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Paper 89
Date: November 9, 2022

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC., CELLTRION, INC., and APOTEX, INC.,
Petitioners,

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner.

IPR2021-00880[1]
Patent 9,669,069 B2

Before ERICA A. FRANKLIN, JOHN G. NEW, and SUSAN L.C. MITCHELL, *Administrative Patent Judges.*

NEW, *Administrative Patent Judge*

JUDGMENT
Final Written Decision
Determining All Challenged Claims Unpatentable
Denying Petitioner's Motion to Exclude Evidence
Denying in part and Dismissing in Part Patent Owner's Motion to Exclude Evidence
35 U.S.C. § 318(a), 37 C.F.R. § 42.64(c)

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[1] IPR2022-00257 and IPR2022-00301 have been joined with this proceeding. *See* Papers 35 and 36.

I. INTRODUCTION

We have jurisdiction to hear this *inter partes* review under 35 U.S.C. § 6, and this Final Written Decision is issued pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. For the reasons set forth below, we determine that Mylan Pharmaceuticals Inc., Celltrion, Inc. and Apotex, Inc. (collectively "Petitioner") have established by a preponderance of the evidence that claims 1 and 8–12 of Patent Owner Regeneron Pharmaceuticals, Inc.'s ("Patent Owner") U.S. Patent No. 9,669,069 B2 (Ex. 1001, "'069 patent") are unpatentable. We additionally deny Petitioner's pending Motion to Exclude Evidence and deny in part and dismiss in part Patent Owner's pending Motion to Exclude Evidence.

A. Procedural History

On May 5, 2021, Mylan Pharmaceuticals, Inc., the original Petitioner, filed a Petition (Paper 1, "Petition") seeking *inter partes* review of claims 1 and 8–12 of the '069 patent. Patent Owner timely filed a Preliminary Response. (Paper 10). We authorized additional briefing (Papers 16 and 19) and pursuant to 35 U.S.C. § 314, on November 10, 2021, we instituted *inter partes* review of all of the challenged claims of the '069 patent (Paper 21, "Institution Decision" or "Dec.").

After institution of trial, Patent Owner filed a corrected Response (Paper 39, "PO Resp."), to which Petitioner filed a Reply[2] (Paper 57, "Pet. Reply"), and Patent Owner, in turn, filed a Sur-Reply (Paper 68, "Sur-Reply").

On February 9, 2022, we instituted an *inter partes* review in IPR2022-00257 and granted the motion for joinder with IPR2021-00880, adding Celltrion, Inc. as a petitioner in the instant proceeding. Paper 35. On the same date, we also instituted an *inter partes* in IPR2022-00301 and likewise granted the motion for joinder with IPR2021-00880, adding Apotex, Inc. as a petitioner in the instant proceeding. Paper 36. We refer to Mylan Pharmaceuticals, Inc., Celltrion, Inc. and Apotex, Inc., collectively, as "Petitioner."

Oral argument was held on August 10, 2022. A transcript of the oral argument is included in the record. (Paper 88, "Hearing Trans.").

B. Related Proceedings

Petitioner and Patent Owner identify *Mylan Pharms. Inc. v. Regeneron Pharms., Inc.*, IPR2021-00881 (PTAB May 5, 2021) (the "-881 IPR") as a related matter. Pet. 4; Paper 5, 2. The -881 IPR challenges

[2] Petitioner filed a Reply containing confidential information (Paper 56), together with a redacted Reply (Paper 57). Although we have reviewed both briefs, in this Decision we quote or cite only to information presented in the redacted brief.

claims of U.S. Patent No. 9,254,338 B2 ("the '338 patent"). The parties further identify *Chengdu Kanghong Biotechnol. Co. v. Regeneron Pharms., Inc.*, PGR2021-00035 (PTAB Jan. 7, 2021) challenging the claims of U.S. Patent No. 10,828,345 B2 ("the '345 patent"), which is related to the '069 patent and the '338 patent. Pet. 5. This latter proceeding has been terminated. *See Chengdu*, PGR2021-00035, Paper 8.

Petitioner also identifies additional patents and patent applications that claim priority to the '069 patent, namely: U.S. Patent Nos. 10,130,681 B2, 10,857,205 B2, 10,828,345 B2, and 10,888,601 B2, and U.S. Application Serial Nos. 17/072,417, 17/112,063, and 17/112,404. Pet. 5.

C. Real Parties-in-Interest

Petitioner states that Viatris Inc. and Mylan Inc. are parent companies of Petitioner Mylan Pharmaceuticals Inc. Paper 87, 1. Accordingly, Petitioner identifies Viatris Inc., Mylan Inc., and Mylan Pharmaceuticals Inc. as real parties-in-interest to the current Petition. *Id.* Petitioner also states that Momenta Pharmaceuticals, Inc. and Janssen Research & Development LLC are wholly-owned subsidiaries of Johnson & Johnson, a publicly held company. *Id.* Consequently, Petitioner also identifies Momenta Pharmaceuticals, Inc., Janssen Research & Development LLC, and Johnson & Johnson as real parties-in-interest to the current Petition. *Id.*

Petitioner Celltrion, Inc. identifies itself, Celltrion Healthcare Co. Ltd., and Celltrion Healthcare U.S.A., Inc. as real parties-in-interest. *See* IPR2022-00257, Paper 2, 3. Petitioner Apotex, Inc. identifies itself, Apotex

Corp., Apotex Pharmaceutical Holdings Inc., and Aposherm Delaware Holdings Corp. as real parties-in-interest. *See* IPR2022-00301, Paper 1, 3.

Patent Owner identifies Regeneron Pharmaceuticals, Inc. as the real party-in-interest. Paper 5, 2.

D. The Instituted Grounds of Unpatentability

Petitioner contends that claims 1 and 8–12 of the '069 patent are unpatentable, based upon the following grounds, all of which have been instituted in this proceeding:

Ground	Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
I	1, 9–12	102	Dixon[3]
II	1, 9–12	102	Heier 2009[4]
III	1, 9–12	102	Regeneron I[5]
IV	1, 8–12	102 and/or 103	Dixon

[3] J.A. Dixon et al., *VEGF Trap-Eye for the Treatment of Neovascular Age-Related Macular Degeneration*, 18(10) EXPERT OPIN. INVESTIG. DRUGS 1573–80 (2009) ("Dixon") Ex. 1006.

[4] J.S. Heier, *Intravitreal VEGF Trap for AMD: An Update*, October 2009 RETINA TODAY 44–45 (2009) ("Heier 2009") Ex. 1020.

[5] Press Release, *Bayer and Regeneron Extend Development Program for VEGF Trap-Eye to Include Central Retinal Vein Occlusion*, April 30, 2009 ("Regeneron I") Ex. 1028.

Ground	Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
V	1, 8–12	103	Heier-2009 and Mitchell[6] or Dixon, and optionally, Papadopolous[7] or Dix[8]

Petitioner also relies upon the Declarations of Dr. Thomas A. Albini (the "Albini Declaration," Ex. 1002, Ex. 1115 (confidential and public, redacted versions)) and Dr. Mary Gerritsen (the "Gerritsen Declaration," Ex. 1003). Patent Owner relies upon Declarations by Lucian V. Del Priore (Ex. 2048), Dr. Alexander M. Klibanov (Ex. 2049), and Dr. David M. Brown (Ex. 2050). We have reviewed the credentials of Petitioners' declarants, Drs. Albini and Gerritsen, and Patent Owner's declarants, Drs. Del Priore, Klibanov, and Brown and consider each of them to be qualified to provide the opinions for which their testimony has been submitted.

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[6] P. Mitchell et al., *Ranibizumab (Lucentis) in Neovascular Age-Related Macular Degeneration: Evidence from Clinical Trials*, 94(2) Br. J. Ophthalmol. 2–13 (2010) Ex. 1030.

[7] Papadopoulos et al. (US 7,374,758 B2, May 20, 2008) ("Papadopolous") Ex. 1010.

[8] Dix et al., (US 2006/0217311 A1, May 20, 2008) ("Dix") Ex. 1033.

E. The ’069 Patent

The ’069 patent is directed to methods for treating angiogenic eye disorders by sequentially administering multiple doses of a vascular epithelial growth factor (“VEGF”) antagonist to a patient. Ex. 1001, Abstr. These methods include the administration of multiple doses of a VEGF antagonist to a patient at a frequency of once every 8 or more weeks, and are useful for the treatment of angiogenic eye disorders such as, *inter alia*, age related macular degeneration. *Id.*

In an exemplary embodiment, a single “initial dose” of VEGF antagonist (“VEGFT”) is administered at the beginning of the treatment regimen (i.e., at “week 0”), two “secondary doses” are administered at weeks 4 and 8, respectively, and at least six “tertiary doses” are administered once every 8 weeks thereafter, i.e., at weeks 16, 24, 32, 40, 48, 56, etc.). Ex. 1001 col. 2, ll. 56–62.

F. Representative Claim

Claim 1 is the sole independent claim of the ’069 patent, and recites:

> 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 on an as needed/

> pro re nata (PRN) basis, based on visual and/or anatomical outcomes as assessed by a physician or other qualified medical professional;
>
> wherein the VEGF antagonist is a receptor-based chimeric molecule comprising (1) a VEGFRl 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.

Ex. 1001, col. 21, ll. 42–60.

G. Prosecution History of the '069 Patent

The '069 patent issued from U.S. Application Ser. No. 14/972,560 (the "'560 application") filed on December 17, 2015, and claims the priority benefit of, *inter alia*, provisional Application Ser. No. Provisional application No. 61/432,245, which was filed on Jan. 13, 2011. Ex. 1001, code (60).

The claims of the '069 patent, including claims 1 and 8–12 were allowed on March 6, 2017, and the patent issued on June 6, 2017. Ex. 1017, 162; Ex. 1001, code (45).

II. ANALYSIS

A. Petitioner's Motion to Exclude

Before turning to our analysis proper of the patentability of claims 1 and 8–12 of the '069 patent, we address the parties' Motions to Exclude

Evidence, turning first to Petitioner's Motion to Exclude. ("Pet. Mot. Exclude"). Paper 76. Patent Owner has filed an Opposition to the Motion to Exclude ("PO Opp.," Paper 79) and Petitioner has filed a Reply ("Pet. Reply MTE," Paper 81).

Specifically, Petitioner seeks to exclude Exhibits 2059, 2060, 2073, 2096, and 2128, and portions of Exhibits 2048–50 (collectively, the "challenged Exhibits"). Pet. Mot. Exclude 1. Petitioner notes that it timely objected to these exhibits through written objections (Paper 40) and/or during deposition. *Id.* Petitioner asserts that, in response to Petitioner's objections, Patent Owner served the declaration of Ms. Doris Weber (Ex. 2131), Patent Owner's in-house, senior litigation support specialist, to authenticate Exhibits 2059–60, 2073, and 2128 as being "true and correct" copies. *Id.* at 2.

1. Exclusion under Fed. R. Evid. 901

Petitioner first argues that challenged Exhibits 2059, 2060, 2073, 2096, and 2128 are not properly authenticated, as required by Federal Rule of Evidence 901. Pet. Mot. Exclude 1. Petitioner argues that Ms. Weber is not a custodian of these exhibits, and has no personal knowledge of the creation, authorship, maintenance, or modification of any of the exhibits or the underlying documents from which they were prepared. *Id.* at 2. Therefore, Petitioner asserts, Ms. Weber's declaration does not "satisfy the requirement of authenticating or identifying an item of evidence under Fed. R. Evid. 901(a). *Id.* (citing *Riverbed Tech., Inc v. Realtime Data LLC*,

IPR2016-00978, Paper 67 at 39–41 (PTAB Oct. 30, 2017); *TRW Auto. U.S. LLC v. Magna Elecs.*, IPR2014-01348, Paper 25 at 5–12 (PTAB Jan. 15, 2016). Petitioner argues that none of the Exhibits are self-authenticating under Fed. R. Evid. 902, and that Exhibits 2060 and 2128 are incomplete and/or excerpted versions of un-produced, allegedly confidential originals, which, Petitioner contends, casts further doubt on their authenticity and reliability. *Id.* at 3.

Specifically, Petitioner contends, with respect to Exhibit 2060, that Ms. Weber could not authenticate the Exhibit, and that Patent Owner's declarant, Dr. Del Priore testified that Exhibit 2060 fails to identify which clinical trial the data come from. Pet. Mot. Exclude 5 (citing Ex. 1111, 175–176). Petitioner notes that Dr. Del Priore also testified that he "[did not] know the source of the document" and refused to answer questions relating to Exhibit 2060 due to his lack of personal knowledge. *Id.* at 5–6 (citing Ex. 111, 175, 174–190).

Concerning Exhibit 2073, Petitioner similarly argues that Ms. Weber's declaration fails to authenticate Exhibit 2073, and that Patent Owner's expert, Dr. Klibanov, was also unable to authenticate Exhibit 2073. Pet. Mot. Exclude 7. Petitioner also notes that, at deposition, Dr. Klibanov could not answer foundational questions about Exhibit 2073. *Id.* Petitioner asserts that Patent Owner has produced no credible evidence to support a finding that Exhibit 2073 is in fact what its expert claims it is. *Id.* at 8.

Petitioner alleges that challenged Exhibit 2128, a confidential (filed under seal), non-public compilation of the VIEW protocol signature pages,

should be excluded under Rule 901 because no witness with personal knowledge has authenticated it. Pet. Mot. Exclude 8. Nor, Petitioner contends, is there evidence that it is an accurate compilation of excerpts as they existed at the time of creation or regarding the maintenance of the documents in the 13–15 years since their alleged creation. *Id.* at 8–9 (citing *Riverbed*, IPR2016-00978, Paper 67 at 39–41; *TRW*, IPR2014-01348, Paper 25 at 5–12).

