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Paper No. 19
Entered: March 6, 2019

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

LUITPOLD PHARMACEUTICALS, INC.,
Petitioner,

v.

APICORE US LLC,
Patent Owner.

Case IPR2018-01640
Patent 9,353,050 B2

Before ZHENYU YANG, CHRISTOPHER G. PAULRAJ, and KRISTI L. R. SAWERT, *Administrative Patent Judges*.

SAWERT, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
35 U.S.C. § 314(a)

I. INTRODUCTION

Luitpold Pharmaceuticals, Inc. ("Petitioner") requests an *inter partes* review of claims 1–18 of U.S. Patent No. 9,353,050 B2 ("the '050 patent," Ex. 1001). Paper 2 ("Pet."). Apicore US LLC. ("Patent Owner") filed a Preliminary Response. Paper 6 ("Prelim. Resp."). Upon our authorization (Paper 12), Petitioner filed a Reply and Patent Owner filed a Sur-reply. Paper 15 ("Reply"); Paper 17 ("Sur-reply").

We have authority to determine whether to institute an *inter partes* review. 35 U.S.C. § 314(b); 37 C.F.R. § 42.4(a). We may not institute an *inter partes* review "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). On April 24, 2018, the Supreme Court held that a decision to institute under 35 U.S.C. § 314(b) may not institute review on fewer than all claims challenged in the petition. *SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, 1355–56 (2018). Moreover, in accordance with USPTO Guidance, "if the PTAB institutes a trial, the PTAB will institute on all challenges raised in the petition." *See Guidance on the Impact of SAS on AIA Trial Proceedings* (April 26, 2018) (available at https://www.uspto.gov/patents-application-process/patent-trial-and-appeal-board/trials/guidance-impact-sas-aia-trial).

Applying those standards, and upon consideration of the information presented in the Petition and the Preliminary Response, we determine that Petitioner has not demonstrated a reasonable likelihood of prevailing with respect to at least one claim of the '050 patent based on the unpatentability challenges presented in the Petition. Accordingly, we do not institute an *inter partes* review.

II. BACKGROUND

A. Related Matters

The ’050 patent was the subject of a civil action captioned *Mylan Institutional LLC v. Aurobindo Pharma Ltd.*, No. 2:16-cv-491 (E.D. Tex.). Paper 16, 2. The district court entered a preliminary injunction against defendant Aurobindo Pharma Limited based on the ’050 patent and two related patents, U.S. Patent No. 7,662,992 (“the ’992 patent”)[1] and U.S. Patent No. 8,969,616 (“the ’616 patent”).[2] *Mylan Institutional LLC v. Aurobindo Pharma Ltd.*, 2017 WL 497593 (E.D. Tex. Feb. 7, 2017) (“district court case”); *see also* Ex. 1032; Ex. 2006. The Court of Appeals for the Federal Circuit affirmed. *Mylan Institutional LLC v. Aurobindo Pharma Ltd.*, 857 F.3d 858 (Fed. Cir. 2017). On remand, the district court granted the parties’ joint motion to dismiss. Pet. 67.

Petitioner AuroMedics Pharma LLC filed a Petition for *inter partes* review of the ’050 patent, which was designed IPR2017-00762. On August 3, 2017, the Board terminated the proceedings before any decision on institution due to the parties’ settlement. *AuroMedics Pharma LLC v. Apicore US LLC*, IPR2017-00762, slip op. at 2 (PTAB Aug. 3, 2017) (Paper 18).

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[1] Ravishanker Kovi et al., U.S. Patent No. 7,662,992 B2 (Feb. 16, 2010). The ’992 patent claims a process of preparing isosulfan blue. Ex. 3002, 9:41–67.

[2] Ravishanker Kovi et al., U.S. Patent No. 8,969,616 B2 (Mar. 3, 2015). The ’616 patent claims a process of preparing isosulfan blue. Ex. 3003, 9:38–64.

According to Petitioner, the ’050 patent has been challenged in a civil action for declaratory judgment captioned *Beloteca, Inc. v. Apicore US LLC,* No. 19-cv-00360 (N.D. Ill. Jan. 17, 2019). Paper 16, 2.

According to Patent Owner, U.S. Patent Application No. 15/801,585 (“the ’585 application) claims priority to the ’050 patent, and U.S. Patent Application No. 16/170,510 claims priority to both the ’585 application and the ’050 patent. Paper 18, 2.

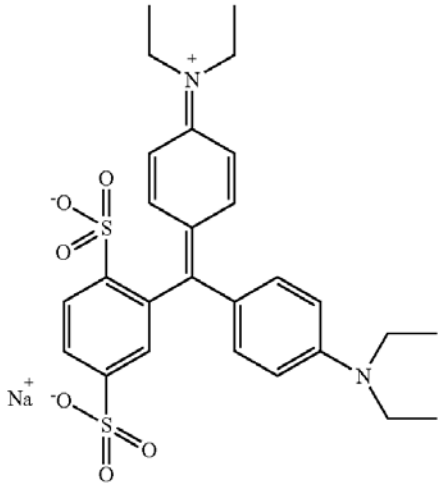
B. Real Parties-In-Interest

Patent Owner argues that the Petition should be denied because Petitioner has failed to name all real parties-in-interest to its Petition. Prelim. Resp. 3, 64–65. On our authorization (Paper 12), Petitioner filed a Reply addressing the real parties-in-interest issue (Paper 15), and Patent Owner filed a Sur-reply (Paper 17). Because we deny the Petition on the merits of the unpatentability challenges presented, we decline to reach the real party-in-interest issue.

C. The ’050 patent

The ’050 patent, titled “Process for Preparation of Isosulfan Blue,” issued on May 31, 2016. Ex. 1001, [45]. The ’050 patent relates to “a process for the production of isosulfan blue, and in particular, to a process for the production of isosulfan blue in a substantially pure form.” *Id.* at 1:17–19. The ’050 patent defines “substantially pure” “as 99.0% or greater.” *Id.* at 2:30–31.

