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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.,
Petitioner,

v.

BAYER PHARMA AKTIENGESELLSCHAFT,
Patent Owner.

IPR2022-00517
Patent 10,828,310 B2

Before TINA E. HULSE, ROBERT A. POLLOCK, and RYAN H. FLAX, *Administrative Patent Judges.*

HULSE, *Administrative Patent Judge*.

DECISION
Granting Institution of *Inter Partes* Review
35 U.S.C. § 314, 37 C.F.R. § 42.4

I. INTRODUCTION

Mylan Pharmaceuticals Inc. ("Petitioner") filed a Petition requesting an *inter partes* review of claims 1–8 of U.S. Patent No. 10,828,310 B2 (Ex. 1001, "the '310 Patent"). Paper 1 ("Pet."). Bayer Pharma Aktiengesellschaft ("Patent Owner") filed a Preliminary Response to the Petition. Paper 11 ("Prelim. Resp."). With our authorization, Petitioner filed a Reply to Patent Owner's Preliminary Response, and Patent Owner filed a Sur-Reply. Paper 13 ("Reply"); Paper 14 ("Sur-Reply").

We have authority under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted "unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). Upon considering the argument and evidence presented in the papers, we determine that Petitioner has established a reasonable likelihood that it would prevail in showing the unpatentability of at least one claim challenged in the Petition. Accordingly, we institute an *inter partes* review of claims 1–8 (all claims) of the '310 Patent.

A. Real Parties-in-Interest

Petitioner identifies itself and also Mylan Inc. and Viatris Inc. as real parties-in-interest. Pet. 1–2. Patent Owner identifies itself and also Bayer Pharma AG, Bayer AG, and Janssen Pharmaceuticals, Inc. as real parties-in-interest. Paper 5, 2.

B. Related Proceedings

Patent Owner has asserted the '310 Patent against Petitioner in a pending case before the U.S. District Court for the Northern District of West Virginia styled *Bayer Pharma AG v. Mylan Pharmaceuticals Inc.*, No. 21-cv-00099 (N.D.W.V). Paper 5, 3. That case is consolidated with four other actions in a multidistrict litigation for pre-trial proceedings only and is pending before the U.S. District Court for the District of Delaware styled *In re: Xarelto (Rivaroxaban) ('310)*

Patent Litigation, No. 1:21-md-03017 (D. Del.). Pet. 2; Paper 5, 4. The four other consolidated actions are: *Bayer Pharma AG v. Lupin Limited*, No. 21-314-RGA (D. Del.); *Bayer Pharma AG v. Dr. Reddy's Laboratories, Inc.*, No. 21-732-RGA (D. Del.); *Bayer Pharma AG v. Taro Pharmaceutical Industries Ltd.*, No. 21-1000-RGA (D. Del.); and *Bayer Pharma AG v. Teva Pharmaceuticals USA, Inc.*, No. 21-1001-RGA (D. Del.).

Patent Owner has also asserted the '310 Patent in *Bayer Pharma AG v. Micro Labs Ltd.*, No. 22-165-RGA (D. Del.), which has been consolidated with the other multidistrict litigation cases in Delaware, as well. Prelim. Resp. 33.

C. The '310 Patent

The '310 Patent relates to methods of treating or preventing cardiovascular events in patients with atherosclerotic vascular disease, coronary artery disease ("CAD"), and/or peripheral artery disease ("PAD"). Ex. 1001, 1:16–19. Both CAD and PAD are caused by atherosclerosis, which occurs when plaque builds up in arteries and narrows or blocks blood flow to various regions of the body. *Id.* at 1:65–67. According to the '310 Patent, CAD is the most common type of heart disease and occurs when plaque builds up in the heart's arteries. *Id.* at 1:49–54. If blood flow to the heart becomes reduced or blocked, angina (i.e., chest pain) or a myocardial infarction (i.e., heart attack) may occur. *Id.* at 1:54–55. PAD results from narrowing of the arteries to the limbs and head, causing symptoms such as pain in the legs or buttocks when exercising, or causing a stroke if there is blockage of vessels in the neck. *Id.* at 1:57–62.

Patients with CAD or PAD are at high risk for major cardiovascular events, such as myocardial infarction, stroke, and cardiovascular death. *Id.* at 2:1–3. Antiplatelet therapy, such as aspirin alone or in combination with newer antiplatelet agents such as clopidogrel, is often used in patients with CAD. *Id.* at

2:23–26. In PAD, the "mainstay of treatment" includes use of a single antiplatelet agent daily to prevent major cardiovascular events. *Id.* at 2:15–17.

Rivaroxaban is a selective inhibitor of coagulation factor Xa (FXa) and serves as an anticoagulant for treatment and prevention of thromboembolic disorders. *Id.* at 1:23–42. According to the '310 Patent, "[a]nticoagulant therapies until the present invention have not been shown to the satisfaction of governmental health authorities to be superior to antiplatelet therapy in PAD and have been rejected as having unacceptably high rates of major bleeding." *Id.* at 2:3–7. As such, the '310 Patent states "there is still a need for new approaches to improve health outcomes in CAD and PAD patients." *Id.* at 2:27–29.

The '310 Patent describes a study that evaluated the potential benefit of rivaroxaban in patients with cardiovascular disease called the "Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome 2—Thrombolysis in Mycoardial Infarction 51" (ATLAS ACS 2-TIMI 51) trial ("the ATLAS trial"). *Id.* at 3:12–17. The '310 Patent states the ATLAS trial administered 2.5 or 5 mg of rivaroxaban twice daily in addition to single or dual antiplatelet therapy in patients with recent acute coronary syndrome. *Id.* at 3:18–21. The dose of 2.5 mg rivaroxaban twice daily resulted in a lower rate of major adverse cardiovascular events and lower mortality than placebo. *Id.* at 3:21–24.

