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Paper No. 24
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.,
Petitioner,

v.

BRISTOL-MYERS SQUIBB COMPANY and PFIZER INC.,
Patent Owners.

Case IPR2018-00892
Patent 9,326,945 B2

Before SHERIDAN K. SNEDDEN, ZHENYU YANG, and KRISTI L. R. SAWERT, *Administrative Patent Judges.*

SNEDDEN, *Administrative Patent Judge.*

DECISION
Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

Mylan Pharmaceuticals Inc. ("Petitioner"), filed a Petition requesting an *inter partes* review of claims 1–38 of U.S. Patent No. 9,326,945 B2 (Ex. 1001, "the '945 patent"). Paper 2 ("Pet."). Bristol-Myers Squibb Company and Pfizer, Inc. (collectively, "Patent Owner") filed a Preliminary Response. Paper 18 ("Prelim. Resp.").

We have authority to determine whether to institute an *inter partes* review under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted unless the information presented in the petition "shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." *See also* 37 C.F.R. § 42.4 (a). Upon consideration of the Petition and the Preliminary Response, and for the reasons explained below, we determine that Petitioner has established a reasonable likelihood that it would prevail with respect to at least one challenged claim. We thus grant Petitioner's request to institute an *inter partes* review of the challenged claims on all grounds set forth in the Petition.

A. Related Matters

The parties provide a list of numerous litigations involving the '945 patent. Pet. 1–3; Paper 7, 1–3.

B. The '945 patent

The '945 patent describes "[c]ompositions comprising crystalline apixaban particles having a D_{90} equal to or less than 89 μm, and a pharmaceutically acceptable carrier." Ex. 1001, Abstract. The compositions

can be used for the treatment and/or prophylaxis of thromboembolic disorders. *Id.*

The '945 patent discloses as follows:

> The aqueous solubility (40 μg/mL at all physiological pH) of apixaban suggests that the tablets with less than 10 mg apixaban (dose/solubility ratio=250 mL) should not demonstrate dissolution rate limited absorption since dissolution rate limitations are only expected when the dose/solubility ratio is greater than 250 mL. Based on this dose and solubility consideration, the particle size of the compound should not be critical for achieving consistent plasma profiles, according to the prediction based on the Biopharmaceutics Classification System (BCS; Amidon, G. L. et al., *Pharmaceutical Research*, 12: 413–420 (1995)). However, it was determined that formulations that were made using a wet granulation process as well as those using large particles of apixaban drug substance resulted in less than optimal exposures, which can present quality control challenges.

Id. at 1:46–60.

The '945 patent discloses as follows:

> Surprisingly and unexpectedly, it has been found that compositions for tablets comprising up to 5 mg, apixaban particles having a D_{90} (90% of the volume) less than 89 microns (μm) lead to consistent in-vivo dissolution in humans (at physiologic pH), hence, consistent exposure and consistent Factor Xa inhibition that will lead to consistency in therapeutic effect.

Id. at 1:64–2:3.

The '945 patent discloses the need for the use of a surfactant in the composition as follows:

> The invention further provides the pharmaceutical composition further comprising a surfactant from 0.25% to 2% by weight, preferably from 1% to 2% by weight. As regards the

> surfactant, it is generally used to aid in wetting of a hydrophobic drug in a tablet formulation to ensure efficient dissolution of the drug, for example, sodium lauryl sulfate, sodium stearate, polysorbate 80 and poloxamers, preferably sodium lauryl sulfate.

Id. at 2:24–31.

The '945 patent further discloses how to perform certain dissolution rate tests. *Id.* at 3:1–19; 6:24–41.

C. Illustrative Claims

Independent claims 1 and 12, reproduced below, are illustrative:

> 1. A solid pharmaceutical composition comprising a therapeutically effective amount of crystalline apixaban particles and a pharmaceutically acceptable diluent or carrier,
>
> wherein the crystalline apixaban particles have a D_{90} equal to or less than about 89 μm, and
>
> wherein at least 77 wt % of apixaban dissolves within 30 minutes in a pH 6.8 phosphate buffer containing 0.05% sodium lauryl sulfate.

> 12. A solid pharmaceutical composition comprising a therapeutically effective amount of apixaban and a pharmaceutically acceptable diluent or carrier,
>
> wherein apixaban comprises crystalline apixaban particles,
>
> wherein the crystalline apixaban particles have a D_{90} equal to or less than about 89 μm, and
>
> wherein, as measured using a USP Apparatus 2 at a paddle rotation speed of 75 rpm in 900 mL, of a dissolution medium at 37° C., at least 77 wt % of apixaban in the pharmaceutical composition dissolves within 30 minutes in the dissolution medium, and the dissolution medium is 0.05 M sodium phosphate at a pH 6.8 containing 0.05% sodium lauryl sulfate.

Ex. 1001, 9:49–57; 10:13–27.

D. Evidence Relied Upon

Petitioner relies upon the following prior art references:

Ex. 1004, Carreiro et al., "Apixaban, an oral direct Factor Xa inhibitor: awaiting the verdict," Expert Opin. Investig. Drugs, 17(12):1937–1945 (2008) ("Carreiro").

Ex. 1007, U.S. Patent No. 6,967,208 B2 to Pinto et al., issued Nov. 22, 2005 ("Pinto").

Ex. 1008, U.S. Patent Publication No. 2006/0160841 A1 by Chenkou Wei et al., published Jul. 20, 2006 ("Wei").

Ex. 1010, Rudnic et al., "Tablet Dosage Forms," in Modern Pharmaceutics, 4th ed., G.S. Banker and C.T. Rhodes, eds., Taylor & Francis Group, Boca Raton, FL, pp. 333–359 (2002) ("Rudnic").

Ex. 1015, "Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms," U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) (Aug. 1997) ("FDA Dissolution Guidance").

Petitioner also relies upon the Declaration of Kinam Park, Ph.D. (Ex. 1002) to support its contentions.

