UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PROVEPHARM INC.,
Petitioner

v.

WISTA LABORATORIES LTD.
Patent Owner

Case IPR2018-00323
Patent 9,675,621

PETITIONER PROVEPHARM INC.'S NOTICE OF APPEAL

Attached hereto as Exhibit A is Petitioner's Notice of Appeal of IPR2018-00323 ("Notice") that was served via United States Express Mail on the Director of the USPTO within 63 days of the PTAB's final decision on September 3, 2019, as required by 37 CFR § 90.3. A copy of the Notice was also filed with the Federal Circuit and served on counsel for WisTa via email and regular mail on September 3, 2019.

The certificate of service indicates at page 3 that a copy of the Notice was filed with the PTAB on September 3, 2019. Petitioner inadvertently did not file a copy of the Notice on September 3. Petitioner is today filing a copy of the complete and original Notice that was previously filed with the Director of the USPTO, along with a certificate of service indicating that the copy is being filed with the PTAB today.

Dated: September 5, 2019

Respectfully submitted,

ALSTON & BIRD LLP

/S. Benjamin Pleune/
S. Benjamin Pleune (Reg. No. 52,421)

Attorney for Petitioner Provepharm, Inc.

CERTIFICATION OF SERVICE

The undersigned hereby certifies that the foregoing **PETITIONER PROVEPHARM INC.'S NOTICE OF APPEAL** was filed electronically with the Board in accordance with 37 CFR § 42.6(b)(1), and e-mailed on September 5, 2019 to the following attorneys for Patent Owner:

Richard F. Giunta: Rgiunta-PTAB@wolfgreenfield.com
Edward R. Gates: EGates-PTAB@wolfgreenfield.com
David F. Cauble: DCauble-PTAB@wolfgreenfield.com
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/S. Benjamin Pleune/
S. Benjamin Pleune (Reg. No. 52,421)

EXHIBIT A

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PROVEPHARM INC.,
Petitioner

v.

WISTA LABORATORIES LTD.
Patent Owner

Case IPR2018-00323
Patent 9,675,621 B2

PETITIONER PROVEPHARM INC.'S NOTICE OF APPEAL

Director of the United States Patent and Trademark Office
c/o Office of the General Counsel
Madison Building East, Room 10B20
600 Dulany Street
Alexandria, VA 22314-5793

Pursuant to 35 U.S.C. §§ 141(c) and 142 and 37 C.F.R. §§ 90.2(a) and 90.3, Petitioner Provepharm Inc. hereby appeals to the United States Court of Appeals for the Federal Circuit from the Patent Trial and Appeal Board's Final Written Decision, entered on July 2, 2019 (Paper 49) (a copy of which is attached), and from all underlying and related findings, orders, decisions, rulings, and opinions that are adverse to Provepharm Inc.

For the limited purpose of providing the Director with the information requested in 37 C.F.R. § 90.2(a)(3)(ii), Provepharm Inc. further indicates that the issues on appeal may include, but are not limited to, whether the Board erred in determining that the prior art did not render the challenged claims unpatentable under 35 U.S.C. § 103 for obviousness. Provepharm Inc. further reserves the right to challenge any finding or determination supporting or relating to the issue above, and to challenge other issues decided adversely to Provepharm Inc.

Pursuant to 37 C.F.R. § 90.2(a), Provepharm Inc. is (1) filing a copy of this Notice of Appeal with the Director; (2) electronically filing a copy of this Notice

with the Federal Circuit, along with the requisite filing fee; and (3) filing this Notice with the Patent Trial and Appeal Board.

DATED: September 3, 2019

Respectfully submitted,

ALSTON & BIRD LLP

By /s/ *Benjamin Pleune*
Benjamin Pleune

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Attorney for Petitioner Provepharm Inc.

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 90.2(a)(1), on September 3, 2019, the foregoing Notice of Appeal was filed electronically with the Board in accordance with 37 C.F.R. § 42.6(b)(1), and mailed to the Director via Priority Mail Express in accordance with 37 C.F.R. §§ 1.10 and 104.2 at the following address:

Director of the U.S. Patent and Trademark Office
c/o Office of the General Counsel
P.O. Box 1450
Alexandria, VA 22313-1450

Pursuant to 37 C.F.R. § 90.2(a)(2); Fed. R. App. P. 15; and Fed. Cir. R. 15, 25, and 52, on September 3, 2019, the foregoing Notice of Appeal was electronically filed with the Court of Appeals for the Federal Circuit via CM/ECF with requisite fees paid via pay.gov. Pursuant to Fed. Cir. R. 15(a)(1), one copy of this Notice of Appeal is being filed by hand with the Clerk's Office of the Federal Circuit on September 3, 2019.

Pursuant to 37 C.F.R. § 42.6(e) and the parties' agreement to accept electronic service, on September 3, 2019 the foregoing Notice of Appeal was served via e-mail on the following attorneys for Patent Owner:

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DATED: September 3, 2019

Respectfully submitted,

ALSTON & BIRD LLP

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Paper 49
Entered: July 2, 2019

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PROVEPHARM INC.,
Petitioner,

v.

WISTA LABORATORIES LTD.,
Patent Owner.

Case IPR2018-00323
Patent 9,675,621 B2

Before JAMES T. MOORE, SUSAN L. C. MITCHELL, and KRISTI L. R. SAWERT, *Administrative Patent Judges.*

SAWERT, *Administrative Patent Judge.*

FINAL WRITTEN DECISION

Determining Claims 1–20 Not Unpatentable in *Inter Partes* Review
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

Denying Patent Owner's Motion to Exclude
37 C.F.R. § 42.64(c)

Denying Petitioner's Motion to Exclude
37 C.F.R. § 42.64(c)

I. INTRODUCTION

This is a Final Written Decision in an *inter partes* review challenging the patentability of claims 1–20 ("the challenged claims") of U.S. Patent No. 9,675,621 B2 ("the '621 patent," Ex. 1002). We have jurisdiction under 35 U.S.C. § 6, and enter this Decision pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. For the reasons set forth below, we determine that Petitioner has not shown, by a preponderance of the evidence, that the challenged claims are unpatentable. *See* 35 U.S.C. § 316(e).

A. Procedural History

Provepharm Inc. ("Petitioner") filed a Petition for an *inter partes* review under 35 U.S.C. § 311. Paper 2 ("Pet."). Petitioner supported its Petition with the Declaration of Daniel W. Armstrong, Ph.D. (Ex. 1003). WisTa Laboratories Ltd. ("Patent Owner") timely filed a Preliminary Response. Paper 10 ("Prelim. Resp.").

On July 6, 2018, pursuant to 35 U.S.C. § 314(a), we instituted trial to determine whether any of the challenged claims of the '621 patent is unpatentable based on the grounds raised in the Petition:

Claims	Basis	References
1–5 and 8–12	35 U.S.C. § 103	WO '720,[1] EP 5.4,[2] Dean,[3] and Akkermans[4]
1–5 and 8–12	35 U.S.C. § 103	WO '720, EP 2001,[5] Dean, and Akkermans
6 and 7	35 U.S.C. § 103	WO '720, EP 5.4, Dean, Akkermans, and Nerenberg[6]
6 and 7	35 U.S.C. § 103	WO '720, EP 2001, Dean, Akkermans, and Nerenberg
13–17, 19, and 20	35 U.S.C. § 103	Therapeutic Drugs,[7] EP 5.4, Dean, and Akkermans
13–17, 19, and 20	35 U.S.C. § 103	Therapeutic Drugs, EP 2001, Dean, and Akkermans

[1] Claude Michel Wischik et al., WO 02/055720 A2 (July 18, 2002) ("WO '720," Ex. 1038).

[2] EUROPEAN PHARMACOPOEIA Supplement 5.4, 3977–79 (Council of Europe ed., 5th ed. 2005) ("EP 5.4," Ex. 1027).

[3] W.W. Dean et al., *The Analysis of Romanowsky Blood Stains by High-Performance Liquid Chromatography*, 124 J. CHROMATOGR. 287–301 (1976) ("Dean," Ex. 1072).

[4] Richard P. Akkermans et al., *Methylene Green Voltammetry in Aqueous Solution: Studies Using Thermal, Microwave, Laser, or Ultrasonic Activation at Platinum Electrodes*, 103 J. PHYS. CHEM. B 9987–95 (1999) ("Akkermans," Ex. 1033).

[5] EUROPEAN PHARMACOPOEIA Supplement 2001, 1131–33 (Council of Europe ed., 3rd ed. 2000) ("EP 2001," Ex. 1028).

[6] C. Nerenberg and Roland Fischer, *Purification of Thionin, Azure A, Azure B and Methylene Blue*, 38(2) STAIN TECHNOL. 75–83 (1963) ("Nerenberg," Ex. 1035).

[7] *Methylene Blue*, *in* THERAPEUTIC DRUGS M117–M118 (Colin Dollery, ed. 1999) ("Therapeutic Drugs," Ex. 1036).

Claims	Basis	References
18	35 U.S.C. § 103	Therapeutic Drugs, EP 5.4, Dean, Akkermans, and Nerenberg
18	35 U.S.C. § 103	Therapeutic Drugs, EP 2001, Dean, Akkermans, and Nerenberg

Paper 15, 9, 35 ("Institution Decision" or "Inst. Dec.").

Patent Owner filed a Response. Paper 25 ("PO Resp."). Patent Owner supported its Response with the Declaration of Jonathan L. Sessler, Ph.D. (Ex. 2062). Petitioner filed a Reply. Paper 28 ("Reply"). On our authorization (Papers 31 and 32), Patent Owner filed a Sur-reply (Paper 35, "Sur-reply"), and Petitioner filed a Sur-sur-reply (Paper 44, "Sur-sur-reply"). Patent Owner's Sur-reply was accompanied by a Second Declaration of Jonathan L. Sessler, Ph.D. (Ex. 2072).

Both parties also filed Motions to Exclude Evidence. Paper 39 ("PO Mot."); Paper 40 ("Pet. Mot."). Each party filed an Opposition to the other's Motion to Exclude (Paper 42, "PO Opp."; Paper 43, "Pet. Opp."), and Replies (Paper 46, "PO Opp. Reply"; Paper 47, "Pet. Opp. Reply").