The '310 Patent states that the findings presented in the Specification were obtained from a phase III COMPASS trial "evaluating the efficacy and safety of rivaroxaban (Xarelto®) for the prevention of major adverse cardiac events including cardiovascular death, myocardial infarction and stroke in patients with CAD or PAD." *Id.* at 3:27–31. According to the Specification, "[t]he invention concerns the discovery that combination therapy of rivaroxaban and aspirin

administered to patients with stable atherosclerotic vascular disease, including coronary artery disease and/or peripheral artery disease, shows efficacy in reducing the risk of myocardial infarction, stroke, and/or cardiovascular death." *Id.* at 3:47–52. The Specification also states that "this combination therapy does not result in unacceptable bleeding, such as an unacceptably high risk of fatal bleeding or bleeding in critical organs." *Id.* at 3:52–55.

D. Illustrative Claim

Petitioner challenges claim 1–8 of the '310 Patent, of which claims 1 and 5 are independent. Claim 1 is illustrative and is reproduced below:

> 1. A method of reducing the risk of myocardial infarction, stroke or cardiovascular death in a human patient with coronary artery disease and/or peripheral artery disease, comprising administering to the human patient rivaroxaban and aspirin in amounts that are clinically proven effective in reducing the risk of myocardial infarction, stroke or cardiovascular death in a human patient with coronary artery disease and/or peripheral arterial disease, wherein the rivaroxaban is administered in an amount of 2.5 mg twice daily and aspirin is administered in an amount of 75-100 mg daily.

Ex. 1001, 18:56–65. Independent claim 5 differs from claim 1 only in specifying that "a first product comprising rivaroxaban and aspirin" and "a second product comprising rivaroxaban" are administered. *Id.* at 19:5–17.

Claims 2, 3, and 4 depend from independent claim 1 and recite the administered aspirin at an amount of "100 mg daily," "81 mg daily," and "75 mg daily," respectively. *Id.* at 18:66–19:4. Claims 6, 7, and 8 depend from independent claim 5 and further require the "first product" (a combination of rivaroxaban and aspirin) of claim 5 to comprise "75 mg aspirin," "81 mg aspirin," and "100 mg aspirin," respectively. *Id.* at 19:18–24.

E. The Asserted Grounds of Unpatentability

Petitioner contends that claims 1–8 of the '310 Patent are unpatentable based upon the following grounds:

Claims Challenged	35 U.S.C. §	Reference(s)/Basis
1–4	102	EMA[1]
1–8	103	EMA
1–2	102	Foley[2]
1–2, 5, 8	103	Foley
3–4, 6–7	103	Foley and Plosker[3]

Petitioner also relies upon the Declaration of Dr. Randall Zusman ("Zusman Declaration," Ex. 1002).

II. DISCRETIONARY DENIAL UNDER 35 U.S.C. § 314(a)

As an initial matter, we consider Patent Owner's request that we exercise our discretion under 35 U.S.C. § 314(a) and deny institution under the Board's precedential decision in *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 11 (PTAB Mar. 20, 2020) (precedential). Prelim. Resp. 32–46. For the reasons discussed below, we decline to exercise our discretion.

A. Legal Standards

Institution of an *inter partes* review under 35 U.S.C. § 314(a) is discretionary. *See Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2140 (2016) (citing § 314(a) and stating "the agency's decision to deny a petition is a matter committed to the Patent Office's discretion"); *see also Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d

[1] European Medicines Agency, *Assessment Report, Xarelto*, EMA/CHMP/794349/2012 (2013). Ex. 1005 ("EMA").
[2] Foley et al., *Antithrombotic therapy in peripheral artery disease*, 21 VASCULAR MED. 156–69 (2016). Ex. 1006 ("Foley").
[3] Plosker, *Rivaroxaban: A Review of Its Use in Acute Coronary Syndromes*, 74 DRUGS 451–64 (2014). Ex 1007 ("Plosker").

1356, 1367 (Fed. Cir. 2016) (explaining that under § 314(a), "the PTO is permitted, but never compelled, to institute an IPR proceeding"). In determining whether to exercise that discretion, the Board may consider the advanced state of a parallel proceeding. *NHK Spring Co., Ltd. v. Intri-Plex Techs., Inc.*, IPR2018-00752, Paper 8 at 19–20 (PTAB Sept. 12, 2018) (precedential).

The Board has set forth certain factors ("the *Fintiv* factors") that may be considered in determining whether to exercise its discretion to deny institution based on the advanced stage of a parallel proceeding:

> 1. whether the court granted a stay or evidence exists that one may be granted if a proceeding is instituted;
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> 2. proximity of the court's trial date to the Board's projected statutory deadline for a final written decision;
>
> 3. investment in the parallel proceeding by the court and the parties;
>
> 4. overlap between issues raised in the petition and in the parallel proceeding;
>
> 5. whether the petitioner and the defendant in the parallel proceeding are the same party; and
>
> 6. other circumstances that impact the Board's exercise of discretion, including the merits.

Fintiv, IPR2020-00019, Paper 11, at 5–6.

On June 21, 2022, the Director of the Office issued a Memorandum to clarify how the Board should apply certain *Fintiv* factors when determining whether to exercise its discretion to deny institution under § 314(a).[4] The

[4] Memorandum Re: Interim Procedure for Discretionary Denials in AIA Post-Grant Proceedings with Parallel District Court Litigation (June 21, 2022), a*vailable at* https://www.uspto.gov/sites/default/files/documents/interim_proc_discretionary_denials_aia_parallel_district_court_litigation_memo_20220621_.pdf. ("Memo").