Isosulfan blue (“ISB”) has the chemical name N-[4-[[4-(diethylamino)phenyl] (2,5-disulfophenyl)methylene]-2,5-cyclohexadien-1-ylidene]-N-ethylethanaminium, sodium salt, and the following chemical structure:



Id. at 1:23–45. ISB is known in the art as "a triarylmethane dye used as a contrast agent for the delineation of lymphatic vessels and is particularly useful as a cancer diagnostic agent." *Id.* at 1:47–49.

According to the '050 patent, "[a]lthough the literature is replete with methods of preparing triarylmethane dyes, most of the methods involve strong acids," "hazardous oxidizing agents," and "crude methods . . . of purification." *Id.* at 1:66–2:5. Thus, "there is a need in the art for an improved method in the process chemistry of isosulfan blue to be prepared in the purest form which is suitable for large scale cGMP production for its pharmaceutical formulation manufacturing." *Id.* at 2:20–23.

The'050 patent teaches a four-step process for the production of ISB. *See id.* at 5:1–7:45. The fourth step of the method "involves conversion of the isoleuco acid (4) to isosulfan blue of the formula (5) under conditions that employ milder oxidizing agents with no strong acidic reagents." *Id.* at 6:62–66. According to the '050 patent, these conditions "are less hazardous than the prior art." *Id.* at 6:66–67. The '050 patent teaches that the isosulfan blue sodium of formula (5) has "purity greater than 99.5% by HPLC [High Performance Liquid Chromatography]." *Id.* at 7:40–42.

D. Illustrative Claim

Of the challenged claims, claims 1, 11, and 15 are independent and illustrative of the claimed subject matter. Claim 1 recites:

> 1. A compound N-[4-[[4-(diethyl amino)phenyl](2,5-disulfophenyl)methylene]-2,5-cyclohexadien-1-ylidene]-N-ethylethanaminium, sodium salt having a purity of at least 99.0% by HPLC.

Ex. 1001, 9:54–57. Claim 11 recites a solution containing ISB, and claim 15 recites a composition consisting essentially of ISB. *Id.* at 12:8–13, 23–29.

E. The District Court Case and Appeal

As noted above, the '050 patent—along with the '992 patent and the '616 patent—was the subject of a district court case in which plaintiffs Mylan Institutional LLC and Patent Owner accused defendant Aurobindo Pharma Limited of importing and selling isosulfan blue formations infringing the '992, '616, and '050 patents. Ex. 1032, 1. Plaintiffs sought a preliminary injunction against the defendant. *Id.* The district court[3] found that plaintiffs had established a likelihood of success on the merits with respect to at least one claim of each patent-in-suit, and that Patent Owner would be irreparably harmed without entry of the preliminary injunction. *Id.*

In so doing, the district court considered whether defendant had "raised a 'substantial question' regarding validity." *Id.* at 26. Defendant alleged that the claims of the '050 patent would have been obvious over various combinations of the prior art, including three out of the four prior-art references asserted in this proceeding. *Id.* at 36. The district court assumed,

[3] A Magistrate Judge issued a Report and Recommendation, Ex. 1032, that the district court adopted, Ex. 2006. We refer to both decisions together as issued from "the district court."

without deciding, that "a person of ordinarily skill in the art would have been motivated to purify existing isosulfan blue even further because, generally speaking, the purer the better." *Id.* at 38. But, the court found, "Plaintiffs have established that it is more likely than not that the state of the art was such that a person of ordinary skill in the art would not have been able to purify isosulfan blue to at least 99% purity before the priority date." *Id.*

Specifically, the district court found that the process for making isosulfan blue described in the '050 patent was new and nonobvious:

> Starting with a commercially-available compound, the specification describes steps for obtaining a benzaldehyde intermediate. This intermediate is then reacted in a subsequent step, after which the isoleuco-acid "with chromatographic purity greater than 98.0% was obtained in the solid form out of the reaction mixture." The isoleuco-acid is then reacted, in the critical step, under unique conditions to obtain isosulfan blue, which can then simply be filtered, precipitated, and recrystallized to obtain the isosulfan blue with greater than 99% HPLC purity.

Id. at 39 (citations omitted). Put differently, "[plaintiffs] did not simply purify the known mixture of isosulfan blue using common methods and then claim the result." *Id.* The court thus concluded that the process "provides patentable weight to the resulting 99% pure isosulfan blue." *Id.*

The district court rejected defendant's argument that it would have been obvious for an ordinarily skilled artisan to purify prior-art 95% pure isosulfan blue mixtures with preparatory HPLC to a purity of 99% or more. *Id.* First, the court, relying on Hirsch and the testimony of defendant's expert, found that closely-related isomers would co-elute from an HPLC column with ISB, and thus ISB would be difficult to separate with HPLC alone. *Id.* at 39–40. Second, the court, relying on Dr. Sessler's testimony,

found that an ordinarily skilled artisan would not have reasonably expected success with repeated chromatography because "[f]or a complex mixture, repeated chromatography will increase the overall purity, but only relative to the impurities for which there is good separation," and because "[r]epeated chromatography comes at the cost of decreased yield." *Id.* at 40. Thus, the district court found "that [defendant] ha[d] not raised a substantial question that the claims of the '050 patent are prima facie obvious." *Id.*

The district court also considered plaintiffs' secondary considerations evidence, including long-felt need, failure of others, commercial success, copying and praise by others, unexpected results, and teaching away. *Id.* at 40–47. At the outset, the court determined that the "objective considerations regarding the patentable process described in the '992 and '616 patents are relevant to the patentability of the '050 patent claims." *Id.* at 41 (quotation omitted). The court ultimately found that evidence of long-felt need, commercial success, copying and praise by others, and unexpected results supported the likelihood that the '616, '992, and '050 patents would not be held obvious at trial.[4] *Id.* at 42–46.

