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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

INNOPHARMA LICENSING, INC., INNOPHARMA LICENSING LLC,
INNOPHARMA INC., INNOPHARMA LLC,
MYLAN PHARMACEUTICALS INC., MYLAN INC.,
LUPIN LTD., and LUPIN PHARMACEUTICALS, INC.,
Petitioner,

v.

SENJU PHARMACEUTICAL CO., LTD., BAUSCH & LOMB, INC., and
BAUSCH & LOMB PHARMA HOLDINGS CORP.,
Patent Owner.

Case IPR2015-00903[1]
Patent 8,129,431 B2

Before FRANCISCO C. PRATS, ERICA A. FRANKLIN, and
GRACE KARAFFA OBERMANN, *Administrative Patent Judges.*

OBERMANN, *Administrative Patent Judge.*

FINAL WRITTEN DECISION
35 U.S.C. § 318 and 37 C.F.R. § 42.73

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[1] IPR2015-01871 has been joined with this proceeding. Specifically, in an Institution Decision dated January 25, 2016, we joined Lupin Ltd. and Lupin Pharmaceuticals, Inc., as parties to this proceeding. Paper 37.

I. INTRODUCTION

This is a Final Written Decision in an *inter partes* review challenging the patentability of claims 1–22 ("the challenged claims") of U.S. Patent No. 8,129,431 B2 (Ex. 1001, "the '431 patent"). We have jurisdiction under 35 U.S.C. § 6(c). For reasons that follow, we determine that Petitioner fails to show by a preponderance of evidence that claims 1–22 are unpatentable. We also address the parties' Motions to Exclude.

A. Procedural History

The Petition (Paper 2, "Pet.") for *inter partes* review was filed pursuant to 35 U.S.C. § 311. We instituted trial on two grounds of unpatentability stated in the Petition:

(1) Whether the subject matter of claims 1–5, 7–14, and 18–19 would have been obvious under 35 U.S.C. § 103 based on the combined disclosures of Ogawa[2] and Sallmann[3]; and

(2) Whether the subject matter of claims 6, 15–17, and 20–22 would have been obvious over Ogawa, Sallmann, and Fu[4]. Paper 15 ("Dec.").

Patent Owner filed a Response (Paper 32, "Resp.") and Petitioner filed a Reply (Paper 49, "Reply").[5] The parties' fully briefed Motions to

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[2] U.S. Patent No. 4,910,225, issued Mar. 20, 1990 (Ex. 1004, "Ogawa").

[3] U.S. Patent No. 6,107,343, issued Aug. 22, 2000 (Ex. 1009, "Sallmann").

[4] Austrl. Patent Application No. AU-B-22042/88, issued Mar. 16, 1989 (Ex. 1011, "Fu").

[5] To the extent that we rely on information in papers and exhibits for which confidentiality is claimed, we determine that the general nature of the discussions of such information herein does not require that this Decision be

Exclude also are pending. Papers 56, 59 (Motions to Exclude); Papers 64, 66 (Oppositions to Motions to Exclude); Papers 69, 70 (Replies to Motions to Exclude). The record includes a transcript of a consolidated final oral hearing conducted on April 19, 2016, in this proceeding and related proceeding IPR2015-00902 ("IPR 902"). Paper 75 ("Tr.").

B. Related Proceedings

Petitioner identifies eight district court actions involving the '431 patent, including two that involve Petitioner as a defendant. Pet. 11–12; *see Senju Pharmaceutical Co. v. Lupin, Ltd*., No. 1:14-CV-00667-MAS-LHG (D.N.J. filed Jan. 31, 2014); *Senju Pharmaceutical Co. v. InnoPharma Licensing, Inc.*, C.A. No. 1:14-CV-06893-JBS-KMW (D.N.J. filed Nov. 3, 2014). Concurrently herewith, we issue a final written decision in IPR 902, which involves the same parties and is directed to U.S. Patent No. 8,669,290 ("the '290 patent"). The '290 patent claims priority to the '431 patent.

C. The '431 Patent (Ex. 1001)

The '431 patent is titled "Aqueous Liquid Preparation Containing 2-Amino-3-(4-Bromobenzoyl) Phenylacetic Acid." Ex. 1001, Title. The claimed invention relates to an aqueous liquid preparation consisting essentially of two components: (1) bromfenac (or its salts and hydrates);

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treated as confidential. The parties are reminded that confidential information that is subject to a protective order ordinarily becomes public 45 days after final judgment in a trial. Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,761 (Aug. 14, 2012). Further, there is an expectation that information will be made public where the existence of the information is identified in a final written decision. *Id*. We provided the parties advance notice "that information subject to a protective order will become public if identified in a final written decision in this proceeding." Paper 77, 4.

and (2) tyloxapol. *Id*. at 11:66–12:10 (independent claim 1). Bromfenac is a non-steroidal anti-inflammatory drug ("NSAID"). *Id*. at 1:24–40. Tyloxapol is added to the claimed formulation "to stabilize an aqueous liquid preparation of" the bromfenac component "and inhibit decrease in preservative effect of" quaternary ammonium compounds in the formulation. *Id*. at 2:4–11. The preparation is useful for ophthalmic administration, for example, in an eye drop to treat blepharitis, conjunctivitis, scleritis, or postoperative inflammation. *Id*., Abstract, 12:5–6. Claim 1 specifies that a quaternary ammonium compound, specifically, benzalkonium chloride ("BAC"), may be included in the liquid preparation. *Id*. at 12:8–9.

An object of the invention is to provide an aqueous liquid preparation of bromfenac that "is stable within a pH range giving no irritation to eyes" when preserved with a quaternary ammonium compound, such as benzalkonium chloride ("BAC"). *Id*. at 2:15–22. The inventors claim to have discovered that the addition of an alkyl aryl polyether alcohol type polymer, such as tyloxapol, provides the sought-after stability, giving no irritation to the eyes. *Id*. at 2:35–49. Specifically, tyloxapol both inhibits the change or degradation of bromfenac "over time" and also inhibits "deterioration in the preservative effect" when a preservative is included in the formulation. *Id*. The inventors describe tyloxapol as "a non-ionic surfactant." *Id*. at 4:37–39.

D. Illustrative Claim

Claim 1, reproduced below, is illustrative of the subject matter.

> 1. An aqueous liquid preparation consisting essentially of the following two components, wherein the first component is 2-amino-3-(4-bromobenzoyl)phenylaceticacid or a

> pharmacologically acceptable salt thereof or a hydrate thereof, wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate and the second component is tyloxapol, wherein said liquid preparation is formulated for ophthalmic administration, and wherein when a quaternary ammonium compound is included in said liquid reparation, the quaternary ammonium compound is benzalkonium chloride.

Ex. 1001, 11:66–12:10.

E. Declaration Testimony

The Petition is supported by the Declaration of Dr. Paul A. Laskar. Ex. 1003.

The Response is supported by the Declaration of Dr. Robert O. Williams, III (Ex. 2082), the Declaration of Mr. Shirou Sawa (Ex. 2098); the Declaration of Dr. Stephen G. Davies (Ex. 2105), the Declaration of Dr. William B. Trattler (Ex. 2116), and the Declaration of Mr. John C. Jarosz (Ex. 2130).

