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Filed: December 28, 2015

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 IPR2015-00903
Patent 8,129,431

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

Table of Contents

Table of Authorities

Page(s)

Cases

Statutes

Other Authorities

Patent Owner Senju Pharmaceutical Co., Ltd. et al. ("Senju") responds to the Petition filed by InnoPharma Licensing, Inc. et al. ("InnoPharma") concerning claims 1-22 of U.S. Patent No. 8,129,431 ("the '431 patent"). The Board instituted trial on InnoPharma's grounds that (a) claims 1-5, 7-14 and 18-19 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), and (b) claims 6, 15-17 and 20-22 are allegedly obvious over Ogawa, Sallmann and AU-B-22042/88 to Fu et al. ("Fu") (EX1011). 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 POSA would have combined any of Ogawa, Sallmann and Fu with any expectation of arriving at the claimed subject matter. InnoPharma, moreover, has wholly failed to prove the existence of any prior art formulation containing 0.02 w/v% tyloxapol, which is an element of claims 6, 15-17 and 20-22. In addition, InnoPharma either ineffectively assails or simply ignores significant objective indicia of patentability, which further support the non-obviousness of the '431 patent claims. The Board accordingly should uphold the patentability of claims 1-22 of the '431 patent.

I. Introduction

The '431 patent discloses and claims aqueous liquid preparations of the non-steroidal anti-inflammatory drug ("NSAID") bromfenac, which are 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, 2:34-47; EX2082, ¶153.)

The inventors successfully formulated these preparations using the non-ionic surfactant tyloxapol. (EX2082, ¶151.) Tyloxapol unexpectedly chemically stabilized bromfenac better than did the surfactant polysorbate 80, even at a low pH known to accelerate bromfenac's degradation. (*Id.*, ¶¶ 156, 166, 171.) 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.*, ¶177.)

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 '431 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]

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 approved by the FDA 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, ¶182.) One of these six, Lupin, which also has filed an IPR petition challenging the '431 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 '431 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 '431 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., 6-7.) As discussed below, InnoPharma offers no reason, other than impermissible hindsight looking backward from the '431 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 failed to identify any prior art formulation containing 0.02 w/v% tyloxapol, which is an element of claims 6, 15-17, and 20-22, 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 '431 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 '431 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, or Ogawa, Sallmann and Fu, with any reasonable expectation of arriving at the claimed subject matter; (ii) it fails to prove the existence of any prior art formulation containing 0.02 w/v% tyloxapol, which is an element of claims 6, 15-17, and 20-22; and (iii) it fails to rebut the compelling objective indicia of non-obviousness of the claimed subject matter.

III. Claim construction

Senju believes that no claim term needs express construction and that the plain and ordinary meaning consistent with the specification and the prosecution history should apply. *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 '431 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, ¶¶41-42.)

V. The '431 patent

The application for the '431 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 '431 patent has two independent claims (claims 1 and 18) and 20 dependent claims, which are separately patentable. The '431 patent is listed in the FDA's Orange Book, and the parties agree that it covers Prolensa® ophthalmic bromfenac (0.07%) solution. (EX1003, ¶42; EX2082, ¶152.)

VI. Background of ophthalmic formulations

As of the 2003 priority date of the '431 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 aqueous liquid preparations of the '431 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 '431 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., 6-7.) 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.*, 27-28.) A POSA therefore would have had no reason or need to focus, for further development, on bromfenac to the exclusion of the other NSAIDs. (EX2082, ¶¶60-61.) 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., 53 (emphasis added).) In fact, Ogawa states that its bromfenac formulations displayed remarkably enhanced stability (EX1004, 8:46-9:3), and Dr. Laskar acknowledged that Ogawa satisfied bromfenac's stability problem. (EX2114, 115:2-116-4.)

Moreover, neither Hara nor Yanni supports a preference for bromfenac over diclofenac, contrary to InnoPharma's position. (EX2082, ¶¶59-62.) 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, ¶60.)

The same applies to Yanni, which actually disparages bromfenac, preferring esters and amides, like nepafenac. (EX1033, 1:54-59, 4:84-52; EX2082, ¶62.) Focusing on a single *in vitro* result from Table 1 of Yanni (EX1003, ¶28), Dr. Laskar ignores important *ex vivo* and *in vivo* data (EX2082, ¶¶61-62), which do not show superiority of bromfenac over diclofenac and in fact show superiority of other compounds. (*Id.*, EX1033, Table 1.)

B. Design need and market demands would not have led a POSA in the direction that the inventors of the '431 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, ¶96.) Dr. Laskar admits, however, that he has no

evidence that any such precipitate actually forms between bromfenac and BAC. (EX2114, 45:18-46:4.] 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, ¶65.) 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." Dr. Laskar also characterized BAC as a "killer," known to cause adverse reactions *in vitro* and *in vivo*. (EX2114, 78:13-25, 79: 13-23.)

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, ¶63.) By January 2003, the art taught using preservative-free formulations and well-tolerated preservatives in place of BAC (EX2082, ¶64; 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). Dr. Laskar did not consider these solutions. He admitted to focusing on BAC because the '431 patent claims recite it. (EX2114, 69:21-70:10.)