As for long-felt need, the district court found that "for over 30 years, isosulfan blue manufacturers had trouble maintaining supply and meeting purity demands," whereas "the claimed invention reliably provides high-purity isosulfan blue." *Id.* at 41. As to commercial success, the court noted that "[t]here is no question that Plaintiffs' commercial isosulfan blue product

[4] On the other hand, the district court found insufficient evidence to support plaintiffs' contentions of failure of others, *id.* at 42–43, and teaching away, *id.* at 46.

was commercially successful." *Id.* at 43. The court noted that, shortly after entering the market, Patent Owner "began generating significant revenue from isosulfan blue sales," despite the presence of the competing isosulfan blue product, Lymphazurin. *Id.* at 43. The sales of Lymphazurin "sharply declined," until it was taken off the market "for reasons other than safety or effectiveness." *Id.* at 43 (quotation omitted). The court found this commercial success "sufficiently tied to the invention claimed in at least the '919 and '616 patents," and that "the nonobviousness of the '919 and '616 patent claims supports the patentability of the '050 patent claims." *Id.* at 44 (citing *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1301–02 (Fed. Cir. 2007)). In this regard, the court found that "[i]f it were not for the process claimed in the '992 and '616 patents, it is likely that neither [Patent Owner] nor [defendant] would be in the market." *Id.*

As to copying and praise by others, the district court found that defendant had made statements to the FDA that constituted "praise," including its admission that it had "searched the literature for a suitable process for preparing isosulfan blue and decided to use the invention disclosed in [Patent Owner's] '992 patent," and that, although "isosulfan blue synthesis is described in a number of patents," defendant "selected the process described in the '992 patent" after "having studied all these patents." *Id.* at 44–45 (quotations omitted). The court also found that defendant "started from something the '992 patent provided," and thus evidence of copying weighed against obviousness. *Id.* at 46. Finally, as to unexpected results and teaching away, the court found "significant evidence that the purity levels achieved by the claimed invention were unexpected." *Id.* at 46.

The district court, in summary, found that defendant had not "raise[d] a substantial question regarding motivation to combine prior art references to achieve the claimed invention with a reasonable expectation of success," and that "objective considerations overwhelmingly weigh against a finding of obviousness." *Id.* at 46–47. Thus, the court determined that defendant "will not likely prove that the patents-in-suit are invalid as obvious." *Id.* at 47; *see also* Ex. 2006, 2 (determining that, "[o]n the basis of a thorough review of the prior art and live testimony from the expert witnesses, the Court concludes that the Report correctly finds that there is not a substantial question regarding validity of the '050 patent").

On May 19, 2017, the Federal Circuit affirmed, holding that the district court did not err in finding that defendant "did not raise a substantial question as to validity of the '050 patent." *Mylan Instit.*, 857 F.3d at 870. The court first noted that it had "previously acknowledged that 'a purified compound is not always prima facie obvious over the prior art mixture' if the process to arrive at the purified compound is itself of patentable weight." *Id.* at 871 (quoting *Aventis*, 499 F.3d at 1301). "Moreover," the court explained, "if the prior art teaches a mixture containing a compound but does not *enable* its purification, then the purified form of the compound may not have been obvious over the prior art mixture." *Id.* (citing *Spectrum Pharm., Inc. v. Sandoz Inc.*, 802 F.3d 1326, 1335–36 (Fed. Cir. 2015)). The court then found "no error in [the district court's] analysis," stating that "[i]t is clear from the record here that, although ISB was known in the prior art, the path to arrive at ISB with a purity of greater than 99.0% was not known before the relevant date of the '050 patent." *Id.*

The Federal Circuit also found "no clear error in the [district] court's findings" as to secondary considerations. *Id.* The court emphasized that "prior to the '050 patent's relevant date, a reliable source of high-purity ISB was so scarce that, at one point, [the seller] was forced to notify its customers that it was completely out of Lymphazurin® until it could find a new supplier for ISB." *Id*. (quotation omitted).

F. The Prior Art

Petitioner advances the following references as prior art on which it relies for the asserted grounds challenging the claims of the '050 patent:

1. Balkrishna K. Kulkarni et al., U.S. Patent Application Publication No. 2006/0224003 A1 (Oct. 5, 2006) ("Kulkarni," Ex. 1007);

2. Lloyd R. Snyder et al., PRACTICAL HPLC METHOD DEVELOPMENT (2nd ed. 1997) ("Snyder," Ex. 1008);

3. J.P. Brown et al., *Synthesis of ^{14}C-Labelled FD & C Blue No. 1 (Brilliant Blue FCF) and its Intestinal Absorption and Metabolic Fate in Rats*, 18 FOOD & COSMETICS TOXICOL. 1–5 (1980) ("Brown," Ex. 1009); and

4. Jerry I. Hirsch et al., *Use of Isosulfan Blue for Identification of Lymphatic Vessels: Experimental and Clinical Evaluation*, 139 AM. J. OF ROENTGENOLOGY 1061–64 (Dec. 1982) ("Hirsch," Ex. 1010).

G. The Asserted Grounds of Unpatentability

Petitioner challenges the patentability of claims 1–18 of the '050 patent on the following grounds:

Claims	Basis	Reference(s)
1–18	35 U.S.C. § 103	Kulkarni and Snyder
1–18	35 U.S.C. § 103	Kulkarni, Snyder, and Brown
1–18	35 U.S.C. § 103	Hirsch and Snyder
1–18	35 U.S.C. § 103	Hirsch, Snyder, and Brown

Pet. 3–4. Petitioner also relies on the Declaration of Geoff Cox, Ph.D. (Ex. 1003), and the Declaration of R. Christian Moreton, Ph.D. (Ex. 1005). *See* Pet. 2. Patent Owner disputes that Petitioner's asserted grounds render the challenged claims unpatentable. *See generally* Prelim. Resp. Patent Owner relies on the Declaration of Jonathan L. Sessler, Ph.D. (Ex. 2001). *See id.* at 11.

III. ANALYSIS

We organize our analysis into four sections. First, we address the level of ordinary skill in the art. Second, we address claim construction. Third, we provide an overview of the asserted references. And fourth, taking account of the information presented, we consider whether the grounds asserted in the Petition meet the threshold showing for instituting an *inter partes* review under 35 U.S.C. § 314(a).

A. Level of Ordinary Skill in the Art

We consider the asserted grounds of unpatentability in view of the understanding of a person of ordinary skill in the art. Petitioner contends, and Dr. Cox testifies, that as of May 11, 2007—the earliest filing date in the priority chain for the '050 patent—a person of ordinary skill in the art:

> would have had an advanced degree (an M.S., Ph.D., or equivalent) in organic, medicinal, or process chemistry or related discipline, including analytical methodology relating to testing active pharmaceutical ingredients, as well as at least about 2 years of experience in developing drug candidates or analyzing pharmaceuticals.

