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

DECLARATION OF ROBERT O. WILLIAMS, III, PH.D.

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I, Robert O. Williams, III, Ph.D., under penalty of perjury, declare as follows:

I. INTRODUCTION

1. I have been retained by Finnegan, Henderson, Farabow, Garrett & Dunner, LLP on behalf of Senju Pharmaceutical, Co., Ltd. in connection with two *inter partes* review ("IPR") proceedings (IPR2015-00903 and IPR2015-00902) before the United States Patent and Trademark Office ("PTO") Patent Trial and Appeal Board ("Board") as an expert in the field of the design, evaluation, and formulation of drug products. My qualifications in these areas, as well as other areas, are established below and by my *curriculum vitae*, which is attached as EX2115.

II. BACKGROUND AND QUALIFICATIONS

2. I am currently the Johnson & Johnson Centennial Chair of Pharmaceutics at the University of Texas at Austin College of Pharmacy in Austin, Texas, where I have been teaching and conducting research for twenty years. Also, I am the Division Head of Pharmaceutics.

3. I received a B.S. degree in biology from Texas A&M University in 1979, a B.S. degree in pharmacy from the University of Texas at Austin in 1981, and a Ph.D. degree in pharmaceutics from the University of Texas at Austin in 1986. I am a licensed pharmacist.

4. I have extensive experience and expertise in pharmaceutical formulation and the use of excipients in formulating various types of drug dosage forms, including aqueous liquid preparations. I have experience with ophthalmic dosage forms including solutions. I am an expert in the field of pharmaceutical development, and I have worked almost exclusively in the field of pharmaceutical development since 1986.

5. Prior to becoming a professor, I worked in the pharmaceutical industry for several companies including Rhone-Poulenc Rorer Pharmaceuticals, Duramed Pharmaceuticals and Eli Lilly and Company. Additionally, from 1996 to 2007 I was co-founder and President of PharmaForm, a contract pharmaceutical laboratory, and from 2007 to mid-2010 I was a director of Akela Pharma. I was the Chief Scientist from 2009 to 2013 and founder of Enavail, a particle engineering contract services company. Accordingly, I have relevant industry experience in addition to my academic qualifications.

6. My current research focuses on the development, formulation, optimization and delivery of drugs by a variety of technologies, including aqueous liquid preparations. I have extensive research experience and have authored numerous publications in this area.

7. I have authored or co-authored over 400 published papers, abstracts and book chapters related to my work in the pharmaceutical sciences. A

significant number of my papers are directed specifically to pharmaceutical formulation techniques and drug dosage forms. I have co-edited two books on the subject of pharmaceutical formulation and drug delivery. I am a co-inventor on over 35 patents and/or patent applications that deal with drug formulation technology.

8. Over the course of my career, I have earned numerous prestigious professional awards and honors, which are described on my curriculum vitae. For example, I was elected as a fellow to the American Association of Pharmaceutical Scientists and the American Institute of Medical and Biological Engineering. I have also received the William J. Sheffield Outstanding Alumnus Award and was named a Dean's Fellow at the University of Texas at Austin College of Pharmacy.

9. I am currently the Editor-in-Chief for *AAPS PharmSciTech,* a joint publication of the American Association of Pharmaceutical Scientists and Springer Publishing. I was the Editor-in-Chief for *Drug Development and Industrial Pharmacy* (an Informa Healthcare publication) from 2000 to 2014. I am a member of the Editorial Advisory Board for *The Open Drug Delivery Journal.* I also have served or currently serve as a reviewer for many scientific journals, including *International Journal of Pharmaceutics*, *Pharmaceutical Research*, *European Journal of Pharmaceutics and Biopharmaceutics*, *Journal of the Controlled Release Society*, *Drug Delivery Science and Technology*, *Pharmaceutical*

Development and Technology, *International Journal of Pharmaceutical Compounding*, *Journal of Membrane Science*, *AAPS PharmSciTech*, *Journal of Pharmaceutical Sciences*, *Journal of Pharmaceutical and Biomedical Analysis* and *Toxicology Letters*.

10. In addition to my research and teaching duties at the University of Texas at Austin, I have consulted for pharmaceutical, chemical and biotechnology companies. I have consulted for both innovator pharmaceutical companies and generic pharmaceutical companies. Most of these consulting activities have dealt specifically with drug formulation issues.

11. On the basis of my education and the experience described above, I believe I am qualified to give the opinion set out herein.

III. INFORMATION CONSIDERED

12. The opinions expressed in this declaration are based on my review of, among other materials, U.S. Patent No. 8,129,431 ("the '431 patent"), the "Petition for *Inter Partes* Review of U.S. Patent No. 8,129,431" ("Petition") and the declarations of Dr. Paul A. Laskar (EX1003), Stephen G. Davies, Ph.D. (EX2105), and Shirou Sawa (EX2098). I also based my opinions on my professional and academic experience in the area of pharmaceutical formulation. I reserve the right to testify about these materials and experience. As I discuss below, I disagree with

Dr. Laskar's conclusions that the subject matter of the claims of the '431 patent would have been obvious.

IV. LEGAL PRINCIPLES

13. I understand that an obviousness analysis involves a review of the scope and content of the prior art, the differences between the prior art and the claims at issue, the level of ordinary skill in the art, and objective indicia of non-obviousness, such as unexpected superior results, copying and commercial success. I understand that for an invention to be regarded as obvious, a person of ordinary skill in the art must have had a reason to modify the prior art or to combine one or more prior art references in a manner that would result in the claimed subject matter with a reasonable expectation of success.

V. THE '431 PATENT

A. Specification and Claims

14. I understand that InnoPharma has challenged claims 1-22 of the '431 patent, EX1001, in this action. I further understand that the '431 patent has a priority date of January 21, 2003.

15. The '431 patent is directed, generally speaking, to aqueous liquid preparations consisting essentially of the non-steroidal anti-inflammatory drug ("NSAID") 2-amino-3-(4-bromobenzoyl)phenylacetic acid ("bromfenac") or its

pharmacologically acceptable salt or hydrate thereof and the non-ionic surfactant tyloxapol. (EX1001.)

16. The '431 patent specification states that "the inventors of the present invention have found that, by adding, for example, [tyloxapol] to an aqueous liquid preparation of [bromfenac], the aqueous solution becomes stable within a pH range giving no irritation to eyes, and change of the [bromfenac] over time can be inhibited, and furthermore, when the aqueous solution contains a preservative, deterioration in the preservative effect of said preservative can be inhibited for a long period of time." (EX1001 at 2:34-47.) This passage's statement that the "change of the [bromfenac] over time can be inhibited" refers to the ability of tyloxapol to stabilize bromfenac from chemical degradation, which Experimental Examples 1-2 and Tables 1-2 of the '431 patent confirm with experimental proof. Similarly, this passage's statement that "deterioration in the preservative effect . . . can be inhibited" refers to the ability of tyloxapol to control and stabilize a bromfenac formulation's microbial growth, which Experimental Example 3 and Tables 3-1 to 3-3 confirm with experimental proof.

17. Thus, the '431 patent specification describes aqueous solutions containing bromfenac and tyloxapol that are chemically stable, with controlled microbial growth, are safe and non-irritating to the eye, and are efficacious and suitable for ophthalmic administration.

