingly, the ’758 Patent is substantially the same as the ’234 Application, which was considered by the Examiner during original prosecution. *Dropworks, Inc. v. Univ. of Chi.*, IPR2021-00100, Paper 9 at 13-14 (May 14, 2021); *NXP USA*, 2020 WL 4805424 at *3-5; *Gardner Denver*, 2020 WL 4529832, at *5-6.

Although Dix was not previously presented to the Office, Dix is cumulative of the ’234 Application. Petitioner asserts that Dix discloses “the VEGF Trap-Eye sequences otherwise known to skilled artisans,” Paper 1 at 61 n.23, yet it is indisputable that the ’234 Application discloses the exact same amino acid sequence as Dix. *Compare* Ex. 2009, SEQ ID NO. 7 *with* Ex. 1033, SEQ ID NO. 3. As discussed, the ’234 Application was provided to the Office in an IDS and marked considered by the Examiner. Ex. 1017, 66, and 112. Thus, substantially

the same art as Dix was previously presented to the Office. *See NXP USA*, 2020 WL 4805424, at *4-5; *see also Dropworks, Inc*, IPR2021-00100, Paper 9 at 13-14; *Gardner Denver*, 2020 WL 4529832 at *5-6.

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

Because the same or 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, LLC v. MED-EL Elektromedizinische Gerate GmbH*, IPR2019-01469, 2020 WL 740292, at *3 n.9 (Feb. 13, 2020). "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" appears nowhere in the Petition. Nor does Petitioner allege that the Examiner overlooked or misapprehended something during prosecution. The Board has repeatedly determined that a petitioner's failure to allege material error is a sufficient basis to determine that the petitioner did not carry its burden as to step two. *E.g.*, *ABS Global*, IPR2021-00306, Paper 13 at 13-14 ("[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).

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 one of the '069 Patent claims is unpatentable for Grounds 1 through 5, and thus, denial of the petition is warranted. 35 U.S.C. § 314(a).

A. Grounds 1-5: Petitioner Fails to Establish the "Assessed by a Physician" Limitation Is Anticipated or Obvious

Each of the Challenged Claims requires "each tertiary dose" to be "administered on an as-needed/*pro re nata* (PRN) basis***, based on visual and/or anatomical outcomes as assessed by a physician or other qualified medical professional***." Ex. 1001, 50-53 (emphasis added). As explained below, this limitation is a positive limitation that should be afforded patentable weight. Consequently, Petitioner fails to satisfy its burden of proof to establish that the "assessed by a physician" limitation is disclosed expressly or inherently in any of the references relied upon in any of its grounds. Additionally, using Petitioner's definition of the POSA, Petitioner fails to establish that Heier-2009, Dixon or Regeneron (30-April-2009) is enabled.

1. Claim Construction

Petitioner's challenge should be disposed of under 35 U.S.C. § 315. However, should the Board consider it necessary to decide whether Petitioner satisfied its threshold burden under 35 U.S.C. § 314, Regeneron respectfully submits that "assessed by a physician or other qualified medical professional" is a positive limitation of the claim that should be afforded patentable weight.

For purposes of this Preliminary Response only, Regeneron has used Petitioner's definition of the person of ordinary skill in the art ("POSA"). Pet., 9. Regeneron reserves the right to propose another definition if this IPR is instituted.

Petitioner also proposes a construction for "tertiary dose" and argues that

the preamble "A method for treating an angiogenic eye disorder in a patient" is not a positive limitation of the claim. Pet., 13-23. While Regeneron disagrees with Petitioner's proposed constructions, Regeneron does not advance claim construction positions for these terms at this time because construction of these terms is not necessary to resolve the arguments presented in this POPR. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (explaining it is only necessary to "construe terms 'that are in controversy, and only to the extent necessary to resolve the controversy'").[2]

Petitioner likewise proposes constructions for (1) "4 weeks" and "*Pro re Nata* (PRN)"; and (2) "VEGFR1 Component," "VEGFR2 Component" and the "Multimerization Component." Pet., 18-19. Again, Regeneron does not advance claim construction positions for these terms because construction of these terms is

[2] If the Board decides to construe "method of treating" or "tertiary dose" in this IPR, it should do so consistently with the constructions Regeneron has proposed in its contemporaneously filed Preliminary Response in IPR2021-00881 relating to the '338 Patent, since the '069 Patent was filed as a continuation from the '338 Patent. *See* IPR2021-00881, Paper 10, at 31-37; *see Samsung Elecs. Co. v. Elm 3DS Innovations, LLC*, 925 F.3d 1373, 1378 (Fed. Cir. 2019) ("Where multiple patents derive from the same parent application and share many common terms, we must interpret the claims consistently across all asserted patents.").

not necessary to resolve the arguments presented in this POPR. *Nidec*, 868 F.3d at 1017. Regeneron reserves the right to propose other constructions of these and other terms if this IPR is instituted.

a. "Based On Visual and/or Anatomical Outcomes as Assessed by a Physician or Other Qualified Medical Professional"

Each of the Challenged Claims requires "wherein each tertiary dose is administered on an as-needed/*pro re nata* (PRN) basis, ***based on visual and/or anatomical outcomes as assessed by a physician or other qualified medical professional***." Ex. 1001, 21:42-60 (emphasis added). In the context of its Ground 5 obviousness argument, Petitioner argues "[t]he 'assessed by a physician' limitation is a pure mental step not entitled to any patentable weight." Pet., 65 (citing *King Pharms.*, 616 F.3d at 1278). However, as discussed below, "assessed by a physician" is a positive limitation of the claim that should be afforded patentable weight. Thus, Petitioner's "mental step" argument fails.

(i) "As Assessed by a Physician" Is a Positive Limitation of the Claim

The phrase "as assessed by a physician or other qualified medical professional" is part of a wherein clause that recites as-needed/*pro re nata* (PRN) administration of each tertiary dose. Petitioner does not dispute that this wherein

clause is a positive limitation of the claim, nor can it.[3] The limitation "wherein each tertiary dose is administered on an as-needed/PRN basis…" supplies the frequency for administration of the tertiary dose, as shown below.

Claim 1 recites:

> A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;
> wherein each secondary dose is administered 2 to 3 weeks after the immediately preceding dose;
> wherein each tertiary dose is administered on an as-needed/pro re nata (PRN) basis, based on visual and/or anatomical outcomes ***as assessed by a physician or other qualified medical professional***;
> ….