Pet. 12–13; Ex. 1003 ¶ 25. Petitioner also contends that "[t]his description is approximate, so a lesser degree with more experience may suffice, and vice versa." Pet. 13; *see also* Ex. 1003 ¶ 25.

Patent Owner contends, and Dr. Sessler testifies, that a person of ordinary skill in the art "would include someone who had, through education or practical experience, the equivalent of a master's degree in chemistry, biochemistry, chemical engineering, or complementary discipline." Prelim. Resp. 11; Ex. 2001 ¶¶ 34–37. Patent Owner also contends, however, that "[t]he outcome of this case should not change even if [Petitioner's] proposed level of skill were adopted." *Id.*

We discern no substantive difference between the parties' respective definitions for a person of ordinary skill in the art. Thus, we adopt Petitioner's definition for our analysis in this decision. We also find, for this decision, that the prior art itself is sufficient to demonstrate 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) (the prior art, itself, can reflect the appropriate level of ordinary skill in art).

Further, based on the information presented at this stage of the proceeding, we consider Petitioner's declarants (Dr. Cox and Dr. Moreton) and Patent Owner's declarant (Dr. Sessler) qualified to opine from the perspective of an ordinary artisan at the time of the invention. *See* Ex. 1004

(Dr. Cox's curriculum vitae); Ex. 1006 (Dr. Moreton's curriculum vitae); Ex. 2002 (Dr. Sessler's curriculum vitae).

B. Claim Construction

For petitions filed before November 13, 2018,[5] the Board interprets claims in an unexpired patent using the "broadest reasonable construction in light of the specification of the patent." 37 C.F.R. § 42.100(b) (2016); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016). "Under a broadest reasonable interpretation, words of the claim must be given their plain meaning, unless such meaning is inconsistent with the specification and prosecution history." *TriVascular, Inc. v. Samuels*, 812 F.3d 1056, 1062 (Fed. Cir. 2016).

Claim 1 of the '050 patent recites an isosulfan blue "having a purity of at least 99.0% by HPLC." Ex. 1001, 9:54–57. Relying on the Declaration of Dr. Cox, Petitioner contends that an ordinarily skilled artisan would understand that phrase "to mean the composition, when analyzed by HPLC under appropriate conditions, results in 'a peak [representing ISB] having at least 99.0% of the area under the curve ('AUC') on a chromatogram.'" Pet. 11–12 (quoting Ex. 1003 ¶ 97; citing *id.* ¶ 48) (brackets in original). In response, Patent Owner does not provide an express interpretation for "having a purity of at least 99.0% by HPLC." *See* Prelim. Resp. 11-12. But, relying on the Declaration of Dr. Sessler, Patent Owner contends that certain aspects of Petitioner's "definition [are] inconsistent with how a POSITA would understand the claim term." *Id.* at 12 (citing Ex. 2001 ¶¶ 40–44).

[5] *See Changes to the Claim Construction Standard for Interpreting Claims in Trial Proceedings Before the Patent Trial and Appeal Board*, 83 FED. REG. 51340 (Oct. 11, 2018) (amending 37 C.F.R. § 100(b) effective November 13, 2018) (to be codified at 37 C.F.R. pt. 42).

To determine whether to institute an *inter partes* review, we need not explicitly interpret every claim term for which the parties propose a construction. *See* 35 U.S.C. § 314(a); *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) ("[O]nly those terms need be construed that are in controversy, and only to the extent necessary to resolve the controversy."). We determine that, to resolve whether Petitioner has demonstrated a reasonable likelihood of prevailing, we need not provide an express interpretation of "having a purity of at least 99.0% by HPLC."

C. Asserted References

Before turning to Petitioner's asserted grounds of unpatentability, we provide a brief summary of the asserted references.

1. Kulkarni

Kulkarni teaches a process for manufacturing ISB from orthochlorobenzaldehyde. Ex. 1007 ¶ 2. The process comprises four steps: (1) sulphonating orthochlorobenzaldehyde with a sulphonating agent to obtain 4-chloro-3-formyl sulphonic acid; (2) treating the 4-chloro-3-formyl sulphonic acid with sodium sulphite, and subsequent basification, to obtain 1-formyl benzene-2,5-sulphonic acid disodium salt; (3) causing condensation of the 1-formyl benzene-2,5-sulphonic acid disodium salt with N,N-diethylaniline using hydrochloric acid, to obtain a 4-[Bis[4-(diethylamino)phenyl]methyl]benzene-2,5-disulphonic acid disodium salt; and (4) oxidizing the 4-[Bis[4-(diethylamino)phenyl]methyl]benzene-2,5-disulphonic acid with an oxidizing agent, using an acid and a solvent, to obtain ISB. *Id.* ¶¶ 21–25. Kulkarni teaches that the oxidizing agent of the final step is "[t]ypically ammonium dichromate." *Id.* ¶ 50. Kulkarni teaches that the commonly used prior-art oxidizing agents—dichromate lead

and potassium dichromate—"lead to over oxidized products" and could "produce toxic effects (lead poisoning) in the recipients." *Id.* ¶¶ 15–16.

On October 15, 2006—during prosecution of the Kulkarni application[6]—named inventor Balkrishna K. Kulkarni submitted a Declaration under 37 C.F.R. § 1.132 purporting to compare the purity of ISB prepared using ammonium dichromate as an oxidizing agent in the final reaction step, with the purity of ISB prepared using potassium dichromate as the oxidizing agent. *See* Ex. 1031 ("the Kulkarni Declaration"). The Kulkarni Declaration asserts that oxidation by ammonium dichromate yielded 25g crude ISB that, when subjected to HPLC analysis, resulted in about 86.4% product and 13.6% total impurities. *Id.* at 2. In contrast, oxidation by potassium dichromate yielded 25g crude ISB that, when subjected to HPLC analysis, resulted in about 79.7% product and 20.3% total impurities. *Id.* at 3.

