

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., and MYLAN INC.
Petitioner,

v.

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

Patent Owner.

Case IPR2015-00902
Patent 8,669,290

**PATENT OWNER RESPONSE
PURSUANT TO 37 C.F.R. § 42.120**

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Patent Owner Senju Pharmaceutical Co., Ltd. et al. (“Senju”) responds to the Petition filed by InnoPharma Licensing, Inc. et al. (“InnoPharma”) concerning claims 1-30 of U.S. Patent No. 8,669,290 (“the ’290 patent”). The Board instituted trial on InnoPharma’s sole ground that claims 1-30 are allegedly obvious over U.S. Patent No. 4,910,225 to Ogawa et al. (“Ogawa”) (EX1004) and U.S. Patent No. 5,891,913 to Sallmann et al. (“Sallmann”) (EX1009). As discussed below, InnoPharma has failed to meet its “burden of proving a proposition of unpatentability by a preponderance of the evidence.” 35 U.S.C. § 316(e).

Indeed, as discussed further below, InnoPharma has failed to prove that a person of ordinary skill in the art would have combined Ogawa and Sallmann with any expectation of arriving at the claimed subject matter. InnoPharma also has failed to prove the existence of all elements of the ’290 patent claims in the art of record and has failed to carry the high burden of proving the inherency of several claim elements in the obviousness context. In addition, InnoPharma either ineffectively assails or simply ignores significant objective indicia of patentability, which further support the non-obviousness of the ’290 patent claims. The Board accordingly should uphold the patentability of claims 1-30 of the ’290 patent.

I. Introduction

The '290 patent discloses and claims stable aqueous liquid preparations of the non-steroidal anti-inflammatory drug (“NSAID”) bromfenac, marketed as Prolensa[®] prescription eye drops for treatment of inflammation and pain in cataract surgery patients.¹ These formulations are chemically stable, lack microbial contamination, and can be administered safely and effectively for ophthalmic use at a pH that does not cause eye irritation. (EX1001, 2:35-47; EX2082, ¶144.)

The inventors successfully formulated these preparations using the non-ionic surfactant tyloxapol. (EX2082, ¶142.) Tyloxapol unexpectedly chemically stabilized bromfenac better than did the surfactant polysorbate 80, even at a low pH known to accelerate bromfenac’s degradation. (*Id.*, ¶¶ 147, 157, 162.) Tyloxapol also unexpectedly maintained preservative efficacy—*i.e.*, prevented microbial contamination—as compared to polysorbate 80, even when measured under the stringent European Pharmacopoeia standards. (*Id.*, ¶167.)

Tyloxapol’s unexpected stabilizing effect translated into significant medical benefits in Prolensa[®]. Tyloxapol’s stabilization effect permitted formulating Prolensa[®] at pH 7.8, down from pH 8.3 in non-prior art Xibrom[®] and Bromday[®]

¹ InnoPharma’s expert admits that Prolensa[®] falls within the scope of the '290 patent claims. (EX2082, ¶149.)

formulations (EX2013, 4; EX2026, 5; EX2027, 4), a substantial reduction on a logarithmic scale and closer to the pH of natural tears. (EX2116, ¶41.) [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Both the reduction in pH [REDACTED] increased ocular comfort and eliminated the burning and stinging associated with all other approved NSAID eye drops. (*Id.*) Lowering the pH also improved bromfenac's intraocular penetration and permitted lowering its concentration to 0.07%, down from 0.09% in Xibrom[®] and Bromday[®], meaning that Prolensa[®] advantageously puts less drug in contact with surgically compromised ocular tissue without a reduction in efficacy. (*Id.*, ¶ 42; EX2030, 1718.) More than a difference in degree, tyloxapol's unexpectedly superior stabilizing effect constitutes a material and substantial difference, producing a more comfortable, non-irritating and more efficacious formulation embodied in Prolensa[®].

As a result, Prolensa[®] has received significant medical industry acclaim by numerous leaders in the field of cataract surgery extolling "the benefits of the new formulation." (EX2116, ¶56.) Since its April 2013 launch, Prolensa[®] has generated \$246.9 million in revenue, despite entering a market with at least six branded drugs

and three generic drugs FDA-approved to treat similar indications. (EX2130, ¶133.) In fact, Prolensa[®] has achieved one of the highest shares of prescriptions and revenue among branded drugs with similar indications. (*Id.*)

Moreover, six generic companies, including InnoPharma, have submitted ANDAs seeking to market exact copies of Prolensa[®]. (EX2082, ¶172.) One of these six, Lupin, which also has filed an IPR petition challenging the '290 patent, has projected Prolensa[®]'s sales to exceed \$100 million annually, which will occur this year. (EX2022, 4; EX2130, ¶75.) Three others, Apotex, Metrics and Paddock, initially challenged the '290 patent in district court (EX2130, ¶¶78-80; EX2023; EX2019; EX2017; EX2018) but licensed the patent and took consent judgments and injunctions, tying their acknowledgement of the '290 patent's validity to their generic copies of Prolensa[®]. (EX2130, ¶¶78-80; EX2024; EX2122; EX2123.)

Against these compelling objective indicia of non-obviousness, InnoPharma contends that tyloxapol in Sallmann's Example 2 would have been "swapped" for polysorbate 80 in Ogawa's Example 6, or alternatively, bromfenac in Ogawa's Example 6 would have been "swapped" for diclofenac in Sallmann's Example 2. (Pet., 6-9.) As discussed below, InnoPharma offers no reason, other than impermissible hindsight looking backward from the '290 patent claims, why a person of ordinary skill in the art ("POSA") would have chosen Ogawa's Example

6 or Sallmann's Example 2 and modified either with any reasonable expectation of arriving at any of the claimed formulations. Indeed, the evidence establishes that a POSA would not have been motivated to pursue bromfenac or tyloxapol at all, and would not have found bromfenac and diclofenac, or tyloxapol and polysorbate 80, interchangeable given their vast chemical, physical and functional differences. Tellingly, InnoPharma has not proffered a scintilla of evidence for the claims that specifically require greater than about 90% [or 92%] bromfenac remaining after four weeks at 60° C., or the claims that identify the preservative efficacy standard of European Pharmacopoeia Criteria B, and thus InnoPharma has wholly failed to meet its burden of proving these claims obvious.

InnoPharma contends that its "swapping" theory allegedly solves the problem of a "complex" that bromfenac purportedly forms with the preservative benzalkonium chloride ("BAC"). Yet InnoPharma's expert Dr. Paul Laskar candidly admits that no prior art shows that bromfenac actually forms a "complex" with BAC, and that he in fact focused on BAC only because the claimed formulations of the '290 patent contain it, exposing InnoPharma's theory as impermissibly based on hindsight. Consistent with the teachings of the art, Dr. Laskar further admits that BAC is a "killer" that should be eliminated from formulations wherever possible. Proceeding contrary to accepted wisdom, the '290

patent's formulations utilize BAC, which alone constitutes strong evidence of non-obviousness.

The Board accordingly should reject the Petition and uphold the patentability of all challenged claims.

II. Statement of relief requested

Senju respectfully requests that InnoPharma's Petition be denied at least because: (i) it fails to prove that a person of ordinary skill in the art would have combined Ogawa and Sallmann with any reasonable expectation of arriving at the claimed subject matter; (ii) it fails to prove the existence of each element of each challenged claim from Ogawa and Sallmann, including the alleged inherency of various claim elements; and (iii) it fails to rebut the compelling objective indicia of non-obviousness of the claimed subject matter.

III. Claim construction

All claims of the '290 patent contain the term "stable," and claims 1-7 further contain the phrase "amount sufficient to stabilize." Senju and InnoPharma disputed the meaning of this term and phrase in parallel district court litigation before Chief Judge Simandle of the U.S. District Court for the District of New Jersey. On behalf of Senju, Dr. Robert Williams, III, Ph.D., who is an expert in the field of pharmaceutical formulation and development and who, based on his

education and experience, is qualified to provide his opinions in this matter (EX2082, ¶¶2-11), has submitted a declaration in this proceeding and in the claim construction proceedings before Chief Judge Simandle (EX2125). Adopting Dr. Williams' construction of the elements "stable" and "amount sufficient to stabilize" (EX2082, ¶¶47-50; EX2125; EX2065, 5-6), Judge Simandle held that "stable" as used in the claims of the '290 patent means having sufficient resistance to degradation (*i.e.*, chemical stability) and having sufficient preservative efficacy to be formulated and maintained for ophthalmic use, and the phrase "amount sufficient to stabilize" as used in the claims of the '290 patent means an amount sufficient to confer sufficient resistance to degradation (*i.e.*, chemical stability) to be formulated and maintained for ophthalmic use. (EX2082, ¶¶51; EX2065, 5-6.) Senju submits that these terms should be similarly construed in this proceeding. *Microsoft Corp. v. Proxyconn, Inc.*, 789 F.3d 1292, 1298 (Fed. Cir. 2015).

IV. Level of ordinary skill in the art

A person of ordinary skill in the art of the '290 patent 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. (EX2082, ¶¶45-46.)

V. The '290 patent

The application for the '290 patent was filed on January 16, 2004, and

claims priority benefit of the January 21, 2003, filing date of JP 2003-012427 under 35 U.S.C. §119. (EX1001; EX2002.) The '290 patent has three independent claims (claims 1, 8 and 14) and 27 dependent claims, which are separately patentable. The '290 patent is listed in the FDA's Orange Book, and the parties agree that it covers Prolensa[®] ophthalmic bromfenac (0.07%) solution. (EX1003, ¶44; EX2082, ¶143.)

VI. Background of ophthalmic formulations

As of the January 21, 2003 priority date of the '290 patent, drug formulation was a difficult and unpredictable endeavor, and it remains so today. The formulation of ophthalmic drugs is particularly complex. Formulating stable ophthalmic dosage forms such as the stable aqueous liquid preparations of the '290 patent is more challenging and critical than with other dosage forms such as tablets or capsules. In addition, the surface area of the eye is extremely small, and the residence time for an eye drop is quite short, which increases the challenge in designing an aqueous dosage form that can pass through the hydrophobic cornea membrane of the eye to reach the intended site of action. Dr. Laskar himself has acknowledged these formulation challenges in sworn testimony in a patent infringement case involving the ophthalmic product Combigan[®]. (EX2135, 989, 1020, 1022.)