18. The '431 patent claims are directed, generally speaking, to aqueous ophthalmic preparations consisting essentially of bromfenac and tyloxapol. (EX1001 at 11:65-14:22.) The '431 patent has two independent claims (claims 1 and 18) and 20 dependent claims. (*Id.*)

19. Generally speaking, independent claim 1 of the '431 patent is directed to an aqueous liquid preparation consisting essentially of bromfenac and tyloxapol, formulated for ophthalmic administration, and when a quaternary ammonium compound is present, it is benzalkonium chloride ("BAC"). (EX1001 at 11:66-12:9.)

20. Generally speaking, dependent claim 2 of the '431 patent is directed to the aqueous liquid preparation of claim 1, wherein the first component is a bromfenac sodium salt. (EX1001 at 12:10-12.)

21. Generally speaking, dependent claim 3 of the '431 patent is directed to the aqueous liquid preparation of claim 1, wherein the second component is tyloxapol and the pharmacologically acceptable salt of bromfenac is a sodium salt, the concentration of tyloxapol is from about 0.01 w/v % to about 0.5 w/v %, the first component is a bromfenac sodium salt, and the concentration of the bromfenac sodium salt is from about 0.01 w/v % to about 0.5 w/v %. (EX1001 at 12:13-23.)

22. Generally speaking, dependent claim 4 of the '431 patent is directed to the aqueous liquid preparation of claim 3, wherein the concentration of tyloxapol is from about 0.01 w/v % to about 0.3 w/v % and the concentration of the bromfenac sodium salt is from about 0.05 to about 0.2 w/v %. (EX1001 at 12:24-28.)

23. Generally speaking, dependent claim 5 of the '431 patent is directed to the aqueous liquid preparation of claim 4, wherein the concentration of bromfenac sodium salt is about 0.1 w/v %. (EX1001 at 12:29-33.)

24. Generally speaking, dependent claim 6 of the '431 patent is directed to the aqueous liquid preparation of claim 4, wherein the concentration of tyloxapol is about 0.02 w/v %. (EX1001 at 12:32-34.)

25. Generally speaking, dependent claim 7 of the '431 patent is directed to the aqueous liquid preparation of claim 1, wherein the formulation further includes one or more additives selected from the group consisting of a preservative, buffer, thickener, stabilizer, chelating agent, and pH controlling agent. (EX1001 at 12:35-39.)

26. Generally speaking, dependent claim 8 of the '431 patent is directed to the aqueous liquid preparation of claim 7, wherein the preservative is BAC, the buffer is boric acid and/or sodium borate, the thickener is polyvinylpyrrolidone

("PVP"), the stabilizer is sodium sulfite, the chelating agent is sodium edetate, and the pH controlling agent is sodium hydroxide. (EX1001 at 12:40-46.)

27. Generally speaking, dependent claim 9 of the '431 patent is directed to the aqueous liquid preparation of claim 8, wherein the pH is from about 7 to about 9. (EX1001 at 12:47-48.)

28. Generally speaking, dependent claim 10 of the '431 patent is directed to the aqueous liquid preparation of claim 8, wherein the pH is from about 7.5 to about 8.5. (EX1001 at 12:49-50.)

29. Generally speaking, dependent claim 11 of the '431 patent is directed to the aqueous liquid preparation of claim 4, where the concentration of bromfenac sodium salt is 0.2 w/v %. (EX1001 at 12:51-53.)

30. Generally speaking, dependent claim 12 of the '431 patent is directed to the aqueous liquid preparation of claim 4, where the concentration of tyloxapol is about 0.3 w/v %. (EX1001 at 12:54-55.)

31. Generally speaking, dependent claim 13 of the '431 patent is directed to the aqueous liquid preparation of claim 12, wherein the formulation further includes one or more additives selected from the group consisting of a preservative, buffer, thickener, stabilizer, chelating agent, and pH controlling agent. (EX1001 at 12:56-60.)

32. Generally speaking, dependent claim 14 of the '431 patent is directed to the aqueous liquid preparation of claim 13, wherein said preservative is BAC, said buffer is boric acid and/or sodium borate, said thickener is PVP, said stabilizer is sodium sulfite, said chelating agent is sodium edetate, and said pH controlling agent is sodium hydroxide. (EX1001 at 12:61-67.)

33. Generally speaking, dependent claim 15 of the '431 patent is directed to the aqueous liquid preparation of claim 11, wherein the concentration of tyloxapol is about 0.02 w/v %. (EX1001 at 13:1-3.)

34. Generally speaking, dependent claim 16 of the '431 patent is directed to the aqueous liquid preparation of claim 15, wherein the formulation further includes one or more additives selected from the group consisting of a preservative, buffer, thickener, stabilizer, chelating agent, and pH controlling agent. (EX1001 at 13:4-8.)

35. Generally speaking, dependent claim 17 of the '431 patent is directed to the aqueous liquid preparation of claim 16, wherein said preservative is BAC, said buffer is boric acid and/or sodium borate, said thickener is PVP, said stabilizer is sodium sulfite, said chelating agent is sodium edetate, and said pH controlling agent is sodium hydroxide. (EX1001 at 13:9-14.)

36. Generally speaking, independent claim 18 of the '431 patent is directed to an aqueous liquid preparation consisting essentially of bromfenac,

tyloxapol, boric acid, sodium tetraborate, EDTA sodium salt, BAC, PVP, and sodium sulfite, formulated for ophthalmic administration, wherein BAC is the only quaternary ammonium compound included. (EX1001 at 13:15-14:9.)

37. Generally speaking, dependent claim 19 of the '431 patent is directed to the aqueous liquid preparation of claim 18, wherein (a) is a bromfenac sodium salt. (EX1001 at 14:10-12.)

38. Generally speaking, dependent claim 20 of the '431 patent is directed to the aqueous liquid preparation of claim 19, where the concentration of bromfenac sodium salt is from about 0.01 to about 0.5% and the concentration of tyloxapol is about 0.02 w/v%. (EX1001 at 14:13-16.)

39. Generally speaking, dependent claim 21 of the '431 patent is directed to the aqueous liquid preparation of claim 20, wherein the concentration of bromfenac sodium salt is about 0.01 w/v %. (EX1001 at 14:17-19.)

40. Generally speaking, dependent claim 22 of the '431 patent is directed to the aqueous liquid preparation of claim 20, wherein the concentration of bromfenac sodium salt is about 0.1 w/v %. (EX1001 at 14:20-22.)

B. Person of Ordinary Skill in the Art

41. As of January 21, 2003, a person of ordinary skill in the art of the '431 patent would have at least a Bachelor's degree in fields such as pharmaceutical chemistry, chemistry, or a related discipline with about three to

five years of work experience in this area, or a comparable level of education and training.

42. I agree with Dr. Laskar that a person of ordinary skill in the art as of January 21, 2003 would have been "think[ing] along conventional wisdom in the art," thereby pursuing clear and objectively rational leads in the prior art, rather than arbitrary pathways not tethered to the realities of rational drug discovery at the time of invention. (EX1003 at ¶ 18.) A person of ordinary skill in the art would have pursued these rational leads to develop pharmaceutical products balancing efficacy, safety and stability.

