

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

Petitioners,

v.

SENJU PHARMACEUTICAL CO., LTD.,

Patent Owner.

Case IPR2015-01105¹
Patent 8,871,813 B2

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

FRANKLIN, *Administrative Patent Judge*.

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

¹ IPR2016-00090 has been joined with this proceeding.

I. INTRODUCTION

Lupin Ltd. and Lupin Pharmaceuticals Inc. (collectively, “Lupin”) filed a Petition requesting an *inter partes* review of claims 1–27 of U.S. Patent No. 8,871,813 B2 (Ex. 1003, “the ’813 patent”). Paper 1 (“Petition” or “Pet.”). Senju Pharmaceutical Co., Ltd. (“Patent Owner”) filed a Preliminary Response to the Petition. Paper 8 (“Prelim. Resp.”).

On October 27, 2015, we instituted an *inter partes* review of claims 1–27 of the ’813 patent. Paper 9 (“Dec. Inst.”). Patent Owner filed a Patent Owner Response to the Petition. Paper 23 (Board Only), Paper 24 (Parties and Board Only), Paper 25 (Public), (collectively, “PO Resp.”).

On February 25, 2016, we instituted an *inter partes* review in IPR2016-00090 and granted the motion for joinder with IPR2015-01105, adding InnoPharma Licensing, Inc., InnoPharma Licensing LLC, InnoPharma Inc., InnoPharma LLC, Mylan Pharmaceuticals, and Mylan Inc. to the Lupin petitioner (collectively “Petitioners”). Paper 22. Petitioners filed a Reply to the Patent Owner Response. Paper 35 (Public), Paper 37 (Parties and Board Only), (collectively, “Reply”).

Both parties filed a Motion to Exclude Evidence. Paper 44 (“Pet. Mot.”) and Paper 46 (“PO Mot.”). Each party filed an Opposition to the other party’s Motion to Exclude Evidence. Paper 49 (“PO Opp.”); Paper 51 (“Pet. Opp.”). Each party filed also a Reply to the other party’s Opposition to the Motion to Exclude Evidence. Paper 55 (“Pet. Reply Opp.”); Paper 56 (“PO Reply Opp.”).

Patent Owner filed a Motion for Observation Regarding Cross Examination of Reply Witnesses, Paper 47, and Petitioners filed a Response to that motion, Paper 52.

On June 9, 2016, the parties presented arguments at an oral hearing. The hearing transcript has been entered in the record. Paper 63 (“Tr.”).

The Board has jurisdiction under 35 U.S.C. § 6(b). In this Final Written Decision, issued pursuant to 35 U.S. C. § 318(a) and 37 C.F.R. § 42.73, Petitioners have not proved by a preponderance of the evidence that claims 1–27 of the ’813 patent are unpatentable.

Petitioners’ Motion to Exclude Evidence is *dismissed* as moot. Patent Owner’s Motion to Exclude Evidence is *denied-in-part* and *dismissed-in-part* as moot.

A. *Related Proceedings*

Petitioners and Patent Owner identify a number of related district court proceedings involving the ’813 patent, including one that involves both parties in this proceeding: *Senju Pharmaceutical Co., Ltd., et al. v. Lupin, Ltd. et al.*, C.A. No. 1:15-cv-00335-JBS-KMW (D.N.J). Pet. 2; Paper 5, 3.

The parties identify also two related *inter partes* proceedings. Pet. 3; Paper 5, 3. An *inter partes* review of claims of U.S. Patent No. 8,669,290 B2 (“the ’290 patent”) was instituted in *Metrics, Inc. v. Senju Pharmaceutical Co., Ltd.*, IPR2014-01043 (trial terminated after settlement, IPR2014-01043, Paper 39) and in *InnoPharma Licensing Inc. v. Senju Pharmaceutical Co., Ltd.*, IPR2015-00902 (claims 1–30 of the ’290 patent were held not to have been shown to be unpatentable in a Final Written Decision, IPR2015-00902, Paper 90). The ’813 patent claims priority to the ’290 patent. An *inter partes* review of claims of U.S. Patent No. 8,129,431 was instituted in *Metrics, Inc. v. Senju Pharmaceutical Co., Ltd.*, IPR2014-01041 (trial terminated after settlement, IPR2014-01041, Paper 39) and in *InnoPharma Licensing Inc. v. Senju Pharmaceutical Co., Ltd.*,

IPR2015-00903 (claims 1–22 of the ’431 patent were held not to have been shown to be unpatentable in a Final Written Decision, IPR2015-00903, Paper 83).

Additionally, an *inter partes* review was instituted for claims of U.S. Patent 8,754,131 (IPR2015-01097), U.S. Patent 8,669,290 (IPR2015-01099), and Final Written Decisions have been entered determining that the challenged claims of those patents have not been shown to be unpatentable. Also, an *inter partes* review was instituted for claims 1–30 of U.S. Patent 8,927,606 (IPR2015-01100) and a Final Written Decision in that case is entered concurrently herewith determining that the challenged claims have not been shown to be unpatentable.

B. The ’813 Patent (Ex. 1003)

The ’813 patent relates to a stable aqueous liquid ophthalmic preparation comprising: (a) 2-amino-3-(4-bromobenzoyl)phenylacetic acid, or a pharmacologically acceptable salt or a hydrate thereof, also known by its generic name, “bromfenac”; and (b) tyloxapol. Ex. 1003, 1:7–31, 2:26–28.

The Specification explains that, prior to the invention, bromfenac was known as a non-steroidal anti-inflammatory agent (“NSAID”) effective against inflammatory diseases of the anterior and posterior segments of the eye, such as blepharitis, conjunctivitis, scleritis, and postoperative inflammation. *Id.* at 1:33–38. According to the Specification, the inventors of the ’813 patent found that by adding an alkyl aryl polyether alcohol type polymer, such as tyloxapol, which is a non-ionic surfactant, to an aqueous liquid preparation of bromfenac, the preparation “becomes stable within a pH range giving no irritation to eyes, and change of the [bromfenac] . . . over

time can be inhibited, and furthermore, when the aqueous solution contains a preservative, deterioration in the preservative effect of said preservative can be inhibited for a long period of time.” *Id.* at 2:24–37, 4:13–15.

Experimental Example 1 of the ’813 patent compares the stability of bromfenac-containing ophthalmic solutions comprising 0.15 w/v% tyloxapol, 0.02 w/v% tyloxapol, 0.15 w/v% polysorbate 80, or 0.15 w/v% polyoxyl 40 stearate. *See id.* at 6:44–7:5. The stability of each preparation was tested under conditions of pH 7.0 at 60° C for 4 weeks. *Id.* at 6:62–64. The results of the comparison are shown in Table 1, reproduced below:

TABLE 1

Component	Comparison Example 1	A-01	A-02	A-03
Sodium 2-amino-3-(4-bromobenzoyl)-phenylacetate	0.1 g	0.1 g	0.1 g	0.1 g
Boric acid	1.5 g	1.5 g	1.5 g	1.5 g
Benzalkonium chloride	0.005 g	0.005 g	0.005 g	0.005 g
Polysorbate 80	0.15 g	—	—	—
Polyoxyl 40 stearate	—	0.15 g	—	—
Tyloxapol	—	—	0.15 g	0.02 g
Sterile purified water	q.s.	q.s.	q.s.	q.s.
Total volume	100 mL	100 mL	100 mL	100 mL
pH	7.0	7.0	7.0	7.0
Remaining rate (%) at 60° C. after 4 weeks	51.3	63.7	73.8	89.6

Id. at 6:43–60, Table 1. As seen in Table 1, the bromfenac activity remaining in each of the tyloxapol-containing preparations (73.8% for the 0.15 w/v% tyloxapol-containing preparation and 89.6% for the 0.02 w/v% tyloxapol-containing preparation) was greater than the remaining activity in either the polysorbate 80-containing preparation (51.3%) or the polyoxyl 40 stearate-containing preparation (63.7%). *Id.*

C. Illustrative Claims

Claims 1 and 7 of the '813 patent are illustrative and reproduced below:

1. A stable aqueous liquid preparation consisting essentially of: (a) a first component; (b) a second component; wherein the first component is 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof; (c) boric acid; (d) sodium tetraborate; and (e) water; wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; the first component is the sole pharmaceutical active ingredient contained in the preparation and is present in the preparation at a concentration from about 0.05 w/v % to about 0.2 w/v %; the second component is tyloxapol and is present in said liquid preparation in an amount sufficient to stabilize said first component; and wherein said stable liquid preparation is formulated for ophthalmic administration.

7. A stable aqueous liquid preparation consisting essentially of: (a) a first component; (b) a second component; wherein the first component is 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof; (c) boric acid; (d) sodium tetraborate; and (e) water; wherein the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate; the first component is the sole pharmaceutical active ingredient contained in the preparation and is present in the preparation at a concentration from about 0.05 w/v % to about 0.2 w/v %; the second component is tyloxapol; wherein said stable liquid preparation is formulated for ophthalmic administration; and wherein the stable aqueous liquid preparation is characterized in that greater than about 90% of the original amount of the first component remains in the preparation after storage at about 60° C. for 4 weeks.

Ex. 1003, 11:30–43, 11:64–12:15.

D. The Cited References

Petitioners rely upon the following prior art references:

Ogawa	Ogawa et al., U.S. Patent No. 4,910,225, issued Mar. 20, 1990.	Ex. 1010
Fu	Fu et al., EP 0 306 984 A1, published Mar. 15, 1989.	Ex. 1014
Sallmann	Sallmann et al., U.S. Patent No. 5,891,913, issued Apr. 6, 1999.	Ex. 1021

Petitioners rely also upon the declarations of M. Jayne Lawrence, Ph.D. (Exs. 1005, 1094), and Ivan T. Hofmann, CPA/CFF, CLP (Exs. 1097, 1122).