E. Asserted Grounds of Unpatentability

Petitioner asserts the following grounds of unpatentability (Pet. 4–5):

Ground	Claims	Basis	References
1	1–38	§ 103(a)	Carreiro, Wei, and FDA Dissolution Guidance
2	1–38	§ 103(a)	Carreiro, Wei, Rudnic, and FDA Dissolution Guidance

Ground	Claims	Basis	References
3	1–38	§ 103(a)	Pinto, Wei, and FDA Dissolution Guidance
4	1–38	§ 103(a)	Pinto, Wei, Rudnic, and FDA Dissolution Guidance

II. ANALYSIS

A. Claim Construction

In an *inter partes* review, the Board interprets claim terms in an unexpired patent according to the broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016) (affirming applicability of broadest reasonable construction standard to *inter partes* review proceedings). Under that standard, and absent any special definitions, we give claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention, in the context of the entire disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

We determine that no explicit construction of any claim term is necessary to determine whether to institute a trial in this case. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) ("[W]e need only construe terms 'that are in controversy, and only 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))).

B. Discretion Whether to Institute Under 35 U.S.C. § 325(d)

Section 325(d) provides: "[i]n determining whether to institute . . . a proceeding . . . , the Director may take into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the Office." Thus, before we decide whether we should exercise our discretion to deny institution for one or more grounds, we first must determine whether any of the grounds asserted in this Petition present the "same or substantially the same prior art or arguments" as those previously presented to the Office.

1. Patent Owner's Contentions

Patent Owner contends that we should exercise our discretion to deny institution on all grounds because "Petitioner relies on the same or substantially the same references applied by the Examiner during prosecution." Prelim. Resp. 15, 21. Specifically, Patent Owner asserts that "the portions of Wei relied upon by Petitioner are ***identical*** to the portions of Wei that were cited by the Examiner" and that "the portions of the Carreiro reference and [Pinto] asserted in the Grounds are cumulative to the Nause[1] reference cited by the Examiner for substantially the ***same*** information." *Id.* at 16, 19.

Regarding Petitioner's reliance on Rudnic and FDA Dissolution Guidance in the Grounds set forth in the Petition, Patent Owner contends that these references

[1] Ex. 2011, Nause, Richard G., U.S. Patent Application Publication No. 2012/0087978 A1, published Apr. 12, 2012 ("Nause").

> add nothing new. The Examiner relied on Nause for the ***same*** material allegedly taught by Rudnic, which is only cited for certain dependent claims. As for the FDA Dissolution Guidance, the Petition uses it to describe information ancillary to the reasons for allowance.

Id. at 16, 22–23.

Lastly, Patent Owner contends that the Park Declaration "largely parrots the Petition" and "contains no new analysis or anything above the attorney argument presented in the Petition." *Id.* at 16.

2. Summary of Relevant Prosecution History

During prosecution of the '945 patent, the examiner rejected the claims as being unpatentable as obvious over the combination of Nause and Wei. Ex. 1003, 397–98 (Non-Final Office Action mailed Aug. 13, 2015). Subsequently, applicants initiated an interview with the examiner and the examiner entered an Applicant-Initiated Interview Summary (Sept. 17, 2015), where the examiner stated the following:

> Applicants discussed different properties observed with claimed invention, including dissolution rate, and stated . . . one skilled in the art would not have expected particle size to have made a difference in in vivo data, since apixaban is a BCS Class III drug (highly soluble)[.] *Applicants stated the dosage form of Nause is directed controlled release, while the claimed invention is directed to immediate release*, noting dissolution property recited in [now independent claim 1]. Applicants discussed [that] Wei is directed to making specific polymorphs, rather than therapeutic properties of apixaban.

Id. at 438 (emphasis added).[2]

After the interview, applicants entered an amendment and traversed the rejection set forth in the Non-Final Office Action mailed Aug. 13, 2015. *Id.* at 456–74 (Amendment entered Nov. 30, 2015). In that Amendment, applicants distinguished Nause from the claimed subject matter on the basis that Nause is directed to controlled release dosage forms, which is "differen[t] from a composition of the present invention, as is evident from, for example, the rate of dissolution recited in [the claims]." *Id.* at 465; *see also id.* at 466–67 (further distinguishing the dissolution rate of the controlled release dosage forms disclosed in Nause from the claimed dosage forms).

Next, the examiner issued a Notice of Allowance (mailed Mar. 4, 2016). *Id.* at 492–499. In that paper, the examiner stated the following reasons for allowance:

> Applicant's data in the specification demonstrates the criticality of the particular size range claimed, wherein the crystalline apixaban particles have a D90 equal to or less than about 89 μm, and the resulting dissolution property, wherein at least 77wt% of apixaban dissolves within 30 minutes in a pH 6.8 phosphate buffer containing 0.05% sodium lauryl sulfate, for establishing bioequivalence of solid apixaban formulations with a solution (see paragraphs [0035]–[0038] of the specification). *It is also noted that Nause teaches 'controlled release' formulations of apixaban, which Nause distinguishes from 'immediate release'*

[2] We note that Patent Owner contends that apixaban was known as a BCS Class III drug, but provides insufficient evidence to support this position. Prelim. Resp. 7, 9.

> *formulations having similar dissolution rates to those of the claimed invention* (see Nause, paragraph [0032]).

Id. at 497–498 (emphasis added).

3. Analysis

Having considered Patent Owner's arguments and the prosecution history of the '945 patent, we are not persuaded to exercise our discretion under § 325(d) to deny the Petition. We agree with Patent Owner that Wei was considered and relied on by the examiner during prosecution, however, we are not persuaded that Carreiro and Pinto are cumulative of Nause. As noted during prosecution, Nause is limited to controlled release dosage forms having a specific dissolution profile. Ex. 2011 ¶ 32. In contrast, the dosage forms disclosed in Carreiro and Pinto do not appear to be limited to controlled release dosage forms. While we acknowledge that Pinto is cited in the '945 patent, we note that the examiner did not raise any ground of rejection involving the combination of Pinto and Wei, and thus, it is unclear whether this combination of references was fully evaluated by the examiner.