VII. The combination of Ogawa and Sallmann, in either direction, does not render any claim of the '290 patent obvious

A. No reason to focus on Ogawa and bromfenac preparations

InnoPharma's central theme of unpatentability is one of "swapping," that is, swapping tyloxapol in Sallmann's Example 2 for polysorbate 80 in Ogawa's Example 6, or alternatively, swapping bromfenac in Ogawa's Example 6 for diclofenac in Sallmann's Example 2, allegedly would have been obvious. (Pet., 6-9.) But this swapping theory is premised on a POSA having had a reason to focus on bromfenac formulations. There was none, absent hindsight.

By January 21, 2003, there were a number of FDA-approved aqueous ophthalmic formulations containing NSAIDs, including diclofenac (Voltaren[®]), ketorolac (Acular[®]), flurbiprofen (Ocufen[®]), and suprofen (Profenal[®]). (*Id.*, 26-27.) A POSA therefore would have had no reason or need to focus, for further development, on bromfenac to the exclusion of other NSAIDs. (EX2082, ¶¶65-66.) Indeed, InnoPharma admits there was no such reason, stating "[t]o the extent there was even *any* need for the claimed bromfenac ophthalmic formulation, it was met by the disclosures of Ogawa and Hara." (Pet., 51 (emphasis added).) In fact, Ogawa states that its bromfenac formulations displayed remarkably enhanced stability (EX1004, 8:46-9:3), [REDACTED]

[REDACTED]

Moreover, neither Hara nor Yanni supports a preference for bromfenac over diclofenac, contrary to InnoPharma's position. (EX2082, ¶¶67-70.) Hara teaches that (1) both have "superior" anti-inflammatory action (EX1002, 2, 3), (2) both treat postoperative inflammation of the eye (*id.*), (3) diclofenac could treat anterior uveitis, while bromfenac was expressly not approved for this indication (*id.*), and (4) no toxicity issues were noted for commercialized diclofenac, while bromfenac had serious liver disorders and even fatalities (*id.*), which prompted the FDA to pull bromfenac's oral form, Duract[®], from the market. (EX2029, 1.) Hara thus certainly does not endorse bromfenac over diclofenac. (EX2082, ¶68.)

The same applies to Yanni, which actually disparages bromfenac, preferring esters and amides, like nepafenac. (EX1028, 1:54-59, 4:84-52; EX2082, ¶¶69-70.) Focusing on a single *in vitro* result from Table 1 of Yanni (EX1003, ¶30), Dr. Laskar ignores important *ex vivo* and *in vivo* data (EX2082, ¶¶69-70), which do not show superiority of bromfenac over diclofenac and in fact show superiority of other compounds. (*Id.*; EX1028, Table 1.)

B. Design need and market demands would not have led a POSA in the direction that the inventors of the '290 patent took

InnoPharma's proffered motivation to substitute polysorbate 80 with tyloxapol is to prevent the alleged formation of a precipitate between an acidic NSAID and BAC. (EX1003, ¶104.) [REDACTED]

[REDACTED]

[REDACTED] But even if such a precipitate did form, which Dr. Laskar has not established, there would have been no motivation to use tyloxapol to address this issue.

BAC was known to have significant toxicity to the eye. (EX2082, ¶74.) In fact, in *Allergan v. Sandoz*, 796 F.3d 1293, 1305 (Fed. Cir. 2015), the defendant's expert referred to BAC as a "natural born killer" that was "from Satan." [REDACTED]

[REDACTED]

[REDACTED]

A POSA objectively viewing this alleged precipitation issue would have sought to eliminate BAC, thereby eliminating its harmful effects and avoiding the precipitation issue entirely, rather than only attempting to reduce it to some extent by adding a surfactant. (EX2082, ¶71.) By January 2003, the art taught using preservative-free formulations and well-tolerated preservatives in place of BAC (EX2082, ¶72; EX2116, ¶¶45-47.) *Depuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (strong inference of non-obviousness when the prior art undermines very reason offered for combining references). [REDACTED]

[REDACTED]

[REDACTED]

Indeed by 2003, market demands sought to eliminate the highly toxic BAC from ophthalmic formulations. The art urged that “[i]t is . . . of *striking importance to become aware of preservative toxicity in order to develop in the near future many more unpreserved drugs.*” (EX2064, 115, emphasis added; EX2082, ¶¶74-75.) The art taught a preservative-free formulation of Fu’s ketorolac “may be a better as a postoperative ocular analgesic” than preserved ketorolac. (EX2090, abstract; EX2116, ¶44.) By November 1997, Acular[®] PF—a preservative-free ketorolac ophthalmic solution—received FDA approval. (EX2061, 1; EX2116, ¶29.)

The art also taught using better-tolerated preservatives in place of BAC. By 2001, published clinical studies demonstrated that the preservative “stabilized oxychloro complex” (“SOC”) could replace BAC in brimonidine ophthalmic formulations. By March 2001, brimonidine-SOC was approved as Alphagan[®] P, with a superior comfort and reduced ocular allergy profile as compared to brimonidine-BAC. (EX2092; EX2116, ¶45.)

Other replacement options for BAC included the preservative lauralkonium chloride (“LAC”), which Dr. Laskar himself admittedly used previously to avoid the interaction of an acidic drug and BAC. IPR2015-00903, EX1003, ¶104; ([REDACTED]); EX2082, ¶60; EX1020, 3:28-4:2, 6:11-7:10). Desai also

teaches the use of a different polymeric quaternary ammonium preservative compound, POLYQUAD[®], w [REDACTED] [REDACTED] (EX1005, 1:27-2:31; [REDACTED]; EX2082, ¶77.) Even if a POSA still would have wanted to use BAC, the art provided a solution that would have addressed the NSAID/BAC interaction that underlies Dr. Laskar's proffered motivation to use a solubilizer. Yanni teaches bromfenac derivatives without free carboxyl groups, which would not interact with BAC and which have better ocular penetration and stability than bromfenac. (EX1028, 1:60-2:29; EX2082, ¶81); *Depuy Spine*, 567 F.3d at 1326.

Notwithstanding these clear teachings, Dr. Laskar selectively relies on Ogawa Example 6, which reported a residual amount of bromfenac of 100.9%. (EX1003, ¶50.) But he ignores Ogawa Example 7, reporting an equally high residual amount of bromfenac (99.2%) and containing methylparaben and ethylparaben instead of BAC, [REDACTED]

[REDACTED] Thus, Ogawa implements a solution to Dr. Laskar's interaction/precipitation problem in a chemically stable formulation, [REDACTED]

Based on a *post hoc* analysis that started with the claims, Dr. Laskar postulated a motivation position premised on the interaction of an NSAID and BAC. Defining a problem by its solution reveals improper hindsight, particularly in selecting the prior art “relevant” to the question of obviousness. *Insite Vision Inc., v. Sandoz, Inc.*, 783 F.3d 853, 859 (Fed. Cir. 2015). Selecting Ogawa, which does not teach that bromfenac had an interaction/precipitation problem (EX2082, ¶110), and focusing on Example 6 rather than Example 7, which admittedly solved his proffered problem, clearly exposes Dr. Laskar’s improper *post hoc* analysis. (*Id.*)

Contrary to Dr. Laskar’s opinion, a POSA as of 2003 would have pursued non-BAC preservatives or unpreserved formulations to entirely eliminate a serious health risk. (EX2116, ¶47.) This also would have addressed any alleged interaction problem. (EX2082, ¶80.) As such, the art led in a direction divergent from the path chosen by the inventors of the ’290 patent, [REDACTED], thereby supporting the non-obviousness of the ’290 patent claims. ([REDACTED]; EX2082, ¶¶77-81); *See Allergan*, 796 F.3d at 1305, *citing In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994) (“A reference may be said to teach away when a person of ordinary skill, upon reading the reference, . . . would be led in a direction divergent from the path that was taken by the [patentee].”);

C. A POSA would not have combined Ogawa and Sallmann

1. Ogawa and the problem it sought to solve

Ogawa successfully formulated ophthalmic bromfenac preparations that are stable for a long period of time without degradation of bromfenac or the formation of red insoluble matters. (EX1004, 2:32-36; EX2082, ¶107.) Ogawa's solution involved a water soluble polymer, *e.g.*, polyvinyl pyrrolidone, and a sulfite, *i.e.*, sodium sulfite. (EX1004, 3:7-15; EX2082, ¶107.) Sodium sulfite is a well-known antioxidant. (EX2014, 3:51-55; EX2082, ¶107.) A POSA would have understood that Ogawa used sodium sulfite because bromfenac chemically degrades by oxidation (EX2105, ¶41), and an antioxidant would prevent that degradation process. InnoPharma acknowledges that sodium sulfite is added "to prevent oxidation reactions." (Pet., 41.)

When bromfenac oxidizes, its forms an oxidation degradant referred to throughout Ogawa as red insoluble matters. (EX1004, 8:3-45; EX2082, ¶108.)

These red insoluble particles do not constitute, therefore, the result of any *physical* interaction such as any precipitation between bromfenac and BAC. (EX2082, ¶109.) In fact, none of the art of record ever states that bromfenac interacts with BAC to form precipitate, and nowhere in Ogawa is

such interaction ever mentioned. (*Id.*) [REDACTED]

[REDACTED] Given the complexities of ophthalmic formulation systems, one cannot predict whether such an interaction does occur. (EX2082, ¶109; EX2105, ¶75-80.)

Polysorbate 80, moreover, plays no role in chemically stabilizing bromfenac from oxidizing. (EX2082, ¶110.) Ogawa is completely silent on the function of polysorbate 80. (*Id.*) It was not used to solubilize bromfenac, for a POSA knew that bromfenac is freely soluble in water. (EX2039, 6; EX2140, 156:20-157:6; EX2082, ¶110.) Nor was it used as a stabilizer, for Ogawa's examples establish that sodium sulfite produces "remarkably enhanced" stability. (EX1004, 8:46-9:3; EX2082, ¶110.) Citing to column 3, lines 49-53 of Ogawa, Dr. Laskar incorrectly states that polysorbate 80 contributes to stabilizing bromfenac. (EX1003, ¶54; EX2082, ¶111.) This passage, however, nowhere refers to polysorbate 80, explicitly or implicitly. (EX2082, ¶111.)

