UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SAMSUNG BIOEPIS CO., LTD.,
Petitioner,

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner.

Case IPR2023-00442

U.S. Patent No. 10,130,681

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 10,130,681

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1006	Dixon JA, Oliver SC, Olson JL, Mandava N. VEGF Trap-Eye for the treatment of neovascular age-related macular degeneration. Expert Opin Investig Drugs. 2009;18(10):1573-1580. ("Dixon")
1007	Press Release, Regeneron, Enrollment Completed in Regeneron and Bayer HealthCare Phase 3 Studies of VEGF Trap-Eye in Neovascular Age-Related Macular Degeneration (Wet AMD) (Sept. 14, 2009), https://newsroom.regeneron.com/node/10806/pdf ("Regeneron September 14, 2009 Press Release")
1008	Halpern MT, Schmier JK, Covert D, Venkataraman K. Resource utilization and costs of age-related macular degeneration. Health Care Financ Rev. 2006;27(3):37-47. ("Halpern 2006").
1009	Holash J, Davis S, Papadopoulos N, et al. VEGF-Trap: a VEGF blocker with potent antitumor effects. Proc Natl Acad Sci U S A. 2002;99(17):11393-11398. ("Holash")
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1016	Heier JS, Brown DM, Chong V, et al. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. Ophthalmology. 2012;119(12):2537-2548. ("Heier 2012")
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1037	U.S. Patent Application Publication No. 2006/0217311 A1 ("Dix")
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1054	Expert Declaration of Lucian V. Del Priore, M.D., Ph.D. submitted in *Mylan Pharmaceuticals Inc. v. Regeneron Pharmaceuticals, Inc.*, IPR2021-00881 as Exhibit 2048.
1055	August 10, 2022 Record of Oral Hearing in *Mylan Pharmaceuticals Inc. v. Regeneron Pharmaceuticals, Inc.*, IPR2021-00880, 00881
1056	File History of U.S. Patent No. 7,374,758 B2, 12/22/2011 Patent Term Extension Application ("'758 FH, 12/22/2011 PTE")
1057	Regeneron Pharm., Inc., Quarterly Report (Form 10-Q) (Sept. 30, 2009) ("Regeneron 10-Q (2009)")
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1062	Eylea Label 2011 available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/125387Orig1s000Lbl.pdf
1063	Overview of Uveitis published by National Health Service, available at: https://www.nhs.uk/conditions/uveitis/

I. INTRODUCTION

Samsung Bioepis Co., Ltd. ("Petitioner") petitions for *inter partes* review ("IPR") under 35 U.S.C. §§ 311-319 and 37 C.F.R. §§ 42 et seq., seeking cancellation of claims 1, 3-11, 13-14, 16-24, and 26 (the "Challenged Claims") of U.S. Patent No. 10,130,681 ("'681 patent") (Ex. 1001), assigned to Patent Owner, Regeneron Pharmaceuticals, Inc.

The Challenged Claims are directed to methods for treating an angiogenic eye disorder. They claim a dosing regimen for administering the anti-VEGF molecule aflibercept in combination with a set of "exclusion criteria." The exclusion criteria are conditions that, if assessed by a clinician to be present, exclude a patient from receiving an intravitreal injection—an injection directly into the vitreous cavity of the eye—of aflibercept.

The aflibercept dosing regimen recited in the Challenged Claims is identical to the aflibercept dosing regimen claimed by an earlier patent in the same family, U.S. Patent No. 9,254,338 ("'338 patent"). Critically, in a Final Written Decision relating to the '338 patent, the Patent Trial and Appeal Board ("Board") recently determined that the Dixon reference anticipates the aflibercept dosing regimen claimed by the '338 patent and repeated in the '681 Challenged Claims. *See* Ex. 1004, *Mylan Pharmaceuticals Inc. v. Regeneron Pharmaceuticals, Inc.*, IPR2021-00881 ("'338 IPR"), Paper 94 ("'338 FWD").

This Petition similarly relies on Dixon as the primary reference and, given that the Challenged Claims recite the identical dosing regimen that the Board already found is disclosed in Dixon (*see, e.g.,* Ex. 1004; Ex. 1002, ¶¶ 111-129, 164-177), the only potential patentable distinction between the Challenged Claims and Dixon is the recited exclusion criteria. But these criteria merely require excluding from treatment patients with three adverse conditions in or near the eye: "(1) active intraocular inflammation," i.e. inflammation inside the eye, such as in the uvea (Ex. 1002, ¶ 92); "(2) active ocular or periocular infection," i.e. infection on or in the eye ("ocular") or in the area surrounding it, such as the conjunctiva ("periocular") (*id*.); and "(3) any ocular or periocular infection within the last 2 weeks prior to treatment," i.e. a recent infection on or in the eye or areas surrounding it. (*id*.).

A person of ordinary skill in the art ("POSA") would have known that these conditions made intravitreal injections, such as those required by the claimed aflibercept dosing regimen, potentially unsafe. *Id*., ¶ 146. Intravitreal injections require insertion of a needle into the eye, which risks bringing flora from on or near the eye's surface into the vitreous cavity. *Id*., ¶¶ 150-160. There, the flora can cause an infection in the vitreous cavity that leads to endophthalmitis, a severe and potentially blinding condition frequently referred to as "the most feared" consequence of medical procedures that penetrate the eye. Ex. 1040, Jaffe, 349; *see also*, Ex. 1002, ¶¶ 150-160. Performing an intravitreal injection in an eye with an

active or recent infection substantially increases the risk of infection in the vitreous cavity. Ex. 1002, ¶¶ 59-66, 150-160.

Similarly, POSAs knew that intravitreal injections of VEGF antagonists could cause intraocular inflammation, in addition to endophthalmitis. *Id*., ¶¶ 150-160. For instance, both endophthalmitis and intraocular inflammation are identified as potential adverse reactions on the 2006 label for ranibizumab (Lucentis®), another VEGF antagonist that is administered via intravitreal injection. Ex. 1026; *see also*, Ex. 1002, ¶ 154.

Not surprisingly, then, the prior art teaches the use of the recited exclusion criteria to minimize these risks associated with intravitreal injections. For instance, three prior art clinical trials, the CATT, MACTEL, and PIER Studies (Exs. 1031-1034) applied nearly identical exclusion criteria for intravitreal injections of two prior art VEGF antagonists, bevacizumab and ranibizumab. *See* Table 1 in Section VII.B.1; *see also*, Ex 1002, ¶¶ 99-110, 130-149. Like the recited exclusion criteria, these references teach to exclude patients with, *inter alia*, "active or recent (within 4 weeks) intraocular inflammation (grade trace or below) in the study eye," "current acute ocular or periocular infection" or a "history within the past 30 days of a chronic ocular or periocular infection." Exs. 1031-1034; *see also* Ex. 1002, ¶¶ 99-110, 130-149.

A POSA would have naturally looked to these exclusion criteria, which were developed to mitigate the same concerns regarding potential complications from intravitreally injected anti-VEGF agents, and would have been motivated to apply them in conjunction with Dixon's dosing regimen for the anti-VEGF agent aflibercept for the same reasons. *See* Ex. 1002, ¶¶ 150-163.

Mylan, one of Petitioner's competitors, filed a petition challenging the claims of the '681 patent as anticipated and obvious on completely different grounds than those presented here. While Mylan presents six grounds of invalidity, it does not present any of the art Petitioner presents as disclosing the exclusion criteria.

Mylan's arguments are also not cumulative of Petitioner's. Mylan relies heavily on arguments that the exclusion criteria are not entitled to patentable weight as a matter of claim construction, or are otherwise inherent. Petitioner presents no such arguments here, and the CATT, MACTEL, and PIER Studies, which Mylan does not rely upon, disclose all three exclusion criteria.

In fact, the only overlap in grounds between this petition and Mylan's petition is Petitioner's assertion of Dixon—the same art the Board found anticipates the '338 claims—as the primary reference for Petitioner's obviousness combination. But that is the natural starting point for the obviousness inquiry here given the overlap between the Challenged Claims and the '338 claims. Indeed, using Dixon as the starting point is efficient for both the Board and the parties given the '338 FWD.

The Board thus should decline to consider a discretionary denial. Petitioner should be allowed to control its own challenge to the '681 patent, using the best art available to it on the key question presented, particularly when that art contains express, relevant disclosures not present in Mylan's prior petition.

There is nothing unfair to Patent Owner about this result. Patent Owner chose to pursue claims that added the trivial variation of exclusion criteria to the dosing regimen already claimed in the '338 patent, and Patent Owner has included those claims in the Purple Book, its listing of patents allegedly covering its drug, EYLEA®. Congress intended the *inter partes* review process to be a quicker and more efficient way of disposing of such trivial claims. To the extent Patent Owner wishes to enjoy the monopoly provided by those claims, it should have to defend them against the best prior art—particularly where that art has not previously been in front of the Patent Office and where Patent Owner previously declined to defend the claims' validity during prosecution, instead terminally disclaiming the claims to the '338 patent which have now been found unpatentable. *See* Section V.C.1.

For these and the foregoing reasons, the Board should institute an *inter partes* review of the Challenged Claims and find those claims unpatentable on the ground presented herein.

II. MANDATORY NOTICES PURSUANT TO 37 C.F.R. § 42.8(a)(1)

A. Real Party-In-Interest (37 C.F.R. § 42.8(b)(1))

The real party-in-interest for Petitioner is Samsung Bioepis Co., Ltd.

B. Related Matters (37 C.F.R. § 42.8(b)(2))

The '681 patent is in the same family as the '338 patent and U.S. Patent No. 9,669,069 ("'069 patent"). In May 2021, Mylan Pharmaceuticals Inc. ("Mylan") filed petitions requesting for *inter partes* review of those two patents. *See* '338 IPR and IPR2021-00880 ("'069 IPR"). The Board instituted petitions for the '338 and '069 patents and found all challenged claims unpatentable in Final Written Decisions issued on November 9, 2022. *See* Ex. 1004, '338 FWD; Ex. 1046, '069 IPR, Paper 89 (Nov. 9, 2022) ("'069 FWD").

Mylan filed a petition requesting IPR of the '681 patent on July 1, 2022 (IPR2022-01225) ("Mylan '681 IPR"). The Board has not yet issued its institution decision.

To the best of Petitioner's knowledge, the following are judicial or administrative matters that potentially would affect, or be affected by, a decision in this proceeding: *Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals Inc.*, NDWV-1-22-cv-00061, a litigation between Regeneron and Mylan under the BPCIA ("Mylan Litigation"), *United States v. Regeneron Pharms., Inc.*, No. 1:20-cv-11217-FDS (D. Mass.).

C. Lead and Backup Counsel (37 C.F.R. § 42.8(b)(3)-(4))

Petitioner hereby identifies its lead and backup counsel as follows:

Lead Counsel	Backup Counsel
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Pursuant to 37 C.F.R. § 42.10(b), a Power of Attorney has been filed herewith.

D. Service Information (37 C.F.R. § 42.8(b)(4))

Please send all correspondence to the lead and backup counsel at the addresses shown above. Petitioner consents to service by e-mail at qe-samsungbioepis@quinnemanuel.com.

E. Payment of Fees (37 C.F.R. §§ 42.103 and 42.15(a))

The requisite filing fee of $43,750 (request fee of $19,750, post-institution fee of $24,000) for a Petition for *Inter Partes* Review is submitted herewith. Claims 1, 3-

11, 13-14, 16-24, and 26 of the '681 patent are being reviewed as part of this Petition. If any additional fees are due during this proceeding, the Office is authorized to charge such fees to Deposit Account No. 505708. Any overpayment or refund of fees may also be deposited in this Deposit Account.

III. GROUNDS FOR STANDING (37 C.F.R. § 42.104(a); 37 C.F.R. §§ 42.101(a)-(c))

Petitioners certify that the '681 patent is available for IPR and that Petitioner is not barred or estopped from requesting this review.