VI. SUMMARY OF OPINIONS

43. I understand that the Board has granted InnoPharma's petition to institute this IPR regarding the purported obviousness of claims 1-22 of the '431 patent on the following grounds:

Ground 1: Obviousness of claims 1-5, 7-14, and 18-19 over U.S. Patent No. 4,910,225 ("Ogawa") (EX1004) and U.S. Patent No. 6,107,343 ("Sallmann") (EX1009)

Ground 2: Obviousness of claims 6, 15-17, and 20-22 over Ogawa, Sallmann, and Australian Patent No. AU-B-22042/88 ("Fu") (EX1011)

44. As discussed further below, Ogawa taught the use of water soluble polymer and a sulfite, particularly sodium sulfite, a well-known antioxidant

(EX2014 at 3:41-55), to chemically stabilize bromfenac from degradation. (EX1004 at Exp. Ex. 6.) From this, a person of ordinary skill in the art would have readily understood that oxidation caused bromfenac's degradation. (EX1021 at 5.) A person of ordinary skill in the art would neither have combined the teachings of Sallmann or Fu with those of Ogawa, nor have reasonably expected the teachings of Sallmann or Fu to remedy bromfenac's oxidative degradation problem.

45. This is at least because Ogawa, Sallmann, and Fu relate to different active ingredients and provide solutions to entirely unrelated problems: Ogawa involves the chemical stability of bromfenac,[1] whereas Fu involves the physical stability of ketorolac formulations, and Sallmann is directed to establishing that diclofenac potassium is more effective therapeutically than diclofenac sodium. As such, a person of ordinary skill in the art would not have looked to Sallmann or Fu to solve bromfenac's oxidative degradation.

[1] To a person of ordinary skill in the art, chemical stability looks to whether a formulation's active ingredient does not change (*i.e.*, degrade) within acceptable limits over a period of time. Physical stability, by contrast, looks to whether the formulation's appearance (*i.e.*, clarity or turbidity) changes within acceptable limits over time.

46. Specifically, Sallmann is directed to formulations of diclofenac potassium, a structurally dissimilar NSAID from bromfenac, and contains no teaching that diclofenac is susceptible to chemical degradation. (EX1009.) Similarly, Fu contains no teaching that its NSAID, ketorolac (also structurally dissimilar to bromfenac), is susceptible to chemical degradation. (EX1011.) Instead, Fu is directed to physically stabilizing formulations of ketorolac and benzalkonium chloride (BAC) by preventing the formation of a precipitate. (EX1011 at, *e.g.*, 14:16-32, 15:12-17:20, 18:8-19:27.) There is no teaching in Ogawa of the formation of any similar precipitate. Ogawa only teaches the formation of a red insoluble oxidative degradation product—clearly not the precipitant salt of an NSAID and BAC. (EX1004 at Exp. Exs. 4-6.) [redacted]

47. Thus, objectively viewing the art, a person of ordinary skill in the art would not have been motivated to selectively pick solubilizers from Sallmann or Fu to solve bromfenac's oxidative degradation, when those solubilizers were used for a completely unrelated purpose. Furthermore, a person of ordinary skill in the art would not have expected that the solubilizers taught in Sallmann and Fu would have prevented or impeded bromfenac's oxidation. As their names suggest,

solubilizers typically solubilize poorly-soluble drugs, whereas antioxidants are used to prevent oxidative degradation of drugs. Even Dr. Lawrence, who serves as InnoPharma's expert in the district court litigation involving the '431 patent as well as Lupin's expert in IPR2015-01099, has testified that solubility and stability are "not synonymous at all." (EX2140 at 43:22-44:12.) Moreover, a person of ordinary skill in the art would have understood that surfactants like polysorbate 80 and tyloxapol would both cause degradation of bromfenac through generation of hydroperoxides and would not have been inclined to switch them, particularly when Ogawa touted its formulations' stability as excellent. (EX2105 at ¶ 72.)

48. A person of ordinary skill in the art, moreover, would also have not simply substituted Ogawa's polysorbate 80 for Sallmann's tyloxapol merely because both are nonionic surfactants. Indeed, even among polysorbates, there are significant differences in properties. (*Id.* at ¶ 81.) Polysorbate 80 and tyloxapol are vastly structurally dissimilar with correspondingly different chemical and physical properties, such that a person of ordinary skill in the art would not consider them so readily interchangeable (*id.* at ¶¶ 79-84), particularly in complex and highly sensitive ophthalmic formulations where seemingly insignificant changes in the formulation's components could affect substantial changes in its properties.

49. In that regard, Ogawa touts its bromfenac formulations as having excellent chemical stability. (EX1004 at 10:49-57.) A person of ordinary skill in the art exercising common sense would not have blindly substituted polysorbate 80 with tyloxapol without considering how it might impact the chemical stability of Ogawa's formulations. None of the art of record suggests using tyloxapol to chemically stabilize an NSAID in an aqueous formulation. And in Ogawa, polysorbate 80 does not function as a stabilizer for bromfenac. (*Id.* at 8:3-9:7; EX2095 at Exp. Exs. 4-6.) That role belongs to PVP and sodium sulfite. (*Id.* at 3:48-62.) Rather than substitute polysorbate 80 with tyloxapol, a person of ordinary skill in the art exercising common sense and engaging in rational drug discovery would have more likely pursued improvements to PVP or sodium sulfite.

50. Additionally, a person of ordinary skill in the art would not have been motivated to substitute Sallmann's diclofenac potassium for Ogawa's bromfenac, for doing so would have been contrary to the entire purpose of the Sallmann patent, *i.e.*, the use of diclofenac potassium. Additionally, Sallmann's use of cyclodextrins (EX1009 at Ex. 2), which were known to complex aryl groups present in bromfenac (EX2105 at ¶ 96), could negatively impact chemical stability, and therefore run afoul of the "consisting essentially of" language in the '431 patent claims. I have been informed and understand that this phrase as it is used in a patent claim means that the claim encompasses the recited elements and only

those non-recited elements that do not materially affect the basic and novel properties of the claimed composition. As such, any non-recited element that materially affects the basic and novel properties of the composition is excluded from the claim's scope.

51. It was completely unexpected that tyloxapol would stabilize bromfenac against chemical degradation. It was similarly unexpected, as discussed below, that it would do so in such a convincing manner compared to Ogawa's polysorbate 80. Tyloxapol's unexpected stabilization benefits translated into similarly unexpected benefits seen in the commercialized product Prolensa®, an ophthalmic bromfenac (0.07%) solution covered by certain claims of the '431 patent. This stabilization benefit permitted formulating Prolensa® at pH 7.8, a comfortable and less irritating pH that is close to that of natural tears (EX2088 at ¶ 66b; [redacted]), that led to enhanced ocular penetration and, without a reduction in efficacy, allowed lowering of the amount of bromfenac from 0.09% to 0.07%, which meant less drug contacting surgically compromised ocular tissue. (EX2030; EX2026; EX2027.) With these new benefits, Prolensa® garnered significant acclaim in the medical community. (EX2113 at 965; EX2118 at 31; EX2119 at 929.) Furthermore, it was marketed and commercialized, despite the availability of generic bromfenac formulations (EX2028 at 1), and in fact, InnoPharma and five other generic companies have sought to market exact copies

of Prolensa®, supporting the successful and non-obvious nature of the formulation. (*See infra* at ¶¶ 181-82.) This objective evidence indicates that tyloxapol's unexpectedly superior stabilizing effect constitutes a material and substantial difference more than in degree, producing a more comfortable, less irritating, more efficacious formulation embodied in Prolensa®, which further supports and enhances the nonobviousness of the claimed preparations.