The data from Ogawa Experimental Examples 4-6 actually confirm that polysorbate 80 does not stabilize bromfenac. (EX2095, 107; EX2082, ¶111.) Upon storage at 60 °C for four weeks, the formulations in Experimental Examples 4-6 containing polysorbate 80 without sodium sulfite exhibited chemical instability, as evidenced by the formation of red insoluble matter; *i.e.*, degradation of bromfenac.

(EX1004, 8:4-9:5; EX2095, 107; EX2082, ¶112.) But adding sodium sulfite prevented the formation of red insoluble matter, prompting Ogawa to comment that bromfenac decomposition was not observed and bromfenac's stability was remarkably enhanced. (EX1004, 8:45-9:4; EX2095, 107, Table 10; EX2082, ¶111.) Thus, polysorbate 80 has no effect on the stability of bromfenac. (EX2082, ¶111.)

Dr. Laskar's attempt to imbue polysorbate 80 with an ability to stabilize bromfenac is fundamental to InnoPharma's position that a POSA would have simply "swapped" tyloxapol for polysorbate 80 with a reasonable expectation of success. (Pet., 7; EX1003, ¶54.) The data in Ogawa Experimental Examples 4-6, however, completely undermine InnoPharma's foundational premise for its obviousness arguments. (EX2082, ¶113.) *See Apotex Inc., v. Wyeth LLC*, IPR2014-00115, slip op. at 22 (Paper 94) (P.T.A.B. Apr. 20, 2015) (it is improper hindsight to "imbue one of ordinary skill in the art with knowledge of the claimed invention, when no prior art reference or references of record conveys or suggests that knowledge.").

2. Sallmann's singular purpose does not align with Ogawa's

Sallmann is uniquely directed to formulations of the potassium salt of diclofenac. (EX2082, ¶136.) The essence of the Sallmann patent, indeed its entire purpose for existing, is the use of diclofenac potassium in treating ocular

inflammation. (*Id.*) The patent was presumably awarded because diclofenac potassium had surprisingly better ocular penetration than diclofenac sodium. (EX1009, 1:1-65; EX2082, ¶115.)

Sallmann formulates diclofenac potassium with a number of additional inactive components, including separate categories of solubilizers, chelating agents, and stabilizers. Tyloxapol is listed as one of a number of solubilizers, but Sallmann identifies the Cremophor[®] solubilizers as “especially preferred,” for they are “tolerated extremely well by the eye.” (EX1009, 4:52-62; EX2082, ¶116.)

A POSA would not have selectively picked Sallmann’s tyloxapol for use in Ogawa. Ogawa teaches instead using antioxidants, like sodium sulfite, to stabilize bromfenac. (EX2082, ¶114.) Sallmann lists tyloxapol as one of many solubilizers, but bromfenac, known to be freely water soluble, does not need a solubilizer and tyloxapol would not be expected to address bromfenac’s oxidative degradation. (EX2082, ¶114, EX2039, 6; EX2140, 156:20-157:6.) Indeed, there would have been no reason to look to Sallmann unless one knew from the ’290 patent that tyloxapol works to stabilize bromfenac. (EX2082, ¶114.)

██

██

██

[REDACTED]

Also, Sallmann separately teaches using stabilizers, such as cyclodextrins. (EX1009, 5:59-6:17.) Sallmann's Example 2 includes both a solubilizer (tyloxapol) and a stabilizer (γ -cyclodextrin). (*Id.*, 8:1-15.) Sallmann does not teach using tyloxapol to stabilize diclofenac, notwithstanding InnoPharma's (Pet., 23) and Dr. Laskar's (EX1003, ¶98) statements to the contrary. (EX2082, ¶119.) As such, there would have been no reason, absent hindsight looking backward from the claimed subject matter of the '290 patent, to combine Sallmann and Ogawa.

3. It would not have been obvious to modify Ogawa Example 6 in view of Sallmann Example 2

InnoPharma asserts that it would have been obvious to substitute polysorbate 80 of Ogawa Example 6 with tyloxapol from Sallmann Example 2. Similarly, the Board has framed the issue as “whether a person of ordinary skill in the art would have had a reason (such as a simple substitution) to use tyloxapol, instead of polysorbate 80, in Ogawa's Example 6 preparation—whether or not that artisan would have recognized any stabilizing benefit of doing so.” (Paper Nos. 17, 10.)

The Board cites *In re Siebentritt*, 372 F.2d 566, 568 (C.C.P.A. 1967), noting that an express suggestion to substitute is not needed. (Paper No. 17, 11.) But the legal viability of a substitution, as indicated by *Siebentritt*, must still be assessed in context of what the prior art reasonably suggests to a POSA. 372 F.2d at 568.

Ogawa discloses chemically stabilized bromfenac formulations, with Ogawa Example 6 described as “stable, excellent for a long period of time.” (EX1004, 10:49-57.) A POSA would not have simply substituted polysorbate 80 in Example 6 without considering how it might impact the chemical stability of a formulation touted as excellent. (EX2082, ¶121); *Eisai Co. Ltd. v. Dr. Reddy’s Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008) (in the unpredictable art of chemistry, KSR’s “predictable solutions” are less likely to be genuinely predictable); *Cadence Pharm. Inc. v. Exela PharmSci Inc.*, 780 F.3d 1364, 1374 (Fed. Cir. 2015) (relying on the problem in the art to be solved in discerning how a POSA would have viewed the proposed combination of prior art teachings). Nor would a POSA exercising common sense have pursued substitutions expected to either lessen or have no effect on the chemical stability of Ogawa Example 6. (EX2082 ¶108); *Unigene Labs. v. Apotex, Inc.*, 655 F.3d 1352, 1361 (Fed. Cir. 2011) (a POSA “interprets the prior art using common sense and appropriate perspective.”). Notably, none of the art of record teaches tyloxapol as a stabilizer for an NSAID in

an aqueous formulation, leaving a POSA with no reason to combine Ogawa and Sallmann, or any reasonable expectation of successfully stabilizing bromfenac's degradation with such a combination. (EX2082, ¶121.)

The Federal Circuit's recent decision in *Cadence*, 780 F.3d 1364, applies to the facts here. There, the patent claimed methods for obtaining stable acetaminophen formulations by deoxygenating to concentrations of oxygen below 2 ppm. 780 F.3d at 1374. The primary prior art '222 patent disclosed formulations of acetaminophen, much like Ogawa discloses bromfenac, but did not decrease the oxygen content to below 2 ppm. *Id.* at 1374. The secondary reference, Palmieri, taught deoxygenating solutions of pyrogallol—a different active ingredient, much like Sallmann's diclofenac—to below 0.05 ppm to increase stability. *Id.* The Federal Circuit held that combining Palmieri with the '222 patent was not obvious because acetaminophen degraded by hydrolysis, whereas Palmieri's pyrogallol degraded by oxidation, and deoxygenation would not have been expected to stabilize acetaminophen's hydrolytic degradation. *Id.* at 1375.

Likewise, it would not have been obvious to modify Ogawa by Sallmann. A POSA would not have expected a solubilizer like tyloxapol to address bromfenac's oxidative degradation. (EX2082, ¶126.) Ogawa teaches that problem was solved by sodium sulfite and that polysorbate 80 had no effect on bromfenac's chemical

stability, giving a POSA no reason to have expected tyloxapol to chemically stabilize bromfenac. (EX1004, 8:3-9:4; EX2095, 107; EX2082, ¶126.) And Sallmann, which does not suggest a stability issue for diclofenac, teaches non-surfactants as stabilizers. (EX1009, 5:59-6:17.) Moreover, a POSA would have realized that tyloxapol generates hydroperoxides in solution. (EX2105, ¶71.) These hydroperoxides would have been expected to oxidize bromfenac, thereby discouraging the substitution of polysorbate 80 with tyloxapol. (EX2082, ¶126; EX2105, ¶¶72-74.) A proposed solution that would not have addressed the problem disclosed in the art is not an obvious solution. *See Cadence*, 780 F.3d at 1375.

Solubilizers, moreover, typically solubilize poorly soluble drugs. (EX2082, ¶47.) Bromfenac was known to readily dissolve in water (EX2039, 6; EX2140, 156:20-157:6; EX2105, ¶47), and there was no evidence in the art of bromfenac and BAC forming a precipitate or otherwise needing addition of a solubilizer. (EX2105, ¶¶75-80; EX2082, ¶109.) No reason existed, other than hindsight, to have used tyloxapol with bromfenac. (*Id.*) *Pfizer Inc. v. Mylan Pharm. Inc.*, 2014 WL 5388100, *9 (D. Del. 2014) (“The court finds that, without data demonstrating a solubility concern, one skilled in the art would have had no reason (and therefore it was not obvious) to add a solubilizing amide.”).

If a POSA would have modified Ogawa, which InnoPharma has not established, she would have followed, if anything, the blaze marks in Ogawa and pursued antioxidants other than Ogawa's to even further improve bromfenac's chemical stability. (EX2082, ¶124.) For example, U.S. Patent No. 5,856,345 to Doi discloses antioxidants to stabilize aqueous solutions of pranoprofen, also an NSAID. (EX2025, abstract; EX2082, ¶124.)

Sallmann also discloses several antioxidants (EX1009, 5:51-54), and InnoPharma admits that Ogawa uses sodium sulfite to prevent oxidation. (Pet., 41.)

[REDACTED]

[REDACTED] InnoPharma ignores Sallmann's disclosure of antioxidants and instead cherry-picks a solubilizer, tyloxapol, that would not have been expected to address bromfenac's oxidation, but rather would have been expected to exacerbate it. (EX2082, ¶126; EX2105, ¶¶72-74.) Picking and choosing only portions of the art to the exclusion of the other parts necessary to fully appreciate what the art fairly suggests to a POSA is "impermissible within the framework of section 103." *In re Wesslau*, 353 F.2d 238, 241 (C.C.P.A. 1965).