The Reply is supported by the Reply Declaration of Dr. Paul A. Laskar (Ex. 1104) and the Declaration of Mr. Ivan T. Hofmann (Ex. 1150).

II. ANALYSIS

A. Claim Construction

In an *inter partes* review, claim terms in an unexpired patent are interpreted according to their broadest reasonable construction in light of the specification of the patent in which they appear. *See Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144-46 (2016) (upholding the use of the broadest reasonable interpretation standard); 37 C.F.R. § 42.100(b). Claim terms generally are given their ordinary and customary meaning, as

understood by one of ordinary skill in the art in the context of the entire disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). If an inventor acts as his or her own lexicographer, the definition must be set forth in the specification with reasonable clarity, deliberateness, and precision. *Renishaw PLC v. Marposs Societa' per Azioni*, 158 F.3d 1243, 1249 (Fed. Cir. 1998). The construction that stays true to the claim language, and most naturally aligns with the inventor's description, is likely the correct interpretation. *Id.* at 1250.

Petitioner addresses the transitional phrase "consisting essentially of" as applied in claims 1–22. Pet. 15–16. Patent Owner proposes no specific claim construction for any claim term. Resp. 6. No claim term requires express construction for the purposes of this decision. *See Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) (only those terms that are in controversy need to be construed, and only to the extent necessary to resolve the controversy).

B. Principles of Law

Petitioner bears the burden of persuasion in proving unpatentability of the challenged claims, and 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). To prevail, Petitioner must establish facts supporting its challenge by a preponderance of the evidence. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d).

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the

time the invention was made to a person of ordinary skill in the art. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). Obviousness is resolved based on underlying factual determinations, including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) objective evidence of nonobviousness, i.e., secondary considerations. *See Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). As explained below, taking account of those factors, including Patent Owner's evidence of secondary considerations, we determine that Petitioner fails to establish the unpatentability of claims 1–22 by a preponderance of the evidence.

C. The Applied Prior Art

We instituted trial on two grounds of unpatentability stated in the Petition; whether the subject matter of claims 1–5, 7–14, 18, and 19 would have been obvious over the combined disclosures of Ogawa and Sallmann, and whether the subject matter of claims 6, 15–17, and 20–22 would have been obvious over the combined disclosures of Ogawa, Sallmann, and Fu. In this case, the prior art itself is representative of the level of ordinary skill in the art. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) ("[T]he absence of specific findings on the level of skill in the art does not give rise to reversible error 'where the prior art itself reflects an appropriate level and a need for testimony is not shown.'" (*quoting Litton Indus. Prods., Inc. v. Solid State Sys. Corp*., 755 F.2d 158, 163 (Fed. Cir. 1985))).

1. Ogawa (Ex. 1004)

Ogawa is directed to an aqueous, stable, ophthalmic preparation for topical administration in the treatment of inflammatory conditions of the

eye, such as uveitis. Ex. 1004, Abstract, 1:60–2:3. Ogawa's Example 6 discloses a stable aqueous liquid preparation, formulated for ophthalmic administration, which comprises bromfenac, as the sole pharmaceutical active ingredient, and polysorbate 80. *Id*. at 10:5–18, 49–57 (for stable aqueous liquid preparation), 10:5–9 (for bromfenac, as sole pharmaceutical active ingredient, and polysorbate 80), 14:45–50 (Table 11, reporting 100% stability for the Example 6 preparation). The ophthalmic preparation of Ogawa's Example 6 also includes BAC, a component that may be included in the formulation of claim 1. Ex. 1004, 10:13; Ex. 1001, 12:6–9. Ogawa does not disclose or suggest a function for the polysorbate 80 in the bromfenac formulation of Example 6. We find that Ogawa's Example 6 meets every limitation of claim 1, but for the recited use of tyloxapol in the formulation. Ex. 1001, 12:4–5; *see* Pet. 21–22 (claim chart for claim 1).

2. Sallmann (Ex. 1009)

Sallmann discloses tyloxapol as a solubilizer in an ophthalmic preparation of a specific NSAID—diclofenac potassium salt. Ex. 1009, 4:52–56. Sallmann's Example 2 discloses an aqueous ophthalmic preparation that includes diclofenac potassium salt and tyloxapol. *Id*. at 8:1–15. The remaining ingredients of Sallmann's Example 2 would not have been expected to adversely affect the stability or preservative efficacy of the preparation. Ex. 1003 ¶ 54. Like Ogawa's Example 6, Sallmann's Example 2 formulation includes BAC. Ex. 1009, 8:1–10. The entire thrust of Sallmann's disclosure, however, is uniquely directed to formulations of diclofenac potassium salt. Ex. 1009, 1:35–3:26 (focusing exclusively on diclofenac potassium salt, which Sallmann describes as "[s]urprisingly" and

"especially suitable" for treating inflammatory ocular processes (*id*. at 1:48–51)); Ex. 2082 ¶ 126. Sallmann does not discuss a formulation of any NSAID other than diclofenac potassium salt. *See generally* Ex. 1009.

The '431 patent discloses that tyloxapol effectively stabilizes an aqueous formulation of bromfenac when included in a range from about 0.01 and 0.5 w/v %. Ex. 1001, 5:36–47. Sallmann's Example 2 formulation of diclofenac potassium salt includes tyloxapol in a concentration of 0.1 w/v %, which falls within the range described in the '431 patent as useful for stabilizing a bromfenac formulation. Pet. 42 (citing Ex. 1009, 8:10, 4:65–67; Ex. 1003 ¶ 71). Sallmann describes tyloxapol as a "solubilizer[]" for diclofenac potassium salt, but does not suggest using tyloxapol to solubilize any other NSAID or assign a stabilizing function to tyloxapol. Ex. 1009, 4:52–53. Sallmann identifies a different component as the stabilizer in the formulation of diclofenac potassium salt. *Id*. at 5:59–6:17, 8:1–15.

3. Fu (Ex. 1011)

Fu discloses an ophthalmic preparation comprising a NSAID, BAC, and an ethoxylated octylphenol, such as Octoxynol 9 or Octoxynol 40. Ex. 1011, 18:5–28, Examples 2, Example 5. Petitioner asserts that tyloxapol is an ethoxylated octylphenol non-ionic surfactant. Ex. 1003 ¶ 33 (citing Ex. 1024, 1:1:1–2:1:2). Petitioner also asserts that Fu "expressly discloses a non-ionic surfactant concentration of 0.02 w/v %." Pet. 44–45 (citing Ex. 1011, 18:5–28, Example 2, Example 5; Ex. 1003 ¶¶ 75, 93). Petitioner applies Fu in a ground of unpatentability raised against certain dependent claims, which limit the concentration of tyloxapol in the formulation. Pet. 1 (asserting Fu in the ground raised as to claims 6, 15–17, and 20–22).