Ex. 1001, 21:41-60 (emphasis added).

It is well-established that a "wherein" clause that provides structure or acts that are necessary to define the invention is a positive limitation of a claim. *See Hoffer v. Microsoft Corp.*, 405 F.3d 1326, 1329-30 (Fed. Cir. 2005) (finding clause limiting where it "is more than the intended result of a process step," "is

[3] Indeed, Petitioner specifically identifies this wherein clause as a limitation of the claim for claim mapping purposes. *See* Pet., 48.

part of the process itself," and is an "integral part of the invention"). Moreover, the claim language makes clear that "assessed by a physician" is part of the process for determining the frequency of tertiary dose administration. It provides the timing of the administration of the tertiary dose by defining how (*i.e.*, assessment of visual and/or anatomical outcomes) and by whom (*i.e.*, physician or qualified medical professional) that determination is made.

(ii) **The "Mental Steps" Doctrine Does Not Apply**

Petitioner cites *King Pharmaceuticals, Inc. v. Eon Labs, Inc.*, 616 F.3d 1267 (Fed. Cir. 2010), to argue that the phrase "assessed by a physician" is purely a mental step. Pet., 65. However, *King Pharms.* and the mental step doctrine — an extension of the printed matter doctrine — do not apply to the "assessed by a physician" limitation.

In *King Pharms.*, the court considered whether "an otherwise anticipated method claim becomes patentable because it includes a step of 'informing' someone about the existence of an inherent property of that method." *Id.* at 1278. Employing a § 101 analysis, the court held that the "informing" limitation was insufficient to transform or render patent eligible an otherwise invalid claim. *Id.* at 1279 (finding that the 'informing' limitation "in no way depends on the [method], and the [method] does not depend on the ['informing' limitation]").

Here, in contrast, to satisfy the claimed methods, the administration of the tertiary dose on a PRN basis must be based on the ***physical acts*** of assessing

visual and/or anatomical outcomes by a physician or other qualified medical professional. Disclosure of the visual or anatomic outcomes alone without disclosure of ***who*** is making the assessment to determine whether and when to administer a tertiary dose is not a disclosure of the entire limitation or step. This limitation is a physical, active, and necessary step in the claimed method of treatment, carried out specifically by a physician or trained medical professional. It is not an informational or instructional step, but rather a limitation that is inexorably linked to the step of administering one or more tertiary doses. Thus, *King Pharms.* and the printed matter/mental step doctrine do not apply.

Indeed, even under a patent eligibility analysis, because the "assessed by a physician" limitation transforms the "tertiary dose" limitation, it is entitled to patentable weight. *King Pharms., Inc.*, 616 F.3d at 1277-78 (noting in dicta that the machine-or-transformation test remains a useful tool to determine whether processes are patent eligible); *Vanda Pharms. Inc. v. W.-Ward Pharms. Int'l Ltd.*, 887 F.3d 1117, 1136 (Fed. Cir. 2018) (affirming patentability of claims directed to a specific method of treatment for specific patients using a specific compound at specific doses to achieve a specific outcome); *see also C R Bard Inc. v. AngioDynamics, Inc.*, 979 F.3d 1372, 1381 (Fed. Cir. 2020) (holding asserted claims directed to "method of performing a power injection procedure" for vascular access ports were patent eligible under § 101 because the claims as a whole were not solely directed to printed matter).

Because the "as assessed by a physician or other qualified medical professional" is a necessary part of a positive limitation of the claim, it is entitled to patentable weight.

2. Grounds 1-4: Petitioner Fails to Establish that Heier-2009, Dixon or Regeneron (30-April-2009) Inherently or Expressly Discloses the "Assessed by a Physician or Other Qualified Medical Professional" Limitation (All Challenged Claims)

Petitioner asserts that Heier-2009 (Ground 1), Dixon (Ground 2 and 4) and Regeneron (30-April-2009) (Ground 3) 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.*, 616 F.3d at 1274 (quotations omitted). Petitioner fails to show that Heier-2009, Dixon or Regeneron (30-April-2009) discloses the "assessed by a physician or other qualified medical professional" limitation either expressly or inherently. Rather, Petitioner simply ignores this portion of the wherein limitation for purposes of anticipation and thus fails to make its threshold showing of anticipation for any of the Challenged Claims, as shown below.

a. Heier-2009 (Ground 1)

Petitioner relies on the following passage in Heier-2009 as allegedly disclosing the "assessed by a physician or other qualified medical professional" limitation:

> Patients with neovascular AMD were randomly assigned to receive monthly intravitreal injections of VEGF Trap-Eye 0.5 mg or 2.0 mg . . . for an initial 3-month fixed-dose period, after which they received the same doses on [a PRN] basis at monthly visits out to 1 year.

Pet., 48 (citing Ex. 1020, 45). Heier-2009 fails to expressly disclose a method where the administration is "based on visual and/or anatomical outcomes as assessed by a physician or other qualified medical professional." Indeed, Petitioner never argues that this limitation is disclosed, either expressly or inherently, in Heier-2009.

Instead, Petitioner — without making these same arguments in its Petition — relies on bare citations to its expert's declaration. Pet., 48 (citing Ex. 1002, ¶121). Specifically, Dr. Albini opines without support that "to determine the need for an injection at each visit during the trial, a physician or other qualified medical professional would have to make an assessment, and that would have been well understood by persons of ordinary skill in the art to include visual and/or anatomical outcomes, such as visual acuity and retinal swelling measurements." Ex. 1002, ¶121.

As an initial matter, the Board should disregard Dr. Albini's opinions since Petitioner fails to argue, let alone establish, within the four corners of its Petition that all limitations of the claims are anticipated based on the disclosure of Dixon, Heier-2009, and/or Regeneron (April-30). *Microsoft Corp. v. Bradium Techs.*

LLC, IPR2015-01435, Paper 15 at 29 (Dec. 23, 2015) ("[W]e will not consider arguments that are not made in the Petition but are instead incorporated by reference to the cited paragraphs and claim charts of [the petitioner's Expert] Declaration."); *Cisco Sys., Inc. v. C-Cation Techs., LLC*, IPR2014-00454, Paper 12 at 7-10 (Aug. 29, 2014) ("[the Board] will not consider arguments that are not made in the Petition, but are instead incorporated by reference to the cited paragraphs and claims charts of [petitioner's expert]").

