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Paper 52
Date: September 20, 2018

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ARGENTUM PHARMACEUTICALS LLC,
Petitioner,

v.

ALCON RESEARCH, LTD.,
Patent Owner.

Case IPR2017-01053
Patent 8,268,299 B2

Before GRACE KARAFFA OBERMANN, SUSAN L. C. MITCHELL, and CHRISTOPHER M. KAISER, *Administrative Patent Judges*.

OBERMANN, *Administrative Patent Judge*.

FINAL WRITTEN DECISION
Determining That Claims 1–28 Have Not Been Proven Unpatentable
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

I. INTRODUCTION

The Petition requests *inter partes* review of claims 1–28 of U.S. Patent No. 8,268,299 B2 (Ex. 1001, "the '299 patent"). Paper 2 ("Pet."). Patent Owner filed no preliminary response. After trial institution, Patent Owner filed a Response (Paper 22, "Resp.") and Petitioner filed a Reply (Paper 35). We held a final hearing on April 17, 2018. Paper 51 ("Tr.").

The Board has jurisdiction under 35 U.S.C. § 6. Petitioner bears the burden of demonstrating unpatentability by a preponderance of the evidence, a burden that never shifts to Patent Owner. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d); *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc*., 800 F.3d 1375, 1378 (Fed. Cir. 2015). We issue this decision pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73.

A. Related Matters

The '299 patent was the subject of seven district court actions and a prior *inter partes* review. *See Apotex Corp. v. Alcon Research, Ltd.*, IPR2013-00428 ("the Apotex IPR"). Pet. 1; Paper 3, 2–3. The Apotex IPR was terminated by settlement after trial institution. Apotex IPR, Papers 9, 58, 60. "Petitioner was not a party to any of these cases." Pet. 1.

B. Illustrative Claim

Claim 1, reproduced below, illustrates the claimed subject matter:

1. A multi-dose, self-preserved ophthalmic composition, comprising:

zinc ions at a concentration of 0.04 to 0.4 mM; and

borate and polyol, the borate being present in the composition at a concentration of 0.1 to 2.0% w/v and the polyol being present in the composition at a concentration of 0.25 to 2.5% w/v, the polyol comprising propylene glycol in the composition at a concentration of 0.25 to 1.25% w/v and sorbitol in the composition at a concentration of 0.05 to 0.5% w/v

wherein: (i) the composition has a concentration of anionic species less than 15 mM; and (ii) the composition exhibits sufficient antimicrobial activity to allow the composition to satisfy USP 27 preservative efficacy requirements.

Ex. 1001, 25:31–47.

C. Grounds of Unpatentability

We instituted trial on the following grounds of unpatentability:

(1) Whether claims 1, 2, 4–8, 16, 17, and 20 of the '299 patent are unpatentable under 35 U.S.C. § 103 over Xia[1], Schneider[2], and Chowhan[3];

(2) Whether claim 28 is unpatentable under 35 U.S.C. § 103 over Xia, Schneider, the Travatan® Label[4], and Chowhan;

(3) Whether claims 1–23, 25, and 26 are unpatentable under 35 U.S.C. § 103 over Xia, Schneider, Chowhan, and Gadd[5]; and

(4) Whether claims 24, 27, and 28 are unpatentable under 35 U.S.C. § 103 over Xia, Schneider, the Travatan® Label, Chowhan, and Gadd.

Dec. 17–18; *see* Pet. 2–3 (statement of grounds).

The Petition is supported by Declarations of Dr. Erning Xia (Ex. 1002) and Dr. Yvonne M. Buys (Ex. 1021). The Petition also is accompanied by Declarations of Dr. Richard P. Parrish (Ex. 1022) and Dr. Henry Grabowski (Ex. 1037), which previously were submitted by Patent

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[1] Xia *et al.*, WO 2005/097067, "Zinc Preservative Composition and Method of Use" (filed March 24, 2005; published October 20, 2005) ("Xia") (Ex. 1003).

[2] Schneider *et al.*, U.S. Patent No. 6,011, 062, "Storage-Stable Prostaglandin Compositions" (Filed February 9, 1999; issued January 4, 2000) ("Schneider") (Ex. 1007).

[3] Chowhan *et al.*, U.S. Patent No. 6,143,799, "Use of Borate-Polyol Complexes in Ophthalmic Compositions" (filed July 2, 1998; issued November 7, 2000) ("Chowhan") (Ex. 1004).

[4] FDA Approved Drug Label "TRAVATAN® (travoprost ophthalmic solution) 0.004% Sterile" (2001) ("TRAVATAN® Label") (Ex. 1006).

[5] Gadd *et al.*, "Microorganisms and Heavy Metal Toxicity," *Microbial Ecology*, 4:303–317 (1978) ("Gadd") (Ex. 1005).

Owner in the Apotex IPR. The Response to the Petition is supported by Declarations of Dr. Bhagwati P. Kabra (Ex. 2006), Dr. Stephen Shannon (Ex. 2007), Dr. Soumyajit Majumdar (Ex. 2023), Dr. George Zhanel (Ex. 2025), as well as newly-prepared Declarations of Dr. Parrish (Ex. 2027), and Dr. Grabowski (Ex. 2029). The Reply is supported by a Second Declaration of Dr. Yvonne M. Buys (Ex. 1092), a Second Declaration of Dr. Erning Xia (Ex. 1093) and a Declaration of Mr. John C. Staines, Jr. (Ex. 1094). Patent Owner filed three motions for observations pertaining to depositions of Dr. Xia, Dr. Buys, and Mr. Staines. Papers 43, 44, 45. Petitioner responded to each motion for observation. Papers 48, 49, 50. In making our final determinations, we have considered Patent Owner's observations concerning those depositions and Petitioner's responses.