With respect to those dependent claims, Petitioner asserts that Fu would have led a person of ordinary skill in the art to modify Ogawa's Example 6 formulation of bromfenac to include tyloxapol in a concentration that meets the claimed concentrations. Pet. 45. Specifically, Petitioner directs us to Fu's disclosure of a class of compounds that allegedly would have been understood to stabilize formulations containing both an NSAID and BAC—and to stabilize such formulations better than polysorbate 80. *Id*.

Claims 1 and 18, the only independent challenged claims, both require an aqueous ophthalmic formulation of bromfenac and tyloxapol. Ex. 1001, 11:64–12:9, 13:16–14:9. The Petition asserts only the combined disclosures of Ogawa and Sallmann to show the obviousness of a formulation of bromfenac and tyloxapol—Fu is not applied in the ground of unpatentability asserted against claim 1 or 18. Pet. 1, 20–26. Petitioner raises Fu, however, as a background reference bearing on the understanding of an ordinary artisan at the time of the invention of those claims. *See id*. at 23–24 (bridging paragraph) (including Fu in a list of background references that allegedly show that the prior art describes "ophthalmic formulations of acidic NSAIDs containing a non-ionic surfactant like tyloxapol") (citing Ex. 1011, 12:1–11). Specifically, Petitioner asserts that Fu, among other background references, would have caused an ordinary artisan to form "a reasonable expectation of success in substituting tyloxapol for polysorbate 80, because the prior art included multiple examples of stable aqueous preparations containing NSAIDs (similar to bromfenac) formulated with BAC and tyloxapol (and other closely related non-ionic surfactants)." *Id*. at 25 (citing, among other background references, Ex. 1011, 18:5–28). In

our analysis below, we consider Fu as a background reference bearing on claims 1 and 18, to the extent that it is raised and discussed in the Petition regarding the ordinary artisan's understanding of the combined disclosures of the two applied references, namely, Ogawa and Sallmann. Pet. 23–25.

4. Background References Cited in the Petition

Petitioner directs us to background references to show the knowledge and understanding of an ordinary artisan at the time of the invention. For example, we are directed to Desai[6] for a disclosure of "a formulation that included bromfenac and tyloxapol, and BAC, in addition to other ingredients." Pet. 17. Desai does not teach a specific formulation containing both bromfenac and tyloxapol, but rather, includes lists of ingredients generally suitable for use in ophthalmic formulations. Ex. 1005, 3:12–45. Desai discloses bromfenac and diclofenac in a list of suitable ophthalmic agents and tyloxapol and polysorbates in a list of suitable surfactants. *Id*. Petitioner also directs us to Yasueda,[7] which relates to the degradation pathway of a non-NSAID active ingredient (pranlukast). Ex. 1012, 1:16–24; Pet. 33.

[6] U.S. Patent No. 5,603,929, issued Feb. 18, 1997 (Ex. 1005, "Desai").

[7] U.S. Patent No. 6,274,609 B1, issued Aug. 14, 2001 (Ex. 1012, "Yasueda").

D. Asserted Grounds of Unpatentability

1. Claim 1: Replacing Polysorbate 80 in Ogawa's Example 6

a. Prior Art Evidence of Obviousness

Claim 1 requires an aqueous liquid preparation consisting essentially of bromfenac (or a pharmacologically acceptable salt or hydrate thereof) and tyloxapol. In addition, BAC may be included in the formulation of claim 1. Ex. 1001, 11:64, 12:9. Ogawa's Example 6 meets every limitation of claim 1, but for the addition of tyloxapol. Ex. 1001, 12:4–5; *see* Pet. 21–22 (claim chart for claim 1). Petitioner directs us to Sallmann for a teaching "that tyloxapol (another non-ionic surfactant) was the preferred surfactant for use in aqueous ophthalmic preparations of diclofenac (another acidic NSAID)." Pet. 24 (citing Ex. 1009, 4:62). Petitioner asserts that a person of ordinary skill in the art "would have known that substituting polysorbate 80 with tyloxapol would successfully, and predictably, result in a stable ophthalmic formulation of bromfenac because tyloxapol and polysorbate 80 had previously been used interchangeably as surfactants in ophthalmic formulations." *Id*. (citing Ex. 1021, 13:8–10; Ex. 1022, 4:24–31; Ex. 1003 ¶ 38). Petitioner further directs us to a disclosure in Desai that includes "poloxamers such as Pluronics; polysorbates such as Tweens; tyloxapol; sarcosinates such as Hamposyl; and polyethoxylated castor oils such as Cremophor." Ex. 1005, 3:38–41; Pet. 17.

In our Institution Decision, we determined that the Petition provides information sufficient to show that an ordinary artisan would have recognized that "tyloxapol and polysorbate 80 had previously been used interchangeably as surfactants in ophthalmic formulations." Dec. 12

(quoting Pet. 24); Ex. 1003 ¶¶ 38, 50 (Dr. Laskar's testimony that, at the time of the invention, "tyloxapol was a widely-used surfactant in aqueous liquid preparations comprising anti-inflammatory agents, and was used interchangeably with polysorbate 80"). We also determined that such known interchangeability, absent persuasive objective evidence to the contrary, was enough to support the proposed substitution, even in the absence of an express suggestion to do so. Dec. 12 (citing *In re Mayne*, 104 F.3d 1339, 1340 (Fed. Cir. 1997); *In re Fout*, 675 F.2d 297, 301 (CCPA 1982); *In re Siebentritt*, 372 F.2d 566, 568 (CCPA 1967)).

We put Patent Owner on notice that, "absent evidence to the contrary, it would have been well within the level of ordinary skill in the art to replace one non-ionic surfactant (polysorbate 80) with another non-ionic surfactant (tyloxapol) in Ogawa's Example 6, because both were known to be useful as surfactants in ophthalmic preparations." Dec. 12 (citing *KSR Int'l*, 550 U.S. at 417 ("If a person of ordinary skill in the art can implement a predictable variation, and would see the benefit of doing so, § 103 likely bars its patentability.")). In that regard, we take account of objective considerations of non-obviousness raised by Patent Owner in the Response, before reaching an ultimate conclusion on whether the subject matter of the challenged claims would have been obvious at the time of the invention.

b. Evidence of Secondary Considerations

Our reviewing court recently rejected the proposition "that objective considerations of non-obviousness can never overcome a strong prima facie case of obviousness." *WBIP, LLC, v. Kohler Co.*, Nos. 2015-1038, 2015-1044, 2016 WL 3902668, at *5 (Fed. Cir. July 19, 2016). Factual inquiries

for an obviousness determination include secondary considerations based on objective evidence of nonobviousness. *See Graham*, 383 U.S. at 17–18. The totality of the evidence submitted may show that the challenged claims would not have been obvious to one of ordinary skill in the art. *In re Piasecki*, 745 F.2d 1468, 1471–72 (Fed. Cir. 1984). Secondary considerations may include long-felt but unsolved need, failure of others, unexpected results, commercial success, copying, licensing, and industry praise. *Graham*, 383 U.S. at 17; *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1349, 1355 (Fed. Cir. 2012). "[E]vidence rising out of the so-called 'secondary considerations' must always when present be considered en route to a determination of obviousness." *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983).