In any event, because Dr. Albini's opinion at paragraph 121 is wholly unsupported by any underlying facts, the Board should not credit his testimony. *See, e.g.*, Practice Guide at 40-41 (citing *Rohm & Haas Co. v. Brotech Corp.*, 127 F.3d 1089, 1092 (Fed. Cir. 1997)); *Merck Sharp & Dohme Corp. v. Wyeth LLC*, IPR2017-01211, Paper 9 at 13-14 (Oct. 20, 2017) (explaining that "[o]ne's expertise, even when draped with a skilled[ ]artisan veil, does not entitle a naked opinion to much weight").

Dr. Albini asserts that Heier-2009 discloses "several measures that physicians were to use in assessing patients for PRN dosing." Ex. 1002, ¶121 (citing Ex. 1020, 45); Ex. 1006, 1576). However, the ***only*** discussion of these measures — *i.e.*, best corrected visual acuity ("BCVA") and retinal thickness — in Heier-2009 relates to the 1-year outcomes of the clinical trial, ***not*** PRN re-treatment criteria. Ex. 1020, 45 ("At 1 year, for all treated groups combined (n=157), there was a significant improvement in BCVA from baseline (mean

improvement 5.3 letters; P<.0001)…." and "Patients receiving initial monthly doses of VEGF Trap-Eye achieved mean decreases in retinal thickness vs baseline at 1 year."). Thus, Heier-2009 does not disclose that PRN dosing in the clinical trial was "based on visual and/or anatomical outcomes as assessed by a physician or other qualified medical professional," as the Challenged Claims require.

Consequently, Petitioner fails to establish that Heier-2009 anticipates, expressly or inherently, the recited limitation "based on visual and/or anatomical outcomes as assessed by a physician or other qualified medical professional."

b. Dixon (Ground 2 and 4)

In Ground 2, Petitioner relies on the following passage in Dixon with respect to the "assessed by a physician or other qualified medical professional" limitation:

> Following this fixed dosing period, patients were treated with the same dose of VEGF Trap-Eye on a p.r.n. basis. Criteria for re-dosing included an increase in central retinal thickness . . . a loss of ≥ 5 ETDRS letters in conjunction with recurrent fluid by OCT, persistent fluid as indicated by OCT, new onset classic neovascularization, new or persistent leak on FA or new macular subretinal hemorrhage.

Pet., 48 (citing Ex. 1006, 1576).

But Dixon provides no disclosure of ***who*** is assessing the disclosed retreatment criteria, and Petitioner has not argued, let alone made any showing

that this is inherent in Dixon. Moreover, since Petitioner's definition of the POSA includes, *inter alia*, a person with "an advanced degree, such as an M.D. ***or*** Ph.D. . . . with practical ***academic*** or medical experience," (Pet., 25) the POSA need not be "a physician or other medical qualified medical professional." Consequently, it cannot be assumed and is not necessarily the case that a "physician or other qualified medical professional" assessed the disclosed retreatment criteria in Dixon.

In Ground 4 (anticipation), Petitioner relies upon Dixon's disclosure of the VIEW dosing regimen, which is three monthly loading doses, followed by monthly or every eight-week maintenance dosing. Dixon's disclosure of the VIEW dosing regimen does not disclose the claimed PRN dosing regimen.[4] As in Ground 2, Petitioner again utterly ignores its burden to establish that the cited references disclose expressly or inherently the requirement that "a physician or otherwise qualified medical professional" assesses the visual and/or anatomic outcomes to determine whether or when to administer a tertiary dose. Thus, Petitioner fails to carry its burden to show that Dixon anticipates the Challenged Claims (Ground 2) or renders them obvious (Ground 4).

[4] Petitioner asserts that Regeneron, during prosecution, equated the eight-week dosing in VIEW with the claimed PRN dosing. Pet., 54-55. Patent Owner did not. *See* Section IV.C.1., *supra*.

c. Regeneron (30-April-2009) (Ground 3)

Petitioner relies exclusively on the following passage in Regeneron (30-April-2009) with respect to the "visual and/or anatomical outcomes as assessed by a physician or other qualified medical professional" limitation:

> Patients in both studies will receive 6 monthly intravitreal injections . . . . At the end of the initial 6 months, all patients will be dosed on a PRN (as needed) basis for another 6 months.

Pet., 51 (citing Ex. 1028, 1).

But this passage provides no disclosure of any retreatment criteria (*e.g.*, "visual and/or anatomical outcomes") or ***who*** is assessing such retreatment criteria. And the Petition makes no attempt to establish that the requirement that the PRN administration is based on "visual and/or anatomical outcomes" by "a physician or other qualified medical professional" is disclosed expressly or inherently by this passage in Regeneron (30-April-2009). Thus, Petitioner fails to carry its burden to show that Regeneron (30-April-2009) anticipates the Challenged Claims.

3. Under Petitioner's Definition of the POSA, Petitioner Fails to Show that Heier-2009, Dixon, or Regeneron (30-April-2009) Is Enabled

Anticipatory references must be enabling. *In re Morsa*, 713 F.3d 104, 110 (Fed. Cir. 2013). For purposes of §102, a prior art publication is enabling if "whether a person of ordinary skill in the art could make or use the claimed invention without undue experimentation." *Id*.; *Elan Pharms., Inc. v. Mayo*

Found. for Med. Educ. & Rsch., 346 F.3d 1051, 1055 (Fed. Cir. 2003) (remanding to district court to determine whether asserted prior art reference was enabled).

As noted above, the Challenged Claims require that each tertiary dose is administered as-needed/PRN "based on visual and/or anatomical outcomes as assessed by a physician or other qualified medical professional." Ex. 1001, 21:50-53. Petitioner defines the POSA to include, *inter alia*, a person with "an advanced degree, such as an M.D. or Ph.D. (or equivalent, or less education but considerable professional experience in the medical, biotechnological, or pharmaceutical field), with practical academic or medical experience." Pet., 25. Petitioner's POSA is, by definition, not "a physician or other medical qualified medical professional." Petitioner fails to show that this POSA, which expressly includes individuals without medical training, could have used the disclosure of Heier-2009, Dixon or Regeneron (30-April-2009) to practice the claimed method without undue experimentation.