VII. THE STATE OF THE ART AS OF JANUARY 21, 2003

52. As of the January 21, 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, because when formulating ophthalmic dosage forms such as the aqueous liquid preparations of the '431 patent, stability 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 at 989, 1020, 1022.)

53. Notwithstanding these formulation challenges, InnoPharma and Dr. Laskar cite Ogawa, Sallmann and Fu, and advance a simple "swapping" theme, which involves 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. (Petition at 6-9.) InnoPharma and Dr. Laskar's contrived and overly simplistic swapping position is not tethered to the realities of rational drug discovery at the time of invention, but is more indicative of already knowing the solution and working backwards to rationalize it. [redacted] As such, Dr. Laskar's analysis ignores 1) other leads or approaches a person of ordinary skill in the art at the time would have been motivated to and more likely to pursue; 2) the important structural and functional differences among non-ionic surfactants like tyloxapol and polysorbate 80 and ethoxylated octylphenols in Fu; and 3) the important structural and functional differences among NSAIDs like bromfenac and diclofenac and ketorolac in Fu, which Dr. Laskar conceded he did not address in his declaration (*Id.* at 40:13-43:1).

54. As of January 2003, formulation chemistry was not as simple as InnoPharma contends, nor is it today. A person of ordinary skill in the art would

have understood that even a single modification to the components of a formulation can yield substantial changes in its properties. Individual formulation components, whether active or inactive, can interact and affect one another in unpredictable ways, impacting the formulation's efficacy, safety, and stability, including preservative efficacy. Changes to ophthalmic preparations in particular require careful consideration and testing, given the sensitivity of the ocular tissue. Dr. Laskar agrees with me. He has testified that "[f]ormulating ophthalmic drugs is a complex matter . . . because there is a number of factors that need to be considered in coming up with a composition. That is to say, it needs to be – needs to be stable, as comfortable as possible and with its therapeutic activity optimized." (*Id.* at 240:19-241:14.) Furthermore, the Court's decision in the patent infringement case involving the ophthalmic drug Combigan®, discussed above, cites to Dr. Laskar's testimony to support that ophthalmic drug formulation is a "challenging and unpredictable endeavor," that it is "a subset with special requirements and special considerations," and that it is "an art full of complexity and unpredictability." (*Id.* at 241:16-246:2; EX2135 at 989, 1020, 1022.)

55. Indeed, addressing a problem arising with one aspect of the formulation can unexpectedly give rise to multiple other problems, often leading to start overs, failures, frustration, and further experimentation, none of which yields obvious solutions. For example, Dr. Jayne Lawrence recognized the

unpredictability of ophthalmic systems and that simply changing one parameter (*e.g.*, temperature) does not yield predictable results, stating "***without further testing, it is not possible to predict*** whether the data related to the elevated temperature will have any relevance to the lower temperature." (EX2088 at ¶ 143, emphasis added.) Dr. Laskar similarly conceded in his Combigan® trial testimony that there is no reliable way of predicting the influence of a particular salt species on the behavior of the parent compound in a given dosage form. ([redacted]; EX2137 at 123:2-7.) When formulating ophthalmic preparations, what is appropriate for one formulation may not work for another. Each drug or excipient must be considered based on its own properties and its compatibility and stability with other components of the formulation for ophthalmic administration.

56. Thus, simply swapping one surfactant for another, or one NSAID for another, when the art does not provide a basis for doing so, and knowing that these components can have vastly different properties, even within a single class, does not constitute rational drug development. Instead, this simplistic "swapping" theory is only based on knowing the solution and working backwards to chart a path through the art that would not have been apparent to a person of ordinary skill in the art at a time when the solution remained unknown. [redacted]

A. A Person of Ordinary Skill in the Art Would Not Have Pursued Bromfenac Formulations Over Other NSAID Formulations

1. No reason to pursue bromfenac formulations

57. InnoPharma's swapping theory, either swapping tyloxapol in Sallmann's Example 2 for polysorbate 80 in Ogawa's Example 6 or swapping bromfenac in Ogawa's Example 6 for diclofenac in Sallmann's Example 2 (Petition at 6-9), is premised on a person of ordinary skill in the art having had a reason to pursue an ophthalmic bromfenac formulation over other ophthalmic NSAID formulations. Dr. Laskar acknowledges that "[a]s of January 21, 2003, a number of NSAIDs, formulated for ophthalmic use, were FDA-approved and sold in the United States," including diclofenac (Voltaren®), flurbiprofen (Ocufen®), ketorolac (Acular®), and suprofen (Profenal®). (EX1003 at ¶¶ 23-27.)

58. Based on the fact that these ophthalmic NSAID formulations are commercially marketed, and thus are apparently well-performing, a person of ordinary skill in the art would have had no reason or need to focus for further development on a bromfenac commercial formulation to the exclusion of others. Indeed, Innopharma readily admits that there was no need to improve on Ogawa's formulations, stating "[t]o the extent there was ***any*** need for the claimed bromfenac ophthalmic formulation, it was met by the disclosures of Ogawa and Hara." (Petition at 53, emphasis added.) Even Ogawa states that its bromfenac

formulations displayed remarkably enhanced stability. (EX1004 at Exp. Ex. 6.) It is worth noting that none of these formulations contains tyloxapol.

59. Despite his acknowledgement that there was no need to improve Ogawa's formulation, Dr. Laskar argues in his declaration that a person of ordinary skill in the art would have still focused on Ogawa's bromfenac formulations over the other commercial formulations, citing to Hara, *Bromfenac sodium hydrate*, CLINICS & DRUG THERAPY 2000, 19:1014-1015 ("Hara") to assert that it was allegedly known that bromfenac is superior to diclofenac and that the use of diclofenac is allegedly "limited." (EX1003 at ¶¶ 60-61.) As discussed below, however, Hara does not promote bromfenac over diclofenac or otherwise support Dr. Laskar's argument that bromfenac was superior to diclofenac.

60. [redacted] Hara discloses both bromfenac and diclofenac have superior anti-inflammatory activity. (EX1002 at 2 ("Diclofenac sodium . . . shows particular efficacy in preventing the generation of fibrin, with superior anti-inflammatory efficacy.").) Hara teaches both bromfenac and diclofenac as alternatives to corticosteroids to prevent inflammation. (EX1002 at 2 ("Diclofenac sodium … shows particular efficacy in preventing the generation of fibrin, with

superior anti-inflammatory efficacy.").) Hara also mentions that diclofenac had been approved for treating inflammation after cataract surgery (*id.* at 3), and it was also believed to treat outer ocular area inflammation and uveitis of the anterior ocular area, such as iritis. (*Id.* at 2.) Bromfenac was not approved for this indication. (*Id.* at 3.) If anything, Hara discloses bromfenac's superiority over indomethacin. (*Id.* at 2.) While Hara does not report toxicity issues for commercialized diclofenac, it does disclose serious liver toxicity for bromfenac, including cases of death, [redacted] In fact, bromfenac's oral form, Duract®, had been pulled from the market for this reason (EX2029 at 1), which would have tended to make a person of ordinary skill in the art shy away from bromfenac.