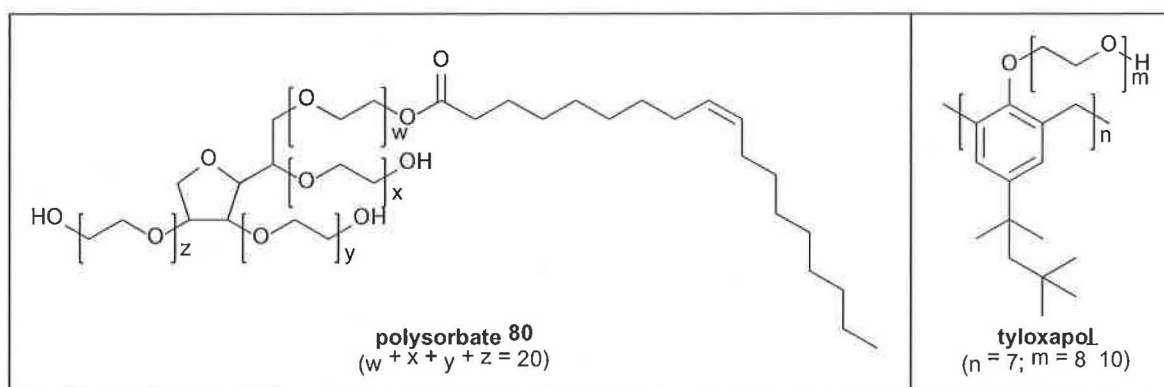
To be sure, Ogawa directs a POSA to use antioxidants to stabilize bromfenac against chemical degradation. (EX2082, ¶127.) A POSA would have also been concerned that tyloxapol's production of hydroperoxides would have added to

bromfenac's degradation. (*Id.*, ¶126; EX2105, ¶¶72-74.) A POSA would have thus been led down a path completely divergent from the one that the inventors of the '290 patent took in arriving at the claimed subject matter. (EX2082, ¶127.) *See In re Gurley*, 27 F.3d at 553 ("A reference may be said to teach away when a person of ordinary skill, upon reading the reference, . . . would be led in a direction divergent from the path that was taken by the [patentee].").

Ophthalmic formulations, moreover, are complex and highly sensitive. (EX2082, ¶¶55-56.) Formulators must carefully balance efficacy, safety, stability and preservative efficacy. With formulations instilled in the eye, additional challenges exist, including small surface area and short residence time to reach the action site. (EX2082, ¶60; ██████████.) Even small changes to a formulation's ingredients can yield substantial changes in its properties and functionality. (EX2082, ¶¶62-63); *Eisai Co. Ltd.*, 533 F.3d at 1359 (potential solutions in the chemical arts are typically unpredictable).

A POSA would have not substituted polysorbate 80 with tyloxapol merely because both are nonionic surfactants, which constitute an enormous category of surfactants, differing greatly in structure and function. (EX2105, ¶81; EX2082, ¶122.) Even among polysorbates, significant differences in properties exist, such as solubilizing ability. (EX2043, 343; EX2105, ¶81); *Syntex LLC v. Apotex Inc.*, 2006

U.S. Dist. Lexis 36089, 45-46 (N.D. Cal. 2006) (wide variability in ability to solubilize demonstrates that all “non-ionic surfactants do not perform alike,” even among the polysorbates), *aff’d* 221 Fed. Appx. 1002 (Fed. Cir. 2007). As shown below, polysorbate 80 and tyloxapol are vastly structurally dissimilar, leading to significant functional differences. (EX2105, ¶¶79-84.)



Polysorbate 80 has a long, single, non-polar linear tail and a complex, triply-branched polar head group. Tyloxapol has seven non-polar aromatic short tails, each containing a single polar head group. (EX2105, ¶81.) These differences impact, for example, their micelle formation, with each forming micelles at different concentrations and with different solubilizing capabilities. (*Id.*) Polysorbate 80 and tyloxapol will also have different three-dimensional structures, causing them to interact differently with other species in aqueous solution. (*Id.*, ¶84) These fundamental functional differences would not have led a POSA to expect these surfactants to be interchangeable, especially in complex, highly

sensitive ophthalmic formulations. (EX2105, ¶79; EX2082, ¶123); *Eisai Co. Ltd.*, 533 F.3d at 1359.

Moreover, tyloxapol is nowhere disclosed in the Handbook of Pharmaceutical Excipients, which [REDACTED] and Dr. Jayne Lawrence, who serves as InnoPharma's expert in district court litigation involving the '290 patent, considered an important reference to an ophthalmic formulator in 2003. (EX2082, ¶¶93, 134; [REDACTED]; EX2140, 188:9-189:6.) The absence of tyloxapol from the Handbook of Pharmaceutical Excipients clearly suggests that a POSA would not have used tyloxapol with an aqueous liquid preparation of bromfenac, absent knowledge of the '290 patent working backward from the claims. *See Syntex*, 2006 U.S. Dist. Lexis 36089, at *30 (absence of Octoxynol 40 from Handbook of Pharmaceutical Excipients supports non-obviousness of patent claims directed to ophthalmic formulations containing Octoxynol 40), *aff'd* 221 Fed. Appx. 1002.

For at least these reasons, InnoPharma has failed to show that it would have been obvious to modify Ogawa Example 6 in view of Sallmann Example 2.

4. InnoPharma's arguments of motivation and expectation of success ring hollow

As part of its central theme of swapping tyloxapol for polysorbate 80 in Ogawa's Example 6 (Pet., 7), InnoPharma relies on a theory of "obvious to try"

(*id.*, 8) and an alleged superiority of tyloxapol compared to polysorbate 80 in solubilizing. (*Id.*, 24.) As discussed below, InnoPharma's arguments wholly lack merit.

Relying on Sallmann, InnoPharma states there were a finite number of surfactants and that tyloxapol, said to be one of three preferred surfactants, was "used to stabilize a similar NSAID (diclofenac)." (*Id.*, 17, 25.) This is entirely wrong. In fact, InnoPharma's district court expert Dr. Lawrence testified that the number of non-ionic surfactants known to exist is effectively limitless. (EX2140, 86:1-8.) Sallmann, moreover, teaches tyloxapol not as a stabilizer for diclofenac, but as one of many solubilizers. (EX1009, 4:52-67; EX2082, ¶129.) Sallmann separately teaches using different types of stabilizers that are not surfactants. (EX1009, 5:59-6:17; EX2082, ¶129.)

InnoPharma alleges that Sallmann teaches that tyloxapol is a better surfactant than polysorbate 80. (Pet., 23.) No basis for this allegation exists, as Sallmann never mentions polysorbate 80. (EX2082, ¶132.) InnoPharma then alleges that tyloxapol and polysorbate 80 are interchangeable, citing Aviv (EX1021.) (Pet., 34.) But Aviv is directed to emulsions, not aqueous solutions. (EX2082, ¶132.) An emulsion is a diphasic system of droplets dispersed within a continuous phase. (*Id.*) Aviv's surfactants prevent the droplets from collapsing into

the continuous phase and destabilizing the emulsion. (*Id.*) A POSA therefore would have gleaned nothing about the ability, if any, of Aviv's non-ionic surfactants to address bromfenac's oxidative degradation. (*Id.*)

Relying on Fu (EX1011), InnoPharma and Dr. Laskar argue that tyloxapol was effective in stabilizing NSAIDs, like bromfenac. Fu, however, is directed to physically stabilizing ophthalmic formulations of ketorolac and BAC using Octoxynol 40 in particular. (EX1011, *e.g.*, 4, 5, 6 and 21.) Fu's formulations are physically stable, as evidenced by their lack of turbidity or cloudiness. (EX1011, 20-; EX2082, ¶132.) Fu contains no data regarding the chemical stability of ketorolac or any NSAID. (EX2082, ¶152.) Fu also does not disclose bromfenac or tyloxapol. And none of the art of record indicates that bromfenac and BAC form any precipitate that leads to cloudiness or turbidity (*id.*), [REDACTED]

[REDACTED] A POSA would not have turned to Fu to address bromfenac's oxidative degradation, *Apotex*, IPR2014-00115, slip op. at 18 (Paper 94) (holding that "a person having ordinary skill in the art would not have looked to a reference that does not mention epimerization in order to solve the problem of epimeric instability"), and certainly would have had no reason use tyloxapol, which is not even taught in Fu, as a solubilizer for the freely soluble bromfenac. (EX2082, ¶¶152-53); *Pfizer*, 2014 WL 5388100, at *9

(without data demonstrating a solubility concern, it would not have been obvious "to add a solubilizing amide.").

InnoPharma further argues that tyloxapol is a better solubilizer than polysorbate 80 based on Yasueda. (EX1012; Pet., 24.) But Yasueda actually teaches in Table 1 that polysorbate 80 (719.6 $\mu\text{g/ml}$) is significantly superior to tyloxapol (551.0 $\mu\text{g/ml}$) for solubilizing pranlukast. (EX1012, 5:10-32; EX2082, ¶133.) Moreover, pranlukast is a poorly water soluble active ingredient that is not an NSAID and is structurally dissimilar from both bromfenac and diclofenac. (EX2082, ¶133; EX2105, ¶¶63-68; EX1012, 1:25-36, Table 1, 5:7-32.) Furthermore, Tables 4 and 5 of Yasueda, relied on by Dr. Laskar, provide no useful information. (EX2082, ¶133.) The polysorbate 80 formulations of those tables contain no BAC, which means the alleged NSAID/BAC interaction—the cornerstone of InnoPharma's motivation position (EX1003, ¶96)—does not occur and a POSA would have gleaned nothing regarding the relative solubilizing effect of polysorbate 80 versus tyloxapol. (EX2082, ¶133); *Depuy Spine*, 567 F.3d at 1326 (strong inference of non-obviousness when the prior art undermines very reason offered for combining references).

In addition, pranlukast and bromfenac degrade by completely different mechanisms: pranlukast by hydrolysis and bromfenac by oxidation. (EX2082, ¶98;

EX2105, ¶74.) A POSA thus could not have drawn any conclusions from pranlukast's chemical stability in Yasueda and applied them to bromfenac. (EX2082, ¶98; EX2105, ¶74.) Nothing in Yasueda would have led a POSA to expect that tyloxapol would favorably impact bromfenac's oxidative degradation. (EX2082, ¶98; EX2105, ¶75.) *Cadence*, 780 F.3d at 1375 (deoxygenation not expected to stabilize compound's hydrolytic degradation). Rather, knowing that tyloxapol produces hydroperoxides that oxidize bromfenac, a POSA would not have substituted polysorbate 80 with tyloxapol. (EX2082, ¶98; EX2105, ¶¶74-75.)