Petitioner argues that Exhibit 2096, a confidential (filed under seal), non-public document alleged to be a clinical study agreement between Vitreoretinal Consultants and Regeneron Pharmaceuticals, Inc., should be excluded under Rule 901. Pet. Mot. Exclude 10 (citing Ex. 1110, 59–62). Petitioner argues that Patent Owner's declarant, Dr. Brown, admitted at his deposition that he did not sign the Exhibit 2096 agreement, nor could he answer foundational questions about it. *Id.* Consequently, Petitioner argues, Exhibit 2096 should be excluded as unauthenticated. *Id.*

Patent Owner responds that, in her sworn declaration, Ms. Weber explained that she has personal knowledge of the facts recited therein, and that each of the Weber Exhibits is a true and correct copy of what it purports to be. PO Opp. 2 (citing Ex. 2131 ¶ 1). Patent Owner explains that, at Petitioner's request, Ms. Weber appeared for deposition, where she testified as to the processes whereby she confirmed the authenticity of the Exhibits. *Id.* According to Patent Owner, Ms. Weber explained that she personally collected the documents addressed in her declaration from Regeneron systems, reviewed them, and confirmed that they are true and correct copies

kept in accordance with Regeneron's procedures. *Id.* (citing, e.g., Ex. 1150 at 25–26, 29–30, 34, 41, 42–43).[9] Patent Owner notes that, where possible, Ms. Weber also personally confirmed these details with individual custodians. *Id.* (citing, e.g., Ex. 1150, 35–37, 40, 44–45).

Petitioner contends that Ms. Weber need not have personally authored or maintained the documents in order to serve as an authenticating witness. PO Opp. 3 (citing, e.g., *Comcast Cable Comms., LLC v. Veveo, Inc.*, IPR2019-002990, 2020 WL 4687062 at *28 (PTAB Aug. 12, 2020)). Furthermore, argues Patent Owner, Petitioner's assertion that certain of the authenticated Weber Exhibits are "incomplete and/or excerpted versions of unproduced" originals is unsupported—and in some cases directly contradicted by the record. *Id.* (citing, e.g., IPR2021-00881, Ex. 1150, 32).

Specifically, Patent Owner contends that Ms. Weber, who spoke with the custodian of Exhibit 2060 in preparation for her deposition, authenticated the Exhibit. PO Opp. 5 (citing IPR2021-00881, Ex. 1150 at 31–33. 35–37; *see also* Ex. 2131 ¶ 3). Petitioner contends that it is not necessary that its

[9] Petitioner deposed Ms. Weber in this proceeding, but only filed that deposition transcript in the parallel proceeding, *Mylan Pharms. Inc. v. Regeneron Pharms., Inc.,* IPR2021-00881. Consequently, our citations to Ms. Weber's deposition transcript reference Exhibit 1150 in IPR2021-00881.

declarant, Dr. Del Priore, separately authenticate, or have personal knowledge of, this Exhibit. *Id.*

Similarly, Patent Owner contends that Exhibit 2073 was authenticated by Ms. Weber, and that Dr. Klibanov need not separately authenticate this document or have "firsthand knowledge" of the experiments it describes, to satisfy the requirements of Rule 901. PO Opp. 6 (citing Ex. 2131 ¶ 4; IPR2021-00881, Ex. 1150, 40–41).

With respect to Exhibit 2128, Patent Owner contends that, in addition to the authentication by Ms. Weber, Patent Owner's declarant Dr. Brown testified at deposition that: (1) he personally recognizes the Exhibit as an Investigator's Agreement; (2) he was a principal investigator for the trial; (3) Exhibit 2128 is signed by Dr. Brown's partner, who was the other principal investigator; and (4) Dr. Brown's practice retains a copy of the agreement that is Exhibit 2128, which is stored at Iron Mountain. PO Opp. 7 (citing Ex. 1110, 62–63). Patent Owner notes that Dr. Brown expressly confirmed that Exhibit 2128 "is our document, from my institution." *Id.* (citing Ex. 1110, 63). Similarly, Patent Owner contends, Dr. Brown testified that Exhibit 2096 is a Clinical Study Agreement between Dr. Brown's institution, Vitreoretinal Consultants of Houston, and Regeneron. *Id.* (citing Ex. 2050 ¶ 71). Patent Owner asserts that Dr. Brown further testified that he has personal knowledge of Exhibit 2096 (because he was the principal investigator in the associated clinical study), that his partner signed Exhibit 2096 (the Clinical Study Agreement), and that his practice maintained a copy of Exhibit 2096 at Iron Mountain in accordance with their

regular, FDA-mandated document retention policies. *Id.* at 9 (citing Ex. 1110, 59–62).

Petitioner replies that the deposition testimony of Ms. Weber revealed authentication deficiencies. Pet. Reply MTE 1. By way of example, Petitioner points to Ms. Weber's lack of personal knowledge concerning the author of Exhibit 2059 and the circumstances under which the document was signed. *Id.* at 1–3 (citing IPR2021-00881, Ex. 1150, 19–29). Furthermore, argues Petitioner, when asked what actions she took "to ensure that [the exhibits were] true and correct cop[ies]," Ms. Weber testified she "had no doubt" that they were, based solely on the fact that she "reviewed them." *Id.* (citing IPR2021-00881, Ex. 1150, 30). Ms. Weber's position and dates of employment at Patent Owner did not provide her with knowledge of Patent Owner's document creation and record-keeping procedure for these exhibits. *Id.* (citing IPR2021-00881, Ex. 1150, 33–37; *Kolmes v. World Fibers Corp.*, 107 F.3d 1534, 1542–43 (Fed. Cir. 1997)). Petitioner also notes that Ms. Weber did not speak to any of the custodians until after she submitted her declaration, allegedly further undermining the reliability of her sworn declaration attesting as to her personal knowledge of the facts and that each Weber Exhibit is a true and correct copy. *Id.* at 4 (citing IPR2021-00881, Ex. 1150, 129).

Petitioner argues further that Patent Owner's reliance on Dr. Brown as an additional source of authentication for Exhibit 2128 only undermines the exhibit's authenticity. Pet. Reply MTE 4. According to Petitioner, Patent Owner's allegation that Dr. Brown confirmed that Exhibit 2128 "is [his]

document, from [his] institution," squarely contradicts its claim that Ms. Weber "personally collected" Exhibit 2128 "from Regeneron systems" and confirmed it was "kept in accordance with Regeneron's procedures." *Id.* (quoting PO Opp. 7, 2). Petitioner argues that, because it is unclear where Exhibit 2128 came from, Patent Owner has not met its burden to establish authenticity. *Id.*

We are not persuaded by Petitioner's argument that the challenged Exhibits are not authenticated. Federal Rule of Evidence 901 sets a relatively low bar for authentication. *See Comcast*, 2020 WL 4687062, at *28. Rule 901(a) states: "To satisfy the requirement of authenticating or identifying an item of evidence, the proponent must produce evidence sufficient to support a finding that the item is what the proponent claims it is." Fed. R. Evid. 901(a). By way of example, Rule 901(b)(1) states that a witness with knowledge can provide authenticating testimony that an item is what it is claimed to be. Fed. R. 901(b)(1).

Patent Owner contends that each of the challenged Exhibits constitutes an internal document in Patent Owner's possession constituting: (1) a Regeneron sample analysis report (Ex. 2059); (2) a portion of the VIEW 1 Clinical Study Report (Ex. 2060); (3) a study from a Regeneron Sanofi Analytical Investigation Workshop (Ex. 2073); (4) Regeneron's VIEW Protocol Signature Pages (Ex. 2128); and (5) a Clinical Study Agreement (Ex. 2096). Ms. Weber, in her capacity as a Senior Litigation Support Specialist with Patent Owner, has declared that the challenged Exhibits are "true and correct cop[ies]" of the original documents. Ex. 2131

¶¶ 1–5. Furthermore, Ms. Weber has testified that the challenged Exhibits were stored on the server at Regeneron, that access to the servers was restricted, and that she collected them for the purpose of this proceeding. *See, e.g.*, Ex. 1135, 26–31. Ms. Weber also testified that, in preparing her Declaration, she consulted with Ms. Karen Chu, custodian of Regeneron's clinical strategy and execution, ophthalmology, to ascertain the location of the documents on Regeneron's regulatory archive. *Id.*, *e.g.*, at 36–37. Ms. Weber also testified that she was not offering any testimony regarding the substance of the challenged Exhibits. *Id.*, *e.g.*, at 31.

Similarly, with respect to Exhibits 2128 and 2096, we find that Dr. Brown is an individual with knowledge who can testify that these exhibits are what they purport to be. Dr. Brown's ability to recognize and authenticate the Exhibits is based upon his personal recognition of the Exhibits as an Investigator's Agreement, his involvement as a principal investigator for the trial, his recognition of the signature of his partner in practice, who was the other principal investigator, on Exhibit 2128, and the retention of a copy of Exhibit 2128 according to his practice of retaining such copies. *See* Ex. 1110, 62–63.

We therefore conclude that Patent Owner has met the standard set forth in Rule 901(b)(1) of presenting a witness with knowledge to authenticate the challenged Exhibits as being true and correct copies of records that are in the possession of Patent Owner. As a Senior Litigation Support Specialist, working in consultation with a Regeneron custodian of records, and with access to the restricted Regeneron server where the

Exhibits at issue are kept, Ms. Weber qualifies as a person with knowledge, under Rule 901(b)(1), that the Exhibits were true and correct copies of the records in Regeneron's possession. Ms. Weber's testimony does not speak to the substance of the challenged Exhibits, but merely that these are accurate copies of records that are in the possession of, and controlled by, Regeneron. As such, her testimony is sufficient to authenticate, under Federal Rule of Evidence 901, the challenged Exhibits as being what Patent Owner claims them to be. Petitioner's Motion to Exclude the challenged Exhibits upon this ground is consequently denied.

In addition to excluding the challenged Exhibits under Rule 901, Petitioner cites additional grounds for excluding certain exhibits. We consider each of these in turn.

2. Exclusion under Fed. R. Evid. 402 and 403

Petitioner moves to exclude challenged Exhibits 2059, 2060, 2073, and 2128 under Rule 402 as being irrelevant. Pet. Mot. Exclude 4, 6, 8, 9. Petitioner also moves to exclude challenged Exhibits 2060 and 2128 under Rule 403 as being unduly prejudicial. *Id.* at 6, 9.

Petitioner asserts that Exhibits 2059, 2060, 2073, and 2128 are non-publicly available, internal documents, and do not demonstrate the knowledge of a person of ordinary skill in the art or are irrelevant prior art teachings, and should therefore be excluded as irrelevant non-prior art under FRE 402. Pet. Mot. Exclude 4, 6, 8. Petitioner also notes that Patent Owner also fails to cite Exhibits 2059, 2060, and 2073 in its Preliminary Response,

Response, or Sur-Reply (Papers 10, 39, 68), demonstrating that they do not have a tendency to make any fact of consequence more or less probable as Rule 401 requires and are therefore irrelevant to this proceeding. *Id.* (also citing *SK Innovation Co. v. Celgard, LLC*, IPR2014-00679, Paper 58, 49 (PTAB Sept. 25, 2015).

Petitioner also argues that any probative value of Exhibits 2060 and 2128, which are excerpted from larger documents, is substantially outweighed by the dangers of unfair prejudice, confusion, and misleading the factfinder, because they could allegedly deny the factfinder a complete set of materials to judge the accuracy of its claim. Pet. Mot. Exclude 6, 9.

Patent Owner argues that it relies on the challenged Exhibits 2059 and 2073 not for their prior art teaching, but, rather, as illustrating the inherent variability in producing VEGF Trap-Eye. PO Opp. 4, 6 (citing Exhibit 2049 at ¶¶ 91–96). Patent Owner also disputes Petitioner's assertion that non-prior art evidence is necessarily irrelevant. *Id.* (citing, e.g., *Organik Kimya AS v. Rohm & Haas Co.*, 873 F.3d 887, 893-94 (Fed. Cir. 2017)). Similarly, Patent Owner argues that Exhibit 2060 is relied upon to rebut Petitioner's arguments on inherent efficacy of the claimed dosing regimen. *Id.* at 5 (citing Ex. 2048 ¶¶ 107–08). Patent Owner also contends that Petitioner's assertion that Exhibit 2128 is irrelevant because it is a non-public document fails because Patent Owner and its expert rely on Exhibit 2128 precisely to

show its confidentiality. *Id.* at 7 (citing, e.g., Ex. 2050 ¶ 71; PO Resp. 9–10, n.6).

With respect to Rule 403, Patent Owner argues that Petitioner's assertion that Exhibit 2128 is unreliable or prejudicial as a "hand-picked excerpt" is wrong because Patent Owner's declarant, Dr. Brown, expressly confirmed the authenticity of the Exhibit. PO Opp. 7 (citing Ex. 1110, 63).