61. Dr. Laskar also opines that bromfenac had already been shown to have an enhanced anti-inflammatory action when compared to other known NSAIDs. (EX1003 at ¶ 28.) Dr. Laskar relies on a single *in vitro* test result from Table 1 of Yanni to conclude bromfenac was more effective than diclofenac. (EX1033 at Table 1.) But Dr. Laskar ignores that Table 1 also includes *ex vivo* and *in vivo* data, data a person of ordinary skill in the art would have considered more valuable than *in vitro* data. The *in vivo/ex vivo* data do not support Dr. Laskar's conclusion that bromfenac is more effective than diclofenac.

62. In fact, as discussed further below, Yanni actually disparages bromfenac and other acids like it, preferring esters and amides such as nepafenac, which is an NSAID without an acid group. (EX1033 at 1:54-59, 4:24-52.) Yanni warns that benzoylphenylacetic acids like bromfenac require high concentrations to achieve sufficient corneal penetration, and such high drug concentrations are not desirable because they provoke ocular irritation and discomfort. (*Id.* at 1:60-2:1.)

[redacted]

Accordingly, based on Yanni, a person of ordinary skill in the art would not have pursued bromfenac formulations for further development.

2. Design needs or market demands would not have supported the solution that InnoPharma proposes

63. Dr. Laskar's alleged motivation for substituting polysorbate 80 with tyloxapol in Ogawa's formulation is premised on using a solubilizer like tyloxapol to prevent the formation of a "complex" between an NSAID and benzalkonium chloride ("BAC") and preventing its precipitation. (EX1003 at ¶ 70.) [redacted] But if such a

precipitate could have formed, which Dr. Laskar has not established, a person of ordinary skill in the art would have more likely avoided its formation entirely rather than add another excipient to only reduce to some extent the precipitate's formation. The art, in fact, provided a person of ordinary skill in the art many routes for avoiding an NSAID-BAC precipitate.

64. For example, a person of ordinary skill in the art would have used a non-BAC preservative or no preservative to avoid the formation of a precipitate. Such a solution would have been particularly attractive given that market demands before January 2003 were pushing for the elimination of harmful preservatives, like BAC, and the development of either replacements for BAC or preservative-free formulations. (EX2089 at 211 (indicating replacement of cytotoxic BAC with another preservative, SOC, approved by FDA in March 2001); EX2064 at 14-115.) For example, Acular® PF was introduced in 1997 as a preservative-free formulation of Acular®. (EX2060 at 9-13; EX2061 at 1.) [redacted]

65. Dr. Laskar argues that BAC was the preservative of choice. (EX1003 at ¶ 30.) But by January 2003, the demand had already surfaced for preservative-free formulations because of BAC's significant toxicity to the eye, even at low concentrations. (EX2064 at 114-15.) In fact, I am aware that in a recent patent infringement case involving the ophthalmic drug Lumigan®, it was noted that the patent challenger's expert summarized the prior art's widespread concern over the toxicity of BAC by describing BAC as "a natural-born killer" that was "from Satan." (EX2134 at 16, which uses "BAK" instead of "BAC" for benzalkonium chloride.) [redacted]

66. Numerous publications confirm BAC's known toxicity. For example, Debbasch et al., published in 2000, referred to BAC's epithelial toxicity and inflammatory infiltration of ocular surface structures, inducing growth arrest and cell death. (EX2064 at bottom of 114.) Pisella et al., published in 2002, indicated that BAC was cytotoxic to trabecular cells and caused unwanted inflammation in the trabeculum. (EX2080 at 418.) Madhu et al. confirmed that BAC was known to cause ocular irritation. (EX2090 at 417, right column.)

67. By January 2003, ophthalmic researchers were urging a heightened awareness of BAC's harmful effects so that many more preservative-free formulations would be developed:

> Studies have shown strong benefits of unpreserved solutions to the ocular surface. However, very few preservative-free ophthalmic solutions are now available. It is therefore of ***striking importance to become aware of preservative toxicity in order to develop in the near future many more unpreserved drugs***, especially for the long-term use and/or for patients with pre-existing ocular surface disorders.
>
> (EX2064 at 115, emphasis added.)

68. Thus, rather than focus on preventing the formation of an alleged "complex" between an acidic NSAID and BAC, the state of the art and market demands at the time of invention were shifting away from using BAC and were more compellingly incentivizing a person of ordinary skill in the art to either replace BAC or pursue preservative-free ophthalmic formulations. These approaches not only would have eliminated the harmful effects of BAC but also would have completely avoided an acidic NSAID/BAC precipitate instead of just reducing it to some extent.

69. Even Dr. Laskar admits as much, particularly as a way of addressing his acidic NSAID/BAC precipitation issue. Based on Dr. Laskar's declaration, a person of ordinary skill in the art would have more likely used a lauralkonium chloride (LAC) preservative because, as Dr. Laskar readily admits, lauralkonium

chloride preservative does not form an insoluble salt with an NSAID, and there would not have been any stability issues associated with an alleged formation of a bromfenac-BAC precipitate. (EX1003 at ¶ 104.) WO 94/15597 to Wong, upon which Dr. Laskar relies, experimentally confirms that LAC does not form an insoluble precipitate with the NSAID flurbiprofen. (EX1020 at 6:11-7:10.) Furthermore, Dr. Laskar himself, in order to solve the issue of an acidic drug (pemirolast) precipitating with BAC, had previously and successfully used LAC (the C12-BAC homologue) instead of BAC, reinforcing that a person of ordinary skill in the art would have more likely used LAC. (EX1003 at ¶ 14; [redacted].) [redacted] Similarly, Desai teaches using a different polymeric quaternary ammonium preservative compound (POLYQUAD®), which is not BAC, to avoid forming insoluble precipitates. (EX1005 at 1:27-2:31.) [redacted]

70. Furthermore, Dr. Laskar's declaration states that Ogawa is the closest prior art (EX1003 at ¶ 95) and selectively relies on Example 6 of Ogawa, which reported the residue amount of bromfenac as 100.9% after four weeks at 60°C. (*Id.* at ¶ 48, claim charts for claims 1 and 18.) But his declaration ignores Ogawa

Example 7, reporting an equally high residue amount of bromfenac at 99.2%. (EX1004 at Ex. 7 &Table 11.) Ogawa Example 7 does not contain BAC, but instead contains the preservatives methylparaben and ethylparaben. [redacted]

71. [redacted] Dr. Laskar could not have objectively considered how a person of ordinary skill in the art would have solved his proposed problem concerning the interaction of an acidic NSAID with BAC. Consequently, Dr. Laskar ignores his own previous work (EX1003 at ¶ 14; [redacted]) and the work of others (Wong, EX1020) with LAC, which Dr. Laskar admitted would have solved the interaction problem (EX1003 at ¶ 104) while simultaneously eliminating BAC's significant health risks. [redacted]

Dr. Laskar further ignores prior art preservative-free formulations and the substantial work done to commercialize formulations using used well-tolerated preservatives in place of BAC. (EX2064 at 114-15; EX2089 at 211, indicating replacement of cytotoxic BAC with another preservative, SOC, approved by FDA in March 2001.) Then, with respect to Ogawa, Dr. Laskar's "closest prior art," which in fact never mentions that bromfenac had an interaction problem with BAC, Dr. Laskar selectively focuses on Example 6 rather than Example 7, [redacted]

[redacted]

72. Objectively speaking, rather than reducing to some extent the formation of an acidic NSAID/BAC precipitate using a solubilizer, the state of the art and market demands by January 2003 would have more compellingly motivated a person of ordinary skill in the art to pursue non-BAC preservatives or preservative-free ophthalmic formulations to entirely avoid potential precipitation and concurrently eliminate a serious health risk. Along these lines, by January 2003, BAC would not have been the preservative of choice, and a person of ordinary skill in the art exercising common sense would have more likely pursued the other literature-based promising alternatives rather than employ a solubilizer, which is a path divergent from the one the inventors of the '431 patent chose.