An oral hearing was held on April 3, 2019. Paper 38. A transcript of the hearing is included in the record. Paper 48 ("Tr.").

B. Related Proceedings

This proceeding is related to IPR2018-00182, which is an *inter partes* review of U.S. Patent No. 9,382,220 B2 ("the '220 patent," Ex. 1001). Petitioner states that the '220 patent is a parent of the '621 patent. Pet. 5. Petitioner identifies U.S. Application No. 15/619,199, filed June 9, 2017, as a related matter under 37 C.F.R. § 42.8(b)(2). *Id.* Petitioner states that this application claims priority to the '621 patent and is currently pending. *Id.*

C. The '621 Patent

The '621 patent relates to methods for the synthesis and purification of 3,7-diamino-phenothiazin-5-ium compounds ("diaminophenothiazinium compounds"), namely methylthioninium chloride (MTC), also known as methylene blue. Ex. 1002, Abstract. The '621 patent discloses and claims methods of treating tauopathy and methemoglobinemia[8] with diaminophenothiazinium compounds that are at least 98% pure. *See, e.g., id.* at 81:64–82:28 (claim 1), 83:28–84:9 (claim 13).

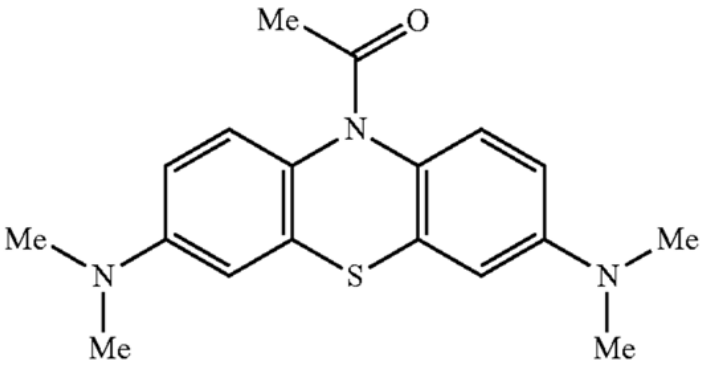
The '621 patent explains that MTC was first described in 1877, and that researchers have disclosed several methods of synthesizing and purifying MTC since that time. *Id.* at 2:65–4:67 (describing prior-art synthesis and purification methods). According to the '621 patent, however, MTC formulations contain substantial amounts of highly undesirable metal impurities, such as aluminum, chromium, iron, and copper. *Id.* at 6:10–13.

[8] Tauopathies are diseases associated with the pathological aggregation of the tau protein, such as Alzheimer's disease. *See* Ex. 1038, Abstract. Methemoglobinemia is a condition in which hemoglobin in the bloodstream is oxidized to methemoglobin, and the blood cannot deliver oxygen to the body. *See* Ex. 1002, 5:2–4; Ex. 1039, 193.

"Consequently," the '621 patent continues, "there is a great need for higher purity (e.g., pharmaceutical grade purity, e.g., a purity safe for human consumption, e.g., with low or reduced organic and/or metal impurity content) diaminophenothiazinium compounds, including MTC." *Id.* at 6:14–18.

The '621 patent states that "[t]he inventors have developed methods for the synthesis of diaminophenothiazinium compounds (including MTC), that yield products with extremely high purity and in particular, products with extremely low levels of undesired impurities (both organic and metal impurities)." *Id.* at 6:19–25. According to the '621 patent, "MTC prepared by the methods described herein is the purest available worldwide." *Id.* at 6:26–27.

The '621 patent teaches that "[t]he methods of synthesis and/or purification of a diaminophenothiazinium compound . . . proceed via an acylated reagent compound (ARC)." *Id.* at 12:26–31. In a preferred embodiment, the ARC is 3,7-di(dimethylamino)-10-acetyl-phenothiazine, shown below:



Id. at 12:65–13:10. The '621 patent explains that ARC compounds are known, and may be obtained through various known synthesis routes. *Id.* at

13:12–16:10. But "[w]hatever synthesis route is taken, an acylation (e.g., acetylation) step is involved, specifically, a step of acylating (e.g., acetylating) an upstream precursor of the acylated (e.g., acetylated) reagent compound, and, ultimately, an acylated (e.g., acetylated) reagent compound (ARC) is obtained." *Id.* at 16:12–17. According to the '621 patent, MTC (or methylene blue) is "an especially preferred" precursor. *Id.* at 17:16–29.

The '621 patent provides an example whereby a commercially available composition of MTC that contains more than 5% by weight of the impurity Azure B serves as the upstream precursor of ARC. *Id.* at 18:64–20:55. According to the '621 patent, removal of Azure B from MTC mixtures is normally very difficult. *Id.* at 18:67–19:2. "However, when such a mixture is used as a starting material, and an acetylation step is employed, acetylation of the Azure B leads to a di-acetylated water-soluble by-product that may easily be separated from the desired organic-soluble acetylated reagent compound, for example, by washing with water and recrystallisation." *Id.* at 19:2–7. The '621 patent states that other impurities, including Azure A and Azure C, "are similarly reduced by the same mechanism." *Id.* at 20:7–8.

The '621 patent states that "the inventors believe that the use of an acylation step (e.g., an acetylation step), and the formation of an acylated reagent compound (ARC) . . . or an acylated upstream precursor of the acylated reagent compound . . . facilitates the easy removal of many undesired impurities and by-products, and leads, ultimately, to an acylated reagent compound (ARC) . . . with higher purity, which, in turn, leads to a

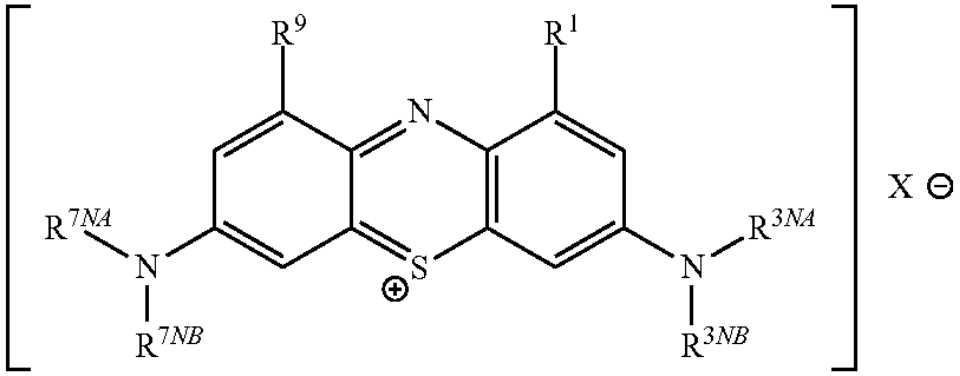
target diaminophenothiazinium compound . . . with a higher purity." *Id.* at 18:51–63.

To obtain the final diaminophenothiazinium compound, in one embodiment, ARC is purified and then deacylated to form "a corresponding deacylated compound." *Id.* at 23:5–8. The deacylated compound is then oxidized to give the diaminophenothiazinium compound. *Id.* at 23:9–10.

D. The Challenged Claims

Petitioner challenges claims 1–20 of the '621 patent. Method claims 1–20 are directed to either a method for treating tauopathy (claims 1–12), or a method of treating methemoglobinemia (claims 13–20). Ex. 1002, 81:64–84:49. Claim 1 is independent and illustrative of claims directed to treating a tauopathy:

> 1. A method of treatment of a tauopathy in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a high-purity diaminophenothiazinium compound of the following formula:



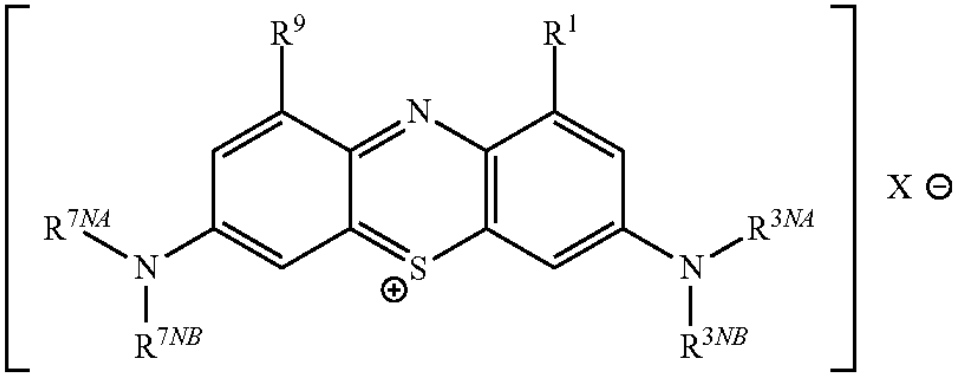
wherein:

each of R^1 and R^9 is independently –H, $C_{1–4}$alkyl, $C_{2–4}$alkenyl, or halogenated $C_{1–4}$alkyl;
each of R^{3NA} and R^{3NB} is independently $C_{1–4}$alkyl, $C_{2–4}$alkenyl, or halogenated $C_{1–4}$alkyl;
each of R^{7NA} and R^{7NB} is independently $C_{1–4}$alkyl, $C_{2–4}$alkenyl, or halogenated $C_{1–4}$alkyl; and
X is one or more anionic counter ions to achieve electrical neutrality;
wherein high-purity is defined by:
at least 98% pure;
less than 1% Azure B as impurity:
less than 0.15% Azure A as impurity;
less than 0.15% Azure C as impurity; and
less than 0.05% Methylene Violet Bernthsen (MVB) as impurity.

Ex. 1002, 81:64–82:26.