II. ANALYSIS

We organize our analysis into four parts. First, we provide an overview of the invention claimed in the '299 patent. Second, we address the level of ordinary skill in the art. Third, we discuss claim construction. Fourth, we assess the merits of the patentability challenge asserted in the Petition, weighing the objective indicia of nonobviousness against the evidence of obviousness.

A. The Invention of the '299 Patent (Ex. 1001)

The '299 patent describes "multi-dose, self-preserved ophthalmic compositions." Ex. 1001, Abstract. The specification states that pharmaceutical compositions, such as irrigating solutions for the eye, "are typically utilized multiple times by the patient, and are therefore frequently referred to as being of a 'multi-dose' nature." *Id.* at 1:44–46. The

specification states that such compositions can be prepared under sterile conditions, but due to "frequent, repeated exposure of multi-dose products to the risk of microbial contamination, it is necessary to employ a means for preventing such contamination from occurring." *Id.* at 1:26–39, 47–50.

The '299 patent discloses "multi-dose products that do not require a conventional antimicrobial preservative" "yet are preserved from microbial contamination." *Id.* at 3:10–13. Such compositions are known in the art as "preservative free" or "self-preserved." *Id*. at 3:14, 19. According to the '299 patent, aqueous ophthalmic compositions may be preserved from microbial contamination, despite the absence of conventional preservatives, by combining low concentrations of zinc ions with a borate-polyol complex and limiting the concentration of anionic species (such as buffering anions and metal cations) other than zinc in the compositions. *Id.* at 3:33–62. The claimed composition is "able to satisfy the USP preservative efficacy requirements" and do so "without employing any conventional antimicrobial preservatives." *Id*. at 4:10–17. The specification identifies prostaglandin analogs (including "travoprost") as therapeutic agents suitable for use with the zinc-based preservation system of the invention. *Id*. at 8:60–65.

B. Level of Ordinary Skill in the Art

We consider each ground of unpatentability in view of the understanding of a person of ordinary skill in the art at the time of the invention. Petitioner submits that such a person would have had a Doctorate in microbiology or chemistry (or a related field) with at least a few years of experience in the development of ophthalmic formulations. Pet. 7. Alternatively, in Petitioner's view, that person would have had a Bachelor's

or Master's Degree combined with significant (5 years or more) practical experience developing ophthalmic formulations. *Id*. Patent Owner, for its part, advances a definition that "does not differ materially" from that proposed by Petitioner. Resp. 5.

Petitioner's definition is comparable to the level of skill reflected in the asserted prior art. The prior art itself is sufficient to demonstrate the level of ordinary skill in the art. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (prior art itself can reflect appropriate level of ordinary skill in the art). To the extent more specified findings are required, we adopt the definition proposed by Petitioner. Pet. 7. We observe, however, that there is no appreciable difference between the parties' respective definitions that would "materially" alter the outcome of this decision based on our acceptance of one definition over the other. Resp. 5.

C. Claim Interpretation

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); *Cuozzo Speed Techs., LLC v. Lee*, *1*36 S. Ct. 2131, 2144–46 (2016). Under that standard, we assign terms their ordinary and customary meaning in view of the specification, as understood by one of ordinary skill in the art at the time of the invention. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). In this section, we adopt the preliminary claim construction set forth in our decision to institute review. Dec. 7–8. Neither party advances evidence supporting a different final claim construction.

Petitioner argues that we should adopt the claim construction resolved in the Apotex IPR, as we did in the decision on institution in this case.

Pet. 5–7; Dec. 7–8. Patent Owner tacitly agrees. *See* Resp. 1 (stating that a "self-preserved" composition is "one that has sufficient antimicrobial activity to pass standard tests for 'preservative efficacy' without needing a conventional preservative"). Accordingly, for reasons set forth in our decision instituting review in the Apotex IPR, we determine that:

(a) The preamble term "self-preserved" breathes life and meaning into the claims, and is construed as a limitation of claims 1–28; and

(b) The broadest reasonable interpretation of "self-preserved" compositions is "compositions that do not contain a conventional antimicrobial preservative." Apotex IPR, Paper 9, 5–6; Dec. 7–8. Schneider, which is asserted in each ground of unpatentability stated in the Petition, informs that edetate disodium ("EDTA") and benzalkonium chloride ("BAC") were conventional antimicrobial preservatives known and available at the time of the invention—an issue not meaningfully disputed by Petitioner. Ex. 1007, 7:14–21; Pet. 15.

Our claim construction findings are supported by the specification of the '299 patent, which states that "[t]he multi-dose compositions of the present invention, which do not contain a conventional antimicrobial preservative, are referred to herein as being 'self-preserved'." Ex 1001, 3:27–29. The specification identifies BAC as an example of a conventional antimicrobial preservative excluded from the self-preserved composition of the challenged claims. *Id.* at 4:23–25. No other claim term requires express construction for the purposes of this decision. *See, e.g.*, *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc*., 200 F.3d 795, 803 (Fed. Cir. 1999) (only claim terms in controversy need be construed, and then only to the extent necessary to resolve the controversy).

D. Analysis of the Asserted Grounds of Unpatentability

In this section, we first analyze the two grounds of unpatentability asserted in the Petition against claim 1. Pet. 2–3 (statement of grounds of unpatentability). We then turn to the remaining challenged claims.