Patent Owner relies upon the declarations of Robert O. Williams, III, Ph.D. (Ex. 2082), Shirou Sawa (Ex. 2098), Stephen G. Davies, D. Phil. (Ex. 2105), William B. Trattler, M.D. (Ex. 2116), Adam C. Myers, Ph.D. (Ex. 2126), Daryl S. Paulson, Ph.D., M.B.A. (Ex. 2128), and John C. Jarosz (Ex. 2130).

E. The Instituted Ground of Unpatentability

We instituted an *inter partes* review as to claims 1–27 of the '813 patent on the following ground:

Claims 1–27 under 35 U.S.C. § 103(a) as obvious over Sallmann and Ogawa.

II. PATENTABILITY ANALYSIS

A. Claim Construction

In an *inter partes* review, the Board interprets claim terms in an unexpired patent according to the broadest reasonable construction in light

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

Petitioners do not propose any specific claim construction for any claim term. *See* Pet. 5; Reply 25. Patent Owner proposes constructions for the terms “stable” and “amount sufficient to stabilize” as used in the claims of the ’813 patent. PO Resp. 6–7. Patent Owner argues that we should assign, as the broadest reasonable interpretations of those terms, the same constructions adopted in related litigation filed in the U.S. District Court for the District of New Jersey. *Id.* (citing Ex. 2065 (*Markman* Opinion)); also citing *Microsoft Corp. v. Proxyconn, Inc.*, 789 F.3d 1292, 1298 (Fed. Cir. 2015)). Petitioners reply that Patent Owner provides no justification for adopting the district court’s claim construction of those terms. Reply 25.

We agree with Petitioners. Only those claim terms that are in controversy need to be construed, and only to the extent necessary to resolve the controversy. *Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999). Patent Owner has not identified any controversy as to the scope of the claim terms for which it seeks construction. Nor does Patent Owner explain specifically why adopting the district court’s

construction of the identified terms is necessary to resolve an issue in this proceeding. Accordingly, we decline to adopt the district court's claim construction. Rather, because the parties identify no controversy as to the scope of any claim terms, we conclude that, for the purposes of this decision, no claim term requires express construction.

B. Level of Ordinary Skill in the Art

The level of skill in the art is a factual determination that provides a primary guarantee of objectivity in an obviousness analysis. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 1324 (Fed. Cir. 1999) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966) and *Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 718 (Fed. Cir. 1991)).

Petitioners assert that a person of ordinary skill in the art “would generally be a pharmaceutical scientist involved in the research and development of pharmaceuticals, and would have a Ph.D. and several years of experience in the field.” Pet. 6. Patent Owner asserts, more broadly, that a person of ordinary skill in the art would have at least a bachelor's degree in a field such as chemistry, pharmaceutical chemistry or a related discipline with 3–5 years of work experience. PO Resp. 7 (citing Ex. 2082 ¶¶ 47–48 (Williams Decl.)).

Based on the record as a whole, we find that Patent Owner's description more appropriately encompasses the broad education that the person of ordinary skill in the relevant art may possess. Thus, we adopt that description. We note, however, that neither party asserts specifically that the ultimate conclusion of obviousness turns on adoption of a particular level of ordinary skill.

C. Analysis of Independent Claims 1, 7, and 13

Petitioners assert that independent claims 1, 7, and 13 of the '813 patent would have been obvious over the combination of Sallmann and Ogawa. Pet. 34–42, 53–60; Reply 1–25. Patent Owner disagrees. PO Resp. 8–59.

When evaluating claims for obviousness, we consider and determine the scope and content of the prior art, the differences between the prior art and the claims at issue, the level of ordinary skill in the pertinent art, and secondary considerations of nonobviousness. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007) (citing *Graham*, 383 U.S. at 17–18).

1. Sallmann

Sallmann is directed to ophthalmic compositions to treat inflammatory conditions of the eye. Ex. 1021, 1:7–10. Sallmann's composition comprises diclofenac potassium, an NSAID, as the only active ingredient. *Id.* at 1:7–8, 29–31. The composition comprises also a solubilizer, wherein tyloxapol is disclosed as one of the preferred solubilizers. *Id.* at 4:64. Sallmann teaches that the concentration of the solubilizer may be from 0.1 to 5000 times the concentration of the active ingredient. *Id.* at 5: 1–2.

2. Ogawa

Ogawa is directed to stable aqueous ophthalmic compositions for treating inflammatory eye disease topically. Ex. 1010, 1:15–17. In Example 6, Ogawa discloses a formulation comprising sodium salt of bromfenac monohydrate, an NSAID, as the only active ingredient, in an amount of 0.1 g/ 100 ml, i.e., 0.1 w/v%, and polysorbate 80 in an amount of 0.15 g/100 ml, i.e., 0.15 w/v%. *Id.* at 10:5–18. The composition comprises also a water-soluble polymer, i.e., polyvinyl pyrrolidone, and a sulfite, both of which

Ogawa credits for the “remarkably enhanced” stability of its compositions. *Id.* at 3:48–52, 10:5–18.

3. Combined Teachings of the Cited References

Petitioners present two different arguments to support their assertion that independent claims 1, 7, and 13 would have been obvious over the combined teachings of Sallmann and Ogawa. Petitioners contend, in an initial obviousness rationale, that Sallmann discloses stable aqueous ophthalmic solutions which include the acidic NSAID diclofenac, in combination with tyloxapol. Pet. 35–37. According to Petitioners, the “only difference between the formulations described by [Sallmann] and the formulation in the claims of the ‘813 patent is the choice of NSAID (diclofenac vs. bromfenac).” *Id.* at 36.

Petitioners rely also upon Example 6 of Ogawa as disclosing an aqueous ophthalmic solution containing bromfenac, boric acid, borax, BAC, water, and the non-ionic surfactant polysorbate 80. *Id.* Petitioners contend that “Example 6 of [Ogawa] includes each of the elements of independent claims 1, 7, and 13 except for the inclusion of tyloxapol.” *Id.* at 37. According to Petitioners, an ordinary artisan would have considered it obvious to substitute Ogawa’s bromfenac for the diclofenac used in Sallmann’s Example 2, thereby arriving at a formulation having all of the ingredients required by the claims of the ’813 patent. *Id.* (citing Ex. 1005 ¶ 443 (Lawrence Decl.)).

Based on the record as a whole, we disagree with Petitioners. As Patent Owner correctly asserts, (PO Resp. 30–32), Sallmann specifically focuses on diclofenac potassium formulations. *See* Ex. 1021, 1:60–65. For example, Sallmann states: “[T]he present invention relates to an ophthalmic

composition for treating inflammatory ocular conditions, for treating glaucoma or for treating ear inflammatory and/or painful conditions (otitis), *which composition comprises a therapeutically effective amount of diclofenac potassium and a carrier.*” *Id.* (emphasis added); *see also id.* at 1:48–54 (background section explaining the significantly superior ocular penetration of diclofenac potassium as compared to diclofenac sodium). Indeed, other than comparative examples advanced to show the superiority of diclofenac potassium over diclofenac sodium, Sallmann does not exemplify or discuss using another active ingredient for its composition. *See id.* at 7:56–14:23 (Examples 1–19).

Given Sallmann’s specific focus on preparing diclofenac potassium formulations, Petitioners do not persuade us that an ordinary artisan having read Sallmann would have considered it obvious to substitute bromfenac for the diclofenac potassium in Sallmann’s formulations. Accordingly, Petitioners do not persuade us that, based on this rationale, a preponderance of the evidence supports a conclusion that claims 1, 7, and 13 of the ’813 patent, or their dependent claims, would have been obvious to a person of ordinary skill in the art.

Alternatively, Petitioners assert that it would have been obvious to a person of ordinary skill in the art to modify Ogawa’s formulation by substituting the tyloxapol used in Sallmann’s formulations for the polysorbate 80 used in Ogawa’s Example 6, thereby arriving at a stable aqueous preparation encompassed by claims 1, 7, and 13 of the ’813 patent. Pet. 37. Petitioners assert that, at the time of the invention, it was known in the art that polysorbate 80 could be substituted for tyloxapol in ophthalmic formulations. *Id.* In support of this assertion, Petitioners rely upon the

Declaration of Dr. Lawrence. *Id.* (citing Ex. 1005 ¶ 444). According to Dr. Lawrence, at the time of the invention, it was known that “polysorbate 80 and tyloxapol could be used interchangeably” and that “substituting tyloxapol for polysorbate 80 in ophthalmic formulations had been shown to improve the stability of acidic group-containing drugs.” Ex. 1005 ¶ 444 (citing Ex. 1022, 6:57–7:45) (“Yasueda”).²

Moreover, Petitioners assert that a person of ordinary skill in the art would have understood from Sallmann that tyloxapol was a suitable additive in a formulation comprising a carboxyl group-containing NSAID, i.e., diclofenac or bromfenac. Pet. 40. As exemplary support, Dr. Lawrence describes a known bromfenac ophthalmic formulation that includes tyloxapol as a suitable surfactant. Ex. 1005 ¶ 444 (citing Ex. 1012, 3:13–45) (“Desai”).³ According to Dr. Lawrence, a skilled artisan would have understood that diclofenac and bromfenac have similar properties and are subject to similar formulation issues, such that the two compounds “could be successfully formulated in the same way.” *Id.*

Having considered the arguments and evidence advanced by Petitioners and Patent Owner, we are persuaded that a person of ordinary skill in the art at the time of the invention would have had a reason to substitute Sallmann’s tyloxapol for the polysorbate 80 used in Ogawa’s formulations. Each of claims 1, 7, and 13 recites a stable aqueous liquid preparation that consists essentially of bromfenac, its salts, or hydrates, as the sole pharmaceutically active ingredient, and tyloxapol. Ex. 1003.