IV. IDENTIFICATION OF CHALLENGE AND RELIEF REQUESTED

A. Identification of Challenge (37 C.F.R. § 42.104(b))

Petitioner requests IPR of claims 1, 3-11, 13-14, 16-24, and 26 of the '681 patent and that the PTAB cancel those claims as unpatentable.

B. Grounds of Challenge (37 C.F.R. § 42.204(b)(2))

Petitioners respectfully request that the Board grant institution of IPR on the Challenged Claims based on the following grounds:

Ground I	Claims 1, 3-11, 13-14, 16-24, and 26 are rendered obvious under 35 U.S.C. § 103 by Dixon in view of the prior art printed publications describing the CATT, MACTEL, and PIER Studies (individually and collectively).

V. THE '681 PATENT

A. Overview

The '681 patent is entitled "Using a VEGF Antagonist to Treat Angiogenic Eye Disorders." Ex. 1001, '681 Patent; Ex. 1002, ¶ 67. The '681 patent issued on November 20, 2018. *Id.* The '681 patent is terminally disclaimed over, *inter alia*, the '338 and '069 patents, and will expire on January 11, 2032. Ex. 1025, '681 patent PH, 488, 511-513.

The '681 patent specification discloses that "the methods of the invention comprise sequentially administering multiple doses of a VEGF antagonist" to treat angiogenic eye disorders, i.e., eye disorders caused by or associated with the formation of new blood vessels, which requires, among other things, the differentiation of endothelial cells that are dependent on Vascular Endothelial growth factor (VEGF). Ex. 1001 at Abstract, 1:23-24, 1:66-2:2; Ex. 1002, ¶ 68.

In particular, the specification teaches that "beneficial therapeutic effects" for angiogenic eye disorders can be achieved "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. Ex. 1001, 2:7-17; Ex. 1002, ¶ 69-70.

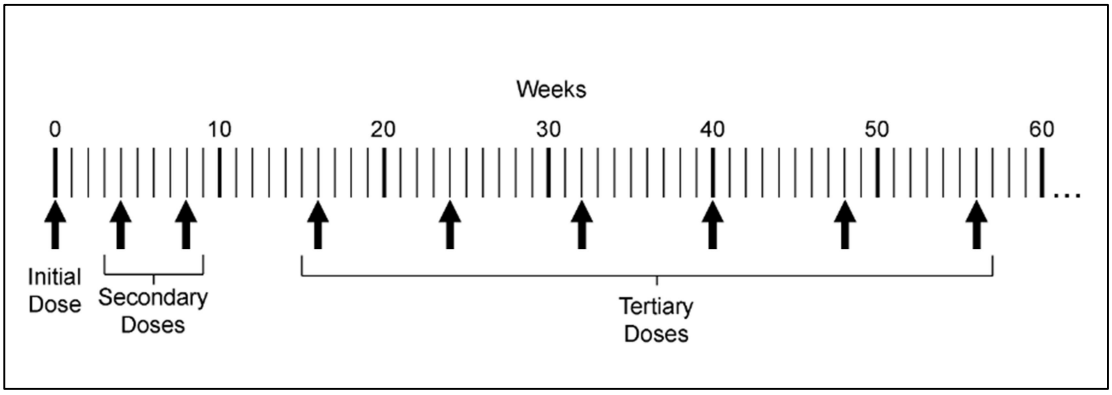
The '681 patent further discloses that "VEGFR1R2-FcΔC1(a) or aflibercept" is a VEGF antagonist "comprising two or more VEGF receptor-based chimeric

molecules." *Id.* at 2:35-40; 2:32-35 (referring to "VEGF-Trap" and "VEGFT"); Ex. 1002, ¶ 71.

Examples 1-6 of the '681 patent describe the results clinical trials using different dosing regimens of aflibercept in subjects with neovascular AMD (Examples 1-4), DME (Example 5), or macular edema secondary to CRVO (Example 6). *See generally id.*, Cols. 7-17; Ex. 1002, ¶ 73. Example 7 of the '681 patent describes additional dosing regimens, but does not contain any test results. Ex. 1001, Cols. 15-17; Ex. 1002, ¶ 73.

Example 4 is particularly relevant here. It describes two Phase III clinical trials of VEGFT for the treatment of neovascular AMD that included a dosing regimen of "2 mg VEGFT administered every 4 weeks to week 8 and then every 8 weeks … (2Q8)." Ex. 1001, 9:55-58, 13:17-31 (describing Table 1); Ex. 1002, ¶¶ 42-46, 74.

The dosing regimen described in Example 4 is, by Patent Owner's own description (*see* Ex. 1004, '338 FWD, 36-37), the dosing regimen of the VIEW1/VIEW2 clinical trials, on which EYLEA®'s (*i.e.*, VEGF Trap-Eye/aflibercept) FDA approval was based. This VIEW1/VIEW2 dosing regimen is described in the specification as "an exemplary dosing regimen of the present invention" and shown graphically in the sole Figure in the patent:



Ex. 1001, Fig. 1, 4:2-4, 2:55-62; Ex. 1002, ¶¶ 72, 75.

The specification's only discussion of "exclusion criteria" is a list of 37 exclusion criteria associated with Example 4. Ex. 1001, 10:58-12:15; Ex. 1002, ¶ 76. Criteria 18 to 20 in the list are the exclusion criteria recited in the claims. Ex. 1001, 11:38-12:8. It also lists the "[p]resence of any contraindications indicated in the FDA Approved label for ranibizumab (Lucentis®)," (*id.*, 12:8-9) which includes "ocular or periocular infections" without specifying whether they are active or recent. Ex. 1027. The specification does not claim anything novel or unexpected related to these exclusion criteria, and does not indicate that the criteria recited in the claims are in any way specifically related to or important for the recited dosing regimen.

B. The Challenged Claims

Independent claims 1 and 14 recite a method of treatment for an angiogenic eye disorder requiring a specific dosing regimen for aflibercept and further including a "wherein" clause reciting three exclusion criteria for excluding a patient from the

claimed treatment. Ex. 1001, 21:40-63, 23:5-23; Ex. 1002, ¶¶ 78-79. Claim 1 recites an amino acid sequence for aflibercept while claim 14 recites a nucleic acid sequence for aflibercept. *Id.*

Dependent claims 3-11, 13, 16-24, and 26 set forth additional limitations for the claimed method, including the nature of the disease treated, the dosing regimen, and the amount of VEGF antagonist. *Id.*, 22:39-68, 23:3-4, 23:28-24:25, 24:29-30; Ex. 1002, ¶ 80.

The Challenged Claims, including the dependent claims, are identical to those of the ’338 patent except for the recitation of the exclusion criteria in independent claims 1 and 14 of the ’681 patent. This is shown in the table below, using claim 1 from each patent as exemplary:

Claim 1 of ’681 patent (additional limitation in bold)	**Claim 1 of ’338 patent**
1. 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 4 weeks after the immediately preceding dose; and	1. 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 4 weeks after the immediately preceding dose; and

wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose; wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule comprising (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130-231 of SEQ ID NO:2; and (3) a multimerization component comprising amino acids 232-457 of SEQ ID NO:2; **wherein exclusion criteria for the patient include all of:** **(1) active intraocular inflammation;** **(2) active ocular or periocular infection;** **(3) any ocular or periocular infection within the last 2 weeks prior to treatment.**	wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose; wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule comprising (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130-231 of SEQ ID NO:2; and (3) a multimerization component comprising amino acids 232-457 of SEQ ID NO:2.

See Ex. 1001, 21:40-63; Ex. 1028, 23:2-18; Ex. 1002, ¶ 81.

C. Prosecution History

The ’681 patent issued from U.S. Application No. 15/471,506 (the “’506 application”), filed on March 28, 2017. Ex. 1001. The key portions of the prosecution history are summarized below.

1. The Applicant Terminally Disclaimed the Claims to the '338 Patent and Never Argued the Exclusion Criteria Rendered the Claims Patentably Distinct

In a preliminary amendment, the applicant canceled the original claims, and added new claims reciting the exclusion criteria in conjunction with the claimed dosing regimen. Ex. 1025, '681 patent PH, 5-10. On April 3, 2018, the examiner issued a non-final office action rejecting the pending claims on the ground of non-statutory obviousness-type double patenting as being unpatentable over the claims of a series of reference patents, including, *inter alia*, the '338 and '069 patents, both of which recite the same aflibercept dosing regimen as the '681 patent. *Id*., 461-469.

On June 25, 2018, the applicant responded by traversing the double patenting rejections as to all patents other than the '338 and '069 patents. The applicant submitted arguments identical to those advanced during prosecution of the '338 patent in support of the traversal. *Compare* Ex. 1025, 488-493 *with* Ex. 1027, '338 patent PH, 287-292. Specifically, the applicant argued that the claimed treatment protocols were not *prima facie* obvious because "[t]here are virtually an infinite number of different treatment protocols that could be tested." Ex. 1025, 488-493.

As to the '338 or '069 patent, however, the applicant did not seek to traverse the obviousness type double patenting rejections by arguing that the exclusion criteria rendered the claims patentably distinct from either patent. Instead, the applicant terminally disclaimed the claims to those patents, which recite the

aflibercept dosing regimen but ***not*** the exclusion criteria, to overcome the double patenting rejection. *See* Ex. 1025, 488, 511-513; Ex. 1002, ¶ 77. Thus, Patent Owner did not contend the exclusion criteria tacked onto the Challenged Claims render them patentable as compared to the '338 patent claims.

2. The Prior Art Presented in This Petition Was Not Before the Examiner During Prosecution

On July 26, 2018, the examiner issued a notice of allowance withdrawing the pending rejections, without further analysis of the art. *Id*., 515-520. None of the references presented here were before the examiner during prosecution, nor were they considered. *See* Section VIII. *infra*. While a single page of Dixon was disclosed during prosecution of the application underlying the '681 patent (Ex. 1025, 118-119), it was not substantively evaluated by the examiner. Based on these same facts, the Board found in connection with the '069 IPR that "the disclosure[s] of Dixon that form the basis of Petitioner's Grounds… were not before the Examiner as prior art during examination (because the relevant disclosures were missing or omitted)." Ex. 1047, '069 IPR, Paper 21, 10-13 (explaining "[i]t would consequently have been impossible for the Examiner to analyze the limitations of the challenged claims in view of the complete teachings of Dixon").

D. The Board's Finding in the '338 FWD that the Dosing Regimen for Aflibercept Is Disclosed by Dixon

The Board instituted Mylan's petition for *inter partes* review of the '338 patent claims 1, 3-11, 13-14, 16-24, and 26 and found all challenged claims unpatentable in its Final Written Decision issued on November 9, 2022. *See* Ex. 1004, '338 FWD. The Board addressed the primary reference presented in this petition—Dixon—finding that it anticipated all of the challenged claims which, as noted above, are identical to the claims of the '681 patent, minus the three recited exclusion criteria. *Id.,* 1.

Specifically, in the '338 FWD, the Board rejected Patent Owner's arguments that Dixon did not disclose two limitations in the independent claims. First, the Board construed a "method of treating an angiogenic eye disorder in a patent" to "not require a particular level of efficacy"—the first limitation challenged by Patent Owner. *Id*., 12-23. On that basis, the Board rejected Patent Owner's argument "that Dixon does not inherently disclose the claimed methods because Dixon's disclosed dosing regimen will not necessarily be effective for some patients." *Id*., 42-45.