(1) Unexpected Results

Patent Owner directs us to evidence that the inventors of the '431 patent discovered that tyloxapol provides a surprising stabilizing effect that inhibits bromfenac degradation in aqueous solution. Resp. 45–60. Specifically, Patent Owner argues that a unique aspect of the claimed invention "is at least the use of tyloxapol with bromfenac." Pet. 46 (citing Ex. 2082 ¶ 151). According to Patent Owner, a second "unique aspect" of the invention "is the use of 0.01 to 0.05 w/v% tyloxapol with bromfenac." *Id*. (citing Ex. 1001, claims 6, 15–17, 20–22; Ex. 2082 ¶ 151). Patent Owner identifies evidence asserted to compare the claimed invention to the closest prior art "admitted by Dr. Laskar [Petitioner's witness] to be Ogawa because it discloses 'examples of ophthalmic formulations containing bromfenac,

BAC, and the non-ionic surfactant polysorbate 80.'" *Id*. (citing Pet. 51; Ex. 1003 ¶ 95; Ex. 2082 ¶ 154).

Petitioner counter argues that Patent Owner's evidence of unexpected results "should be afforded no weight" because it focuses on Ogawa's Example 4 formulation instead of Ogawa's Example 6 formulation. Reply 20. That argument is unpersuasive for several reasons. First, Petitioner's own witness explicitly refers to Ogawa's Example 4 formulation in a discussion of "the closest prior art." Ex. 1003 ¶ 94 (citing Ex. 1004, 8:3–14 (Ogawa's Example 4)). Second, as explained below, Patent Owner shows persuasively that the claimed formulation achieved surprising results compared to both Ogawa's Example 4 and Example 6 formulations. Resp. 48–46.

Ogawa's Example 4 formulation contains bromfenac, BAC, and polysorbate 80. Ex. 1004, 8:3–14. Patent Owner directs us to evidence that bromfenac's chemical stability—that is, the ability to resist degradation—is "44% better" when tyloxapol is used in place of polysorbate 80 in Ogawa's Example 4. Ex. 2082 ¶ 164; *see id*. at ¶ 163 (chart tabulating experimental results); Resp. 49. Patent Owner, moreover, establishes a further unexpected result—that by replacing polysorbate 80 with tyloxapol, and decreasing the amount of the non-ionic surfactant from about 0.15 g to about 0.02 g, the inventors increased significantly the stability of the bromfenac formulation. Ex. 2082 ¶ 163–171 (Dr. Williams, explaining the test results showing that when tyloxapol is added to an aqueous formulation of bromfenac and BAC in an amount of 0.02 g, the tyloxapol stabilizes bromfenac better than when tyloxapol is added in the greater amounts of 0.05 g, 0.1 g, or 0.15 g—and

that all of the tyloxapol formulations stabilize bromfenac better than a comparable formulation containing polysorbate 80 at 0.17 g), ¶ 165 (explaining that those results would have been unexpected by a person of ordinary skill in the art). Specifically, when the amount of tyloxapol added to the formulation is lowered to 0.02 g, or about one-eighth the amount of polysorbate 80 (0.17 g), tyloxapol is about 75% better at stabilizing bromfenac against degradation. Resp. 41; Ex. 2082 ¶ 164. We are persuaded by Dr. Williams' testimony that those results would have been "entirely unexpected" to one of ordinary skill in the art at the time of the invention. Ex. 2082 ¶¶ 160, 164–165.

Ogawa's Example 6 formulation, by contrast, includes not only polysorbate 80 but also two additional components—polyvinyl pyrrolidone and sodium sulfite—which, according to Ogawa, "remarkably enhance[]" bromfenac stability. Ex. 1004, 3:50–51; *see id*. at 8:47–51; 10:12–18 (further discussing the remarkable enhancement of bromfenac stability accomplished by those two additional components). Patent Owner shows persuasively that tyloxapol stabilizes bromfenac as effectively as Ogawa's Example 6 formulation even when the tyloxapol formulation lacks polyvinyl pyrrolidone and sodium sulfite. Ex. 2082 ¶¶ 167–171; Ex. 2098, Sections III.B and C. We find credible Dr. Williams' testimony that those "results are highly unexpected" and "materially contribute to the art as a whole in potentially eliminating sodium sulfite from being administered to a patient's surgically compromised eye." Ex. 2082 ¶¶ 165, 170.

Petitioner disagrees and contends that Patent Owner's evidence of unexpected results is not commensurate in scope with the claimed invention.

Reply 20. On that point, however, we find that Patent Owner's evidence is sufficient to establish a trend demonstrating a surprising stabilizing effect of tyloxapol that is not suggested by the prior art. Ex. 2082 ¶ 163 (comparative chart, showing unexpected result that tyloxapol at amount of 0.02 g stabilizes bromfenac better than tyloxapol at 0.05 g, 0.1 g, and 0.15 g—and that all of the tyloxapol formulations unexpectedly stabilize bromfenac better than a comparable formulation containing polysorbate 80 at 0.17 g). Further, we are persuaded by Dr. Williams' testimony that the comparative data shows a superior stabilizing effect of tyloxapol across "disparate pH ranges, which are representative of the useable pH range" and "effectively demonstrate tyloxapol's unexpectedly superior stabilizing effect commensurate with the scope of the claims." *Id*. at ¶ 172.

(2) Commercial Success

Patent Owner comes forward with additional evidence that "[t]he unexpected stabilization benefits of tyloxapol translated into unexpected medical benefits in the commercial product Prolensa." Resp. 53. On that point, Patent Owner directs us to specific information pertaining to the composition of Prolensa, indicating that the commercial product falls within the scope of claims 1–4, 6–10, and 18–20. *Id*. at 55–56 (citing Ex. 2082 ¶¶ 152, 178). Petitioner admits that "[t]he subject matter of many of the challenged claims of the '431 patent is commercially embodied by Prolensa." Pet. 9. At the final oral hearing, Petitioner confirmed that Prolensa falls within the scope of the '431 patent claims. Tr. 27:15–19. In the absence of persuasive evidence to the contrary, we presume that the commercial success of Prolensa is attributable to the claimed invention of

the '431 patent. *See PPC Broadband, Inc. v. Corning Optical Commc'ns RF, LLC*, 815 F.3d 734, 746–47 (Fed. Cir. 2016) (evidence showing that a commercial product embodies the claimed invention gives rise to a presumption that the commercial success of that product is due to the claimed invention, absent persuasive evidence to the contrary).

Patent Owner identifies evidence that tyloxapol's stabilizing effect permitted the formulation of Prolensa at a pH lower than other commercially available bromfenac formulations, representing "a substantial reduction on a logarithmic scale" that was "beneficially closer to the pH of natural tears." Resp. 56 (citing Ex. 2030, 1; Ex. 2026, 5; Ex. 2027, 4; Ex. 2082 ¶ 178). According to Patent Owner, the stabilizing effect of tyloxapol further permitted the use of substantially less surfactant in Prolensa than in other commercial products. *Id.*; Ex. 2082 ¶ 178. Patent Owner directs us to evidence that "[b]oth the reduction in pH and lower amount of surfactant eliminated the burning and stinging upon administration present with all approved NSAID ophthalmic eye drops besides Prolensa." Resp. 56 (citing Ex. 2082 ¶ 179; Ex. 2116 ¶ 41). Patent Owner further identifies evidence that other commercially available eye drops "are limited by their burning and stinging side effects." *Id*. (citing Ex. 2116 ¶ 36; Ex. 2057, 6; Ex. 2060, 7–8; Ex. 2111, 1, col. 2; Ex. 2026, 5–6; Ex. 2027, 6).