Indeed, the Petition provides no explanation for how an individual with a Ph.D. and "practical academic" experience would be able to assess visual and/or anatomic outcomes, let alone how such a person would use that information to determine whether or when to administer a tertiary dose to carry out the claimed method without undue experimentation. And Heier-2009, Dixon, and Regeneron (30-April-2009) provide no guidance in that regard. In addition, Heier-2009 and Regeneron (30-April-2009) also provide no guidance on specific re-treatment

criteria. Petitioner provides no evidence to suggest that a Ph.D.-trained individual with no clinical training or experience would be qualified to assess visual and/or anatomical outcomes, even with the disclosure of retreatment criteria, let alone qualified to make assessments or decisions about whether or when to administer a tertiary dose. Thus, applying Petitioner's definition of the POSA, Petitioner fails to establish that Heier-2009, Dixon and Regeneron (30-April-2009) would have enabled the POSA to practice the claimed invention without undue experimentation.

4. Ground 5: Petitioner Fails to Satisfy Its Burden that the "Assessed by a Physician or Other Qualified Medical Professional" Is Obvious (All Challenged Claims)

In Ground 5, Petitioner argues "[t]he 'assessed by a physician' limitation is a pure mental step not entitled to any patentable weight." Pet., 65 (citing *King Pharms.*, 616 F.3d at 1278). While Petitioner cites to retreatment criteria disclosures of Mitchell and Dixon, it fails to identify any disclosure regarding ***who*** is assessing the retreatment criteria. Pet., 65. Just as in Grounds 1-4, Petitioner does not identify any express or inherent disclosure of this limitation. Thus, Petitioner fails to carry its burden in showing that Dixon renders the Challenged Claims obvious.

B. Grounds 1-4 (§ 102 Anticipation): Petitioner Fails to Establish that the Disclosure of "VEGF Trap-Eye" in Heier-2009, Dixon, or Regeneron (30-April-2009) Anticipates the Recited Amino Acid or Nucleic Acid Sequences

Petitioner asserts that Heier-2009 (Ground 1), Dixon (Grounds 2 and 4), and

Regeneron (30-April-2009) (Ground 3) 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.*, 616 F.3d at 1274 (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." 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 to show inherent anticipation of the amino acid and nucleic acid limitations of claims 1 and 14, respectively.

Petitioner's anticipation Grounds 1-4 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 to 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 Correspond to SEQ ID NO: 2 (Claims 1 and 8-11)

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, 21:54-60. Because Heier-2009, Dixon, and Regeneron (30-April-2009) do not expressly disclose any sequence information for "VEGF Trap-Eye," Petitioner argues that

references to "VEGF Trap-Eye" in Heier-2009, Dixon and Regeneron (30-April-2009) inherently constitute such disclosure based on sequence information present in various other references.

But Petitioner has not identified ***any*** prior art that discloses the amino acid sequence for "VEGF Trap-Eye." Therefore, Petitioner argues that Heier-2009, Dixon, and Regeneron (30-April-2009)'s use of the term "VEGF Trap-Eye" would have been understood by the POSA to refer to aflibercept — and only to aflibercept — and that aflibercept's amino acid sequence was well-known in the art. Pet., 48-49, 52.

Petitioner's burden to demonstrate 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).

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 evidence discussed below showing different molecular weights "VEGF Trap-Eye" and "aflibercept", and inconsistent

descriptions of "VEGF Trap," "VEGF Trap-Eye," and "aflibercept" in the art. Consequently, Petitioner fails to show that the POSA would have understood "VEGF Trap-Eye" to necessarily have the same amino acid sequence as aflibercept and, as a result, that SEQ ID NO:2 was inherently disclosed by Heier-2009, Dixon, or Regeneron (30-April-2009).

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

Petitioner relies on disclosures in Heier-2009, Dixon and Regeneron (30-April-2009) that refer to administration of "VEGF Trap-Eye" as anticipating the claimed sequence information. But these references do not disclose the amino acid sequence of "VEGF Trap-Eye" and none of Petitioner's cited references states that "VEGF Trap-Eye" and aflibercept have an identical amino acid sequence.

The full extent of Dixon's disclosure regarding the molecular characteristics of "VEGF Trap-Eye" is that "VEGF Trap-Eye" is "a fusion protein of binding domains of VEGF receptors-1 and -2 attached to 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 protein comprising an hVEGF-R1 domain 2, hVEGF-R2 domain 3, and a human Fc region. For example, Dixon does not specify which amino acids of the VEGF receptor-1 or receptor-2 domains are included in "VEGF Trap-Eye," and Dixon does not specify which amino acids of which Fc domain form "the Fc fragment" of "VEGF

Trap-Eye." As explained below, this is not a disclosure of VEGF Trap-Eye's amino acid sequence.

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 a shared "molecular structure" indicates an identical amino acid sequence.[5] 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.

Heier-2009 and Regeneron (30-April-2009) provide even less information

[5] 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.

regarding the nature of "VEGF Trap-Eye" than Dixon. Heier-2009 simply states: "VEGF Trap-Eye is a purified formulation of VEGF Trap, a vascular endothelial growth factor (VEGF) receptor fusion protein that binds all forms of VEGF-A." Ex. 1020, 44-45 (Fig. 1). Likewise, Regeneron (30-April-2009) states "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). Investigational VEGF Trap-Eye is a specific blocker of VEGF-A and PIGF that has been demonstrated in preclinical models to bind these growth factors with greater affinity than their natural receptors." Ex. 1028, 1.

Given the absence of any sequence disclosure in Dixon, Heier-2009 and Regeneron (30-April-2009), 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-TrapR1R2, and AVE0005 are simply different names for the ***same molecule***." Pet., 26 (emphasis added); Ex. 1002, ¶39. However, by equating "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. *Id.* 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.[6] Yet, Petitioner equates "aflibercept" with various

[6] Petitioner relies on Regeneron's PTE Application (Ex. 1024), filed nearly a year after the priority date, to connect "VEGF Trap-Eye" to "aflibercept" (Pet., 15), 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 v. Amgen*, 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

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 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***…") (emphasis added); 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***

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if it later acquires a different meaning). Accordingly, the term "VEGF Trap-Eye" must embrace all possible molecules to which that term referred as of the priority date.