Second, Patent Owner argued that Dixon did not expressly or inherently disclose the amino acid sequence or nucleic acid sequence of aflibercept/VEGF Trap-Eye. *Id.*, 29-32. The Board rejected this argument, finding that "VEGF Trap-Eye disclosed in Dixon necessarily comprised the same amino acid sequence and nucleic acid sequence recited in claims 1 and 14 of the '338 patent…." *Id*., 39. The

Board further explained that "Patent Owner has acknowledged, repeatedly, that the VEGF Trap-Eye used in the VIEW 1 and VIEW 2 clinical studies disclosed by Dixon is the same drug disclosed by the '338 patent, with the same amino acid sequence recited by claim 1." *Id*., 40. In accord with these findings, the Board found that Dixon inherently disclosed the claimed amino acid sequence because "the claimed amino acid sequence was necessarily present in the VEGF Trap-Eye used in the studies…." *Id*.

The Board thus found that "Petitioners have shown by a preponderance of the evidence that claims 1, 3-11, 13, 14, 16-24 and 26 are anticipated by Dixon." *Id.*, 45.

With respect to the portion of the Challenged Claims that are identical to the '338 patent claims, i.e. everything other than the exclusion criteria, Petitioner relies on an analysis of Dixon's disclosures herein that is substantially the same as that supporting the Board's '338 FWD.

E. Level of Ordinary Skill in the Art

In the '338 IPR, the petitioner proposed the following definition for the relevant POSA:

> A person of ordinary skill in the art at the time of the invention would have had (1) knowledge regarding the diagnosis and treatment of angiogenic eye disorders, including the administration of therapies to treat said

> disorders; and (2) the ability to understand results and findings presented or published by others in the field, including the publications discussed herein. Typically, such a person would have an advanced degree, such as an M.D. or Ph.D. (or equivalent, or less education but considerable professional experience in the medical, biotechnological, or pharmaceutical field), with practical academic or medical experience in (i) developing treatments for angiogenic eye disorders (such as AMD), including through the use of VEGF antagonists, or (ii) treating of same, including through the use of VEGF antagonists.

Ex. 1004, '338 FWD, 9-10. In the '338 FWD, the Board found that petitioner's definition was "reasonable and consistent with the '338 patent and the prior art or record." *Id.*, 10. Patent Owner proposed a more restrictive definition "limited to those having 'firsthand experience' regarding the diagnosis and treatment of angiogenic eye disorders…." *Id.,* 10 (citing PO Resp. at 15 n.7).

For the purposes of this petition, Petitioner proposes that these differences are not relevant to the evaluation of the grounds presented herein, but that the definition adopted in the '338 FWD should be applied as consistent with the '681 patent as summarized above, as well as the prior art described herein. Specifically, a POSA would not necessarily be an ophthalmologist, but would have similar knowledge

regarding the diagnosis and treatment of angiogenic eye disorders, including the administration of therapies to treat said disorders. Ex. 1002, ¶ 21-24, .

F. Construction of the Challenged Claims

For the purposes of this petition, Petitioner proposes the constructions adopted by the Board in the '338 FWD. Ex. 1004; Ex. 1002, ¶¶ 25-29, 82-93. Petitioner further proposes that no additional constructions are necessary for the purpose of resolving this petition.

1. "*A method for treating an angiogenic eye disorder in a patient*"

For the purposes of this petition only, Petitioner does not dispute that the preamble is limiting. Further, Petitioner agrees with the Board's rejection of Patent Owner's position that the preamble requires a particular level of efficacy. The plain and ordinary meaning of the term "treating" does not require a specific level of efficacy—just that the method be administered for the purpose of treatment of an angiogenic eye disease. Ex. 1002, ¶ 84.

Specifically, in the '338 FWD, the Board found that "the preambles of method claims 1 and 14 are limiting insofar as they require 'treating an angiogenic eye disorder in a patient.'" Ex. 1004, 18. The Board further rejected Patent Owner's position that the preamble "required such 'treating'" to achieve any particular level of effectiveness, much less a 'high level of efficacy' as was argued by Patent Owner. Instead, the Board properly found "that the intrinsic evidence supports finding that

it is the administration of the VEGF antagonist to such patient ***for the purpose*** of providing an improvement of or beneficial effect on their angiogenic eye disorder that satisfies the "treating" portion of the preamble." *Id.*, 19, 23 (emphasis added); *see, e.g.*, *Eli Lilly & Company v. Teva Pharms. Int'l GmbH,* 8 F.4th 1331, 1340 (Fed. Cir. 2021).

For the purposes of this petition, Petitioner concurs with the Board's construction for the same reasons articulated by the Board.[1] Specifically, the plain and ordinary meaning of the term "treating" requires only that the method be administered for the purpose of treatment of an angiogenic eye disease. Reading in any level of efficacy, including from the specification, would violate the fundamental rule of claim construction that prohibits reading in limitations from the specification. *SciMed Life Sys., Inc. v. Advanced Cardiovascular Sys., Inc.*, 242 F.3d 1337, 1340 (Fed. Cir. 2001).

There is no reason to read in limitations requiring efficacy from the specification here. Indeed, "efficacy" is a defined term in the specification (Ex. 1001, 7:24-34), and neither it nor any related term is recited in the claims—merely the word "treatment," which requires only that the method have the purpose of treating a patient, not that it achieves a level of efficacy. Moreover, the claims do

[1] Petitioner reserves the right to argue that the preamble is non-limiting, but for the purposes of this IPR, such argument is unnecessary as even if limiting, it is disclosed by the art.

not recite any dosage amounts. Instead, the claimed method focuses on treating an angiogenic eye disorder with a specific compound based on a specific temporal regimen—not any specific level of efficacy. *Id.*, Cols. 21-24; Ex. 1002, ¶ 85.

Similarly, the specification supports finding that the administration of the VEGF antagonist to a patient for the purpose of providing an improvement of or beneficial effect satisfies the "treating" portion of the preamble. The specification only refers to "a high level of efficacy" in one instance, i.e., in the "Background" section. *See* Ex. 1001, 1:55-62. Otherwise, the specification describes administration of anti-VEGF agents for treating an angiogenic eye disorder in a manner that encompasses dosing methods that result in disclosed improvements and benefits ("therapeutically effective amounts") and doses that do not. *Id.*

For instance, the specification discusses the "Amount of VEGF Antagonist Administered" (*see* Ex. 1001, 6:29-7:14) as follows: "The amount of VEGF antagonist administered to the patient in each dose is, ***in most cases***, a therapeutically effective amount." *Id*. (emphasis added); *see also id*. at 6:55-58 (teaching "a therapeutically effective amount ***can be*** from about 0.05 mg to about 5 mg," but not teaching that any dose within that range of dosage amounts will necessarily be "therapeutically effective," and without limiting the treatment methods based upon such results); Ex. 1002, ¶¶ 86-87. Similarly, the specification states that "[a]s used herein, the phrase 'therapeutically effective amount' means a dose of VEGF

antagonist that results in a ***detectable improvement*** in one or more symptoms or indicia of an angiogenic eye disorder, ***or*** a dose of VEGF antagonist that ***inhibits, prevents, lessens or delays the progression*** of an angiogenic eye disorder." Ex. 1001, 6:48-55 (emphasis added); Ex. 1002, ¶¶ 86-87.

A POSA thus would have understood that treatment according to the patent may, in some cases, result in a detectable improvement, or it may not. In either case, as the Board found, the specification teaches that "the method of treating the patient with the eye disorder is performed upon administration of the VEGF antagonist to the patient ***for the purpose*** of achieving an improvement or beneficial effect in the eye disorder, regardless whether the dosage amount administered actually achieves that intended result." Ex. 1004, 22; Ex. 1002, ¶¶ 86-88.

2. "*Initial dose*," "*secondary dose*," and "*tertiary dose*"

Petitioner proposes that the terms "initial dose," "secondary dose," and "tertiary dose," be construed to refer to their temporal sequence of administration, consistent with the express definition in the specification. Ex. 1001, 3:31-38; Ex. 1002, ¶¶ 89-90.

In the '338 FWD, the Board construed these terms consistent with that express definition. Ex. 1004, 24-25. That definition "unequivocally states that "[t]he terms 'initial dose, 'secondary doses,' and 'tertiary doses,' refer to the *temporal sequence of administration* of the VEGF antagonist," and that "the 'tertiary doses' are the

doses which are administered after the secondary doses." *Id.* (citing Ex. 1001, 3:31-38 (emphasis in original)); Ex. 1002, ¶¶ 89-90. In adopting that definition, the Board properly rejected Patent Owner's position that these terms included an efficacy requirement. Any such requirement is unsupported by any portion of the claims, specification, or extrinsic evidence. Ex. 1004, 25.

3. The Exclusion Criteria

In the patent litigation between Patent Owner and Mylan, both sides have proposed a construction of "exclusion criteria" in the context of another family member, the '601 patent (though not the '681 patent). Ex. 1030, Mylan Litigation CC Chart, 13-14. For the purposes of this petition, Petitioner has applied the plain and ordinary meaning of "exclusion criteria." Ex. 1002, ¶¶ 91-93.

Mylan argues in the district court that "wherein exclusion criteria for the patient include" should be limited to excluding patients from clinical trials. Ex. 1030. Patent Owner, on the other hand, argues the "patient" is not limited to a clinical trial subject. *Id.* For the purposes of this petition, it is not necessary to resolve this dispute, as it would be obvious to exclude patients from receiving intravitreal injections in infected/inflamed or recently infected eyes, whether the patient was a clinical trial subject or not. Ex. 1002, ¶¶ 91-93.

VI. PRIOR ART

A. Dixon

Dixon et al., "VEGF Trap-Eye for the Treatment of Neovascular Age-Related Macular Degeneration," Expert Opn. Investig. Drugs, 18(10): 1573-80 (2009)) ("Dixon") is a peer reviewed publication describing, *inter alia*, the Regeneron Phase Phase 3 clinical trials known as VIEW 1 and VIEW 2. The VIEW 1 and VIEW 2 trials studied the use of aflibercept/VEGF Trap-Eye for the treatment of age-related macular degeneration (AMD). Ex. 1006, Dixon; Ex. 1002, ¶¶ 42-46, 94. Dixon was published in 2009, and thus constitutes prior art under 35 U.S.C. § 102(b).[2] *Id.*

Dixon reviews clinical trial data regarding administering VEGF Trap-Eye to treat neovascular AMD. *Id.* 1573; Ex. 1002, ¶ 95. Dixon discloses that "VEGF Trap-Eye is a novel anti-VEGF therapy, with Phase I and II trial data indicating safety, tolerability and efficacy for the treatment of neovascular AMD." *Id.* Dixon discloses that in a Phase II trial, patients treated with monthly doses of 2.0 or 0.5 mg VEGF Trap-Eye achieved improvements according to the Early Treatment of Diabetic Retinopathy Study ("ETDRS") scale. *Id*.

[2] Dixon was already found to be available as prior art as part of the '338 and '069 FWDs. It lists on its face a 2009 copyright. Its entry in the Expert Opinion on Investigational Drugs journal page further lists an online publication date of August 20, 2009. Ex. 1048 (https://www.tandfonline.com/doi/abs/10.1517/13543780903201684?journalCode=ieid20).

Dixon further describes VEGF Trap-Eye as "a fusion protein of key binding domains of human VEGFR-1 and -2 combined with a human IgG Fc fragment." Ex. 1006, 1575; Ex. 1002, ¶ 96. Dixon also discloses that "VEGF Trap-Eye and aflibercept (the oncology product) have ***the same molecular structure***, but there are substantial differences between the preparation of the purified drug product and their formulations." *Id.* (emphasis added).

Dixon discloses that a Phase III trial of aflibercept "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), compared with 0.5 mg of ranibizumab administered every 4 weeks." Ex. 1006, 1576; Ex. 1002, ¶¶ 97-98.