Petitioner disagrees, directing us to evidence that the prescribing information for Prolensa states that adverse reactions "are limited to the 'most commonly reported adverse reactions,'" which, according to Petitioner, indicates "that less common adverse reactions were not included." Reply 21–22 (emphasis omitted) (citing Ex. 2013, 3). To the

extent that Petitioner suggests that Prolensa may cause burning and stinging, but that it remains unreported as a "less common adverse reaction[]" (*id*.), we find that suggestion to be speculative and unsupported by the evidence to which we are directed. Ex. 2013, 3.

Petitioner also argues that certain other asserted benefits of Prolensa are not shown to be commensurate in scope with the challenged claims because Patent Owner fails to come forward with evidence showing that "other embodiments" would "exhibit similar benefits." Reply 22–23. Petitioner, however, admits that Prolensa embodies "many of the challenged claims." Pet. 9. Under the circumstances, Petitioner must overcome a presumption that the benefits of Prolensa flow from the claimed invention. *PPC Broadband, Inc.*, 815 F.3d at 746–47. Petitioner has not established persuasively that a lack of evidence regarding the benefits of "other claimed embodiments" detracts from the force of the evidence showing the benefits of Prolensa. Reply 22.

Patent Owner comes forward with persuasive evidence that Prolensa is the only approved NSAID-containing eye drop that is not limited by "significant, painful side effects that adversely impact patient compliance." Resp. 56; Ex. 2116 ¶ 36. Patent Owner's witness, Dr. Trattler, provides credible testimony that non-compliant post-operative patients are at risk of developing a serious complication involving retinal swelling and reduced vision. Ex. 2116 ¶ 36. We find that the stabilizing benefits of tyloxapol in an aqueous formulation of bromfenac permitted the formulation of a commercial product, represented by Prolensa, at a lower pH than other commercially available bromfenac formulations—specifically, at a pH

beneficially closer to that of natural tears. Resp. 56; Ex. 2030, 1; Ex. 2026, 5; Ex. 2027, 4; Ex. 2082 ¶ 178.

By using a lower amount of surfactant and bringing the pH of the formulation closer to that of natural tears, the claimed invention resulted in a commercial product that effectively eliminated the burning and stinging associated with other approved NSAID ophthalmic eye drops. Ex. 2082 ¶ 178; Ex. 2116 ¶ 41; *see* Resp. 56 (identifying other commercial eye drops that all were limited by their side effects of burning and stinging). Prolensa represented a new therapy for comfortably treating postoperative inflammation and pain after cataract surgery without burning or stinging upon administration. Ex 2013, 6; Ex. 2116 ¶¶ 36, 39, 52; Resp. 56–57; *see Allergan, Inc. v. Sandoz, Inc.*, 796 F.3d 1293, 1306 (Fed. Cir. 2015) (unexpected difference in kind between safe and effective drug and one with serious side effects causing patients to become non-compliant).

Patent Owner also directs us to testimony of Mr. Jarosz to establish that Prolensa has enjoyed commercial success, achieving one of the highest shares of prescriptions and revenue among branded drugs with similar indications. Ex. 2130 ¶¶ 62, 72–75, 85, 132–135; Resp. 58–59. Petitioner, on the other hand, attempts to undercut Mr. Jarosz's testimony that the commercial success of Prolensa is attributable specifically to tyloxapol's stabilizing effect on bromfenac. Reply 23.

Petitioner argues that the performance of Prolensa in the marketplace is primarily attributable to a life-cycle management strategy employed by Patent Owner. *Id*. at 24. On that point, Petitioner directs us to declaration testimony that the introduction of Prolensa "did not increase the overall level

of total prescriptions" but simply "replaced the prescriptions of the previous generation products." Ex. 1150 ¶ 61. Petitioner's argument, however, appears as a tacit admission of the success of Prolensa. We are directed to no evidence that the introduction of a superior product would increase the overall number of patients requiring treatment for conditions of the eye (or, thus, the overall number of prescriptions written for such conditions). The fact that Prolensa replaced such prescriptions suggests commercial success.

We have considered but find unpersuasive Petitioner's other arguments that Patent Owner's evidence of secondary considerations lacks probative value. Reply 24–25. For example, Petitioner argues that Patent Owner overstates the purported success of Prolensa by relying exclusively on its gross sales. Reply 24–25 (bridging paragraph) (citing Ex. 1150 ¶ 33; Ex. 1149, 76:16–78:7). That argument depends on Mr. Hofmann's bare opinions regarding "historical experience" and "estimated gross-to-net sales adjustments"—opinions that are not adequately explained or supported by objective evidence. Ex. 1150 ¶ 33; *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"). Patent Owner, by contrast, presents persuasive declaration testimony, which we credit, that Prolensa has, in fact, achieved substantial marketplace success—which Petitioner tacitly acknowledges by seeking to replicate that success by copying exactly the claimed invention. Resp. 58–92; Ex. 2130 ¶¶ 62, 72–75, 85, 132–135; *see* Ex. 2082 ¶ 181 (indicating Petitioner's intention to market a generic bromfenac product that is an exact copy of Prolensa).

(3) Industry Acclaim

Patent Owner directs us to additional objective evidence of non-obviousness. Resp. 55–60. For example, Patent Owner identifies objective evidence that Prolensa received significant medical industry acclaim by others in the field of cataract surgery based on benefits flowing from tyloxapol's ability to stabilize the formulation at relatively low amounts of addition. Ex. 2116 ¶¶ 51–61; Ex. 2130 ¶ 125; Resp. 58. Specifically, Dr. Trattler provides a detailed discussion, supported by objective evidence, indicating that Prolensa's benefits, including its lack of a burning or stinging side effect, increased patient comfort and compliance—and that those benefits flowed from "tyloxapol's unexpected ability to stabilize bromfenac." Ex. 2116 ¶ 51; *see id*. at ¶¶ 52–54 (further explaining those benefits). Dr. Trattler details the resulting industry acclaim, supported by objective evidence indicating that Prolensa was praised by a "renowned ophthalmologist" Dr. Steven M. Silverstein, "leading cataract surgeon" Dr. Thomas R. Walters, and "leader in the field of cataract surgery" Dr. Rahesh Rajpal. Ex. 2116 ¶¶ 56–57, 59–60. Patent Owner identifies additional evidence, moreover, that Prolensa's superior degree of efficacy and ocular comfort trace back "to tyloxapol's ability to chemically stabilize bromfenac at a reduced pH," as evidenced by a Medscape report. *Id*. at ¶ 58; Ex. 2066, 1; Ex. 2082 ¶¶ 178–180. Patent Owner also directs us to evidence that Prolensa "has received acclaim in numerous peer-reviewed medical journal articles." Ex. 2116 ¶ 61 (citing Ex. 2051, 6–8). Petitioner does not address that evidence. Reply 20–24. On this record, we are persuaded that Prolensa has received significant acclaim within the medical industry.

c. Conclusions on Obviousness

We weigh the above objective evidence of non-obviousness en route to ruling on Petitioner's obviousness challenge. We do so mindful that secondary considerations can be the most probative evidence of non-obviousness in the record, enabling a court to avert the trap of hindsight. *Crocs, Inc. v. Int'l Trade Comm'n*, 598 F.3d 1294, 1310 (Fed. Cir. 2010).