(a) The Grounds Asserted Against Claim 1

The Petition asserts two grounds of unpatentability against claim 1, both of which are based on obviousness. Pet. 2, 3. The first ground is based on obviousness over Schneider, Xia, and Chowhan. *Id*. at 8–23. The second ground adds Gadd to the analysis. *Id*. at 33–35, 37–42. Because the two grounds raise substantially similar issues, we address them together in this section, discussing Gadd only as necessary to resolve the second ground.

Petitioner argues that a person of ordinary skill in the art would have selected Schneider's Formulation A as the starting point for modification. Pet. 9–10 (claim chart, identifying Schneider's Formulation A), 14–15, 17, 33–35; Tr. 8:7–11. According to Petitioner's witness, Dr. Xia, one would have made that selection because Formulation A was "already in the marketplace" and had demonstrated "both safety and effectiveness." Resp. 11 (citing Ex. 2121, 18:12–16); Pet. 15; *see* Ex. 1002 ¶¶ 46–47 (Dr. Xia's declaration). Significantly, Petitioner acknowledges that one undertaking to improve Formulation A "would have retained as much of" the original composition "as feasible." Pet. 14–15 (bridging sentence). Yet the challenge to claim 1 depends on at least six modifications to Formulation A—which, in unmodified form, bears little resemblance to the composition specified in claim 1. Pet. 14–20; *compare* Ex. 1001, claim 1, *with* Ex. 1007, 9:25–42 (Table, Formulation A).

Claim 1 requires a combination of zinc, borate, sorbitol, and propylene glycol, and of those four ingredients, Formulation A includes only borate. *Compare* Ex. 1001, claim 1 (requiring "borate"), *with* Ex. 1007, 9:25–42 (including "boric acid"); *see* Ex. 1001, 6:6 ("[a]s used herein, the term "borate" includes "boric acid"). Further, Formulation A includes two conventional preservatives (BAC and EDTA) that are excluded from the "self-preserving" composition of claim 1. Ex. 1001, claim 1; *see* Ex. 1007, 7:14–21 (Schneider, identifying BAC and EDTA as conventional preservatives), 9:25–42 (Table, Formulation A).

Petitioner asserts that an ordinarily skilled artisan, notwithstanding a desire to retain as much of the original composition "as feasible" (Pet. 15), would have undertaken at least six modifications necessary to bring Formulation A within the scope of claim 1: (1) replacing BAC with zinc ions; (2) replacing mannitol with sorbitol; (3) adding propylene glycol; (4) adjusting the amounts of zinc ions, sorbitol, and propylene glycol to fall within specific concentration ranges required by claim 1; (5) removing EDTA; and (6) limiting anionic species present in the modified composition to a concentration that is less than 15 mM. Pet. 14–20.

We address each of those proposed modifications in sections (1) through (6) below. In section (7), we discuss a further limitation of claim 1 that requires a composition that meets USP 27 preservative efficacy requirements; in section (8), we consider Patent Owner's evidence of secondary considerations of nonobviousness; and, in section (9), we provide our conclusions regarding the challenge to claim 1.

(1) Replacing BAC with Zinc Ions

First, Petitioner proposes that an ordinarily skilled artisan would have recognized the advantage of replacing BAC (a conventional preservative excluded in the "self-preserved" composition of claim 1) with a zinc compound disclosed in Xia. Pet. 14–16. Petitioner submits that this modification would have been undertaken to improve Formulation A "by removing BAC, a known source of toxicity, discomfort, and irritation to the eye." *Id*. at 14; Ex. 1002 ¶¶ 36, 47.

Patent Owner responds that the use of Xia's zinc compound in place of BAC in Formulation A would have been a "more complicated and less obvious route" than selecting one of many conventional BAC alternatives known and available in the art at the time of the invention. Resp. 10; Ex. 2023 ¶ 45 (identifying known and available conventional preservatives that would have been recognized as less toxic than BAC). Patent Owner's witness, Dr. Majumdar, identifies zinc as "an unconventional preservative" in a field rife with "conventional" BAC alternatives. Ex. 2023 ¶ 45. Patent Owner further observes that zinc "had never before been the sole preservative in a marketed ophthalmic drug." Resp. 9; Ex. 2023 ¶ 46; Ex. 2025 ¶ 30. Already, with this first modification, a glimmer of doubt creeps in, regarding whether Petitioner's selection of zinc is driven by disclosures in the prior art or impermissible hindsight reconstruction.

(2) Replacing Mannitol with Sorbitol

Second, Petitioner proposes that one would have replaced mannitol in Formulation A "with sorbitol." Pet. 18; Ex. 1002 ¶ 54. The Petition does not articulate any particular reason why an ordinarily skilled artisan would

have resolved on that substitution, except to argue that "mannitol and sorbitol are sugars . . . differing only in their stereochemistry at a single carbon and therefore share many similar physical properties." Pet. 17 (citing Ex. 1017, 5767, 8797)[6]. Petitioner stops short of arguing, much less presenting evidence, that an ordinarily skilled artisan would have identified sorbitol and mannitol as interchangeable alternative ingredients that would serve a common function in the modified composition of Formulation A. Pet. 15–17. Nor does Petitioner identify an express suggestion in the art to substitute one polyol for the other in the modified composition. *Id*.