² Yasueda et al., U.S. Patent No. 6,274,609 B1, issued Aug. 14, 2001 (“Yasueda”).

³ Desai et al., U.S. Patent No. 5,603,929, issued Feb. 18, 1997 (“Desai”).

We find that Ogawa discloses ophthalmic solutions containing the sodium salt of bromfenac monohydrate as the sole pharmaceutically active ingredient, meeting the “first component” of the preparation recited by claims 1, 7, and 13. Ex. 1010, 1:60–2:3, Example 6.

We find also that Ogawa discloses that the solution described in Example 6 contains 0.15 w/v% polysorbate 80 (0.15 g/100ml). *Id.* According to Ogawa, after four weeks at 60° C, the solution described in Example 6 maintained 100.9 % of its original bromfenac activity. *Id.* at 10:49–51, 14:45–48 (Table 11). Accordingly, the solution of Ogawa’s Example 6 meets the stability requirements of independent claims 1 and 13, as well as claim 7’s additional stability requirement of greater than 90% bromfenac activity present after four weeks at 60° C.

Thus, as Petitioners contend, Example 6 of Ogawa differs from claims 1, 7, and 13 only in that Ogawa’s solution contains polysorbate 80 instead of tyloxapol. As Petitioners assert, however, Example 2 of Sallmann describes using 0.1 mg/ml tyloxapol, i.e., 0.1 w/v%, in an aqueous eye drop formulation that also contains an acidic group-containing NSAID diclofenac potassium. Ex. 1021, 8:1–13.

Petitioners rely upon the declaration testimony of Dr. Lawrence to support their contention that an ordinary artisan would have considered Sallmann’s tyloxapol and Ogawa’s polysorbate 80 to be interchangeably useful in aqueous ophthalmic solutions. Pet. 38 (citing Ex. 1005 ¶ 444). Given her qualifications, experience, and explanation, we credit her testimony on this issue. *See* Ex. 1005 ¶¶ 3–15. Dr. Lawrence’s testimony in this regard, moreover, is supported by the Yasueda and Desai references

cited in Dr. Lawrence's Declaration. Ex. 1005 ¶ 444 (citing Exs. 1012 and 1022).

In particular, Yasueda describes the use of both tyloxapol and polysorbate 80 as solubilizing surfactants in ophthalmic solutions containing the anti-allergic drug pranlukast. Ex. 1022, 4:61–65, *see also id.* at 1:16–24 (pranlukast used to treat allergic diseases in ophthalmology). In the experiment cited by Petitioners and Dr. Lawrence, Yasueda discloses that aqueous tyloxapol-containing formulations showed more than 98% residual drug activity after 2 weeks at 60° C, and that solutions containing polysorbate 80 had more than 95% remaining drug activity, with no deposition of insoluble material in solutions using either surfactant. *Id.* at 7:34–44.

Desai describes stabilizing aqueous acidic NSAID-containing ophthalmic solutions with the combination of a polymeric quaternary ammonium compound and boric acid. Ex. 1012, 2:18–30. As Petitioners and Dr. Lawrence note, Desai discloses that the NSAID in its compositions may be diclofenac or bromfenac, and that polysorbates and/or tyloxapol may be used as surfactants in the ophthalmic solutions. *Id.* at 3:12–38.

Given these prior art teachings, Petitioners persuade us that an ordinary artisan would have recognized that tyloxapol and polysorbate 80 were interchangeably useful as non-ionic surfactants in acidic NSAID-containing ophthalmic aqueous solutions, and, therefore, absent persuasive objective evidence to the contrary, that is enough to support the proposed substitution, even in the absence of an express suggestion to do so. *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)).

As to the stability requirements in claims 1, 7, and 13, the '813 patent discloses that the tyloxapol range effective to stabilize a bromfenac-containing solution is between about 0.01 and 0.5 w/v %. Ex. 1003, 5:19–25. Both the tyloxapol concentration described in Sallmann (0.1 w/v %) and the polysorbate 80 concentration described in Ogawa (0.15 w/v %), fall within the stabilizing range set out in the '813 patent.

Therefore, in addition to having a reason to substitute the tyloxapol recited in claims 1, 7, and 13 of the '813 patent for the polysorbate 80 in Ogawa's Example 6, an ordinary artisan also had a reason to include the tyloxapol at a concentration encompassed by each of those claims.

Patent Owner's arguments do not convince us otherwise.

Patent Owner contends that a number of NSAID ophthalmic compositions other than Ogawa's bromfenac compositions would have been viewed as suitable for modification, and would have been preferred over the bromfenac compositions. PO Resp. 8–10 (citing Ex. 2082 ¶¶ 68–77 (Williams Decl.)). Patent Owner contends, moreover, that because of the benzalkonium chloride ("BAC") in Ogawa's formulations, an ordinary artisan would have been led away from Ogawa's compositions to non-BAC-containing compositions. PO Resp. 10–13 (citing *Allergan v. Sandoz*, 796 F.3d 1293, 1305 (Fed. Cir. 2015); Ex. 2082 ¶¶ 74–78, 80, 82, 87 (Williams Decl.)).

As our reviewing court has explained, however, when evaluating claims for obviousness, "a finding that the prior art as a whole suggests the desirability of a particular combination need not be supported by a finding that the prior art suggests that the combination claimed by the patent applicant is the preferred, or most desirable, combination." *In re Fulton*,

391 F.3d 1195, 1200 (Fed. Cir. 2004). Given Ogawa's undisputed disclosure that its compositions are useful for ophthalmic administration, that an ordinary artisan might not have viewed Ogawa as describing the most art-preferred NSAID-containing ophthalmic formulations does not convince us that an ordinary artisan would have considered Ogawa's compositions unsuitable for the disclosed use or unsuitable for further modification, such as the substitution of known interchangeably useful ophthalmically acceptable non-ionic surfactants.

We acknowledge that Ogawa does not disclose expressly why it included polysorbate 80 in its compositions. PO Resp. 15 (citing Ex. ¶ 125). Ogawa, nonetheless, includes polysorbate 80, a well known non-ionic surfactant, in every one of the exemplified bromfenac-containing compositions that is described as an ophthalmic solution, including Example 6. *See* Ex. 1010, 9:5–10:68 (Examples 1, 2, 4, and 5–9).

Accordingly, although Ogawa does not expressly state its reason for including polysorbate 80 in its compositions, we agree with Petitioners that an ordinary artisan would have recognized from Ogawa that its compositions included a non-ionic surfactant in bromfenac-containing ophthalmic solutions, and that such non-ionic surfactant had well known ophthalmically acceptable equivalents. That Ogawa's reason for including a non-ionic surfactant in its bromfenac-containing solutions *may have* differed from the stabilization effect discovered by the inventors of the '813 patent, discussed above, does not demonstrate a deficiency in Petitioners' contention that, based on the cited prior art, an ordinary artisan would have recognized Sallmann's tyloxapol as an ophthalmically acceptable non-ionic surfactant

that would be an interchangeably useful equivalent to the polysorbate 80 in Ogawa's compositions.⁴

Patent Owner contends that, given the complex and sensitive nature of preparing ophthalmic solutions, and given the significant differences in structure between tyloxapol and polysorbate 80, which are among numerous other non-ionic surfactants that were available for use, an ordinary artisan would not have viewed tyloxapol and polysorbate 80 as interchangeably substitutable equivalents and, therefore, would not have been motivated to substitute one for the other. PO Resp. 18–36.

Even acknowledging the complexities of ophthalmic solution formulation, however, because Sallmann and Ogawa, as discussed above, describe the use of tyloxapol and polysorbate 80 in similar acidic NSAID-containing ophthalmic solutions, Petitioners persuade us that an ordinary artisan would have recognized that both were non-ionic surfactants that would be useful in acidic NSAID-containing ophthalmic formulations. As also discussed above, Yasueda describes the use of both tyloxapol and polysorbate 80 as solubilizing surfactants in separate ophthalmic solutions containing an anti-allergy drug, thereby suggesting that both surfactants would be interchangeably useful in the same ophthalmic formulation and that no significant adverse effects would be expected when substituting one for the other. Thus, that many non-ionic surfactants may have existed in the prior art does not convince us that an ordinary artisan would have failed to

⁴ In our following analysis of secondary considerations of nonobviousness, we consider whether the preponderance of the evidence demonstrates that tyloxapol performs as a true equivalent yielding the same result as polysorbate 80 in Ogawa's formulation, or instead yields an unexpected result.

recognize, based on the cited prior art, that tyloxapol specifically would have been useful in the particular type of formulation described in Ogawa's Example 6.

In sum, for the reasons discussed, having considered the prior art, evidence, and arguments advanced by Petitioners in light of Patent Owner's arguments and evidence regarding the cited references' teachings, we find that an ordinary artisan had a reason to substitute Sallmann's tyloxapol, recited in claims 1, 7, and 13 of the '813 patent, for the polysorbate 80 in Ogawa's Example 6, and to include the tyloxapol at a concentration encompassed by each of those claims.

We next analyze and weigh the secondary considerations of nonobviousness asserted by Patent Owner to determine if, on balance, that evidence renders nonobvious the challenged claims.

4. Secondary Considerations

We have also considered Patent Owner's contention that objective evidence exists establishing that an ordinary artisan would not have considered the claimed aqueous formulations obvious. *Id.* at 36–52. Factual inquiries for an obviousness determination include secondary considerations based on evaluation and crediting of objective evidence of nonobviousness. *Graham*, 383 U.S. at 17. Notwithstanding what the teachings of the prior art would have suggested to one with ordinary skill in the art at the time of the invention, the totality of the evidence submitted, including objective evidence of nonobviousness, may lead to a conclusion that the claimed invention 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).