In addition, Carreiro, FDA Dissolution Guidance, and Rudnic were not cited by the Examiner during prosecution and none are cited on the face of the patent. FDA Dissolution Guidance, for example, discloses routine tests for dissolution testing that are specifically relevant to the claim elements added during prosecution to overcome the examiner's rejection over Nause and Wei. In this regard, we do not agree with Patent Owner that FDA Dissolution Guidance merely provides "information ancillary to the reasons for allowance." Prelim. Resp. 16.

Thus, with the exception of Wei, it is unclear to the extent that the examiner considered the subject matter disclosed in any of Carreiro, Pinto, FDA Dissolution Guidance, and Rudnic and relied upon by Petitioner in Grounds 1–4 of the Petition. Accordingly, based on our evaluation of the entirety of the record before us, we are unable to determine that any of the grounds asserted in this Petition present the "same or substantially the same prior art or arguments" as those previously presented to the Office.

C. Whether to Institute Based on Information Presented in the Petition

1. Summary of Asserted Prior Art

a. Carreiro

Carreiro is a "review article discuss[ing] the discovery, pharmacokinetics, attributes, and current clinical trials of [apixaban]." Ex. 1004, Abstract. Carreiro discloses apixaban as "a potent, selective, reversible, and orally bioavailable FXa inhibitor that demonstrates antithrombotic efficacy with a favorable pharmacokinetic profile." *Id.* at 1938.

Carreiro further discloses the results of the APROPOS Phase II trial, examining the efficacy of apixaban in preventing deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing total knee replacements (TKR). *Id.* at 1941. Carreiro teaches that "the optimal dose of apixaban was determined to be either 2.5 mg twice daily or 5 mg once daily, both of which had a promising benefit–risk profile compared with the current standards of care following TKR." *Id.*

Carreiro also discloses that "[a]pixaban has no ionizable groups and therefore does not exhibit pH-dependent aqueous solubility," which

Petitioner contends is an indication to a person of ordinary skill in the art the drug would have had poor solubility. *Id.* at 1940; Ex. 1002 ¶¶ 120, 163, 173.

b. Pinto

Pinto discloses a class of compound inhibitors of trypsin-like serine protease enzymes, especially Factor Xa, useful for the prevention and treatment of thromboembolic diseases. Ex. 1005, Abstract, 1:19–22. Pinto discloses that the compounds of the invention can be administered in oral dosage forms, including tablets or capsules. *Id.* at 154:65–155:3. Pinto further provides that the daily oral dosage of the compounds of the invention "will range between about 0.001 to 1000 mg/kg of body weight, preferably between about 0.01 to 100 mg/kg of body weight per day, and most preferably between about 1.0 to 20 mg/kg/day." *Id.* at 155:23–28.

Pinto identifies apixaban ("1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxo-l-piperidinyl) phenyl-4,5,6,7-tetrahydro-1H-pyrazole-[3,4-c] pyridine-3-carboxamide") as a member of the disclosed class of compounds. *Id.* at 269:1–6 (claim 13). Pinto discloses a pharmaceutical comprising apixaban (*id.* at 270:5–9 (claim 27)) and further discloses apixaban in crystalline form (*id.* at Certificate of Correction, page 11 (claim 104)).

c. Wei

Wei discloses "a process or apparatus for transforming a first polymorph of a chemical material into a second polymorph of the same chemical material." Ex. 1008, Abstract. Wei discloses that "[i]t is well known in the pharmaceutical industry that the bioavailability of a sparingly

soluble organic compound is often enhanced when the compound is very pure and the molecules of the compound have a small, uniform particle size, high surface area, and short dissolution time." *Id.* ¶ 3. Thus, one object of the process of Wei is to "provide crystalline particles of high surface area, high chemical purity, and high stability, without the need for post-crystallization milling." *Id.* ¶ 5.

Wei discloses that "the present invention can be especially effective for transforming a first polymorph which consists of large crystals into a second polymorph which consists of small crystals." *Id.* ¶ 20. Large and small crystals are described as follows:

> Generally, large crystals have a particle size D[90] greater than about 100 μm, and small crystals have a particle size D[90] less than about 30 μm. In addition, large crystals can have a particle size D[90] greater than about 60 μm, and small crystals can have a particle size D[90] less than about 50 μm.

Id.

Example 1 of Wei discloses the preparation of small crystals of apixaban (1-(4-methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidine-1-yl)phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide). *Id.* ¶ 41. In Example 1, Wei produces "small, granular crystals which have a particle size $D_{[90]}$ less than about 20 μm." *Id.* ¶ 42.

d. FDA Dissolution Guidance

The FDA Dissolution Guidance was prepared by the Immediate Release Expert Working Group of the Biopharmaceutics Coordinating Committee in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration and is an industry guidance document

> developed for immediate release (IR) dosage forms and is intended to provide (1) general recommendations for dissolution testing; (2) approaches for setting dissolution specifications related to the biopharmaceutic characteristics of the drug substance; (3) statistical methods for comparing dissolution profiles; and (4) a process to help determine when dissolution testing is sufficient to grant a waiver for an in vivo bioequivalence study.

Ex. 1015, 1.

FDA Dissolution Guidance discloses the Biopharmaceutics Classification System, which classifies drugs into 4 categories based on drug solubility and permeability, as follows:

Case 1: High Solubility - High Permeability Drugs

Case 2: Low Solubility - High Permeability Drugs

Case 3: High Solubility - Low Permeability Drugs

Case 4: Low Solubility - Low Permeability Drugs

Id. at 2–3.

FDA Dissolution Guidance discloses that a drug substance is considered to be highly soluble under the BCS when the dose/solubility volume of solution are less than or equal to 250 mL. *Id.* A drug substance is considered to be highly permeable with an extent of absorption that is greater than 90% in the absence of documented instability in the GI tract or those whose permeability have been determined experimentally. *Id.*

FDA Dissolution Guidance provides the following guidance with regard to Case 2 and Case 3 drugs:

> In the case of low solubility/high permeability drugs (case 2), drug dissolution may be the rate limiting step for drug absorption and an IVIVC may be expected. A dissolution profile in multiple

> media is recommended for drug products in this category. In the case of high solubility/low permeability drugs (case 3), permeability is the rate controlling step and a limited IVIVC may be possible, depending on the relative rates of dissolution and intestinal transit.