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 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. Thus, Petitioner fails to show that Heier-2009, Dixon, or Regeneron (30-April-2009) anticipates claims 1 and 8-11.

2. Petitioner Fails to Establish that "VEGF Trap-Eye" Was Known in the Art to Be Encoded by SEQ ID NO: 1 (Claim 12)

Claim 12 requires that the recited VEGF antagonist is a receptor-based chimeric molecule encoded by the nucleic acid sequence of SEQ ID NO:1. Ex. 1001, 22:63-66. Petitioner argues that "[b]oth the amino acid and nucleotide sequences [for VEGF Trap-Eye] were disclosed in the prior art and well known to skilled artisans." Pet., 50 (citing Ex. 1002, ¶¶136-37). 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 Heier-2009 and Dixon anticipate and that the "nucleotide sequences [of claim 12] were disclosed in the prior art and well known to skilled artisans" based on the '758 patent (Ex. 1010) and Dix (Ex. 1033). Pet., 50. However, none of these references discloses the nucleic acid sequence of "VEGF Trap Eye."

None of Heier-2009, Dixon, or Regeneron (30-April-2009) discloses any nucleic acid sequence information, let alone the nucleic acid sequence for "VEGF Trap-Eye." Their 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 or Dix 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].

The mere possibility that "VEGF Trap-Eye" or "aflibercept" could comprise a nucleic acid sequence meeting the limitation of claim 12 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").

C. Ground 4: Petitioner Fails to Demonstrate that There Is a Reasonable Likelihood that at Least One of the Challenged Clams Is Anticipated or Rendered Obvious by VIEW1/2 as Disclosed in Dixon

Petitioner's Ground 4 also fails to show that there is a reasonable likelihood that at least one of the Challenged Claims is unpatentable for anticipation or rendered obvious by VIEW1/2 as disclosed by Dixon (Ground 4).

1. Petitioner Fails to Establish that the 8-Week Dosing Arm of the VIEW Clinical Trial Anticipates the Claimed PRN Dosing Regimen (All Challenged Claims)

In Ground 4, Petitioner argues that Dixon's disclosure of an 8-week dosing regimen in VIEW1/2 anticipates the claimed PRN method of treatment. But Dixon's VIEW1/2 disclosure fails to disclose a "tertiary dose" that "is administered on an as-needed/*pro re nata* PRN basis," as required by each of the Challenged Claims. Tellingly, Petitioner's claim chart does not even purport to rely on Dixon for this limitation. Pet., 55. Instead, Petitioner relies on a tortured reading of the '069 Patent's prosecution history to argue that 8-week dosing and PRN dosing are the same thing. Petitioner's argument is both factually incorrect and legally unsound. Because Petitioner fails to show in Dixon's disclosure a critical limitation of each of the Challenged Claims, its Ground 4 anticipation challenge fails. *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000) ("[I]nvalidity by anticipation requires that the four corners of a single, prior art document describe every element of the claimed invention ….").

Petitioner argues that Dixon anticipates the Challenged Claims of the '069 Patent because Dixon discloses a two-part Phase 3 study that "will evaluate the safety and efficacy of … 2.0 mg at an 8-week dosing interval (following three monthly doses)." Pet., 55 (citing Ex. 1006, 1576). But eight-week, fixed dosing is ***not*** a disclosure of the limitation "wherein each tertiary dose is administered on

an as-needed/*pro re nata* (PRN) basis." Because Dixon does not disclose the claimed dosing regimen, it cannot anticipate the Challenged Claims of the '069 Patent. *Verdegaal Bros. v. Union Oil Co. of Cal.*, 814 F.2d 628, 631 (Fed. Cir. 1987) ("A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference."). Petitioner does not satisfy its threshold burden for institution of this IPR.

Petitioner instead premises its anticipation argument on Regeneron's prosecution history statements, which Petitioner argues equated the 8-week dosing regimen of VIEW with a PRN treatment protocol:

> Dixon discloses the exact VIEW1/VIEW2 dosing regimens that Regeneron told the Examiner represented a "PRN treatment protocol" "as claimed" in independent claim 1. ***Applying Regeneron's interpretation of the Challenged Claims***, Dixon discloses each and every element of Challenged Claim 1…

Pet., 54 (emphasis added).

As a threshold matter, Petitioner's argument is factually flawed. Petitioner misconstrues Regeneron's statements in prosecution and ignores important differences between Dixon's disclosures, relied upon by Petitioner, and the Heier 2012 paper that was discussed in prosecution. Contrary to Petitioner's assertion, Regeneron did not argue during prosecution that 8-week dosing and PRN dosing were the same thing. Pet. at 12. Instead, Regeneron explained that the Heier 2012

reference showed that extended dosing regimens with VEGF Trap-Eye were unexpectedly noninferior to the prevailing standard of care (*i.e.*, monthly injections of ranibizumab). Ex. 1017, 136.

While Heier 2012 reports the clinical trial results from Year 1 of the VIEW1/2 trials, which tested fixed dosing regimens (including an 8-week dosing regimen), it also sets forth the clinical trial results for Year 2, which tested PRN dosing. Ex. 1018, 10 ("The results of this second year were recently presented … and reveal … comparable visual acuity maintenance (91-92%) in each group at the 96-week time point"). Thus, by the time Heier 2012 published the clinical trial results for Year 2 of VIEW1/2, it was known that the second-year PRN dosing regimen resulted in extended dosing. *Id*. ("The total number of active injections (baseline to week 96) was 16.0 to 16.2 in the monthly intravitreal aflibercept groups … and 11.2 in the original 2q8 group").[7] As a consequence, Regeneron's statements during prosecution of the '069 Patent that "the PRN treatment protocol as encompassed by the presently pending independent claim 1 achieves results which are as good or better than the results obtained with monthly treatment" were fully supported by Heier 2012. Ex. 1017, 137

Additionally, Regeneron's prosecution history statements about a different publication are not legally relevant to Petitioner's anticipation arguments

[7] The actual mean number of injections in year 2 of VIEW was approximately four.

regarding the Dixon reference in this IPR. Petitioner offers no authority for its suggestion that anticipation can be based on prosecution history estoppel rather than on prior art, and Regeneron is aware of none. Because Petitioner fails to make a *prima facie* case for anticipation, its challenge must be rejected.