The Kulkarni Declaration also asserts that the crude ISB samples were purified using column chromatography and then subjected to HPLC analysis. *Id.* at 2–3. Column purification of the ammonium dichromate-prepared ISB yielded 15g of purified product, whereas column purification of the potassium dichromate-prepared ISB yielded 10.5g of purified product. *Id.* HPLC analysis of the ISB prepared with ammonium dichromate exhibited 5 peaks, the fifth having an area of about 98.5%. *Id.* at 2. In contrast, HPLC analysis of the ISB prepared with potassium dichromate exhibited 11 peaks, the eleventh peak having an area of about 99.4%. *Id.* at 3.

[6] The Kulkarni application was filed on April 4, 2006 and designated Application No. 11/278,641. Ex. 1007, [21], [22].

The Kulkarni Declaration asserts that the comparative experimental data shows "[c]rude yield in both cases was [the] same," but that "the purity of the product was higher when ammonium dichromate was used as the oxidizing agent." *Id.* at 4. The Kulkarni Declaration concludes that "[t]he advantageous effect of selection [sic] ammonium dichromate which is a mild oxidizing agent over the use of potassium dichromate (relative stronger oxidizing agent) for the process of the present invention is substantiated by the comparative experimental data." *Id.*

2. Snyder

Snyder is a reference textbook for HPLC comprising 15 chapters and several appendices. *See* Ex. 1008, v–xviii.[7] Chapter 13 of Snyder provides an overview of preparative HPLC separation, "where the goal is the isolation of purified material (product) for further use." *Id.* at 616.

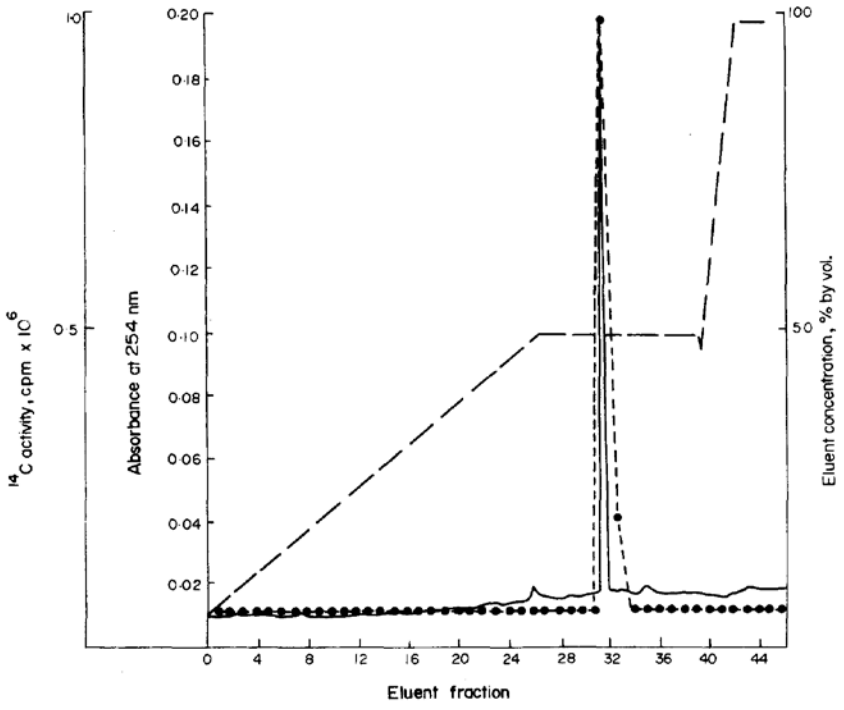
3. Brown

Brown provides a study of the "intestinal absorption, tissue distribution, and biliary, urinary and pulmonary excretion of FD & C Blue No. 1 and its metabolites" in rats "using radiolabelled dye." Ex. 1009, 1 (Introduction). Brown first synthesized the radiolabeled FD & C Blue No. 1 dye in eight steps from a barium [^{14}C]carbonate. *Id.* at 1–2 (Experimental). Brown states that, although yield was high, "HPLC analysis showed that the crude product was of low purity." *Id.* at 2. Thus, "the dye was purified by preparative high performance liquid chromatography." *Id.*

Brown then injected into an HPLC 200 µl aliquots "of an approximately 0.1% solution of crude [^{14}C]FD & C Blue No. 1," and

[7] Exhibit 1008 consists of certain excerpts of Synder, including Chapters 1, 2, 13, and 14.

collected the eluent fractions. *Id.* Brown states that "[e]leven injections were required to purify the entire reaction mixture," and the "purest fractions from each injection were combined." *Id.* But analytical C_{18} column analysis indicated that "further purification was necessary." *Id.* Thus, Brown prepared three preparative HPLC injections, collected the eluent fractions, and combined the purest fractions obtained. *Id.* Subsequent analytical C_{18} column analysis, however, showed that "11% of the total radioactivity was found eluting with other than the main peak of [^{14}C]FD & C Blue No. 1." *Id.* at 2–3. "Therefore," Brown states, "this sample needed further purification." *Id.* at 3. Brown then prepared five preparative HPLC injections, collected the eluent fractions, and combined the purest fractions obtained. *Id.* "A 10 µl aliquot of this approx. 1 mg/ml solution was injected onto the analytical column," and the "purity of the resultant [^{14}C]FD & C Blue No. 1 was determined to be more than 99%," as shown in Figure 2, reproduced below. *Id.*



Brown states that "[t]he labelled dye produced after this exhaustive purification contained less than 1% labelled impurities." *Id.* at 4 (Results and Discussion). Although "[t]he overall yield [was] very low (approx. 0.2%)," Brown states that it was sufficient to "provide[] material for absorption studies which far exceeded commercial FD & C Blue No. 1 in purity." *Id.* Brown concludes that, "[w]ithout HPLC techniques, material of this purity would be almost impossible to obtain." *Id.*

4. Hirsch

Hirsch describes clinical trials relating to the use of ISB for identifying lymphatic vessels in volunteers and patients under an investigational new drug application. Ex. 1010, 1061. Hirsch describes ISB as "the monosodium salt of a 2,5 disulfonated triphenylmethane dye." *Id.* Hirsch teaches that "[t]he compound was prepared in high purity of 94.5%[8] dye content of the 2,5 isomer as determined by high-pressure liquid chromatography." *Id.* Hirsch teaches that "[t]he remaining 5.5% consists of closely related isomers produced during synthesis." *Id.* at 1061–62. As a result of the clinical trials, Hirsch reports that "[i]sosulfan blue injection (1%) is a safe and efficacious drug for the identification of lymphatics during lymphangiography. FDA approval for human use has been obtained. Commercial introduction of this drug is forthcoming under the trade name Lymphazurin (1%)." *Id.* at 1064.