Id. at 3. FDA Dissolution Guidance further provides that "for high solubility, high permeability (case 1) drugs and in some instances for high solubility, low permeability (case 3) drugs, 85% dissolution in 0.1N HCl in 15 minutes can ensure that the bioavailability of the drug is not limited by dissolution." *Id.*

2. Petitioner's Ground 1: Obviousness over the Combination of Carreiro, Wei, and FDA Dissolution Guidance

Petitioner asserts that claims 1–38 are unpatentable under § 103 as obvious over the combination of Carreiro, Wei, and FDA Dissolution Guidance. Pet. 33–40. In support of its assertion that the combination of Carreiro, Wei, and FDA Dissolution Guidance renders claims 1–38 obvious, Petitioner sets forth the foregoing teachings of Carreiro, Wei, and FDA Dissolution Guidance and provides a detailed discussion explaining how each claim limitation is disclosed in the combination of references. *Id.*

For the elements of independent claim 1, Petitioner contends that Carreiro discloses the development of oral dosage forms of apixaban for treatment and prophylaxis of thromboembolic disorders, and therefore, a person of ordinary skill in the art would have been motivated to optimize known oral apixaban dosages based on clinical results. Pet. 34–35 (citing Ex. 1002 ¶¶ 160–62); *see also* Ex. 1004, 1940 (apixaban shows a "pharmacokinetic profile . . . consistent with rapid oral absorption and

bioavailability"). Also, on this issue, Dr. Park states that optimal dissolution is important for drugs like apixaban because "the drug is being developed for treating thromboembolic disorders and events, which often require immediate action of the drug to help treat or prevent clotting in an emergency situation." Ex. 1002 ¶¶ 161–62.

Emphasizing apixaban's solubility profile, Petitioner contends that a person of ordinary skill in the art would have understood that the drug's poor solubility "could pose a challenge to developing a bioavailable oral pharmaceutical dosage formulation, and would thus be motivated to improve the dissolution rate of apixaban." Pet. 36. Petitioner contends also that

> a POSA, in view of the potential clinical usefulness of an oral dosage form of apixaban as disclosed by Carreiro, and the solubility and dissolution issues associated with apixaban as disclosed by Wei, would have been motivated to optimize the *solubility and dissolution* of apixaban by reducing the crystalline apixaban's particle size as taught by Wei to provide a quick-acting immediate release formulation of apixaban with increased solubility, and consequently, better *dissolution* and bioavailability.

Id. (emphasis added). Such a desire to improve the dissolution rate of apixaban would have lead a person of ordinary skill in the art "to apply the Wei process to the oral dosage forms being clinically tested as disclosed by Carreiro to optimize a smaller particle size, such as the crystalline apixaban, form N-1 disclosed in the examples of Wei." *Id.* at 40–41 (citing Ex. 1008 ¶¶ 6–8, 20, 41–46; Ex. 1002 ¶ 173). Petitioner further contends that, "in an effort to improve dissolution and solubility, and consequently, the bioavailability of apixaban . . . a POSA would seek to apply the Wei process

to the oral dosage forms being clinically tested as disclosed by Carreiro." *Id.* at 40.

To support its argument that apixaban was known to be poorly soluble, Petitioner relies on Wei and contends that Wei discloses apixaban as an example of a "sparingly soluble" molecule and that the bioavailability of a "sparingly soluble organic compound is often enhanced when the compound is very pure and the molecules of the compound have a *small*, uniform particle size, high surface area, and short dissolution time." *Id.* at 26 (emphasis added) (citing Ex. 1008 ¶¶ 3, 41–46). *See also id.* at 36 (citing Ex. 1002 ¶¶ 26, 135, 163–164, 173, 176); Ex. 1008 ¶ 20 (defining "small crystals" as having a D_{90} of less than 30 μm). Petitioner further contends that Carreiro's disclosure that apixaban has no ionizable groups and therefore does not exhibit pH-dependent aqueous solubility would inform a person of ordinary skill in the art that "the drug may have poor solubility." Pet. 35–36 (citing Ex. 1004, 1940; Ex. 1002, ¶¶ 120, 163, 173; Ex. 1011, 252).

Thus, Petitioner contends that a person of ordinary skill in the art would have sought to optimize or improve the dissolution rate of apixaban due to the drug's solubility profile. *Id.* at 35–36. In this regard, Petitioner further contends that, "[t]o test the optimization of the dissolution and solubility of the apixaban formulation, a POSA would have consulted the published FDA guidance, including the FDA Dissolution Guidance, which teaches the use of routine dissolution testing." *Id.* at 55; Ex. 1015, A-1.

Furthermore, in its discussion of the reasonable expectation of success, Petitioner contends as follows:

> The general state of the art during the time frame leading up to the priority date of the '945 patent made clear to a POSA that two of the most common ways for improving solubility of a drug were: (1) to decrease the particle size of the drug; and (2) add a surfactant. Therefore, the prior art provided a POSA seeking to develop an immediate release apixaban formulation with a reasonable expectation of success that a reduction in particle size, along with the addition of a surfactant, would result in increased dissolution and solubility, and consequently, bioavailability. (*See* Exs. 1009 and 1010; Ex. 1002, ¶¶ 166–170, 226, 264.)
>
> . . . .
>
> Finally, a POSA seeking FDA approval for an immediate release formulation would look to known industry standard dissolution methods, including the FDA Guidance for recommendations on the routine equipment and methods for dissolution testing and follow those recommendations. (*See generally* Ex. 1015; Ex. 1002, ¶¶ 154, 161, 170.) As discussed below, the FDA Guidance teaches to a POSA each of the claim limitations for dissolution testing. (*Id*.)

Pet. 37–39.

Petitioner contends that "FDA Dissolution Guidance recommends that for sparingly soluble drugs, such as apixaban, sodium lauryl sulfate should be used in the dissolution medium." *Id.* at 43 (citing Ex. 1015, A-1).