Memorandum explains that the Board should decline to exercise its discretion to deny institution where: (1) a petition presents compelling evidence of unpatentability; (2) a request for denial under *Fintiv* is based on a parallel ITC proceeding; or (3) a petitioner stipulates not to pursue in a parallel district court proceeding the same grounds as in the petition or any grounds that could have reasonably been raised in the petition. Memo 2–3. Moreover, when analyzing *Fintiv*'s second factor, the Board will consider the published median time to trial in the district court in which the parallel litigation resides. *Id.* at 3.

B. Analysis of the Relevant Fintiv Factors

As explained further below, we find the Petition presents compelling evidence of unpatentability with respect to the challenges over the EMA reference, which precludes us from exercising our discretion to deny institution under *Fintiv*. Memo 4–5. Although that factor alone is sufficient to end our analysis, we further note that several other factors support declining to exercise our discretion, as well.

For example, we agree with Petitioner that the investment in the parallel proceeding in Delaware has been relatively low. Reply 7. As explained above, the West Virginia proceeding between Petitioner and Patent Owner was consolidated with five other cases for pre-trial proceedings in a multidistrict litigation in Delaware ("the Delaware MDL"). Pet. 2; Paper 5, 4. In the Delaware MDL, the parties resolved the claim construction issues without briefing or a hearing (Ex. 2019, 2), fact discovery is still ongoing, and expert reports have not yet been served. Ex. 2008, 3, 11.

Moreover, although Patent Owner asserts that trial in the related Delaware MDL is set for May 30, 2023—several months before our projected Final Written Decision would be due (Prelim. Resp. 34)—the median time to trial in the District

of Delaware is 36.3 months.[5] Because the Delaware action was filed on March 1, 2021, this results in a projected trial date of July 2024, almost one year after the deadline for the Final Written Decision in this proceeding. And, although statistics on the median time to trial are not available for the Northern District of West Virginia, because that case has been consolidated with the Delaware MDL for pre-trial proceedings, the trial in West Virginia involving Petitioner presumably would not occur until after those pre-trial proceedings conclude in Delaware. Accordingly, we find these factors further weigh against exercising our discretion to deny institution.

Patent Owner argues that institution would amount to an inefficient and repetitive proceeding because Petitioner is seeking its third round of challenging the '310 Patent. Prelim. Resp. 32–33. As explained further below, however, we are not persuaded that we should exercise our discretion under § 325(d), nor are we persuaded that the Petition has no merit, as Patent Owner asserts. Moreover, we acknowledge Patent Owner's policy argument that we should exercise our discretion to deny institution to avoid giving Petitioner multiple bites at the apple. Prelim. Resp. 33. We note, however, that the Office did not consider EMA or the ATLAS trial during Supplemental Examination. Thus, our approach "strikes a balance among the competing concerns of avoiding potentially conflicting outcomes, avoiding overburdening patent owners, and strengthening the patent system by eliminating patents that are not robust and reliable." Memo 5.

Accordingly, having considered the specific facts and circumstances of this case, we find the balance of factors weighs against exercising our discretion to deny institution under 35 U.S.C. § 314(a).

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[5] *See* https://www.uscourts.gov/sites/default/files/data_tables/fcms_na_distcomparison0331.2022.pdf

Next, we turn to Patent Owner's assertion that we should exercise our discretion and deny institution under § 325(d).

III. DISCRETIONARY DENIAL UNDER 35 U.S.C. § 325(d)

Patent Owner also urges us to exercise our discretion to deny institution under 35 U.S.C. § 325(d). Prelim. Resp. 2. For the reasons discussed below, we decline to exercise such discretion.

A. Legal Standards

Under § 325(d), we have discretion to deny a petition that presents the same or substantially the same prior art or arguments as previously presented to the Office. *See* 35 U.S.C. § 325(d).

In performing an analysis under § 325(d), the Board uses a two-part framework:

> (1) We consider whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office; and
>
> (2) If either condition of the first part of the framework is satisfied, we consider whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims.

Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH, IPR2019-01469, Paper 6 at 8 (PTAB Feb. 13, 2020) (precedential).

To help us evaluate the *Advanced Bionics* framework, we consider a number of non-exclusive factors, as set forth in our decision in *Becton, Dickinson and Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 at 17–18 (PTAB Dec. 15, 2017) (precedential) ("the *Becton, Dickinson* factors"):

> (a) the similarities and material differences between the asserted art and the prior art involved during examination;

(b) the cumulative nature of the asserted art and the prior art evaluated during examination;

(c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection;

(d) the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or Patent Owner distinguishes the prior art;

(e) whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and

(f) the extent to which additional evidence and facts presented in the Petition warrant reconsideration of the prior art or arguments.

Becton, Dickinson, IPR2017-01586, Paper 8 at 17–18.

According to *Advanced Bionics*, *Becton, Dickinson* factors (a), (b), and (d) relate to whether the same or substantially the same art or arguments previously were presented to the Office, and factors (c), (e), and (f) relate to whether the petitioner has demonstrated a material error by the Office. *Advanced Bionics*, Paper 6 at 9–11. On this record, we are not persuaded that we should exercise our discretion to deny institution under § 325(d) in this case for the reasons below. Because it is dispositive to this issue, we focus our analysis on the unpatentability challenges over the EMA reference.

B. Analysis

There can be no dispute that EMA was previously presented to the Office during prosecution of the ’310 Patent. EMA is on the face of the ’310 Patent (Ex. 1001, 1) and appears to have been considered by the Examiner during prosecution, as the reference was cited in an IDS, which the Examiner signed

without indicating that EMA was not considered (Ex. 1004, 524). Thus, part one of the *Advanced Bionics* framework has been satisfied, and we move on to part two to determine whether Petitioner has demonstrated that the Office erred in a manner material to the patentability of the challenged claims.