Instead, the Petition raises a third reference (Chowhan) and advances conclusory opinion testimony that "[i]t would have been obvious to combine Chowhan and Xia and Schneider in order to optimize the borate-polyol portion of the self-preservation system and to arrive at the claimed invention." Pet. 15 (citing Ex. 1002 ¶ 48) (repeating that conclusory assertion). That conclusory opinion is not persuasive to show how or why one would have resolved to replace mannitol with sorbitol in Formulation A. We discuss Chowhan in more detail below, in connection with the third proposed modification to Formulation A.

(3) Adding Propylene Glycol in Combination with Sorbitol

Third, Petitioner proposes adding propylene glycol, which is present in the composition of claim 1 but not in Formulation A. Pet. 17. For support, Petitioner directs us to Chowhan, which concerns the use of borate-polyol complexes in ophthalmic compositions that employ "small organic

[6] The cited pages do not exist in Exhibit 1017, which consists of three pages from the Merck Index that do not appear to relate to the proposition asserted.

compounds" such as "BAC" as antimicrobial preservatives. *Id*.; Ex. 1004, Title, 1:49–63. Chowhan uses the borate-polyol complexes "as adjunctive disinfecting agents" to improve the antifungal activity of conventional preservatives. Ex. 1004, 1:49–63, 2:26–36; *see* Resp. 20–21; Ex. 2025 ¶¶ 41, 65; Ex. 2025 ¶¶ 48–49; Ex. 2021 86:19–87:7, 93:5–9. Chowhan does not mention zinc, much less suggest that a polyol-borate complex would boost the antimicrobial efficacy of zinc ions in an ophthalmic composition. *See*, *e.g.*, Ex. 1004, Examples 1–12; Tr. 38:7–20.

Petitioner submits that Chowhan would have supplied "a reason to optimize" the polyol selection in Formulation A and, in so doing, would have prompted an ordinarily skilled artisan to arrive at a polyol mixture of "propylene glycol and sorbitol" to improve the antimicrobial efficacy of zinc ions in the modified composition of Formulation A. Pet. 17. The Petition assumes, but does not establish, that polyol selection was a result-effective variable for that function, and that an ordinarily skilled artisan would have been equipped to "optimize" that variable by routine experimentation. *Id*. at 15, 17; *see* Resp. 30–38 (for persuasive opposing argument and evidence on that point); Tr. 7:1–16.

Petitioner does not establish how or why one would have resolved to include propylene glycol and sorbitol together in Formulation A. None of Chowhan's examples uses sorbitol, only one uses propylene glycol; and, where Chowhan selects a mixture of polyols, propylene glycol is used in combination with mannitol. Ex. 1004, Example 5; Ex. 2023 ¶ 88; Resp. 34; *see* Resp. 30–38 (Patent Owner's position that the selection of sorbitol and propylene glycol, in combination with the other specified ingredients and the express limitation on anionic species, is based on impermissible hindsight).

It is not clear on this record why an ordinarily skilled artisan, seeking to improve the preservative efficacy of zinc, would have turned to Chowhan, which does not mention zinc. Resp. 21; *see* Ex. 1004 (Chowhan). In a nutshell, the Petition directs us to no rational reason why the combined disclosures of the prior art would have suggested including a polyol mixture of sorbitol and propylene glycol in the composition of Formulation A as modified to include zinc ions in place of BAC. Pet. 13–17. Having considered the second and third modifications proposed in the Petition, that glimmer of doubt, regarding impermissible hindsight, glows brighter.

(4) Removing EDTA

Formulation A also includes EDTA, a conventional preservative that is excluded from the "self-preserved" composition of claim 1. Ex. 1001, claim 1; Ex. 1007, 7:14–21, 9:25–42. And as Petitioner acknowledges, EDTA is an anionic species. Pet. 19; *see* Ex. 1001, claim 1 (limiting the concentration of anionic species). Petitioner proposes that an ordinarily skilled artisan would have been prompted to remove EDTA from the modified composition of Formulation A, led by a desire "to avoid chelation of the zinc and interference with its antimicrobial properties." Pet. 19 (citing Ex. 1007, 9:21–42, claims 8, 11; Ex. 1002 ¶ 55).

That position runs counter to the disclosure of Xia—the very reference upon which Petitioner relies for a suggestion to include zinc in Formulation A in the first modification. Pet. 10, 14–15. Xia itself identifies EDTA as a "preferred" chelating or sequestering agent suitable for use in a zinc-preserved ophthalmic composition. Resp. 12–13; Ex. 2023 ¶ 49; Ex. 1003, 11. Although EDTA is not a required ingredient of Xia's

composition, the fact that Xia contemplates the use of EDTA as a "preferred" optional ingredient undercuts Petitioner's view that EDTA would have been understood to interfere with zinc ions in an ophthalmic formulation. Ex. 1003, 11; Pet. 19. With this fourth modification, we discern that Petitioner is picking and choosing ingredients in Xia's formulation to include those required, and remove those precluded, by the terms of claim 1. Petitioner's rationale appears to be "entirely hindsight-driven." Resp. 13, *see id*. at 30–41 (and evidence cited therein).

(5) Employing Zinc Ions, Sorbitol, and Propylene Glycol in the Specified Concentration Ranges

Even if we accept that an ordinarily skilled artisan would have replaced BAC with zinc, substituted sorbitol for mannitol, added propylene glycol, and removed EDTA from Formulation A, we are not persuaded that the artisan also would have recognized the necessity of maintaining the zinc ions, sorbitol, and propylene glycol within the specific concentration ranges required for each component in claim 1. Ex. 1001, claim 1.