We are not persuaded by Petitioner's arguments that Exhibits 2059, 2060, 2073, and 2128 should be excluded under Rule 402 as being irrelevant. We acknowledge Petitioner's point that Exhibits 2059, 2060, and 2073 are not cited in Patent Owner's Preliminary Response, Response, or Sur-Reply. Nevertheless, they are cited in the various Declarations of Patent Owner's experts. Specifically, Exhibit 2059 is cited by Dr. Klibanov (*see* Ex. 2049 ¶¶ 95, 97, 98, 101) and Dr. Del Priore (*see* Ex. 2048 ¶¶ 98, 99, 100–103). Exhibit 2060 is also cited by Dr. Del Priore (*see* Ex. 2048 ¶ 107) and Dr. Del Priore also testified about the Exhibit at his deposition. *See* Ex. 1111, 174–175. Dr. Klibanov testified with respect to Exhibit 2073 at his deposition (*see* Ex. 1108, 198). Exhibit 2128 was cited in Dr. Brown's Declaration (*see* Ex. 2050 ¶ 71), and Dr. Brown testified about the Exhibit in his deposition. *See* Ex. 1110, 62–63, 122. We consequently find that these Exhibits are relevant to this proceeding because these exhibits have a tendency to make a fact more or less probable. Fed. R. Evid. 401.

Nor are we persuaded by Petitioner's argument that Exhibits 2060 and 2128 should be excluded under Rule 403 as unduly prejudicial. Rule 403 states that "[t]he court may exclude relevant evidence if its probative value

is substantially outweighed by a danger of one or more of the following: unfair prejudice, confusing the issues, misleading the jury, undue delay, wasting time, or needlessly presenting cumulative evidence." Petitioner's generalized allegation that "[a]llowing [Patent Owner] to cherry-pick a portion of a document denies the factfinder a complete set of materials to judge the accuracy of its claim" (*see* Pet. Mot. Exclude 6, 9) by itself, lacks particularity as to the potential unfair prejudice posed by admission of these particular Exhibits, particularly when weighed against the relatively minor, if relevant, role played by the Exhibits in Patent Owner's arguments. We consequently deny Petitioner's motion to exclude challenged Exhibits 2059, 2060, 2073, and 2128 under Fed. R. Evid. 402 and/or 403.

3. Exclusion under Fed. R. Evid. 802

Finally, Petitioner urges us to exclude challenged Exhibits 2059, 2060, 2128 and 2096 as inadmissible hearsay under Rule 802 because they constitute out-of-court statements offered for the truth of the matters asserted.[10] Pet. Mot. Exclude 5, 6–7, 9, 10.

[10] Petitioner also moves to exclude Exhibit 2059 under Rule 801. Pet. Mot. Exclude 5. Rule 801 addresses "Definitions That Apply to This Article; Exclusions From Hearsay." Petitioner makes no separate arguments for Rule 801, and we therefore address Petitioner's combined Rules 801-802 argument as being under Rule 802.

Patent Owner contends that Exhibit 2059 falls within the business records exception to the Rule, as demonstrated by Ms. Weber's Declaration. PO Opp. MTE 3. Patent Owner states that Exhibit 2059 is a scientific report that was stored on Regeneron servers, and bears facial indications of trustworthiness (e.g., written on Regeneron letterhead and dated and signed by Dr. Koehler-Stec, a study director and Regeneron employee). *Id.* at 4 (citing Ex. 2059; IPR2021-00881, Ex. 1150 at 24–26; Ex. 2131 ¶ 2).

Patent Owner similarly argues that Exhibit 2060 is a clinical study protocol, stored in Regeneron's regulatory archive, and bears facial indicia of trustworthiness (Regeneron protocol headers and file path information on each page), and was authenticated by Ms. Weber. PO Opp. MTE (citing Ex. 2060; Ex. 2131 ¶ 3; IPR2021-00881, Ex. 1150, 24–26).

With respect to Exhibits 2128 and 2096, Patent Owner argues that Dr. Brown's and Ms. Weber's testimony support the position that the Exhibits falls within the business records exception under Rule 803. PO Opp. MTE 8–9. Patent Owner contends that both Exhibits 2128 and 2096 were generated in the ordinary course of regularly conducted activity (i.e., a clinical investigation), was stored by Regeneron in its regulatory archives and by Dr. Brown's practice at Iron Mountain, and bears facial indications of trustworthiness (i.e., dated signatures by Dr. Brown's partner on every page). *Id.* (citing Ex. 1110, 62–63).

Petitioner replies that Ms. Weber's testimony does not demonstrate sufficient personal knowledge of Patent Owner's business practices for her to testify regarding these practices. Pet. Reply MTE 5. According to

Petitioner, Ms. Weber cannot testify about whether the records were made or kept in the course of a regularly conducted business activity because she was never a custodian of Patent Owner's records or otherwise a qualified witness. *Id.* (citing Fed. R. Evid. 803(6) (stating that records of a regularly conducted activity must be "shown by the testimony of the custodian or another qualified witness")). Similarly, Petitioner argues, Dr. Brown's testimony regarding Exhibit 2128 fails for the same reason. *Id.* Petitioner asserts that Patent Owner's reliance on Exhibits 2059, 2060, 2096, and 2128 as either "scientific report[s]" or clinical trial documents does not support application of FRE 803(6). *Id.* (citing *Corning Inc. v. DSM IP Assets B.V.*, IPR2013-00043, Paper 97 at 4–7 (PTAB May 1, 2014) (declining to invoke a Rule 803(6) exception to reports of scientific research/tests).

We are not persuaded by Petitioner's arguments. Rule 803 states, in relevant part:

> The following are not excluded by the rule against hearsay, regardless of whether the declarant is available as a witness:
> ….
>
> (6) Records of a Regularly Conducted Activity.
>
> A record of an act, event, condition, opinion, or diagnosis if:
>
> (A) the record was made at or near the time by—or from information transmitted by—someone with knowledge;
>
> (B) the record was kept in the course of a *regularly conducted activity of a business*, organization, occupation, or calling, whether or not for profit;

> (C) making the record was a regular practice of that activity;
>
> (D) all these conditions are shown by the testimony of the custodian or another qualified witness, or by a certification that complies with Rule 902(11) or (12) or with a statute permitting certification; and
>
> (E) neither the source of information nor the method or circumstances of preparation indicate a lack of trustworthiness.

(emphasis added).

Despite Petitioner's invocation of *Corning*, we are not persuaded by its argument that challenged Exhibits 2059, 2060, 2096, and 2128 constitute inadmissible hearsay evidence. As an initial matter, Exhibits 2096 and 2128 are not "laboratory notebooks" or "laboratory generated data of properties of compositions" of the sort that *Corning* finds to be inadmissible as hearsay. *See Corning*, IPR2013-00043, Paper 97 at 4. Rather, Patent Owner explains that those exhibits represent agreements between Regeneron and third-party investigators. *See* PO Opp. 8. Such an agreement between a pharmaceutical company and third-party investigators sounds more in contract than in "laboratory notebooks" and are typical of the sort of routine business conducted by such corporations. Moreover, the fact that such records were maintained in an access-restricted, searchable electronic archive of Regeneron, as well as in the records of Dr. Brown's practice, also speaks to the routine nature of such records kept in the ordinary course of business.

See, e.g., Ex. 2131 ¶¶ 1–5. As such, we conclude that challenged Exhibits 2128 and 2096 fall into the business records exception of 803(6).

We also find that challenged Exhibits 2059 and 2060 are covered by Rule 803(6). These Exhibits are similarly not laboratory notebooks; rather, we agree with Patent Owner that these Exhibits are best characterized as sample analysis report and a clinical study report. *See* PO Opp. 3. These Exhibits were also stored in the Regeneron database of records and appear to be the type of report that would be routinely made by a pharmaceutical company to summarize and memorialize laboratory tests.

That said, even laboratory notebooks, if kept as part of a company's regular record keeping activity, may well fall into the exception to the hearsay rule of 803(6)(B). *See, e.g.*, *Shu-Hui Chen v. Bouchard*, 347 F.3d 1299, 1313 (Fed. Cir. 2003) (holding that laboratory notebooks are admissible when "it was the regular practice to keep research notebooks" (citing *Air Land Forwarders, Inc. v. United States*, 172 F.3d 1338, 1344 (Fed. Cir. 1999)); *see also Conoco v. Dep't of Energy*, 99 F.3d 387, 391 (Fed. Cir. 1996) (stating that "[b]ecause of the general trustworthiness of regularly kept records and the need for such evidence in many cases, the business records exception has been construed generously in favor of admissibility")).

We consequently conclude that Petitioner has failed to demonstrate that challenged Exhibits 2059, 2060, 2128, and 2096 should be excluded as inadmissible hearsay under Fed. R. Evid. 802.

4. Conclusion

We conclude that Petitioner has failed to demonstrate that challenged Exhibits 2059, 2060, 2073, 2096, and 2128 should be excluded. Furthermore, because we so conclude, we also decline to exclude the corresponding portions of Declaration Exhibits 2048, 2049, and 2050 relying on those exhibits. Petitioner's Motion to Exclude is consequently DENIED.

B. Patent Owner's Motion to Exclude

We next turn to Patent Owner's Motion to Exclude. ("PO Mot. Exclude"). Paper 77. Petitioner has filed an Opposition to the Motion to Exclude ("Pet. Opp.," Paper 78) and Patent Owner has filed a Reply ("PO Reply MTE," Paper 80).

Patent Owner moves to exclude Exhibits 1118, 1121, 1124 in their entirety, and portions of Petitioner's Reply (Paper 56). Pet. Mot. 1, 13. Petitioner opposes the motion. Pet. Opp. MTE 1.

1. Petitioners' Reply

Patent Owner asserts that Petitioners' Reply improperly contains a new argument that VEGF Trap-Eye was publicly distributed before the critical date. PO. Mot. Exclude 1–2 (citing Pet. Reply 22, 29). According to Patent Owner, that argument by Petitioners should be excluded as it attempts to alter the grounds presented in the Petition. *Id.* at 5–6. Patent Owner requests, as an alternative to excluding the Reply argument that we strike it.

See id. at 3 n.3 (asserting that "[i]f the Board deems appropriate, this portion of Patent Owner's motion to exclude may be treated as a motion to strike.").

We deny the motion to exclude the referenced argument in Petitioners' Reply, as well as the invitation to consider the motion as one to strike the argument. As Patent Owner notes in the motion, Patent Owner raised this issue previously in this proceeding. PO Mot. Exclude 5. At that time, we denied Patent Owner's request for authorization to file a motion to strike the referenced argument in the Reply. It is improper for Patent Owner to now seek to strike the argument in a motion to exclude. A motion to exclude is not the proper vehicle to address arguments or evidence that a party believes exceeds the proper scope of a reply. *See* USPTO, *Consolidated Trial Practice Guide* (2019) at 79, available at: https://www.uspto.gov/sites/default/files/documents/tpgnov.pdf?MURL= (last visited October 27, 2022) ("CTPG"). Moreover, as Petitioners correctly assert, Patent Owner has failed to satisfy the prerequisite for filing a motion to exclude by failing to timely file an objection. *See* 37 C.F.R. 42.64(b)(1); CTPG 78–79.

Patent Owner has not been left without an opportunity to address the Reply argument. When we denied authorization to file a motion to strike, we authorized Patent Owner to file, with its Sur-Reply, a table identifying any portion of the Reply that Patent Owner considers to have exceeded the scope of the Reply. Further, we explained that Patent Owner, alternatively, may address that contention, or the merits of any newly-raised arguments or evidence in its Sur-Reply. Indeed, Patent Owner addressed the issue in its

Sur-Reply for our consideration. Thus, Patent Owner had sufficient opportunity to identify in its Sur-Reply its contentions regarding Petitioners' allegedly inappropriate Reply argument and took advantage of that opportunity. That is sufficient for us to consider the issue and determine whether such argument should be disregarded. *See* CTPG 80.

Patent Owner also alleges that Petitioner attempts to make no arguments with respect to Ground 4 by arguing for the first time on Reply that Dixon's prospective disclosure of the intended 2-year dosing regimen of VIEW's 2Q8 arm (3 monthly loading doses, followed by fixed Q8 dosing through the end of Year 1, followed by PRN dosing in Year 2) anticipates the challenged claims. PO Mot. Exclude 6. Similarly, Patent Owner argues that Petitioner improperly alters its Ground 5 obviousness arguments, using several new theories raised for the first time on Reply. *Id.*

As with Patent Owner's prior arguments, we determine that Patent Owner had sufficient opportunity to identify in its Sur-Reply its contentions regarding Petitioners' allegedly inappropriate Reply argument. Indeed, Patent Owner has done so. *See, e.g.*, Sur-Reply 28. That is sufficient for us to consider the issue and determine whether such argument should be disregarded. *See* CTPG 80.

2. Exhibits 1118, 1121 and 1124

Patent Owner asserts that Petitioners' Exhibits 1118, 1121 and 1124 should be excluded because they are not cited in the pleadings and are irrelevant. PO Mot. Exclude 9 (citing Fed. R. Evid. 402). Additionally,

Patent Owner seeks to exclude certain paragraphs in the declarations of Drs. Albini and Gerritsen that Patent Owner asserts are not cited in the pleadings. *Id.* at 6–7 (citing portions of Ex. 1002, Ex. 1003 and Ex. 1137). According to Patent Owner, the referenced declaration paragraphs were not relied upon by Petitioners and should be excluded as irrelevant. *Id.*

We dismiss as moot the motion to exclude Exhibits 1118, 1121 and 1124. Because Exhibits 1118, 1121 and 1124 were not cited or relied upon by Petitioners, we have not considered them in rendering our Final Written Decision. Accordingly, we dismiss the motion as moot with regard to these exhibits.