2. Petitioner Fails to Establish that the 8-Week Dosing Arm of the VIEW Clinical Trial Renders Obvious the Claimed PRN Dosing Regimen (All Challenged Claims)

Petitioner's obviousness argument fares no better. Petitioner fails to show that the POSA would have been motivated to modify monthly dosing followed by 8-week dosing to monthly dosing followed by PRN dosing. "It was [Petitioner's] burden to demonstrate … that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention." *Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367-1368 (Fed. Cir. 2016); *see also* 35 U.S.C. § 314(a).

But here, Petitioner provides no rationale for why the POSA would replace VIEW's 8-week tertiary fixed dosing with PRN dosing. In VIEW's 8-week dosing arm, after three monthly loading doses, patients were only seen by their physicians when they were treated — *i.e.*, once every 8-weeks. In contrast, under a PRN treatment protocol, even if the patient is not treated at each visit, the patient is still required to be monitored by his/her physician on a regular (*i.e.*, monthly) basis. Thus, PRN is more burdensome than extended fixed dosing.

Indeed, as of the priority date of the '069 Patent, PRN was considered, at

best, inconvenient and, in some cases, unsafe as compared to other dosing regimens. *See e.g.*, Ex. 1025, 1369 (referring to PRN dosing: "Nonetheless, this strategy does require monthly visits, clinical examinations, and OCTs, and patients are uncertain if or when they will need treatment. In addition, there have been more recent concerns that patients who are no longer receiving regular maintenance intravitreal anti-VEGF injections can occasionally experience sudden sight-threatening macular hemorrhages within days or weeks after a stable clinical examination and an OCT showing no apparent sub- or intraretinal fluid.").

Petitioner must provide a motivation to modify the 8-week dosing regimen — with the benefit of requiring visits only every 8 weeks — to PRN dosing, which requires patients to make monthly monitoring visits to their physician. "[T]he benefits, both lost and gained, should be weighed against one another. That is consistent with the longstanding principle that the prior art must be considered for all its teachings, not selectively." *Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1331-32 (Fed. Cir. 2019) (affirming final IPR decision that claims were not proven invalid for obviousness where "[c]onsidering the prior art as a whole, we conclude that substantial evidence supports the Board's finding of no motivation to combine") (citations omitted); *AstraZeneca AB v. Aurobindo Pharma Ltd.*, 232 F. Supp. 3d 636, 646-47 (D. Del. 2017) (holding that the asserted patent claims were not obvious and finding that expert's testimony was flawed for failing to consider the prior art as a whole, but instead only "looked to

a selection of prior art ***handpicked*** by [accused infringer's] counsel in order to select the compound for his obviousness analysis. This is evidence of classic hindsight bias") (emphasis in original). Petitioner provides none.

The fact that PRN dosing was practiced in the art does not mean that the POSA would have been motivated to modify an extended fixed dosing regimen to make it PRN dosing, particularly because PRN was repeatedly reported to be inferior to the monthly fixed dosing standard of care. Ex. 1030, 7 (SUSTAIN study showed a maximum visual acuity ("VA") gain after the three consecutive monthly doses and then a decrease in VA gains over time in the PRN phase.); *id.* at 9 ("However, some VA loss occurred after month 3 [in PRN], whereas fixed monthly injections resulted in further VA improvement during the maintenance phase."); Ex. 2029, 803 [HORIZON] (resulting in inferior therapeutic outcomes with PRN dosing as compared to monthly dosing of ranibizumab); Ex. 2032, 1737-38 [SAILOR] (resulting in inferior therapeutic outcomes with PRN dosing as compared to monthly dosing of ranibizumab).

Petitioner has not met its burden to show that the POSA would have been motivated to modify 8-week dosing by replacing it with PRN dosing and, thus, fails to show that Dixon renders the Challenged Claims obvious.

D. Ground 5: Petitioner Fails to Demonstrate that There Is a Reasonable Likelihood that at Least One of the Challenged Clams Is Rendered Obvious

Petitioner also fails to show that there is a reasonable likelihood that any

Challenged Claim is rendered obvious by Heier-2009 in combination with either Mitchell or Dixon and, optionally, either the '758 Patent or Dix (Ground 5).[8]

Petitioner asserts that the POSA would have been motivated to modify Regeneron's Phase 2 CLEAR-IT 2 dosing regimen by reducing the number of loading doses from four loading doses, as reported in Heier-2009, to three loading doses based on (a) ranibizumab dosing regimens, as reported in Mitchell, or (b) the prospective VIEW trial, as reported in Dixon. Pet., 65.

It is fundamental that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 418 (2007). Here, if there is any so-called motivation to reduce the four loading doses of CLEAR-IT 2 to three, Petitioner has wholly failed to articulate "a reason, suggestion, or motivation in the prior art that would lead one of ordinary skill in the art to combine the references, and that would also suggest a reasonable likelihood of success." *Forest Lab'ys, LLC v. Sigmapharm Lab'ys, LLC*, 918 F.3d 928, 934 (Fed. Cir. 2019) (quoting *Smiths Indus. Med. Sys., Inc. v. Vital Signs,*

[8] Because Petitioner has not sufficiently disclosed its alternative obviousness theories (*see* Section II.B., *supra*), Regeneron addresses Petitioner's failures in Ground 5 only as it relates to Heier-2009 in combination with either Mitchell or Dixon and, optionally, either the '758 Patent or Dix.

Inc., 183 F.3d 1347, 1356 (Fed. Cir. 1999)).