In that regard, Claim 1 requires a composition that includes zinc ions, sorbitol, and propylene glycol in these concentration ranges: (1) zinc ions must be present "at a concentration of 0.04 to 0.4 mM"; (2) propylene glycol "at a concentration of 0.25 to 1.25% w/v"; and (4) sorbitol "at a concentration of 0.05 to 0.5% w/v." Ex. 1001, claim 1. In addition, polyols must be present in a concentration range "of 0.25% to 2.5% w/v." *Id.*

Xia discloses "minimum" and "maximum" concentration ranges for the zinc employed in its composition, and there is no dispute that the "minimum" concentration falls within the range of claim 1. Ex. 1003, 5; Pet. 9, 15–16; Ex. 1002 ¶ 50; Resp. 16. But Xia discloses two preservation

methods; one using zinc alone, and another using zinc in combination with a "primary preservative agent" such as Polymer JR, "which provides the preservative efficacy" when zinc is employed at the disclosed "minimum" concentrations. Ex. 1003, 3–5; Resp. 16–17; Ex. 1002 ¶ 50; Ex. 2023 ¶ 59; Ex. 2166, 72:17–73:5. Xia makes plain that when the "minimum" concentrations for zinc are employed in an ophthalmic composition, the zinc is not an effective preservative on its own, and a "primary preservative agent" must be included to attain a useful preservation system. Ex. 1003, 4. Accordingly, we agree with Patent Owner that Xia does not suggest using zinc ions, at the concentrations required by claim 1, as a useful alternative to BAC in Formulation A. Resp. 16–17; Ex. 2023 ¶¶ 42–44; Ex. 1003, 5.

Further, as Petitioner's counsel confirmed during the final hearing, "the polyol in" Formulation A "isn't within the claimed range and it's not even the same polyol." Tr. 17:15–17; *see* Ex. 1007, 9:25–42 (Table, Formulation A, incorporating mannitol in a concentration of 4.6% w/v). The Petition includes no coherent explanation of why or how a person of ordinary skill in the art would have been led to incorporate sorbitol or propylene glycol in concentrations that fall within the ranges required for each of those ingredients or maintain the specified limit on total polyol concentration. *See* Pet. 11 (claim chart).

This fifth proposed modification rests on conclusory argument that the concentrations of zinc, sorbitol, and propylene glycol were result-effective variables and, further, that an ordinarily skilled artisan would have recognized a need, and understood how, to optimize those concentrations by routine experimentation to improve the efficacy of zinc ions in the modified composition of Formulation A. Pet. 17–18. Patent owner persuasively

argues that an ordinarily skilled artisan would not "have recognized a connection between the concentrations of sorbitol or propylene glycol (let alone both) and zinc's preservative efficacy, much less" would have known "how to modify those concentrations to enhance preservative efficacy" of zinc ions in a formulation that lacks a conventional preservative. Resp. 39; *see id*. at 30–41 (and evidence cited therein).

We agree that the asserted prior art does not suggest a "relationship between polyol concentrations and the preservative efficacy of zinc ions." Resp. 40; Ex. 2023 ¶¶ 89, 92–93, 95. Chowhan's disclosure says nothing about optimizing the concentrations of individual polyols in a mixed-polyol composition. *See* Ex. 1004 (Chowhan). And Petitioner identifies no prior-art driven suggestion that the concentrations of sorbitol and propylene glycol (selected to form a mixed-polyol complex with borate) would have been understood to affect the preservative efficacy of zinc ions in an ophthalmic composition. Pet. 17–18; *see* Resp. 30–41 (and evidence cited therein).

(6) Limiting Anionic Species to Less Than 15 mM

Petitioner advances a sixth modification, which pertains to a limitation on anionic species. According to claim 1, anionic species, to the extent present, must be limited to a concentration that is "less than 15 mM." Ex. 1001, claim 1. In Petitioner's view, Xia and Chowhan would have led an ordinarily skilled artisan to limit the amount of anionic species in the modified composition of Formulation A to fall below a concentration of 15 mM as required by claim 1. Pet. 12 (claim chart). On that point, Petitioner argues that compositions disclosed in Xia and Chowhan "encompass formulations" that include anionic species in "concentrations of

zero or at least less than 15 mM." *Id*. at 19 (citing Ex. 1002 ¶ 56); *see id*. at 12 (claim chart). That observation, however, does not speak to whether one would have recognized a desire or need to maintain anionic species in the modified composition of Formulation A at less than 15 mM.

Petitioner directs us to Chowhan's disclosure "that phosphate anions can interfere with antimicrobial activity." *Id*. at 19–20 (Ex. 1004, 1:45–48). From there, Petitioner asserts that Chowhan "would have guided a [person of ordinary skill in the art] to keep the concentration of anionic species as low as possible" when added to any "ophthalmic compositions"—including the modified composition of Formulation A. *Id*. at 20 (citing Ex. 1002 ¶ 57). For support, Petitioner directs us to opinion testimony that is not tethered adequately to disclosures in the prior art or other objective proof. *Id*.