Petitioner's challenge rests on an assertion that a person of ordinary skill in the art would have recognized that substituting tyloxapol for polysorbate 80 in Ogawa's Example 6 "would successfully, and predictably, result in a stable ophthalmic formulation of bromfenac." Pet. 24 (citing Ex. 1021, 13:8–10; Ex. 1022, 4:24–31; Ex. 1003 ¶ 38). A preponderance of evidence, however, persuades us that the inventors of the '431 patent made the surprising and unexpected discovery that tyloxapol serves a stabilizing function in an ophthalmic formulation of bromfenac. Ex. 2082 ¶¶ 163–173; Resp. 45–60.

On that point, we find that bromfenac's chemical stability is "44% better" when tyloxapol is used in place of polysorbate 80 in Ogawa's Example 4. Ex. 2082 ¶ 164; *see id*. at ¶ 163 (chart tabulating experimental results). The inventors further discovered that a reduction in the concentration of tyloxapol, "in an unexpected and counterintuitive manner," increased the stabilizing effect. Ex. 2082 ¶ 164; *see id*. at ¶ 165 (in general, one would expect an effect to "become more powerful as you increase concentration") (quotation omitted) ¶¶ 165–171 (further explaining the experimental data). We find that those results would have been "entirely unexpected" to one of ordinary skill in the art at the time of the invention.

Id. at ¶ 165. Given the significant evidence of unexpected results, we find that the proposed substitution of tyloxapol for polysorbate 80 in Ogawa's Example 6 of bromfenac would have done more than yield a predictable result. *See KSR Int'l*, 550 U.S. at 416 ("[W]hen a patent claims a structure already known in the prior art that is altered by the mere substitution of one element for another known in the field, the combination must do more than yield a predictable result.").

We further find that tyloxapol stabilizes bromfenac as effectively as Ogawa's Example 6, even when the tyloxapol formulation lacks polyvinyl pyrrolidone and sodium sulfite—the two components that, according to Ogawa, "remarkably enhance[]" bromfenac stability. Ex. 1004, 3:50–51; *see id*. at 8:47–51; 10:12–18 (further discussing the remarkable enhancement of bromfenac stability accomplished by those two additional components); Ex. 2082 ¶¶ 167–173; Ex. 2098, Sections III.A, B, and C; *see* Ex. 2082 ¶ 169 (chart tabulating experimental results); *see id*. at ¶ 154 (chart tabulating experimental results); Resp. 51–52 (Patent Owner's argument regarding the comparative data relating to Ogawa's Example 6 formulation). We find that those "results are highly unexpected" and "meaningfully and materially contribute to the art as a whole in potentially eliminating sodium sulfite from being administered to a patient's surgically compromised eye." Ex. 2082 ¶ 170.

The use of tyloxapol facilitates, among other things, a lowering of the pH of the formulation to more closely approximate the pH of natural tears. Ex. 2082 ¶¶ 178; Ex. 2030, 1; Ex. 2026, 5; Ex. 2027, 4; Resp. 56. The use of tyloxapol also enables a reduction in the amounts of irritating ingredients,

including the surfactant and bromfenac. Ex. 2082 ¶¶ 168, 178, 179; Ex. 2116 ¶ 41; Resp. 56. The claimed invention is embodied in a commercially successful product, Prolensa, which reduces the stinging sensation associated with other products that contain higher levels of irritating ingredients. Pet. 9; Tr. 27:15–19 (admission of nexus); *see* Ex. 2130 ¶¶ Ex. 2130 ¶¶ 62, 72–75, 85, 132–135; Resp. 58–59 (evidence and persuasive argument that Prolensa is commercially successful); *see also* Ex. 2116 ¶ 36; Ex. 2057, 6; Ex. 2060, 7–8; Ex. 2111, 1, col. 2; Ex. 2026, 5–6; Ex. 2027, 6 (evidence that other commercial products are limited by their side effects of burning and stinging). Moreover, Prolensa received significant medical industry acclaim by others in the field of cataract surgery based on benefits flowing from tyloxapol's ability to stabilize the formulation at relatively low amounts of addition. Ex. 2116 ¶¶ 51–61; Ex. 2130 ¶ 125; Resp. 58.

We hold that the objective evidence of non-obviousness outweighs Petitioner's evidence of obviousness based on the prior art. *See, e.g.*, Pet. 21–22 (claim chart for claim 1, advancing the alleged interchangeability of tyloxapol for polysorbate 80 in Ogawa's Example 6 in view of Sallmann). In reaching that conclusion, we take account of the combined disclosures of Ogawa and Sallmann along with the teachings of the background prior art references advanced in the Petition. *See, e.g.*, Ex. 1005, 3:12–45 (Desai's disclosure of lists of NSAIDs and surfactants useful in aqueous ophthalmic preparations); Ex. 2082 ¶ 81 (Dr. Williams' testimony relating to Desai's teachings). Desai does not teach a specific formulation containing both

bromfenac and tyloxapol, but rather, includes lists of ingredients generally suitable for use in ophthalmic formulations. Ex. 1005, 3:12–45.

Petitioner argues that "Yasueda teaches that tyloxapol is superior to polysorbate 80 in solubilizing acidic ophthalmic drugs." Pet. 33 (citing Ex. 1012, Tables 4 & 5; Ex. 1003 ¶ 59). Yasueda, however, relates to the degradation pathway of a different active ingredient (pranlukast). Ex. 1012, 1:16–24. Petitioner's argument regarding the background teaching of Yasueda relies on opinion testimony that lacks adequate discussion of the similarities and differences between pranlukast and bromfenac. Ex. 1003 ¶ 59. Specifically, that testimony is not credible because it lacks adequate explanation for why an ordinary artisan would have expected those different active ingredients to behave similarly in an aqueous formulation. *Id*.