“Indeed, evidence of secondary considerations may often be the most probative and cogent evidence in the record. It may often establish that an invention appearing to have been obvious in light of the prior art was not.” *Eurand, Inc. v. Mylan Pharm. Inc.*, 676 F.3d 1063, 1075–76 (Fed. Cir. 2012) (quoting *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983)). In *Eurand v. Mylan*, the court explained further that, “not only is *Stratoflex* the law, it is sound in requiring that a fact finder consider the objective evidence before reaching an obviousness determination. The objective considerations, when considered with the balance of the obviousness evidence in the record, guard as a check against hindsight bias.” *Id.* at 1079.

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).

a. Unexpected Results

Patent Owner contends that comparisons between the closest prior art and compositions encompassed by claims 1, 7, and 13 of the ’813 patent show that including tyloxapol in bromfenac-containing aqueous solutions unexpectedly inhibits bromfenac degradation. PO Resp. 36–45. Having reviewed Patent Owner’s evidence and arguments regarding unexpected results, in light of Petitioners’ responsive evidence and arguments on that issue, we agree with Patent Owner that the evidence of record supports a finding that the claimed compositions exhibit properties that an ordinary artisan would not have expected.

To show unexpectedness, Patent Owner directs us to several sets of comparative data. Patent Owner presents data from a first comparison, which includes data from Table 1 of the '813 patent shown above, in the following table:

Formulation	Amount of surfactant	Remaining rate (%) bromfenac at 60° C. after 4 weeks
Comparison Example 1 (A-20)	0.17 g polysorbate 80	51.3%
Formulation A-02 (A-21)	0.15 g tyloxapol	73.8%
Formulation A-03 (A-27)	0.02 g tyloxapol	89.6%
Formulation A-28	0.05 g	86.0%
Formulation A-29	0.1 g	82.0%
Formulation A-2 from Ogawa	0.3 g polysorbate 80	54.2% (after 3 weeks)

PO Resp. 40; *see also* Ex. 2098 ¶¶ 7–9 (Declaration of co-inventor Shirou Sawa describing conditions of comparative tests, complete ingredient lists, and results underlying data presented in Table 1 of the '813 patent). The table shows a comparison of bromfenac formulations containing either tyloxapol, or the polysorbate 80 used in Ogawa, stored for four weeks at 60° C at pH 7. *Id.* As is evident from the table, and as Patent Owner contends, after storage for four weeks under those conditions, the amount of bromfenac activity remaining in each of the tyloxapol-containing formulations, which include formulations A-28 and A-29, is significantly higher than the polysorbate 80-containing formulations.

Patent Owner's expert witness, Dr. Williams, characterizes these as "vastly superior chemical stability results . . . [which] were entirely unexpected because, based on Ogawa, substituting one non-ionic surfactant for another would not have been expected to impact chemical stability at

all.” Ex. 2082 ¶ 189 (Williams Decl.). Dr. Williams testifies, moreover, that “tyloxapol’s ability to dramatically improve bromfenac’s chemical stability at significantly lower amounts than polysorbate 80 formulations in Ogawa was completely unexpected and much more than a mere difference in degree.” *Id.* In view of his education and experience, we credit Dr. Williams’s testimony on this issue. *See id.* ¶¶ 2–10; *see also* Ex. 2115 (Dr. Williams’s curriculum vitae).

Patent Owner presents a summary of the data from a second comparison in the following table:

Formulation	Amount of surfactant	Remaining rate (%) bromfenac at 60° C. after 4 weeks
Bronuck (BF(PE))	0.15 g polysorbate 80	91.45%
A-01 (PE)	0.02 g tyloxapol	93.61%
A-03 (PE)	0.03 g tyloxapol	95.07%

PO Resp. 42–43; *see also* Ex. 2098 ¶ 11 (Sawa Declaration describing conditions of comparative tests, complete ingredient lists, and results). The table shows a comparison between: (a) two tyloxapol-containing bromfenac formulations, and (b) Bronuck, a bromfenac formulation closely resembling Ogawa’s Example 6, which included polysorbate 80 and sodium sulfite, the formulations having been stored for four weeks at 60° C at about pH 8.2–8.3. *Id.* As is evident from the table, and as Patent Owner contends, after storage for four weeks under those conditions, the amount of bromfenac activity remaining in each of the tyloxapol-containing formulations was at least comparable to, if not slightly greater than, the bromfenac activity remaining in the polysorbate 80-containing formulation, Bronuck.

Patent Owner notes that this result was achieved despite the fact that, unlike Bronuck, neither tyloxapol-containing formulation contained sodium sulfite. PO Resp. 43. As Patent Owner explains (*id.*), Ogawa teaches that sodium sulfite is necessary to achieve a bromfenac solution of acceptable stability. *See* Ex. 1010, 8:47–50 (Ogawa) (“[A]s a result of searching for more stable solutions, the inventors obtained the finding that by further inco[r]porating sodium sulfite . . . *the stability was remarkably increased.*”) (emphasis added); *see also id.* at 8:66–9:4 (emphasis added):

In the solution containing [bromfenac] in which polyvinyl pyrrolidone and sodium sulfite coexist, the change of appearance was not observed at all and the decomposition of [bromfenac] was not observed either. *It was found that the stability was remarkably enhanced.* Thus, there can be successfully obtained a stable aqueous composition containing the [bromfenac] compounds.

As to the experiments underlying the data in the table shown on page 43 of Patent Owner’s Response, Patent Owner’s witness, Dr. Williams, testifies that “[i]n view of Ogawa, these results are completely unexpected and suggest the possibility of eliminating a chemical component from a formulation to be instilled on surgically compromised ocular tissue, another substantial and material benefit attributable to the use of tyloxapol.” Ex. 2082 ¶ 189 (Williams Decl.).

Patent Owner contends that Table 2 of the ’813 patent (Ex. 1003, 7:17–38) also shows unexpectedness, by listing three tyloxapol-containing formulations with a bromfenac stability comparable to Example 6 of Ogawa, despite the absence of Ogawa’s sodium sulfite, and despite using tyloxapol at a concentration about one-third, one-fifth, and one-eighth, respectively, the amount of polysorbate 80 in Ogawa’s Example 6. PO Resp. 43–44

(citing Ex. 2082 ¶¶ 192–94). Dr. Williams testifies that “in light of what Ogawa teaches persons of ordinary skill in the art, these 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 ¶ 194.

Patent Owner presents the results from another comparison between polysorbate 80-containing and tyloxapol-containing bromfenac formulations in the following table:

Formulation	Amount of surfactant	European Pharmacopoeia A standard	European Pharmacopoeia B standard
Bronuck	0.15 g polysorbate 80	Failed	Failed
A-04	0.02 g tyloxapol	Satisfied	Satisfied
A-05	0.05 g tyloxapol	Failed	Satisfied

PO Resp. 46; *see also* Ex. 2098 ¶¶ 12–17 (Sawa Declaration describing conditions of comparative tests, complete ingredient lists, and results). As is evident from the table, and as Patent Owner contends, the polysorbate 80-containing Bronuck formulation did not satisfy either the European Pharmacopoeia (“EP”) A or B standard (measurements of preservative agent efficacy against specific microorganisms over a certain number of days (Ex. 2098 ¶ 16)), whereas the formulation containing 0.02 g of tyloxapol satisfied both standards, and the formulation containing 0.05 g tyloxapol satisfied the EP B standard.

Dr. Williams testifies that this result is “unexpected for surfactants that Dr. Lawrence argues should have no material effect on stability

(EX2253 at ¶ 115;⁵ EX2316 at 281:18-282:8)⁶] and also because the art taught that polysorbate 80 was a better solubilizer than tyloxapol (EX1022 [Yasueda] at Table 1).” Ex. 2082 ¶ 200. Dr. Williams testifies that, “this is not merely a difference in degree. Satisfying the more stringent EP preservative efficacy test would meaningfully contribute to the claimed compositions having a significantly longer shelf life than bromfenac formulations containing polysorbate 80, which did not satisfy this test.” *Id.*

In addition, Patent Owner contends that tyloxapol’s stabilizing effect, discussed above, allowed formulation of a commercial embodiment, “Prolensa[®],” at a lower pH of 7.8, closer to that of natural tears, and using less surfactant, thus resulting in a formulation exhibiting less burning and stinging as a side effect than other commercial ophthalmic NSAID eye drops, a result that would have been unexpected, given the presence of BAC in Prolensa[®]. PO Resp. 47–49. Patent Owner’s witness, Dr. Trattler, testifies that the improved side effect profile of Prolensa[®] as compared to other commercial formulations was unexpected (Ex. 2116 ¶ 51 (Trattler Decl.)) particularly “given that it contains the preservative BAK [benzalkonium chloride, also known as BAC], which had long been known to be toxic to the eye, even at concentrations significantly lower than those used in Prolensa[®]” (*id.* ¶ 53). In view of his education and experience, we credit Dr. Trattler’s testimony on this issue. *See id.* ¶¶ 2–12; *see also* Ex. 2051 (Dr. Trattler’s curriculum vitae).

⁵ Opening Expert Report of M. Jayne Lawrence, Ph.D., *Senju Pharmaceutical Co., Ltd., et al. v. Lupin, Ltd., et al.*, No. 1:14-cv-06893, (D.N.J. Dec. 30, 2015).

⁶ Deposition of M. Jayne Lawrence, Ph.D. (Ex. 2316).