At this point in the analysis, faced with a challenge that depends on at least six modifications to Formulation A, our steadily brightening glimmer of doubt catches fire. The challenge appears to be based on impermissible hindsight rather than a course recommended by the combined disclosures of the prior art or the understanding of an ordinarily skilled artisan. Patent Owner observes, and we agree, that "[t]here is no suggestion anywhere in Xia, Schneider, or Chowhan that anionic species interfere with zinc ions, or that anionic species are to be avoided." Resp. 25. On the contrary, Xia—the very reference asserted to provide an impetus for introducing zinc ions into Formulation A—identifies "anionic surfactants" and "anionic" counterions as "suitable for use" in a composition that includes zinc ions. Ex. 1003, 5, 13; Resp. 25. Petitioner does not explain adequately how or why Chowhan would have prompted an ordinarily skilled artisan to avoid using anions, given that anions are freely employed in Xia's own formulation.

Here, the Petition pulls in yet another reference—Gadd—to show that a person of ordinary skill in the art would have undertaken this sixth modification to Formulation A. Pet. 34. In Petitioner's view, Gadd would have provided a reason to avoid "anions and multivalent metal cations other than zinc" as ingredients in the modified composition. Pet. 33. Petitioner argues that Gadd discloses that "ions can interfere with the activity of antimicrobial agents" but directs us to no mention in Gadd of the use of zinc in an ophthalmic formulation. *Id*. at 34. In fact, Gadd relates to the bioavailability of organic materials that bind to heavy metals, such as zinc, when present in soil or clay. Ex. 1005, 304.

Patent Owner responds that, "[a]bsent hindsight knowledge" of the claimed invention, one "would have had no reason to go looking for information about whether anions or multivalent cations could interfere with the preservative efficacy of zinc" in an ophthalmic formulation. Resp. 48. That argument has merit, given that Petitioner identifies nothing in the combined disclosures of Xia, Schneider, or Chowhan that suggests "any concern with the concentrations of anions or cations in a formulation containing zinc, borate, and polyol." *Id*. Here again, we find significant that "Xia affirmatively suggests using certain anionic components" in an ophthalmic formulation that contains zinc. Resp. 48; *see* Ex. 1003, 5, 13 (Xia, disclosing numerous anions, including "anionic organic or inorganic counterion[s]" (*id*. at 5) as well as "anionic surfactants" (*id*. at 13) that are useful for inclusion in the zinc-based preservative system); Ex. 2023 ¶ 36 and n.3 (Dr. Majumdar, observing that all of Xia's example formulations contain an anionic species (sodium chloride) and all but one example

incorporates that anionic species in concentrations well above the 15 mM limitation imposed by claim 1); Ex. 1003, 16–19, 22–23 (Xia's examples).

The lack of an art-based suggestion to limit the anionic species is important to our analysis. The '299 patent identifies the discovery made by the inventors thusly; when combining zinc ions with a borate-polyol in an ophthalmic preservation system, certain anionic species, especially anionic borate-polyol complexes, interfere with the antimicrobial activity of the zinc ions. Ex. 1001, 3:45–53, 4:57–5:8, 5:14–31, 6:54–65. The inventors discovered that zinc ions, present in relatively low concentrations, would deliver adequate preservative efficacy when combined with borate and specific polyols in a composition wherein anionic species are limited to less than 15 mM. Resp. 24–25, 30–31; Ex. 1001, claim 1. Based on the evidence developed during trial, we are not persuaded that the prior art illuminates a path toward that particular combination.

Gadd is concerned with anions because of their proclivity "to reduce metal toxicity by precipitation"—a problem that Petitioner does not establish as relevant in the modified composition of Formulation A. Resp. 49; *see* Ex. 1005, 307 (Gadd, explaining that "[a]nions are able to reduce metal toxicity by precipitation"); Ex. 2023 ¶¶ 109. And as Patent Owner observes, "Gadd says nothing whatsoever about the concentration of anionic species that may give rise to precipitation with zinc." Resp. 49; Ex. 1005, 307; Ex. 2121, 114:9–15. On the contrary, Petitioner's position, that an ordinarily skilled artisan would have avoided anions in the composition of Formula A, as modified to include Xia's zinc compound, is refuted by Xia's own use of a variety of anionic species, without limit or restraint, in formulations employing that very same zinc compound. Ex. 1003, 5, 13.

Even if an ordinarily skilled artisan would have turned to Gadd, and even if that artisan would have appreciated Gadd's "generic warning as to possible precipitation" when employing zinc ions and anions (Resp. 49), Petitioner does not explain adequately how or why the disclosure of Gadd (or any other asserted prior art reference) would have guided an ordinarily skilled artisan to a concentration of anions in the modified composition of Formulation A below 15 mM as specified in claim 1. Resp. 49–50; Ex. 2023 ¶¶ 110, 112.

(7) Achieving USP 27 Preservative Efficacy Requirements

There is another weakness in Petitioner's case. Even if we accept that an ordinarily skilled artisan would have undertaken the six modifications to Formulation A discussed above, Petitioner fails to direct us to persuasive evidence that the modified composition would have met the further limitation of claim 1 that requires a composition that satisfies "USP 27 preservative efficacy requirements." Ex. 1001, claim 1. Petitioner argues (without objective proof) that the modified composition "would have inherently satisfied" the claimed "USP 27 preservative efficacy requirements." Pet. 21. In the alternative, Petitioner argues that one would have been led, by routine optimization, to adjust the modified composition to satisfy USP 27 efficacy requirements—in other words, Petitioner advances an alternative, seventh modification that would have been required to meet claim 1. *Id.*