We deny the motion to exclude the identified paragraphs of the declarations of Dr. Albini (Ex. 1002) and Dr. Gerritsen (Ex. 1003). Each declaration has been cited in pleadings. Although every paragraph in the declarations of these expert may not be cited in pleadings, those portions of the declaration may serve to provide context for the cited paragraphs, or the testimony as a whole. Indeed, as Petitioners note, and Patent Owner does not dispute, some of the challenged portions of the declaration testimony that Patent Owner seeks to exclude are referenced in the declaration testimony of another expert. *See, e.g.*, Pet. Opp. MTE 13; PO Reply 4. Further, we do not find that Patent Owner has established that keeping the complete declaration testimony of these experts in the record to be unduly prejudicial under Fed. R. Evid. 403. It is unclear how Patent Owner alleges that Petitioners could use the evidence in the future. It is also unclear and unpersuasive that keeping the referenced paragraphs in the record serves to

clutter the record in a prejudicial manner. In any event, we do not find that Patent Owner has met its burden of proof to establish that the identified paragraphs of the declarants' testimony should be excluded as irrelevant.

C. Level of Ordinary Skill in the Art

Petitioner contends that a person of ordinary skill in the art 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). Pet. 25. Such a person, Petitioner asserts, would have 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 angiogenic eye disorders (such as AMD), including through the use of VEGF antagonists. *Id.* (citing Ex. 1002 ¶¶ 26–28).

Patent Owner disagrees with Petitioner's definition of a person of ordinary skill in the art, contending that, for purposes of the '069 Patent, a skilled artisan would be an ophthalmologist with experience in treating angiogenic eye disorders, including through the use of VEGF antagonists. PO Resp. 7–8, n.4. Patent Owner states, however, that it does not believe that the parties' differing definitions of a person of ordinary skill in the art matter for any argument in this Patent Owner's Response. *Id.*

We find that Petitioner's definition is the better definition for purposes of this proceeding. We acknowledge that the claims of the '069 patent are directed to a "method for treating an angiogenic eye disorder in a patient"

and that the actual practice of the method would therefore seem to be limited to those who have the ability to treat patients, i.e., physicians, etc. However, we find Patent Owner's definition to be unduly limiting. Individuals who are involved in drug development or sub-clinical level testing of drugs for treating eye disorders may be extremely knowledgeable about the development of the treatment of eye disorders and drug development, and able to comprehend and evaluate the teachings of the prior art. *See, e.g.*, Pet. 25. Such individuals might not possess an M.D. degree, but instead possess a Ph.D. in a "biotechnological, or pharmaceutical field," or a lesser degree with a corresponding increased depth of experience, as suggested by Petitioner. We agree that such individuals should be considered persons of ordinary skill in the art.

We also find that Petitioner's definition is commensurate with the level of skill reflected in the prior art. *See, e.g.*, Exs. 1006, 1010, 1030, 1033; *see also Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required "where the prior art itself reflects an appropriate level and a need for testimony is not shown" (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985))). We consequently adopt Petitioner's definition of a person of ordinary skill in the art has having an M.D. or Ph.D. or equivalent, or less education but considerable professional experience in the medical, biotechnological, or pharmaceutical field, and having practical academic or medical experience in developing treatments

for angiogenic eye disorders or treating angiogenic eye disorders including through the use of VEGF antagonists.

D. Claim construction

The Board applies the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. § 282(b). *See* 37 C.F.R. § 100(b) (2020). Under that standard, claim terms "are generally given their ordinary and customary meaning" as understood by a person of ordinary skill in the art at the time of the invention. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc). "In determining the meaning of the disputed claim limitation, we look principally to the intrinsic evidence of record, examining the claim language itself, the written description, and the prosecution history, if in evidence." *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 469 F.3d 1005, 1014 (Fed. Cir. 2006) (citing *Phillips*, 415 F.3d at 1312–17). Extrinsic evidence is "less significant than the intrinsic record in determining 'the legally operative meaning of claim language.'" *Phillips*, 415 F.3d at 1317 (quoting *C.R. Bard, Inc. v. U.S. Surgical Corp.*, 388 F.3d 858, 862 (Fed. Cir. 2004)).

Petitioner advances proposed claim constructions for the claim terms "initial dose," "secondary dose," and "tertiary dose," "4 weeks" and "*pro re nata*," "VEGFR1 component," "VEGFR2 component," and "multimerization component." Pet. 15–19. We consider each in turn.

1. "initial dose," "secondary dose," and "tertiary dose"

Petitioner urges us to adopt the definitions of these claim terms as they are expressly set forth in the Specification of the '069 patent:

> The terms "initial dose," "secondary doses," and "tertiary doses," refer to the temporal sequence of administration of the VEGF antagonist. Thus, the "initial dose" is the dose which is administered at the beginning of the treatment regimen (also referred to as the "baseline dose"); the "secondary doses" are the doses which are administered after the initial dose; and the "tertiary doses" are the doses which are administered after the secondary doses. The initial, secondary, and tertiary doses may all contain the same amount of VEGF antagonist, but will generally differ from one another in terms of frequency of administration. In certain embodiments, however, the amount of VEGF antagonist contained in the initial, secondary and/or tertiary doses will vary from one another (e.g., adjusted up or down as appropriate) during the course of treatment.

Ex. 1001, col. 3, ll. 34–48.

Patent Owner does not propose claim construction positions for these terms because construction of these terms is not necessary to resolve the arguments presented in Mylan's Petition. PO Resp. 8 (citing *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017)).

We agree that it is unnecessary to construe these claim terms in view of the express definitions set forth in the Specification. *DePuy*, 469 F.3d at 1014. Because the claim terms are undisputed, we adopt the definition of the claim terms "initial dose," "secondary dose," and "tertiary dose" as expressly defined by the Specification of the '069 patent. *Nidec*, 868 F.3d at 1017.

2. "four weeks," "*pro re nata*," "VEGFR1 component," "VEGFR2 component," and "multimerization component"

Petitioner argues that a skilled artisan would understand "4 weeks" as "monthly" administration. Pet. 18 (citing Ex. 1001, col. 7, ll. 58–59 ("'[M]onthly' dosing is equivalent to dosing once every four weeks."), col. 14, ll. 47–48 (patients received "monthly injections," which "means patients who received . . . injections once every four weeks"); Ex. 1002 ¶ 41).

Petitioner proposes that the claim term "*pro re nata*" be defined as "as-needed," as expressly recited in the claims. Pet. 19 (citing Ex. 1001 col. 21, ll. 50–51 ("administered on an as-needed/*pro re nata* (PRN) basis")). Petitioner contends that the use of the term in the '069 patent's Specification is consistent with the claim language and with the term's use among skilled artisans. *Id.* (citing Ex. 1001, col. 14, l. 43, col. 16, ll. 9–49; Ex. 1002 ¶ 43).

Petitioner proposes that "VEGFR1 component," "VEGFR2 component," and "multimerization component" all refer to separate amino acid domains of recited SEQ ID NO:2. Pet. 19. According to Petitioner, a person of ordinary skill in the art would understand these terms to collectively refer to aflibercept (i.e., VEGF Trap, VEGF Trap-Eye, or VEGFR1R2-FcΔC1(a)). *Id.* (citing Ex. 1001, col. 2, ll. 34–38; Ex. 1002 ¶ 39).

Patent Owner does not contest Petitioner's proposed claim construction for these terms because, it contends, that the Board does not

need to construe these terms to resolve the arguments presented in this POR. PO Resp. 9

Because we find that, upon review of the record before us, that it is unnecessary to construe any of these claim terms to resolve the issues presented in this proceeding, we decline to construe these claim terms. *Nidec*, 868 F.3d at 1017.

3. Assessed by physician or qualified medical professional

Patent Owner argues that the limitation of claim 1 reciting "assessed by a physician or other qualified medical professional" is a positive limitation of the claim that should be accorded patentable weight. PO Resp. 7–8. Petitioner disagrees, contending that the term is "a pure mental step." Pet. Reply 6 (citing *King Pharms., Inc. v. Eon Labs, Inc.*, 616 F.3d 1267, 1278 (Fed. Cir. 2010).

We find that it is not necessary, for the purposes of this *inter partes* review, to determine whether this limitation should be accorded patentable weight. The limitation plays no substantial part in either parties' arguments, nor in our analysis below. *See generally*, Pet., PO Resp., Pet. Reply, Sur-Reply. Neither party disputes that when the claimed method is practiced, a physician or other qualified medical professional will be overseeing the treatment of an angiogenic eye disorder in a patient. We consequently decline to address this issue. *See Nidec*, 868 F.3d at 1017 (explaining it is only necessary to "construe terms 'that are in controversy, and only to the extent necessary to resolve the controversy'").

E. Patentability: Principles of Law

To prevail in its challenges to the patentability of all claims of the '069 patent, Petitioners must demonstrate by a preponderance of the evidence that the claims are unpatentable. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d) (2019). "In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable." *Harmonic Inc. v. Avid. Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016); *see also* 35 U.S.C. § 312(a)(3) (2012) (requiring inter partes review petitions to identify "with particularity . . . the evidence that supports the grounds for the challenge to each claim"). That burden of persuasion never shifts to Patent Owner. *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015); *see also In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1375–78 (Fed. Cir. 2016) (discussing the burden of proof in *inter partes* review).

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Schering Corp. v. Geneva Pharms*, 339 F.3d 1373 (Fed. Cir. 2003) (quoting *Verdegaal Bros., Inc. v. Union Oil Co. of Cal.*, 814 F.2d 628, 631 (Fed. Cir. 1987)). It is well settled that "a reference can anticipate a claim even if it 'd[oes] not expressly spell out' all the limitations arranged or combined as in the claim, if a person of skill in the art, reading the reference, would 'at once envisage' the claimed arrangement or combination."

Kennametal, Inc. v. Ingersoll Cutting Tool Co., 780 F.3d 1376, 1381 (Fed. Cir. 2015) (quoting In re Petering, 301 F.2d 676, 681 (1962))

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F. Grounds I and IV: Anticipation of claims 1 and 9–12 by Dixon

Ground I of the Petition argues that claims 1 and 9–12 are anticipated by Dixon. Pet. 8. Ground IV also argues claims 1 and 9–12 are anticipated by Dixon or, alternatively, are obvious over Dixon. *Id.* Ground IV also adds claim 8 as being anticipated and/or obvious. *Id.* In its response, Patent Owner contends, with respect to Ground I and IV, that the claims are not anticipated because Petitioner allegedly fails to demonstrate that VEGF Trap-Eye, as disclosed by Dixon, was known to correspond to claimed SEQ ID NO:1 or SEQ ID NO:2. PO Resp. 9–21. With respect to Ground IV, Patent Owner argues that Dixon neither anticipates nor renders obvious the challenged claims because Dixon fails to teach or suggest the claimed dosing schedules. *Id.* at 22–27. Because both Grounds I and IV each rely on Dixon as anticipating claims 1 and 9–12, albeit for different reasons, as we have explained, in Grounds I and IV, we address together both of Patent Owner's arguments with respect to both Grounds I and IV. We then consider whether claims 1 and 9–12 are obvious over Dixon. Finally, we address claim 8 separately.

1. Overview of Dixon

Dixon was published in October, 2009, and is prior art to the '069 patent. Ex. 1006, 1573. Dixon discloses that a new drug for the treatment of age-related macular degeneration ("AMD") is aflibercept ("VEGF Trap-Eye"), a fusion protein that blocks all isoforms of VEGF-A and placental growth factors-1 and -2. *Id.* Abstr. 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.*

Relevantly, Dixon discloses that, structurally, VEGF Trap-Eye is a fusion protein consisting of key binding domains of human VEGFR-1 and -2 combined with a human IgG Fe fragment. Ex. 1006, 1575, Fig. 1. Dixon also discloses the PrONTO, CLEAR-IT-1, CLEAR-IT-2, and VIEW 1/VIEW 2 clinical trials. *Id.* at 1574–76, Ex. 1002 ¶ 74. Dixon identifies "[d]esirable attributes for emerging therapies for neovascular AMD include higher visual improvement rates and decreased dosing intervals" as a motivation for the "development of new drugs for neovascular AMD . . . focused on both improving efficacy and extending duration of action," Ex. 1006, 1574, 1577; Ex. 1002 ¶ 78.

Dixon further discloses results from the phase II clinical trial CLEAR-IT-2, which included four monthly doses (at weeks 0, 4, 8 and 12) followed by *pro re nata* ("PRN") administration. Ex. 1006, 1576. Dixon reports that CLEAR-IT-2 subjects treated with that regimen exhibited mean improvement in visual acuity of nine letters and a mean decrease in retinal

thickness of 143 μm. *Id.*; Ex. 1002 ¶¶ 79–80. Dixon further reports that "patients dosed at 2.0 mg during the initial monthly dosing period required 1.6 injections on average during the p.r.n. dosing phase." Ex. 1006, 1577. Dixon discloses that, in the CLEAR-IT-2 trial:

> Two groups received monthly doses of either 0.5 or 2.0 mg for 12 weeks (at weeks 0, 4, 8 and 12) and three groups received quarterly doses of either 0.5, 2.0 or 4.0 mg for 12 weeks (at weeks 0 and 12). Following this fixed dosing period, patients were treated with the same dose of VEGF Trap-Eye on a p.r.n. basis. Criteria for re-dosing included an increase in central retinal thickness of ≥ 100 μm by OCT, a loss of ≥ 5 ETDRS letters in conjunction with recurrent fluid by OCT, persistent fluid as indicated by OCT, new onset classic neovascularization, new or persistent leak on FA or new macular subretinal hemorrhage.