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, ¶¶67-68.) The art taught that a preservative-free formulation of Fu's ketorolac "may be 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. (EX1003, ¶104; EX2114, 33:4-34:1; EX2082, ¶52; EX1020, 3:28-4:2, 6:11-7:10.) Desai also teaches the use of a

different polymeric quaternary ammonium preservative compound, POLYQUAD®, which Dr. Laskar admits would avoid the interaction problem. (EX1005, 1:27-2:31; EX2114, 93:3-16; EX2082, ¶69.) 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. (EX1033, 1:60-2:29; EX2082, ¶73); *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, ¶¶48.) But he ignores Ogawa Example 7, reporting an equally high residual amount of bromfenac (99.2%) and containing methylparaben and ethylparaben instead of BAC, which Dr. Laskar testified do not interact and precipitate with bromfenac. (EX2114, 229:6-21.) Thus, Ogawa implements a solution to Dr. Laskar's interaction/precipitation problem in a chemically stable formulation, yet Dr. Laskar ignores it because, as he testified, he focused on the fact that the claims of the '431 patent recite BAC. (EX2114, 69:21-70:10.)

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, ¶100), 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, ¶71.) As such, the art led in a direction divergent from the path chosen by the inventors of the '431 patent, as Dr. Laskar admitted, thereby supporting the non-obviousness of the '431 patent claims. (EX2114, 32:22-34:1; EX2082, ¶¶69-73); *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, ¶97.) Ogawa's solution involved a water soluble polymer, *e.g.*, polyvinyl pyrrolidone, and a sulfite, *i.e.*, sodium sulfite. (EX1004, 3:7-15; EX2082, ¶97.) Sodium sulfite is a well-known antioxidant. (EX2014, 3:51-55; EX2082, ¶97.) A POSA would have understood that Ogawa used sodium sulfite because bromfenac chemically degrades by oxidation (EX2105, ¶37), and an antioxidant would prevent that degradation process. InnoPharma acknowledges that sodium sulfite is added "to prevent oxidation reactions." (Pet., 49.)

When bromfenac oxidizes, its forms an oxidation degradant referred to throughout Ogawa as red insoluble matters. (EX1004, 8:3-45; EX2082, ¶98.) Dr. Laskar agrees that red insoluble matters indicate that bromfenac is ***chemically*** degrading. (EX2114, 228:16-24.) These red insoluble particles do not constitute, therefore, the result of any ***physical*** interaction such as any precipitation between bromfenac and BAC. (EX2082, ¶99.) 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.*) Dr. Laskar admitted that he cited no prior art and conducted no test to establish bromfenac interacts with BAC. (EX2114, 45:18-46:4.) Given the complexities of ophthalmic formulation systems, one cannot predict whether such an interaction does occur. (EX2082, ¶99; EX2105, ¶77.)

Polysorbate 80, moreover, plays no role in chemically stabilizing bromfenac from oxidizing. (EX2082, ¶97.) 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, ¶100.) 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, ¶100.) Citing to column 3, lines 49-53 of Ogawa, Dr. Laskar incorrectly states that polysorbate 80 contributes to stabilizing bromfenac. (EX1003, ¶50; EX2082, ¶101.) This passage, however, nowhere refers to polysorbate 80, explicitly or implicitly. (EX2082, ¶101.)

The data from Ogawa Experimental Examples 4-6 actually confirm that polysorbate 80 does not stabilize bromfenac. (EX2095, 107; EX2082, ¶101.) 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, ¶102.) 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, ¶101.) Thus, polysorbate 80 has no effect on the stability of bromfenac. (EX2082, ¶101.)

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., 51-52; EX1003, ¶¶98-99.) The data in Ogawa Experimental Examples 4-6, however, completely undermine InnoPharma's foundational premise for its obviousness arguments. (EX2082, ¶103.) *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, ¶126.) 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, ¶105.)

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, ¶106.)

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, ¶104.) 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, ¶104; EX2039, 6; EX2140, 156:20-157:6.) Indeed, there would have been no reason to look to Sallmann unless one knew from the '431 patent that tyloxapol works to stabilize bromfenac. (EX2082, ¶104.) Dr. Laskar candidly admitted as much, while also acknowledging that there are many other surfactants used in ophthalmic formulations (EX2114, 94:15-20):

> Q: And you focused on tyloxapol because it's identified in the claims of the '431 and '290 patents, correct?
> A (Dr. Laskar): Yes, yes. I mean, there is certainly a number of other non-ionic surfactants that are employed in -- in ophthalmic formulations.

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., 32) and Dr. Laskar's (EX1003, ¶98) statements to the contrary. (EX2082, ¶109.) As such, there would have been no reason, absent hindsight looking backward from the claimed subject matter of the '431 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. 15, 11.) 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. (Inst. Dec., 12.) 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, ¶111); *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, ¶111); *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, ¶111.)

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, ¶116.) 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, ¶116.) 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, ¶116; EX2105, ¶¶71-72.) 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 is no evidence in the art of bromfenac and BAC forming a precipitate or otherwise needing addition of a solubilizer. (EX2105, ¶ 73-78; EX2082, ¶116.) There was no reason, 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, ¶114.) 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, ¶114.)