The Federal Circuit addressed inherency in the obviousness context in *Par Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186 (Fed. Cir. 2014). Our reviewing court there explained that a party asserting inherency in an

obviousness challenge must show sufficiently that "the limitation at issue necessarily must be present, or the natural result of the combination of elements explicitly disclosed by the prior art." *Par Pharm.*, 773 F.3d at 1195. The Petition does not direct us to persuasive evidence that the limitation at issue (specifying a composition that satisfies USP 27 preservative efficacy requirements) would have been "necessarily" present or "the natural result" of combining "elements explicitly disclosed by the prior art." *Id.*; *see* Pet. 21. That failure of proof disposes of Petitioner's further argument that the limitation pertaining to USP 27 preservative efficacy requirements "does not impart patentability" to claim 1. Pet. 21–22. On that point, Petitioner relies on *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344 (Fed. Cir. 2012), which is consistent with the Federal Circuit's decision in *Par Pharm*. Pet. 21–22. As Petitioner acknowledges, the *Santarus* decision concerned "an inherent property" of a formulation. *Id*. at 22 (quoting *Santarus*, 694 F.3d at 1354). The formulation was suggested in a single prior art reference and there was no dispute that the claimed property at issue was expected. *Santarus*, 694 F.3d at 1354.

Petitioner's alternative argument is no more persuasive. Petitioner asserts that an ordinarily skilled artisan would have recognized a need, and understood how, to optimize the modified composition of Formulation A "with the expectation of meeting" USP 27 preservative efficacy requirements. Pet. 21. By way of support, however, Petitioner directs us to conclusory opinion testimony. *Id*. (citing Ex. 1002 ¶¶ 60–62) (opinion backed up by no objective proof on the matter asserted); *see* 37 C.F.R. § 42.65(a) (opinion testimony that does not disclose underlying facts or data "is entitled to little or no weight"). In any event, Petitioner does not identify

a variable that would have been recognized as result effective, much less explain whether or how that variable could or would have been optimized through routine experimentation by an artisan exercising no more than ordinary skill in the art. *Id*. at 22–23.

(8) Secondary Considerations of Nonobviousness

Patent Owner comes forward with evidence that its commercial product, TRAVATAN Z, embodies the claimed invention and has enjoyed considerable commercial success as a direct result of the claimed invention. Resp. 55–56; Ex. 2029 ¶¶ 25, 30–31, 37–41. Specifically, Patent Owner directs us to persuasive evidence that TRAVATAN Z (a zinc-preserved travoprost composition) achieved the same market share and number of prescriptions as TRAVATAN (a BAC-preserved travoprost composition) in a shorter length of time after launch; and, thereafter, continued to significantly outperform TRAVATAN's peak performance—even though the formulations contain the same active ingredient in the same concentration. Resp. 55; Ex. 2027 ¶¶ 22, 27, 29, 32; Ex. 2029 ¶ 38–40; Ex. 1006, 1.

Patent Owner provides evidence that the commercial success of TRAVATAN Z is attributable to the only material difference between the two products; that is, the use of the zinc-based preservation system that is claimed in the '299 patent in place of BAC. Resp. 55; Ex. 2029 ¶¶ 38–40. Patent Owner also provides evidence that TRAVATAN Z has enjoyed a competitive edge over several conventionally-preserved alternatives—an edge that derives from the "self-preserved" feature of the claimed invention. Resp. 55–56; Ex. 2027 ¶¶ 21–22, 29, 32–34; Ex. 2029 ¶¶ 40–41, 44, 54.

Petitioner counters that Schneider and Chowhan would have "blocked earlier development of a product containing the technology claimed in the '299 patent, even if that technology had been obvious." Ex. 1094 ¶ 20; Ex. 1093 ¶ 86. From there, Petitioner asserts that "the alleged success is driven by blocking patents" rather than "any benefits connected to the claimed invention"—an argument not fully developed and, therefore, unpersuasive. Reply 27. The Federal Circuit recently observed that "a 'blocking patent'" may impact the obviousness analysis "where the practice of a later invention would infringe the earlier patent." *Acorda Therapeutics, Inc. v. Roxane Labs., Inc.*, Nos. 2017–2078, 2017–2134, 2018 WL 4288982 at *18 (Fed. Cir. Sept. 10, 2018). Chowhan is not a patent. Ex. 1004. Schneider is a patent, but claims a composition that requires polyethoxylated castor oil, which is not an ingredient of the composition claimed in the '299 patent. *Compare* Ex. 1007, claims 1–20, *with* Ex. 1001, claims 1–28. Petitioner does not explain how or why Schneider or Chowhan are "blocking patents" under the facts of this case. Reply 27. Petitioner raises other arguments in response to Patent Owner's evidence of commercial success, but develops none of them adequately in the Reply. Reply 27–28.

Patent Owner also comes forward with persuasive evidence that TRAVATAN Z met a long-felt need in the marketplace for an effective, self-preserved antiglaucoma medication that is BAC-free. Resp. 56–58; Ex. 2027 ¶¶ 21, 24–27, 29, 33, 35, 37–38, 40. Petitioner counter argues that Xia's formulation met that need, but directs us to no objective proof on point. Reply 25 (citing Pet. 13–14, which directs us to no objective evidence supporting Petitioner's position on that issue).

Petitioner raises other arguments that are similarly unpersuasive. For example, Petitioner argues that consumers would have viewed "surgery and laser" treatments as acceptable alternatives to the claimed medical therapy, which involves, for example, topical application of a drug in an eye drop. Reply 25–26; Ex. 1001, 1:33–36, 4:1; Pet. 9 (claim chart). That argument is unpersuasive. Even Petitioner's own witness, Dr. Buys, admitted that "medical therapy" is a more common intervention than "surgery and laser treatments," which carry "higher risks." Ex. 2167, 10:11–15.