Id. at 1576. Dixon also discloses that "[p]atients initially treated with 2.0 or 0.5 mg of VEGF TrapEye monthly achieved mean improvements of 9.0 ($p < 0.0001$) and 5.4 ($p < 0.085$) Early Treatment Diabetic Retinopathy Study ("ETDRS") letters with 29 and 19% gaining, respectively, ≥ 15 ETDRS letters at 52 weeks." *Id.*

Dixon also describes the then-ongoing VIEW 1/VIEW 2 phase III clinical trials. Ex. 1006, 1576. Dixon discloses that, with respect to the VIEW 1 trial:

> This non-inferiority study will evaluate the safety and efficacy of intravitreal VEGF Trap-Eye at doses of 0.5 and 2.0 mg administered at 4-week dosing intervals and 2.0 mg at an 8 week dosing interval (following three monthly doses), compared with 0.5 mg of ranibizumab administered every 4 weeks. After the first year of the study, patients will enter a second year of p.r.n.

> dosing evaluation. The VIEW 2 study has a similar study design….

Id. (internal citations omitted).

2. Petitioner's contentions of invalidity against claims 1 and 9–12 on the grounds of anticipation by Dixon

a. Claim 1

Petitioner argues that the disclosures of Dixon teach each of the limitations of independent claim 1 and dependent claims 9–12. Pet. 26–33. Petitioner has provided a claim chart of the limitations of claim 1, and what it contends are the corresponding disclosures of Dixon that teach those limitations, which, for convenience, is reproduced below:

Claim 1	**Dixon**
1. A method for treating an angiogenic eye disorder in a patient	"VEGF Trap-Eye is a novel anti-VEGF therapy, with Phase I and Phase II trial data indicating safety, tolerability and efficacy for the treatment of [AMD]." (Ex. 1006, 1573; *id.*, 1575). "Phase I data demonstrated acceptable safety and tolerability of VEGF Trap-Eye in the treatment of neovascular AMD." (*Id.*, 1577). Phase 2 patients "treated with 2.0 mg or 0.5 mg of VEGF Trap-Eye monthly achieved mean improvements of 9.0 ($p<0.0001$) and 5.4 ($p<0.085$) ETDRS letters." (*Id.*, 1576). "[P]atients … demonstrated stabilization of their vision that was similar to previous studies of ranibizumab at 1

Claim 1	**Dixon**
	year." (*Id.*, 1577). (Ex. 1002 ¶¶ 116, 120).
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;	Two groups received monthly doses of either 0.5 or 2.0 mg for 12 weeks (at weeks 0, 4, 8 and 12) …. Following this fixed dosing period, patients were treated with the same dose of VEGF Trap-Eye on a p.r.n. basis." (Ex. 1006, 1576). (Ex. 1002, ¶¶ 121–123).
wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and	(Ex. 1006, 1576). (Ex. 1002 ¶¶ 121–23).
wherein each tertiary dose is administered on an as-needed/pro re nata (PRN) basis, based on visual and/or anatomical outcomes as assessed by a physician or other qualified medical professional	"Following this fixed dosing period, patients were treated with the same dose of VEGF Trap-Eye on a p.r.n. basis. Criteria for redosing included an increase in central retinal thickness . . . a loss of ≥ 5 ETDRS letters in conjunction with recurrent fluid by OCT, persistent fluid as indicated by OCT, new onset classic neovascularization, new or persistent leak on FA or new macular subretinal hemorrhage." (Ex. 1006, 1576)
wherein the VEGF antagonist is a 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.	VEGF Trap-Eye is "a fusion protein of binding domains of VEGF receptors-1 and -2 attached to the Fc fragment of human IgG." (*Id.*, 1576 (Fig.1)). "VEGF Trap-Eye and aflibercept (the oncology product) have the same molecular structure." (*Id.*, 1575). (Ex. 1002 ¶ 125).

Pet. 46–49.

b. Claims 9 and 10

Claim 9 is exemplary and recites:

9. The method of claim **1**, wherein the angiogenic eye disorder is selected from the group consisting of: age related macular degeneration, diabetic retinopathy, diabetic macular

> edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization.

Ex. 1001 col. 22, ll. 53–57.

Petitioner contends, Heier 2009 discloses CLEAR-IT-2 data confirming that the trial's PRN regimen was successful at treating AMD. *Id.* (citing Ex. 1020, 2). Dixon similarly discloses the PRN regimen and results of CLEAR-IT-2 (Phase 2) to treat AMD. *Id.* (citing Ex. 1006, 1573, 1576, 1579).

c. Claim 11

Dependent claim 11 recites:

> 11. The method of claim **1**, wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration.

Ex. 1001, col. 22, ll. 60–62.

Petitioner contends that "intraocular administration" refers to administration to the eye generally, whereas intravitreal administration, a subset of intraocular administration, refers to administration directly into the vitreous chamber of the eye. Pet. 49 (citing Ex. 1002 ¶¶ 132–33; Ex. 1001, col. 2, ll. 39–41). Petitioner argues that Dixon discloses monthly intravitreal injections of VEGF Trap-Eye. *Id.* (citing Ex. 1020, 1–2; Ex. 1006, 1575; Ex. 1002 ¶¶ 134–135).

d. Claim 12

Claim 12 recites:

> 12. The method of claim 1, wherein the VEGF antagonist is VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO: 1.

Ex. 1001, col. 22, ll. 63–65.

Petitioner argues that both the amino acid and nucleotide sequences of VEGF Trap-Eye were disclosed in the prior art and were well known to skilled artisans. Pet. 50 (citing Ex. 1002 ¶¶ 136–137; Ex. 1010, Figs. 24A–C (disclosing the nucleotide sequence and deduced amino acid sequence), col. 10, ll. 15–17 (specifying that this molecule is termed "VEGFR1R2-FcΔC1(a)"); Ex. 1033, SEQ ID NO:3; Ex. 1083). Petitioner asserts that the CLEAR-IT 2 trials disclosed by Dixon employed VEGF Trap-Eye, and therefore disclose the "VEGF antagonist" recited by claim 12. *Id.*

3. Patent Owner's argument that VEGF Trap-Eye, as disclosed by Dixon, was not known to correspond to the claimed SEQ ID NO:1 or SEQ ID NO:2

a. Patent Owner's contentions

Patent Owner argues that it is undisputed that VEGF Trap-Eye was not publicly available before EYLEA's FDA approval on November 18, 2011. PO Resp. 9. (citing Ex. 2130 319–320; Ex. 2050, ¶¶ 70–72). According to Patent Owner, its clinical trials involving VEGF Trap-Eye were conducted under strict confidentiality, as was its submission of information to FDA regarding VEGF Trap-Eye preapproval. *Id.* at 9–10. Consequently, argues Patent Owner, the amino acid or nucleic acid sequence

of VEGF Trap-Eye was not available before the priority filing date of the '069 Patent unless the identity of those sequences was publicly disclosed. *Id.* Patent Owner argues that, because Dixon does not expressly disclose the amino acid sequence of VEGF Trap-Eye, the burden thus falls on Petitioner to show that Dixon inherently discloses the claimed sequence. *Id.* at 10–11.

Patent Owner contends that, to demonstrate inherency, Petitioner must establish that the amino acid or nucleic acid sequence of VEGF Trap-Eye "is necessarily present" in Dixon. PO Resp. 11 (citing *Continental Can Co. USA v. Monsanto*, 948 F.2d 1264, 1268 (Fed. Cir. 1991)). Specifically, argues Patent Owner, Petitioner must demonstrate that "one skilled in the art would read the [prior art reference] as inherently disclosing the invention." *Id.* at 12 (citing *Rosco, Inc. v. Mirror Lite Co.*, 304 F.3d 1373, 1380-81 (Fed. Cir. 2002).

Patent Owner notes that Petitioner relies on Dixon's statement that "VEGF Trap-Eye" and aflibercept share a "molecular structure" to show inherency of the VEGF Trap-Eye amino acid sequence. PO Resp. 13 (citing Ex. 1006, 1575). Patent Owner contends that Dixon does not expressly say that "VEGF Trap-Eye" and aflibercept have the same amino acid sequence and argues that a shared "molecular structure" does not necessarily mean an identical amino acid sequence. *Id.* Patent Owner contends that the term "molecular structure" was repeatedly used in the literature to refer to the three-dimensional structure of the protein, rather than the protein's amino acid sequence. *Id.* at 13–14 (citing Ex. 2049 ¶¶ 57–63 (citing Ex. 2067,

1449) (stating that "[t]his study was designed to disclose the molecular structure of tau" proteins that have rod-like three-dimensional structure))).

Patent Owner argues that a skilled artisan would have known that proteins with different amino acid sequences may have the same molecular structure, or *vice versa*. PO Resp. 14 (citing Ex. 2049 ¶ 61–63 (citing Ex. 2076 at 1292) (noting that thioesterases can have "very different primary structures but common tertiary structures"), ¶ 58 (citing Ex. 2069, 1019, 1026) (noting that over 1000 pairs of proteins with similar molecular structures but dissimilar amino acid sequences have been cataloged); *id.* ¶ 59 (citing Ex. 2070, 41) (murine and bovine antibody domains have "surprisingly similar structures and stabilities, considering the marginal sequence conservation between the two molecules"), ¶ 63 ("[A] protein with a given amino acid sequence expressed in *E. coli* may have a different overall structure when it is expressed in a mammalian host cell."); *see also* Ex. 2048 ¶¶ 68–69).

Patent Owner also points to Dixon, which, Patent Owner contends, suggests that the "molecular structure" of VEGF Trap-Eye refers to a more general selection and arrangement of receptor binding domains and an Fc region, not a precise amino acid or nucleic acid sequence. PO Resp. 14 (citing Ex. 2049 ¶¶ 65–66; Ex. 2048 ¶¶ 71–72; Ex. 2130, 337 (stating that "Dixon is describing the structure of VEGF Trap-Eye by its key binding domains in the Fc region")). According to Patent Owner, Dixon uses the term "molecular structure" right after explaining that: "Structurally, VEGF Trap-Eye is a fusion protein of key binding domains of human VEGFR-1

and -2 combined with a human IgG Fc fragment (Fig. 1)." *Id.* at 14–15 (citing Ex. 1006, 1573, 1576, Fig. 1). Patent Owner contends that Figure 1 of Dixon also shows a stylized version of VEGF receptors 1 and 2 and the binding domains that lead to the creation of a VEGF Trap molecule. *Id.* at 15 (citing Ex. 1006, 1576).

Summarizing, Patent Owner argues that a skilled artisan would have understood that Dixon's statements concerning the "molecular structure" of VEGF Trap-Eye could have referred to the protein's three-dimensional structure, or overall configuration of VEGF binding domains, rather than its primary structure (i.e., amino acid sequence). PO Resp. (citing Ex. 2049 ¶¶ 49–66; Ex. 2048, ¶¶ 66–72; Ex. 2129 73–74; Ex. 2130, 107).

Patent Owner next argues that a person of skill in the art, at the time of filing of the '069 patent, would have had reason to doubt that VEGF Trap-Eye corresponded to only aflibercept. PO Resp. 15. Petitioner bases this contention upon four arguments.

First, Patent Owner suggests that a skilled artisan could have concluded that VEGF Trap-Eye was a genus of proteins with different amino acid sequences. PO Resp. 15. Patent Owner argues that the structural information that Dixon provides for VEGF Trap-Eye was insufficient to distinguish VEGF Trap-Eye from any other protein comprising a VEGFR1 domain 2, VEGFR2 domain 3, and a human Fc region. *Id.* at 15–16. Patent Owner suggests that a skilled artisan would have understood Dixon's description to correspond to a genus of protein sequences reported in the art. *Id.*

Patent Owner notes that Regeneron developed, tested, and published a variety of engineered VEGF fusion proteins that it called "VEGF Trap" molecules, only some of which included both the VEGFR1 and VEGFR2 binding domains. PO Resp. 16 (citing Ex. 2049 ¶¶ 68–75 (citing Ex. 1004, 11394)). Patent Owner notes that even the term "VEGF $Trap_{R1R2}$," which is a subset of VEGF Trap proteins, was known to encompass a genus of protein sequences, any one of which could satisfy Dixon's structural definition, but would not necessarily possess the amino acid sequence of the challenged claims. *Id.* (citing Ex. 2049 ¶¶ 68–75). By way of example, Patent Owner points to the '758 Patent (Ex. 1010) and Dix (Ex. 1033) that disclose the amino acid and nucleic acid sequences for a VEGF $Trap_{R1R2}$ protein that does not satisfy the sequence limitations of the challenged claims. *Id.* (citing Ex. 2049 ¶¶ 69–74; Ex. 1010, 10).

Second, Patent Owner contends that a person of ordinary skill in the art would have been aware of different molecular weights for "VEGF Trap-Eye" reported in the prior art. PO Resp. 17. Patent Owner points to reports that "VEGF Trap-Eye is a 110-kDa recombinant protein," and that "VEGF Trap-Eye (Regeneron Inc.) is a 115-kDa recombinant fusion protein." *Id.* (citing Ex. 2049 ¶¶ 76–78 (citing Ex. 1075, 403); Ex. 2048 ¶¶ 87–91). Patent Owner contrasts this with the molecular weight of aflibercept, which was was routinely reported as 115 kDa. Ex. 2049 ¶ 77; Ex. 2014, 596; Ex. 2015 ¶ 10; Ex. 2048 ¶ 88). Patent Owner argues that a person of ordinary skill in the art could have recognized that reported differences in molecular weights among VEGF Trap-Eye proteins, as well as those

between the reported molecular weights of VEGF Trap-Eye and aflibercept, could reflect differences in the amino acid sequence. *Id.* (citing Ex. 2049 ¶ 78; Ex. 2048 ¶¶ 89–91).