Claim 13 is independent and illustrative of claims directed to treating methemoglobinemia:

13. A method of treatment of a methemoglobinemia in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a high-purity diaminophenothiazinium compound of the following formula:



wherein:

each of R_1 and R_9 is independently –H, $C_{1–4}$alkyl, $C_{2–4}$alkenyl, or halogenated $C_{1–4}$alkyl;
each of R_{3NA} and R_{3NB} is independently $C_{1–4}$alkyl, $C_{2–4}$alkenyl, or halogenated $C_{1–4}$alkyl;
each of R_{7NA} and R_{7NB} is independently $C_{1–4}$alkyl, $C_{2–4}$alkenyl, or halogenated $C_{1–4}$alkyl; and
X is one or more anionic counter ions to achieve electrical neutrality; and
wherein high-purity is characterized by:
a purity of greater than 98%;
less than 1% Azure B as impurity:
less than 0.15% Azure A as impurity;
less than 0.15% Azure C as impurity; and
less than 0.05% Methylene Violet Bernthsen (MVB) as impurity.

Id. at 83:28–84:9.

II. PATENTABILITY ANALYSIS

We have reviewed the parties' respective briefs as well as the relevant evidence discussed in those papers. We determine that Petitioner has not shown by a preponderance of the evidence that the claims of the '621 patent as challenged are unpatentable under 35 U.S.C. § 103(a) for two independent reasons. First, upon consideration of the record following trial, Petitioner has failed to prove by a preponderance of the evidence its factual premise that the prior art taught commercially available high-purity methylene blue compositions. Second, upon consideration of the record following trial, Petitioner has failed to prove by a preponderance of the evidence that an ordinarily skilled artisan would have had a reasonable expectation of success in using routine chromatography methods (e.g., high-performance liquid chromatography (HPLC)) to further purify methylene blue compositions to obtain at least 98% purity.

A. Principles of Law

To prevail in its challenges to the patentability of all claims of the '621 patent, Petitioner must demonstrate by a preponderance of the evidence that the claims are unpatentable. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d). "In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable." *Harmonic Inc. v. Avid. Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016); *see also* 35 U.S.C. § 312(a)(3) (requiring *inter partes* review petitions to identify "with particularity . . . the evidence that supports the grounds for the challenge to each claim"). That burden of persuasion never shifts to Patent Owner. *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015); *see also In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1375–78 (Fed. Cir. 2016) (discussing the burden of proof in *inter partes* review).

A claim is unpatentable for obviousness if, to one of ordinary skill in the pertinent art, "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made." 35 U.S.C. § 103(a) (2006); *see also 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 the scope and content of the prior art, any differences between the claimed subject matter and the prior art, the level of ordinary skill in the art, and objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). A petitioner cannot satisfy its burden of proving obviousness by employing "mere conclusory statements."

Magnum Oil, 829 F.3d at 1380. Moreover, a decision on the ground of obviousness must include "articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR*, 550 U.S. at 418 (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)). We analyze the asserted grounds of unpatentability in accordance with the above-stated principles.

B. Level of Ordinary Skill in the Art

We begin with the level of ordinary skill in the art. The ordinarily skilled artisan is a hypothetical person who is presumed to have known the relevant art at the time of the invention. *In re GPAC, Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995). Petitioner asserts, and Patent Owner does not dispute, that the relevant "time of the invention" in this case is July 11, 2006—the effective filing date of the application leading to the '621 patent. *See* Pet. 7; *see generally* PO Resp.

Petitioner asserts that an ordinarily skilled artisan at the time of the invention would have had "a bachelor of science degree plus five years of relevant work experience," or an "advanced degree[]—e.g., Ph.D. or Pharm.D.—while having fewer years of experience." Pet. 7 (citing Ex. 1003 ¶ 56). Petitioner also asserts that "a POSA in the relevant field would have had education and/or experience in the field of small molecules and purification methods, with knowledge of the scientific literature concerning the same, including some understanding of methylene blue and routine separation techniques such as high performance liquid chromatography, ion exchange chromatography, and thin layer chromatography." *Id.* Patent

Owner does not dispute this definition of the level of ordinary skill in the art. *See generally* PO Resp.

At institution, we preliminarily determined that the prior art itself was sufficient to demonstrate the level of ordinary skill in the art at the time of the invention. Inst. Dec. 10. For this Decision, we maintain that the prior art demonstrates the appropriate level of ordinary skill in the art. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (the prior art, itself, can reflect appropriate level of ordinary skill in art).

Nevertheless, for further clarity, we also find that an ordinarily skilled artisan would have had a doctorate degree in a scientific discipline related to small molecules and purification methods, such as chemistry and biochemistry. We agree with Petitioner that, in some cases, the ordinarily skilled artisan may have had less formal education, e.g., a bachelor's degree, but more relevant work experience, e.g., five or more years in a laboratory setting. We also find that an ordinarily skilled artisan would have had skills and/or knowledge related to the use of HPLC. Ex. 1003 ¶¶ 14–16; Ex. 2062 ¶¶ 31–32.

Finally, we consider each parties' declarant—Dr. Armstrong and Dr. Sessler—qualified to opine as to the perspective of an ordinarily skilled artisan at the time of the invention. *See* Ex. 1004 (curriculum vitae of Dr. Armstrong); Ex. 2035 (curriculum vitae of Dr. Sessler).

C. Broadest Reasonable Interpretation

Having defined the ordinarily skilled artisan, we now turn to claim construction. For petitions filed before November 13, 2018,[9] 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) (2017); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016). Under that standard, we presume that a claim term carries its "ordinary and customary meaning," which "is the meaning that the term would have to a person of ordinary skill in the art in question" at the time of the invention. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007).

At the conclusion of trial, we discern no dispute between Petitioner and Patent Owner over the meaning of any claim term. We agree with the parties that no claim term requires express interpretation here to resolve the issues in this *inter partes* review. *See Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) (stating that only those claim terms or phrases that are in controversy need be construed, and only to the extent necessary to resolve the controversy).

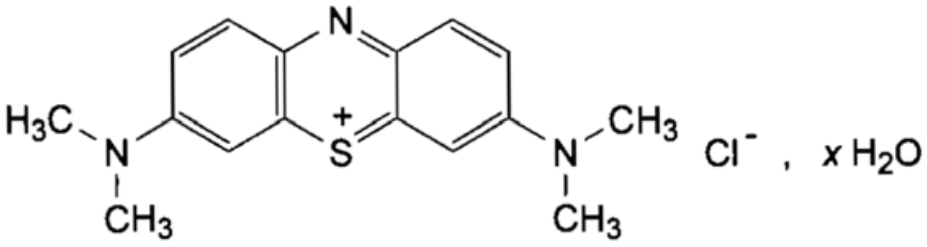
[9] *See Changes to the Claim Construction Standard for Interpreting Claims in Trial Proceedings Before the Patent Trial and Appeal Board*, 83 Fed. Reg. 51,340 (Oct. 11, 2018) (amending 37 C.F.R. § 42.100(b) effective November 13, 2018 to require a federal district court claim construction approach) (to be codified at 37 C.F.R. pt. 42).

D. Overview of Asserted References

Before turning to Petitioner's asserted grounds of unpatentability, we provide an overview of the asserted references.

1. EP 5.4

EP 5.4 provides a monograph for MTC that sets forth the chemical structure, definition, and characteristics of MTC, as well as means for identifying, tests, assay, storage, and impurities information. Ex. 1027, 3977–79.[10] Specifically, EU 5.4 provides the following structure for MTC:



Id. at 3977. For the "Definition," EP 5.4 states that MTC is "3,7-Bis(dimethylamino)phenothiazin-5-ylium chloride (methylene blue)" and has a "[c]ontent" of "95.0 per cent to 101.0 per cent (dried substance)." *Id.*

2. EP 2001

EP 2001 also provides a monograph for MTC that sets forth the chemical structure, definition, and characteristics of MTC, as well as means for identifying, tests, assay, storage, and impurities information. Ex. 1028, 1131–33. Under "Definition," EP 2001 states:

> Methylthioninium chloride (methylene blue) contains not less than 95.0 per cent and not more than the equivalent of 101.0 per

[10] For this and other references, to the extent possible, we use the original page numbers rather than those added by Petitioner.

> cent of 3,7-bis(dimethylamino)phenothiazin-5-ylium chloride, calculated with reference to the dried substance.

Id. at 1132.

3. Akkermans

Akkermans provides a comparison study of the voltammetry of the aqueous two-electron reduction of methylene green and methylene blue. Ex. 1033, Abstract. Akkermans states that these experiments used methylene blue in salt form ($C_{16}H_{18}N_3S^+ \bullet Cl— \bullet 3H_2O$), and further states "Aldrich, 99%." *Id.* at 9989.

4. Nerenberg

Nerenberg describes the purification of four thiazin dyes, including methylene blue. Ex. 1035, Abstract. Nerenberg explains that "[i]t is generally known that most dyes employed in the biological laboratory contain considerable amounts of contaminants." *Id.* at 75. Even so, "no major attempt has been made in the past to devise proper methods for the isolation of substantial amounts of these compounds in a purity comparable to that of drugs." *Id.* at 76. Thus, Nerenberg set out "to work out a relatively simple and reliable analytical method for detecting inorganic and organic impurities in" methylene blue, and "to devise an efficient purification procedure for" this dye. *Id.* Nerenberg detected both organic impurities and inorganic impurities in the thiazine dyes via paper chromatography, and purified the dyes via ion-exchange resins and alumina columns. *Id.* Specifically, Nerenberg determined that commercial preparations of methylene blue contained Azure B as an organic contaminant, and metallic cations as inorganic contaminants. *Id.* at 82.

5. Therapeutic Drugs

Therapeutic Drugs provides a description of methylene blue. Ex. 1036, M117–M118. Therapeutic Drugs states that methylene blue "is used in the treatment of drug-induced and some forms of genetic methemoglobinemia." *Id.* at M117. Therapeutic Drugs also states that methylene blue pharmaceuticals are "available from several manufacturers" for both "oral and parenteral administration." *Id.* In oral form, one manufacturer provides coated tablets that contain 65 mg methylene blue. *Id.* Therapeutic Drugs explains that to treat methemoglobinemia, methylene blue should be administered orally in an amount of 3 to 6 $mg.kg^{-1}$, which is generally 300 mg daily in adults. *Id.*

6. WO '720

WO '720 relates to tauopathies—diseases associated with the pathological aggregation of the tau protein, such as Alzheimer's disease. Ex. 1038, Abstract. WO '720 discloses a method for screening for modulators of the aggregation process. *Id.* WO '720 states that methylene blue "inhibit[s] pathological induced conformational polymerisation of proteins such as tau," and is of "particular interest as [a] potential therapeutic agent[] for use in the prevention of tautau aggregation in diseases such as Alzheimer's Disease." *Id.* at 29.