[8] As discussed by the district court, Hirsch reported later in a letter to the FDA that the same lot of ISB in fact contained only 83.4% ISB and 8.2% "other organics." Ex. 1032, 3–4.

D. Asserted Grounds of Unpatentability Based on Kulkarni

Petitioner contends that claims 1–18 are unpatentable as obvious over Kulkarni in view of Snyder, and as obvious over Kulkarni in view of Snyder and Brown. Pet. 13–46. A claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time of the invention to a person having ordinary skill in the art. *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. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

1. Petitioner's Arguments

Claim 1 of the '050 patent recites an isosulfan blue "having a purity of at least 99.0% by HPLC." Ex. 1001, 9:54–57. Petitioner acknowledges that Kulkarni "does not expressly disclose the level of purity of the synthesized ISB product" claimed, but argues that Kulkarni's ISB has an inherent purity of 86.4% by HPLC as evidenced by the Kulkarni Declaration. Pet. 13–14. Specifically, Petitioner contends that "Kulkarni declared (under penalty of a fine, imprisonment, or both) that his claimed process for synthesizing ISB using ammonium dichromate resulted in a crude product of 86.3689% purity, as assessed by analytical HPLC." Pet. 14 (citing Ex. 1031, 2; Ex. 1003 ¶ 80). "Thus," Petitioner contends, "the process described in Kulkarni . . . inherently produces an ISB product of around 86% purity," and "[a]ny POSITA could have readily performed the same analytical HPLC test

to determine the purity level of the crude ISB." *Id.* at 14–15 (citing Ex. 1003 ¶ 80).

Relying on the Declaration of Dr. Cox, Petitioner then contends that an ordinarily skilled artisan "could have used Snyder to scale up known analytical HPLC conditions into a preparative HPLC to obtain a purified [ISB] product." *Id.* at 16 (citing Ex. 1003 ¶ 92). Specifically, Petitioner contends that "Snyder provides a roadmap for the POSITA to follow in developing a preparative HPLC method for purifying ISB to 99.0% or higher." *Id.* at 19–20 (citing Ex. 1003 ¶¶ 101–102). Petitioner contends that "the '050 patent does not disclose how to assess ISB purity by HPLC, thereby admitting that the use of HPLC was well known in the art at the critical date," *id.* at 17 (citing Ex. 1032, 17–18; Ex. 1002, 120–121), and that Snyder evidences that preparative HPLC is performed "in the same general way" as analytical HPLC, *id.* (citing Ex. 1008, 620). Thus, Petitioner contends, "a POSITA readily could have developed the analytical HPLC starting point" from Kulkarni into a "preparative HPLC . . . to purify ISB, even from its known isomers that were generated during synthesis." *Id.* at 17–19 (citing Ex. 1008, 617, 620; Ex. 1003 ¶¶ 90–92).

Finally, Petitioner contends that an ordinarily skilled artisan would have had a reasonable expectation of success in scaling up to preparative HPLC because "[b]y 2007, preparative HPLC was a mature technique that would have been routine to the POSITA." *Id.* at 32 (citing Ex. 1009; Ex. 1025; Ex. 1026). Petitioner contends that "there are no fundamental differences between analytical and preparative chromatography, and a POSITA could have exercised routine skill to scale up an analytical HPLC method to a preparative HPLC method." *Id.* at 33 (citing Ex. 1003 ¶ 39).

Petitioner contends that the Kulkarni Declaration demonstrates the ease of which crude ISB can be purified, *id.* (citing Ex. 1031; Ex. 1003 ¶¶ 123–24), and also relies on "a 2017 paper [that] utilizes preparative HPLC conditions from the teachings of Snyder to purify ISB to a purity of 99.96%," *id.* (citing Ex. 1036; Ex. 1003 ¶¶ 125). Petitioner thus concludes that the ordinarily skilled artisan, "relying only on the guidance in Snyder and routine skill, would have successfully purified ISB with the claimed purity of at least 99% using HPLC." *Id.* at 34 (citing Ex. 1003 ¶ 125).

2. Discussion

Having considered the arguments and evidence before us, we find that the Petition does not establish a reasonable likelihood that Petitioner would prevail on its asserted grounds of obviousness based on Kulkarni. *See* Prelim. Resp. 17 (citing Ex. 1002 ¶ 98).

First, we agree with Patent Owner that Petitioner has not established sufficiently for institution that Kulkarni's method inherently produces an ISB compound having a purity of about 86.4%. Although "inherency may supply a missing claim limitation in an obviousness analysis," its use "must be carefully circumscribed in the context of obviousness." *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1194–95 (Fed. Cir. 2014) (citations omitted). That is "because that which may be inherent is not necessarily known and that which is unknown cannot be obvious." *Honeywell Int'l Inc. v. Mexichem Amanco Holding S.A. DE C.V.*, 865 F.3d 1348, 1354 (Fed. Cir. 2017) (quotation omitted). Thus, "[i]nherency . . . may not be established by probabilities or possibilities"; "[t]he mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Par Pharm.*, 773 F.3d at 1195 (quotations omitted).