B. The CATT, MACTEL, and PIER Studies

Multiple prior art publications describe the exclusion criteria recited in the '681 patent claims in relation to clinical trials of the two leading anti-VEGF agents used to treat angiogenic eye diseases at the time, both of which were administered via intravitreal injections. Ex. 1002, ¶¶ 99-100. These publications describe exclusion criteria for the CATT study involving bevacizumab (Avastin®) and ranibizumab (Lucentis®) (Ex. 1031), the MACTEL Phase II pilot study for ranibizumab (Ex. 1032-33), and the PIER study evaluating the efficacy and safety of ranibizumab (Ex. 1034). *Id.*

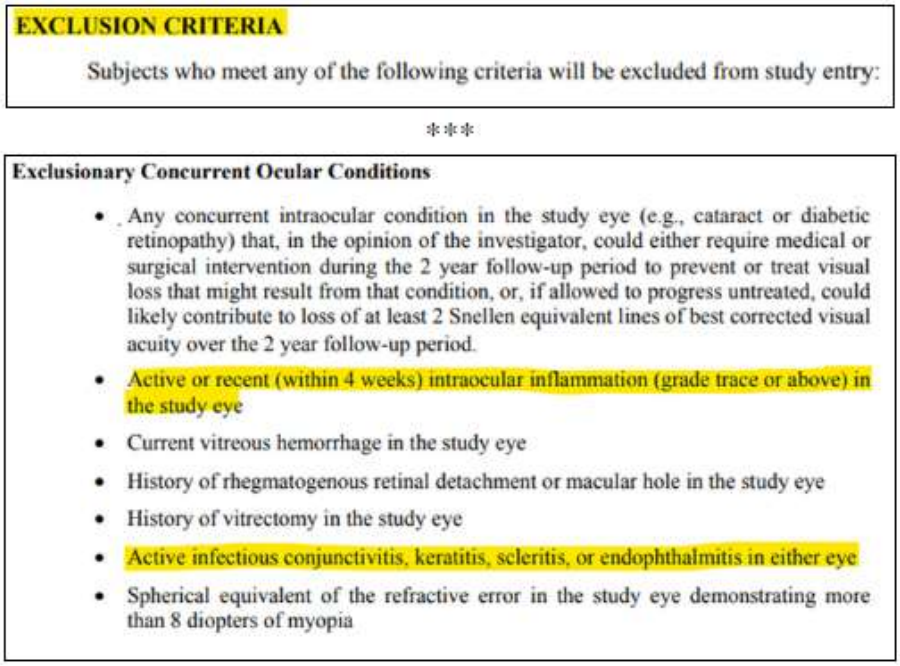
Petitioner describes the publications documenting the exclusion criteria for these studies in detail below.

1. The CATT Study

The CATT study evaluated the efficacy and safety of intravitreal injections of bevacizumab relative to ranibizumab, the two major anti-VEGF treatments for angiogenic diseases at the time. *See* Ex. 1035, NCT00593450, ClinicalTrials.gov (available at www.clinicaltrials.gov/ct2/show/NCT00593450); Ex. 1002, ¶¶ 101-103. The University of Pennsylvania was the sponsor of the study, and the web archive of its website provides a document (the "CATT Study") listing exclusion criteria for CATT as of July 13, 2010. Ex. 1031, CATT Study; Ex. 1002, Ex. 1002, ¶¶ 101-103. Thus, the CATT Study is prior art to the '681 patent under 35 U.S.C. § 102(a).[3]

Among other exclusion criteria, the CATT Study expressly lists both active inflammation and active infections (the first two exclusion criteria listed in claims 1 and 14), and it also calls out "recent (within 4 weeks) intraocular inflammation," which as explained in detail in Section VII would exclude recent infections (which cause and are characterized by inflammation):

[3] To the extent Patent Owner seeks to antedate the CATT Study, the MACTEL Study and PIER Study's disclosure of the recited exclusion criteria are sufficient alone or in combination. Additionally, the CATT Study would still be evidence of the standard of care at the time.



EXCLUSION CRITERIA

Subjects who meet any of the following criteria will be excluded from study entry:

***

Exclusionary Concurrent Ocular Conditions

- Any concurrent intraocular condition in the study eye (e.g., cataract or diabetic retinopathy) that, in the opinion of the investigator, could either require medical or surgical intervention during the 2 year follow-up period to prevent or treat visual loss that might result from that condition, or, if allowed to progress untreated, could likely contribute to loss of at least 2 Snellen equivalent lines of best corrected visual acuity over the 2 year follow-up period.
- Active or recent (within 4 weeks) intraocular inflammation (grade trace or above) in the study eye
- Current vitreous hemorrhage in the study eye
- History of rhegmatogenous retinal detachment or macular hole in the study eye
- History of vitrectomy in the study eye
- Active infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye
- Spherical equivalent of the refractive error in the study eye demonstrating more than 8 diopters of myopia

Ex. 1031, CATT Study, 2; Ex. 1002, ¶ 103.

The CATT Study (an electronic publication) was "accessible to persons concerned with the art to which the document relates." MPEP § 2128. The CATT study was available and was captured by the Internet Archive, more commonly known as the WayBack Machine, at the link in the footnote below, as of at least July 13, 2010.[4]

The public accessibility of the CATT study is confirmed by an authenticating affidavit from the Internet Archive, submitted herewith, showing it was available no later than July 13, 2010. Ex. 1031, 1-2. *See, e.g., Int'l Bus. Machines Corp. v. Intellectual Ventures LLC*, No. IPR2015-00089, 2016 WL 3598306, at *28

[4] Ex. 1031 (available at https://web.archive.org/web/20100713035617/http://www.med.upenn.edu/cpob/studies/documents/CATTEligibilityCriteria_000.pdf).

(P.T.A.B. Apr. 25, 2016); *Sandoz Inc. v. Abbvie Biotechnology Ltd.*, No. IPR2018-00156, 2018 WL 2735468, *4-5 (P.T.A.B. June 5, 2018).; *see also* Ex. 1002, ¶ 102.

2. The MACTEL Study

The MACTEL Phase II study (NCT00685854) was a pilot study for intravitreal injection of ranibizumab (Lucentis®). An electronic document describing the MACTEL study (NCT00685854) (the "MACTEL Study"), was available on May 24, 2008 according to ClinicalTrials.gov, which includes first posted information recorded with each study. Ex. 1032, MACTEL Study; Ex. 1002, ¶¶ 104-107. Thus, the MACTEL Study is prior art to the '681 patent under 35 U.S.C. § 102(b).

Among the exclusion criteria included in the MACTEL Study are "current acute ocular or periocular infection," and "[h]istory within the past 30 days of a chronic ocular or periocular infection….":

EXCLUSION CRITERIA:

***

- History within the past 30 days of a chronic ocular or periocular infection (including any history of ocular herpes zoster).
- Current acute ocular or periocular infection.

Ex. 1032, MACTEL Study at "Exclusion Criteria"; Ex. 1002, ¶ 104.

The MACTEL Study (an electronic publication) "was accessible to persons concerned with the art to which the document relates." MPEP § 2128. The U.S. National Library of Medicine maintains, by law, the public ClinicalTrials.gov results database, and has since September 2008. Exs. 1049-50 ("ClinicalTrials.gov

Background"; "About the Results Database"). "The full history of the changes made to a record can be accessed by clicking on the History of Changes link near the bottom of the full text view of each record." *Id*. "Historical views show you when a record was updated and how it was changed." Ex. 1051 ("How to Read a Study Record").

The record for the MACTEL study can be accessed by searching the study record identifier "NCT00685854" or other terms relevant to the study. The MACTEL Study record lists a "First Posted" date of May 28, 2008, which the record explains is "[t]he date on which the study record was first available on ClinicalTrials.gov after National Library of Medicine (NLM) quality control (QC) review has concluded." Ex. 1044, NCT00685854. The "History of Changes" for the MACTEL study also shows a first submitted date of May 24, 2008. Ex. 1045, History of Changes.

As explained on "History of Changes for Study" page for the MACTEL study, the "Submitted Date" link for any version of the study can be selected "to see a rendering of the study for that version." Exs. 1032. Clicking on the May 24, 2008 entry in the History of Changes shows the MACTEL Study record for that date (*id.*), and confirms that the relevant exclusion criteria were disclosed in the May 24, 2008 record. *Id.*

Additionally, the Wayback Machine first archived the MACTEL Study record on November 7, 2008, and the record of that archive is available at the link in the footnote below.[5] It further confirms that the exclusion criteria were part of the record for the MACTEL Study made available by at least November 7, 2008, and it similarly lists a "first received" date for the MACTEL study as May 24, 2008. Ex. 1033, MACTEL Study Wayback Machine.

Accordingly, the evidence confirms that the MACTEL Study was publicly available on the ClinicalTrials.gov website by at least May 24, 2008, and no later than November 7, 2008. *See also* Ex. 1002, ¶¶ 105-107.

3. The PIER Study

Finally, the PIER study (NCT00090623) evaluated the efficacy and safety of ranibizumab (Lucentis®) administered monthly for three months and then quarterly in patients with subfoveal choroidal neovascularization secondary to age-related macular degeneration. Ex. 1034; Ex. 1002, ¶¶ 108-110. Regillo et al., "Randomized, Double-Masked, Sham-Controlled Trial of Ranibizumab for Neovascular Age-related Macular Degeneration: PIER Study Year 1," Am. J. Ophthalmol., 145(2): 239-248 (Feb. 2008) ("PIER Study"), published February

[5] Ex. 1033, MACTEL Study Wayback Machine, available at: https://web.archive.org/web/20081107014243/https:/clinicaltrials.gov/ct2/show/NCT00685854.

2008, describes the PIER study and is prior art to the '681 patent under § 102(b).[6] *Id.*

The PIER Study discloses the following exclusion criteria that include "any intraocular condition" such as active infections that could require medical intervention, as well as active inflammation:

- Active intraocular inflammation (grade trace or above) in the study eye.
- Current vitreous hemorrhage in the study eye.
- History of rhegmatogenous retinal detachment or macular hole (stage 3 or 4) in the study eye.
- History of idiopathic or autoimmune-associated uveitis in either eye.
- Infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye.

Id. at Supplemental Table A; Ex. 1002, ¶¶ 109-110.

VII. GROUND 1: THE CHALLENGED CLAIMS ARE OBVIOUS UNDER 35 U.S.C. § 103 OVER DIXON IN VIEW OF THE CATT, MACTEL, AND PIER STUDIES (INDIVIDUALLY OR COLLECTIVELY)

For the reasons set forth below, the Challenged Claims are obvious over the prior art. Ex. 1002, ¶¶ 31-41, 111-185.

[6] The PIER Study includes a February 2008 publication date (Ex. 1034, 240) and a 2008 copyright, and notes the paper was accepted for publication on Oct. 5, 2007. The entry for the American Journal of Ophthalmology lists its online publication date as December 3, 2007, with publication in Volume 145 on February 1, 2008. Ex. 1052 (https://www.ajo.com/article/S0002-9394(07)00881-1/fulltext). The ClinicalTrials.gov entry for the PIER study similarly lists the relevant exclusion criteria as part of the first record, which was entered as of June 23, 2005 and made available no later than September 2008. Ex. 1053 (https://clinicaltrials.gov/ct2/history/NCT00090623?V_1=View#StudyPageTop; Exs. 1049-50 ("ClinicalTrials.gov Background"; "About the Results Database").

A. Dixon Discloses All of the Limitations of Independent Claims 1 and 14 Other than the Three Recited Exclusion Criteria

Dixon discloses all of the limitations of independent claims 1 and 14, other than the three recited exclusion criteria. *Id.*, ¶¶ 112-129.

1. Dixon Discloses The Preamble of Claims 1 and 14

The preamble of claims 1 and 14 recites "[a] method for treating an angiogenic eye disorder in a patient, said method comprising…." Dixon discloses the recited method, as demonstrated in Section VII.A.2-B below, which is incorporated herein. Ex. 1006, Dixon; Ex. 1002, ¶¶ 112-118.