73. Furthermore, if a person of ordinary skill in the art would have wanted to maintain the use of BAC, and not have it decrease pharmaceutical activity or have a reduced preservative effect as Dr. Laskar contends (EX1003 at ¶ 31), he/she would have more likely used an ester or a prodrug of bromfenac without a carboxylic acid moiety to avoid the alleged formation of a precipitate. For example, Yanni teaches using bromfenac derivatives without free carboxyl groups, which would not interact with BAC based on Dr. Laskar's theory but are also said to beneficially improve ocular penetration and stability over benzoylphenylacetic acids, like bromfenac. (EX1033 at 1:60-2:29; EX1003 at ¶ 27.)

B. A Person of Ordinary Skill in the Art Would Not Have Considered Different Non-Ionic Surfactants Interchangeable

74. In connection with his combination of Ogawa and Sallmann, Dr. Laskar argues that polysorbate 80 and tyloxapol are interchangeable as surfactants in ophthalmic formulations generally and that a person of ordinary skill in the art would have expected that substituting tyloxapol for polysorbate 80 would predictably solubilize bromfenac to produce a stable ophthalmic formulation of bromfenac and BAC. (EX1003 at ¶¶ 38, 56.) But Dr. Laskar does not substantiate his opinion and does not account for the vastly different structural and physiochemical properties of these surfactants. (EX2105 at ¶¶ 79-84.) Furthermore, Dr. Lawrence has testified that different nonionic surfactants possess a variety of different physical and chemical properties in aqueous liquid

preparations, based on the hydrophobic and hydrophilic moieties of the surfactant, the concentration and the state of dispersal of the surfactant, pH and temperature of the formulation, and the presence of the active ingredient, excipients and salts within the formulation. (EX2140 at 75:16-76:20.) How a given non-ionic surfactant will perform functionally depends on its unique properties, the desired role for it in a particular formulation, and the other formulation components.

1. No teaching of interchangeability of polysorbate 80 and tyloxapol in aqueous solutions of NSAIDs

75. Dr. Laskar has identified no references supporting the interchangeability of polysorbate 80 and tyloxapol in an aqueous solution of a freely-water soluble drug, like bromfenac sodium, contrary to his contention that "it also was known that polysorbate 80 and tyloxapol were interchangeable in many ophthalmic preparations." (EX1003 at ¶ 38.) As discussed further below, in connection with his interchangeability theory, Dr. Laskar instead relies on references where polysorbate 80 and/or tyloxapol are used as dispersing agents in suspensions and emulsions or as solubilizers for water-insoluble compounds. These references provide a person of ordinary skill in the art no information regarding the interchangeability of polysorbate 80 and tyloxapol in the context of bromfenac sodium solutions, especially given that there is no role ascribed to polysorbate 80 in Ogawa. (EX1004.)

76. Dr. Laskar relies on several references where surfactants are used as dispersing agents in suspensions and emulsions (EX1003 at ¶¶ 38, 56), but these references are irrelevant to aqueous *solutions* of bromfenac sodium, such as those of the '431 patent claims. For example, Dr. Laskar relies on the Aviv reference (EX1003 at ¶ 56), but Aviv is directed to sub-micron emulsions. (EX1026 at abstract.) Emulsions are biphasic systems with immiscible droplets of a discontinuous phase dispersed within a continuous phase. In emulsions like those disclosed in Aviv, non-ionic surfactants are included to physically stabilize and prevent the droplets from coalescing into the two phases, *e.g.*, the continuous phase and the discontinuous phase. (EX1026 at 5.) Aqueous solutions do not have a continuous phase and a discontinuous phase like the emulsions of Aviv. Thus, Aviv, which is directed to the physical stability of sub-micron emulsions, is not applicable to the chemical or physical stability of aqueous solutions.

77. Dr. Laskar's reliance on the Kawabata reference (EX1003 at ¶ 38) is similarly misplaced, because Kawabata teaches the inclusion of surfactants as suspending agents to ensure "uniform microparticulate and satisfactorily dispersed aqueous suspension." (EX1043 at 13:7-15.) Dr. Laskar further relies on Guy (EX1003 at ¶ 37), but Guy is directed to physically stable suspensions of water-insoluble drugs, including the steroid loteprednol. (EX1038 at 2:60-3:9.) Guy tests the ability of various surfactants to physically stabilize these suspensions,

measuring the time to re-suspend, *i.e.*, physical stability. (*Id.* at Table 1 & Table 3.) All of the above references directed to emulsions or suspensions are simply irrelevant to bromfenac solutions and would have given a person of ordinary skill in the art no guidance regarding the interchangeability of polysorbate 80 and tyloxapol in such a solution. [redacted]

78. Indeed, nearly all of the commercial ophthalmic formulations identified by Dr. Laskar as containing tyloxapol, none of which is an NSAID preparation, are water-insoluble steroid suspensions. (EX1003 at ¶ 36.) Azopt® is a brinzolamide (non-NSAID, anhydrase inhibitor) ophthalmic suspension. (EX1035 at 2.) Alrex® is a loteprednol etabonate (steroid) ophthalmic suspension. (EX1039 at 1.) Lotemax® is a loteprednol etabonate ophthalmic suspension. (EX1040 at 1.) Tobradex® is a tobramycin and dexamethasone (steroid) ophthalmic suspension and ointment. (EX1041 at 2.) Alomide® is a lodoxamide tromethamine ophthalmic solution, but lodoxamide tromethamine is a mast-cell stabilizer, not an NSAID. (EX1042 at 2.)

79. Dr. Laskar further relies on several references in which non-ionic surfactants are used to solubilize water-insoluble compounds. (EX1003 at ¶¶ 38, 56.) These references are also irrelevant to aqueous solutions of bromfenac sodium, because bromfenac sodium is freely water soluble (EX2039 at 29;

EX2140 at 156:20-157:6; EX2105 at ¶ 47), and thus does not require the inclusion of a solubilizer. Indeed, Dr. Lawrence stated in a peer-reviewed journal article published in 1994 that "it is no use trying to increase the aqueous solubility of a water-soluble hydrophilic drug in an aqueous-based surfactant system." (EX2139 at 423; EX2140 at 286:4-15.) I agree with Dr. Lawrence that a person of ordinary skill in the art would have had no need to use a solubilizer for bromfenac sodium ophthalmic formulations.