Patent Owner contends also that Prolensa[®]'s reduced pH improved bromfenac's intraocular penetration, allowing a significant reduction in the concentration of bromfenac as compared to other bromfenac-containing formulations, "advantageously put[ting] less drug in contact with surgically compromised ocular tissue without a reduction in efficacy." PO Resp. 49. As to this feature, Dr. Williams testifies that "[i]t would not have been expected that tyloxapol's surprising stabilizing effect could also result in lowering the amount of bromfenac without a corresponding reduction in ocular penetration and efficacy." Ex. 2082 ¶ 202.

In sum, in light of the discussed comparisons, the advantageous properties inhering to tyloxapol-containing bromfenac formulations, and the supporting testimony of Patent Owner's witnesses, we find that Patent Owner has advanced evidence sufficient to support its contentions that the compositions recited in claims 1, 7, and 13 of the '813 patent exhibit unexpected properties.

Petitioners' arguments do not persuade us to the contrary.

Petitioners contend that certain commercial products covered by Ogawa's Example 6, including Bronuck, passed the Japanese Pharmacopeia ("JP") and U.S. Pharmacopeia ("USP") standards. Reply 5 (citing Ex. 1104, 146:17–147:9 (Williams Deposition)). Therefore, Petitioners contend, Patent Owner's comparison, discussed above, showing that Bronuck did not meet the EP A or B standard, "makes no sense." Reply 5.

Petitioners do not, however, direct us to persuasive evidence suggesting that a product that meets the JP and USP standards would necessarily meet the EP A or B standard. Moreover, that Ogawa's Example 6 formulation is similar to other compositions that meet the EP B standard

except for the inclusion of tyloxapol (*see* Reply 5), does not persuade us that Bronuck necessarily met the EP B standard, given the side-by-side comparison between Bronuck and tyloxapol-containing formulations advanced by Patent Owner (*see* PO Resp. 43). Indeed, Petitioners direct us to no persuasive evidence suggesting that any of the comparative experiments advanced by Patent Owner were inadequately performed or used substandard procedures such that the data might be considered unreliable.

Petitioners contend that the improved preservative efficacy shown by Patent Owner was not unexpected, because the bromfenac formulation of Ogawa's Example 6 included ingredients taught by Desai as yielding compositions that pass both the USP and EP. Reply 5 (citing Ex. 1012, 5:32–37 (Desai)). We acknowledge that Desai attributes the loss of antibacterial activity (and, therefore, preservative effect) of BAC to complexation between BAC and acidic NSAIDs. Ex. 1012, 1:26–34. Desai, however, remedies that problem, at least in part, by using a polymeric quaternary ammonium compound *instead* of BAC. *See* Ex. 1012, 5:32–37 (“[A]n ophthalmic formulation of an acidic drug can be globally preserved, that is, can comply with the USP and Ph. Eur. A preservative effectiveness requirements for ophthalmic preparations, using a combination of a *polymeric quaternary ammonium compound* and boric acid.”) (emphasis added). Petitioners do not direct us where Ogawa describes its Example 6 as containing a polymeric quaternary ammonium compound such that an ordinary artisan might have expected that example to meet both the EP A and B standards.

Petitioners contend that an ordinary artisan would have expected that switching polysorbate 80 with tyloxapol would improve preservative efficacy because polysorbate 80 was known to neutralize BAC. Reply 5 (citing Exs. 1107 (Fassihi), 1108 (Sigma-Aldrich), 1109 (Kohn)).^{7,8,9} Petitioners do not explain specifically, however, which teachings in the cited references support this assertion. Moreover, although the portion of Fassihi cited by Petitioners discusses specific examples in which a number of surfactants inhibited the action of certain preservatives (Ex. 1107, 878–879), Fassihi discloses also, more generally, that “nonionic surfactant can inhibit the interaction between preservative and cell membrane” (*id.* at 878). This disclosure suggests that because tyloxapol, like polysorbate 80, is a non-ionic surfactant, tyloxapol also would have been expected to reduce preservative efficacy. Contrary to this suggestion in Fassihi, however, tyloxapol enhances preservative efficacy, as seen in the side-by-side comparison advanced by Patent Owner.

In addition, even assuming that the Sigma-Aldrich reference is prior art, that reference as well as the Kohn reference discloses that the inhibitory effect of polysorbate 80 on BAC occurs when lecithin is also included in the

⁷ Reza A. Fassihi, *Preservation of Medicines Against Microbial Contamination*, in *Disinfection, Sterilization, and Preservation*, 871–886 (Chapter 50) (Seymour S. Block, Ph.D., ed., Lea & Febiger, 1991) (Ex. 1107).

⁸ Sigma-Aldrich Product Information, Benzalkonium Chloride (no date provided) (Ex. 1108).

⁹ S. Robert Kohn et al., *Effectiveness of Antibacterial Agents Presently Employed in Ophthalmic Preparations as Preservatives Against Pseudomonas aeruginosa*,” 52 *Journal of Pharmaceutical Sciences* 967–974 (1963) (Ex. 1109).

composition. *See* Ex. 1108 (“The preservative effect of B[A]C can be neutralized by the addition of TWEEN® 80 *and lecithin*.”) (citing Fassihi 884) (emphasis added); *see also* Ex. 1109, 973 (“The subculture medium found to have the greatest neutralizing activity against benzalkonium chloride contained polysorbate 80 (Tween 80) *and lecithin* as the inactivating agents.”) (emphasis added). Petitioners do not identify specifically where any of Ogawa’s formulations, including that of Example 6, contained lecithin, such that an ordinary artisan would have expected Ogawa’s formulations to have a reduced preservative efficacy as compared to tyloxapol-containing preparations.

We acknowledge, but are not persuaded by, Petitioners’ contentions that tyloxapol’s stabilizing effect on bromfenac solutions would have been expected, even at lower concentrations of tyloxapol. Reply 8–9, 16–17. As an initial matter, inasmuch as Petitioners seek, in their Reply, to supplement the original obviousness rationale over Sallmann and Ogawa presented in the Petition by advancing new evidence supporting “further motivation” for including tyloxapol in bromfenac formulations (*see, e.g., id.* at 8–9), we decline to consider the newly presented obviousness rationale. *See Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1369–70 (Fed. Cir. 2016) (Board did not err or abuse its discretion in declining to consider new contentions and evidence in Reply advanced to supplement unpatentability rationale presented in Petition).

We do not find convincing Petitioners’ contention that tyloxapol, due to its antioxidant properties, would have been expected to improve bromfenac stability. Reply 8–9, 16–17. Neither the “red insoluble matters” appearing during extended storage (Ex. 1010, 8:20–21 (Ogawa)), nor the

“decomposition” of bromfenac described in Ogawa (*id.* at 9:1), has been shown on this record by either party to be the result of oxidation, as Petitioners’ expert witness Dr. Lawrence acknowledges. *See* Ex. 1094 ¶ 31 (Lawrence Reply Decl.) (asserting that Patent Owner’s witnesses “Drs. Davies and Williams comment that the ‘red insoluble matters’ discussed in Ogawa are a degradation product of bromfenac caused by an oxidation reaction, *although neither has offered any proof or cited to any reference that indicates that the ‘red matters’ discussed in Ogawa are caused by oxidation*”) (emphasis added).

Indeed, even if we were to assume that the red insoluble matters in Ogawa were attributable to oxidation, Ogawa discloses that substantially all bromfenac activity remained during storage for three weeks, despite the appearance of the red insoluble matters. *See* Ex. 1010, 8:19–21 (“In the formula, the change in [bromfenac] residue rate were not almost observed but in three weeks red insoluble matters were observed.”). Thus, even if an ordinary artisan had expected tyloxapol, due to its antioxidant properties, to remedy the problem of red insoluble matters, we are not persuaded that tyloxapol would have been expected to stabilize bromfenac to the extent shown above by Patent Owner. To the contrary, given the lack of clarity on this record as to the mechanism of loss of bromfenac activity during storage of Ogawa’s formulations, Petitioners do not persuade us that an ordinary artisan would have expected the improved stability properties of the tyloxapol-containing bromfenac formulations discussed above.

We acknowledge, but for similar reasons are not persuaded by, Petitioners’ contention that tyloxapol would have been expected to inhibit complexation between bromfenac and BAC and, therefore, would have been

expected to improve bromfenac stability. Reply 12–15. Although Dr. Lawrence opines that Ogawa used polysorbate 80 to inhibit bromfenac/BAC complexation (Ex. 1094 ¶ 31), Petitioners do not advance specific persuasive evidence suggesting that the loss in bromfenac activity in Ogawa’s formulations during storage, or the formation of insoluble red matters, involved the alleged complexation between bromfenac and BAC.

Rather, as noted above, Ogawa solved the issues of both bromfenac decomposition and red insoluble matter formation by including sodium sulfite and polyvinylpyrrolidone (PVP) in its formulations. Ex. 1010, 8:66–9:4 (Ogawa). Petitioners do not advance specific persuasive evidence suggesting that the alleged complexation issue would or could be resolved using sodium sulfite and PVP. Thus, Ogawa did not resolve the loss of bromfenac activity through the use of components shown on this record to inhibit bromfenac/BAC complexation. Petitioners do not persuade us, therefore, that any allegedly expected complex-inhibiting properties of tyloxapol would have led an ordinary artisan to also expect tyloxapol to stabilize Ogawa’s formulations in the manner shown by Patent Owner. To the contrary, again, given the lack of clarity on this record as to the mechanism of loss of bromfenac activity in Ogawa’s formulations during storage, Petitioners do not persuade us that an ordinary artisan would have expected the improved stability properties of the tyloxapol-containing bromfenac formulations discussed above.