Third, Patent Owner notes that Petitioner, and its declarant, Dr. Albini, rely on various Regeneron patents and published applications to show correspondence between the recited VEGF antagonist fusion protein and amino acid sequences and sequences disclosed in the art. PO Resp. 18–19 (citing Pet. 26–27). However, Patent Owner argues, none of its cited patents identifies any of its disclosed sequences as "VEGF Trap-Eye." *Id.* at 19. Patent Owner asserts that other VEGF Trap sequences, including other VEGF-$Trap_{R1R2}$ sequences, were known in the art, and published in some of those same references. *Id.* (citing Ex. 2049 ¶¶ 69–74, 84–89; Ex. 2130, 325–326). Consequently, argues Patent Owner, disclosure of the sequences recited in claim 1 of the '069 patent among other disclosed VEGF Trap sequences in Petitioner's cited references would not have informed the skilled artisan that VEGF Trap-Eye necessarily possessed the amino acid sequence or nucleic acid sequence of the challenged claims. *Id.* at 19–20.

Fourth, argues Patent Owner, Regeneron consistently characterized "VEGF Trap-Eye" as an ophthalmology product and "aflibercept'" as an oncology drug. PO Resp. 20 (citing Ex. 2048 ¶¶ 73–79). Patent Owner characterizes Dixon as stating that Dixon discloses that aflibercept is a promising new anti-VEGF agent. *Id.* (citing Ex. 1006, Abstr.). Patent Owner notes that Dixon then states that the objective of the paper is to "review the current literature and clinical trial data regarding VEGF Trap-

Eye for the treatment of neovascular AMD," and states 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.* Patent Owner contends that Dixon thus characterizes VEGF Trap-Eye as a novel anti-VEGF therapy for neovascular AMD, but identifies aflibercept as an "oncology product." *Id.* (citing Ex. 2049 ¶ 40; Ex. 2048 ¶ 81; Ex. 1006, 1575).

Patent Owner also points to the testimony of Petitioner's declarant, Dr. Albini, who Patent Owner contends stated that it was "certainly possible" that a skilled artisan, reading Dixon, could have concluded that VEGF Trap-Eye and aflibercept were different products. PO Resp. 21 (quoting Ex. 2130, 333–335, 342–343). Additionally, Patent Owner argues, a person of ordinary skill in the art would have known that Genentech's anti-VEGF oncology drug (Avastin®) had a different protein sequence than its anti-VEGF ophthalmology drug (Lucentis®), even though Avastin was used off-label in ophthalmology. *Id.* (citing Ex. 2048 ¶¶ 82–85; Ex. 2130, 342). Therefore, argues Patent Owner, it would have been reasonable for a skilled artisan to conclude that Regeneron's anti-VEGF oncology product, aflibercept, was different from its ophthalmology product, "VEGF Trap-Eye." *Id.* at 22 (citing Ex. 2048 ¶ 86).

b. Analysis

With respect to Grounds I and IV, Patent Owner's first argument is that Dixon does not anticipate the limitation of claim 1 reciting:

> wherein the VEGF antagonist is a 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.

Ex. 1001, col. 21, ll. 54–60.

Dixon 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. Both aflibercept and VEGF Trap-Eye are manufactured in bioreactors from industry standard Chinese hamster ovary cells that overexpress the fusion protein. However, VEGF Trap-Eye undergoes further purification steps during manufacturing to minimize risk of irritation to the eye. VEGF Trap-Eye is also formulated with different buffers and at different concentrations (for buffers in common) suitable for the comfortable, non-irritating, direct injection into the eye.

Ex. 1006, 1575 (emphasis added). Patent Owner argues that the language alluding to the "same molecular structure" of aflibercept and VEGF Trap-Eye refers only to the three-dimensional structures of the fusion protein, rather than the protein's amino acid sequence. PO Resp. 13–14 (citing Ex. 2049 ¶¶ 57–63). We decline to accept such a limited and unduly arbitrary definition of "molecular structure."

We here take judicial notice that it is axiomatic of protein chemistry that proteins have primary, secondary, tertiary, and quaternary structure. *See* Fed. R. Evid. 201; W.H. Brown et al., *Polypeptides and Proteins*, Chapter 27.3, 1075–96, in ORGANIC CHEMISTRY (Fourth Ed.) (2005) Ex. 3002. Indeed, Patent Owner's declarant, Dr. Del Priore, recognizes that "[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. 2048 ¶¶ 50, 67. Primary structure is the sequence of the amino acids constituting a polypeptide chain. Ex. 3002, 1075. Secondary structure refers to spontaneously self-organizing ordered arrangements (conformations) of amino acids in localized regions of a polypeptide chain, such as an α-helix or β-pleated sheet. *Id.* at 1089-90. Secondary structure is ordained by the patterns of the amino acid distribution (sequence) within the polypeptide chain. *Id.* The tertiary structure of a protein refers to the overall folding pattern and arrangement in space of all of the atoms in a single polypeptide chain. Such three-dimensional structure is caused by the interactions of amino acids in the chain, including that caused by disulfide bonds between cystine residues, hydrophobic interactions, hydrogen bonding, and salt linkages. *Id.* at 1091. Quaternary structure is formed by the interactions of multiple polypeptide monomers into aggregate arrangements. *Id.* at 1095.

All of these structures are intensely interrelated in defining the final three-dimensional shape of the protein, which is, in turn, critical to the role played by the protein, whether as a structural protein, enzyme, etc. The

location of specific amino acids in the polypeptide chain (the primary structure) determines the ability of those amino acids to interact with each other, and these interactions form the final complex, three-dimensional shape of the chain (secondary and tertiary structures), and also helps determine the quaternary structure of aggregated polypeptide chains in the final protein molecule. Ex. 3002, 1093–1094. Consequently, primary, secondary, tertiary, and quaternary structures are all interrelated, and primary structure necessarily drives secondary, tertiary, and quaternary structures. *Id.* at 1095. Indeed, Patent Owner's declarant, Dr. Klibanov, testified that primary structure is a determinant of the three-dimensional conformation of a protein:

> Q. Then do you agree with the statement here set forth in your declaration that: "The 3D arrangement in the a [sic] protein, its shape or conformation, and its properties are determined by its primary structure and the aqueous medium in which the protein is dissolved"?
> ….
>
> [Dr. KLIBANOV]: Yes, I agree with the proviso that, of course, the post-translation modification, which is mentioned in the first sentence of that paragraph, also may play a role in that, which is why, of course, that sentence has to be read in the context of at least the entire paragraph and ideally in a broader context presented here in my 2007 declaration.

Ex. 1108, 32, ll. 2–15 (citing Ex. 1103 ¶ 76); *see also* Hearing Trans., 60, ll. 12–14.

Further, Dr. Klibanov agreed that substitution at a single amino acid locus, such as in a mutation, can alter the three-dimensional conformation of

a protein, significantly altering, or disabling, its function. Ex. 1103 ¶¶ 76, 82–83.

Dixon expressly teaches that aflibercept and VEGF Trap-Eye have the "same molecular structure." Ex. 1006, 1575. Patent Owner argues that this disclosure should exclude the primary structure, i.e., the amino acid sequence, from this definition of molecular structure, and offers examples of how proteins having different amino acid sequences can have similar shapes. *See, e.g.*, PO Resp. 13–14. We agree with Patent Owner to the extent that protein molecules, or more often, the active sites of protein molecules can have similar shapes; this is how molecular agonists and antagonists of proteins work. Indeed, it is how VEGF Trap-Eye works, the active site of the VEGF molecule binds to the active site of endogenous vascular endogenous growth factor A ("VEGF-A") isoforms, preventing VEGF-A from binding to the VEGF receptor and inhibiting its angiogenic effects, i.e., VEGF Trap-Eye is a VEGF-A antagonist. *See* Ex. 1001, col. 1, ll. 44–49, col. 2, ll. 29–39, Ex. 1006, 1575.

But to argue, as Patent Owner does, that proteins, or parts of proteins, *can* have similar, or the same, three-dimensional shapes is not the same as saying that aflibercept and VEGF Trap-Eye have the *same* molecular structure, i.e., are the same molecule, as disclosed by Dixon. Patent Owner offers no plausible reason why a protein's primary structure should be omitted from any definition of "molecular structure" and, given the interrelatedness of primary, secondary, and tertiary structure in determining

the shape of a polypeptide chain, we can see no reason to omit primary structure from the definition of "molecular structure."

There is even further reason to conclude that Dixon inherently discloses the amino acid sequence of VEGF Trap-Eye. Petitioner points to Patent Owner's repeated statements to the Patent Office during prosecution that the sequence of "the active ingredient of EYLEA™" [aflibercept ophthalmic solution]—namely, "aflibercept, also known as VEGF trap, VEGF-trap, VEGF Trap-Eye and VEGF-$Trap_{R1R2}$" is set forth in Patent Owner's prior art '758 and '959 patents. Pet. Reply 7–8 (citing Ex. 1024, 2, 5–7, 8 ("aflibercept meets all of the limitations of claims 1 and 2 of the '758 patent"); Ex. 1115 ¶¶ 10–32; Ex. 1010, Figs. 24A–C, SEQ ID NOS: 15 and 16; Ex. 1102, 2, 5–7; Ex. 1023, Figs. 24A–C, SEQ ID NOS: 15 and 16). Petitioner also points to Patent Owner's statement to the Patent Office, during prosecution of the '069 patent, that the data in the '069 Specification's Example 4 correspond to the VIEW 1/VIEW 2 clinical trials. *Id.* at 8 (citing Ex. 1017, 136–138). In other words, the '069 Specification discloses the same trials, and thus the same molecule, as disclosed by Dixon.

It is therefore Petitioner's position that, because VEGF Trap-Eye, as used in the VIEW 1/VIEW 2 studies, was admitted by Patent Owner to have the amino acid sequence recited in claim 1, Dixon, which discloses the use of VEGF Trap-Eye in the VIEW 1/VIEW 2 studies, inherently discloses the claimed amino acid sequence. *Id.*

Patent Owner disagrees that Dixon discloses the claimed amino acid sequence inherently. Patent Owner argues that a person of ordinary skill in

the art would have had reason to doubt that the VEGF Trap-Eye disclosed by Dixon could only have been aflibercept, but could rather have been one of a possible genus of VEGF compounds, and not necessarily aflibercept. PO Resp. 14. Patent Owner advances four arguments in support of this contention: (1) The skilled artisan could have concluded that VEGF Trap-Eye was a genus of proteins with different amino acid sequences; (2) The prior art reported VEGF Trap-Eye to have different molecular weights than aflibercept; (3) Dixon does not discloses that "VEGF Trap Eye" corresponds to only the recited sequence; an (4) Patent Owner Regeneron consistently characterized "VEGF Trap-Eye" as an ophthalmology product and "aflibercept'" as an oncology drug. Patent Owner's position, therefore, is that because a person of ordinary skill could not be certain that the VEGF Trap-Eye disclosed by Dixon had the claimed amino acid sequence recited in claim 1 of the '069 patent, Dixon does not anticipate the challenged claims.

Patent Owner's arguments are unavailing. The test for whether a reference inherently anticipates a claim is whether a claim limitation that is not expressly disclosed "is *necessarily* present, or inherent, in the single anticipating reference." *Verizon Servs. Corp. v. Cox Fibernet Va., Inc.*, 602 F.3d 1325, 1337 (Fed. Cir. 2010) (emphasis added). Patent Owner has made multiple acknowledgements that the VEGF Eye-Trap used in the VIEW 1/VIEW 2 test disclosed by Dixon possessed the amino acid sequence recited in claim 1 of the '069 patent.

For example, during prosecution of the '069 patent, Patent Owner admitted to the Patent Office that:

> The [Heier 2012][11] paper shows results of a treatment protocol of the type claimed on over 2,400 patients. The 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."

Ex. 1020, 136. Heier 2012 describes results of the VIEW 1/VIEW 2 phase III clinical studies, which are also disclosed in Dixon. *Compare* Ex. 1018, 2539–2540, *with* Ex. 1006, 1579, refs. 46–47. Patent Owner thus acknowledged, during prosecution, that VEGF Trap-Eye with the claimed amino acid sequence used in Example 4 of the '069 patent is the same drug used in the VIEW 1/VIEW 2 studies disclosed by both Dixon and Heier 2012.

Similarly, Patent Owner stated in its November 3, 2009 Form 10-Q submission to the United States Securities and Exchange Commission ("SEC," Ex. 1021):

> We also have six product candidates currently in clinical development, including three in late-stage clinical development. Our late stage programs are aflibercept (VEGF Trap), which is being developed in oncology in collaboration with the sanofi-aventis Group, VEGF Trap-Eye, which is being developed in

[11] J.S. Heier et al., *Intravitreal Aflibercept (VEGF Trap-Eye) in Wet Age-related Macular Degeneration*, 119(112) OPHTHALMOLOGY 2537-48 (2012) ("Heier 2012") (Ex. 1018).

> eye diseases using intraocular delivery in collaboration with Bayer HealthCare LLC, and ARCALYST which is being developed for the treatment of gout.