Patent Owner asserts that Petitioner has failed to show any material error by the Examiner during prosecution. Prelim. Resp. 23–32. We disagree. Although the Examiner considered EMA in an IDS, EMA was not discussed in any Office Action or Response, as Petitioner notes. Reply 3–4. Thus, according to *Becton, Dickinson* factor (c), we find that EMA was not extensively evaluated during examination and was not the basis for a rejection. Although Patent Owner is correct that the Examiner appears to have run prior art searches for "acute coronary syndrome" (Prelim. Resp. 27), we cannot speculate as to why the Examiner did not apply the references from those search results to the claims. Regardless, as explained further below, we are persuaded that Petitioner has presented compelling evidence that the Examiner overlooked disclosures in EMA that anticipate and render obvious the '310 Patent claims. *See infra*. We, therefore, agree with Petitioner that the Office erred in a manner material to the patentability of the challenged claims.

C. Conclusion

Having considered the respective arguments and evidence of the parties and applied the *Advanced Bionics* framework, we decline to exercise our discretion to deny institution under 35 U.S.C. § 325(d).

We now turn to the merits of Petitioner's challenge.

IV. PATENTABILITY ANALYSIS

A. A Person of Ordinary Skill in the Art

Petitioner asserts that a person of ordinary skill in the art at the time of the invention would have had "the equivalent of an M.D. degree, knowledge, and experience regarding the diagnosis and treatment of patients with CAD and PAD, including administering antiplatelet and anticoagulant agents to such patients." Pet. 10 (citing Ex. 1002 ¶¶ 50–52, 89–95).

Patent Owner does not contest Petitioner's definition of the level of ordinary skill in the art for purposes of its Preliminary Response. Prelim. Resp. 10.

We adopt Petitioner's definition as it appears to be consistent with the prior art's demonstration of the level of ordinary skill in the art at the time of the invention. *See 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))).

Moreover, we find on this record that Dr. Zusman, Petitioner's witness, is qualified to opine from the perspective of a skilled artisan as he is a person of at least ordinary skill in the art. *See* Ex. 1002 ¶¶ 1–14; Ex. 1003.

B. Claim Construction

The Board applies the same claim construction standard in these proceedings 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)).

1. "clinically proven effective"

Independent claims 1 and 5 each recite administering rivaroxaban and aspirin "in amounts that are clinically proven effective in reducing the risk of myocardial infarction, stroke or cardiovascular death in a human patient with coronary artery disease and/or peripheral artery disease." Ex. 1001, claims 1 and 5. Petitioner asserts that because the claims recite administering rivaroxaban and aspirin "in amounts that are clinically proven effective," those specific doses must satisfy that functional element. Pet. 11 (Ex. 1002 ¶ 55). Petitioner also cites the '310 Patent Specification, which defines "effective" and "efficacy" as preferably referring to "a dosage determined by the US FDA as acceptable for administration to reduce the risk of major cardiovascular events (cardiovascular death, myocardial infarction, or stoke) in CAD and/or PAD patients." Pet. 11–12 (quoting Ex. 1001, 10:57–63). Petitioner notes, however, that the FDA did not approve the claimed regimen until after the February 2018 priority date. *Id.* at 12 (citing Ex. 1016). Finally, Petitioner asserts that the claim phrase should be construed to encompass both individual and joint-efficacy. Pet. 12 (citing Ex. 1002 ¶ 56).

Patent Owner asserts that Petitioner's construction is erroneous because it is unsupported by its expert's testimony, ignores the claim language, and cherry picks

portions of the Specification discussing "efficacy" and "effective." Prelim. Resp. 10–11. Patent Owner does not, however, propose an alternative construction for the term.

The '310 Patent Specification states, "[a]ccording to the invention, the terms 'effective' or 'efficacy' . . . refer to reducing the risk of myocardial infarction, stroke, or cardiovascular death in patients with CAD and/or PAD or other atherosclerotic vascular disease, such as by reducing the risk when compared to therapy with aspirin alone." Ex. 1001, 10:50–57. Although the Specification also states that the terms "[p]referably" refer to a dosage that has been approved by the FDA, we do not construe the claim language to be limited to FDA approval.[6] Moreover, we agree with Patent Owner that, when reading the claims and Specification as a whole, the "clinically proven effective" amounts refer to the amounts of aspirin and rivaroxaban in combination and not individually. Ex. 1001, claims 1 and 5, Abstract (referring to "[c]ombination therapy with rivaroxaban and aspirin").

At this stage of the proceeding, we construe the term "clinically proven effective" according to its plain and ordinary meaning as it would have been understood by the ordinarily skilled artisan—the amounts of aspirin and rivaroxaban in combination that have clinically been shown to reduce the risk of myocardial infarction, stroke, or cardiovascular death in patients with CAD and/or PAD.

2. "first product" / "second product"

Independent claim 5 recites once daily administration of a "first product" comprising 2.5 mg rivaroxaban and 75–100 mg aspirin and a "second product"

[6] We note that in the Delaware MDL, the parties have since stipulated that claim 1 "does not require FDA approval." Ex. 2019, 2.

comprising 2.5 mg rivaroxaban. Ex. 1001, claim 5. Petitioner notes that the terms "first product" and "second product," other than in the claims themselves, do not appear in the '310 Patent Specification, and "product" is not expressly defined. Pet. 13. Petitioner's expert, Dr. Zusman, opines that a person of ordinary skill in the art would have understood the "first product" to be combination therapy, which the Specification describes "may be administered using separate dosage forms for rivaroxaban, or using a combination dosage form containing both rivaroxaban and aspirin." Pet. 13; Ex. 1002 ¶ 67 (quoting Ex. 1001, 8:65–9:20). Moreover, Dr. Zusman notes that the '310 Patent Specification states that "combinations" include "components administered simultaneously or sequentially as long as they are employed for the prophylaxis and/or treatment of the same disease." Ex. 1002 ¶ 67 (quoting Ex. 1001, 8:65–9:20). Accordingly, Petitioner asserts that a person of ordinary skill in the art "would have understood simply administering one 2.5 mg rivaroxaban pill and one aspirin pill at approximately the same time could constitute claim 5's 'first product.'" Pet. 14.