In the '338 FWD, the Board correctly rejected Patent Owner's position that the preamble required a specific level of efficacy, finding only that "the intended purpose of the claimed methods is to treat an angiogenic eye disorder and that such treatment only requires administering the recited dosing regimen to a patient for that purpose, without any requirement that such treatment achieves any particular level of efficacy." Ex. 1004, '338 FWD. The same construction should be applied here as set out above in Section V.F.1. *See* Ex. 1002, ¶ 113.

Dixon teaches administering the recited dosing regimen (as set out further in Section VII.A.2-3 below) to a patient for the purpose of treating an angiogenic eye disorder. Ex. 1002, ¶ 114. Dixon teaches that "VEGF Trap-Eye is a novel anti-VEGF drug currently in commercial development ***for the treatment*** of neovascular

AMD by Regeneron Pharmaceuticals, Inc. (Tarrytown, NY, USA)…." Ex. 1006, Dixon, 1573, 1577 (emphasis added).

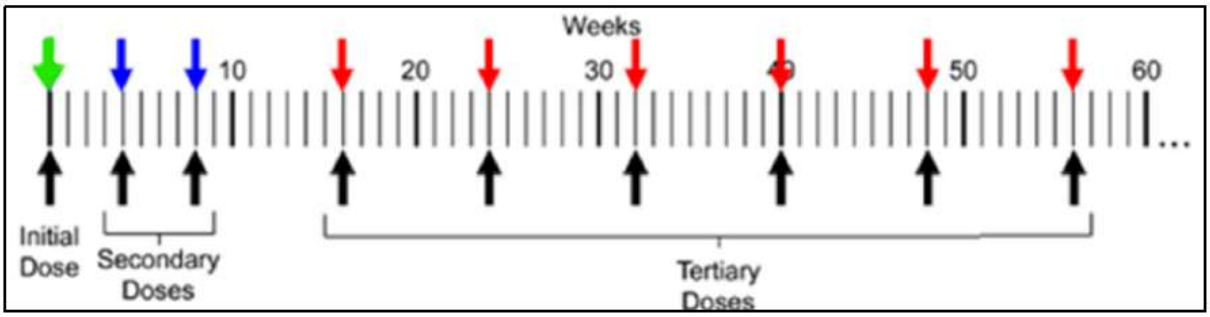
Dixon further teaches that the Phase I and Phase II trial data for VEGF-Trap Eye "indicat[e] safety, tolerability and efficacy ***for the treatment*** of neovascular AMD." *Id*. (emphasis added); *see also id*., 1576 (describing prior success in visual acuity stabilization and reduction in retinal thickness); *see generally* Ex. 1002, ¶ 113-118. On the basis of these prior successful treatments, Dixon further discloses that Phase III studies were in progress using the dosing regimen recited in the '681 patent for the treatment of AMD. *Id*., 1577-78 (describing DME and RVO studies)). Ex. 1002, ¶ 116; *see also* Ex. 1004, '338 FWD, 40-45.

2. Dixon Discloses the Aflibercept Dosing Regimen Recited in Claims 1 and 14

Claims 1 and 14 require "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 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose." This limitation is disclosed by Dixon. Ex. 1002, ¶¶ 119-120.

Dixon discloses that the Phase III study "will evaluate the safety and efficacy of intravitreal VEGF Trap-Eye at doses of… 2.0 mg at ***an 8 week dosing interval***

(***following three monthly doses***)…." Ex. 1006, 1576 (emphasis added). As shown below in an annotated version of the sole '681 Figure, Dixon discloses an initial dose (green), followed by two secondary doses (blue) (for a total of "three monthly doses"), further followed by tertiary doses (red) given at an "8 week dosing interval":



This is the dosing regimen recited by the claims, *i.e.*, an initial dose at day 0 and two secondary doses at weeks 4 and 8, followed by tertiary dosing every 8 weeks. Ex. 1006, 1576; Ex. 1002, ¶ 120.

3. Dixon Discloses the VEGF Antagonist Recited by Claims 1 and 14

Claim 1 recites "wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule comprising (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130-231 of SEQ ID NO:2; and (3) a multimerization component comprising amino acids 232-457 of SEQ ID NO:2." Claim 14 merely recites the nucleotide sequence, rather than the amino acid sequence, of the same molecule. Ex. 1002, ¶ 121. Dixon discloses these limitations. Ex. 1002, ¶¶ 47-54, 121-129.

(a) Dixon Teaches that VEGF Trap-Eye Has the Same Structure as Aflibercept, and Thus Necessarily Discloses It Has the Same, Known Amino and Nucleic Acid Sequences

Dixon expressly discloses the use of VEGF Trap-Eye in the claimed dosing regimen. Dixon further explains 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, Dixon, 1576 (Fig. 1); Ex. 1002, ¶ 122. And Dixon teaches that "VEGF Trap-Eye and aflibercept (the oncology product) have the ***same molecular structure***" as part of its broader description teaching that VEGF Trap-Eye and aflibercept are the same fusion protein. Ex. 1006, 1575 (emphasis added); Ex. 1002, ¶ 122.

The amino acid/nucleic acid sequence and structural information for aflibercept that are recited in claims 1 and 14 were well-known and widely-published to POSAs at the time. *See, e.g.,* Ex. 1036, '758 patent, Fig. 24A-C, 10:15-17; Ex. 1037, Dix, [0013]-[0014], [0030]; Ex. 1002, ¶¶ 47-58, 123.

Given Dixon's disclosure that VEGF-Trap-Eye and aflibercept share "the same molecular structure," a POSA would have understood that Dixon, at a minimum, inherently discloses the recited amino acid sequence and structural information for aflibercept that were known in the art. Ex. 1002, ¶ 124.

As in the '338 FWD, the Board can properly take judicial notice that "it is an axiom of protein chemistry that proteins have primary, secondary, tertiary, and

quaternary structure." Fed. R. Evid. 201; Ex. 1038, Brown, *see also* Ex. 1002, ¶ 125.

As Patent Owner's own expert in the '338 IPR admitted, "[i]t is well established that protein molecules, like VEGF Trap-Eye, have multiple levels of 'structure,' including primary, secondary, tertiary, and quaternary structures." Ex. 1054, ¶¶ 50, 67. Dr. Chaum provides a detailed description of each of these structures in his declaration. Ex. 1002, ¶¶ 125-127.

Of critical importance, the primary structure is ***the sequence of the amino acids*** constituting a polypeptide chain. Ex. 1038, 1075; *see also id.* at 1091, 1095; *see also, generally*, Ex. 1002, ¶ 126-127. The primary structure "determines the ability of [the] amino acids to interact with each other" and thus determines the remaining structures, including "final complex, three-dimensional shape of the chain (secondary and tertiary structures)" that are dependent on the primary structure. Ex. 1004, 33; *see also* Ex. 1038, 1093-1094; Ex. 1002, ¶ 126-127. The primary structure thus "necessarily drives the secondary and tertiary structures," and the completed protein molecule will then "consist of an aggregation of folded polypeptide chains, and that provides the final, quaternary structure of the protein molecule." Ex. 1038, 1095; Ex. 1002, ¶ 126-127.

Accordingly, because Dixon expressly teaches that aflibercept and VEGF Trap-Eye have the "same molecular ***structure***" (Ex. 1006, 1575), Dixon teaches that

they are the same molecule with at least the same primary structure—i.e. the same amino acid and nucleic acid sequence. Ex. 1004, 34. Ex. 1002, ¶¶ 128-129 . They are thus necessarily disclosed.

To the extent Patent Owner argues that the conclusion here should be different from that reached in the '338 FWD because Petitioner here presents Dixon as part of an obviousness analysis, not as an anticipatory reference, Patent Owner is wrong. "The inherent teaching of a prior art reference is a question of fact." *Hospira, Inc. v. Fresenius Kabi USA, LLC*, 946 F.3d 1322, 1329 (Fed. Cir. 2020) (citing *Par Pharm. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1194 (Fed. Cir. 2014) (quotation omitted)). The teaching of a prior art reference is not dependent on the theory of invalidity asserted: "[w]hen the prior art does not expressly disclose a claim limitation, 'inherency may supply a missing claim limitation in an obviousness analysis.'" *Hospira*, 946 F.3d at 1329 (citing *Par*, 773 F.3d at 1194-95 (collecting cases)). Inherency is established in the context of obviousness, as in anticipation, when "the limitation at issue ***necessarily must be present***, or the natural result of the combination of elements explicitly disclosed by the prior art." *Id*. at 1195-96.[7]

[7] To the extent Patent Owner argues the presence of the limitation must not be "unexpected" to be inherent in an obviousness analysis, given that the precise sequence of the aflibercept/VEGF Trap-Eye molecule was taught in the art, it was expected. Ex. 1002, ¶ 47-54, 122-129.

Dixon teaches that aflibercept and VEGF Trap-Eye have the same molecular structure, as set out above, and thus the amino and nucleic acid sequences that form the primary structure of aflibercept—sequences that were known in the art—must "necessarily be present" in VEGF Trap-Eye; they are the same molecule. Ex. 1002, ¶ 129.

(b) Patent Owner Has Repeatedly Admitted that VEGF Trap Eye Has the Same Amino and Nucleic Acid Sequences as the Known Sequence for Aflibercept

In addition to Dixon's express disclosure that VEGF Trap-Eye and aflibercept are the "same molecule," Patent Owner has repeatedly taken the position that VEGF Trap-Eye used in the VIEW 1/VIEW 2 study (as disclosed by Dixon) has the ***same*** sequence as recited in the claims and in Patent Owner's prior art patents relied on here. Patent Owner did so, for instance, during prosecution of the '338 patent and in the '338 IPR, both of which form part of the prosecution history.

For instance, during prosecution of the '338 patent, Patent Owner discussed the Heier 2012 reference, which describes the VIEW 1 and VIEW 2 phase III clinical studies—the same studies disclosed in Dixon. *Compare* Ex. 1016, Heier 2012, 2539-2540 (describing VIEW 1/2) with Ex. 1006, 1576 (describing same). Patent Owner stated that Heier 2012 "shows results of a treatment protocol ***of the type claimed*** on over 2,400 patients." Ex. 1027, 289, 293-304 (emphasis added). A "treatment protocol of the type ***claimed***" must necessarily include treatment with a

drug having the ***sequence recited in the claim***. *See also* Ex. 1017, 136, 289 (stating "[t]he studies summarized in the Heier [2012] paper correspond to the clinical trials disclosed in Example 4 of the present application ***which involve the use of the VEGF receptor-based chimeric molecule known as aflibercept*** or 'VEGF Trap.") (emphasis added); Ex. 1055 (Tr. at 37:6-15) (acknowledging same); Ex. 1056 ("***aflibercept, also known as*** VEGF trap, VEGF-trap, ***VEGF Trap-Eye*** and VEGF-TrapR1R2'"); Ex. 1057, 17.

4. Dixon Discloses Every Element of the Dependent Claims, As Was Found in the '338 FWD

The Board has already determined that Dixon discloses every element of the dependent claims of the '338 patent, which are identical to the dependent claims of the '681 patent. Ex. 1004, '338 FWD, 28-46; Ex. 1002, ¶¶ 164-177.

(a) Claims 3 and 16

Claims 3 and 16 recite "wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose." Dixon discloses that the relevant study "will evaluate the safety and efficacy of intravitreal VEGF Trap-Eye at doses of… 2.0 mg at an 8 week dosing interval (***following three monthly doses***)…." This is the exact regimen described in claims 3 and 16, *i.e.*, an initial dose at day 0 and two secondary doses at weeks 4 and 8, followed by tertiary dosing every 8 weeks. Ex. 1006, 1576; Ex. 1002, ¶¶ 165-167.