The Petition cites to a single paragraph in Dr. Albini's declaration in purported support of a motivation to modify CLEAR-IT 2:

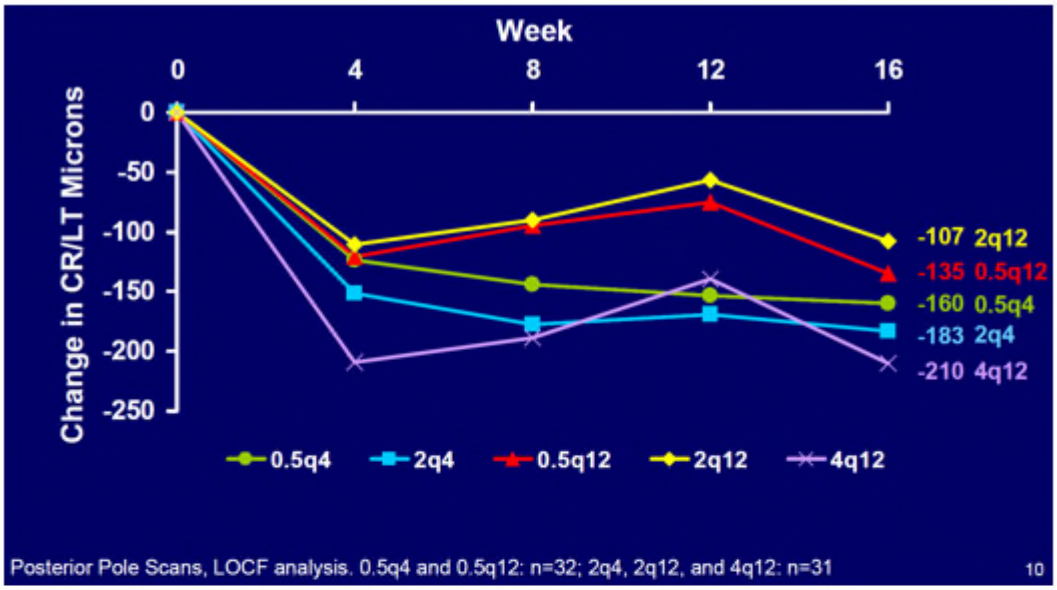
> Given the valid concerns over dosing frequency and the motivation to reduce the number of doses patients received, a person of ordinary skill in the art would have been motivated to reduce the four monthly loading doses of the Phase 2 CLEAR-IT-2 trial to the three monthly loading doses planned for the Phase 3 VIEW regimens.

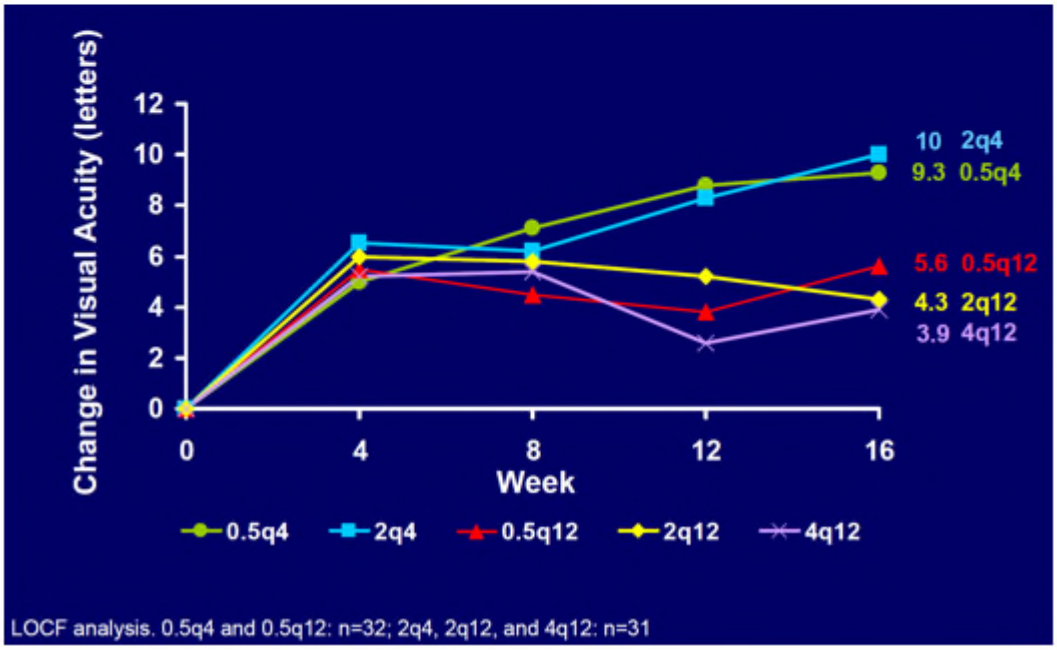
Ex. 1002, ¶199; *see* also Pet., 64. This wholly conclusory, unsupported opinion is contradicted by the evidence for the following reasons.

First, neither Petitioner nor Dr. Albini provides a motivation to explore fewer ***loading*** doses. Rather, the prior art that Dr. Albini relies upon consistently and repeatedly described a motivation to reduce the number of maintenance injections required to treat a chronic disorder. *See, e.g.*, Ex. 1006, 1577 ("However, limitations of current therapy include the need for frequent intraocular injections, as often as monthly, ***without a defined stopping point***. Each injection subjects patients to risks of cataract, intraocular inflammation, retinal detachment and endophthalmitis. A significant time and financial burden falls on patients ***during their treatment course***.") (emphases added).

Second, the results of CLEAR-IT 2 demonstrated the importance of loading doses in establishing the best visual acuity and anatomical outcomes. The figures

below are from a 2007 report on the 12-week results from CLEAR-IT 2, presented at the September 30, 2007 Retina Society Conference in Boston, Massachusetts. Ex. 2028, 10, 12:





The top panel reports the change in the retinal thickness and the bottom

panel reports the change in visual acuity. Importantly, the patients receiving monthly (q4) dosing experienced improvements in both anatomical outcomes and visual acuity following the injection at week 12 (*i.e.*, at the fourth loading dose) as shown by the curves at week 16. This continued improvement would have discouraged the POSA from dropping the fourth loading dose. Petitioner does not explain why the POSA would be motivated to pursue an ostensibly less efficacious treatment that required extra patient visits, all in order to save a single intravitreal injection over the course of treatment of a chronic disease.

Third, Petitioner fails to explain why Dixon's disclosure of the VIEW regimen, which was designed to evaluate fixed monthly or 8-week dosing for the first year following the loading doses, would motivate the POSA to alter the loading dose period for a monthly loading dose direct-to-PRN regimen. The skilled artisan would have known that PRN dosing was less effective than fixed monthly dosing. *See, e.g.*, Ex. 1030, 7 (SUSTAIN study showed a maximum VA gain after the three consecutive monthly doses and then a decrease in VA gains over time in the PRN phase.).