Sallmann also discloses several antioxidants (EX1009, 5:51-54), and InnoPharma admits that Ogawa uses sodium sulfite to prevent oxidation. (Pet., 49.) Consistent with Dr. Laskar's admission that he focused on tyloxapol because the '431 patent claims recite it (EX2114, 94:15-20), 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, ¶116; EX2105 ¶¶71-72.) 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).

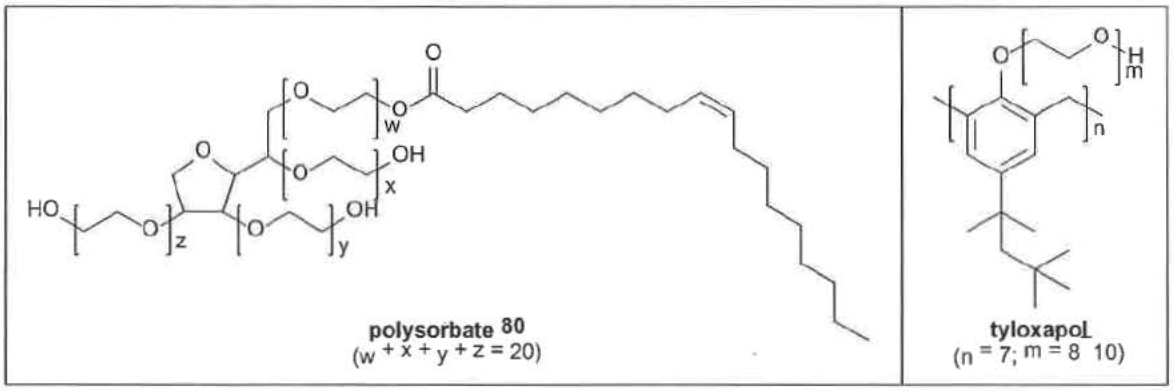
To be sure, Ogawa directs a POSA to use antioxidants to stabilize bromfenac against chemical degradation. (EX2082, ¶117.) A POSA would have also been concerned that tyloxapol's production of hydroperoxides would have added to bromfenac's degradation. (*Id.*, ¶116; EX2105 ¶¶71-72.) A POSA would have thus been led down a path completely divergent from the one that the inventors of the

'431 patent took in arriving at the claimed subject matter. (EX2082, ¶117.) *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, ¶¶54-55.) 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, ¶52; EX2114, 240:19-241:14.) Even small changes to a formulation's ingredients can yield substantial changes in its properties and functionality. (EX2082, ¶¶54-55; *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, ¶112.) 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, ¶113); *Eisai Co. Ltd.*, 533 F.3d at 1359.

Moreover, tyloxapol is nowhere disclosed in the Handbook of Pharmaceutical Excipients, which both Dr. Laskar and Dr. Jayne Lawrence, who serves as InnoPharma's expert in district court litigation involving the '431 patent, considered an important reference to an ophthalmic formulator in 2003. (EX2082, ¶¶85, 125, 142; EX2114, 247:25-249:23; 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 '431 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., 22), InnoPharma relies on a theory of "obvious to try" (*id.*, 25) and an alleged superiority of tyloxapol compared to polysorbate 80 in solubilizing. (*Id.*) 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 diclofenac." (*Id.*, 25-26.) 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, ¶119.) Sallmann separately teaches using different types of stabilizers that are not surfactants. (EX1009, 5:59-6:17; EX2082, ¶119.)

InnoPharma alleges that Sallmann teaches that tyloxapol is a better surfactant than polysorbate 80. (Pet., 24.) No basis for this allegation exists, as Sallmann never mentions polysorbate 80. (EX2082, ¶122.) InnoPharma then alleges that tyloxapol and polysorbate 80 are interchangeable, citing Aviv (EX1026). (Pet., 24.) But Aviv is directed to emulsions, not aqueous solutions. (EX2082, ¶122.) 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.*)

InnoPharma further argues that tyloxapol is a better solubilizer than polysorbate 80 based on Yasueda. (EX1012; Pet., 25.) But Yasueda actually teaches in Table 1 that polysorbate 80 (719.6 μg/ml) is significantly superior to tyloxapol (551.0 μg/ml) for solubilizing pranlukast. (EX1012, 5:10-32; EX2082, ¶123.) Moreover, pranlukast is a poorly water soluble active ingredient that is not an NSAID and is structurally dissimilar from both bromfenac and diclofenac. (EX2082, ¶123; 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, ¶123.) 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, ¶123); *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, ¶88; EX2105, ¶71.) A POSA thus could not have drawn any conclusions from pranlukast's chemical stability in Yasueda and applied them to bromfenac.

(EX2082, ¶88; EX2105, ¶71.) Nothing in Yasueda would have led a POSA to expect that tyloxapol would favorably impact bromfenac's oxidative degradation. (EX2082, ¶88; EX2105, ¶72.) *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, ¶88; EX2105, ¶¶71-72.)

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., 26.) This alternative position is untenable and impermissibly relies on hindsight. (EX2082, ¶126.)