The Kulkarni Declaration is not prior art. Pet. 19. Thus, the relevant question is whether Kulkarni itself teaches a method that necessarily and inevitably produces an ISB having a purity of about 86.4%. *See In re Montgomery*, 677 F.3d 1375, 1380 (Fed. Cir. 2012) ("The inherent result must inevitably result from the disclosed steps . . . ."). But neither Petitioner nor Dr. Cox allege that performing the steps described in Kulkarni results in such a purity level *each and every time* those steps are performed. *See In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1372 (Fed. Cir. 2007) (finding the claimed in situ separating layer inherent because that layer would result each and every time a skilled artisan followed the prior-art process steps). Instead, Dr. Cox testifies only that he "*understand[s]* that the crude isosulfan blue product obtained by the synthetic process described in Kulkarni . . . inherently would have been around 86%." Ex. 1003 ¶ 80 (emphasis added). This unsupported statement is insufficient to demonstrate a reasonable likelihood that Kulkarni inherently discloses an ISB having about 86.4% purity.

Moreover, we find the conclusory and self-serving statements in the Kulkarni Declaration to be insufficient evidence that Kulkarni's method necessarily produces an ISB having about 86.4% purity. While we recognize that the statements were made under penalty of perjury, the Kulkarni Declaration fails to provide any specificity as to the steps taken to achieve a purity of 86.4%; nor does the declaration provide independent evidentiary support for the claimed purity level. *See* 37 C.F.R. § 42.65(b) ("If a party relies on a technical test or data from such a test, the party must provide an affidavit explaining: (1) Why the test or data is being used; (2) How the test was performed and the data was generated; (3) How the

data is used to determine a value; (4) How the test is regarded in the relevant art; and (5) Any other information necessary for the Board to evaluate the test and data."). And although Dr. Cox testifies that "[a]ny person of skill in the art readily could have performed the same analytical HPLC test to determine the purity level of the crude isosulfan blue," Ex. 1003 ¶ 80, he provides no independent testing data to support Petitioner's inherency theory. Thus, we are not persuaded—on this record and for institution—that Kulkarni discloses an isosulfan blue having an inherent purity of about 86.4%.

Second, even if we accepted that Kulkarni discloses an ISB having about 86.4% purity, Petitioner does not persuade us sufficiently for institution that an ordinarily skilled artisan would have reasonably expected success in further purifying that compound to a purity of at least 99%. Petitioner relies on the general teachings of Snyder to provide "a roadmap to scale up an analytical HPLC method to a preparative HPLC method," Pet. 15, but fails to explain adequately for institution why the ordinarily skilled artisan would have reasonably expected success under the particular facts of this case, especially where, as the Federal Circuit noted, "the path to arrive at ISB with a purity of greater than 99.0% *was not known* before the relevant date of the '050 patent." *Mylan Instit.*, 857 F.3d at 871 (emphasis added).

Indeed, given the district court's findings that the ordinarily skilled artisan would have understood that common purification methods would not have resulted in 99% pure ISB before the priority date of the '050 patent, Ex. 1032, 38, Petitioner's reliance on the generalized HPLC teachings of Snyder is unpersuasive. Snyder provides no guidance for the skilled artisan to overcome the failures of the prior art to achieve an ISB having at least

99% purity. *See* Ex. 2001, ¶¶ 132–39, 259–60. Snyder also expressly states that its teachings are "not intended as a detailed guide for the design of process-scale separations." Ex. 1008, 640.

Third, Petitioner does not persuade us sufficiently for institution that Brown evidences an ordinarily skilled artisan would have had a reason to use conventional and iterative preparative HPLC to purify the ISB of Kulkarni to at least 99% purity. *See* Pet. 23–25. As explained above, Brown's synthesis reactions produced "a crude product . . . of low purity." Ex. 1009, 2. And, although Brown eventually purified that product by preparative HPLC, Brown was forced to go through an "exhaustive purification process" that involved several rounds of injections, fraction collections, and analytical analyses, and which nevertheless resulted in "very low" overall yield. *Id.* at 2–4. Thus, even if "[a] POSITA would have understood from Brown that *it was possible* to obtain a high purity for ISB . . . using conventional HPLC conditions" as Petitioner contends, Pet. 25 (emphasis added), we find that Brown would not have provided the skilled artisan a reason to pursue conventional and iterative preparative HPLC techniques under the particular facts of this case. *See Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1073 (Fed. Cir. 2015) ("[O]bviousness concerns whether a skilled artisan not only *could have made* but *would have been motivated to make* the combinations or modifications of prior art to arrive at the claimed invention.").

The Kulkarni Declaration fares no better, as Petitioner conflates the "column chromatography" used by Kulkarni to purify ISB with the preparative HPLC that Petitioner alleges an ordinarily skilled artisan would have used to purify ISB. *See* Pet. 33 (stating that "[p]ost-filing evidence

confirms that the preparative HPLC procedures described in Snyder would have worked," but omitting that the Kulkarni Declaration's utilizes "column purification" to purify the crude isosulfan blue); Ex. 1031, 2 (describing the use of analytical HPLC to test the purity of crude ISB and the pure yield ISB product obtained by "[c]olumn purification"). There is no evidence suggesting that Kulkarni used HPLC for purification, as opposed to analytical, purposes.

Accordingly, for the reasons set forth above, we are not persuaded that Petitioner establishes a reasonable likelihood of prevailing in showing that the subject matter of claims 1–18 would have been obvious over any asserted ground of unpatentability requiring the combination of Kulkarni with Snyder and/or Brown.[9]

[9] The parties debate the impact of Patent Owner's secondary considerations evidence on the obviousness *vel non* of the claimed invention. *See* Pet. 59–62; Prelim. Resp. 53–63. We need not analyze that evidence in this case because we are not persuaded, for the reasons explained, that Petitioner establishes a reasonable likelihood of prevailing in showing that the subject matter of claims 1–18 would have been obvious. *See Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1349 (Fed. Cir. 2012) (stating that evidence of secondary considerations "must always when present be considered *en route to a determination of obviousness*" (emphasis added)); *see also Apple Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1048 (Fed. Cir. 2016) (en banc) ("A determination of whether a patent claim is invalid as obvious under § 103 requires consideration of all four *Graham* factors, and it is error to *reach a conclusion of obviousness* until all those factors are considered." (emphasis added)).

E. Asserted Grounds of Unpatentability Based on Hirsch

Petitioner contends that claims 1–18 are unpatentable as obvious over the combination of Hirsch in view of Snyder, Pet. 46–54, and as obvious over the combination of Hirsch in view of Snyder and Brown, *id.* at 55–59. Having considered the arguments and evidence before us, we find that the record does not establish a reasonable likelihood that Petitioner would prevail on its asserted grounds of obviousness based on Hirsch.