Petitioner contends that "a POSA would also understand that the 77% wt dissolution after 30 minutes to be the inherent result of the claimed 'crystalline apixaban particles' from a well-known and routine dissolution test." *Id.* (citing Ex. 1002 ¶¶ 178–180 ("[T]he percent of apixaban dissolved in the dissolution medium chosen after a certain period of time is an inherent characteristic of the drug itself.")). Thus, to meet the 77% wt dissolution after 30 minutes element of claim 1, Petitioner contends that "nothing more

is required to achieve this dissolution profile than having apixaban with particle sizes as recited in the claims." *Id.*

Independent claim 12 contains the same limitations as claim 1, but recites alternative dissolution test parameters, as follows: "wherein, as measured using a USP Apparatus 2 at a paddle rotation speed of 75 rpm in 900 mL, of a dissolution medium at 37° C., at least 77 wt % of apixaban in the pharmaceutical composition dissolves within 30 minutes in the dissolution medium, and the dissolution medium is 0.05 M sodium phosphate at a pH 6.8 containing 0.05% sodium lauryl sulfate." Ex. 1001, 10:21–27. For this claim element, Petitioner contends as follows:

> [A] POSA would have been motivated to look to the FDA's guidance on routine dissolution testing provided in the FDA Dissolution Guidance. (Ex. 1015.) The FDA Dissolution Guidance teaches that the most commonly employed dissolution test methods are (1) the basket method (Apparatus 1); and (2) the paddle method (Apparatus 2), which should be used unless shown to be unsatisfactory. (*Id*., A-1.) As the paddle method recommended by the FDA Dissolution Guidance is the same as that in claim 12, a POSA would consider claim 12 to be obvious for the same reasons as claim 1.

Pet. 45.

3. Petitioner's Ground 2: Obviousness over the Combination of Carreiro, Wei, Rudnic, and FDA Dissolution Guidance

For substantially similar reasons, Petitioner contends that claims 1–38 are unpatentable under § 103 as obvious in view of the combination of Carreiro, Wei, Rudnic, and FDA Dissolution Guidance. Pet. 49–54. For this ground, Petitioner adds Rudnic because the reference allegedly provides "additional motivation to a POSA to utilize the common lubricant and

surfactant sodium lauryl sulfate in the claimed formulation at the claimed concentrations," which is allegedly relevant to challenged claims 7, 8, 18, and 19. *Id.* at 49–50. In particular, Petitioner contends that

> Rudnic discloses the design and formulation of compressed tablets for oral dosage, and teaches use of the well-known surfactant sodium lauryl sulfate as a lubricant and a wetting agent to improve solubility. (Ex. 1010, 354-355, 30; Ex. 1002, ¶169.) Accordingly, a POSA would have a reasonable expectation of success that the combination of prior art references discussed herein would result in a crystalline apixaban formulation with an increased solubility and dissolution properties as claimed in the '945 patent. (Ex. 1002, ¶¶166-171.)

Id. at 38.

4. Petitioner's Ground 3: Obviousness over the Combination of Pinto, Wei, and FDA Dissolution Guidance

Ground 3 is substantially similar to Ground 1. For this ground, Petitioner substitutes Pinto for Carreiro for, *inter alia*, its disclosure of oral dosage forms of Factor Xa inhibitors, including apixaban. Pet. 52–54. In particular, Petitioner contends as follows:

> Claim 13 of [Pinto] recites apixaban by its known chemical name. (Ex. 1007, 269:1-6.) Claim 27 depends from claim 13 and claims a pharmaceutical composition comprising a therapeutically effective amount of apixaban and a pharmaceutically acceptable carrier. (*Id.*, 270:5-9.) [Pinto] further discloses that the compounds disclosed therein, including apixaban, could be administered in oral dosage forms such as tablets and capsules. (*Id.*, 154:65-155:3.) Claim 104 also depends from claim 13 adding the limitation that the "compound according to claim 13 is a crystalline compound." (*Id.*, 276:31.)

> Thus, [Pinto] clearly contemplated formulating crystalline apixaban, disclosing both tablet and capsule formulations that included apixaban and an inert carrier.

Pet. 53–54.

As in Ground 1, Petitioner relies on Wei for its disclosure that "apixaban is a sparingly soluble molecule, and that the bioavailability of such a compound can be increased by decreasing the particle size, resulting in very pure molecules of the compound with a small, uniform particle size, high surface area, and short dissolution time." *Id.* at 52–53 (citing Ex. 1008 ¶¶ 3, 41–46). Petitioner contends that

> a POSA seeking FDA approval for an immediate release formulation would look to the FDA Dissolution Guidance for recommendations on the equipment and methods for routine dissolution testing and follow such recommendations as being industry standard. (*See generally* Ex. 1015, A-1; Ex, 1002, ¶260.) Once that routine dissolution testing was conducted, a POSA would immediately appreciate the improved release characteristics of such a formulation with a uniform population of small apixaban particles, that would satisfy the inherent release rate (77 wt.% in 30 minutes achieved by that formulation.)

Id. at 53.

> Lastly, relying on the testimony of Dr. Park, Petitioner contends that
>
> a formulator is always striving to maximize the dissolution kinetics when developing an immediate release formulation, such as for apixaban, a POSA would turn to Wei to optimize the apixaban formulations of [Pinto] and use the working examples to make small, granular particles of apixaban polymorphic form N-1 having a D90 of less than 20 μm that would improve solubility and dissolution, and hence bioavailability. (*See, e.g.*, Ex. 1008, ¶¶[0041]–[0046]; Ex. 1002, ¶¶ 265–266.)

Id. at 54.

5. Petitioner's Ground 4: Obviousness over the Combination of Pinto, Wei, Rudnic, and FDA Dissolution Guidance

For substantially similar reasons set for in Ground 3, Petitioner contends that claims 1–38 are unpatentable under § 103 as obvious in view of the combination of Pinto, Wei, Rudnic, and FDA Dissolution Guidance. Pet. 59–61. For this ground, Petitioner adds Rudnic because the reference allegedly provides "additional motivation to utilize the common lubricant and surfactant sodium lauryl sulfate in the claimed formulation," which is allegedly relevant to challenged claims 7, 8, 18, and 19. *Id.* at 59. In particular, Petitioner contends that "a POSA would know that the surfactant sodium lauryl sulfate is commonly included in oral dosage forms at 1–4% as a lubricant that 'ha[s] been used in tablets containing very poorly soluble drugs to enhance their rate of dissolution.'" *Id.* at 60 (citing Ex. 1010, 354–555, 359).