(b) Claims 4 and 17

Claims 4 and 17 recite "wherein each tertiary dose is administered 8 weeks after the immediately preceding dose." As illustrated in the annotated figure in Section VII.A.2, Dixon expressly discloses "an 8 week dosing interval" for the tertiary doses. Ex. 1006, 1576; Ex. 1002, ¶¶ 168-169.

(c) Claims 5 and 19

Claims 5 and 19 recite "wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and wherein the first four tertiary doses are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose." Dixon describes that the relevant study will continue with the described tertiary dosing for a year ("***After the first year of the study***, patients will enter a second year of p.r.n. dosing evaluation."). Ex. 1006, 1576. Under the proposed regimen, that would yield "at least 5 tertiary doses" administered eight weeks apart (as is illustrated in the annotated figure in Section VII.A.2 above, showing five red arrows representing tertiary doses before week 52). Ex. 1002, ¶¶ 170-171.

(d) Claims 6, 7, 18, and 20

Claims 6, and 18 recite a Markush group of angiogenic eye disorders including age related macular degeneration (AMD), while claims 7 and 20 specifically recite that the angiogenic eye disorder is AMD. Dixon discloses

administering VEGF Trap-Eye according to the claimed dosing regimen to patients with AMD. Ex. 1006, 1573, 1576 ("The first part, VIEW 1… will enroll ~1200 patients with neovascular AMD"); Ex. 1002, ¶ 172.

(e) Claims 8-10 and 21-23

Claims 8 and 21 recite administering the VEGF antagonist either via topical or intraocular administration; claims 9 and 22 recite administering the VEGF antagonist via intraocular administration; and claims 10 and 23 specifically recite administering the VEGF antagonist via intravitreal administration. Intravitreal administration is a subset of intraocular administration and refers to administration directly into the vitreous cavity of the eye. Ex. 1006; Ex. 1001 2:40-43; Ex. 1002, ¶ 174. Dixon discloses that the claimed dosing regimen is administered intravitreally: "This non-inferiority study will evaluate the safety and efficacy of ***intravitreal VEGF Trap-Eye***…." Ex. 1006, 1576; Ex. 1002, ¶¶ 173-174.

(f) Claims 11, 13, 24, and 26

Claims 11 and 24 recite a dosing range "from about 0.5 mg to about 2 mg of the VEGF antagonist." Claims 13 and 26 specifically recite a "2 mg" dose of the VEGF antagonist. Dixon discloses 2.0 mg VEGF Trap-Eye/aflibercept doses are used in the dosing regimen: "***2.0 mg*** at an 8 week dosing interval (following three monthly doses)…." Ex. 1006, 1576; Ex. 1002, ¶¶ 175-177.

B. The Claimed Exclusion Criteria Are Obvious

The exclusion criteria recited in claims 1 and 14 are as follows:

wherein exclusion criteria for the patient include all of:

(1) active intraocular inflammation;

(2) active ocular or periocular infection;

(3) any ocular or periocular infection within the last 2 weeks prior to treatment.

Dixon does not disclose the exclusion criteria for the recited dosing regimen. But the claimed exclusion criteria were well known in the art for treatments involving intravitreal injections of VEGF antagonists. Ex. 1002, ¶¶ 130-163.

1. The Claimed Exclusion Criteria Are Disclosed in the Prior Art

The CATT, MACTEL, and PIER Studies (Exs. 1031-1034) describe the exclusion criteria for clinical trials of the leading prior art anti-VEGF treatments—bevacizumab (Avastin®) and ranibizumab (Lucentis®). Ex. 1002, ¶¶ 99-110, 130-149. Like aflibercept, bevacizumab and ranibizumab were both administered via intravitreal injection. As shown in the table below, the prior art discloses the same exclusion criteria as the Challenged Claims:

Table 1	
Exclusion Criteria Recited in Independent Claims	**Prior Art Exclusion Criteria for Anti-VEGF Intravitreal Injections Relied on by Petitioner**
"(1) ***active intraocular inflammation***" – i.e. current inflammation within the eye. Ex. 1002, ¶¶ 91, 133.	"***Active*** or recent (within 4 weeks) ***intraocular inflammation*** (grade trace or below) in the study eye." Ex. 1031, CATT Study. "***Active intraocular inflammation*** (grade trace or above) in the study eye." Ex. 1034, PIER Study.
"(2) ***active ocular or periocular infection***" – i.e. a current infection anywhere on/in the eye (ocular) or surrounding it within its orbit (periocular). *Id*.	"***Current acute ocular or periocular infection***." Exs. 1032-33, MACTEL Study. "***Active*** infectious conjunctivitis, keratitis, scleritis, or endophthalmitis ***in either eye***." Ex. 1031, CATT Study. "***Infectious*** conjunctivitis, keratitis, scleritis, or endophthalmitis ***in either eye***." Ex. 1034, PIER Study.
"(3) any ***ocular or periocular infection within the last 2 weeks*** prior to treatment" – i.e. a ***recent*** infection anywhere on/in or surrounding the eye *Id*.	"***History within the past 30 days of a chronic ocular or periocular infection*** (including any history of ocular herpes zoster)" and "***[c]urrent acute ocular or periocular infection***." Exs. 1032-33, MACTEL Study. "Active or ***recent (within 4 weeks) intraocular inflammation*** (grade trace or below) in the study eye." Ex. 1031, CATT Study.

See Ex. 1002, ¶ 133.

Specifically, with respect to the first claimed exclusion criterion, "active intraocular inflammation," the CATT and PIER Studies disclose the criterion verbatim: "[a]ctive or recent (within 4 weeks) intraocular inflammation" and "[a]ctive intraocular inflammation (grade trace or above) in the study eye," respectively. Ex. 1031, CATT Study, at Exclusion Criteria; Ex. 1034, PIER Study, at Supplemental Table A. As explained by Dr. Chaum, these prior art exclusion criteria would exclude the same patients as the first claimed exclusion criterion. Ex. 1002, ¶¶ 133-137.

With respect to the second claimed exclusion criterion, "active ocular or periocular infection," the prior art again includes nearly verbatim exclusion criteria. The MACTEL Study excludes patients with "[c]urrent acute ocular or periocular infection" (Exs. 1032-33, MACTEL Study, Exclusion Criteria) while the CATT and PIER exclude patients with "infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye." (Ex. 1031, CATT Study, Exclusion Criteria; Ex. 1034, PIER Study, Supplemental Table A.). Again, Dr. Chaum explains that these prior art exclusion criteria would exclude the same patients as the claimed second exclusion criterion. Ex. 1002, ¶¶ 133-137, 140.

Finally, for the third claimed exclusion criterion, "any ocular or periocular infection within the last 2 week***s*** prior to treatment," the prior art MACTEL Study discloses the claimed exclusion criterion. The MACTEL Study excludes patients

with a "[h]istory within the past 30 days of a chronic ocular or periocular infection (including any history of ocular herpes zoster)," as well as "[c]urrent acute ocular or periocular infection." Exs. 1032-33, MACTEL Study at Exclusion Criteria. Thus, because the MACTEL Study excludes patients with a history of "chronic" ocular or periocular infection ***in the last 30 days*** (i.e. infections lasting for longer durations, such as four weeks or more, including ones have been recently symptomatic) or current "acute" ocular or periocular infection (i.e. infections that had the initial onset of symptoms within the last few weeks), it would exclude all of the patients excluded by the claimed third exclusion criterion, which is limited to fourteen days—whether their infection is chronic or acute. Ex. 1002, ¶¶ 140-144.

Specifically, as Dr. Chaum explains, while a POSA would understand that "chronic" and "acute" are not generally given precise definitions in the art, they generally refer to the length of time an infection is present from presentation and whether they have reoccurred. Ex. 1002, ¶¶ 142-143; *see, e.g.* Exs. 1023-1024, 1063. Excluding patients with a "history" of a chronic infection within the past 30 days would thus exclude any infection in the past 14 days that was present long enough to be considered "chronic" (or had otherwise reoccurred), while excluding current "acute" infections would exclude any other infections that had presented within the weeks immediately before treatment (i.e. generally one to three weeks).

Id. This would result in excluding "any ocular or periocular infection within the last 2 weeks prior to treatment." *Id*.

Additionally, the CATT Study excludes patients with "[r]ecent (within 4 weeks) intraocular inflammation (grade trace or below) in the study eye." Ex. 1002, ¶ 137. As explained by Dr. Chaum, intraocular inflammation is a "hallmark" indicator for ocular and periocular infections, which cause such inflammation. Ex. 1002, ¶¶ 138-139; *see e.g.* Ex. 1018, Martin 2012, 1394 (disclosing that endophthalmitis implicates both inflammation and infection – "endophthalmitis [is] defined as severe inflammation that was presumed infectious…"); Ex. 1017, Brown 2009, 62 ("[I]ntraocular inflammation that [was] reported as uveitis…was classified as presumed endophthalmitis because it was treated with systemic antibiotics."). Thus, by excluding patients with recent intraocular inflammation, the CATT Study would also exclude patients with ocular or periocular infections within the past two weeks. Ex. 1002, ¶¶ 138-139.

Further, to the extent Patent Owner argues these criteria do not disclose the third criterium *in haec verba*, it would have been obvious to modify them to apply to "any" ocular or periocular infection within the past two weeks for the reasons discussed above. Ex. 1002, ¶ 140-144. A POSA interpreting these exclusion criteria would understand that their purpose was avoid complications from intravitreal injections into infected or recently infected eyes, as active and recent infections are

associated with increased risks of adverse reactions. *Id*., ¶¶ 55-66, 140-144. Indeed, a POSA would understand it was routine practice to exclude ocular or periocular infections generally without reference to the specific timing of the infection at the time of the alleged invention. *Id*., ¶ 144. For instance, the Lucentis® label indicated, as a contraindication at the time, to exclude for "ocular or periocular infections," without specifying further the timing of the infection. Ex. 1026, Lucentis Label 2006.

Finally, the '681 patent does not identify anything unique or novel about the combination of the exclusion criteria together or with the claimed method. Ex. 1002, ¶ 145. Instead, they are merely listed along with 34 other exclusion criteria in the specification, without any further discussion. *See* Ex. 1001, '681 Patent, 10:58-12:15; Ex. 1002, ¶ 145. That is because there is nothing unique or novel about them. Assessing for and excluding patients from treatment via intravitreal injection of anti-VEGF agent on the basis of current or recent infection or inflammation was part of the standard of care. Ex. 1006, Dixon; Ex. 1059, Jager 2004; Ex. 1026, Lucentis Label 2006; Ex. 1034, PIER Study; Ex. 1040, Jaffe; Ex. 1041, Steps for a Safe intravitreal Injection Technique (2009). The exclusion criteria recited in the '681 patent merely reflect this practice. Ex. 1002, ¶¶ 145-149.

2. A POSA Would Have Been Motivated to Make the Claimed Combination

Intravitreal injections of anti-VEGF agents were not new at the time of the '681 patent, nor were the risks associated with such injections. POSAs understood that the exclusion criteria disclosed in the CATT, MACTEL, and PIER studies reflected basic safety precautions designed to minimize the known risks. A POSA would have been motivated to adopt the exclusion criteria from these studies in order to mitigate potential complications for intravitreal injections of aflibercept, which posed the same potential risks as prior anti-VEGF agents that were administered intravitreally. *See* Ex. 1002, ¶¶ 150-160.

First, at the time of the patent, POSAs understood that intravitreal injections involve penetration by a needle into the eye, and thus there is a risk of bringing flora from the eye ("ocular") or surrounding area ("periocular") into the vitreous cavity. This can potentially cause endophthalmitis, a severe and potentially blinding condition, along with associated intraocular inflammation. Ex. 1002, ¶¶ 151-152. Endophthalmitis was "the most feared" consequence of medical procedures that penetrate the eye. Ex. 1040, Jaffe, 349.