Patent Owner opposes Petitioner's proposed construction of "first product," asserting that it "ignores that claim 5 itself describes the 'first product' as 'comprising' specified amounts of rivaroxaban and aspirin." Prelim. Resp. 10. Again, Patent Owner does not provide its own proposed construction of either "first product" or "second product."

Without further explanation, it is unclear why Patent Owner disputes Petitioner's proposed construction. Thus, at this stage of the proceeding, we find Petitioner's proposed construction is consistent with the intrinsic evidence. That is, the "first product" of claim 5 refers to "combination therapy," which encompasses administering "separate dosage forms for rivaroxaban and aspirin" or "a combination dosage form containing both rivaroxaban and aspirin" in the

recited amounts.[7] *See* Ex. 1001, 8:26–9:1. If administered as separate dosage forms, we agree with Petitioner that the Specification supports administering the "first product" dosage forms "simultaneously or sequentially as long as they are employed for the prophylaxis and/or treatment of the same disease." *See id.* at 9:17–19.

3. Remaining Claim Terms

Petitioner notes that the preambles of independent claims 1 and 5 recite "peripheral artery disease," whereas the claim bodies refer to "peripheral arterial disease." Pet. 13. Because the '310 Patent uses the terms interchangeably, Petitioner asserts that a person of ordinary skill in the art would have understood those terms to refer to the same disease. *Id.* (citing Ex. 1002 ¶¶ 62–65).

There does not appear to be any dispute over construing these terms as synonyms. *See* Ex. 2019, 2 (stipulating in the Delaware MDL that the terms are interchangeable). For clarity, however, we adopt Petitioner's proposed construction as consistent with the plain and ordinary meaning of the terms. *See Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) ("[C]laim terms need only be construed 'to the extent necessary to resolve the controversy.'" (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc*., 200 F.3d 795, 803 (Fed. Cir. 1999))).

We now turn to the patentability challenges presented by Petitioner.

C. Alleged Anticipation by EMA

Petitioner asserts that claims 1–4 are anticipated by EMA. Pet. 21–33. Patent Owner does not address the substantive grounds in its Preliminary Response

[7] In the Delaware MDL, the parties stipulated that claim 1 "does not require that the amounts of rivaroxaban and aspirin be in a single/combined dosage form (e.g., a tablet containing both rivaroxaban and aspirin)." Ex. 2019, 2.

beyond its discretionary denial arguments. *See generally* Prelim. Resp. On this record, we determine that Petitioner has established a reasonable likelihood that it would prevail in showing the challenged claims are anticipated by EMA.

1. EMA (Ex. 1005)

EMA is an assessment report of the European Medicines Agency approving the use of rivaroxaban (the active ingredient in XARELTO film-coated tablets) with aspirin alone or with aspirin plus a thienopyridine (clopidogrel or ticlopidine) to prevent cardiovascular death, myocardial infarction, and stent thrombosis in patients after an acute coronary syndrome ("ACS"), which is defined as a non-ST elevation or ST elevation myocardial infarction or unstable angina. Ex. 1005, 6, 10. On its first page, EMA indicates it published March 21, 2013, more than a year before the earliest indicated priority date for the '310 Patent; thus, EMA is prior art to the challenged claims. *Id.* at 1; *see also* Ex. 1001, codes (56) (References Cited), (60) (Related U.S. Application Data). Patent Owner does not, at present, dispute this. *See generally* Prelim. Resp.

EMA notes that "[c]oronary heart disease (CHD) is a common clinical and pathological condition." Ex. 1005, 8. EMA further states that following an ACS event, patients are at high risk of another morbid event of ACS or stroke or dying from a cardiovascular cause. *Id.* EMA then describes the results of the phase III ATLAS trial in which subjects with ACS who were currently receiving 75–100 mg aspirin daily alone (Stratum 1) or in combination with a thienopyridine (Stratum 2) were given 2.5 mg or 5 mg rivaroxaban twice a day (or a placebo). *Id.* at 26.

EMA found that "a statistically significant and clinically relevant reduction of the primary composite endpoint was demonstrated in the 2.5 mg b.i.d. [twice daily] dose group driven by a reduction in mortality." *Id.* at 72. EMA notes, however, that the proportion of patients treated with aspirin only (i.e., Stratum 1)

was small so "no firm conclusions can be drawn for that stratum." *Id.* at 69. EMA states, however, that it can be "speculated based on the hazard ratios observed in the phase II and phase III study results that the additional benefit is larger if rivaroxaban is added to less intensive platelet inhibition." *Id.* Thus, based on the date submitted, EMA states "it is finally considered acceptable to approve Xarelto for patients with ASA [aspirin] only and taking into account the more restricted indication in patients with elevated cardiac biomarkers." *Id.*

2. Analysis

Anticipation requires that "each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999) (citation omitted). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.'" *Id.* (citation omitted). Moreover, to anticipate, a prior art reference must "disclose[] within the four corners of the document not only all of the limitations claimed but also all of the limitations arranged or combined in the same way as recited in the claim." *Net MoneyIN, Inc. v. Verisign, Inc.*, 545 F.3d 1359, 1371 (Fed. Cir. 2008).