7. Dean

Dean discloses the use of HPLC for "separating and quantitating the components of thiazine dyes," including methylene blue, "and compound blood stains." Ex. 1072, Abstract. Dean teaches that degradation products of methylene blue include Azure A, Azure B, Azure C, and methylene violet. *Id.* at 288. Dean reports that resolution of a commercial sample of methylene blue composition by HPLC shows that the composition was contaminated with Azure B. *Id.* at 300.

E. Alleged Obviousness of Claims 1–5 and 8–10

Petitioner contends that claims 1–5 and 8–10 are unpatentable as obvious over WO '720, EP 5.4 or EP 2001, Dean, and Akkermans. *See* Pet. 20–45. These claims are directed to method of treatment with a high-purity methylene blue. Thus, we focus our analysis on the method of treatment with methylene blue (i.e., a method of treatment of a methemoglobinemia or of a tauopathy), rather than the process by which the high-purity methylene blue was made.

Although there can be no dispute that methylene blue is an old compound, the issue in this case is whether Petitioner has shown by a preponderance of the evidence that treatment with a methylene blue having at least 98% purity would have been obvious. *See Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1301 (Fed. Cir. 2007) ("[I]solation of interesting compounds is a mainstay of the chemist's art. *If it is known how to perform such an isolation*, doing so 'is likely the product not of innovation but of ordinary skill and common sense.'" (quoting *KSR*, 550 U.S. at 421 (emphasis added))). In this, Petitioner fails.

1. Brief summary of Petitioner's obviousness contentions

Petitioner contends that a high-purity methylene blue compound, as recited in the challenged claims, would have been obvious to an ordinarily skilled artisan. *E.g.*, Pet. 20–27, 35–45. Petitioner contends that, before July 11, 2006, skilled artisans knew that methylene blue compositions included organic impurities (e.g., Azure A, Azure B, Azure C, and MVB), as well as inorganic impurities (e.g., metals). *Id.* at 10–12, 23. Petitioner contends that the ordinarily skilled artisan would have been motivated to use conventional separation techniques, such as HPLC, to remove those impurities from methylene blue compositions. *Id.* at 12–20, 24–26. Specifically, Petitioner contends that high-purity methylene blue compositions were known and commercially available, as evidenced by EP 5.4, EP 2001, and Akkermans. *Id.* at 12–13, 22, 41.

Starting with these high-purity methylene blue compositions, Petitioner contends, the skilled artisan would have been prompted to use HPLC "to purify methylene blue well beyond the claimed ranges." *Id.* at 23–24; *see also id.* at 25 (stating that an ordinarily skilled artisan "would have conducted routine experimentation starting with a methylene blue composition such as 95% methylene blue or 99% methylene blue and ultimately arrived at the recited 'at least 98%' methylene blue"). Petitioner contends that the skilled artisan would have had a reasonable expectation of success in doing so, because "[t]here would be nothing challenging with using HPLC by the time of the '621 patent," i.e., routine experimentation was all that was required, and because the use of HPLC to purify methylene blue was suggested by EP 5.4 and EP 2001. *Id.* at 25; *see also id.* at 19–20.

2. The prior-art methylene blue compositions

At the outset, we find Petitioner's contention that the prior art taught high-purity methylene blue, Pet. 12–13, unsupported by the record evidence at the conclusion of trial. Specifically, Petitioner contends that, "[b]y 2006, highly pure methylene blue compositions, such as those comprising greater than 98% methylene blue, were commercially available." *Id.* at 12.

As evidence, Petitioner relies in its claim charts on (1) EP 5.4 as "recit[ing] methylene blue contains 'not less than 95.0 per cent and not more than the equivalent of 101.0 per cent of 3,7-bis(dimethylamino) phenothiazine-5-ylium chloride [methylene blue],'" *id.* at 22 (quoting Ex. 1027, 3–4[11]); (2) Akkermans as "disclos[ing] a commercial 99% methylene blue composition," *id.* (citing Ex. 1033, 9989); and (3) EP 2001 as "recit[ing] methylene blue contains 'not less than 95.0 per cent and not more than the equivalent of 101.0 per cent of 3,7-bis(dimethylamino) phenothiazine-5-ylium chloride [methylene blue],'" *id.* at 41 (quoting Ex. 1028, 5).

We agree with Patent Owner, however, and find that the percentages recited in these references do not, as a matter of fact, refer to the purity of methylene blue. *See* PO Resp. 4–5. We discuss what the disclosures of each reference teach below.

[11] Here, Petitioner confuses the disclosure of EP 5.4 with that of EP 2001. *Compare* Ex. 1027, 3977 (stating "95.0 per cent to 101.0 per cent"), *with* Ex. 1028, 1132 (stating "not less than 95.0 per cent and not more than the equivalent of 101.0 per cent").

a. EP 5.4 and EP 2001

EP 5.4 sets forth a monograph for methylene blue, and, under the heading "Definition," states that the "[c]ontent" is "95.0 per cent to 101.0 per cent (dried substance)." Ex. 1027, 3977. EP 2001 also sets forth a monograph for methylene blue, which states, under the heading "Definition," that methylene blue "contains not less than 95.0 per cent and not more than the equivalent of 101.0 per cent of 3,7-bis(dimethylamino)phenothiazine-5-ylium chloride calculated with reference to the dried substance." Ex. 1028, 1132.

Petitioner contends that these references teach a methylene blue composition having at least 95% purity. Pet. 22, 41. Dr. Armstrong also testifies that EP 5.4 and EP 2001 disclose a purity of at least "95% to 101% methylene blue." Ex. 1003 ¶¶ 106, 204. The preponderance of the evidence adduced at trial, however, does not support these contentions.

To begin, we credit and rely on Dr. Sessler's explanation as supported by the evidence of record that EP 5.4 and EP 2001 (collectively, "the EP references") provide a content for methylene blue that is determined using a non-specific assay. Ex. 2062 ¶¶ 80–84. Specifically, EP 5.4 states, in the footer, that "General Notices (1) apply to all monographs and other texts." *See* Ex. 1027, 3977. These "General Notices" are found in European Pharmacopoeia 5.0. *See* Ex. 2045, 5–10.[12] Under "Limits of content," the

[12] Although Petitioner did not provide a copy of the European Pharmacopoeia 5.0, EP 5.4 is a supplement of the fifth edition of the European Pharmacopoeia, and is meant to be read in conjunction with that reference. *See* Ex. 2062 ¶ 80; Ex. 2045, third page (stating that European Pharmacopoeia 5.0 "will be complemented by *non-cumulative supplements*" including supplement 5.4 (emphasis in original)).

General Notices state that "[w]here limits of content are prescribed, they are those determined by the method under Assay." *Id.* at 7. Turning back to the monographs, the "Assay" is described as a thiosulfate titration that utilizes potassium dichromate to determine the amount of methylene blue in a composition. Ex. 1027, 3978 (EP 5.4); Ex. 1028, 1133 (EP 2001); *see also* Ex. 2062 ¶ 84.

Of importance here, the record supports Patent Owner's argument that a thiosulfate titration is not capable of distinguishing between methylene blue and its closely related thiazine impurities, i.e., Azure B and Azure A. PO Resp. 56–57. This is because the potassium dichromate used in the thiosulfate titration reacts with not only methylene blue, but also with Azure B and Azure A, because these impurities "contain the same functional group on which the titration of the drug material is based." Ex. 2044, 932[13]; Ex. 2043, 744–45[14]; Ex. 2062 ¶ 84; *see also* Ex. 2058 (stating that Azure B is "structurally identical with Methylene Blue itself").

Put together, then, we find that the preponderance of the evidence supports Dr. Sessler's testimony that the Assay disclosed in the EP references measures *total dye content*, i.e., the sum of the active ingredient and its closely related impurities, rather than the purity of the methylene blue in the composition. Ex. 2062 ¶ 84; *see also* Ex. 2044, 934.

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[13] Sándor Görög, *The sacred cow: the questionable role of assay methods in characterising the quality of bulk pharmaceuticals*, 36 J. PHARM. BIOMED. ANAL. 931–37 (2005) (Ex. 2044).

[14] W. J. MacNeal and J.A. Killian, *Chemical Studies on Polychrome Methylene Blue*, 48 POLYCHROME METHYLENE BLUE 740–47 (1926) (Ex. 2043).

We also note that Dr. Armstrong, during his cross-examination, admitted that potassium dichromate would react with both methylene blue and Azure B, and thus could not distinguish between methylene blue and that impurity. Ex. 1096[15], 121:18–122:19. Put differently, the "95% to 101%" content in the EP references provides, as Dr. Armstrong admitted, "a total amount of dye content." *Id.* at 122:14–19. Similarly, during our oral hearing, counsel for Petitioner conceded that the "95% to 101%" range in the EP references may refer to total dye content. Tr. 28:6–13 ("And the EP Pharmacopoeia, it's true, that is a nonspecific assay. . . . [A]nd so what that means is that it could be total dye content.").

For these reasons, we find—consistent with Dr. Sessler's testimony—that an ordinarily skilled artisan would not have understood "95% to 101%" in the EP references to teach a purity of at least 95% to 101% methylene blue. Instead, that skilled artisan would have understood "95% to 101%" to refer to total dye content, including impurities such as Azure B and Azure A. Ex. 2062 ¶¶ 193, 222–27; PO Resp. 57.

b. Akkermans

As explained above, Akkermans provides a comparison study of the voltammetry of the aqueous two-electron reduction of methylene green and methylene blue. Ex. 1033, Abstract. Akkermans states that these experiments used "methylene blue (as the salt $C_{16}H_{18}N_3S^+ \bullet Cl^- \bullet 3H_2O$) (Aldrich, 99%)." *Id.* at 9989. Petitioner relies on this statement for its

[15] Two transcripts of Dr. Armstrong's September 13, 2018, testimony have been entered into the record. *See* Ex. 1096 (entered by Petitioner); Ex. 2036 (entered by Patent Owner). Because both transcripts appear to be identical, we refer to Exhibit 1096 for convenience.

contention that "Akkermans provided a commercially available methylene blue composition comprising 99% methylene blue." Pet. 36. Again, we find that Petitioner fails to meet its burden to prove, by a preponderance of the evidence, that Akkermans teaches a 99% *pure* methylene blue.