POSAs were aware of the risk of endophthalmitis from intravitreal injections. It was acknowledged as a risk on, for instance, the 2006 label for ranibizumab (Lucentis®), one of the two leading anti-VEGF treatments at the time. Ex. 1026, 1. Similarly, the PIER study describes endophthalmitis as having a "hypothesized or

documented relationship to ranibizumab, based [] on the route of administration," i.e. intravitreal injection. Ex. 1034, PIER Study, 247.

POSAs were similarly aware of the risk of exacerbating intraocular inflammation with an injection of an anti-VEGF agent. For instance, prior studies of anti-VEGF intravitreal injections of ranibizumab taught that a primary complication from such injections was intraocular inflammation. *See, e.g.*, Ex. 1034, PIER Study, 247; Ex. 1002, ¶ 152-154. Indeed, the Lucentis label lists "intraocular inflammation" as one of the "most common adverse reactions" which were "reported ≥ 6% higher in LUCENTIS-treated subjects than control subjects." Ex. 1026, 2. And the PIER study describes intraocular inflammation, like endophthalmitis, as having a "hypothesized or documented relationship" to anti-VEGF intravitreal injections. Ex. 1034, 247; Ex. 1002, ¶ 152-154.

Neither of these concerns were specific to the anti-VEGF drug injected. Instead, injecting any anti-VEGF (or other) drug into an eye with an active or recent infection in or around the eye substantially increases the risk of endophthalmitis and associated inflammation because of the potential increase in available flora. Ex. 1002, ¶ 152-153; *see also* Ex. 1041 (2009). Indeed, Dixon taught that aflibercept may allow for reduced dosing which would be desirable because "[e]ach injection subjects patients to risks of cataract, ***intraocular inflammation***, retinal detachment and ***endophthalmitis***." Ex. 1006, 1577. Thus, POSAs knew that intravitreal

injections of anti-VEGF agents, including aflibercept, could cause endophthalmitis and intraocular inflammation, and were motivated to take safety precautions to avoid these known complications. *Id.*[8]; Ex. 1002, ¶ 150-155.

The prior art exclusion criteria were developed to minimize these risks, as a POSA would have easily understood. As set out above, the CATT, MACTEL, and PIER Studies disclosed the same safety precautions as are recited in the '681 patent claims. These were routine precautions for limiting the risks of endophthalmitis, intraocular inflammation, and other complications from intravitreal injections of any anti-VEGF agent. Ex. 1002, ¶¶ 146-147. POSAs would have understood their purpose was to minimize the known risks, and that they could be implemented through basic procedures before each injection, including the "slit-lamp biomicroscopy" procedure described in the PIER Study. Ex. 1034, PIER Study, 240; Ex. 1002, ¶¶ 147-147; Ex. 1039.

POSAs thus would have had a strong motivation to look to exclusion criteria from prior studies involving anti-VEGF intravitreal injections such as those disclosed by the CATT, MACTEL, and PIER studies, and to apply to them to the aflibercept dosing regimen recited by Dixon.

[8] POSAs also understood at the time that intraocular inflammation is a hallmark of active or recent ocular infection, and thus were motivated to assess for and exclude patients with this condition on this basis as well. Ex. 1034, PIER Study; Ex. 1002, ¶ 139, 146.

Moreover, POSAs would have recognized the prior art exclusion criteria as reflecting basic safety precautions developed to address the risks associated with intravitreal injections generally, regardless of the specific anti-VEGF agent injected. Ex. 1002, ¶ 150. These safety concerns apply equally to all VEGF agents that are administered via intravitreal injection. Indeed, the specific VEGF agent being administered does not affect the risks associated with the intravitreal injection. It is the injection itself that creates the risk of introducing harmful flora into the vitreous cavity. A POSA would have been motivated to apply the prior art exclusion criteria to the aflibercept dosing regimen described by Dixon because that dosing regimen raises the same safety concerns as the prior art VEGF antagonists. *See* Ex. 1002, ¶ 151-156.

POSAs also would have been motivated to adopt the exclusion criteria for additional reason. In the context of a Phase III trial as described in Dixon, performing an intravitreal injection on an actively inflamed or actively infected or recently infected eye could interfere with study of the effect of aflibercept on the patient, including the assessment of the safety of those injections. Ex. 1002, ¶ 157. As Dr. Chaum explains, an active or recent infection or inflammation can negatively impact the study of the effect of a drug in a number of ways, including, for instance, increasing the risk of a serious adverse event (*e.g.*, endophthalmitis) and skewing

conclusions regarding the risk and seriousness of complications such as intraocular inflammation. *Id.* (citing Ex. 1059, Jager 2004, 680).

Finally, to the extent Patent Owner argues that there were various studies of intravitreal injections that did not apply these criteria, Patent Owner is wrong. First, as Dr. Chaum explains, assessing and excluding patients from treatment for the claimed criteria was part of the standard of care. Ex. 1002, ¶ 158. To the extent the exclusion criteria are not explicitly disclosed by other prior art studies involving intravitreal injections, that is because the standard of care involves an evaluation of any patient for active inflammation and active and recent infections before ***any*** intravitreal injection, and would have resulted in excluding patients from the study based on these criteria, whether expressly stated in the exclusion criteria or not. *Id.*

Additionally, even if these criteria were not applied in all studies, the criteria are part of a "finite number of identified, predictable solutions" to the problems associated with intravitreal injections—inflammation and further complication from infection—and "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." *KSR* 550 U.S. at 420. In other words, a POSA would have been motivated to select these criteria because, to address the problem of complications from intravitreal injections of anti-VEGF agents, there were only a finite number of solutions. Accordingly, excluding patients with active

inflammation and infection or recent infections from treatment is "the product not of innovation but of ordinary skill and common sense." *KSR*, 550 U.S. at 421.

3. A POSA Would Have Had a Reasonable Expectation of Success in Making the Claimed Combination

A POSA would have had a reasonable expectation of success in applying the prior art exclusion criteria to the Dixon dosing regimen. As noted above, the exclusion criteria are designed to address the known risks associated with intravitreal injections, the same route of administration as described in Dixon. Ex. 1002, ¶ 161. These safety concerns are common to all intravitreal injections, including injections of VEGF antagonists. *Id*., ¶ 156-158. A POSA would therefore reasonably expect that the exclusion criteria developed for prior art VEGF antagonists could be successfully applied to aflibercept. *Id*.[9]

C. There Are No Secondary Considerations

Finally, though it is not Petitioner's burden, Patent Owner cannot establish secondary considerations that would support a finding of non-obviousness. Ex. 1002, ¶¶ 178-185.

No Unexpected Results. The Challenged Claims do not require any particular levels of efficacy. Accordingly, Patent Owner's anticipated argument—asserted

[9] To the extent Patent Owner argues that motivation to adopt or reasonable expectation of success as to treatment via the dosing regimen disclosed in Dixon is necessary, a POSA would have one based on the disclosures of treatment success in Dixon. *See* Ex. 1002, ¶¶ 55-58, 159-163; Ex. 1006.

during prosecution (Ex. 1025, 488-494)—that the less frequent regimen of the Challenged Claims produced "unexpected results" is entirely irrelevant.

In addition, based on the success of prior clinical trials, Patent Owner had announced as early as 2008 that "an 8-week dosing schedule may be feasible." Ex. 1042, Regeneron April 28, 2008 Press Release, 1. There was nothing unexpected about any alleged successful results from the claimed dosing regimen. Ex. 1002, ¶ 181.

No Long-Felt, Unmet Need. Patent Owner cannot establish a "need" or show that any such need was "long-felt." The prior art taught the '681 dosing regimen no later than 2009. Ex. 1002, 182. Regardless, POSAs had been implementing such regimens well before the priority date, and other successful, intravitreally injected anti-VEGF treatments existed. *Id*.

Additionally, to the extent Patent Owner argues (incorrectly) that EYLEA® satisfied a long felt need, there is no nexus to the alleged invention. Ex. 1002, ¶ 183. Patent Owner has not shown use of the EYLEA® product according to its FDA-approved label practices the claimed invention. *Id.* To the extent Patent Owner disputes the exclusion criteria were disclosed in the art, they are also not on the EYLEA® label, which lists only contraindications, not exclusion criteria, and only for "[o]cular or periocular infection," "[a]ctive intraocular inflammation," and "[h]ypersensitivity." Ex. 1062.

No Commercial Success. As noted immediately above, Patent Owner has not shown the EYLEA® product practices the Challenged Claims, and thus Patent Owner cannot otherwise establish any commercial success. *Id.*, ¶ 184.

No Nexus. Patent Owner cannot establish nexus to the "merits of the claimed invention" of the '681 patent because the art discloses all of the claimed elements. *Novartis AG v. Torrent Pharms. Ltd.*, 853 F.3d 1316, 1330–31 (Fed. Cir. 2017). There is no "novel combination or arrangement of known individual elements" in the selection of the exclusion criteria (*id.*)—rather, they are routine. Ex. 1002, ¶ 185.

VIII. DISCRETIONARY DENIAL IS UNWARRANTED

As set out below and in Section V.C.2 above, Petitioner's art is not the same or substantially the same as the art previously presented to the Patent Office, and the examiner never considered the arguments presented in this petition. Moreover, while Mylan filed a petition challenging the claims of the '681 patent on six grounds, Petitioner and Mylan have no relationship whatsoever, and did not coordinate in any way regarding their petitions. As a consequence, Petitioner presents a single ground of invalidity that is completely different and non-cumulative in comparison to Mylan's grounds, in particular as to the third exclusion criterion. Thus, the Board should not consider a discretionary denial of this petition, as further set out below.

A. The *Becton Dickinson* Factors Do Not Favor Denial Under 35 U.S.C. § 325(d)

The Board uses a two-part framework to analyze whether denial under § 325(d) is proper. *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 at 7 (PTAB Feb. 13, 2020). The Board considers several nonexclusive factors ("*Becton Dickinson* factors") within this framework to provide useful insight into how to apply each prong, each of which is discussed below. *Id.* at 4; *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8, 17-18 (Dec. 15, 2017) (precedential as to Section III.C.5, first paragraph) ("*Becton, Dickinson*").

Becton Dickinson factors (a), (b), and (d) relate to whether the art or arguments presented in the Petition are the same or substantially the same as those previously presented to the Office. *Advanced Bionics* at 10. Factors (c), (e), and (f) are only considered if the same or substantially the same art or arguments were previously presented to the Office. *Id.*

1. *Becton Dickinson* Factors (a), (b), and (d)

Petitioner's arguments and prior art here are neither the same nor substantially the same art or arguments previously before the Office during prosecution of the '681 patent.

As set out in Section V.C., the examiner only issued non-statutory double patenting rejections during prosecution and no § 102 or § 103 rejections. Petitioner

asserts a single ground—a combination involving four references never considered during prosecution that provide additional, non-cumulative disclosures. In other words, the art and arguments presented here were neither "involved" nor "evaluated" during prosecution, and therefore, they are not the same or substantially the same as that previously considered by the Office. *Becton, Dickinson*, IPR2017-01586, Paper 8, 17; 35 U.S.C. § 325(d).

Moreover, the disclosures of Petitioner's references are not cumulative of the references that were in front of the examiner. Based on the same facts as present here, the Board already found in connection with the '069 IPR that "the disclosure[s] of Dixon that form the basis of Petitioner's Grounds…were not before the Examiner as prior art during examination (because the relevant disclosures were missing or omitted)." '338 IPR, Paper 21 at 13, 10-13.

And Petitioner further relies on the CATT, MACTEL, and PIER Studies. Those references were not in front of the examiner, nor were any references describing the same exclusion criteria, including the third criterion, and the examiner did not consider any combinations with them or any obviousness arguments regarding them.