Petitioner asserts that EMA discloses each limitation of claim 1. Pet. 22–32. For example, to the extent the preamble is limiting—which we need not resolve for purposes of our Decision—Petitioner asserts that EMA discloses it because EMA approves rivaroxaban (XARELTO) in addition to standard care antiplatelet therapy that reduces the risk of cardiovascular death, myocardial infarction, or stroke in subjects with a recent ACS event compared with placebo. *Id.* at 23 (citing Ex. 1005, 25, 26, 39–45; Ex. 1002 ¶¶ 114–115). Petitioner further asserts that a person

of ordinary skill in the art "would have readily appreciated that ACS is a form of CAD." *Id.* (citing Ex. 1008, e146; Ex. 1011, 170; Ex. 1002 ¶ 117).

Petitioner also asserts that EMA discloses the remaining limitations of claim 1 because EMA describes a clinical trial in which patients with a recent ACS event received aspirin at "75 to 100 mg/day" in combination with 2.5 mg rivaroxaban twice daily. Pet. 24–31 (citing Ex. 1005, 25–26, 40, 42, 48, 51, FIG. E1). Petitioner asserts that EMA's description of the Phase III ATLAS trial discloses the "clinically proven effective" limitation of claim 1, as it describes the exact same regimen claimed by the '310 Patent. *Id.* at 25 (citing Ex. 1005, 16, 25, 26, 39–45; Ex. 1002 ¶¶ 120–125). Moreover, Petitioner's expert opines that a person of ordinary skill in the art would have understood the regimen approved by EMA to be "clinically proven effective." *Id.* at 27–28 (citing Ex. 1002 ¶¶ 129–131). Accordingly, Petitioner asserts that EMA discloses each limitation of claim 1.

At this stage of the proceeding, we find Petitioner presents a compelling unpatentability challenge to claim 1. That is, we find "the evidence, if unrebutted in trial, would plainly lead to a conclusion that one or more claims are unpatentable by a preponderance of the evidence." Memo 4. We find Petitioner has shown that EMA discloses the claimed regimen of administering 2.5 mg rivaroxaban twice daily and 75–100 mg aspirin daily to patients with ACS—a form of CAD—which was clinically proven effective to reduce myocardial infarction, stroke, or cardiovascular death by the ATLAS trial. Pet. 22–32.

In urging the Board to exercise our discretion to deny institution, Patent Owner argues that the '310 Patent Specification explains how the ATLAS and COMPASS trials were "two separate clinical trials conducted in different patients." Prelim. Resp. 21. As such, according to the Specification, the ATLAS trial

"involved patients who had recently been hospitalized following an acute event," whereas COMPASS involved "stable patients who had no history of an acute event, or were years removed from an acute event." *Id.* (citing Ex. 1001, 7:49–58). Patent Owner further asserts that "the claimed invention is based on the COMPASS trial, a separate clinical trial with different parameters than the ATLAS ACS clinical trial." *Id.* at 27. Patent Owner then argues that Petitioner has failed to show how a regimen that is "'clinically proven effective' in patients with an acute condition (ACS) anticipates a regimen that is 'clinically proven effective' in patients with a stable condition (CAD and/or PAD)." *Id.* at 29.

At this stage of the proceeding and on this record, we are not persuaded. Although not expressly stated as such, Patent Owner appears to argue that patients with CAD do not include patients who have ACS. In doing so, Patent Owner repeatedly qualifies its assertion by distinguishing "*acute* coronary syndrome" from "*stable* cardiovascular disease." *See, e.g.*, Prelim. Resp. 22 (noting the differences between the ATLAS and COMPASS trials). Nowhere, however, does the '310 Patent expressly limit CAD to "stable" CAD. Nor do the claims expressly limit the "human patient" to a stable one, but only one "with coronary artery disease and/or peripheral artery disease." *See* Ex. 1001, claims 1 and 5. As the Specification explains, CAD "occurs when plaque builds up in the heart's arteries, a condition called atherosclerosis. . . . If blood flow becomes reduced or blocked, angina (chest pain) or heart attack may occur." *Id.* at 1:49–55. Thus, the Specification acknowledges that angina and heart attack—which are signs of ACS—are caused by CAD. *See* Ex. 1005, 10 (defining ACS as "non-ST elevation or ST elevation myocardial infarction or unstable angina"); *see also* Ex. 1002 ¶ 117 ("ACS is a form of, and often the initial presentation of, coronary artery

disease (also known as coronary heart disease).") (citing Ex. 1008, e146; Ex. 1011, 170).

Although the COMPASS trial evaluated the rivaroxaban and aspirin treatment regimen in patients with stable cardiovascular disease, the claims are not so limited. Rather, we agree with Petitioner that a person of ordinary skill in the art would understand that CAD encompasses both acute and stable cardiovascular disease. *See* Ex. 1002 ¶ 71 (citing Ex. 1012, 1155; Ex. 1011, 170). Accordingly, we find Petitioner has presented compelling evidence that EMA anticipates claim 1.

Petitioner also asserts EMA anticipates claims 2–4. Claims 2–4 depend from claim 1 and further recite 100 mg, 81 mg, and 75 mg aspirin, respectively. Ex. 1001, claims 2–4. Petitioner asserts that EMA's disclosure of administering 75–100 mg aspirin anticipates those claims, as there is nothing critical about those amounts of aspirin, which are commercially available dosages in various parts of the world. Pet. 32–33 (citing Ex. 1005, 26, 51; Ex. 1002 ¶¶ 149–150; Ex. 1013, 2656).