6. Patent Owner's Contentions

Patent Owner sets forth several arguments to support its position that Petitioner fails to establish a reasonable likelihood that challenged claims 1–38 of the '945 patent would have been obvious over any combination of the references asserted in the grounds of the Petition. Prelim. Resp. 32–40. Specifically, Patent Owner contends Petitioner's grounds are flawed because "[a]ll four grounds in the Petition rely on the argument that a person of ordinary skill would be motivated to decrease apixaban's particle size to increase its solubility and dissolution rate, thus improving its bioavailability." *Id.* at 32.

First, Patent Owner contends that Petitioner's arguments are flawed because they depend on the general assumption that low solubility equates to low bioavailability, but Petitioner does not establish that this assumption applies to apixaban. *Id.* at 32–36. Patent Owner contends that Petitioner's evidence does not even establish that apixaban had poor solubility. *Id.* at 36–38. In particular, Patent Owner contends that Carreiro's description of apixaban as non-ionizable does not provide evidence that apixaban has poor solubility. *Id.* at 36. According to Patent Owner, Carreiro states, apixaban "does not exhibit pH-dependent aqueous solubility," which Patent Owner argues simply means apixaban's solubility remains the same across all aqueous pH values and is not a measure of low solubility. *Id.* (quoting Ex. 1004, 1940 (emphasis omitted). Patent Owner also argues that Wei never states that apixaban has low bioavailability, but that Wei's use of the phrase "sparingly soluble" is used in the background section of the document to set forth general principles. *Id.* at 37 (citing Ex. 1008 ¶ 3).

Second, Patent Owner contends that Petitioner's arguments are flawed because they depend on the general assumption that low solubility equates to low bioavailability and that increasing the dissolution rate of a compound increases its bioavailability. *Id.* at 32–36. Patent Owner contends that the record shows that "reducing particle size to increase dissolution rate can increase bioavailability when the bioavailability of a drug *is limited by* the dissolution rate," however, "Petitioner fails to provide any evidence that a person of ordinary skill would have expected that apixaban's bioavailability was limited by its dissolution rate." *Id.* at 39 (citing Ex. 1009, 288; Ex. 1010, 335).

Patent Owner concludes with the following:

> Given that both critical assumptions—that low solubility compounds have low bioavailability and that increasing the dissolution rate increases bioavailability—are flawed, Petitioner's evidence cannot support its motivation to modify the prior art and reduce the particle size of apixaban.

Id. at 40.

7. Discussion

Independent claims 1 and 12 are directed to solid pharmaceutical compositions comprising crystalline apixaban particles having a D_{90} equal to or less than about 89 μm. Ex. 1001, 9:49–57; 10:13–27. The claims further recite that the apixaban present in the recited pharmaceutical compositions achieve certain dissolution rate parameters. *Id.*

The parties do not dispute that either Carreiro or Pinto disclose solid pharmaceutical compositions comprising apixaban. The parties do not dispute that Wei discloses small crystalline apixaban particles having a D_{90} of less than 20 μm. The parties do not dispute that FDA Dissolution Guidance discloses methods of routine dissolution testing. Rather, the dispute between the parties is whether a person of ordinary skill in the art would have combined the teachings of Carreiro or Pinto with the teachings of Wei to achieve a solid pharmaceutical composition comprising crystalline apixaban particles having a D_{90} equal to or less than about 89 μm with a reasonable expectation of success. Pet. 33–39, 51–53; Prelim. Resp. 34–40.

Upon consideration of the respective arguments presented and evidence of record, we find that Petitioner has offered sufficient evidence to institute trial, and Patent Owner's arguments do not persuade us that we

should decline to go forward with a trial. It is well settled that "where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Applied Materials, Inc.*, 692 F.3d 1289, 1295 (Fed. Cir. 2012) (quoting *In re Aller*, 220 F.2d 454, 456 (CCPA 1955). "This rule is limited to cases in which the optimized variable is a 'result-effective variable.'" *Id.* (citing *In re Antonie*, 559 F.2d 618, 620 (CCPA 1977)). Here, the current record shows that the general conditions of at least the challenged independent claims are disclosed in the prior art. In particular, the current record shows that solid oral dosage forms of apixaban were known (Ex. 1004; Ex. 1007), that a method for producing small crystals ($D_{90} < 20$ μm) of apixaban was known (Ex. 1008 ¶ 42), and that crystal particle size of a drug can be modified to potentially improve the bioavailability of that drug (Ex. 1008 ¶¶ 3, 20; Ex. 1002 ¶¶ 167–170).

We are persuaded by Patent Owner's arguments that Petitioner has not established that apixaban's lack of ionizable groups equates to poor solubility. Prelim. Resp. 35. Although we agree with Patent Owner that Wei does not expressly disclose apixaban as a "sparingly soluble" compound (*id.* at 37–38), we do find that Wei implies that apixaban is such a compound. Furthermore, regardless of what Wei suggests to a person of ordinary skill in the art about the solubility of apixaban, we find that Wei provides adequate motivation to a person of ordinary skill in the art to

produce small crystals[3] of apixaban. Wei discloses that reducing the particles of a drug to small crystals can improve the bioavailability of a drug and then discloses the production of small crystals of apixaban as the example provided in the reference. Ex. 1008 ¶¶ 3, 20, 42.

We further note that none of the cited references disclose dissolution tests of solid pharmaceutical compositions achieving the recited dissolution rate parameters specific for apixaban. Here, we adopt Petitioner's position that a person of ordinary skill in the art would understand that the dissolution rate of apixaban present in a pharmaceutical composition is an inherent characteristic of the drug itself. Pet. 43, 45, 53; Ex. 1002 ¶¶ 178–180, 227, 260, 267–268, 301, 335; *see also Allergan Inc. v. Sandoz, Inc*., 726 F.3d 1286, 1294 n. 1 (Fed. Cir. 2013) (suggesting that where the evidence establishes a claimed limitation is the necessary result or inherent property of a claimed administration it does not render an otherwise obvious claim nonobvious); *In re Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011) (finding an inherent property of a compound used in a claimed method did not render the obvious claimed method nonobvious even though the property was unknown in the prior art).