As with its grounds of unpatentability based on Kulkarni, Petitioner contends that Hirsch discloses an ISB having a certain purity level,[10] and that it would have been obvious to an ordinarily skilled artisan "to purify the ISB disclosed in Hirsch using the roadmap provided by Snyder to make a preparative HPLC method to purify ISB to at least 99.0% by HPLC." *Id.* at 46–51. And Petitioner contends that "the POSITA would have been motivated to improve the purity of the ISB disclosed by Hirsch for the same five reasons she would have been motivated to combine Kulkarni with Snyder," *id.* at 49, and would have had a reasonable expectation of success "[f]or the same reasons," *id.* at 51.

We are not persuaded by these arguments for the reasons explained above. *Supra* §§ III.D.2. In particular, Petitioner does not persuade us sufficiently for institution that an ordinarily skilled artisan would have reasonably expected success in purifying Hirsch's compound to a purity of at least 99% from the teachings of Snyder. *Id.* Nor does Petitioner persuade

[10] Petitioner contends that an ordinarily skilled artisan "would have been motivated to combine Hirsch and Snyder to arrive at the claimed purity regardless of whether the known purity [of Hirsch] was 94.5% or 83.6%." Pet. 49 n.7 (citing Ex. 1003 ¶¶ 162–163). Because our decision is the same regardless of Hirsch's starting purity, we need not address this issue.

us sufficiently for institution that Brown evidences an ordinarily skilled artisan would have had a reason to use conventional and iterative preparative HPLC as disclosed in Brown to purify Hirsch's ISB to at least 99% purity. *Id.*

Moreover, as noted above, Hirsch teaches that its ISB contains at least 5.5% "closely related isomers produced during synthesis." Ex. 1010, 1061–62. Relying on the testimony of defendant's own expert witness, the district court found that those "closely related isomers would be difficult to separate with HPLC alone because closely related isomers have similar affinities for the stationary phase, and could co-elute from an HPLC column at the same time as isosulfan blue." Ex. 1032, 40 (citation omitted); *see also* Ex. 2001 ¶¶ 147, 174–76, 256.

Petitioner does not directly challenge this finding, but appears to imply that the district court was incorrect by pointing to Lee (Ex. 1024), Kusaka (Ex. 1025), and Ngang (Ex. 1026) as "literature describing the successful separations of triarylmethane dyes." Pet. 25 (citing Ex. 1003 ¶¶ 51–54). Specifically, Petitioner contends that these triarylmethane dyes "are structurally very similar to ISB," and that the literature describes their separation "from closely-related isomers of the respective compounds." Pet. 25 (citing Ex. 1003 ¶¶ 51–54). Petitioner alleges that these examples "would have given the POSITA confidence that ISB could be separated from its isomers by HPLC as well." *Id.* (citing Ex. 1003 ¶ 55); *see also id.* at 25–31, 50–51.

We are not persuaded, however, because as we discussed above, Petitioner's argument ignores the district court's findings that the ordinarily skilled artisan would have understood that common purification methods

such as HPLC would not have resulted in 99% pure ISB before the priority date of the '050 patent. *Supra* §§ III.D.2; *see also* Ex. 1032, 38. Critical to the district court's analysis was its finding that that the process itself results in 99% pure ISB without further HPLC purification. Ex. 1032, 39 (explaining that the disclosed process contains, in the critical step, the reaction of isoleuco-acid "under unique conditions to obtain isosulfan blue, which can then simply be filtered, precipitated, and recrystallized to obtain the isosulfan blue with greater than 99% HPLC purity" (citing Ex. 1001, 7:24–45)). Put differently, Patent Owner "did not simply purify the known mixture of isosulfan blue using common methods and then claim the result." *Id.* Relying on *Aventis*, the court thus concluded that the process "provides patentable weight to the resulting 99% pure isosulfan blue." *Id.* (citing *Aventis*, 499 F.3d at 1301). We see no reason to decide differently from the district court in this case, especially where the Federal Circuit found no error in the district court's analysis and reliance on *Aventis*. *Mylan Instit.*, 857 F.3d at 871; *see also id.* ("It is clear from the record here that, although ISB was known in the prior art, the path to arrive at ISB with a purity of greater than 99.0% was not known before the relevant date of the '050 patent.").

Accordingly, for the reasons set forth above, we are not persuaded that Petitioner establishes a reasonable likelihood of prevailing in showing that the subject matter of claims 1–18 would have been obvious over any asserted ground of unpatentability requiring the combination of Hirsch with Snyder and/or Brown.

F. 35 U.S.C. §§ 312(a)(3), 314(a), 325(d)

Patent Owner requests that we deny institution of a trial in this proceeding under 35 U.S.C. §§ 314(a) and 325(d). Prelim. Resp. 12–22.

Petitioner opposes. Pet. 62–66. We do not exercise our discretion to deny institution under these statutory bases in this case because, as explained above, we deny the Petition on its merits.

Patent Owner also argues that we should deny institution under 35 U.S.C. § 312(a)(3) because Petitioner's asserted grounds of unpatentability were not identified with particularity, as required by the statute. Prelim. Resp. 29–31. Again, because we deny institution on the merits, we need not address this issue in detail. We note, however, that additional references may be relevant, for example, to an ordinarily skilled artisan's reason to combine prior-art references and expectation of success. *See, e.g.*, *Novartis AG v. Torrent Pharm. Ltd.*, 853 F.3d 1316, 1326–27 (Fed. Cir. 2017) (finding no APA violation from Board's use of additional references as evidence supporting its factual findings underlying the obviousness conclusion).

IV. CONCLUSION

Taking account of the information presented in the Petition and the Preliminary Response, and the evidence of record, we determine that Petitioner fails to demonstrate a reasonable likelihood of prevailing at trial as to any challenged claim. Accordingly, the Petition is *denied* and no trial is instituted.

V. ORDER

Accordingly, it is

ORDERED that the Petition is *denied* as to all challenged claims of the '050 patent, and no trial is instituted.

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