Patent Owner introduced into the record fifteen editions of the Aldrich Catalog dating from 1973 to 2001, i.e., both well before and immediately after Akkermans' 1999 publication date. *See* Ex. 2013, 2, 4–63; *see also* PO Resp. 60–61. As Dr. Sessler explains and the record supports, beginning with the 1984–1985 edition, the Aldrich Catalog offered for sale a methylene blue product having the product number "No. 86,124–3." Ex. 2062 ¶ 197; Ex. 2013. In each of those catalogs, the "[d]ye content" of the methylene blue product is described as "~85%." Ex. 2062 ¶ 197; Ex. 2013, 30 (1984–1985 edition), 35 (1986–1987 edition), 38 (1988–1989 edition), 43 (1990–1991 edition), 46 (1992–1993 edition), 51 (1994–1995 edition), 54 (1996–1997 edition), 59 (1998–1999 edition), 62 (2000–2001 edition). Thus, no Aldrich Catalog either before or immediately after the Akkermans' publication date refers to a "99%" methylene blue product. *Id.*[16]

Taking into account the record as a whole, we find the Aldrich Catalogs themselves to be specific and credible evidence that Aldrich did

[16] And, for the reasons explained above, we agree with Patent Owner that an ordinarily skilled artisan would have understood "dye content" in the Aldrich Catalogs as referring to *total dye content*, i.e., methylene blue and its impurities, rather than the purity of the methylene blue itself. Ex. 2062 ¶ 197.

not, in fact, provide a 99% pure methylene blue composition, notwithstanding the disclosure of Akkermans. This evidence refutes the contentions of Petitioner and Dr. Armstrong that "Akkermans provided a commercially available methylene blue composition comprising 99% methylene blue." Pet. 36; Ex. 1003 ¶ 83.

In its Sur-sur-reply, Petitioner reiterates its argument that Akkermans discloses a 99% pure methylene blue, stating that Akkermans "is unequivocal in [reciting] 99% pure MB," and that Akkermans "recites the chemical formula for MB and that it is 99% pure." Sur-sur-reply, 13 (emphasis omitted). We are not persuaded. We are not pointed to any disclosure in Akkermans that uses the word "pure"; Akkermans simply states, "(Aldrich, 99%)." Ex. 1033, 9989. Petitioner points to no credible, supporting evidence in its Sur-sur-reply that an ordinarily skilled artisan would have understood that "(Aldrich, 99%)" refers to the purity of methylene blue. And, as explained above, the preponderance of the evidence in this record contradicts this assertion.

In its Opposition to Patent Owner's Motion to Exclude, Petitioner advances a new theory that Akkermans is not quoting an Aldrich Catalog. Pet. Opp. 10 (stating that "Patent Owner assumes that Akkermans is quoting an Aldrich catalog"). This new argument lacks credible evidentiary support, and is, in any event, contradicted by Dr. Armstrong's statement in his Declaration that "Akkermans provided a *commercially available* methylene blue composition comprising 99% methylene blue," Ex. 1003 ¶ 106 (emphasis added), and by Dr. Armstrong's deposition testimony that "*Aldrich* also made a 99 percent" methylene blue "that was published in . . .

Akkermans," Ex. 1097, 72:6–12 (emphasis added); *see also id.* at 80:1–81:24 (testifying that Akkermans "obtained 99 percent pure methylene blue from a commercial source"). These statements necessarily indicate that Petitioner's position was that Akkermans references an Aldrich product.

For all these reasons, we find that Petitioner fails to prove that an ordinarily skilled artisan would have understood "(Aldrich, 99%)" in Akkermans as teaching or suggesting the purity of methylene blue.

c. Other references cited in the Petition

Although not part of its obviousness grounds, in its Petition, Petitioner refers to other alleged examples of high-purity methylene blue commercially available before July 11, 2006. *See* Pet. 3 (citing Exs. 1031, 1032, and 1073); *id.* at 12–13 (citing Exs. 1030, 1031, and 1032); *see also* Ex. 1003 ¶¶ 83–84 (stating that "[p]rior to 2006, high-purity methylene blue compositions were commercially available–touting purity levels such as 98% and 99%"). These examples, however, suffer from the same deficiencies highlighted above: Petitioner fails to prove that the percentages, in fact, refer to the purity of the methylene blue.

Petitioner cites to Exhibit 1031[17] and Exhibit 1032[18] (collectively "the Tuite references") as evidence for prior-art methylene blue compositions

[17] Eimer Tuite et al., *Femtosecond deactivation of thionine singlet states by mononucleotides and polynucleotides,* 226 CHEM PHYS LETT., 517–24 (1994) (Exhibit 1031).

[18] Eimer Tuite and John M. Kelly, *The Interaction of Methylene Blue, Azure B, and Thionine with DNA: Formation of Complexes with Polynucleotides and Mononucleotides as Model Systems,* 35 BIOPOLYMERS 419–33 (1995) (Ex. 1032).

having 98% purity. Pet. 12–13; *see also* Ex. 1003 ¶ 83 (citing to the Tuite references as evidence of commercially available "high-purity methylene blue compositions"). The Tuite references describe experiments performed to determine the binding affinities of phenothiazinium dyes, such as methylene blue, to nucleic acids. *See generally* Ex. 1031, Ex. 1032. The Tuite references teach that the experiments used "methylene blue (Fluka puriss grade; 98%)," Ex. 1031, 517, or "methylene blue (98%; Fluka puriss grade)," Ex. 1032, 421. We find, however, that Petitioner presents no credible evidence that "98%" refers to the purity of methylene blue, as opposed to the total dye content. Instead, we credit and rely on Dr. Sessler's testimony that an ordinarily skilled artisan "would have understood that, as with Akkermans, the Fluka 98% figures in the Tuite references refer to total dye content, and not to [methylene blue] purity." Ex. 2062 ¶ 201.

Petitioner cites to Exhibit 1073, the 2004–2005 Aldrich Catalog, as evidence that "500 g of ≥97% methylene blue [was] available for $118.60." *See* Pet. 3 (citing Ex 1073, 1299). But again, we find Petitioner's contention lacks credible support, because the record shows that "≥97%" refers to total dye content, rather than the purity of methylene blue. As Patent Owner explains, and Dr. Sessler's testimony supports, the Aldrich Catalog clearly states that the "≥97%" figure was calculated by "AT." Ex. 1073, 1299. We credit and rely on Dr. Sessler's unrebutted testimony, which is supported by the record evidence, that those skilled in the art would have understood that "AT" stands for "argentometric titration," a titration that measures total dye content rather than purity. PO Resp. 61; *see also* Ex. 2054, 2 (referring to "argentometric (AT)" titration); Ex. 2062 ¶¶ 198–200.

We also credit and rely on Dr. Sessler's unrebutted testimony, which is also supported by record evidence, that an argentometric titration measures chloride ions, and that, because the impurities Azure A, Azure B, and Azure C exist as chloride salts, an argentometric titration would provide—just like a thiosulfate titration—a measure of total dye content, i.e., the sum of methylene blue and its closely related thiazine impurities. Ex. 2062 ¶¶ 199–200; *see also* Ex. 2055, 3273 (describing the argentometric titration of chloride ions), Ex. 2040, 109, 112, 118 (showing that Azure A, Azure B, and Azure C exist as chloride salts). Thus, like the EP references, Petitioner fails to prove that the 2004–2005 Aldrich Catalog teaches a ≥97% pure methylene blue.

Finally, Petitioner cites to Exhibit 1030, the 1980 United States Pharmacopeia, as disclosing "that methylene blue compositions should comprise 'not less than 98.0 percent and not more than 103.0 percent of $C_{16}H_{18}ClN_3S$ [i.e., methylene blue], calculated on the dried basis.'" Pet. 12. Petitioner's contention that the United States Pharmacopeia discloses a 98% to 103% pure methylene blue, however, is undermined by its own statements made to the Australian Patent Office in 2014.

Specifically, Dr. Sessler testifies without rebuttal that Petitioner's parent company is the owner of Australian Patent Application No. 2007274213 ("the Australian application"). Ex. 2062 ¶ 205; *see also* Ex. 2021 ¶ 5. The Australian application was prosecuted by an entity named "Provepharm Life Solutions." *See* Ex. 2038, 1 (stating that "the name of the applicant has been amended to PROVEPHARM LIFE SOLUTIONS"). The Petition lists "Provepharm Inc., Provepharm Life Solutions, and Provepharm

SAS" as each real party-in-interest under 37 C.F.R. § 42.8(b)(1), Pet. 5, and the evidence shows that Petitioner "is the U.S. subsidiary of Provepharm Life Solutions based in Marseille, France," Ex. 2021 ¶ 5. Thus, as a real party-in-interest to this proceeding, we attribute statements made by Provepharm Life Solutions during prosecution of the Australian application to Petitioner.

During prosecution of the Australian application, Petitioner submitted a declaration from Dr. Babak Sayah, Head of the Chemistry Department, dated December 2014 ("the Sayah Declaration"). Ex. 2034, 1–27. Petitioner stated that it had "obtained a sample of the US Pharmacopeia reference standard for methylene blue and the sample has been analysed by the chemistry department of the applicant." *Id.* at 1. Dr. Sayah averred that: "The analysis showed that the chromatography purity of the sample was only 85.792%. Azure B, the main impurity, represented 11.544% of the sample." *Id.* at 5.