Ex. 1021, 18. Specifically, Patent Owner stated that:

> Aflibercept is a protein-based product candidate designed to bind all forms of Vascular Endothelial Growth Factor-A (called VEGF-A, also known as Vascular Permeability Factor or VPF), VEGF-B and the related Placental Growth Factor (called P1GF), and prevent their interaction with cell surface receptors. VEGF-A (and to a less validated degree, VEGF-B and PlGF) is required for the growth of new blood vessels (a process known as angiogenesis) that are needed for tumors to grow and is a potent regulator of vascular permeability and leakage.

Id. at 19. Furthermore:

> *VEGF Trap-Eye is a specially purified and formulated form of VEGF Trap for use in intraocular applications*. We and Bayer HealthCare are testing VEGF Trap-Eye in a Phase 3 program in patients with the neovascular form of age-related macular degeneration (wet AMD). We and Bayer HealthCare also are conducting a Phase 2 study of VEGF Trap-Eye in patients with diabetic macular edema (DME).

Id. at 20 (emphasis added). Patent Owner further states that:

> The Phase 3 trials in wet AMD, known as VIEW 1 and VIEW 2 (VEGF Trap: Investigation of Efficacy and Safety in Wet age-related macular degeneration), are comparing VEGF Trap-Eye and Lucentis® (ranibizumab injection), marketed by Genentech, Inc., an antiangiogenic agent approved for use in wet AMD. VIEW 1 is being conducted in North America and VIEW 2 is being conducted in Europe, Asia Pacific, Japan, and Latin America. The VIEW 1 and VIEW 2 trials are both evaluating VEGF Trap-Eye doses of 0.5 milligrams (mg). and 2.0 mg at dosing intervals of four weeks and 2.0 mg at a dosing interval of eight weeks (after three monthly doses) compared with Lucentis

> dosed according to its U.S. label, which specifies doses of 0.5 mg administered every four weeks over the first year. As-needed dosing (PRN) with both agents will be evaluated in the second year of the studies. VIEW 1 and VIEW 2 are now fully enrolled, and initial data are expected in late 2010.

Id.

Patent Owner thus admits, in the passages quoted above, that VEGF Trap-Eye is its drug being used in the VIEW1 and VIEW 2 studies disclosed by Dixon. Patent Owner makes it clear that VEGF Trap-Eye is a single drug (of three in late-stage clinical testing), and not, as Patent contends, a genus of drugs.

Counsel for Patent Owner also admitted at oral argument that the VEGF Trap-Eye used in the VIEW 1/VIEW 2 phase III clinical studies had the same amino acid sequence as recited in claim 1 of the '069 patent:

> JUDGE NEW: …. So in other words, if I say, here's VEGF Trap-Eye. Go use it in your VIEW 1 test. And you use it in your VIEW 1 test, it's going to have that sequence, is it not?
>
> MS. FISHMAN: I guess I'm a little confused by your question. Yes, we know today that VEGF Trap-Eye has the same sequence as the claims. And yes, when that was given to the clinical investigators in the studies that were performed, it had that sequence.
>
> JUDGE NEW: So in other words, it was inherent. It was necessarily part of that drug.
>
> MS. FISHMAN: It was the drug that was tested.

Hearing Trans., 42.

Finally, as the above discussion and common sense strongly suggest, a drug that is reported in late Phase III clinical testing on human subjects is going to be a well-characterized single drug, rather than, as Patent Owner suggests, possibly a member of a vaguely defined genus of drugs, all called "VEGF Trap-Eye."

There can be little doubt, then, that the VEGF Trap-Eye disclosed in Dixon possessed the amino acid sequence recited in claim 1 of the '069 patent. And, as such, the claimed amino acid sequence was necessarily present, i.e., inherent, in the VEGF Trap-Eye disclosed by Dixon.

Whether a person of ordinary skill in the art at the time of filing would have known the exact amino acid sequence of VEGF Trap-Eye, even when using it in a clinical test, is irrelevant to its determining whether it is inherently disclosed. *See* Hearing Trans., 42–43 (Patent Owner arguing that use of VEGF Trap-Eye in VIEW 1 study not anticipatory because "it was an experimental use under confidentiality restrictions"). The test for inherency, rather, is whether the limitation of the claim is *necessarily* present in the anticipating reference. *Verizon*, 602 F.3d at 1337. Patent Owner has acknowledged, repeatedly, that the VEGF Trap-Eye used in the VIEW 1/VIEW 2 clinical studies disclosed by Dixon is the same drug disclosed by the '069 patent, with the same amino acid sequence recited by claim 1. Therefore, the claimed amino acid sequence was necessarily present in the VEGF Trap-Eye used in the studies, whether a person of skill in the art at that time would have known it or not. That is sufficient to meet the requirements of an inherent disclosure. *See Abbott Labs. v. Baxter Pharm.*

Prods., Inc., 471 F.3d 1363, 1367 (Fed. Cir. 2006) (holding that "[o]ur cases have consistently held that a reference may anticipate even when the relevant properties of the thing disclosed were not appreciated at the time").

Finally, we find that Patent Owner's contention that Petitioner's argument that VEGF Trap-Eye was disclosed publicly is largely irrelevant. Even if the amino acid sequence was not disclosed publicly, there can be no doubt that VEGF Trap-Eye was made available to the researchers in the VIEW 1 and VIEW 2 studies. Our inherency analysis therefore applies as to whether VEGF Trap-Eye was disclosed publicly or not, and Petitioner's argument is not necessary to our determination.

We find that a person of ordinary skill in the art would understand that Dixon's disclosure that "VEGF Trap-Eye and aflibercept (the oncology product) have the same molecular structure" to mean that VEGF Trap-Eye and aflibercept have the same primary, secondary, and tertiary structure. Therefore, a person skilled in the art would understand that VEGF Trap-Eye and aflibercept have the same amino acid sequence, and that sequence is the same as recited in claim of the '069 patent. *See, e.g.*, Ex. 1024, 2, 5–7, 8; Ex. 1127, 1; Ex. 1128, 1–2; Ex. 1017, 136–138. We consequently conclude that Dixon thus inherently discloses the amino acid sequences recited in claim 1 of the '069 patent.

We consequently conclude that Petitioner has demonstrated, by a preponderance of the evidence, that Dixon discloses this limitation of claims 1 and 9–12 of the '069 patent.

4. Patent Owner's argument that Dixon's disclosure of dosing schedules does not the dosing schedules recited in claims 1 and 9–12 of the '069 patent

We next turn to Patent Owner's argument that Dixon does not disclose the dosing schedules recited in claims 1 and 9–12 of the '069 patent (we address claim 8 separately below).

a. Petitioner's contentions

Petitioner contends that the VIEW 1/VIEW 2 trial extended dosing arm 2Q8[12] schedule was designed to test a monthly loading dose regimen of three monthly injections. Pet. 20 (citing Ex. 1006, 1576). According to Petitioner, the 2Q8 schedule was also designed to test two different maintenance phases: (1) an every-8-week dosing in the first year, and (2) PRN dosing in the second year. *Id.* at 20–21 (citing Ex. 1006, 1576 ("After the first year of the study, patients will enter a second year of p.r.n. dosing evaluation.")). Therefore, argues Petitioner, given that monthly loading doses (i.e., a single initial dose followed by one or more secondary doses) followed by PRN treatment (i.e., "tertiary doses" "administered on an as-needed/*pro re nata* (PRN) basis, based on visual and/or anatomical outcomes") were both disclosed by Dixon's disclosure of the aflibercept

[12] i.e., VIEW 1/ VIEW 2's group receiving 2.0 mg of VEGF Trap-Eye administered at an 8 week dosing interval (following three monthly doses), followed by *pro re nata* administration in the second year. *See* Ex. 1017, 137 (quoting Ex. 1018, 2540); Ex. 1006, 1576.

VIEW trial, challenged claims 1 and 9–12 are anticipated. *Id.* at 21 (citing Ex. 1114 ¶¶ 19–20).

b. Patent Owner's response

Patent Owner disputes Petitioner's contention that that Dixon's disclosure of a prospective fixed 8-week dosing regimen (following three monthly doses) in the VIEW 1/VIEW 2 clinical trials anticipates the claimed PRN method of treatment. PO Resp. 22–23 (citing Pet. 53–58 (citing Ex. 1006, 1576)). Patent Owner contends that Dixon's disclosures concerning the VIEW1/ VIEW 2 studies fail to disclose a "tertiary dose" that "is administered on an as-needed/*pro re nata* PRN basis," as required by each of the challenged claims. *Id.* at 23 (citing Ex. 2050 ¶ 131). Specifically, Patent Owner disputes Petitioner's reading of the '069 patent's prosecution history to argue that 8-week dosing and PRN dosing are the same thing. *Id.* (citing Pet. 1, 55). According to Patent Owner, a fixed dosing every 8 weeks (following three monthly doses), as disclosed by Dixon, is not a disclosure of recited tertiary dosing "administered on an as-needed/*pro re nata* (PRN) basis." PO Resp. 23 (citing Ex. 2050 ¶ 131; Ex. 2130, 285–286).

Furthermore, argues Patent Owner, and contrary to Petitioner's contention, during prosecution of the '069 Patent, Patent Owner did not describe the VIEW 1/VIEW 2 studies' fixed, 8-week dosing regimen as a PRN regimen. PO Resp. 24. To the contrary, Patent Owner asserts, Regeneron explained that the Heier 2012 reference showed that extended

dosing regimens with VEGF Trap-Eye were unexpectedly non-inferior to the prevailing standard of care (i.e., monthly injections of ranibizumab). *Id.* (citing Ex. 1017, 136).

Patent Owner additionally contends that, although Heier 2012 reports the clinical trial results from Year 1 of the VIEW 1/VIEW 2 trials, which tested fixed dosing regimens (including an 8-week dosing regimen), it also sets forth the clinical trial results for Year 2, which tested PRN dosing. *Id.* (citing Ex. 1018, 10). Therefore, Patent Owner argues, by the time Heier 2012 published the clinical trial results for Year 2 of the trials, it was known that the second-year PRN dosing regimen resulted in extended dosing. *Id.* As a consequence, Patent Owner argues, Regeneron's statements during prosecution that "the PRN treatment protocol as encompassed by the presently pending independent claim 1 achieves results which are as good or better than the results obtained with monthly treatment" were fully supported by Heier 2012. *Id.* at 24–25 (citing Ex. 1017, 137).

Patent Owner also argues that Regeneron's prosecution history statements about a different publication are not legally relevant to Petitioner's anticipation arguments regarding the Dixon reference in this IPR. PO Resp. 25.

c. Petitioner's Reply and Patent Owner's Sur-Reply

Petitioner replies that the VIEW 1/VIEW 2 trials 2Q8 extended dosing schedule was designed to test a monthly loading dose regimen of three monthly injections. Pet. Reply 20 (citing Ex. 1006, 1576). Petitioner asserts

that the VIEW trials was also designed to test two different maintenance phases: (1) every-8-week dosing in the first year; and (2) PRN dosing in the second year. *Id.* at 20–21 (citing Ex. 1006, 1576). According to Petitioner, given that monthly loading doses (i.e., a single initial dose followed by one or more secondary doses) followed by PRN treatment (i.e., "tertiary doses" "administered on an as-needed/*pro re nata* (PRN) basis, based on visual and/or anatomical outcomes") were both disclosed in Dixon's disclosure of the aflibercept VIEW 1/VIEW 2 trial. *Id.* at 21 (citing Ex. 1114, ¶¶ 19–20).

In its Sur-Reply, Patent Owner argues that Petitioner's argument was not made in its Petition, and should be disregarded as untimely and in violation of 37 C.F.R. § 42.23(b). Sur-Reply 19 (citing *Intelligent Bio-Sys, Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1369 (Fed. Cir. 2016).

Patent Owner contends that Dixon's disclosure of the VIEW 2Q8 dosing arm does not include tertiary PRN dosing. Sur-Reply 20. Patent Owner contends that the tertiary dosing in VIEW 1/VIEW 2 clinical trial's 2Q8 regimen is fixed 8-week dosing, as acknowledged by Petitioner's own expert. *Id.* (citing Ex. 1002, 84–85; Ex. 2287, 147–148). Therefore, argues Patent Owner, "each tertiary dose" is not administered PRN in Dixon's disclosure of VIEW 1/VIEW 2; rather, PRN dosing in the second year of VIEW comes after the 2Q8 dosing and would be, in effect, quaternary dosing. *Id.* Patent Owner asserts that Dixon's disclosure of VIEW's 2Q8 arm dosing regimen thus does not anticipate the challenged claims. *Id.* (citing, e.g., *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359,

1369 (Fed. Cir. 2008).

d. Analysis

We find that the preponderance of the evidence supports Petitioner's argument that Dixon also teaches the dosing schedules recited in challenged claims 1 and 9–12. As an initial matter, we reject Patent Owner's argument that Petitioner failed to timely make its argument. *See* Sur-Reply 19. Petitioner expressly relied upon Dixon's disclosure of the VIEW 1/VIEW 2 trials as disclosing the claimed dosing regimen in its Petition. *See* Pet. 47–48. For that reason, Petitioner may permissibly develop that argument in its Reply in response to arguments made in Patent Owner's Response.

Claim 1 of the '069 patent recites, in relevant part:

> [A] 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 on an as-needed/*pro re nata* (PRN) basis…."

Ex. 1001, col. 21, ll. 42–53. Claim 1 thus requires: (1) an initial dose of the VEGF antagonist; (2) one or more secondary doses administered at 2–4 week intervals, and; (3) one or more tertiary doses administered on a PRN basis.