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, ¶126), 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, ¶127; 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, ¶127.) For this reason alone, InnoPharma has failed to prove obviousness of claims 2-6, 11-17 and 19-22 of the '431 patent requiring bromfenac sodium.

There is also no 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). In fact, Dr. Laskar admitted on cross examination that even though many other surfactants were known for use in ophthalmic formulation, he focused on tyloxapol because the '431 patent claims recite it. (EX2082, ¶129; EX2114, 94:15-20.)

Unlike Dr. Laskar, however, a POSA would not have engaged in hindsight using the claims of the '431 patent and instead would have focused on, if anything, Sallmann's Examples 8 and 11. (EX2082, ¶¶130-31.) 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, ¶¶130-31; 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, ¶130.) *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, ¶128.) 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 "consisting essentially of," 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, ¶131.) 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, Inc.*, 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., 27-28.) 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.)

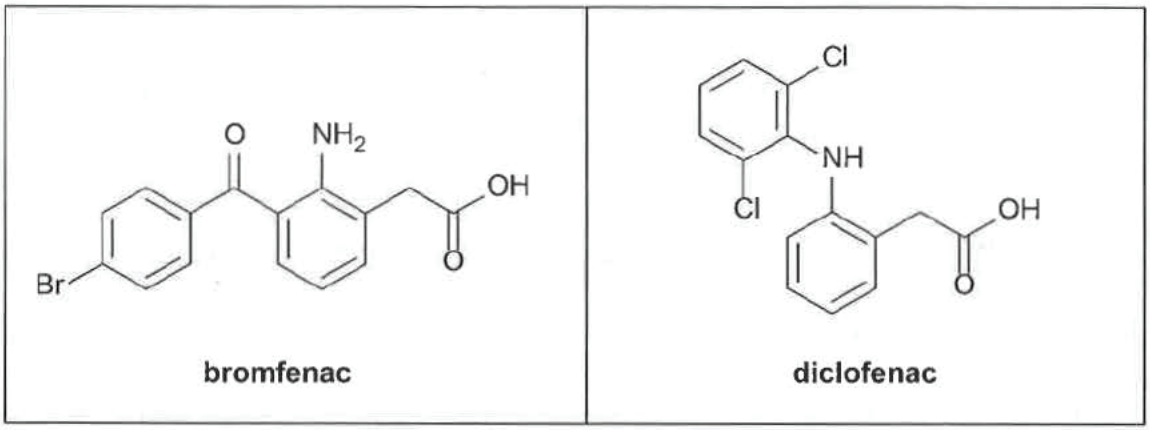
InnoPharma then argues that there allegedly would have been a design need to formulate a stable bromfenac solution and it allegedly would have been obvious to try to formulate bromfenac with tyloxapol. (Pet., 30.) But InnoPharma contradicts itself, having unequivocally stated that there would not have been ***any*** need to design a new bromfenac formulation, and all that was needed was embodied in Ogawa or Hara. (Pet., 53.) 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, as evidenced by Dr. Laskar's clear admissions that he only focused on BAC and tyloxapol, even though other excipients for ophthalmic use were well known, because both are recited in the claims of the '431 patent. (EX2114, 69:21-70:10, 94:15-20.) Regarding alleged design need, InnoPharma and Dr. Laskar make inconsistent statements that undermine their basic obviousness position, ultimately betraying and exposing their analysis as *post hoc* and entirely improper. *KSR Int'l Co. v. Teleflex Inc.*, 550

U.S. 398, 421 (2007) ("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning.").

InnoPharma further relies on Hara (EX1002) as alleged support for using bromfenac instead of diclofenac in Sallmann. (Pet., 28.) That reliance is similarly misplaced. As discussed above, Hara teaches that both bromfenac and diclofenac have "superior" anti-inflammatory action (EX1002, 2, 3), that both treat postoperative inflammation of the eye (*id.*), that diclofenac could treat anterior uveitis, while bromfenac was not approved for this indication (*id.*), and that diclofenac had no toxicity issues, 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.) For at least these reasons, a POSA would not have interpreted Hara as endorsing bromfenac over diclofenac. (EX2082, ¶60.)

InnoPharma further argues that a POSA would have expected success in substituting bromfenac for diclofenac solely because these NSAIDs allegedly have similar physical and pharmacological properties. (Pet., 29.) InnoPharma again is wrong. As shown below, bromfenac and diclofenac have significant structural differences, which lead to important functional differences. (EX2105, ¶¶43-44.)



Bromfenac is a primary amine (NH_2 group), whereas diclofenac is a secondary amine (NH group). (*Id.*, ¶44.) 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 (C=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.*, ¶¶45-46.)

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.*, ¶49.) A POSA would have expected bromfenac to be better solvated than diclofenac in solution and less likely than diclofenac to form insoluble salts. (*Id.*, ¶50.) Indeed, bromfenac sodium "is freely water soluble"

and does not need a solubilizer. (*Id.*, ¶48.) Dr. Laskar admittedly addressed none of these properties. (*Id.*, ¶44; EX2114, 41:7-41:15.)

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 1-5, 7-14 and 18-19 should be maintained over Ogawa and Sallmann.