Accordingly, we determine that Petitioner has shown that there is a reasonable likelihood that it would prevail with regard to establishing that claims 1 and 12 would have been unpatentable as obvious over the

[3] Wei defines small crystals as having a D_{90} of less than 50 μm. Ex. 1008 ¶ 20.

combined teachings of the references relied upon by Petitioner in any one of Grounds 1 to 4 as presented in the Petition.

D. Status of Asserted Prior Art as Printed Publications

"A petitioner in an *inter partes* review may request to cancel as unpatentable 1 or more claims of a patent only on a ground that could be raised under section 102 or 103 and *only on the basis of prior art consisting of patents or printed publications*." 35 U.S.C. § 311(b) (emphasis added); *see also* 37 C.F.R. § 42.104(b)(2). A petitioner has the burden to establish in its petition a reasonable likelihood of showing that any asserted prior art is a "printed publication" within the meaning of 35 U.S.C. §§ 102 and 311(b). 35 U.S.C. § 314(a); *In re Wyer*, 655 F.2d 221, 227 (C.C.P.A. 1981) ("[W]hether information is printed, handwritten, or on microfilm or a magnetic disc or tape, etc., *the one who wishes to characterize the information, in whatever form it may be, as a 'printed publication' . . .* should produce sufficient proof of its dissemination or that it has otherwise been available and accessible to persons concerned with the art to which the document relates and thus most likely to avail themselves of its contents." (emphasis added)).

"A reference will be considered publicly accessible if it was 'disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence, can locate it.'" *Blue Calypso, LLC v. Groupon, Inc.*, 815 F.3d 1331, 1348 (Fed. Cir. 2016) (quoting *Kyocera Wireless Corp. v. Int'l Trade Comm'n*, 545 F.3d 1340, 1350 (Fed. Cir. 2008)). The status of a reference as a printed publication is a legal conclusion "based on underlying

factual determinations." *Id.* (citing *In re Lister*, 538 F.3d 1307, 1311 (Fed. Cir. 2009)).

Petitioner acknowledges that "[t]he '945 patent issued May 3, 2016, and claims priority back through a series of applications dating to February 25, 2010." Pet. 8 (citing Ex. 1001). Petitioner challenges the earliest effective filing date for certain claims, but contends that "the Board need not address the priority date on a claim-by-claim basis because all prior art references relied on in Grounds 1–4 qualify as prior art under the earliest possible priority date." *Id.* at 9. Specifically, Petitioner contends that "Carreiro, . . . Rudnic and FDA Dissolution Guidance are all prior art references under pre-AIA 35 U.S.C. § 102(b)." Pet. 49.

Patent Owner contends that Petitioner has not met its burden of production to establish that Carreiro, FDA Dissolution Guidance, and Rudnic are "printed publications" under 35 U.S.C. §102(b). Prelim. Resp. 42. We consider Patent Owner's contention with regard to each of these references in the following.

1. Carreiro

Patent Owner contends:

> Exhibit 1004 bears no library stamp and the face of the exhibit identifies that it was downloaded from the internet in August 2017, i.e., more than seven years after the priority date. Ex. 1004, Carreiro at 1.
>
> While the Exhibit has a copyright date of 2008, that alone is not enough to establish that the document is a "printed publication."

Id. at 44. Patent Owner further contends that the copyright notice, which appears as a watermark on the first pages of Ex. 1004, expressly states that the document is for "Authorised users" and is "Not for Commercial Use or Commercial Distribution," thereby suggesting that any availability of the document was limited. *Id.* at 45.

As presented by Petitioner, Carreiro is a paper titled "*Apixaban, an oral direct Factor Xa inhibitor: awaiting the verdict*." Ex. 1004, 1. The identified authors are Jennifer Carreiro and Jack Ansell. *Id*. The cover page shows a copyright notice of 2008, which identifies the publisher as Inform UK Ltd. The cover page also provides an ISSN[4] number and provides the following citation: "*Expert Opin. Investig. Drugs (2008) 17(12):1937–1945*." Each of the remaining pages of Carreiro provide the following citation: "*Expert Opin. Investig. Drugs* (2008) **17**(12)."

We weigh the evidence presented by the parties to determine that, on this record, it is reasonably likely that Carreiro is a printed publication. First, we note that a copyright notice is some evidence of publication.[5] Second, Carreiro appears to have been published by an established publisher, and thus, there is no reason to suspect that it would not have been publicly available to one skilled in the art absent evidence to the contrary. *See Coriant (USA) Inc. v. Oyster Optics, LLC*, IPR2018-00258, slip op. at 11

[4] International Standard Serial Number.

[5] "[A] notice of copyright . . . *may be placed on publicly distributed copies* from which the work can be visually perceived . . . ." 17 U.S.C. § 401(a) (emphasis added).

(PTAB June 6, 2018) (Paper 13) ("For established publishers, demonstrating a date of publication is alone sufficient for showing accessibility to the public."). We also note that the record is absent any evidence supporting a position that Carreiro was not published. *See In re Hall*, 781 F.2d 897, 899 (Fed. Cir. 1986) (considering the absence of "rebuttal evidence" in determining whether a document was public accessibility); *see also Giora George Angres, Ltd. v. Tinny Beauty & Figure, Inc*., 1997 WL 355479, at *7 (Fed. Cir. June 26, 1997) (unpublished) (finding "no reason to suspect that [a reference published by an established publisher] was not publicly available, including to one skilled in the art" when "no evidence was presented that it was not").

Third, we are not persuaded by Patent Owner's argument that Carreiro's copyright notice suggests that "any availability of the document was limited." Patent Owner does not explain how "limited availability" of a document would impact our analysis of what would constitute sufficient accessibility to interested persons exercising reasonable diligence.