We acknowledge, but are not persuaded by, Petitioners’ contentions that Patent Owner did not demonstrate unexpected bromfenac stability as compared to the closest prior art formulation, Ogawa’s Example 6. Reply 17–18, 24. As Patent Owners contend, and as noted above, a side-by-

side comparison between tyloxapol-containing bromfenac compositions and the Bronuck formulation closely similar to Ogawa's Example 6 showed the compositions to have comparable stabilities. PO Resp. 43. As also noted above, however, Dr. Williams testifies that this comparable stability was completely unexpected because it was achieved despite the fact that the tyloxapol-containing formulations did not contain sodium sulfite, the agent taught by Ogawa as yielding bromfenac formulations of acceptable stability. Ex. 2082 ¶¶ 192–94 (Williams Decl.).

Petitioners contend that Dr. Williams's testimony in this regard is discredited by the fact that Ogawa discloses at least one other formulation, lacking sodium sulfite, that exhibited a bromfenac stability comparable to that seen in the table on page 43 of Patent Owner's Response. Reply 18 (citing Ex. 1094 ¶¶ 87–88. (Lawrence Reply Decl.)). Dr. Williams's testimony, however, is based on a direct side-by-side comparison to the formulation recognized by Petitioners to be the closest prior art embodiment of the claims. *See* Pet. 55 (explaining that Ogawa is considered the closest prior art). The fact that a distinct prior art composition exhibited similar stability in a different experiment by Ogawa does not persuade us that we should discredit Dr. Williams's testimony, which is based on a side-by-side comparison. Moreover, as seen above, Patent Owner's assertions of unexpectedness are supported by a number of comparisons, the totality of which convinces us that tyloxapol-containing bromfenac formulations encompassed by independent claims 1, 7, and 13 of the '813 patent possess unexpected properties.

We acknowledge, but are not persuaded by, Petitioners' contention that Ogawa discloses that stable bromfenac formulations at lower pH can be

achieved simply by adjusting the pH with hydrochloric acid. Reply 18–19. As discussed above, side-by-side comparison shows that tyloxapol provides significantly and unexpectedly increased bromfenac stability as compared to Ogawa’s polysorbate 80 at pH 7.0. *See* PO Resp. 42–44 and exhibits cited therein. In that regard, moreover, Ogawa discloses that “the stability of an aqueous composition containing the above compounds is remarkably enhanced by incorporating a water-soluble polymer *and sulfite*, and adjusting the pH to 6.0–9.0, preferably about 7.5–8.5.” Ex. 1010, 3:49–53 (emphasis added). As discussed above, Dr. Williams testifies that inclusion of tyloxapol unexpectedly allows the elimination of sodium sulfite from stable bromfenac formulations. Ex. 2082 ¶ 194 (Williams Decl.). Lastly, that Dr. Trattler acknowledged low incident side effects for Prolensa® other than burning or stinging, (Reply 19), does not persuade us that we should discredit his testimony that the greatly reduced burning and stinging exhibited by Prolensa® was unexpected.

We acknowledge, but are not persuaded by, Petitioners’ contention that Dr. Sawa’s Declaration, upon which Dr. Williams relies, should be given no weight under 37 C.F.R. § 42.65(a).¹⁰ Reply 19–20 (citing Ex. 1090 58:8–63:11 (Sawa Deposition)).¹¹ That Dr. Sawa did not assemble the materials presented in the appendices in his Declaration does not undercut his express testimony that he himself prepared and tested, or was involved in the testing and review of the data regarding the formulations for which the

¹⁰ 37 C.F.R. § 42.65(a) states, in relevant part, that “[e]xpert testimony that does not disclose the underlying facts or data on which the opinion is based is entitled to little or no weight.”

¹¹ Deposition of Shirou Sawa (Ex. 1090).

data above is presented. *See* Ex. 2098 ¶¶ 7, 10–13 (Sawa Decl.). To the extent Petitioners intimate that Dr. Sawa’s lack of access to certain information “call[s] into question the completeness and reliability of the evidence,” Reply 19–20 (citing Ex. 1090, 90:21–95:12), Petitioners do not identify any specific persuasive evidence of record suggesting that Patent Owner’s evidence of unexpected results is incomplete or unreliable.

We acknowledge, but are not persuaded by, Petitioners’ contention that Patent Owner’s evidence of unexpected results is not commensurate in scope with the subject matter of the challenged claims of the ’813 patent. Reply 22–24.

As our reviewing court has explained in the context of patent prosecution, that “[e]vidence of secondary considerations must be reasonably commensurate with the scope of the claims . . . does not mean that an applicant is required to test every embodiment within the scope of his or her claims.” *In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011). Rather, “[i]f an applicant demonstrates that an embodiment has an unexpected result and provides an adequate basis to support the conclusion that other embodiments falling within the claim will behave in the same manner, this will generally establish that the evidence is commensurate with scope of the claims.” *Id.*

In the instant case, Dr. Williams testifies that, in the experiments discussed above, “tyloxapol was tested at both the harsher pH (with respect to bromfenac degradation) of 7 and the milder pH of more than 8 and showed unexpectedly superior stabilizing effects compared to polysorbate 80 at these disparate pH ranges, which are representative of the usable pH range.” Ex. 2082 ¶ 196 (Williams Decl.). Petitioners do not provide a

specific persuasive evidentiary basis to question Dr. Williams's testimony in this regard. We note, moreover, that in addition to the differing pH conditions of the comparisons discussed, tyloxapol was tested at a number of different concentrations. *See* PO Resp. 40–45. Accordingly, Petitioners do not persuade us that the evidence of record fails to support Patent Owner's assertion that the evidence of unexpected results discussed above is commensurate in scope with claims 1, 7, and 13, the independent claims of the '813 patent.

We are also unpersuaded that Dr. Trattler's deposition testimony (Ex. 1120, 100:1–102:9) and the Baklayan article¹² show that Prolensa® did not exhibit an unexpected increase in intraocular penetration. *See* Reply 23–24. As explained in Baklayan, Prolensa® at pH 7.8 delivered the same amount of bromfenac to ocular tissues as a pH 8.3 formulation, despite the fact that Prolensa® contained significantly less drug than the pH 8.3 formulation. *See* Baklayan, 1 (“Bromfenac ophthalmic solution 0.07%, pH 7.8 readily penetrated ocular tissues with levels similar to those of bromfenac ophthalmic solution 0.09%, pH 8.3.”).

In sum, having reviewed Patent Owner's evidence and arguments regarding unexpected results, in light of Petitioners' responsive evidence and arguments, we agree with Patent Owner that the evidence of record supports a finding that preparation of bromfenac and tyloxapol, as recited in claims 1, 7, and 13 of the '813 patent, yield results that an ordinary artisan would not have expected, and that Patent Owner's evidence of unexpectedness is

¹² George A Baklayan and Mauricio Muñoz, *The ocular distribution of ¹⁴C-labeled bromfenac ophthalmic solution 0.07% in a rabbit model*, 8 Clinical Ophthalmology 1717–1724 (2014) (Ex. 2033).

commensurate in scope with the subject matter encompassed by those claims.

b. Industry Praise/Commercial Success/Copying

Patent Owner advances evidence to show that Prolensa®, the commercial embodiment encompassing claims 1, 7, and 13 of the '813 patent, elicited significant industry praise, experienced substantial commercial success, and was directly copied by its competitors. PO Resp. 47–52. Having reviewed Patent Owner's evidence and arguments on those issues, in light of Petitioners' responsive evidence and arguments, we find that the evidence of record further supports Patent Owner's contention that, despite the prior art advanced by Petitioners, the preparations recited in claims 1, 7, and 13 of the '813 patent would not have been obvious to an ordinary artisan.

As to industry praise, Patent Owner advances the testimony of Dr. Trattler (PO Resp. 49), who testifies that Prolensa® “is widely recognized in the medical community as a major improvement on existing therapies for its efficacy in treating inflammation post cataract surgery while maintaining a favorable side effect profile” (Ex. 2116 ¶ 54 (Trattler Decl.)). Dr. Trattler cites to statements by Dr. Steven M. Silverstein, “a renowned ophthalmologist and leader in the field of cataract surgery” (*id.* ¶ 55) that Prolensa® had been shown to be potent and clinically effective in treating post cataract surgery inflammation. *Id.* ¶¶ 55–56 (citing Exs. 2014, 2113).

Dr. Trattler also cites to published studies in which Prolensa® was described as maintaining significant efficacy and ocular comfort, exhibiting a safety profile better than placebo, and exhibiting properties likely to be beneficial as to patient compliance. Ex. 2116 ¶¶ 57–59 (citing Exs. 2066,

2118, 2119). Dr. Trattler testifies also that, because Prolensa® does not elicit the burning and stinging side effects of all other available NSAID eye drops, he routinely prescribes Prolensa®, despite the fact that less expensive generic versions of a number of the other NSAID eye drops are currently available. Ex. 2116 ¶ 51.

Significantly, Petitioners do not dispute specifically Dr. Trattler’s characterization of Prolensa® as being widely recognized in the field as a major improvement over existing treatments for post cataract surgery inflammation. Nor do Petitioners direct us to persuasive evidence suggesting that the statements of praise identified by Dr. Trattler and Patent Owner are unfounded.