80. Dr. Laskar relies on Bergamini (EX1003 at ¶ 56), but Bergamini teaches the use of various surfactants in high amounts as solubility agents "to keep the Diclofenac and Tobramycin in solution." (EX1019 at 4:24-36.) Dr. Laskar further relies on two Johnson references (EX1003 at ¶ 38) where surfactants are included in high amounts (up to 25%) to solubilize insoluble steroids and physically stabilize steroid solutions. (EX1044 at 3:18-39 & Table 1; EX1045 at 3:18-39 & Table 1.) Guttmann, upon which Dr. Laskar further relies (EX1003 at ¶ 37), is directed to using tyloxapol to solubilize water-insoluble steroids. (EX1010 at 307.) Dr. Laskar additionally relies on Yasueda (EX1003 at ¶ 39), but Yasueda is directed to "promot[ing] solubilization or suspension of pranlukast in water," a drug which has very low water-solubility, and compares the relative solubilizing ability of various surfactants for pranlukast. (EX1012 at 1:36-48 & Table 1.)

81. Dr. Laskar further relies on references in which tyloxapol is merely listed generally as a surfactant with no disclosed role, including Desai (EX1005) and Kapin (EX1016). Desai lists tyloxapol among many possible surfactants that may optionally be included as one of many identified classes of excipients in a formulation with many different and diverse active ingredients. (EX1005 at 3:13-45.) A person of ordinary skill in the art would not have read this very broad disclosure as a suggestion to formulate bromfenac with tyloxapol. Additionally, Desai does not describe a particular function or role for tyloxapol, and Desai does not include tyloxapol in any examples or provide any data concerning tyloxapol. [redacted] Therefore, I completely disagree with Dr. Laskar's overreaching and unsupported statements in his declaration that Desai teaches "stable aqueous ophthalmic preparations of bromfenac," or that Desai includes "tyloxapol as one surfactant which could be formulated together with bromfenac." (EX1003 at ¶ 37.) Similarly, in Kapin, tyloxapol is included in one example, Example 3, with nepafenac, an acetamide NSAID derivative, which does not include a carboxylic acid moiety. (EX1016 at 8; *see also*, [redacted].) Kapin also discloses no role for tyloxapol. I thus disagree with Dr. Laskar that a person of ordinary skill in the art as of January 2003 would have

considered polysorbate 80 and tyloxapol interchangeable in aqueous liquid preparations of bromfenac sodium, based on Desai, Kapin or any other reference Dr. Laskar cites.

2. No teaching of polysorbate 80 or tyloxapol as a stabilizer of aqueous ophthalmic preparations of NSAIDs

82. Dr. Laskar further contends that both polysorbate 80 and tyloxapol were known to stabilize aqueous ophthalmic preparations of NSAIDs and other acidic drugs. (EX1003 at ¶¶ 32, 34.) I disagree with Dr. Laskar's contentions for at least the reasons discussed below.

83. First, Dr. Laskar states that "[i]n the late 1980's, a group of Japanese investigators succeeded in stabilizing bromfenac by using polysorbate 80, polyvinylpyrrolidone (PVP), and a sulfite at a pH of 6-9 – a pH range suitable for topical administration to the eye," relying on Ogawa (EX1004 and EX2095). (EX1003 at ¶ 32.) This statement is entirely incorrect and a gross mischaracterization of Ogawa, which, as discussed in detail below, teaches no role for polysorbate 80 in the disclosed bromfenac formulations and presents data that confirm that polysorbate 80 does not stabilize bromfenac in aqueous liquid preparations. (EX2095 at Exp. Exs. 5 & 6.)

84. Dr. Laskar then relies on Fu to argue that tyloxapol was known to stabilize aqueous NSAID ophthalmic preparations (EX1003 at ¶ 34), but tyloxapol is not disclosed or alluded to anywhere in Fu. (EX1011.) Dr. Laskar argues that

tyloxapol is an ethoxylated octylphenol like Octoxynol 9 and Octoxynol 40 disclosed in Fu, which he contends "could eliminate instability caused by the interaction of an acidic NSAID with BAC." (EX1003 at ¶ 33.) Dr. Laskar is wrong and ignores that tyloxapol, Octoxynol 9 and Octoxynol 40 have significant structural and chemical differences. (EX2105 at ¶¶ 85-92.) Dr. Laskar further contends that tyloxapol is an oligomer of Octoxynol 9.[2] Dr. Laskar again is wrong, and, as discussed above, tyloxapol and Octoxynol 9 in fact are structurally and chemically different. *(Id.* at ¶¶ 85-89.) [redacted] Indeed, Octoxynol 9, Octoxynol 40 and tyloxapol have different three-dimensational shapes. (EX2105 at ¶ 91.) From these differences, a person of ordinary skill in the art would

[2] Dr. Laskar cites Schott (EX1024) for this proposition. (EX1003 at ¶ 64.) Schott actually states that "[t]yloxapol is ***essentially*** an oligomer of octoxynol 9." (EX1024 at 496 (emphasis added).) Dr. Laskar further cites Regev (EX1025) for this proposition. (EX1003 at ¶ 64.) Similarly, Regev actually states that tyloxapol has "a repeating unit ***close to*** Triton X-100," which is one manufacturer's version of Octoxynol 9. (EX1025 at 8 (emphasis added).) These statements thus confirm that tyloxapol is ***not*** an oligomer of Octoxynol 9.

understand that these compounds exhibit significantly different functional and chemical properties, making their interaction with other components in ophthalmic solutions uncertain and unpredictable. (*Id.*) The unpredictable nature of these interactions further undermines Dr. Laskar's suggestion that Octoxynol 9, Octoxynol 40 and tyloxapol are somehow interchangeable.

85. Furthermore, nowhere in the Handbook of Pharmaceutical Excipients, which [redacted] Dr. Lawrence considered an important reference to an ophthalmic formulator in 2003, is tyloxapol or any Octoxynol disclosed. ([redacted]; EX2140 at 188:9-189:6.) The omission of tyloxapol and Octoxynols from the Handbook of Pharmaceutical Excipients clearly suggests that a person of ordinary skill in the art would not have used tyloxapol with an aqueous liquid preparation of bromfenac, absent knowledge of the '431 patent working backward from the claims.

86. Moreover, as discussed in detail below, Fu does not teach that ethoxylated octylphenols eliminate instability in formulations of NSAIDs and BAC. Rather, Fu is directed to ketorolac tromethamine formulations in particular, and only narrowly demonstrates under certain conditions that Octoxynol 40 physically stabilized these formulations. Fu contains no data regarding Octoxynol 9, and Fu never mentions tyloxapol.

87. Dr. Laskar further relies on Yasueda to argue that tyloxapol was better than polysorbate 80 at stabilizing acidic drugs in ophthalmic solutions. (EX1003 at ¶ 39.) I disagree with Dr. Laskar's position for several reasons. First, solubility is the cornerstone to Dr. Laskar's position that tyloxapol would allegedly stabilize bromfenac better than would polysorbate 80. (EX1003 at ¶¶ 39, 59, 99.) Yet Yasueda's Table 1 actually teaches that polysorbate 80 (719.6 μg/ml) is clearly superior to tyloxapol (551.0 μg/ml) for solubilizing pranlukast. (EX1012 at Table 1 .) Second, pranlukast is so structurally and chemically dissimilar to bromfenac (EX2105 at ¶¶ 63-68) that a person of ordinary skill in the art would not have applied any of Yasueda's findings to bromfenac. Third, no conclusion regarding the relative stabilizing effect of polysorbate 80 and tyloxapol can be drawn from Yasueda. As seen from the data in Tables 4 of Yasueda, there is no head-to-head comparison of pranlukast solutions where only tyloxapol and polysorbate 80 are varied. (EX1012 at Table 4; *see also*, EX2088 at ¶ 260 (Dr. Lawrence has stated that "[g]ood science requires only one variable to be altered at a time in order for a proper comparison to be made between formulations.").)