D. Sallmann in view of Ogawa: another hindsight-laden combination

InnoPharma contends, as an alternative to swapping non-ionic surfactants between Ogawa and Sallmann, that it allegedly would have also been obvious to switch their NSAIDs, swapping diclofenac in Sallmann's Example 2 with bromfenac from Ogawa's Example 6. (Pet., 25.) This alternative position is untenable and impermissibly relies on hindsight. (EX2082, ¶136.)

1. The proposed combination destroys the essential purpose of Sallmann and ignores the blaze marks in the art

As discussed, Sallmann is directed uniquely to formulations of diclofenac potassium, patentably distinguished from diclofenac sodium because of its superior ocular penetration. (EX1009, 1:48-59.) A POSA would not have replaced diclofenac potassium with bromfenac sodium. Doing so would have destroyed the

entire purpose and essence of Sallmann's invention (EX2082, ¶136), thus making InnoPharma's proposed modification non-obvious as a matter of law. *See In re Gordon*, 733 F.2d 900, 902 (Fed. Cir. 1984) (holding that modification of a reference is not obvious if it would render the reference inoperable for its intended purpose).

Sallmann's teachings extoll the benefits of diclofenac potassium over the corresponding sodium salt. (EX2082, ¶ 137; EX1009, 1:48-59, 10:49-11:6.) If a POSA were to have forced Ogawa's bromfenac into Sallmann, which InnoPharma has not established, Sallmann's indisputable preference for diclofenac potassium would have led, if anywhere, to a bromfenac potassium formulation. (EX2082, ¶ 137.) For this reason alone, InnoPharma has failed to prove obviousness of claims 3-5, 7, 11, 13, 16-19 and 23-25 of the '290 patent requiring bromfenac sodium.

There is also no particular reason, other than hindsight, for InnoPharma to focus on Sallmann's Example 2 containing tyloxapol, while ignoring the many other examples in Sallmann containing solubilizers more preferred than tyloxapol. *See Wesslau*, 353 F.2d at 241 (impermissible to pick and choose isolated teachings contrary to what the reference fairly suggests). [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Unlike Dr. Laskar, however, a POSA would not have engaged in hindsight using the claims of the '290 patent and instead would have focused on, if anything, Sallmann's Examples 8 and 11. (EX2082, ¶¶126-27.) These examples contain Sallmann's "especially preferred" solubilizer Cremophor[®], identified as well-tolerated by the eye. (*Id.*; EX1009, 4:56-62.) Sallmann, moreover, provides data for the formulation of Example 8, demonstrating its superior anti-inflammatory efficacy and ocular penetration. (EX2082, ¶¶139-40; EX1009, 10:25-12:37.) It provides no such data for Example 2. A POSA would have been motivated, if at all, to focus on Sallmann's formulations substantiated by data, rather than make an unsubstantiated selection of Example 2 proffered by InnoPharma. (EX2082, ¶140.) *Insite*, 783 F.3d at 862 (upholding non-obviousness where the prior art was too general and lacked sufficient data to motivate a POSA to combine the prior art.); *Pfizer*, 2014 WL 5388100, at *9 (the skilled person would not have found optimization argument obvious without some data to support it).

In addition, Sallmann's Example 2 contains a cyclodextrin stabilizer. Cyclodextrins are known to complex aryl groups, such as those present in bromfenac and BAC, negatively impacting the stability of bromfenac. (EX2105,

¶96; EX2082, ¶138.) Because the chemical stability constitutes a basic property of the claimed formulations (EX1001, 2:15-22), modifying Sallmann by Ogawa would violate the exclusionary effect of the transition term “consists essentially of,” for claims 7, 13, 19 and 25 of the '290 patent, making this modification improper as a matter of law. *Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 750 F.2d 1569, 1573-74 (Fed. Cir. 1984).

Furthermore, as discussed, a POSA would have recognized from Ogawa that bromfenac degrades via oxidation. (EX2082, ¶141.) Sallmann's Example 2 contains neither PVP nor sodium sulfite—Ogawa's solution to bromfenac's degradation. (*Id.*) After replacing diclofenac potassium with bromfenac in Sallmann Example 2, a POSA would have expected the oxidative degradation to persist, for Example 2 contains no excipient not already in Ogawa's formulations that would have prevented the oxidative degradation of bromfenac. (*Id.*) The modification would have been a step backward from Ogawa, and a POSA simply would have not have done this. (*Id.*) *See, e.g., Depuy Spine*, 567 F.3d at 1326 (obviousness requires not only an “expectation that prior art elements are capable of being physically combined, but also that the combination would have worked for its intended purpose”).

2. InnoPharma's arguments to modify Sallmann in view of Ogawa are legally insufficient, internally inconsistent, and belied by the very art InnoPharma cites

InnoPharma argues that a POSA would have switched diclofenac with bromfenac, pointing to various NSAID ophthalmic formulations available in the art. (Pet., 26-27.) InnoPharma also points to the commercially available bromfenac formulations Xibrom[®] and Bromday[®] to misleadingly imply they were prior art. They were not. Both were marketed in the United States well after January 21, 2003. (EX2116, ¶¶32, 34; EX2062, 1; EX2063, 1.)

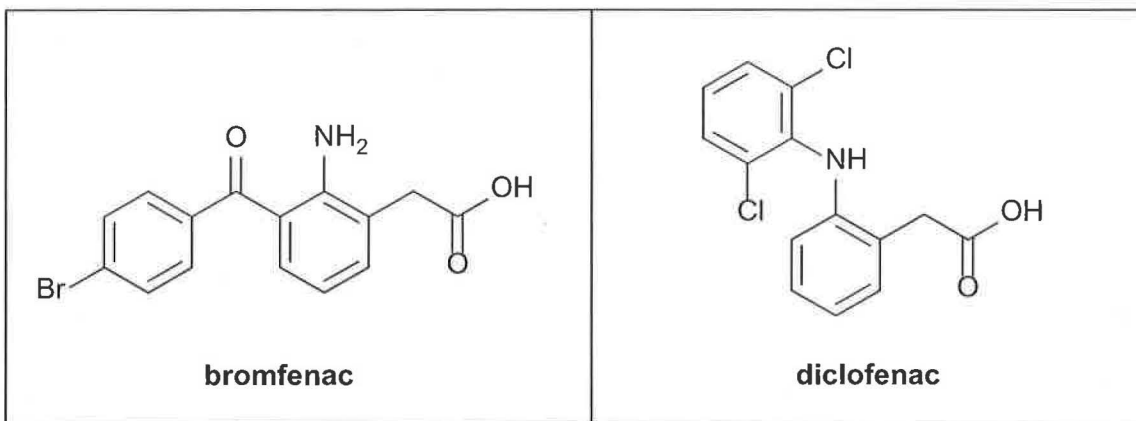
InnoPharma then argues that there allegedly would have been a design need to formulate a stable bromfenac solution and it allegedly would have been obvious to try to formulate bromfenac with tyloxapol. (Pet., 28-29.) But InnoPharma contradicts itself, having unequivocally stated that there would not have been *any* need to design a new bromfenac formulation, and all that was needed was embodied in Ogawa or Hara. (Pet., 51.) Dr. Laskar agrees, stating that “[a]ny such need was already met by aqueous ophthalmic formulations of NSAIDs known as of January 21, 2003.” (EX1003, ¶110.)

InnoPharma's arguments are riddled with hindsight, [REDACTED]

[REDACTED]

[REDACTED]

similar physical and pharmacological properties. (Pet., 28.) InnoPharma again is wrong. As shown below, bromfenac and diclofenac have significant structural differences, which lead to important functional differences. (EX2105, ¶¶45-46.)



Bromfenac is a primary amine (NH_2 group), whereas diclofenac is a secondary amine (NH group). (*Id.*, ¶46.) Bromfenac has a 4-bromobenzoyl group attached adjacent to the NH_2 group, whereas diclofenac has a 2,5-dichlorophenyl group attached directly to the NH group. (*Id.*) Bromfenac has a carbonyl ($\text{C}=\text{O}$) group, whereas diclofenac does not. (*Id.*) These structural differences result in significant differences in electron density distribution and thus hydrogen bonding ability, leading to different lipophilicities and solubilities in water. (*Id.*, ¶¶47-48.)

Bromfenac also contains more strong hydrogen bonding sites than diclofenac and is more polar because of its single bromine as compared to diclofenac's two chlorines. (*Id.*, ¶51.) A POSA would have expected bromfenac to

be better solvated than diclofenac in solution and less likely than diclofenac to form insoluble salts. (*Id.*, ¶52.) Indeed, bromfenac sodium “is freely water soluble” and does not need a solubilizer. (*Id.*, ¶50.) [REDACTED]

[REDACTED]

In short, bromfenac and diclofenac are significantly disparate in structure and function, and thus a POSA would not have simply substituted them in complex and highly sensitive ophthalmic formulations and expected to produce a stable, efficacious, and well-tolerated eye drop. For at least these reasons, the patentability of claims 1-30 should be maintained over Ogawa and Sallmann.

VIII. Compelling objective evidence of patentability

Objective evidence of nonobviousness “is not just a cumulative or confirmatory part of the obviousness calculus, but constitutes independent evidence of nonobviousness.” *Ortho-McNeil Pharm. Inc. v. Mylan Labs, Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008). Indeed, the Federal Circuit has stated that “it may often be the most probative and cogent evidence of nonobviousness in the record.” *Catalina Lighting, Inc. v. Lamps Plus, Inc.*, 295 F.3d 1277, 1288 (Fed. Cir. 2002) (citations omitted). Here, compelling objective evidence supports patentability of all challenged claims.