Given that the key question remaining after the '338 FWD is whether the claimed exclusion criteria are an obvious addition to the '681 patent claims, and given Petitioner's prior art references directly address that question, Petitioner

should be allowed to present its new art and argument to the Board. *Becton Dickinson* factors (a), (b), and (d) thus favor institution.

2. *Becton Dickinson* Factors (c), (e), and (f)

As explained above, factors (c), (e), and (f) are only considered if the same or substantially the same art or arguments were previously presented to the Patent Office. As set out above, the Office has never considered Petitioner's art or argument, and thus there is no need to consider these factors.

B. The *General Plastic* Factors Do Not Support Denial Under 35 U.S.C. § 314(a)

In *General Plastic*, the Board articulated a non-exhaustive list of factors to be considered in determining whether to exercise discretion under § 314(a) to deny a petition that challenges the same patent as a previous petition. IPR2016-01357, Paper 19 (PTAB Sept. 6, 2017) (precedential), slip op. 9-10. Those factors favor institution.

1. Mylan's Petition Against the '681 Patent

On July 1, 2022, Mylan filed an IPR petition against the '681 Patent. Mylan does not present the same ground of invalidity that petitioner presents here, nor any evidence or argument that is cumulative of it. *See, e.g.*, Ex. 1058, 12-13 (grounds). Specifically, Mylan's prior art does not include the CATT, MACTEL, and PIER Studies or directly disclose the third exclusion criterion: "(3) any ocular or periocular infection within the last 2 weeks prior to treatment."

Specifically, while Mylan presents six grounds of invalidity compared to the single ground of invalidity presented herein, Mylan primarily argues that the exclusion criteria are not entitled to patentable weight as a matter of claim construction and thus argues that three references—Dixon, Adis, and a Regeneron press release—anticipate the claims. Ex. 1058, 12-13, 25-28, 58. Mylan also argues that, to the extent the exclusion criteria are entitled to patentable weight "excluding patients exhibiting the recited 'exclusion criteria' was a necessary, and thus inherent outcome, of VIEW," the study described by all three of its references. *Id*. at 49, 54, 58. This accounts for Grounds I-IV in Mylan's petition, as Mylan's fourth ground relies on the same theory but presents a combination as to the aflibercept sequence recited in the claims and argues that the exclusion criteria are obvious based on the disclosures of Dixon alone. *See id*., 61-62.

Here, Petitioner is not presenting an argument that the exclusion criteria are not entitled to patentable weight, nor does Petitioner argue that the exclusion criteria are inherent or disclosed by Dixon alone.[10]

As to Grounds V and VI in Mylan's petition, Mylan presents two obviousness combinations involving Dixon.

Mylan relies on Rosenfeld-2006 for Ground V, which reports the results of MARINA a trial of monthly doses of ranibizumab. Unlike Petitioner's art here,

[10] Petitioner reserves the right to make such arguments in separate proceedings.

Rosenfeld-2006 does not directly disclose "(3) any ocular or periocular infection within the last 2 weeks prior to treatment." Instead, it discloses (1) "[a]ctive intraocular inflammation (grade trace or above)," (2) "[i]nfectious conjunctivitis, keratitis, scleritis, or endophthalmitis," or (3) a "[h]istory of other disease…" that contraindicates treatment or may confound the study results Ex. 1058, 63-64.

The same is true of Mylan's Ground VI. Mylan relies on a combination with Heimann 2007, which "discloses guidelines and strategies for the administration of intravitreal injections," but not exclusion criteria. Ex. 1058, 46.

Unlike Mylan's petition, Petitioner here presents prior art references that include an express disclosure of all of the recited exclusion criteria, including "(3) any ocular or periocular infection within the last 2 weeks prior to treatment." For instance, one of Petitioner's references includes the exclusion criterion "[h]istory within the past 30 days of a chronic ocular or periocular infection (including any history of ocular herpes zoster)." Exs. 1032-33, MACTEL Study; *see also* Table 1, Section VII.B. Petitioner's references are, therefore, non-cumulative of Mylan's as to the most significant issue raised by this petition—whether the recited exclusion criteria render the claims patentable.

2. *General Plastic* Factor 1

Because the *General Plastic* factors were articulated in response to a petitioner that filed serial, harassing petitions against a patent owner, the primary

factor examines "whether the ***same petitioner*** previously filed a petition directed to the same claims…." *Qualcomm Inc. v. Monterey Research, LLC*, IPR2020-01493, Paper 11, 15 (March 8, 2021) ("*Qualcomm*") (emphasis added). The remaining factors "bear little relevance" if there is no relationship or evidence of coordination. *Id*.; *Alcatel-Lucent USA Inc. v. Oyster Optics, LLC*, Case IPR2017-02146, Paper 12 at 12 (Feb. 28, 2018); *see also Twitter, Inc. v. Palo Alto Research Center Inc.*, Case IPR2021-01458 (April 6, 2022) (Paper 11).

Though Mylan previously filed a petition challenging the '681 patent, Petitioner has no relationship with Mylan and has not communicated with or planned the filing of any petitions with Mylan. Petitioner and Mylan are unrelated competitors, and Petitioner did not contribute in any way to Mylan's IPR filing and Mylan has not contributed in any way to Petitioner's filing.

Accordingly, this is not a case that raises the "potential inequity based on a petitioner's filing of serial attacks" against a patent—the concern at the heart of *General Plastic*. *Id*. Petitioner has never filed any attack on the '681 patent previously. Petitioner is not a party, real party-in-interest, or privy to any other Patent Office proceedings or litigation concerning the '681 patent, and this is Petitioner's first challenge to the '681 patent. *See Sony et al. v. Ancora Technologies, Inc.*, IPR2021-00663, Paper 17 at 7-10 (June 10, 2021).

This lack of any relationship "weighs especially heavily against a discretionary denial." *See Unified Patents, Inc. v. Certified Measurement, LLC*, IPR2018-00548, Paper 7 at 7-8 (Sept. 5, 2018).

3. *General Plastic* Factors 2-5

Absent "extenuating circumstances" such as a showing of coordination between petitioners, "[o]nce resolution of factor 1 indicates that Petitioner had not previously filed a petition against the same patent, factors 2-5 bear little relevance…." *Qualcomm*, Paper 11, 15 (March 8, 2021).

There are no such extenuating circumstances here. There was no coordination between Mylan and Petitioner nor is there any relationship between them. Thus factors 2-5, which focus on the petitioner's prior knowledge of the art and of the patent owner's response to it, bear no relevance.

Even if they did, the concerns regarding efficiency and fairness generally addressed by those factors are not present here. Specifically, Petitioner knew of the primary references asserted in this petition at least from the '338 IPR, not from Mylan's petition against the '681 patent. In the interests of efficiency, Petitioner waited until the resolution of the '338 IPR to bring its challenge, not for any reason related to Mylan's petition against the '681 IPR. Petitioner recognized that—much like Patent Owner did in taking a terminal disclaimer to the '338 patent—the issue comes down to whether the prior art discloses the claimed aflibercept dosing

regimen, and the addition of the claimed exclusion criteria to what was claimed in the '338 patent was trivial. Petitioner filed its Petition on a timely basis after the '338 FWD, doing so on essentially the same bases as presented in the '338 IPR, with the addition of references expressly disclosing the claimed exclusion criteria (references not relied on by Mylan).

Moreover, Petitioner did not gain any unfair advantage by the timing of its petition. Petitioner presents a single ground of invalidity here based on entirely new obviousness combinations with the CATT, MACTEL, and PIER Studies. Petitioner thus did not receive Patent Owner's or the Board's position on its arguments in advance.

Institution is favored under these circumstances, where differences in the issues raised between co-pending petitions mean the "Petitioner could not have received any insight into the Board's position on the merits of the arguments [in the Petition] in that proceeding….." *The Data Company Technologies Inc, v. Bright Data Ltd.*, IPR2022-00135, Paper 12 at 14. Thus, if considered, Factors 2 through 5 also weigh in favor of institution. *See, e.g. Sony*, 13-15.

4. *General Plastic* Factors 6-7

Factors 6-7 consider the Board's finite resources and requirement to issue a final determination within a year of institution. *Qualcomm*, 18. Petitioner here has intentionally presented a single ground based on a primary reference (Dixon) that

the Board already considered and found to disclose the recited aflibercept dosing regimen. '338 FWD. Resolving the issues presented by the single ground Petitioner proposes will not require any more of the Board's resources than a standard IPR in which a prior petition has not been filed.

Finally, there is no risk the Board could not issue a final determination within a year of institution merely by instituting on Petitioner's petition.

Factors 6 and 7 thus favor institution.

5. Additional Factors

As some panels have observed, when a subsequent petitioner is different from the previous petitioner "the following additional considerations have been considered relevant…8. potential prejudice to the subsequent petitioner if institution is denied and the pending instituted proceedings involving the first petitioner are terminated. 9. whether multiple petitions filed against the same patent is a direct result of Patent Owner's litigation activity." *Microsoft Corp. v. Iron Oak Techs.,* LLC, IPR2019-00107, Paper 8, 53-54, 58 (May 15, 2019).

Here, Petitioner would be prejudiced if institution is denied based on Mylan's petition. Mylan and Patent Owner may settle their IPR before the Board reaches a Final Written Decision. In that case, Petitioner would have to re-file a petition, delaying its ability to invalidate the claims of the '681 patent. While Petitioner could join Mylan's IPR if instituted, Petitioner presents different, non-cumulative

arguments for invalidity here based on the best art available to it. It should not be at the mercy of Mylan's choice of arguments and art for its IPR—particularly where Petitioner does not present the core arguments advanced by Mylan, including its arguments regarding the patentable weight and inherency of the exclusion criteria. And Petitioner should not have to risk having to file a petition to invalidate the claims much later in time should Mylan and Patent Owner settle their issues prior to a Final Written Decision. That would unacceptably delay matters and frustrate one of the primary purposes of IPRs—to provide an expedient alternative to litigation.

Finally, multiple petitions have been filed against the '681 patent because of Patent Owner's litigation activity in listing it in the Purple Book for EYLEA®. This indicates Patent Owner's belief its label for EYLEA® is covered by the '681 patent. *See also* Ex. 1060, Mylan Litigation Complaint; Ex. 1061, EYLEA® Purple Book Patent List. These factors thus weigh in favor of institution.

C. The *Fintiv* Factors Do Not Support Denial Under 35 U.S.C. § 314(a)

The *Fintiv* factors are not applicable here because '681 patent is not being litigated in any other proceeding, including the district court litigation between Mylan and Patent Owner. IPR2022-01225, Paper 19 at 4; *Apple Inc. v. CPC Patent Technologies PTY, Ltd.*, IPR2022-00601, Paper 11 at 43 (Sept. 28, 2022).

IX. CONCLUSION

For the foregoing reasons, Petitioner respectfully requests that *inter partes* review of the Challenged Claims of the ’681 patent be granted and the Challenged Claims be found unpatentable.

DATED: January 6, 2023

Respectfully submitted,

By /Raymond N. Nimrod/

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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(a) and (d), the undersigned hereby certify that the **PETITION FOR *INTER PARTES* REVIEW** complies with the type-volume limitation of 37 C.F.R. § 42.24(a)(i) and (b)(i) permitting a preliminary response of up to 14,000 words because, exclusive of the exempted portions, it contains 13,969 words as counted by the word processing program used to prepare the paper.

Date: January 6, 2023

Respectfully submitted,

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CERTIFICATE OF SERVICE

In accordance with 37 C.F.R. §§ 42.6(e) and 42.105, I hereby certify that true and correct copies of the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 10,130,681 and Exhibits 1001-1063 were served on January 6, 2023, via FedEs Priority Overnight on Patent Owner at the correspondence address of record for U.S. Patent No. 10,130,681 as evidenced in Patent Center:

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