This is so even though the monograph for methylene blue in the 2000 United States Pharmacopeia—like the 1980 United States Pharmacopeia—states that "Methylene Blue contains not less than 98.0 percent and not more than 103.0 percent of $C_{16}H_{18}ClN_3S$ [i.e., methylene blue], calculated on the dried basis." *Compare* Ex. 2034, 16 (2000 United States Pharmacopeia), *with* Ex. 1030, 519 (1980 United States Pharmacopeia); *see also* Ex. 2062 ¶ 208. Thus—contrary to its arguments made in this *inter partes* review—Petitioner represented to the Australian Patent Office that the United States Pharmacopeia does not disclose a methylene blue purity of 98% or greater. The Sayah Declaration, instead, suggests that an ordinarily skilled artisan

would not have understood "not less than 98.0 percent and not more than 103.0 percent" to refer to the purity of a methylene blue composition.

We observe that neither Petitioner nor Dr. Armstrong appears to address or acknowledge Petitioner's statements to the Australian Patent Office about the teachings of the United States Pharmacopeia. We consider the Sayah Declaration as containing a statement against interest, and find that Petitioner's current contentions based on the 1980 United States Pharmacopeia lack credible support. *See Gillette Co. v. Energizer Holdings, Inc.*, 405 F.3d 1367, 1374 (Fed. Cir. 2005) (holding party to a "blatant admission" made to the European Patent Office); *see also Garrido v. Holt*, 547 F. App'x 974, 979 n.3 (Fed. Cir. 2013) ("[T]he Board may rely on a patentee's repeated concessions against interest.").

3. The obviousness case fails because it is premised on errors in fact

"[T]he petitioner is master of its complaint." *SAS Inst. Inc. v. Iancu*, 138 S. Ct. 1348, 1355 (2018). Here, Petitioner premises its obviousness grounds of unpatentability on its contention that "[b]y the time of the priority date of the '[621] patent, commercial methylene blue was cheaply available at 97% to 99% purity," Pet. 3, and that an ordinarily skilled artisan "would have conducted routine experimentation starting with a methylene blue composition such as 95% methylene blue or 99% methylene blue and ultimately arrived at the recited 'at least 98%' methylene blue," *id.* at 25.

Petitioner also distinguishes its obviousness case presented in the Petition from that presented by the Examiner during prosecution of the application leading to the '621 patent. *See* Pet. 27. Specifically, Petitioner contends that none of the prior-art references the Examiner cited during

prosecution—unlike here—"actually provided a percentage of methylene blue in the composition and instead simply referred to 'pure' compounds." *Id.* (citing Ex. 1005, 3–11). Thus, in every instance, Petitioner ties its unpatentability analysis to the alleged teachings of methylene blue compositions having specific purity levels that simply could be further purified to the purity levels recited in the claims. *Id.* at 25. And because Petitioner fails to prove, by a preponderance of the evidence, that the prior art teaches those alleged purities of methylene blue, we find that Petitioner fails to demonstrate by a preponderance of the evidence that the challenged claims are unpatentable for obviousness.

In its Reply, Petitioner asserts that its prior-art references "specifically recite high purity, both nominally and in fact, and any potential difference is merely a matter of degree." Reply 14. But Petitioner cites to no specific record evidence supporting this argument. Petitioner also does not define what an ordinarily skilled artisan would consider "a matter of degree."

In sum, we discern no specific and separate argument in the Petition that the claims would have also been obvious if the skilled artisan started with a methylene blue composition having an unknown purity of methylene blue. *See SAS Inst.*, 138 S. Ct. at 1358 ("the petition [is] the centerpiece of the proceeding both before and after institution"). We decline to parse the Petition to make these arguments for Petitioner. *Cf. Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1369 (Fed. Cir. 2016) ("It is of the utmost importance that petitioners in the IPR proceedings adhere to the requirement that the initial petition identify 'with particularity' the 'evidence

that supports the grounds for the challenge to each claim.'" (quoting 35 U.S.C. § 312(a)(3))).

4. Petitioner also fails to adequately establish a reasonable expectation of success

As noted above, we find that Petitioner has failed to prove by a preponderance of the evidence that an ordinarily skilled artisan would have had a reasonable expectation of success in using routine HPLC to purify methylene blue to obtain at least 98% purity. Thus, the Petition also fails for this additional independent reason.

"The reasonable expectation of success requirement refers to the likelihood of success in combining references to meet the limitations of the claimed invention." *Intelligent Bio-Sys.*, 821 F.3d at 1367. It is a subsidiary requirement for obviousness subsumed within the *Graham* factors. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007). In making our findings as to "reasonable expectation of success," we keep in mind that we cannot demand absolute certainty. *See Intelligent Bio-Sys.*, 821 F.3d at 1367 ("While the definition of 'reasonable expectation' is somewhat vague, our case law makes clear that it does not require a certainty of success.").

Petitioner contends that an ordinarily skilled artisan would have had a reasonable expectation that using routine HPLC would purify the methylene blue compositions taught in the EP references or in Akkermans to successfully produce a methylene blue of at least 98% purity. *See, e.g.*, Pet. 24–26. Upon consideration of the entire record, we find again that Petitioner's contentions lack credible support, such that Petitioner has failed to meet its burden to prove unpatentability of the challenged claims by a preponderance of the evidence.

a. Petitioner's contentions as to reasonable expectation of success are contradicted by its previous statements to the USPTO and the EPO

We agree with Patent Owner that Petitioner's contentions in this case are directly contradicted by its previous arguments about the ease (or lack thereof) of using routine purification methods to obtain high-purity methylene blue from conventional methylene blue compositions. To begin, we note that Patent Owner provides evidence, without rebuttal, that Provepharm Life Solutions, a real party-in-interest to this proceeding, is the owner of domestic and foreign patents and patent applications directed to high-purity methylene blue compositions. PO Resp. 22–23; Ex. 2021 ¶ 5 (stating that Provepharm Inc. "is the U.S. subsidiary of Provepharm Life Solutions based in Marseille, France"). For example, Petitioner's parent company is the owner of U.S. Patent No. 8,815,850 ("the '850 patent")[19,20], the Australian application, and European Patent Application No. 11191749.7 ("the EP application").[21,22] Again, we attribute statements made by Provepharm Life Solutions to Petitioner.

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[19] Michel Feraud and Babak Sayah, U.S. Patent No. 8,815,850 (Aug. 26, 2014) (Ex. 1069).

[20] Provepharm Life Solutions was previously named "Provence Technologies," which is listed on the face of the '850 patent as the original Assignee. *See* Ex. 2070 ¶¶ 10–12; Ex. 1069, (73). In 2018, Provence Technologies informed this Office it had changed its name first to "Provepharm Solutions" in 2016, and then to "Provepharm Life Solutions" in 2017. Ex. 2024. Provence Technologies also filed similar notices in a European counterpart to the '850 patent. Ex. 2070 ¶¶ 10–12.

[21] European Patent Application No. 11191740.7 (Dec. 2, 2011) (Ex. 2065).

The ’850 patent is directed to a methylene blue “comprising less than 3% of impurities measured by HPLC under the conditions of the European Pharmacopeia 5.4.” Ex. 1069, 10:48–51. Despite Petitioner’s contentions here, the ’850 patent suggests insufficient purification processes existed in the art before 2006: “Despite the subsequent purification steps, these various processes inevitably produce a methylene blue comprising many metal impurities and also organic impurities, in particular azure B, azure C and azure A.” *Id.* at 2:12–16. The ’850 patent also states that “[t]he European Pharmacopeia was recently amended (April 2006) in terms of an increase in the tolerance thresholds for metal impurities since *no producer of methylene blue was able to produce*, and even less to produce in an industrial amount, a methylene blue of a quality meeting its previous requirements.” *Id.* at 2:26–31 (emphasis added).

In our view, these previous statements to the Office cast considerable doubt on Petitioner’s repeated assertions here that using HPLC in 2006 to purify methylene blue would have been obvious and routine. *See, e.g.*, Pet. 19 (stating that “achieving purity levels greater than 99% prior to the ’621 patent would have been obvious and routine to a POSA”).

Petitioner’s previous statements to the European Patent Office (EPO) are similar, and again, undermine its contentions here. The EP application, like the ’850 patent, is directed to a high-purity methylene blue having less than 3% impurities. *See* Ex. 2020, 3 (claim 15). In a written statement

[22] Each of these documents claim priority to French Patent Application No. 06/06330 having has a priority date of July 12, 2006, which is one day after the July 11, 2006, priority date of the ’220 patent. Ex. 2070 ¶ 3; Ex. 1069, (62); Ex. 2038, (31); Ex. 2065, 2 (25).

appealing the EPO's rejection of the EP application, Petitioner asserted that "[s]eparating MB from its organic and metallic impurities by physico-chemical separation techniques is . . . difficult" because (1) methylene blue "possesses a structure and physico-chemical characteristics that are very close to those of its organic impurities (Azure A, B and C)," and (2) methylene blue "is extremely sensitive to its environment and is readily transformed into Azure B through demethylation." Ex. 2020, 6.

Petitioner further asserted that "metallic and organic impurities *are difficult or impossible* to eliminate once the MB molecule has formed" from conventional processes for making methylene blue. *Id.* at 7 (emphasis added). Petitioner characterized its invention as a high-purity methylene blue that could only be obtained through its novel process providing "passage through an acylated intermediate" that "makes it possible to eliminate the metallic impurities and organic impurities." *Id.*

Of critical importance here, Petitioner asserted that normal physico-chemical separation techniques could *not* purify a methylene blue produced by conventional processes. *See id.* (stating that "the process for obtaining the MB strongly affects the nature and quantity of impurities present in an MB composition"). Instead, Petitioner's new process providing a "passage through an acylated intermediate allows the organic impurities to be eliminated easily by conventional physico-chemical separation methods." *Id.*

We agree with Dr. Sessler that an ordinarily skilled artisan would have understood normal or conventional physico-chemical separation techniques to include HPLC. Ex. 2062 ¶ 210. Indeed, in another document

filed with the EPO in connection with the EP application, Petitioner stated that "[t]he physico-chemical methods of separation are: organic extraction, recrystallization, distillation and chromatography/filtration." Ex. 2016, 18.