A. Tyloxapol's unexpectedly superior chemical stabilizing effect

1. Testing against the closest prior art

A unique aspect of the aqueous liquid preparations of the '290 patent is at least the use of tyloxapol with bromfenac. (EX2082, ¶142.) Another unique aspect differing from the prior art is the use of 0.01 to 0.05 w/v% tyloxapol with bromfenac. (EX1001, claims 4, 11, 17-18, 23-24; EX2082, ¶142.) Embodiments of these unique claimed aspects were compared against the closest prior art, admitted by Dr. Laskar to be Ogawa because it discloses "examples of ophthalmic formulations containing bromfenac, BAC, and the non-ionic surfactant polysorbate 80." (Pet., 48; EX1003, ¶103; EX2082, ¶145.) Dr. Laskar also admits that additional formulation ingredients, including boric acid, borax, sodium edetate, BAC, PVP and sodium sulfite, would be understood by a POSA not to affect a formulation's stability. (EX1003, ¶56; EX2082, ¶145.) Therefore, consistent with Dr. Laskar admissions, a formulation that contains at least bromfenac, BAC and polysorbate 80, is a proper comparator against which to evaluate unexpected results commensurate in scope with the claimed subject matter. (EX2082, ¶145.)

Dr. Williams reviewed comparative studies that used the same stability test as in Ogawa (EX1004, *e.g.*, 8:39-45, 10:50-52) to evaluate the relative ability of tyloxapol and polysorbate 80 to stabilize bromfenac from chemical degradation

under the highly stressed conditions of 60 °C. for four weeks. (EX2082, ¶146.) Some experiments were run at pH 7 because this pH severely challenges the formulations and effectively differentiates the relative stabilization capabilities of these surfactants. (*Id.*) Bromfenac becomes vulnerable to degradation at a pH below about 8 and degrades precipitously as the pH approaches 7, passing through the pH of natural tears at 7.4. (EX1004, 8:3-22, Exp. Ex. 4, 13:60-14:32, Table 8; EX2082, ¶147-48.) Because only the surfactant was varied in these experiments, they constitute proper head-to-head comparisons. (EX2082, ¶146.)

At a higher pH, the difference in chemical stabilization between the surfactants becomes smaller and less observable. (EX2082, ¶149.) This can be seen from Ogawa's Experimental Example 4 and Table 8, where the stability increases towards 100% bromfenac remaining at a pH of 8 and 9. (EX1004, 8:3-22, Table 8; EX2082, ¶149.) Dr. Williams opines on other comparisons that manifest tyloxapol's unexpectedly superior chemical stabilization at these milder pH conditions. (EX2082, ¶¶158-62.)

2. A POSA's expectation, if anything, of polysorbate 80

InnoPharma and Dr. Laskar have argued that, as non-ionic surfactants, polysorbate 80 and tyloxapol are interchangeable and would have been expected to behave equivalently. (Pet., 23-24; EX1003, ¶¶ 38, 56.) The art describes tyloxapol

only as a solubilizer, which says nothing about whether it would chemically stabilize bromfenac. (EX2082, ¶151.) Ogawa ascribes no role to polysorbate 80, and its data confirm that polysorbate 80 certainly does not stabilize bromfenac. (EX2082, ¶151; EX1004 at 8:3-9:4; EX2095, 107.) On this record, therefore, a POSA would not have substituted tyloxapol for polysorbate 80 at all, and a POSA would not have expected that substituting tyloxapol for polysorbate 80 would have enhanced bromfenac's chemical stability. (EX2082, ¶151.)

InnoPharma cites Fu and Yasueda and argues otherwise. (Pet., 46.) InnoPharma is wrong. Fu is directed exclusively to physical stability, which tells a POSA nothing about the relative ability of polysorbate 80 or tyloxapol to inhibit the chemical degradation of bromfenac. (EX2082, ¶152.) InnoPharma argues that Yasueda teaches that tyloxapol solubilizes pranlukast better than polysorbate 80 and would be expected to be a better stabilizer. (Pet., 46.) Although a surfactant's ability to solubilize says nothing about whether it would chemically stabilize, Yasueda's Table 1 clearly teaches that polysorbate 80 (719.6 $\mu\text{g/ml}$) solubilizes pranlukast better than tyloxapol (551.0 $\mu\text{g/ml}$). (EX1012, Table 1; EX2082, ¶153.)

3. Tyloxapol's unexpectedly superior stabilizing effect

The following table (*see* Declaration of Mr. Shirou Sawa, EX2098, Section A) provides the results from a chemical stability test, conducted at pH 7 at 60 °C

for four weeks, that compared formulations containing bromfenac, BAC and polysorbate 80 (A-20), said by Dr. Laskar to constitute the closest prior art, to formulations containing bromfenac, BAC and tyloxapol. (EX2082, ¶154.) It also includes an additional test result from Ogawa (EX1004, A-2, Exp. Ex. 4) on a solution containing bromfenac, BAC and polysorbate 80. “Remaining rate” refers to the amount of bromfenac remaining at the conclusion of the test.

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)

As seen from the results in this table, when compared with polysorbate 80 at 0.17 g, tyloxapol at 0.15 g was 44% better at stabilizing bromfenac from degradation. (EX2082, ¶155.) And in a completely unexpected and counterintuitive manner, when the amount of tyloxapol was lowered to 0.02 g, about 1/8 the amount of polysorbate 80 (0.17 g), tyloxapol was 75% better at stabilizing bromfenac degradation. (*Id.*) Also, at 0.1 g (82.01% bromfenac remaining) and 0.05 g (85.96% bromfenac remaining), tyloxapol stabilized

bromfenac 60% (A-29) and 68% (A-28), respectively, better than polysorbate 80 at 0.17 g (51.27% bromfenac remaining). (*Id.*)

As Dr. Williams has opined, this is a truly remarkable and surprising result constituting a substantial and material difference—more than merely a difference in degree—especially considering the harsh pH conditions and the significantly reduced amount of tyloxapol versus polysorbate 80. (*Id.*, ¶ 156.) These results are further unexpected given InnoPharma’s interchangeability argument, indicating that substituting one non-ionic surfactant for another would have been expected to have no impact. (*Id.*, ¶¶151, 156); *Allergan*, 796 F.3d at 1306 (unexpected difference in kind for excipient to increase an active ingredient’s permeability when the art taught no impact or decrease in permeability expected.)

Additionally, the other ingredients in the tested formulations do not impact bromfenac’s chemical stability, as acknowledged by Dr. Laskar (EX1003, ¶56) and confirmed by Dr. Williams (EX2082, ¶155 n.7), and are, in any event, present in each formulation. These experiments thus constitute proper head-to-head comparisons commensurate in scope with the broadest claims to effectively evaluate the relative chemical stabilizing effect of tyloxapol and polysorbate 80. (*Id.*, ¶¶155-56.) Tyloxapol’s unexpectedly superior chemical stabilization effect would also be present in claimed formulations containing tyloxapol and other

excipients not present in the compositions evaluated above. (*Id.*); *Cadence*, 780 F.3d at 1376 (secondary consideration attendant to a broader claimed embodiment used to support patentability of more narrowly claimed formulations).

The results reported for Ogawa's Formulation A-2 in the table above further corroborate the results of tyloxapol's unexpected chemical stabilizing effect. At 1/2 and 1/15 the amount of polysorbate 80 used in Ogawa's Formulation A-2, and at one extra week of high stress and harsh pH conditions, tyloxapol unexpectedly and surprisingly stabilized bromfenac from degradation 36% and 65%, respectively, better than did polysorbate 80. (EX2082, ¶157.)

At a higher pH of about 8.2 to 8.3 (*see* Declaration of Mr. Shirou Sawa, EX2098, Section C), one less conducive to degrading bromfenac, formulations were compared containing bromfenac sodium, boric acid, borax, BAC, polyvinylpyrrolidone, disodium edetate, sodium hydroxide and either polysorbate 80 or tyloxapol at 60° C. for 4 weeks. (EX2082, ¶158.) In the following table, the Bronuck formulation, which contains polysorbate 80, also contains sodium sulfite, recognized in Ogawa as instrumental in achieving "remarkably enhanced" stability results (EX1004, 8:63-9:3). Formulations A-01 and A-3, which contain tyloxapol, do not contain sodium sulfite. (EX2098, ¶¶158-59.)

Formulation	Amount of surfactant	Remaining rate (%) bromfenac at 60° C. after 4 weeks
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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%

The Bronuck formulation containing 0.15 g of polysorbate 80, said by Dr. Laskar to be an embodiment of Ogawa (EX1003, ¶42) and closely resembling Ogawa Example 6, had 91.45% residual bromfenac. By contrast, the formulations containing substantially less tyloxapol at 0.02 g and 0.03 g, and lacking Ogawa's sodium sulfite, had 93.61% and 95.07% residual bromfenac, respectively, which was completely unexpected. (EX2082, ¶159.) Eliminating a chemical component from a formulation to be instilled on surgically compromised ocular tissue, with a significantly reduced amount of tyloxapol, constitutes a substantial and material difference in kind attributable to the use of tyloxapol. (*Id.*); *Allergan*, 796 F.3d at 1306. [REDACTED]

[REDACTED]

[REDACTED]

Further corroboration of tyloxapol's unexpected chemical stabilizing effect at a high pH is shown in the tests in Table 2 of the '431 patent. (EX2098, Section B; EX2082, ¶160.) Despite using an amount of tyloxapol that was about 1/3, 1/5 and 1/8 the amount of polysorbate 80 used by Ogawa, these formulations achieved comparable stabilization results to Ogawa's Example 6. (EX2082, ¶160.)

Specifically, Formulations A-04, A-06 and A-05, using 0.02 g, 0.03 g and 0.05 g of tyloxapol, respectively, achieved 92.6%, 92.0% and 90.9% remaining rate of bromfenac, compared to 100.9% reported in Ogawa's Example 6. (*Id.*, 164 n.8.) Achieving these results without using Ogawa's sodium sulfite confirms that the significant contribution made by the '290 patent to the art as whole was a difference in kind, *Allergan*, 796 F.3d at 1306, applicable to all claimed formulations containing tyloxapol, whether they recite sodium sulfite or not. (EX2082, ¶¶161-62); *Cadence*, 780 F.3d at 1375; *In re Papesch*, 315 F.2d 381, 392 (C.C.P.A. 1963) (a composition and its properties are inseparable).

InnoPharma argues that Senju allegedly has not demonstrated unexpected superior results over the full pH range. (Pet., 50.) This argument lacks merit. Senju tested at the harsher pH of 7.0 and the milder pH higher than 8.0 and showed unexpectedly superior stabilizing effect for tyloxapol compared to polysorbate 80 throughout the usable pH range and thus the full scope of the claims. (EX2082, ¶163.) Senju need not have tested every conceivable embodiment. *See In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011) (demonstrating an embodiment had an unexpected result and providing basis for expecting other claimed embodiments would behave similarly will suffice).