As to commercial success, Patent Owner contends that, despite having been projected originally by Lupin to reach \$100 million in annual sales after two to three years, Prolensa®, from its April 2013 launch to August 2015, “had generated \$246.9 million in revenue . . . and is on target to surpass Lupin’s forecast.” PO Resp. 50 (citing Ex. 2130 ¶¶ 17, 58 (Jarosz Decl.)). Patent Owner’s witness Mr. Jarosz testifies that, since its introduction, Prolensa® “has achieved the second highest share of revenues and prescriptions among branded drugs with similar indications.” Ex. 2130 ¶ 17. Mr. Jarosz testifies that Prolensa® “achieved this success despite being introduced into a marketplace in which at least six branded drugs and three generic drugs had already received U.S. Food and Drug Administration (‘FDA’) approval to treat similar indications.” *Id.*

As our reviewing court has explained, “[w]hen a patentee can demonstrate commercial success, usually shown by significant sales in a relevant market, and that the successful product is the invention disclosed

and claimed in the patent, it is presumed that the commercial success is due to the patented invention.” *J.T. Eaton & Co. v. Atlantic Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997). Once a patentee makes the required showing, “the burden shifts to the challenger to prove that the commercial success is instead due to other factors extraneous to the patented invention, such as advertising or superior workmanship.” *Id.*

Petitioners do not dispute specifically Patent Owner’s assertion (PO Resp. 7, 46–47), that Prolensa® is the commercial embodiment encompassing claims 1, 7, and 13 of the ’813 patent. Rather, Petitioners contend that Patent Owner’s evidence of commercial success lacks factual support and a causal nexus with the claims because “Mr. Jarosz [does not] mention that any purported success is directly the result of tyloxapol’s stabilizing effect on bromfenac, or any other claimed and allegedly novel aspect of the ’813 patent.” Reply 21 (citing Ex. 2130 ¶¶ 81, 147 (Jarosz Decl.)).

Contrary to Petitioners’ assertion, however, Mr. Jarosz opines that, based on Prolensa®’s lower pH, improved ocular penetration of bromfenac, reduced amount of surfactant, elimination of burning and stinging as side effects as compared to other ophthalmic NSAID formulations, and superior shelf life over other bromfenac formulations, the “claimed features of the ’813 patent have been a critical driver of the success of Prolensa®. That is, Prolensa® is consistently marketed based on the benefits made possible by the ’813 patent.” Ex. 2130 ¶ 18.

Thus, in addition to the evidence that Prolensa® is a commercial embodiment of claims 1, 7, and 13 of the ’813 patent, Patent Owner advances Mr. Jarosz’s opinion that the impetus behind the sales and market

share of Prolensa® are the advantageous features, discussed above, of Prolensa® as compared to other available NSAID formulations, and as embodied by claims 1, 7, and 13. We are persuaded, therefore, that Patent Owner has advanced evidence sufficient to shift to Petitioners the burden of showing that the commercial success is due to factors “extraneous to the patented invention.” *J.T. Eaton v. Atlantic Paste & Glue*, 106 F.3d at 1571.

To that end, Petitioners contend that, rather than the merits of the claimed invention, the commercial success of Prolensa® is based in part on a life-cycle product management strategy, in which Patent Owner replaced its previous discontinued bromfenac formulations with Prolensa®. Reply 21–22 (citing Ex. 1122 ¶¶ 60, 66–70 (Hofmann Decl.)). Petitioners contend further that “significant evidence proves that Prolensa®’s marketplace performance is highly dependent on extrinsic factors, such as extensive and strategic marketing efforts.” Reply 22 (citing Ex. 1122 ¶¶ 61, 81–96). Moreover, Petitioners contend that Patent Owner’s gross sales figures for Prolensa® do not account for certain expenses suggesting that “Prolensa appears to have incurred a cumulative net loss since its release in 2013 through the third quarter of 2015, which far from illustrates any cognizable commercial success.” *Id.* (citing Ex. 1122 ¶¶ 37–40).

Petitioners do not persuade us that Patent Owner’s evidence in relation to commercial success lacks persuasive weight. That Patent Owner employed a life-cycle product management strategy does not negate the significant sales and market share, discussed above, that Prolensa® experienced in just over two years after its launch. Moreover, that Prolensa® might have replaced an also-successful previous generation bromfenac formulation does not demonstrate that the sales and market share

success was primarily due to factors unrelated to the claimed formulation, given that practitioners had other ophthalmic NSAID choices, and given, particularly, Dr. Trattler's undisputed testimony, noted above, that Prolensa® was widely recognized in the field as a major improvement over existing treatments for post cataract surgery inflammation. *See* Ex. 2116 ¶ 54 (Trattler Decl.).

Petitioners direct us to numerous paragraphs in Mr. Hofmann's Declaration to support its assertion that Prolensa®'s performance in the market place depends highly "on extrinsic factors, such as extensive and strategic marketing efforts." Reply 22 (citing Ex. 1122 ¶¶ 61, 81–96). However, Petitioners provide no specific discussion of the cited testimony or underlying evidence, explaining why that testimony supports its assertion.

In any event, we acknowledge Mr. Hofmann's testimony that Patent Owner spent significantly more in marketing on Prolensa® than was spent on a comparable ophthalmic formulation, Ilevro. *See* Ex. 1122 ¶ 89 (Hofmann Decl.). That evidence, however, must be weighed against other evidence relating to commercial success, including Mr. Jarosz's testimony, discussed above, that the lower pH, improved ocular penetration of bromfenac, reduced amount of surfactant, elimination of burning and stinging as side effects as compared to other ophthalmic NSAID formulations, and superior shelf life, were crucial to Prolensa®'s sales and market share. *See* Ex. 2130 ¶ 18 (Jarosz Decl.).

As noted above, Petitioners assert that Prolensa® "appears" to have suffered a net loss. Reply 22 (citing Ex. 1122 ¶¶ 37–40; Ex. 1121, 76:16–

78:7 (Jarosz 902 Deposition)).¹³ In that regard, we first note that Mr. Hoffman's testimony is based largely on estimates as to the incurred expenses, including the critical total value of rebates, discounts, allowances, coupons, chargebacks, and returns, asserted by Petitioners and Mr. Hofmann as having been ignored by Patent Owner when reporting gross sales. *See* Ex. 1122 ¶¶ 34, 36, 38, 39. As support for the estimated total value of rebates, discounts, allowances, coupons, chargebacks, and returns, Mr. Hofmann identifies Exhibit 1154.¹⁴ *See* Ex. 1122, Exhibit A. Mr. Hofmann, however, does not explain with any specificity how the information appearing in Exhibit 1154 substantiates the accuracy of his estimate.

More significantly, Petitioners do not direct us to persuasive evidence refuting Mr. Jarosz's statement in the cited portion of his deposition testimony that gross sales is "what the pharmaceutical industry examines in order to assess the performance of a drug relative to other drugs and over time," and that comparative value does not include chargebacks and returns in the data. Ex. 1121, 78:2–7 (Jarosz 902 Deposition).

Accordingly, on the record before us, Petitioners do not persuade us that the marketing or other expenditures attendant to Prolensa® warrant giving little or no weight to the evidence of commercial success. Indeed, our reviewing court has recognized that marketing expenditures are simply a factor to be considered alongside all the relevant evidence pertaining to commercial success. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802

¹³ Deposition of John C. Jarosz in IPR2015-00902 (Ex. 1121) ("Jarosz 902 Deposition").

¹⁴ Exhibit 1154 is identified only as "Confidential Patent Owner Document." Paper 53, 12 (Petitioners' Updated Exhibit List).

F.2d 1367, 1383 (Fed. Cir. 1986) (“[W]hile there is evidence that marketing and financing played a role in the success of Hybritech’s kits, *as they do with any product*, it is clear to us on the entire record that the commercial success here was due to the merits of the claimed invention.”) (emphasis added).

Lastly, having considered Patent Owner’s contentions and evidence regarding copying and licensing by certain of its competitors (PO Resp. 50–52), in light of Petitioners’ countervailing arguments, we agree with Petitioners that, in this instance, the asserted copying and licensing are of little probative value as to whether the compositions of claims 1, 7, and 13 of the ’813 patent would have been obvious. *See Bayer Healthcare Pharm., Inc. v. Watson Pharm., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013) (“[E]vidence of copying in the ANDA context is not probative of nonobviousness because a showing of bioequivalence is required for FDA approval.”); *see also Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1324 (Fed. Cir. 2004) (“[L]icenses may constitute evidence of nonobviousness; however, only little weight can be attributed to such evidence if the patentee does not demonstrate a nexus between the merits of the invention and the licenses of record.”) (internal quotations omitted).

5. Conclusion Regarding Analysis of Independent Claims

In sum, as discussed above, having considered the cited references, along with the arguments and evidence advanced by Petitioners and Patent Owner, Petitioners persuade us that an ordinary artisan had a reason to substitute Sallmann’s tyloxapol for the polysorbate 80 used in Ogawa’s formulations. Nonetheless, having considered Patent Owner’s evidence and arguments regarding objective indicia of nonobviousness, also discussed

above, in light of Petitioners' countervailing arguments and evidence, we agree with Patent Owner that, despite the prior art evidence of obviousness, the compositions recited in independent claims 1, 7, and 13 of the '813 patent exhibit unexpectedly superior properties not suggested by the prior art, and having those properties, those compositions achieved significant industry praise and commercial success, and therefore would not have been obvious to an ordinary artisan. Accordingly, based on the totality of the record, we conclude that Petitioners have not shown by a preponderance of the evidence that claims 1, 7, and 13 of the '813 patent are unpatentable under 35 U.S.C. § 103(a).

C. Analysis of Dependent Claims 2–6, 8–12, and 14–27

Petitioners assert that dependent claims 2–6, 8–12, and 14–27 of the '813 patent would have been obvious over the combination of Sallmann and Ogawa. Pet. 42–53; Reply 1–25. Patent Owner disagrees. PO Resp. 8–59.