At this stage of the proceeding, we are persuaded that Petitioner has also presented a compelling unpatentability challenge to claims 2–4 over EMA. We find that EMA's disclosure of the narrow range of 75–100 mg aspirin daily (Ex. 1005, 26), in combination with the known commercially available aspirin dosages of 100 mg, 81 mg, and 75 mg (*see* Ex. 1002 ¶ 150), anticipates the specific doses of claims 2–4, as a person of ordinary skill in the art would "at once envisage each member of this limited class." *See In re Petering*, 301 F.2d 676, 681 (CCPA 1962).

Accordingly, we find Petitioner has shown a reasonable likelihood of prevailing on its assertion that EMA anticipates claims 1–4 of the '310 Patent.

D. Alleged Obviousness over EMA

Petitioner asserts claims 1–8 would have been unpatentable as obvious over EMA. Pet. 33–51. Patent Owner does not address the substantive grounds on the merits in its Preliminary Response beyond its discretionary denial arguments. *See generally* Prelim. Resp. On this record, we determine that Petitioner has established a reasonable likelihood that it would prevail in showing the challenged claims would have been unpatentable as obvious over EMA.

A claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which that subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness when presented. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

In analyzing the obviousness of a combination of prior art elements, it can be important to identify a reason that would have prompted one of skill in the art "to combine . . . known elements in the fashion claimed by the patent at issue." *KSR*, 550 U.S. at 418. A precise teaching directed to the specific subject matter of a challenged claim is not necessary to establish obviousness. *Id.* Rather, "any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.* at 420. Accordingly, Petitioner must show that "a skilled artisan would have been motivated to combine the teachings of the prior art

references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016) (quotations and citations omitted).

Regarding claims 1–4, Petitioner asserts EMA anticipated each claim. With the understanding that the requirements for obviousness and anticipation are not identical, because we find above that Petitioner has shown sufficiently that EMA anticipates claims 1–4, we find Petitioner has also shown for the same reasons a reasonable likelihood of succeeding on its assertion that EMA renders those claims obvious. *See Realtime Data, LLC v. Iancu*, 912 F.3d 1368, 1373 (Fed. Cir. 2019) ("[I]t is well settled that a disclosure that anticipates under § 102 also renders the claim invalid under § 103, for anticipation is the epitome of obviousness.") (internal quotations and citations omitted).

As for independent claim 5, Petitioner asserts EMA teaches or suggests each limitation of the claim. For the same reasons as claim 1, Petitioner asserts EMA teaches the preamble and administering rivaroxaban and aspirin in amounts that are clinically proven effective in reducing the risk of myocardial infarction, stroke, or cardiovascular death in a human patient with CAD and/or PAD. *See supra*. Claim 5 further recites administering a "first product" comprising 2.5 mg rivaroxaban and 75–100 mg aspirin and a "second product" comprising 2.5 mg rivaroxaban. Ex. 1005, claim 5. Petitioner asserts "the first product" would have been obvious because although EMA does not specify whether the aspirin was specifically required to be taken at the same time as the rivaroxaban, Petitioner's expert, Dr. Zusman, explains that "unless there is cause for concern in terms of potential drug interactions, concomitant administration of multiple drugs in a dosing regimen is preferred for patient-compliance reasons." Pet. 48–49 (citing Ex. 1002 ¶¶ 234–235; Ex. 1009, 981). Moreover, Dr. Zusman notes that a person of

ordinary skill in the art "would have readily understood that it is easier for patients to take two drugs at the same time . . . than to have to remember to take them at different times throughout the day." Pet. 49–50 (citing Ex. 1002 ¶¶ 234–235). Dr. Zusman concludes that "it thus would have been obvious to administer aspirin along with the first of two daily doses of rivaroxaban in carrying out the method described by EMA." Ex. 1002 ¶ 234.

On this record, we are persuaded that Petitioner has shown sufficiently that claim 5 would have been obvious over EMA. As explained above with respect to claim 1, we are persuaded that Petitioner has shown that EMA expressly teaches each limitation of claim 5 except the "first product." We are persuaded, however, that Petitioner has shown sufficiently that a person of ordinary skill in the art would have had a reason to administer rivaroxaban and aspirin at the same time because it is easier for patients to remember and to comply with the regimen. *See* Ex. 1002 ¶¶ 234–235. Moreover, Petitioner has shown that a person of ordinary skill in the art would have had a reasonable expectation of success in doing so, as it was known that the two drugs could be administered together. Pet. 49 (citing Ex. 1009, 981).

Regarding claims 6–8, which recite the first product comprises 75 mg, 81 mg, and 100 mg aspirin, respectively, Petitioner asserts that EMA teaches or suggests those specific dosages by teaching administering 75–100 mg once daily in addition to 2.5 mg rivaroxaban. For the same reasons given above for claims 2–4 being anticipated, Petitioner asserts claims 6–8 would have been obvious from the teachings of EMA. Pet. 51 (citing Ex. 1002 ¶¶ 243–245). We are similarly persuaded that Petitioner has shown sufficiently that EMA renders obvious claims 6–8 in light of the narrow range of aspirin taught by EMA and the known

commercially available dosages of aspirin that match the recited dosages of claims 6–8. *See* Ex. 1002 ¶ 150.

Thus, on this record, we are persuaded that Petitioner has shown sufficiently that claims 1–8 would have been unpatentable as obvious over EMA. *See* Pet. 44–51 (citing Ex. 1002 ¶¶ 230–245).

E. Alleged Unpatentability over Foley, Individually or in Combination

Petitioner asserts that claims 1 and 2 of the '310 Patent are anticipated by Foley; that claims 1, 2, 5, and 8 are unpatentable as obvious over Foley; and that claims 3, 4, 6, and 7 are unpatentable as obvious over Foley and Plosker. Pet. 52–71. Patent Owner does not directly address the substantive grounds in its Preliminary Response beyond its discretionary denial arguments. *See generally* Prelim. Resp. On this record, we determine that Petitioner has not established a reasonable likelihood that it would prevail in showing the challenged claims are unpatentable over Foley alone or in combination with Plosker.