InnoPharma also argues that tyloxapol's stabilizing effects were expected relying on Fu's disclosure of Octoxynol 40 and Octoxynol 9. (Pet., 49-50.) InnoPharma again is wrong. As discussed above, a POSA would not have looked to Fu, and would not have expected tyloxapol to increase chemical stability of bromfenac, because Fu only addresses physical stability, and not chemical stability, of ketorolac tromethamine and BAC formulations. (EX2082, ¶¶92-95.) Moreover, ethoxylated octylphenols effectively constitute an infinite class of compounds having significant structural and chemical differences such that a POSA would not have made any predictions of tyloxapol's effect on bromfenac's chemical stability from either Octoxynol 40 or Octoxynol 9. (*Id.*)

4. Tyloxapol's unexpectedly better maintenance of preservative efficacy

With respect to preservative efficacy, no prior art discloses or suggests that tyloxapol would have had a more favorable effect than polysorbate 80 on preservative efficacy. (EX2082, ¶164.) Because Dr. Laskar contends that both surfactants are interchangeable (EX1003, ¶¶38, 56), they should, according to Dr. Laskar, behave similarly, including with respect to preservative efficacy. (EX2082, ¶164.) But surprisingly, at a significantly lower concentration, tyloxapol unexpectedly improves the preservative efficacy of bromfenac formulations as compared to polysorbate 80. (EX2098, Section D; EX2082, ¶¶165-67.)

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

In the table above, only the tyloxapol formulations satisfied the European Pharmacopoeia standards, which are more stringent than the US Pharmacopoeia standards. (EX2082, ¶166.) Formulation A-04 (0.02 g tyloxapol) satisfied the European Pharmacopoeia A and B standard, and A-05 (0.05 g tyloxapol) satisfied the European Pharmacopoeia B standard. (*Id.*) The Bronuck formulation, which had about eight times more polysorbate 80 (0.15 g) than did Formulation A-04, did not satisfy either the European Pharmacopoeia A or B standard. (*Id.*)

These results are surprising not only because Dr. Laskar argues that a POSA would have expected the surfactants to behave similarly, but also because tyloxapol so convincingly outperformed polysorbate 80 at substantially lesser amounts, a material and significant benefit by any metric. (*Id.*, ¶167.) [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] More than a mere difference in degree, these results

meaningfully contribute to the claimed compositions [REDACTED]

[REDACTED]

[REDACTED]

B. Additional compelling objective evidence of patentability

The unexpected stabilization benefits of tyloxapol translated into unexpected medical benefits, manifested in the commercial product Prolensa[®]. (EX2116, ¶¶51-52.) Prolensa[®], which contains 0.07 w/v% bromfenac [REDACTED] [REDACTED] (EX2082, ¶¶143, 168.) Tyloxapol's stabilization effect permitted formulating Prolensa[®] at pH 7.8, down from pH 8.3 in non-prior art commercially available bromfenac formulations (EX2030, 1; EX2026, 5; EX2027, 4)—a substantial reduction on a logarithmic scale—and beneficially closer to the pH of natural tears. (EX2082, ¶168.)

[REDACTED]

[REDACTED]

[REDACTED]

Both the reduction in pH [REDACTED] eliminated the burning and stinging upon administration present with all other approved NSAID ophthalmic eye drops besides Prolensa[®]. (EX2082, ¶168; EX2116, ¶41.) Each of Ocufer[®] (1986), Profenal[®] (1988), Voltaren[®] (1991), Acular[®] (1992), Acular[®] PF

(1997), Bronuck in Japan (non-prior art), and even Xibrom[®] and Bromday[®] (non-prior art) are limited by their side effects of burning and stinging. (EX2116, ¶36; EX2057, 6; EX2060, 7-8; EX2111, 1, col. 2; EX2026, 5-6; EX2027, 6.) These are significant, painful side effects that adversely impact patient compliance. (EX2116, ¶36.) Non-compliant post-operative patients have a high risk of developing CME, a serious complication involving retinal swelling and reduced vision. (*Id.*)

Prolensa[®] represented a new therapy for effectively and comfortably treating postoperative inflammation and pain after cataract surgery without burning or stinging upon administration. (EX2013, 6; EX2116, ¶¶39, 52.) Being comfortable to administer and well-tolerated is a major benefit, for Prolensa[®] increases patient compliance and minimizes the potential for CME. (EX2116, ¶36, 39, 52.) This favorable side effect profile traces back to tyloxapol's superior chemical stabilizing effect on bromfenac, permitting a reduction in both pH [REDACTED] and representing a significant difference in kind. (*Id.*) *Allergan*, 796 F.3d at 1306 (unexpected difference in kind between safe and effective drug and one with serious side effects causing patients to become non-compliant). This favorable side effect profile also was unexpected given that Prolensa[®] contains BAC, which is toxic to eye cells and which the prior art taught away from using in ophthalmic formulations. *Allergan*, 796 F.3d at 1305 (defendant's expert referring to BAC as a

“natural born killer” that was “from Satan”); ([REDACTED]
[REDACTED]; EX2116, ¶¶43-47, 54.)

Lowering the pH also improved bromfenac’s intraocular penetration and permitted a lowering of its concentration to 0.07%, down from 0.1% in Ogawa and 0.09% in non-prior art Bromday[®], meaning that Prolensa[®] advantageously puts less drug in contact with surgically compromised ocular tissue without a reduction in efficacy. (EX2116, ¶42; EX2030, 1718.) This significant reduction in the amount of active ingredient—30% and 22%, respectively—without a corresponding reduction in ocular penetration and efficacy, is another unexpected difference in kind. (EX2082, ¶169); *Allergan*, 796 F.3d at 1306.

Indeed, Prolensa[®] has received significant medical industry acclaim by numerous leaders in the field of cataract surgery extolling “the benefits of the new formulation.” (EX2116, ¶¶55-61.) These key opinion leaders also recognized Prolensa[®]’s high efficacy with a reduced amount of bromfenac on healing ocular tissue, its ocular comfort, its lower incidence rates, and its high degree of patient compliance, which all trace back to tyloxapol’s superior chemical stabilization effect on bromfenac. (*Id.*) Doctors and patients alike quickly gravitated to Prolensa[®], despite the availability of lower-priced generic versions of non-prior art

bromfenac formulations and other ophthalmic NSAIDs. (EX2116, ¶¶51-52; EX2130, ¶123.)

With these attributes, Prolensa[®] has achieved substantial marketplace success. (EX2130, ¶¶58, 129.) Lupin, a company seeking to market generic Prolensa[®], had projected sales for Prolensa[®] to reach \$100 million annually after two to three years. (EX2022, 4.) Since its April 2013 launch, Prolensa[®] has generated \$246.9 million in revenue, despite entering a market with at least six branded drugs and three generic drugs FDA approved to treat similar indications, and is on target to surpass Lupin's forecast. (EX2130, ¶¶70-72, 130.) Prolensa[®] has achieved one of the highest shares of prescriptions and revenue among branded drugs with similar indications. (EX2130, ¶16.) Prolensa[®]'s commercial success is attributable to tyloxapol's stabilizing effect on bromfenac. (EX2130, ¶¶82, 133.)

Six generic companies, including InnoPharma, have submitted ANDAs seeking to market exact copies of Prolensa[®]. Their Paragraph IV Letters advance no non-infringement positions, indicating their intention to copy Prolensa[®]. (EX2082, ¶171.)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] The FDA expressly permits variations in inactive ingredient in ophthalmic

drug products. (EX2107, § 314.94(b)(9)(iv).) Accordingly, “[c]opying the claimed invention, rather than one in the public domain,” which InnoPharma could have also done with Bromday[®], is evidence that the claimed subject matter would not have been obvious. *Specialty Composites v. Cabot Corp.*, 845 F.2d 981, 991 (Fed. Cir. 1988) (citations omitted). Filing ANDAs by generic manufacturers constitutes copying, which the Federal Circuit has affirmed as objective evidence of non-obviousness. *Janssen Pharm. NV v. Mylan Pharm., Inc.*, 456 F. Supp. 2d 644, 671 (D.N.J. 2006), *aff’d per curiam*, 223 Fed. Appx. 999 (Fed. Cir. 2007).

The ophthalmic industry also has recognized ’290 patent’s merit through Prolensa[®]. As mentioned, even before Prolensa[®] was marketed, Lupin projected its sales to reach \$100 million annually. (EX2022, 4.) Apotex, Metrics, and Paddock, all of which sell ophthalmic products, initially challenged the ’290 patent in district court. (EX2130, ¶¶75-77; EX2019; EX2017; EX2018.) But each licensed the patent and took a consent judgment and injunction, importantly tying their acknowledgement of the ’290 patent’s validity to their generic versions of Prolensa[®]. (EX2130, ¶¶75-78; EX2024; EX2122; EX2123.) *Institut Pasteur v. Focarino*, 738 F.3d 1337, 1347 (Fed. Cir. 2013) (Pasteur’s licensing activities provide ‘probative and cogent evidence’ of non-obviousness of the claims at issue.”).

Accordingly, these compelling objective indicia support the non-obviousness of all the challenged claims of the '290 patent.

IX. Separate patentability of individual claims

A. Separate patentability of claims 4-5, 11-12, 17-18 and 23-24

The stable aqueous preparation of claims 4-5, 11-12, 17-18 and 23-24 require, among other recited elements, bromfenac and tyloxapol, wherein the amount of tyloxapol is from about 0.01 w/v % to about 0.05 w/v %. (EX2082, ¶173.) Claims 4 and 5 further require that this amount be “sufficient to stabilize” bromfenac, as both either directly or indirectly depend from claim 1. InnoPharma has not identified any teaching in the art of any amount of tyloxapol sufficient to chemically stabilize bromfenac. Both InnoPharma and Dr. Laskar merely argue in their claim charts that “Ogawa Table 11 describes that Example 6 Ophthalmic Solution, after 4 weeks at 60° C is not less than 90% of the original amount of bromfenac.” (Pet., 21; EX1003, ¶80.) Because Ogawa does not disclose tyloxapol, however, it cannot disclose amounts of tyloxapol “sufficient to stabilize” bromfenac (EX2082, ¶175), leaving InnoPharma with a failure of proof regarding this claimed element. *See Unigene*, 655 F.3d at 1361-62 (affirming nonobviousness where prior art disclosed only “vague” discussions of piecemeal elements).