Each of claims 2–6, 8–12, and 14–27 requires a stable aqueous liquid preparation consisting essentially of bromfenac and tyloxapol. Petitioners' challenge to the patentability of each of those claims relies ultimately on the same obviousness rationale advanced in connection with independent claims 1, 7, and 13, i.e., that the combination of Sallmann and Ogawa would have suggested a preparation of bromfenac and tyloxapol in the manner claimed. Pet. 42; *see also* Reply 25 (“[T]he elements of the dependent claims are taught by the prior art, or simply adjusting variables using routine optimization.”) (citing Ex. 1094 ¶¶ 93–99 (Lawrence Reply Decl.)).

For the reasons discussed above in connection with claims 1, 7, and 13, based on the totality of the record, we conclude that Petitioners have not shown by a preponderance of the evidence that claims 2–6, 8–12, and 14–27 of the '813 patent are unpatentable under 35 U.S.C. § 103(a).

III. MOTIONS TO EXCLUDE

A. *Petitioners' Motion*

Petitioners move to exclude Exhibit 2323, “as well as all testimony relating to Exhibit 2323 elicited from Mr. John Jarosz, Patent Owner’s expert, during redirect following the cross-examination on March 16, 2016. See EX1089 at 178:9–203:6.” Pet. Mot. 1. In our decision, however, we do not rely on Exhibit 2323 or the deposition testimony allegedly relating to it. We, therefore, dismiss Petitioners’ Motion to Exclude as moot.

B. *Patent Owner's Motion*

Patent Owner moves to exclude portions of Exhibits 1094 and 2342, and the entirety of Exhibits 1096–1098, 1100–1102, 1107–1109, 1122, 1172–1174, and 1176. PO Mot. 1. Petitioners oppose the motion. Pet. Opp. 1. As the moving party, Patent Owner has the burden of proof to establish that it is entitled to the requested relief. 37 C.F.R. § 42.20(c).

1. Dr. Lawrence's Reply Declaration (Ex. 1094)

Patent Owner moves to exclude under Federal Rule of Evidence (FRE) 702 “at least” ¶¶ 31, 33, 36, 37, 48, 49, 51, 52, 73, and footnote 5 of Dr. Lawrence’s Reply Declaration, as well as allegedly supporting Exhibits 1174 and 1176 and her related deposition testimony (Ex. 2342). PO Mot. 1. In particular, Patent Owner contends that Dr. Lawrence “completely lacks expertise in organic or medicinal chemistry and, thus, she is not qualified by knowledge, skill experience, training or education necessary to form an opinion under FRE 702.” *Id.*

We deny Patent Owner’s motion to exclude the aforementioned portions of Dr. Lawrence’s Reply Declaration, allegedly supporting exhibits, and her related deposition testimony. As Petitioners contend (Pet. Opp. 1), Dr. Lawrence testifies that she has a Ph.D. in Pharmacy, is Head of the Pharmaceutical Biophysics Group of the Institute of Pharmaceutical Science at Kings College, London, has been the Chief Scientist at the Royal Pharmaceutical Society since 2007, has taught multiple courses including physical chemistry of micelles, physical chemistry of emulsions and biopharmaceutics, and biopharmacy, and has performed research and published in the field of physical and colloid chemistry. Ex. 1005 ¶¶ 5–13 (Lawrence Decl.). Given her education and experience, Patent Owner does not persuade us that Dr. Lawrence fails to qualify as an expert in the art relevant to this proceeding.

To the extent Patent Owner further identifies alleged deficiencies and inconsistencies in Dr. Lawrence’s testimony (PO Mot. 2–6), we find that such matters go to the probative weight of her testimony, as opposed to its admissibility. As to the Board’s asserted ““gatekeeping role”” of excluding

unqualified expert testimony (PO Mot. 7), we note that, generally unlike a lay jury, the Board by statutory definition has competent scientific ability (35 U.S.C. § 6), and has significant experience in evaluating expert testimony. Accordingly, the danger of prejudice in this proceeding is considerably lower than in a conventional district court trial.

Therefore, for the reasons discussed, we deny Patent Owner's motion to exclude under FRE 702 the cited portions of Dr. Lawrence's Reply Declaration, supporting exhibits, and her related deposition testimony.

Patent Owner also moves to exclude, under FRE 402 and 403, ¶¶ 31–33, 37, 38, and footnote 5 of Dr. Lawrence's Reply Declaration, as well as allegedly supporting Exhibits 1096–1098, 1100–1102, 1107–1109, 1172, and 1173. PO Mot. 1. Patent Owner contends that the cited evidence should be excluded under FRE 402 and 403 because it exceeds the proper scope of Petitioners' Reply under 37 C.F.R. § 42.23(b). *Id.* at 1, 9–11.

Petitioners reply that the cited portions of Dr. Lawrence's Reply Declaration were submitted only to rebut contentions made in Patent Owner's Response. Pet. Opp. 4–10.

However, as noted above, Petitioners sought in their Reply to supplement the original obviousness rationale over Sallmann and Ogawa in the Petition by advancing new evidence supporting "further motivation" for including tyloxapol in bromfenac formulations. *See, e.g.*, Reply 8–9. Accordingly, Patent Owner persuades us that the evidence allegedly supporting Petitioners' assertions of "further motivation" is impermissibly raised for the first time in the Reply. *See* 37 C.F.R. § 42.23(b) ("A reply may only respond to arguments raised in the corresponding opposition or patent owner response."); *see also Intelligent Bio-Systems, Inc. v. Illumina*

Cambridge Ltd., 821 F.3d at 1369–70 (Board did not err or abuse its discretion in declining to consider new contentions and evidence in Reply advanced to supplement unpatentability rationale presented in Petition).

We, therefore, accord no weight to ¶¶ 31–33, 37, 38, and footnote 5 of Dr. Lawrence’s Reply Declaration, or to Exhibits 1096–1098, 1100–1102, 1107–1109, 1172, and 1173, to the extent that evidence is discussed in the Reply and relates to the new rationale of unpatentability. Patent Owner’s motion to exclude that evidence, therefore, is dismissed as being rendered moot.

2. Mr. Hofmann’s Reply Declaration (Ex. 1122)

Patent Owner moves to exclude the entirety of Mr. Hofmann’s Reply Declaration (Ex. 1122) “because of Mr. Hofmann’s improper behavior during cross examination.” PO Mot. 1. Patent Owner also moves to exclude under FRE 702 “at least” ¶¶ 25–27, 42, 59, 60, 62, 69, 70, 72–80, 86, 87, 99, 102, and 110 of Mr. Hofmann’s Reply Declaration as well as his related deposition testimony (Ex. 2343), because he “provides opinions on technical and medical matters for which he is not qualified by knowledge, skill, experience, training or education necessary to form an opinion under FRE 702.” PO Mot. 1.

We deny Patent Owner’s motion to exclude either the entirety of, or the aforementioned paragraphs of, Mr. Hofmann’s Declaration. As to his qualifications, Mr. Hofmann testifies that he has a number of professional accreditations, including as a Certified Public Accountant (“CPA”), a Certification in Financial Forensics (“CFF”), membership in the Licensing Executives Society (“LES”), and a Certified Licensing Professional (“CLP”) designation, “which is granted by the LES to professionals with

demonstrated knowledge and experience in the areas of intellectual property and licensing.” Ex. 1122 ¶ 10.

Additionally, Mr. Hofmann testifies that he has significant experience consulting as an expert, including performing “financial and economic analysis for over one hundred prescription pharmaceutical products, including virtually every major therapeutic class of drugs” (*id.* ¶ 12), having been engaged by the United States Patent and Trademark Office (“USPTO”) and Office of the Solicitor to testify on issues involving objective indicia of nonobviousness, including commercial success and nexus (*id.* ¶ 14), and having been designated as a testifying expert in federal and state courts (*id.* ¶ 15).

Patent Owner does not dispute the accuracy of that testimony. Given his accreditations and experience, Patent Owner does not persuade us that Mr. Hofmann fails to qualify as an expert as to the issues for which his testimony was presented.

Given his accreditations and experience, moreover, that Mr. Hofmann relied on technical disclosures outside his economic expertise when testifying as to economically related matters pertinent to this proceeding (PO Mot. 12–14) does not persuade us that he is unqualified to testify as to those economically related matters, or that his testimony should be excluded under FRE 702. To the contrary, that during his deposition Patent Owner might have been able to identify weaknesses or inconsistencies in Mr. Hofmann’s prior testimony in this proceeding or elsewhere goes to the probative weight of this testimony, not its admissibility. In addition, as noted above, because the Board, unlike a lay jury, has significant experience in evaluating expert

testimony, the danger of prejudice in this proceeding is considerably lower than in a conventional district court trial.

As to Mr. Hofmann's alleged improper behavior during his cross examination (PO Mot. 1, 12, 15), it is not evident from the cited portions of his deposition that Patent Owner was unable to conduct an effective cross examination. Patent Owner, moreover, fails to explain why Hofmann's alleged membership in an investigated auditing team demonstrates that his testimony in this proceeding is inadmissible under any rule of evidence. PO Mot. 14–15.

In sum, for the reasons discussed, we deny Patent Owner's Motion to Exclude Mr. Hofmann's testimony.

IV. CONCLUSION

For the foregoing reasons, we conclude that Petitioners have not established by a preponderance of the evidence that claims 1–27 of the '813 patent are unpatentable under 35 U.S.C. § 103 as obvious over Sallmann and Ogawa. Additionally, we conclude that neither Petitioners nor Patent Owner have established that they are entitled to have any exhibits excluded.

ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 1–27 of the '813 patent have not been shown by a preponderance of the evidence to be unpatentable;

FURTHER ORDERED that Petitioners' Motion to Exclude is *dismissed* as moot; and

FURTHER ORDERED that Patent Owner's Motion to Exclude is *denied-in-part* and *dismissed-in-part* as moot; 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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