Patent Owner, by contrast, identifies credible and persuasive testimony that explains why Yasueda does not suggest that tyloxapol is superior to polysorbate 80 in an aqueous formulation of bromfenac, and why the absence of BAC in Yasueda's formulation undercuts Petitioner's argument in that regard. Resp. 27–28; Ex. 2082 ¶ 123 (Dr. Williams' testimony); Ex. 2015 ¶¶ 63–68 (Dr. Davies' testimony). On that point, we find credible Patent Owner's evidence that pranlukast and bromfenac degrade by different mechanisms. Ex. 2082 ¶ 88; Ex. 2105 ¶ 71. We further find that "pranlukast is not an NSAID and is structurally and chemically dissimilar to bromfenac, and thus a person of ordinary skill in the art would not have applied to bromfenac any stability conclusions reached with respect to pranlukast." Ex. 2105 ¶ 63 (Dr. Davies' testimony). We also credit Dr. Davies' explanation of the chemical differences between pranlukast and

bromfenac and why they would have led an ordinary artisan to expect them to exhibit "significantly different functional and chemical properties." *Id*. at ¶ 67; *see id*. at ¶¶ 63–72 (for a full and cogent explanation of the differences between pranlukast and bromfenac). A preponderance of evidence does not support Petitioner's position that Yasueda would have prompted a person of ordinary skill in the art to substitute tyloxapol for polysorbate 80 in Ogawa's Example 6 formulation of bromfenac. Ex. 2082 ¶ 123; Ex. 2105 ¶¶ 63–72.

Petitioner also argues that Fu, among other background references, would have caused an ordinary artisan to form "a reasonable expectation of success in substituting tyloxapol for polysorbate 80, because the prior art included multiple examples of stable aqueous preparations containing NSAIDs (similar to bromfenac) formulated with BAC and tyloxapol (and other closely related non-ionic surfactants)." Pet. 25 (citing Ex. 1011, 18:5–28). On that point, however, Petitioner directs us to opinion testimony (Ex. 1003 ¶¶ 33, 35–36) that is undercut by the best objective evidence on point—the disclosure of Fu itself. Fu does not mention tyloxapol or bromfenac. *See generally* Ex. 1011. Furthermore, we credit the testimony of Patent Owner's witness, explaining why Fu's disclosed formulation—containing the NSAID ketorolac and the solubilizer Octoxynol 40—would not have suggested the unexpected result that tyloxapol would inhibit the degradation of bromfenac in the aqueous formulation of Ogawa's Example 6. Ex. 2082 ¶¶ 84–86, 132–147. Petitioner's discussion of whether tyloxapol would have been understood to inhibit complexation of bromfenac and BAC does not undercut that evidence, which relates to

tyloxapol's unexpected ability to inhibit the chemical degradation of bromfenac. Reply 1–16.

Taking account of the objective indicia of non-obviousness, including Patent Owner's significant evidence of unexpected results, we are not persuaded that Petitioner demonstrates sufficiently that the combined disclosures of Ogawa and Sallmann, when considered in light of the teachings of the asserted background prior art references, establish the obviousness of the claimed invention. Petitioner's proposed substitution of tyloxapol for polysorbate 80 produced a surprising and unexpected stabilizing effect on bromfenac. The other objective indicia of non-obviousness flow from that surprising result. Accordingly, we hold that Petitioner fails to establish that it would have been obvious at the time of the invention to prepare a bromfenac formulation comprising tyloxapol in the manner claimed.

2. Claim 1: Substituting Bromfenac for Diclofenac in Sallmann

In our decision instituting trial, we preliminarily determined that Petitioner had shown sufficiently that it would have been obvious at the time of the invention to replace the diclofenac potassium salt in Sallmann's Example 2 with a bromfenac component based on argument that one would have simply substituted the NSAIDs to serve a common function. Dec. 13–15. Upon consideration of the full trial record, however, we reach a different final determination on that point. Specifically, we agree with Patent Owner that Sallmann's disclosure reveals an exclusive focus on diclofenac potassium salt as the NSAID. Resp. 16–18, 28–35 (and evidence cited therein).

On that point, we are persuaded that the entire thrust of Sallmann's disclosure is uniquely directed to formulations of diclofenac potassium salt. Ex. 1009, 1:35–3:26 (focusing exclusively on diclofenac potassium salt, which Sallmann describes as "[s]urprisingly" and "especially suitable" for treating inflammatory ocular processes) (*id*. at 1:48–51); Ex. 2082 ¶ 126. We are not persuaded that the background prior art references advanced by Petitioner would have led an ordinary artisan to substitute diclofenac potassium salt with any other NSAID—given the exclusivity of Sallmann's focus on diclofenac potassium salt. Pet. 26–30 (and references cited therein).

We find that a person of ordinary skill in the art would not have been prompted to replace diclofenac potassium salt with a bromfenac compound in Sallmann's Example 2 formulation, because "doing so would have been contrary to the entire purpose and essence of Sallmann's invention." Ex. 2082 ¶ 126; *see, e.g.*, Ex. 1009, 7:54–14:41 (Sallman's disclosure of 19 examples, all of which are directed to a formulation of diclofenac potassium salt). *See generally* Ex. 1009 (nowhere suggesting that any active ingredient, other than diclofenac potassium salt, is suitable for use in Sallmann's invention); Resp. 28–35 (and evidence cited therein).

A person of ordinary skill in the art would have understood that even small changes to an ophthalmic formulation's ingredients can yield substantial changes in its properties and functionality—and changing the active ingredient would not have been viewed as a small change. Ex. 2082 ¶¶ 52–56, 104–105, 126. For example, bromfenac was known to be freely soluble in water and, therefore, would have required no ingredient such as

the tyloxapol, which Sallmann incorporated to solubilize the diclofenac potassium salt. Ex. 2082 ¶ 104; Ex. 2039, 6; Ex. 2140, 156:20–157:6. Patent Owner directs us to persuasive evidence, moreover, that Sallmann does not use tyloxapol to stabilize diclofenac potassium salt, as that function is achieved by a different component in Sallmann's formulation. Resp. 18 (citing Ex. 1009, 5:59–6:17, 8:1–15; Ex. 2082 ¶ 109).

We are not persuaded that Petitioner shows by a preponderance of evidence that it would have been obvious to substitute a bromfenac compound for the diclofenac potassium salt employed in Sallmann's Example 2. In that regard, we take account of the evidence of secondary considerations discussed above in the context of the challenge based on the alleged interchangeability of tyloxapol and polysorbate 80 in Ogawa's Example 6 formulation. The totality of the evidence leads us to conclude that Petitioner fails to show that the subject matter of claim 1 would have been obvious over the combined disclosures of Ogawa and Sallmann.

3. Obviousness of Claims 2–5, 7–14, and 18–19 over Ogawa and Sallmann

Each of claims 2–5, 7–14, and 18–19 requires an aqueous preparation of bromfenac and tyloxapol. Ex. 1001, 12:10–14:22. Petitioner's challenge to the patentability of those claims relies on the same reasoning raised in connection with claim 1 based on the combined disclosures of Ogawa and Sallmann for a reason to combine bromfenac and tyloxapol. Pet. 20–50. For reasons discussed above in connection with claim 1, Petitioner fails to establish that the combined disclosures of Ogawa and Sallmann would have suggested an aqueous formulation of bromfenac and tyloxapol.

Accordingly, we hold that Petitioner fails to establish by a preponderance of evidence the unpatentability claims 2–5, 7–14, and 18–19.