Moreover, Petitioner relied on the United States Pharmacopoeia and a certificate of analysis for methylene blue to assert that "it is common to have significant quantities of Azure B associated with MB." Ex. 2020, 15 (citing Ex. 2056 (referred to as "D22"); Ex. 2057 (referred to as "D23")). Petitioner asserted that these documents "show that the reference which was being offered for sale by the American Pharmacopoeia until February 2015 to analyze MB is a product whose organic purity is less than 85% and which contains 11% of Azure B." *Id.* "This document," Petitioner asserted, "illustrates the difficulty of obtaining pure MB." *Id.*

In its Reply, Petitioner contends that its statements to the EPO have been mischaracterized. Pet. 35. We disagree. Petitioner's statements that methylene blue could not be purified to a high purity using conventional techniques could not be clearer. Ex. 2020, 14–15. Petitioner also implies that this *inter partes* review is distinguishable because the EPO proceeding did not include consideration of the prior-art references Dean, Lapen,[23] and Gaudette.[24] Pet. 35.

[23] Daniel Lapen, *A Standardized Differential Stain for Hematology*, 2(5) CYTOMETRY 309–315 (1982) ("Lapen," Ex. 1071).

[24] Norman F. Gaudette & Jon W. Lodge, *Determination of Methylene Blue and Leucomethylene Blue in Male and Female Fischer 344 Rat Urine and B6C3F1 Mouse Urine*, 29 J. ANAL. TOXICOL. 28–33 (2005) ("Gaudette," Ex. 1052).

As to Lapen and Gaudette, we note that neither is included in any of the grounds of unpatentability in this case, and neither is discussed with particularity in the Petition as required by 35 U.S.C. § 312(a)(3). In any event, we find that Petitioner's own experimental evidence submitted in the EPO directly contradicts its assertions in this case that Dean, Lapen, and Gaudette evince the feasibly of using routine HPLC to purify methylene blue. *See* Ex. 2023, 1–2 (stating that HPLC could not separate commercially available methylene blue from its organic impurities).

In sum, the record in this case contains several contradictory statements made by Petitioner in both this Office and the EPO. Those statements provide strong evidence that, contrary to Petitioner's contentions here, those skilled in the art would not have reasonably expected success in purifying methylene blue from its closely related impurities using conventional separation techniques such as HPLC. Ex. 2020, 14–15; Ex. 2062 ¶ 213; *see also Tanabe Seiyaku Co. v. U.S. Int'l Trade Comm'n*, 109 F.3d 726, 733 (Fed. Cir. 1997) (finding that "representations made to foreign patent offices are relevant to determine whether a person skilled in the art would consider butanone or other ketones to be interchangeable with acetone"). And, at the very least, Petitioner's contradictory statements significantly weaken and undermine the credibility of Petitioner's case, as well as the credibility of Dr. Armstrong's testimony, which is also in direct contradiction to Petitioner's earlier assertions.

b. Petitioner's contentions as to reasonable expectation of success lack credible and persuasive support

The parties present extensive arguments and testimony about an ordinarily skilled artisan's expectation as to whether routine HPLC could be

used to purify methylene blue to the purity level claimed in the '621 patent. *See, e.g.*, Pet. 24–26 (setting forth Petitioner's reasonable-expectation-of-success arguments); PO Resp. 5–9, 31–56; Reply 15–22, 23–35; Sur-reply 5–6, 9–15; Sur-sur-reply, *passim*. After considering the entirety of the arguments, evidence, and the testimony of the respective experts, we are unpersuaded that Petitioner has shown a reasonable expectation of success by a preponderance of the evidence.

To begin, we find Petitioner's generalized and conclusory statements in its Petition that "there would be nothing challenging with using HPLC by the time of the '621 patent—including with methylene blue compositions," because "HPLC was known to achieve purity levels of greater than 99% . . . across a variety of compounds" insufficient to support a reasonable expectation of success. Pet. 25–26. These statements are also contradicted by record evidence that it would have been "difficult or impossible" to purify methylene blue via routine HPLC because (1) methylene blue "possesses a structure and physico-chemical characteristics that are very close to those of its organic impurities (Azure A, B and C)," and (2) methylene blue "is extremely sensitive to its environment and is readily transformed into Azure B through demethylation." Ex. 2020, 6.

We also find unpersuasive Petitioner's reliance on EP 5.4 as supporting a reasonable expectation of success. Specifically, Petitioner argues that "a POSA would have had a reasonable expectation of success because a composition comprising at least 98% methylene blue was within the range of acceptable methylene blue compositions as shown by [EP] 5.4." Pet. 25. But, as explained above, an ordinarily skilled artisan would not

have understood "95% to 101%" in the EP 5.4 to teach a purity of at least 95% to 101% methylene blue. *Supra* § II.E.2.a.

Next, we find ourselves in agreement with Patent Owner that the contentions of Petitioner and Dr. Armstrong—as set forth in the Petition—that each HPLC fraction shown in the chromatograms reproduced in the Petition represents "a purified sample" of the components of a methylene blue composition conclusory and misleading. *See* Pet. 18 (asserting that the peak in Figure 8G of Dean is a "purified fraction[] of methylene blue"); 25 (stating that "a POSA would have had a reasonable expectation of success in purifying methylene blue by HPLC resulting in a highly pure methylene blue composition meeting or exceeding the composition of Claim 1").

We instead credit and agree with Dr. Sessler's testimony that the analytical HPLC process disclosed in Dean would have produced an eluate having significantly greater amounts of glycine and other impurities than methylene blue. *See* Ex. 2062 ¶¶ 107, 112–122. We contrast Dr. Sessler's testimony with Dr. Armstrong's, who states in a conclusory manner that "part of the methylene blue peak" shown "in Figure 8G as well as Figures 6A-6H [of Dean] could be separated to obtain highly pure methylene blue." Ex. 1003 ¶ 103.

Indeed, Dr. Armstrong concludes that, even though Dean teaches that the methylene blue shown on the chromatogram was contaminated with Azure B, "[p]art or all of the methylene blue peak could be separated and re-shot in the chromatograph" without explanation. *Id.* ¶¶ 103–104. We also note that Dr. Armstrong appeared to acknowledge in his deposition the lack

of purity in Dean's fractions. Ex. 1096, 80:1–4, 91:9–22.[25] We find that Dr. Armstrong's testimony amounts to "conclusory statements and unspecific expert testimony" that are insufficient to support Petitioner's obviousness theories. *Arendi S.A.R.L. v. Apple Inc.*, 832 F.3d 1355, 1366 (Fed. Cir. 2016).

Drilled down, Petitioner has at most shown with the teachings of Dean, Lapin, and Gaudette that an ordinarily skilled artisan would have expected HPLC to *resolve* methylene blue from its impurities on a chromatogram. We credit and agree with Dr. Sessler's testimony, however, that Petitioner (and Dr. Armstrong) failed to adequately explain—in its Petition—how an ordinarily skilled artisan would have gone from observing resolved, possibly overlapping, fractions on a chromatogram to obtaining a methylene blue composition of at least 98% purity. Ex. 2062 ¶¶ 107, 117,133–135, 144, 153, 162.[26] We consider such an explanation (with

[25] In its Reply, Petitioner points to a new figure in Dean (Figure 1) to support its reasonable expectation of success argument. Because Petitioner relied on Figures 6 and 8 only in the Petition, however, we decline at this time to consider Figure 1 of Dean. *Compare* Pet. 2–4, 16–18, 22–23, 41 (relying on Figures 6A–6H and 8G of Dean), *with* Reply, 28–29 (relying on Figure 1). *See Ariosa Diagnostics v. Verinata Health, Inc.*, 805 F.3d 1359, 1367–68 (Fed. Cir. 2015) (holding that the Board may refuse to consider different embodiments first identified in a petitioner's reply). In any event, Table III of Dean labels its findings in Figure 1 as "tentative." Ex. 1072, 291.

[26] Dr. Sessler persuasively points to Dr. Armstrong's deposition testimony as containing new procedures for running HPLC wholly absent from the Petition. *See* Ex. 2062 ¶¶ 125–126. We therefore will not consider this testimony.

supporting evidence) critical in this case, given Petitioner's earlier contradictory statements that "metallic and organic impurities *are difficult or impossible* to eliminate once the MB molecule has formed." Ex. 2020, 7 (emphasis added).

c. The Federal Circuit's decision in Mylan is instructive here

That the '621 patent describes a chemical process for obtaining highly pure methylene blue is another factor weighing against a reasonable expectation of success. As explained above, Petitioner argued in the EPO that conventional processes for making methylene blue resulted in a methylene blue that, once formed, could not be separated from its metallic and organic impurities. Ex. 2020, 7. The '621 patent, presumably like Petitioner's EP application, discloses a process "that yield[s] [methylene blue] products with extremely high purity and in particular, products with extremely low levels of undesired impurities (both organic and metal impurities)," by way of an acylated intermediate. Ex. 1002, 6:19–25, 12:25–30; *see also* Ex. 2020, 7 (asserting that the EP application discloses a novel process providing "passage through an acylated intermediate" that "makes it possible to eliminate the metallic impurities and organic impurities"). And, as also explained above, Petitioner told the EPO that commercially available methylene blue obtained by conventional chemical processes could not result in a product that could then be purified by conventional purification techniques.[27]

[27] In a footnote, Petitioner states that the '621 patent "actually uses HPLC to determine the purity of the compositions in its examples." Pet. 13 n.2 (citing Ex. 1002, 71:32–36, 72:57–60). That HPLC may be used to

In this regard, the facts in this case are similar to those presented in *Mylan Institutional LLC v. Aurobindo Pharma Ltd.*, 857 F.3d 858 (Fed. Cir. 2017). The Federal Circuit's decision in that case arose from an appeal from the entry of a preliminary injunction against the defendant for importing and selling isosulfan blue products covered by a certain "purity patent" claiming isosulfan blue "having a purity of at least 99.0% by HPLC." *Id.* at 861–62. The court explained 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). The court found "no error in [the district court's] analysis," stating that "[i]t is clear from the record here that, although [isosulfan blue] was known in the prior art, the path to arrive at [isosulfan blue] with a purity of greater than 99.0% was not known before the relevant date of the '050 patent." *Id.*

We find that the Federal Circuit's reasoning in *Mylan* applies here. As in *Mylan*, Petitioner has failed to adequately show that "the path to arrive" at methylene blue having at least 98% purity was known in the art, especially given the strong evidence that an ordinarily skilled artisan would have considered the purification of methylene blue via HPLC "difficult or impossible" due to methylene blue's close physico-chemical properties and structure to Azure A, Azure B, and Azure C, as well as methylene blue's ready demethylation into Azure B. Ex. 2020, 6–7. Put differently, Petitioner has not shown adequately that "it [was] known how to perform an

confirm purity, however, does not provide us persuasive evidence that HPLC may be used *to purify* methylene blue to the level claimed in the '621 patent.

isolation" of a high-purity methylene blue given the state of the art in 2006. *Aventis*, 499 F.3d at 1301.