E. Fu does not remedy the deficiencies of Ogawa and Sallmann

1. A POSA would not have looked to Fu

Fu 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, 20-21; EX2082, ¶132.) Fu contains no data regarding the chemical stability of ketorolac or any NSAID. (EX2082, ¶132.) 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.*), which Dr. Laskar conceded on cross examination. (EX2114, 45:18-46:4.) 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 with bromfenac. (EX2082, ¶¶132-34); *Pfizer*, 2014 WL 5388100, at *9 (without data demonstrating a solubility concern, it would not have been obvious "to add a solubilizing amide.").

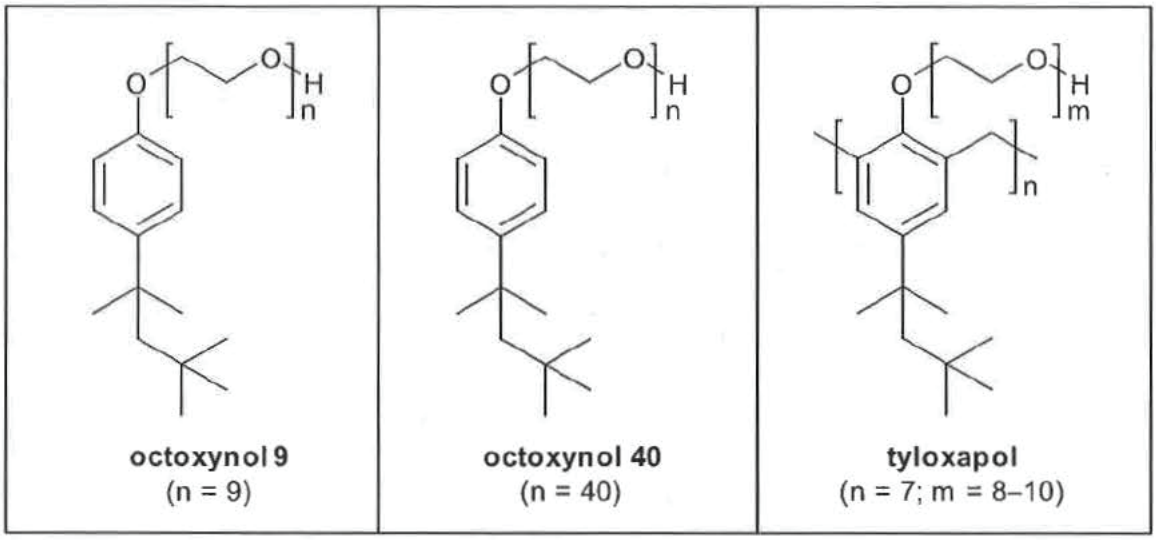
2. InnoPharma's attempted connection between Fu and tyloxapol is untenable

InnoPharma's path to tyloxapol from Fu is not straightforward even in hindsight, which Dr. Laskar admittedly used when acknowledging that, even though the art taught many different surfactants for ophthalmic formulations, he focused on tyloxapol because the '431 patent claims recite it. (EX2114, 94:15-20; EX2082, ¶136.)

Fu's Example 5 compares the ability of polysorbate 80 (Tween 80), Myrj 52 and Octoxynol 40, its most preferred surfactant and the only one for which it provides data, to physically stabilize formulations of ketorolac and BAC. (EX1011, 10, 20-21; EX2082, ¶137.) Under certain conditions, Octoxynol 40 physically stabilized these formulations to a greater extent than did polysorbate 80. (EX1011, 10, 20-21; EX2082, ¶137.) Using hindsight, however, InnoPharma focuses on Octoxynol 9, relying on broad patent scrivener language that groups Octoxynol 9

with Octoxynol 12, Octoxynol 13 and Octoxynol 40. (EX2082, ¶137.) Yet Fu provides no data for Octoxynol 9, and thus there would have been no reason to choose Octoxynol 9 over any of Octoxynols 12, 13 or 40. (EX2082, ¶137); *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).

From Octoxynol 9, InnoPharma jumps to tyloxapol, even though tyloxapol is not disclosed in Fu. InnoPharma alleges that tyloxapol is in the same broad family as Fu's Octoxynols, and "[s]tructurally, tyloxapol is an oligomeric form of Octoxynol 9 (Triton X-100)." (Pet., 51-52; EX1003, ¶¶34.) InnoPharma is absolutely wrong. Octoxynol 40, Octoxynol 9 and tyloxapol are significantly structurally and functionally different. (EX2105, ¶90; EX2082, ¶140.) As shown below, Tyloxapol is ***not*** an oligomer of Octoxynol 9. (EX2105, ¶¶87-88; EX2082, ¶140.) Tyloxapol contains a repeating substituted phenyl group with a methylene bridge, whereas neither Octoxynol 9 nor Octoxynol 40 contains the methylene bridge, and the substituted phenyl group does not repeat. (EX2105, ¶¶86-87.)