1. Foley (Ex. 1006)

Foley is a journal article entitled "Antithrombotic therapy in peripheral artery disease," which "reviews current data on antithrombotic therapy in PAD and discusses the implications of this data for current practice and future research." Ex. 1006, 156. At its first page, Foley indicates a publication date of 2016, which makes it prior art to the challenged claims; Patent Owner does not assert otherwise. *Id.*; *see generally* Prelim. Resp. Foley describes a variety of treatment regimens for patients with PAD, including the use of aspirin for symptomatic and asymptomatic PAD. Foley states "[d]espite the advent of newer agents, aspirin remains the most widely used antiplatelet drug in the world." Ex. 1006, 157.

Foley also describes anticoagulant therapy in PAD. Specifically, Foley describes the Warfarin Antiplatelet Vascular Evaluation (WAVE) study. *Id.* at

164. In this randomized controlled trial, the study compared combination therapy with warfarin and an antiplatelet agent to an antiplatelet agent alone in patients with PAD. *Id.* The WAVE study found there was no significant difference between the treatment groups in the occurrence of heart attack, stroke or death from cardiovascular causes. *Id.* According to Foley, the WAVE findings "suggest that combination therapy with warfarin and an antiplatelet agent yields no significant benefit in patients with PAD when compared to antiplatelet therapy alone, and is associated with an increased risk of moderate and severe bleeding." *Id.*

Finally, Foley describes the COMPASS trial and states that it was ongoing and studies the effects of rivaroxaban in patients with CAD or PAD. *Id.* at 167. Foley states the COMPASS patients are randomized into one of three arms: (1) 2.5 mg rivaroxaban twice daily and aspirin (100 mg once daily); (2) 5 mg rivaroxaban twice daily and aspirin (same dosage); and (3) placebo twice daily and aspirin (same dosage). *Id.* Foley notes that the COMPASS trial was estimated to be completed in February 2018. *Id.*

2. Plosker (Ex. 1007)

Plosker is a journal article entitled "Rivaroxaban: A review of Its Use in Acute Coronary Syndromes." Ex. 1007, 451. At its first page, Plosker indicates it published in 2014, which makes it prior art to the challenged claims; Patent Owner does not argue otherwise. *Id.*; *see generally* Prelim. Resp. Plosker describes the ATLAS trial, including the dosing regimen of 2.5 mg rivaroxaban twice daily, co-administered with aspirin alone or aspirin plus either clopidogrel of ticlopidine. Ex. 1007, 451. Plosker notes the dosing regimen was approved for use in the EU for patients with a recent ACS. *Id.*

3. Analysis

Petitioner asserts that Foley discloses a method of preventing major cardiovascular events in CAD and PAD by administering 2.5 mg rivaroxaban twice daily and 100 mg aspirin once daily. Pet. 54 (citing Ex. 1006, 166–167; Ex. 1002 ¶ 157). Regarding the "clinically proven effective" limitation, Petitioner asserts Foley teaches this limitation because "the efficacy of this known regimen is inherent to the regimen itself." *Id.* Moreover, Petitioner asserts the regimen was known to be clinically proven effective by the ATLAS trial for ACS patients, as taught by Plosker. *Id.* at 55, 60–61, 66, 69.

We are not persuaded. Because Foley does not disclose the clinical results of the COMPASS trial, we find Petitioner has not shown that Foley teaches or suggests the "clinically proven effective" limitation of the claims. The Examiner came to the same result in the Supplemental Examination of the '310 Patent application. Ex. 2001, BAYX310-0001578–BAYX310-0001579 ("None of the items of information discloses information regarding the efficacy of the claimed treatment methods, i.e. results of the clinical trial, which was available prior to the critical date of February 2, 2017. Therefore none of the items of information raises a [substantial new question of patentability] for any of claims 1–8."). We are also not persuaded, on this record, that Petitioner has shown sufficiently that a person of ordinary skill in the art would have combined the clinical efficacy results from Plosker's ATLAS trial for ACS patients with Foley's COMPASS method of treating patients with stable CAD with a reasonable expectation of success.

Accordingly, on this record, we are not persuaded that Petitioner has shown a reasonable likelihood of prevailing on its assertions that claims 1–8 are unpatentable over Foley alone or in combination with Plosker.

V. CONCLUSION

For the foregoing reasons, we determine that Petitioner has established a reasonable likelihood of prevailing on its assertion that at least one of the challenged claims of the '310 Patent is unpatentable. Accordingly, we institute an *inter partes* review of claims 1–8 of the '310 Patent on the grounds raised in the Petition.

Our determination in this Decision is not a final determination on the construction of any claim term or the patentability of any challenged claim and, thus, leaves undecided any factual issues necessary to determine whether sufficient evidence supports Petitioner's contentions by a preponderance of the evidence in the final written decision. *See TriVascular, Inc. v. Samuels*, 812 F.3d 1056, 1068 (Fed. Cir. 2016) (noting that "there is a significant difference between a petitioner's burden to establish a 'reasonable likelihood of success' at institution, and actually proving invalidity by a preponderance of the evidence at trial") (quoting 35 U.S.C. § 314(a) and comparing § 316(e)).

VI. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that, pursuant to 35 U.S.C. § 314(a), an *inter partes* review of claims 1–8 of U.S. Patent No. 10,828,310 B2 is instituted with respect to all challenged claims and all grounds set forth in the Petition; and

FURTHER ORDERED that, pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial, which will commence on the entry date of this decision.

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