Undeterred, InnoPharma wrongly alleges that it would have been obvious to optimize the amount of tyloxapol to meet these claims. It is well settled that it is not obvious to optimize a variable when 1) the parameter optimized was not art-recognized to be result-effective or 2) the parameter was known to be result-effective, but the results in optimizing it were unexpectedly good. *In re Antonie*, 559 F.2d 618, 620 (C.C.P.A. 1977); *see also, Ex parte Whalen et al.*, Appeal 207-4423, at 14 (B.P.A.I. July 23, 2008). Here, tyloxapol was not an art-recognized result-effective variable and, compared to polysorbate 80, tyloxapol was unexpectedly superior in chemically stabilizing bromfenac's degradation.

First, tyloxapol was not an art-recognized variable for chemically stabilizing any NSAID. (EX2082, ¶175.) Not a single reference of record describes the use of tyloxapol as a stabilizer in an aqueous liquid preparation containing an NSAID. (*Id.*, ¶90.) Sallmann describes tyloxapol as a solubilizer, not as a stabilizer. (EX1009, 4:52-67; EX2082, ¶114.) Sallmann separately ascribes the stabilizer function to non-surfactants, like cyclodextrins. (EX1009, 5:59-6:17; EX2082, ¶119.) Yasueda uses tyloxapol with pranlukast, which is not an NSAID, is vastly structurally different from bromfenac and diclofenac, and degrades by hydrolysis rather than oxidation, making any conclusions about stability drawn from Yasueda inapplicable to bromfenac. (EX2105, ¶¶66-67; EX2082, ¶98.) Moreover, a POSA

would have been concerned that tyloxapol's generation of hydroperoxides would have degraded bromfenac by oxidation—the antithesis of a result-effective variable for optimization purposes. (EX2105, ¶¶71-72; EX2082, ¶98.)

Second, as discussed above, tyloxapol has demonstrated an unexpected superiority over polysorbate 80 in chemically stabilizing bromfenac, particularly at the lower amounts of 0.01 to 0.05%. (EX2082, ¶¶154-70.) The unexpected stabilization effects of tyloxapol were a difference in kind, translating into real-world medical benefits manifested in Prolensa[®]. (EX2082, ¶¶168-70.)

The amounts of tyloxapol used in the art are for solubilizing, not stabilizing, and, importantly, are all much higher than 0.01 to 0.05 w/v%. *Ex parte Whalen*, at 14-15 (art's teaching of low viscosities would not have led the POSA to optimize known compositions to increase viscosity). Sallmann's Example 2 uses 0.1 w/v% tyloxapol, which is twice the upper endpoint of the claimed range. (EX1009, 8:1-15; EX2082, ¶176.) Five of Sallmann's six eye drop formulations that contain tyloxapol use 0.1 w/v%. (EX1009, Exs. 2, 15, and 17.) Indeed, InnoPharma has argued “that a person of ordinary skill in the art, when replacing polysorbate 80 with tyloxapol in Ogawa's Example 6, would have used the concentration of tyloxapol that is disclosed in Sallmann's Example 2” (Paper 15, 16 (citing Pet., 19-22; EX1003, ¶¶50-51)), which is 0.1 w/v%. The only example using less tyloxapol,

Example 3, does not contain BAC and thus does not address InnoPharma's proposed motivation for selecting tyloxapol. (EX2082, ¶176.) Though Sallmann's solubilizers can range from 0.1 to 5000 times the concentration of the active ingredient (EX1009, 4:65-67), that disclosure relates to the myriad of solubilizers taught in Sallmann and is so broad as to encompass patentably distinct compositions, as the evidence here establishes. (EX2082, ¶¶154-170); *Allergan*, 796 F.3d at 1305-06, distinguishing *Galderma Labs. v. Tolmar, Inc.*, 737 F.3d 731 (Fed. Cir. 2013).

Yasueda similarly teaches using much higher amounts of tyloxapol than the 0.01 to 0.05 w/v% claimed in the '290 patent. (EX2082, ¶179.) As Dr. Laskar acknowledges, Yasueda teaches 0.5-8 w/v% tyloxapol. (EX1003, ¶¶73, 88.) Yasueda's examples of aqueous solutions, including those relied on by Dr. Laskar (Table 4), consistently use 4.0 g of tyloxapol (4.0%), 80 times greater than 0.05 w/v%. (EX1012, Tables 4 & 5; EX2082, ¶179.)

In sum, a POSA would not have been led to optimize the teachings of Ogawa and Sallmann to use 0.01 to 0.05 w/v% of tyloxapol. Tyloxapol is not an art-recognized result-effective variable, it unexpectedly chemically stabilized bromfenac better than polysorbate 80, *in re Antonie*, 559 F.2d at 620, and the art divergently taught using significantly higher amounts of tyloxapol. *Ex parte*

Whalen, Appeal 207-4423, at 14; *Allergan*, 796 F.3d at 1305-06. For these reasons, the Board should confirm the patentability of claims 4-5, 11-12, 17-18 and 23-24.

B. Separate patentability of claims 8-13, 20-25, 27, 29 and 30

Among these claims, independent claims 8 and 20 recite stable aqueous liquid preparations of bromfenac and tyloxapol, wherein “greater than about 90% of the original amount of [bromfenac] remain[ing] in the preparation after storage at about 60° C. for 4 weeks.” Moreover, claim 11, which depends from claim 8, and claim 23, which depends from claim 20, also recite a tyloxapol concentration from about 0.01 w/v % to about 0.05 w/v%. Dr. Laskar has identified no disclosure in Ogawa or Sallmann meeting any of these elements, [REDACTED]

[REDACTED] InnoPharma nonetheless argues the claimed stability would have been inherent in an obviousness context. (Pet., 31.) InnoPharma is wrong.

“The inherency of an advantage and its obviousness are entirely different questions Obviousness cannot be predicated on what is unknown.” *In re Shetty*, 566 F.2d 81, 86 (C.C.P.A. 1977). Indeed, the Federal Circuit has set a high standard to show inherency in an obviousness context. *Par Pharm, Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1195-96 (Fed. Cir. 2013).

Without any evidence to establish inherency, InnoPharma has failed to meet this high burden. *Sandoz, Inc. v. EKR Therapeutics, LLC*, IPR2015-00005, slip op. at 11 (P.T.A.B. Apr. 24, 2015) (Paper 20) (petitioner failed to present evidence to show that formulations allegedly suggested in the art inherently satisfy the claimed element). In any event, as discussed above, tyloxapol's unexpected chemical stabilization effect on bromfenac, particularly at 60°C for four weeks, as well as at the lower amounts of 0.01 to 0.05 w/v, differed in kind from the prior art. (EX2082, ¶¶154-70, 185; EX2116, ¶¶ 37-43.) *Allergan*, 796 F.3d at 1306 (unexpected properties differing in kind, even if inherent, support a conclusion of non-obviousness.) InnoPharma's mere attorney argument and unsubstantiated opinion testimony from Dr. Laskar should be rejected. *See, e.g., Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 294 (Fed. Cir. 1985) (expert opinion lacking factual support is entitled to little probative value in a validity determination). InnoPharma has failed to prove obviousness of claims 8-13, 20-25, 27, 29 and 30, and the Board should confirm their patentability.

C. Separate patentability of claims 26-30

Claims 26-30 require that the aqueous liquid preparations meet the European Pharmacopoeia Criteria B ("EP-Criteria B") standard for preservative efficacy. Claims 27 and 29 depend from claims 8 and 20 (discussed in Section VIII.B.,

supra), respectively, and further require that the aqueous liquid preparations have “greater than about 90% of the original amount of [bromfenac] remain[ing] in the preparation after storage at about 60° C. for 4 weeks.”

Neither InnoPharma nor Dr. Laskar has pointed to anything in Ogawa or Sallmann disclosing this claim element, and without proffering a scintilla of evidence, InnoPharma and Dr. Laskar merely argue that the claimed preservative efficacy would have been inherently obvious. (Pet., 46-47; EX1003, ¶99.) InnoPharma and Dr. Laskar again are wrong. Although Dr. Laskar cites to examples in Sallmann and Fu (EX1003, ¶98), none of them discloses a formulation that satisfied EP Criteria B and that contained tyloxapol. (EX2082, ¶187.)

Moreover, the Bronuck formulation, said by Dr. Laskar to be described in Ogawa (EX1003, at ¶44), did not meet the European Pharmacopoeia A or B standards, whereas the claimed formulations of the '290 patent unexpectedly did. (EX2082, ¶¶ 164-67, 189.) Not only is this unexpected given Dr. Laskar's view that polysorbate 80 and tyloxapol are interchangeable (EX2098, ¶189; Pet., 23; EX1003, ¶40), but also the art taught polysorbate 80 as a better solubilizer than tyloxapol. (EX2082, ¶189.) Based on Dr. Laskar's arguments, this would have led a POSA to believe that formulations containing polysorbate 80 would have exhibited better preservative efficacy. The opposite unexpectedly occurred. (*Id.*)

Claims 26-30, therefore, recite unknown and unexpected properties of new and nonobvious formulations, completely undermining InnoPharma's unsubstantiated position that a POSA would have expected the combined teachings of Ogawa and Sallmann to satisfy the European Pharmacopeia B standard. *Allergan*, 796 F.3d at 1307. InnoPharma therefore has failed to prove obviousness of claims 26-30, and the Board should confirm their patentability. Moreover, in view of InnoPharma's compounded failures of proof with respect to claims 27 and 29, which further recite the chemical stability element recited in claims 8 and 20, the patentability of these claims should be confirmed.

X. Conclusion

InnoPharma's petition should be denied for at least: (i) failing to prove that a POSA would have made any combination of Ogawa and Sallmann with any reasonable expectation of arriving at the claimed subject matter; (ii) failing to prove the existence of each claimed element from Ogawa and Sallmann, including the alleged inherency of various claim elements; and (iii) failing to rebut the compelling objective indicia of non-obviousness of the claimed subject matter.

Respectfully submitted,

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing **Patent Owner Response (PUBLIC)** was served on December 28, 2015, via email directed to counsel of record for the Petitioner at the following:

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