Additionally, Octoxynol 9 and Octoxynol 40 have a single non-polar, linear tail with a single polar head group, the length of which is longer for Octoxynol 40 than for Octoxynol 9. (*Id.*, ¶87.) By contrast, tyloxapol has seven non-polar, short tails, each containing a single polar head group and connected by methylene groups. (*Id.*) Also, Octoxynol 9 and Octoxynol 40 have one hydroxyl group in their single polar head group, whereas tyloxapol has seven. (*Id.*)

A POSA would expect these structural differences to lead to important functional differences in aqueous formulations. Octoxynol 9, Octoxynol 40 and tyloxapol will form micelles at different concentrations, and their micelles will have different solubilizing capabilities. (*Id.*, ¶90.) Each surfactant will also have different three-dimensional structures, impacting their interactions with other species in the complex, highly sensitive milieu of ophthalmic solutions. (*Id.*, ¶91.)

Indeed, the methylene bridging group unique to tyloxapol generates hydroperoxides that would contribute to bromfenac's oxidation. (*Id.*, ¶71.)

Ethoxylated octylphenols effectively constitute an infinite class of compounds. (EX2082, ¶84.) Given the above-elucidated structural and functional differences, a POSA would not have traveled InnoPharma's contorted path from Octoxynol 40 to Octoxynol 9 to tyloxapol, which is not even mentioned in Fu. This is particularly the case given that Fu clearly prefers Octoxynol 40, it is the only surfactant for which Fu presents data, and it—not Octoxynol 9—was used in the prior commercialized ketorolac formulation covered by Fu. (EX2059, 1; EX2060, 1.) And, as discussed above, tyloxapol and Octoxynols are nowhere disclosed in the Handbook of Pharmaceutical Excipients (EX2114, 247:25-249:23; EX2140, 188:9-189:6), further undermining InnoPharma's argument that it allegedly would have been obvious to look to these excipients for use in an ophthalmic formulation as of 2003. *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.

Recognizing these fatal deficiencies in its argument, InnoPharma further cites Ali (EX1052), contending that tyloxapol and Octoxynol 9 have been used

interchangeably "in manufacturing ophthalmic preparations." (EX1003, ¶64.) InnoPharma misrepresents the teachings of Ali. Ali actually teaches that tyloxapol and Octoxynol 9 can be used as surfactants for milling raw crystal materials to keep them suspended. (EX1052, 2:1-20; EX2082, ¶139.) Ali has nothing to do with using surfactants to chemically stabilize a formulation and accordingly fails to support InnoPharma's flawed swapping theory. (EX2082, ¶139.)

3. InnoPharma has failed to prove unpatentability of claims 6, 15-17 and 20-22, requiring about 0.02 w/v % tyloxapol

Each of claims 6, 15-17 and 20-22 requires bromfenac sodium salt and about 0.02 w/v % tyloxapol. Claims 17 and 20-22 also require BAC. InnoPharma argues that the combination of Ogawa, Sallmann and Fu renders these claims obvious (Pet., 44), proposing to substitute polysorbate 80 in Ogawa Example 6 with tyloxapol from Sallmann's Example 2, present at the much higher concentration of 0.1 w/v%. InnoPharma argues that a POSA would have been motivated to lower the amount of tyloxapol to 0.02 w/v% based on Fu's use of 0.02% Octoxynol 40 in a solution containing the NSAID ketorolac and BAC. InnoPharma is wrong.

As discussed above, Octoxynol 40 and tyloxapol are entirely different compounds. Moreover, Fu never mentions tyloxapol and it is only alleged to belong to an enormous class of surfactants that includes the structurally dissimilar Octoxynol 40. (EX2082, ¶136) Indeed, InnoPharma has identified no prior art

reference disclosing any formulation containing 0.02 w/v% tyloxapol, and InnoPharma thus has wholly failed to prove obviousness of claims 6, 15-17 and 20-22 of the '431 patent.

Undeterred, InnoPharma argues that it allegedly would have been obvious to optimize the amount of tyloxapol to meet these claims. InnoPharma again is wrong. 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, it would not have been obvious to optimize tyloxapol to the amount recited in claims 6, 15-17 and 20-22, for tyloxapol was not an art-recognized result-effective variable, and tyloxapol was unexpectedly superior in chemically stabilizing bromfenac against degradation as compared with polysorbate 80.

First, tyloxapol was not an art-recognized variable for chemically stabilizing any NSAID. (EX2082, ¶160.) Not a single reference of record describes the use of tyloxapol as a stabilizer in an aqueous liquid preparation containing an NSAID. (*Id.*, ¶111.) Sallmann describes tyloxapol as a solubilizer, not as a stabilizer. (EX1009, 4:52-67; EX2082, ¶119.) 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, ¶123.) 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, ¶162.)

Second, tyloxapol has demonstrated an unexpected superiority over polysorbate 80 in chemically stabilizing bromfenac, particularly at the lower amount of 0.02%, which was completely counterintuitive and remarkably unexpected. (*See infra* Section VIII.A; EX1001, 2:34-39, Tables 1-2; EX2082, ¶¶163-73.) Though the claims of the '431 patent do not recite the term "stable," a proper obviousness assessment of a composition claim requires consideration of the subject matter as whole, which goes beyond the claim's literal words and includes the properties disclosed in the specification. *Antonie*, 559 F.2d at 619. Indeed, a composition and its properties are inseparable. *In re Papesch*, 315 F.2d 381, 392 (C.C.P.A. 1963).