Petitioner argues that *Mylan* is not applicable because "[t]here did not appear to be any prior art, as is the case here, disclosing HPLC of the patented compound." Reply 12. "In addition," Petitioner argues, "the District Court was further convinced that the presence of isomers would make HPLC difficult." *Id.* at 12–13 (citing *Mylan Institutional LLC v. Aurobindo Pharma. Ltd.*, 2016 WL 7587325, *19 (E.D. Tex. 2016)). Petitioner argues that methylene blue "is not an isomer of the Azures or MVB." *Id.* at 13.

Again, we find Petitioner's arguments lack persuasive, credible support. First, Petitioner has already stated that methylene blue "possesses a structure and physico-chemical characteristics that are very close to those of its organic impurities (Azure A, B and C)." Ex. 2020, 6. Thus, Petitioner's assertion otherwise in this case lacks credibility. Second, as discussed above, we have considered and rejected Petitioner's argument that *resolving* a composition by HPLC on a chromatograph is the same as *obtaining* a high-purity compound by HPLC.[28] *Supra* II.E.4.b. Third, although methylene blue is not an isomer of its thiazine impurities, there can be no dispute that the Azures A, B, and C are structurally similar to methylene blue.

[28] In any event, it is not clear to us that the prior art of record in the district court case lacked such evidence, as the district court noted that defendant's expert testified that the prior art "teaches that triarylamine dyes can be purified in a range from 96% to 98%." *Mylan*, 2016 WL 7587325 at *19.

Dr. Armstrong, for example, testifies that "methylene blue, Azures A, B, and C, and MVB[] have very similar structures, differing by only a methyl group in the case of methylene blue and Azure B." Ex. 1003 ¶ 71. In addition, Dean identifies Azure B as the first product of methylene blue degradation. Ex. 1072, 288.

For all these reasons, we are not persuaded by Petitioner's arguments and evidence that the ordinarily skilled artisan would have reasonably expected success in using HPLC to obtain high-purity methylene blue based on the teachings of Dean, the EP references, Lapin, and Gaudette.

5. Conclusion as to obviousness of claims 1–5 and 8–12

In sum, we find that Petitioner has failed to prove by a preponderance of the evidence its factual premise that the prior art taught high-purity methylene blue. We also find that Petitioner has failed to prove by a preponderance of the evidence that an ordinarily skilled artisan would have had a reasonable expectation of success in using routine HPLC to further purify methylene blue to obtain at least 98% purity.[29]

[29] We note that the parties debate the impact of Exhibit 2059 ("Aldrich Letter") as secondary evidence of long-felt need and failure of others. *See, e.g.*, PO Resp. 2–3; Reply 22–23. We need not analyze that evidence in this case, however, because we are not persuaded, for the reasons explained, that Petitioner establishes by a preponderance of the evidence that the subject matter of the challenged claims is taught by the art of record. *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*

After carefully considering the arguments and evidence, therefore, we determine that the record as a whole does not weigh in favor of a conclusion of obviousness. Our conclusion is further confirmed by Petitioner's contradictory statements and evidence submitted to the USPTO, the EPO, and the Australian Patent Office. For these reasons, we conclude that Petitioner has not satisfied its burden of demonstrating, by a preponderance of the evidence, the unpatentability of claims 1–5 and 8–12 of the '621 patent as obvious over WO '720, EP 5.4 or EP 2001, Akkermans, and Dean.

F. Alleged Obviousness of Claims 6 and 7

Petitioner contends that claims 6 and 7 are unpatentable as obvious over WO '720, EP 5.4 or EP 2001, Dean, Akkermans, and Nerenberg. Pet. 45–52. Claims 6 and 7 depend from claim 2, and recite limits on the amounts of inorganic (i.e., metal) impurities in the claimed diaminophenothiazinium compounds. Ex. 1002, 82:47–83:7. Petitioner relies on Nerenberg only for teaching the metal limits recited in claims 6 and 7. Pet. 46 (citing Ex. 1035, 1–2). Because Nerenberg does not remedy the deficiencies of the WO '720, EP references, Dean, and Akkermans, this ground of unpatentability fails for the same reasons discussed above.

G. Alleged Obviousness of Claims 13–17 and 19–20

Petitioner contends that claims 13–17 and 19–20 are unpatentable as obvious over Therapeutic Drugs, EP 5.4 or EP 2001, Dean, and Akkermans. Pet. 52–61. Petitioner relies on Therapeutic Drugs only for a teaching of treating methemoglobinemia with methylene blue. *See, e.g.*, Pet. 52 (citing

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conclusion of obviousness until all those factors are considered." (emphasis added)).

Ex. 1036, 3). Because Therapeutic Drugs does not remedy the deficiencies of the EP references, Dean, and Akkermans, this ground of unpatentability fails for the same reasons discussed above.

H. Alleged Obviousness of Claim 18

Petitioner contends that claim 18 is unpatentable as obvious over Therapeutic Drugs, EP 5.4 or EP2001, Dean, Akkermans, and Nerenberg. Pet. 61–62. Claim 18, like claims 6 and 7, recites limits on the amounts of inorganic (i.e., metal) impurities in the claimed diaminophenothiazinium compounds. Ex. 1002, 84:29–42. Petitioner relies on Nerenberg only for teaching the metal limits recited in claim 18. Pet. 62–63. Because Nerenberg does not remedy the deficiencies of the Therapeutic Drugs, the EP references, Dean, and Akkermans, this ground of unpatentability fails for the same reasons discussed above.

III. EVIDENTIARY MOTIONS

Petitioner and Patent Owner each filed a motion to exclude certain evidence. We address Patent Owner's motion first and then turn to Petitioner's motion.

A. Patent Owner's Motion to Exclude

Patent Owner moves to exclude Akkermans (Ex. 1033) under Federal Rules of Evidence ("FRE") 801 and 802 as impermissible hearsay not subject to the hearsay exceptions in FRE 803 or FRE 804. PO Mot. 1. Petitioner opposes. *See generally* Pet. Opp.

Akkermans states: "methylene blue (as the salt $C_{16}H_{18}N_3S^+ \bullet Cl^- \bullet 3H_2O$) (Aldrich, 99%)." Ex. 1033, 9989. As explained in detail above, Petitioner relies on Akkermans as evidence of "a commercial 99% methylene blue

composition." Pet. 22, 41. Although Patent Owner's arguments for inadmissibility are not without merit, we determine that Akkermans is relevant to the state of the art and whether an ordinarily skilled artisan would have understood "(Aldrich, 99%)" as teaching a 99% pure methylene blue, and not whether the underlying composition was actually of that purity level. Because we are not considering Akkermans' statements for the truth of the matter asserted, we deny Patent Owner's motion to exclude.

B. Petitioner's Motion to Exclude

Petitioner moves to exclude Exhibit 2062 in its entirety, or alternatively, to exclude paragraphs 46–49 and 147–154. Pet. Mot. 1. Patent Owner opposes. *See generally* PO Opp. Exhibit 2062 is the Declaration of Dr. Sessler, filed with Patent Owner's Response.

1. The Entirety of Dr. Sessler's Declaration

As an initial matter, we deny Petitioner's motion to exclude the entirety of Dr. Sessler's declaration. All of Petitioner's arguments go to the admissibility of Dr. Sessler's testimony relating to the solubility of methylene blue, as determined by test results described in paragraphs 48 and 49 of Exhibit 2062, and relating to the isolation of methylene blue from certain nonvolatile solvents, as determined by test results described in paragraphs 149–151 of Exhibit 2062. Petitioner provides no persuasive reason to exclude the entirety of Dr. Sessler's Declaration based on these paragraphs.

2. Paragraphs 46–49 and 147–154

Petitioner moves to exclude paragraphs 46–49 and 147–154 as insufficiently authenticated, relying on insufficient facts and data, and as

containing inadmissible hearsay. Pet. Mot. 1–2. We do not rely on paragraphs 46–49 of Dr. Sessler's Declaration in this Decision, and thus Petitioner's arguments as to those paragraphs are moot.

As to paragraphs 147–154, we rely on paragraph 153 in this Decision. But, even if we accepted as true Petitioner's assertions about the tests described in paragraphs 149–150, those deficiencies do not infect Dr. Sessler's testimony contained in paragraph 153. Specifically, Dr. Sessler describes Dr. Armstrong's testimony and points to deficiencies in that testimony that are not dependent on the testing described in the preceding paragraphs.

In any event, Petitioner's arguments go to the weight we should accord Dr. Sessler's testimony, not to the admissibility of the entire declaration. *See, e.g.*, *Liberty Mut. Ins. Co. v. Progressive Cas. Ins. Co.*, Case CBM2012-00002, slip op. at 70 (PTAB Jan. 23, 2014) (Paper 66) (stating that "the Board, sitting as a non-jury tribunal, is well-positioned to determine and assign appropriate weight to the evidence presented in this trial"). We have considered Petitioner's arguments in weighing Dr. Sessler's testimony.

For these reasons, we deny Petitioner's motion to exclude.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 1–20 of U.S. Patent 9,675,621 B2 have not been shown to be unpatentable under 35 U.S.C. § 103 for obviousness;

FURTHER ORDERED that Patent Owner's Motion to Exclude Evidence is denied;

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

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

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