Furthermore, with respect to the primary, secondary and tertiary doses, the Specification of the '069 patent discloses that:

> The initial, secondary, and tertiary doses may all contain the same amount of VEGF antagonist, *but will generally differ from one another in terms of frequency of administration*. In certain embodiments, however, the amount of VEGF antagonist contained in the initial, secondary and/or tertiary doses will vary from one another (e.g., adjusted up or down as appropriate) during the course of treatment.

Ex. 1001, col. 3, ll. 41–48 (emphasis added). Dependent claims 9–12 do not further recite additional limitations with respect to the dosing regimen recited by claim 1.

The initial dose is distinguished, naturally, from the secondary and tertiary doses by virtue of its being the first dose administered. Both the claims and the Specification tell us that what distinguishes the secondary and tertiary doses from each other is primarily the "terms of frequency of administration," i.e., secondary doses are administered regularly at 2–4 week intervals, and tertiary doses are administered *pro re nata*.

Dixon describes, *inter alia*, the VIEW 1/VIEW 2 phase III clinical trials. Specifically, Dixon discloses that:

> A two-part Phase III trial of VEGF Trap-Eye was initiated in August of 2007. The first part, VIEW 1 (VEGF Trap: Investigation of Efficacy and safety in Wet age-related macular degeneration) will enroll ~ 1200 patients with neovascular AMD in the US and Canada. This non-inferiority study will evaluate the safety and efficacy of intravitreal VEGF Trap-Eye at doses of 0.5 and 2.0 mg administered at 4-week dosing intervals and 2.0 mg at an 8 week dosing interval (following three monthly doses), compared with 0.5 mg of ranibizumab administered every 4 weeks. After the first year of the study, patients will enter a second year of p.r.n. dosing evaluation. The VIEW 2 study has a similar study design.

Ex. 1006, 1576 (internal references omitted). Dixon thus discloses an initial (first) dose, followed by doses (of either 2.0 or 5.0 mg) administered at 4-week intervals. Because these latter are administered regularly at 4-week intervals for the remainder of the first year of the study, we find that these doses succeeding the initial dose correspond to claim 1's recited "one or more secondary doses of the VEGF antagonist, … wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose."

Dixon also discloses that, after the first year of such treatment, patients will enter "a second year of p.r.n. dosing evaluation." Ex. 1006, 1576. We find that this statement directly discloses the limitation of claim 1 requiring "follow[ing the one or more secondary doses] by one or more tertiary doses of the VEGF antagonist;… wherein each tertiary dose is administered on an as-needed/*pro re nata* (PRN) basis."

We note that the claims do not specify a given number of secondary doses other than "one or more," nor do they require a specific interval during which secondary doses may be given before transitioning to the tertiary *pro re nata* doses. We consequently find that Dixon's disclosure of the VIEW 1/VIEW 2 VEGF Trap-Eye administration schedule of (1) an initial dose; (2) administration of a dose at succeeding 4-week intervals for the remainder of the first year of the study (i.e., "one or more secondary doses"); and (3) *pro re nata* administration following completion of a year of

secondary dosing (i.e., "tertiary doses") reads directly upon the language of claim 1.[13]

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[13] We note that Heier 2012 (which is not prior art to the '069 patent, but which was cited by Patent Owner during prosecution (*see* Ex. 1017, 136–137)) characterizes the second year of the VIEW 1/VIEW 2 study slightly differently:

> After the 1-year primary end point of VIEW 1/VIEW 2 presented in this article, all treatment groups' dosing intervals were changed to a common protocol of modified quarterly dosing with their originally randomized dose and drug (all patients were monitored monthly and received a minimum of dosing every 12 weeks with interim as-needed monthly intravitreal injections).

Ex. 1018, 2546. Heier 2012 thus teaches that, in the second year of the VIEW 1/VIEW 2 studies, mandatory 12 week (i.e., "quarterly") doses are given in combination with monthly administration of VEGF Eye-Trap given on a PRN basis. This does not affect our reasoning, or the outcome of the Decision, for two reasons.

First, because Heier 2012 is not prior art to the '069 patent, its disclosures would not have been available to a person of ordinary skill in the art at the time of invention. A skilled artisan's understanding of the VIEW 1/VIEW 2 protocols would have been guided by Dixon's express disclosure of second year PRN dosing, and Dixon expressly discloses that "After the first year of the study, patients will enter a second year of p.r.n. dosing evaluation." Ex. 1106, 1576. A person of skill in the art would therefore have understood that Dixon discloses administration of tertiary doses on a PRN basis at monthly examinations.

Second, and more importantly, the language of claim 1 recites "method for treating an angiogenic eye disorder in a patient, said method *comprising*…." (emphasis added). Use of "[t]he transitional term 'comprising' creates a presumption that the recited elements are only a part of the device, that the claim does not exclude additional, unrecited

We therefore conclude that Dixon expressly discloses the dosage schedule recited in the challenged claims 1 and 9–12.

5. Conclusion

For the reasons we have explained above, we conclude that Petitioner has demonstrated, by a preponderance of the evidence, that challenged claims 1 and 9–12 are anticipated by Dixon on Grounds I and IV.

6. Obviousness of claims 1 and 9–12 (Ground IV)

We have explained above our reasoning as to why we conclude that Petitioner has demonstrated by a preponderance of the evidence why challenged claims 1 and 9–12 are anticipated by Dixon. For those same reasons, we conclude that the Petitioner has concurrently established, by a preponderance of the evidence, that claims 1 and 9–12 are obvious over Dixon upon Ground IV. *See In re McDaniel*, 293 F.3d 1379, 1385 (Fed. Cir. 2002) (holding that "[i]t is well settled that 'anticipation is the epitome of obviousness'" (quoting *In re Fracalossi*, 681 F.2d 792, 794 (C.C.P.A. 1982)).

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elements." *Crystal Semiconductor Corp. v. TriTech Microelectronics Int'l, Inc.*, 246 F.3d 1336, 1348 (Fed. Cir. 2001). Consequently, the administration of mandatory quarterly doses *in addition to* monthly doses administered on a PRN basis in the second year of VIEW 1/VIEW 2 does not fall outside of the scope of the claimed method.

7. Claim 8 of the ’069 patent (Ground IV)

Claim 8 of the ’069 patent recites: “The method of claim 1, wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose.” Ground IV of the Petition challenges the patentability of claims 1 and 8–12 of the ’069 patent as being anticipated by, or obvious over, Dixon. We have addressed the patentability of claims 1 and 9-12 as anticipated or obvious over Dixon in the preceding sections. We now address the patentability of claim 8

a. Petitioner’s assertions of unpatentability under § 102

Petitioner acknowledges that Claim 8 limits the claimed regimen to “only two secondary doses” “wherein each secondary dose is administered 4 weeks after the immediately preceding dose,” i.e., doses at weeks 0 (initial dose), 4, and 8 (two secondary doses). Pet. 56. Petitioner argues that, applying Patent Owner’s interpretation that the challenged claims encompass the VIEW 1/VIEW 2 dosing regimen (and thus can be supported by unexpected results from that study), means that Dixon expressly discloses the claim limitations of claim 8. *Id.* at 56–57 (citing Ex. 1006, 1576 (“three

monthly doses," i.e., an initial dose at day 0 and two secondary doses at weeks 4 and 8); also citing Ex. 1002 ¶¶ 175–178).

b. Patent Owner's Response

With respect to anticipation upon Ground IV, Patent Owner contends that the 2Q8, eight-week, fixed dosing (following three monthly doses), as disclosed by Dixon, is not a disclosure of recited tertiary dosing "administered on an as-needed/*pro re nata* (PRN) basis." PO Resp. 23 (citing Ex. 2050 ¶ 131; Ex. 2130, 285–286). Therefore, argues Patent Owner, Dixon cannot anticipate challenged claim 8, because it does not disclose the claimed dosing regimen. *Id.*

c. Petitioner's Reply and Patent Owner's Sur-Reply

Petitioner replies, with respect to claim 8, that Dixon discloses and recommends 3 monthly loading doses. Pet. Reply 26. Petitioner contends that Patent Owner selected 3 monthly loading doses for its phase III VIEW 1/VIEW 2 clinical trials after using 4 monthly loading doses in its phase II studies. *Id.* (citing Ex. 1006, 1576, 1574, 1577; Ex. 1002 ¶¶ 59–62, 168, 193, 197, 199–200, 205).

In its Sur-Reply, Patent Owner repeats its argument that the VIEW 1/VIEW 2 fixed Q8 dosing regimen described in Dixon is not a disclosure of tertiary dosing "administered on an as-needed/*pro re nata* (PRN) basis," and that Dixon therefore fails to disclose this required

limitation of challenged claim 8. PO Sur-Reply 26–30 (citing Ex.1001, claim 1).

d. Analysis

We conclude that, by a preponderance of the evidence, Petitioner has shown that Dixon anticipates claim 8. Dixon discloses the PrONTO study, which: "looked at as needed (p.r.n.) dosing of ranibizumab (a VEGF antagonist) after three consecutive monthly [i.e., 4-week] doses." Ex. 1006, 1574. The PrONTO study, then, teaches an initial dose, followed by "only two secondary doses [] administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose," followed by PRN dosing, as required by independent claim 1 and its dependent claim 8.

The PrONTO study employed ranibizumab (LUCENTIS®), a different VEGF antagonist in the treatment of AMD, and not VEGF Trap-Eye, as required by the claims. *See* Ex. 1006, 1574. However, Dixon also expressly teaches that VEGF Trap-Eye was successfully administered under the same dosing schedule as the PrONTO study:

> The most effective dosing regimen and monitoring program for anti-VEGF therapy has yet to be firmly established but new treatments are aimed at extending and improving on the efficacy of ranibizumab. VEGF Trap-Eye differs from established anti-VEGF therapies in its higher binding affinity for VEGF-A and its blockage of placental growth factors-I and -2. Phase I data demonstrated acceptable safety and tolerability of VEGF Trap-Eye in the treatment of neovascular AMD. In Phase II study data, *patients dosed in a similar fashion to the PrONTO trial*

> *demonstrated stabilization of their vision that was similar to previous studies of ranibizumab at 1 year*. Of the greatest interest, patients dosed at 2.0 mg during the initial monthly dosing period required 1.6 injections on average during the p.r.n. dosing phase.

Id. at 1577 (emphasis added). This passage discloses administering VEGF Trap-Eye in a manner similar to the PrONTO study, i.e., as an initial dose, followed by "only two secondary doses [] administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose," followed by PRN dosing, as required by independent claim 1 and its dependent claim 8. Dixon thus discloses all of the limitations of challenged claim 8.

We consequently conclude that the preponderance of the evidence demonstrates that Dixon anticipates challenged claim 8. Furthermore, because claim 8 is anticipated by Dixon, we further conclude that it is also obvious over Dixon. *See McDaniel*, 293 F.3d at 1385.

G. Grounds II, III, and V

Because we find that Petitioner has demonstrated, by a preponderance of the evidence, that all of the challenged claims are unpatentable over Dixon upon Grounds I and IV, we need not address whether the challenge claims are unpatentable upon remaining Grounds II, III, IV. *See SAS Inst. Inc. v. Iancu*, 138 S. Ct. 1348, 1359 (2018) (holding that a petitioner "is entitled to a final written decision addressing all of the claims it has challenged"); *Bos. Sci. Scimed, Inc. v. Cook Grp. Inc.*, 809 F. App'x 984,

990 (Fed. Cir. 2020) (non precedential) (recognizing that the "Board need not address issues that are not necessary to the resolution of the proceeding" and therefore agreeing that the Board has "discretion to decline to decide additional instituted grounds once the petitioner has prevailed on all its challenged claims").

III. CONCLUSION

For the foregoing reasons, and after having analyzed the entirety of the record and assigning appropriate weight to the cited supporting evidence, we determine that Petitioner has established, by a preponderance of the evidence, that claims 1 and 8–12 of the '069 patent are unpatentable. We also deny, for the reasons we have explained, both Petitioner's Motion to Exclude Evidence and we den-n-part and dismiss-in-part Patent Owner's Motions to Exclude Evidence.

IV. ORDER

Accordingly, it is

ORDERED that Petitioner has shown by a preponderance of the evidence that claims 1 and 8–12 of the '069 patent are unpatentable; [14]

FURTHER ORDERED that Petitioner's Motion to Exclude Evidence is DENIED;

FURTHER ORDERED that Patent Owner's Motion to Exclude Evidence is DENIED IN PART and DISMISSED IN PART; and

FURTHER ORDERED that, because this is a Final Written Decision, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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[14] Should Patent Owner wish to pursue amendment of the challenged claims in a reissue or reexamination proceeding subsequent to the issuance of this decision, we draw Patent Owner's attention to the April 2019 *Notice Regarding Options for Amendments by Patent Owner Through Reissue or Reexamination During a Pending AIA Trial Proceeding*. *See* 84 Fed. Reg. 16,654 (Apr. 22, 2019). If Patent Owner chooses to file a reissue application or a request for reexamination of the challenged patent, we remind Patent Owner of its continuing obligation to notify the Board of any such related matters in updated mandatory notices. *See* 37 C.F.R. § 42.8(a)(3), (b)(2).

Claim(s) Challenged	35 U.S.C. §	Reference(s)/ Basis	Claims Shown Unpatentable	Claims Not Shown Unpatentable
1, 9–12	102	Dixon	1, 9–12	
1, 9–12	102	Heier 2009		
1, 9–12	102	Regeneron I		
1, 8–12	102 and/or 103	Dixon	1, 8–12	
1, 8–12	103	Heier-2009 and Mitchell or Dixon, optionally, Papadopolous or Dix		
Overall Outcome			1, 8–12	

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