Petitioner also argues that "single-use" products, already available in the marketplace, satisfied any need for a "multi-use" product. Pet. 26. That argument ignores specific advantages of "multi-use" products. *See*, *e.g.*, Ex. 1001, 1:26–46 (explaining need for a product that retains its antimicrobial efficacy after the packaging is opened); *see also* Ex. 2167, 22:16–20 (Petitioner's own witness, Dr. Buys, admitting "the advantages" of multi-dose products "over single unit dose medications"). Dr. Buys, Petitioner's own witness, casts doubt on several other arguments, raised in the Reply, which are aimed at offsetting Patent Owner's persuasive evidence of long-felt need. Resp. 26; *see* Ex. 2167, 27:20–30:6 (Dr. Buys, on cross-examination, explaining why she selectively declined to quote or cite data that supported studies advanced by Patent Owner), 37:25–38:16 (Dr. Buys, providing further testimony that undercuts Petitioner's argument that TRAVATAN Z made certain symptoms worse not better).

We have considered Petitioner's information that Patent Owner's evidence of long-felt need is not commensurate in scope with certain claims of the '299 patent. Reply 25–27. Taking account of the parties' respective positions on that issue, however, we find that Patent Owner's evidence on

long-felt need is entitled to some weight. *See Rambus Inc. v. Rea*, 731 F.3d 1248, 1257 (Fed. Cir. 2013) (evidence "need only be 'reasonably commensurate' with the scope of the claims," and does not require objective evidence "for every potential embodiment of the claim").

(9) Conclusions Regarding the Challenge to Claim 1

We instituted trial without the benefit of a preliminary response to the Petition. During the trial, Patent Owner came forward with information that casts serious doubt on Petitioner's evidence. The sheer number and nature of the modifications necessary to convert Formulation A into a composition that meets claim 1 speak against a conclusion of obviousness.

The objective indicia of nonobviousness, when weighed against Petitioner's relatively weak evidence of obviousness, tip the scales further in favor of Patent Owner. When we "balance of the obviousness evidence in the record" against the objective indicia of nonobviousness, the objective indicia provide a useful "check against hindsight bias." Resp. 54 (quotation omitted). We are convinced that Petitioner's challenge is based on a "hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention." *Id*. at 36 (quoting *Cheese Sys., Inc. v. Tetra Pak Cheese & Powder Sys., Inc.*, 725 F.3d 1341, 1352 (Fed. Cir. 2013).

A patent claim "is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 418 (2007). A conclusion of obviousness requires finding "both 'that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed

invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.'" *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367–68 (Fed. Cir. 2016) (citation omitted); *see KSR*, 550 U.S. at 418 ("it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does").

Petitioner asserts that an ordinarily skilled artisan "would have retained as much of" Formulation A "as feasible, as this was already an FDA-approved formulation, marketed as Travatan®." Pet. 15; Ex. 1002 ¶¶ 46–47. But Petitioner's challenge incongruously depends on at least six modifications to Formulation A; seven, if attaining UPS preservative efficacy requirements is not an inherent property of the modified composition. Petitioner does not address, much less explain, how or why an ordinarily skilled artisan, undertaking those six or seven modifications, would have done so with a reasonable expectation of success in arriving at a "self-preserved" composition using zinc as the sole preservative—in a field where zinc "had never before been the sole preservative in a marketed ophthalmic drug." Resp. 9; Ex. 2023 ¶ 46; Ex. 2025 ¶ 30.

The Petition does not articulate a rational reason why a person of ordinary skill in the art, setting out to improve Formulation A, would have selected the particular combination of ingredients required by claim 1. Formulation A bears almost no resemblance to the composition of claim 1, lacking three of the four required ingredients (zinc ions, sorbitol, and propylene glycol) and containing two others (BAC and EDTA) that are excluded by the "self-preserving" terms of the claim. *Compare* Ex. 1001, claim 1, *with* Ex. 1007, 9:25–42 (Table, Formulation A). And even if we set

aside those hurdles, the challenge fails for lack of persuasive evidence showing how or why an ordinarily skilled artisan would have resolved to include the claimed ingredients in the specified concentrations, while at the same time limiting anionic species (to the extent included) to a concentration of "less than 15 mM." Ex. 1001, claim 1.

Petitioner fails to establish that the subject matter of claim 1 would have been obvious over the combined disclosures of Schneider, Xia, and Chowhan—with or without the additional disclosure of Gadd. Pet. 2–3.

(b) The Remaining Challenged Claims

The Petition also states challenges against claims 2–28 of the '299 patent. Pet. 2–3. Those challenges, however, depend on arguments and evidence presented in the context of claim 1, regarding the combined teachings of Schneider, Xia, and Chowhan. *See, e.g.*, Pet. 9–12, 29–31, 37–42, 53–55 (claim charts). Our above reasoning applies with equal force to each of the other patent claims challenged in the Petition. Based on that reasoning, we find that Petitioner also has failed to show unpatentability of claims 2–28 by a preponderance of the evidence.

III. CONCLUSION

Petitioner has not shown by a preponderance of the evidence that claims 1–28 of the '299 patent are unpatentable under 35 U.S.C. § 103(a).

IV. ORDER

It is

ORDERED that Petitioner has not shown by a preponderance of the evidence that claims 1–28 of the '299 patent are unpatentable under 35 U.S.C. § 103(a); and

FURTHER ORDERED that, because this is a final written decision, any party 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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