It is not enough for Petitioner to explain that the two references could be combined; it must supply a motivation for why the POSA would have picked out those two references and combined them to arrive at the claimed invention. *Pers. Web Techs., LLC v. Apple, Inc.*, 848 F.3d 987, 993–94 (Fed. Cir. 2017); *Belden Inc. v. Berk–Tek LLC*, 805 F.3d 1064, 1073 (Fed. Cir. 2015) ("[O]bviousness

concerns whether a skilled artisan not only ***could have made*** but ***would have been motivated to make*** the combinations or modifications of prior art to arrive at the claimed invention.") (emphases in original). Here, Petitioner has done nothing more than show that Heier-2009 ***could*** have been combined with Mitchell or Dixon. Thus, Petitioner's Ground 5 challenge should be rejected.

E. 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.

Here, the Board should deny institution because Petitioner fails to establish a reasonable likelihood of establishing a *prima facie* case of obviousness regardless of objective evidence of nonobviousness. *See, e.g., Luye Pharma Grp. Ltd. v. Alkermes Pharma Ir. Ltd.*, IPR2016-01096, Paper 74 at 29 (Nov. 28, 2017) ("As we conclude that the preponderance of evidence of record does not support Petitioner's obviousness challenge, we need not address Patent Owner's evidence of secondary indicia"). Regeneron reserves the right to present objective evidence of nonobviousness in the unlikely event that an IPR of the '069 Patent is instituted.

Regeneron nevertheless responds to Petitioner's incorrect assertion that

Regeneron omitted "highly pertinent" information from the Examiner in arguing unexpected results during prosecution. Pet., 70.

First, Petitioner argues that Regeneron somehow misled the Examiner by relying on the VIEW1/2 clinical trial results reported in Heier 2012 for unexpected results because the VIEW1/2 dosing regimen was disclosed in the prior art. *Id.* Petitioner ignores the critical distinction that the clinical trial results of VIEW1/2 were not known in the prior art. Petitioner also incorrectly suggests that Regeneron failed to disclose the VIEW1/2 dosing regimen to the Examiner. *Id.* However, as discussed *supra* at Section III.A, this is simply untrue: Regeneron submitted numerous references to the Examiner that disclosed the design of its VIEW1/2 trials.

Second, Petitioner contends that Regeneron mischaracterized "the standard of care at the time as monthly dosing and sought to distinguish the claims from that 'standard of care,' ignoring that PRN dosing could result in monthly injections." Pet., 70-71.

As an initial matter, before Regeneron's invention, there were two approved anti-VEGF therapies in use in clinical practice — Lucentis® and Avastin®.[9] Avastin, approved only for oncology indications, was used off-label. And the

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

FDA-approved recommended dosing regimen for Lucentis®, which was approved for the treatment of angiogenic eye disorders, was monthly intravitreal injections. Ex. 1003, 5 ("recommended to be administered by intravitreal injection once a month (approximately 28 days)"). Indeed, there was no satisfactory extended dosing regimen available at the time of the invention. Even today, the recommended administration of Lucentis remains monthly injections. Ex. 2033, 4.

Next, Regeneron's unexpected results argument in prosecution was based on Heier 2012, which showed that, based on the Year-2 clinical trial results of VIEW 1/2, PRN dosing resulted in extended dosing as compared to monthly dosing of ranibizumab. So, while PRN dosing could have resulted in, *e.g.*, monthly injections of VEGF Trap-Eye, by the time Heier 2012 was published, it was known that the PRN dosing in the VIEW 1/2 trial in fact resulted in extended dosing relative to the standard of care.

Third, Petitioner attempts to point 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. Pet., 70-71.

In fact, several failed attempts to achieve extended dosing using ranibizumab had been reported by the time Regeneron undertook its Phase 3 testing of EYLEA®. 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. Heier 2012 cites the same clinical trials on which Petitioner attempts to rely — HORIZON (Ex. 2029, 803) (resulting in inferior therapeutic outcomes with PRN dosing as compared 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).

These studies, and reports that some patients on a PRN regimen had developed sight-threatening macular hemorrhage, undermined the results reported for PrONTO, a small, open-label, prospective, single-center, non-randomized, investigator-sponsored clinical study. Ex. 2042, 1074. Yet, Dr. Albini relies on the PrONTO study and his own uncorroborated experience for his opinion that monthly dosing was not the standard of care as of 2010. Ex. 1002, ¶220. Regardless, the scientific evidence unequivocally demonstrated that PRN or quarterly dosing after three loading doses with ranibizumab was not as effective as monthly dosing. *Compare* Ex. 1002, ¶¶60-61, 220 *with* Ex. 2032, 1735-36 *and* Ex. 2029, 801-03.

Fourth, 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., 71. This argument belies the facts. Regeneron's Phase 2 results were submitted to and considered by

the Examiner, including Dixon, which was presented to the Office in an IDS and was marked considered by the Examiner. Ex. 1017, 121, 168.

Fifth, Petitioner also argues that Regeneron ignored "practical realities facing physicians at the time" in explaining that an infinite number of different treatment protocols existed. Pet., 71-72. While it is unclear how this statement is relevant to unexpected results, Regeneron made this statement in response to an obviousness-type double patenting rejection based on the Weigand Patents,[10,11]

[10] 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").

[11] Petitioner improperly refers to the Wiegand patents as "Monthly-Dosing Patents." Pet., 11 n.7. As noted, the Examiner recognized that the claims of the Wiegand patents did ***not*** "disclose the dosing schedules set forth in the instant claims." *Id.* at 266. Indeed, the '746 Patent does not claim any particular dosing regimen or dosing interval. Ex. 1016 at 57. Further, the '747 Patent, the '799 Patent, and the '049 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. 1016 at 89-90, 122, 154-55. Thus, there is nothing to suggest that the Wiegand patents are directed to "monthly dosing regimens."

which even the Examiner recognized did not "disclose the dosing schedules set forth in the instant claims." Ex. 1017, 266. Additionally, Petitioner's argument that a "new entrant to the anti-VEGF market would have considered a PRN dosing regimen" (Pet., 72) is contradicted by the fact that PRN dosing had been repeatedly shown to be inferior to fixed dosing. Petitioner's argument and Dr. Albini's opinions thus disregard the scientific evidence that would have led the POSA to conclude that PRN dosing would not be as effective as monthly dosing.

V. CONCLUSION

For the foregoing reasons, the Board should deny institution of MPI's petition for IPR of all '069 Patent Challenged Claims.

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 12,865 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.

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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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