Fu teaches physical stability of a solution of ketorolac and BAC with a vastly different surfactant than tyloxapol. (EX1011, 10, 20-21; EX2082, ¶132.) Moreover, there is no evidence in the record that bromfenac and BAC interact and form a precipitate, which Dr. Laskar conceded. (EX2082, ¶132; EX2114, 45:18-46:4.) Nor is there any evidence in Fu that ketorolac degrades, let alone by oxidation. (EX2082, ¶146.) A POSA therefore would not have looked to Fu's amount of Octoxynol 40, used in physically stabilized ketorolac/BAC formulations, and expected it to work to chemically stabilize bromfenac from oxidation. (*Id.*); *Cadence*, 780 F.3d at 1375 (a proposed solution that does not address the problem disclosed in the art is not obvious).

Although InnoPharma relies on Octoxynol 9 to bridge to tyloxapol, no amounts are provided in Fu for Octoxynol 9. (EX2082, ¶145.) InnoPharma then drops Octoxynol 9 and points instead to amounts of Octoxynol 40. (Pet., 44.) But the structural and physical differences are even greater between Octoxynol 40 and tyloxapol. (EX2105, ¶92.) Their critical micelle concentrations are so disparate that a POSA would not have expected that concentration amounts of Octoxynol 40 would have translated to tyloxapol. (EX2082, ¶145.) Additionally, from the structurally different NSAIDs to the diverse excipient packages used by Fu and Ogawa, a POSA would have realized that their formulations contain different ions

in solution capable of interacting so that the amounts of Octoxynol 40 in Fu would not have translated to tyloxapol with bromfenac. (EX2082, ¶146.)

Moreover, the amounts of tyloxapol used in the art are for solubilizing, not stabilizing, and, importantly, are all much higher than 0.02 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 five times as much tyloxapol at 0.1 w/v%. (EX1009, 8:1-15; EX2082, ¶148.) Five of Sallmann's six eye drop formulations that contain tyloxapol use 0.1 w/v%. (EX1009, Examples 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, ¶148.)

Similarly, Yasueda teaches the use of 25 to 400 times more tyloxapol than the 0.02 w/v% claimed in the '431 patent. (EX2082, ¶149.) 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

(Tables 4 and 5) consistently use 4.0 g of tyloxapol (4.0%), 200 times greater than 0.02 w/v%. (EX1012, Tables 4 & 5; EX2082, ¶149.)

In sum, a POSA would not have been led to optimize the teachings of Ogawa or Sallmann in view of Fu to use 0.02 w/v% tyloxapol. Tyloxapol is not an art-recognized result-effective variable, and it unexpectedly chemically stabilized bromfenac better than polysorbate 80. Moreover, the art taught using significantly higher amounts of tyloxapol than 0.02 w/v%, and in fact, as discussed above, InnoPharma argues that the art taught using 0.1 w/v%. (EX2082, ¶148); *In re Antonie*, 559 F.2d at 620; *Ex parte Whalen*, at 14. For these reasons, InnoPharma has failed to prove obviousness of claims 6, 15-17 and 20-22.

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 '431 patent is at least the use of tyloxapol with bromfenac. (EX2082, ¶151.) Another unique aspect differing from the prior art is the use of 0.02 w/v% tyloxapol with bromfenac. (EX1001, claims 6, 15-17, 20-22; EX2082, ¶151.) 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., 51; EX1003, ¶95; EX2082, ¶154.) 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, ¶52; EX2082, ¶154.) 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, ¶154.)

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, ¶155.) 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, ¶156-57.) Because only the surfactant was varied in these experiments, they constitute proper head-to-head comparisons. (EX2082, ¶155.)

At a higher pH, the difference in chemical stabilization between the surfactants becomes smaller and less observable. (EX2082, ¶158.) 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, ¶158.) Dr. Williams opines on other comparisons that manifest tyloxapol's unexpectedly superior chemical stabilization at these milder pH conditions. (EX2082, ¶¶167-71.)

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. (Paper No. 15, 12:17-21; EX1003, ¶¶38, 56.) The art

describes tyloxapol only as a solubilizer, which says nothing about whether it would chemically stabilize bromfenac. (EX2082, ¶160.) Ogawa ascribes no role to polysorbate 80, and its data confirm that polysorbate 80 certainly does not stabilize bromfenac. (EX2082, ¶160; 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, ¶160.)

InnoPharma cites Fu and Yasueda and argues otherwise. (Pet., 33.) InnoPharma is wrong. Fu is directly 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, ¶161.) InnoPharma argues that Yasueda teaches that tyloxapol solubilizes pranlukast better than polysorbate 80 and would be expected to be a better stabilizer. (Pet., 33.) Although a surfactant's ability to solubilize says nothing about how it will chemically stabilize, Yasueda's Table 1 clearly teaches that polysorbate 80 (719.6 μg/ml) solubilizes pranlukast better than tyloxapol (551.0 μg/ml). (EX1012, Table 1; EX2082, ¶162.)