4. Obviousness of Claims 6, 15–17, and 20–22 over Ogawa, Sallmann, and Fu

Each of claims 6, 15–17, and 20–22 requires an aqueous preparation of bromfenac and tyloxapol. Ex. 1001, 12:10–14:22. Petitioner's challenge to the patentability of those claims relies on the same reasoning raised in connection with claim 1 based on the combined disclosures of Ogawa and Sallmann for a reason to combine bromfenac and tyloxapol. Pet. 20–50. Petitioner does not show sufficiently that Fu cures the deficiencies of Ogawa and Sallmann as applied to claims 6, 15–17, and 20–22. *Id*. For reasons discussed above in connection with claim 1, Petitioner fails to establish that the combined disclosures of Ogawa, Sallmann, and Fu would have suggested an aqueous formulation of bromfenac and tyloxapol. Accordingly, we hold that Petitioner fails to establish by a preponderance of evidence the unpatentability claims 6, 15–17, and 20–22.

III. MOTIONS TO EXCLUDE

We next turn to the parties' fully briefed Motions to Exclude. Papers 56, 59. We first address Petitioner's Motion to Exclude. Paper 56. We then address Patent Owner's Motion to Exclude. Paper 59.

Petitioner moves to exclude Exhibits 2266, 2267, and 2268,[8] and related testimony of Dr. Laskar, based on argument that those materials were

[8] Exhibits 2266 and 2268 are, respectively, deposition transcripts of Dr. Clayton Heathcock and Dr. Robert C. Cykiert recorded in related district court litigation. Paper 72, 21. Exhibit 2267 is an expert report Dr. Stephen G. Davies from related district court litigation. *Id*.

submitted in violation of a Board ruling and under Federal Rules of Evidence 801 and 802. Paper 56, 3–8.

We deny Petitioner's Motion to Exclude. Patent Owner introduced Exhibits 2266, 2267, and 2268 during the cross-examination of Dr. Laskar on March 25, 2016, nearly three months after Patent Owner filed its Response. Paper 56, 1. The filing of those exhibits does not represent a "backdoor alleged sur-reply" in violation of the Board's order denying Patent Owner's request to file a sur-reply, because we will not consider those exhibits to the extent that they are not discussed adequately in a substantive paper. *Id*.

Petitioner's argument that Exhibits 2266, 2267, and 2268 should be excluded as impermissible hearsay is presented without adequate analysis. *Id*. at 6, 8–9. For example, Petitioner directs us to no instance in which Patent Owner refers—in a substantive brief filed in this proceeding—to any disclosure in Exhibits 2266, 2267, or 2268 for the purpose of establishing the truth of a matter asserted. *Id*.; Paper 69, 3 (directing us only to Patent Owner's Opposition to Petitioner's Motion to Exclude, and there, only to a general statement by Patent Owner that Exhibit 2267 is advanced "as evidence of material fact" that remains unidentified). Patent Owner, moreover, submits that those exhibits were used to question the veracity and credibility of Dr. Laskar's opinion during cross-examination at his deposition. Paper 64, 3–4. We are not persuaded that Exhibits 2266, 2267, or 2268 should be excluded under these circumstances. Accordingly, Petitioner's Motion to Exclude is *denied*.

Patent Owner seeks to exclude the Reply Declaration of Dr. Laskar (Ex. 1104) as well as his deposition testimony (Ex. 2114 and Ex. 2272) on the basis that "Dr. Laskar completely lacks expertise in organic or medicinal chemistry," therefore, he lacks the background necessary to form an opinion under Federal Rule of Evidence 702. Paper 59, 1–8. Patent Owner's argument goes to the weight and not the admissibility of the evidence sought to be excluded. *Id*. We are not persuaded by Patent Owner's argument that our "gatekeeping role" under *Daubert v. Merrell Dow Pharm., Inc*., 509 U.S. 579, 597 (1993) and Federal Rule of Evidence 702 compels us to exclude Dr. Laskar's testimony. Paper 59, 7. To the extent Patent Owner identifies weaknesses in Dr. Laskar's testimony, we take that into account when weighing the evidence in this case. *Id*. at 1–8.

Patent Owner also argues that Dr. Laskar's Reply Declaration (Ex. 1104) as well as eight prior art references identified in Petitioner's Reply (Paper 51, 11) represent entirely new argument that exceeds the scope of a proper rely. Paper 59, 9–10 (citing Ex. 1089, Ex. 1106, Ex. 1091, Ex. 1094, Ex. 1080, Ex. 1105, Ex. 1148, Ex. 1092, Ex. 1093). In Patent Owner's view, Dr. Laskar devotes 30 paragraphs of his 39-paragraph Reply Declaration to the new argument that those eight newly-cited prior art references establish that tyloxapol is an antioxidant and, based on that function, would have been recognized as an interchangeable alternative to polysorbate 80 in Ogawa's Example 6. Paper 59, 10. Petitioner counters that "Patent Owner's principle theory of the purported non-obviousness of the claims" is that a person of ordinary skill in the art "would have known bromfenac degrades by oxidative degradation and thus would have used an

antioxidant—and associated factual allegations (e.g., that polysorbate 80 and tyloxapol are both oxidizing agent[s]).” Paper 66, 8. That statement is provided without any citation to Patent Owner’s Response. *Id*. We are persuaded that Petitioner’s argument regarding the alleged antioxidant function of tyloxapol is impermissibly raised for the first time in the Reply. Paper 59, 9–10. The Petition nowhere suggests that polysorbate 80 and tyloxapol would have been understood to serve the common function of an antioxidant in Ogawa’s Example 6 formulation. *See generally* Pet. Rather than excluding Dr. Laskar’s Reply Declaration or the eight new prior art references, however, we accord that evidence no weight to the extent that it is discussed in the Reply and relates to the new argument. *See* Ex. 1104 (Dr. Laskar’s Reply Declaration); Ex. 1089, Ex. 1106, Ex. 1091, Ex. 1094, Ex. 1080, Ex. 1105, Ex. 1148, Ex. 1092, Ex. 1093 (eight new prior art references).

Patent Owner also seeks to exclude portions of Dr. Laskar’s deposition testimony on the basis that Dr. Laskar allegedly discussed his testimony with Petitioner’s counsel during a break and other alleged irregularities. Paper 59, 11–13. Here again, Patent Owner’s raises argument that goes not to admissibility, but rather, to the weight that should be accorded Dr. Laskar’s testimony—argument that we take into account when weighing the evidence. We decline to exclude Dr. Laskar’s testimony on that basis. Patent Owner’s motion to exclude is *denied*.

IV. CONCLUSION

Taking account of the arguments and evidence presented during trial, including Patent Owner’s evidence of secondary considerations, we

determine that Petitioner fails to establish by a preponderance of the evidence that claims 1–5, 7–14, 18, and 19 of the ’431 patent are unpatentable under 35 U.S.C. § 103(a) as obvious over the combination of Ogawa and Sallmann, and claims 6, 15–17, and 20–22 of the ’431 patent are unpatentable under 35 U.S.C. § 103(a) as obvious over the combination of Ogawa, Sallmann, and Fu.

IV. ORDER

It is

ORDERED that Petitioner has not shown by a preponderance of the evidence that claims 1–22 of the ’431 patent are unpatentable;

FURTHER ORDERED that Petitioner’s Motion to Exclude is *denied*;

FURTHER ORDERED that Patent Owner’s Motion to Exclude 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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