Consequently, on this record, we are persuaded that Petitioner has provided sufficient evidence to demonstrate a reasonable likelihood that Carreiro is a printed publication.

2. FDA Dissolution Guidance

Patent Owner contends that the "Petition does not include any evidence supporting Exhibit 1015's status as a printed publication beyond the document itself." Prelim. Resp. 43.

As presented by Petitioner, FDA Dissolution Guidance is a paper titled "*Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms*." Ex. 1015. The paper states:

> This guidance has been prepared by the Immediate Release Expert Working Group of the Biopharmaceutics Coordinating Committee in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on the dissolution testing of immediate release solid oral dosage forms. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public.

Id. at 1 n1. The paper is dated August 1997 and provides that additional copies are available from the "Office of Training and Communications" and provides relevant contact information, which includes an address, phone number, and URL directing the reader to a FDA webpage.

We weigh the evidence of record and determine that, based on the evidence of record at this stage, it is reasonably likely that FDA Dissolution Guidance was publically accessible before the priority date of the '945 patent (February 25, 2010). The information contained in the document, summarized above, indicates that FDA Dissolution Guidance is an industry guidance document distributed by a government agency beginning in August 1997.

This determination on the sufficiency of Petitioner's evidence is for purposes of this Decision only, and does not signify that Petitioner's evidence would be adequate under the preponderance standard applicable at the Final Written Decision stage. 35 U.S.C. § 316(e); *see also TriVascular, Inc. v. Samuels*, 812 F.3d 1056, 1068 (Fed. Cir. 2016) ("[T]he Board is not

bound by any findings made in its Institution Decision. At that point, the Board is considering the matter preliminarily without the benefit of a full record. The Board is free to change its view of the merits after further development of the record, and should do so if convinced its initial inclinations were wrong."). Patent Owner's criticisms of FDA Dissolution Guidance may have merit, and the parties may further develop the evidentiary record during the course of trial on the issue of whether and when FDA Dissolution Guidance became publicly accessible. *See Genzyme Therapeutic Prods. Ltd. P'ship v. Biomarin Pharma. Inc.*, 825 F.3d 1360, 1367 (Fed. Cir. 2016) ("The purpose of the trial in an *inter partes* review proceeding is to give the parties an opportunity to build a record by introducing evidence—not simply to weigh evidence of which the Board is already aware."). However, at this stage, we need only decide whether Petitioner has shown a reasonable likelihood of prevailing in its challenge. 35 U.S.C. § 314.

3. Rudnic

As presented by Petitioner, Rudnic is Chapter 10 of the 4th edition of the book "Modern Pharmaceutics." Ex. 1010. The first 3 pages of Rudnic indicate that the text was published by the CRC Press, provides a copyright date of 2002, and provides an ISBN[6] number. *Id.*

Patent Owner contends that Rudnic "bears no library stamp and the face of the exhibit does not appear to be a photocopy of a hardcopy

[6] International Standard Book Number.

textbook." Prelim. Resp. 42. Patent Owner further contends that "the pages of the Exhibit purporting to be the Rudnic chapter (pages 4–30) include markings in the footer and headers of the document that are ***not*** on the first three pages of the Exhibit—suggesting that the document is an aggregate of multiple documents that was compiled by Petitioner." *Id.* at 42–43. Finally, Patent Owner provides the Table of Contents for the 2002 version of Rudnic (Ex. 2019) and contends that Chapter 10 of Rudnic begins on page 287, while Ex. 1010 shows that Chapter 10 begins on page 333.

We weigh the evidence presented by the parties and determine that Petitioner has presented sufficient evidence to persuaded us to proceed to trial. First, even if Patent Owner can show that Rudnic is not a printed publication, we are persuaded that Petitioner has established a reasonable likelihood that it will prevail with Grounds 1 and 3, which do not rely on Rudnic.

Second, although Patent Owner has provided information suggesting that the Chapter 10 that appears in Ex. 1010 may not be from the 2002 version of "Modern Pharmaceutics," the information provided is not dispositive on the issue because Patent Owner does not provide us with a copy of Chapter 10 that appears in its version of "Modern Pharmaceutics." We are therefore unable to make any comparison to reach a definitive conclusion on whether the information provided in Ex. 1010 was indeed published in 2002 or at some other time. Thus, the issue remains a factual dispute that may be resolved during trial. For example, after institution of trial, Petitioner will have an opportunity to address this subject, for example, by filing supplemental information to correct its citation, if appropriate.

37 C.F.R. § 42.123; *see also Genzyme*, 825 F.3d at 1367 ("The purpose of the trial in an *inter partes* review proceeding is to give the parties an opportunity to build a record by introducing evidence—not simply to weigh evidence of which the Board is already aware.").

III. CONCLUSION

After considering the evidence and arguments presented in the Petition and Preliminary Response, we determine that Petitioner has demonstrated a reasonable likelihood that it will succeed on at least one of its challenges to patentability. Under the Office's Guidance implementing *SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348 (2018): "[a]t this time, if the PTAB institutes a trial, the PTAB will institute on all challenges raised in the petition." Guidance on the Impact of *SAS* on AIA Trial Proceedings ("Guidance"), available at https://www.uspto.gov/patents-application-process/patent-trial-and-appeal-board/trials/guidance-impact-sas-aia-trial (April 26, 2018). Accordingly, we institute trial as to all claims and all grounds presented in the Petition.

At this preliminary stage in the proceeding, we have not made a final determination with respect to the patentability of any challenged claim or the construction of any claim term. Any findings of fact and conclusions of law made herein are not final, but are made for the sole purpose of determining whether Petitioner meets the threshold for initiating review. Any final decision shall be based on the full trial record, including any response timely filed by Patent Owner. Any arguments not raised by Patent Owner in a timely filed response shall be deemed waived, even if they were presented in the Preliminary Response.

IV. ORDER

Accordingly, it is

ORDERED that pursuant to 35 U.S.C. § 314(a), an *inter partes* review of claims 1–38 of U.S. Patent No. 9,326,945 B2 is instituted with respect to 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, *inter partes* review of the '945 patent shall commence on the entry date of this Order, and notice is hereby given of the institution of a trial.

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