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, ¶163.) 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, ¶164.) 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 did 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.*, ¶165.) 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.*, ¶¶160, 165); *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, ¶52) and confirmed by Dr. Williams (EX2082, ¶151 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.*, ¶¶164-65.) 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, ¶166.)

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, ¶167.) 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, ¶¶167-68.)

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%

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, ¶165.) 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. Even Dr. Laskar has recognized as much. (EX2114, 238:19-25 (a formulator would want to use "the minimum number [of] excipients and the minimum amount of those excipients to accomplish the goal for that particular formulation.").)

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, ¶169.) 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, ¶169.)

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 '431 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, ¶¶170-71); *Cadence*, 780 F.3d at 1375; *In re Papesch*, 315 F.2d at 392 (a composition and its properties are inseparable).

InnoPharma argues that Senju allegedly has not demonstrated unexpected superior results over the full pH range. (Pet., 52-53.) 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, ¶172.) 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 wrongly argues that Senju has not shown unexpected results over the entire range of BAC homologues claimed. (EX1003, ¶¶103-04.) A POSA would not have expected that BAC would affect bromfenac's chemical stability. (EX2082, ¶173.) Even Dr. Laskar agrees, confirming that BAC would not have been expected to affect its chemical stability. (EX1003, ¶52; EX2082, ¶173.)

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, ¶174.) 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, ¶171.) 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, ¶¶175-75.)

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, ¶176.) 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 alleges that the surfactants are interchangeable and expected to behave similarly, but also because tyloxapol so convincingly outperformed polysorbate 80 at substantially lesser amounts, a significant benefit by any metric. (*Id.*, ¶177.) Even Dr. Laskar would agree, having testified that formulators want "the minimum amount of those excipients to accomplish the goal for that particular formulation." (EX2114, 238:19-25.) More than a mere difference in degree, these results meaningfully contribute to the claimed compositions [redacted]

B. Additional compelling objective evidence of patentability

The unexpected stabilization benefits of tyloxapol translated into unexpected medical benefits in the commercial product Prolensa®. Prolensa®, which contains

0.07 w/v% bromfenac [redacted] (EX2082, ¶¶152, 178.) 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, ¶178.) [redacted]

Both the reduction in pH [redacted] eliminated the burning and stinging present with all other approved NSAID ophthalmic eye drops besides Prolensa®. (EX2082, ¶179; EX2116, ¶41.) Each of Ocufen® (1986), Profenal® (1988), Voltaren® (1991), Acular® (1992), Acular® PF (1997), Bronuck in Japan (non-prior art), and Xibrom® and Bromday® (non-prior art) are limited by their burning and stinging side effects. (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 and risk development of CME, a serious complication involving retinal swelling and reduced vision. (EX2116, ¶36.)

Prolensa® represented a new therapy for effectively and comfortably treating postoperative inflammation and pain after cataract surgery without burning or

stinging. (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, ¶¶39, 41-42, 51.) 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). It was also was unexpected given that Prolensa® contains BAC, taught in the art as toxic to eye cells and taught away from in ophthalmic formulations. *Allergan*, 796 F.3d at 1305 (BAC called a "natural born killer" and "from Satan"); (EX2114, 78:13-25, 79: 13-23 (Dr. Laskar characterizing BAC as a "killer"); 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, ¶176); *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 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, ¶125.)

With these attributes, Prolensa® has achieved substantial marketplace success. (EX2130, ¶¶62, 132.) 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, ¶¶73-75, 133.) Prolensa® has achieved one of the highest shares of prescriptions and revenue among branded

drugs with similar indications. (EX2130, ¶72.) Prolensa®'s commercial success is attributable to tyloxapol's stabilizing effect on bromfenac. (EX2130, ¶¶85, 135.)

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, ¶181.) [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 '431 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 '431 patent in district court. (EX2130, ¶¶78-80; EX2019; EX2017; EX2018.) But each licensed the patent and took a consent judgment and injunction, importantly tying their acknowledgement of the '431 patent's validity to their generic versions of Prolensa®. (EX2130, ¶¶78-80; EX2024; EX2122; EX2123.) *See Institut Pasteur v. Focarino*, 738 F.3d 1337, 1347 (Fed. Cir. 2013) (licensing activities provide probative and cogent evidence). Accordingly, these compelling objective indicia support the non-obviousness of all the challenged claims of the '431 patent.

IX. Conclusion

InnoPharma's petition should be denied for at least: (i) failing to prove that a POSA would have made any combination of Ogawa, Sallmann and Fu with any reasonable expectation of arriving at the claimed subject matter; (ii) failing to prove the obviousness of a formulation containing 0.02 w/v% tyloxapol, as recited in claims 6, 15-17 and 20-22; 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 (BOARD AND PARTIES ONLY)** was filed on PRPS and served on December 28, 2015, via email directed to the following counsel of record for the Petitioner. At the time of the filing, Jitendra Malik and Hidetada James Abe were the only counsel that executed an Acknowledgment Form of the Proposed Stipulated Protective Order.

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The undersigned hereby certifies that a copy of the foregoing re-designated **Patent Owner's Response** was served on July 29, 2016, via email directed to counsel of record for the Petitioner at the following:

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