88. [redacted]

[redacted]

I further understand that pranlukast and bromfenac degrade by different mechanisms. Pranlukast degrades by hydrolysis and is not susceptible to oxidation, whereas bromfenac degrades by oxidation and is not susceptible to hydrolysis. (*Id.* at ¶¶ 67, 71.) Because Yasueda's pranlukast degrades by hydrolysis, any conclusions drawn from Yasueda would not have been applicable to bromfenac, which degrades by oxidation. (*Id.* at ¶ 71.) Moreover, there is no basis for a person of ordinary skill in the art to expect that tyloxapol would favorably impact bromfenac's oxidative degradation because both surfactants generate hydroperoxides, which would be expected to contribute to bromfenac's oxidative degradation. (*Id.* at ¶¶ 71-72.)

C. A Person of Ordinary Skill in the Art Would Not Have Considered Different NSAIDs Interchangeable.

89. Dr. Laskar alternatively argues for "swapping" bromfenac sodium from Ogawa's Example 6 for diclofenac in Sallmann's Example 2 by arguing that NSAIDs share certain structural characteristics, namely a carboxylic acid moiety. (EX1003 at ¶¶ 27, 55.) A person of ordinary skill in the art, however, would have

known that NSAIDs, including bromfenac, diclofenac and ketorolac, would not be interchangeable, given their vastly different structures and properties. (EX2105 at ¶¶ 42-62.) For example, based on their structures, a person of ordinary skill in the art would expect the bromfenac anion to be more solvated than both the diclofenac and ketorolac anion and thus less likely to form a precipitate in solution. (*Id.* at ¶¶ 49-51, 59-61.) [redacted] As discussed above, it is my opinion that these NSAIDs are not interchangeable and that a person of ordinary skill in the art would understand that a formulation suitable for diclofenac, for example, would not necessarily be suitable for bromfenac.

90. Moreover, a person of ordinary skill in the art as of January 2003 would not have assumed, without more information or data, that a given NSAID would form a precipitate with BAC based solely on its carboxylic acid moiety. (EX2105 at ¶¶ 73-78.) Dr. Laskar argues that the "NSAID anion can interact with the BAC cation. In most cases this results in a turbid or hazy drug product not suitable for use having diminished antimicrobial preservative effectiveness of the BAC." (EX1003 at ¶ 27.) I disagree with Dr. Laskar's unsupported argument, because whether a precipitate will form depends on many factors, including the structure of the NSAID and the type and concentration of other formulation components. (EX2105 at ¶¶ 73-78.) Because there is no evidence in the art of bromfenac and BAC forming a precipitate, contrary to Dr. Laskar's unsupported declaration statement (EX1003 at ¶¶ 31, 96), a person of ordinary skill in the art would not have been motivated to use solubilizers disclosed in Sallmann and Fu with bromfenac. [redacted]

For at least these reasons, I disagree entirely with the premise of Dr. Laskar's "swapping" theory.

VIII. THE TEACHINGS OF OGAWA, SALLMANN, AND FU WOULD NOT HAVE BEEN COMBINED WITH ANY REASONABLE EXPECTATION OF ARRIVING AT THE CLAIMED SUBJECT MATTER OF THE '431 PATENT

A. A Person of Ordinary Skill in the Art Would Have Had No Reason to Focus on Ogawa and its Bromfenac Formulations

91. As discussed above, by January 21, 2003, there were a number of FDA-approved aqueous ophthalmic formulations containing NSAIDs on sale in the United States, including diclofenac (Voltaren®), flurbiprofen (Ocufen®), ketorolac (Acular®) and suprofen (Profenal®). (EX1003 at ¶¶ 24-26.) A bromfenac ophthalmic solution called Bronuck was on sale in Japan.[3] (EX1003 at ¶ 111; EX1007 at 4-6.) But there was no need to focus on improving the bromfenac solution because, as InnoPharma and Dr. Laskar readily admit, "[t]o the extent there was ***any*** need for the claimed bromfenac ophthalmic formulation, it was met by the disclosures of Ogawa and Hara." (Petition at 53, emphasis added; *see also*, EX1003 at ¶¶ 111-12.)

[3] I understand that the sale of Bronuck in Japan does not constitute prior art to the '431 patent.

92. Moreover, design needs or market demands would not have led a person of ordinary skill in the art in the direction chosen by the inventors of the '431 patent. According to Dr. Laskar, a person of ordinary skill in the art would have been motivated to substitute polysorbate 80 with tyloxapol in Ogawa's formulation to prevent the alleged formation of a precipitate between an acidic NSAID and BAC or to solubilize that precipitate. (EX1003 at ¶ 70.) I disagree with Dr. Laskar's unsupported statement for at least the reasons discussed above. But even if a person of ordinary skill in the art would have been motivated to take that approach, which Dr. Laskar has not established, it would have only potentially reduced, to some extent, the formation of any precipitate. It would not have eliminated it.

93. Given BAC's recognized significant toxicity to the eye, even at low concentrations, market demands were pushing to eliminate harmful preservatives, like BAC, and either replace BAC with better tolerated preservatives or develop preservative-free formulations. (EX2064 at 115 ("It is therefore of striking importance to become aware of preservative toxicity in order to develop in the near future many more unpreserved drugs, especially for a long-term use and/or for patients with pre-existing ocular surface disorders."); EX2080 at 422 ("Overall, preservative free eye drop products have a significant medical advantage."); EX2089 at 211 ("Another approach is to reformulate existing products with better-

tolerated preservatives. One such product, a brimonidine compound approved by the FDA in March 2001, has replaced BAK with SOC in the current formulation."); EX2090 at abstract ("Therefore, the formulation with ketorolac alone may be better as a post-operative ocular analgesic.").) Indeed, some preservative-free formulations or non BAC-containing formulations, such as Acular® PF and Alphagan® P, had been successfully brought to market, and more were being sought. (*See, e.g.*, EX2089 at 211; EX2092 at 1; EX2090 at abstract; EX2061 at 1.)

94. Thus, by January 2003, rather than preventing the formation of a precipitate between an acidic NSAID and BAC, the state of the art and market demands at the time of invention would have more compellingly motivated and led a person of ordinary skill in the art to pursue non-BAC preservatives or develop preservative-free ophthalmic formulations.

95. Indeed, only because the claims of the '431 patent signal out BAC (see claim 1 "when a quaternary ammonium compound is included . . . [it] is benzalkonium chloride", as well as claim 18 "benzalkonium chloride is the only quaternary ammonium . . . included") does Dr. Laskar apparently postulate a motivation position based on addressing the alleged acidic NSAID/BAC precipitation issue. [redacted]

[redacted] Yet the state of the art by January 2003 thoroughly indicated that BAC and its significant health and formulation problems could be successfully eliminated. This undermines Dr. Laskar's focus on Ogawa in general, and also of Dr. Laskar's selection of Ogawa Example 6 over, for instance, Ogawa Example 7. Both of these examples had essentially the same chemical stability (99.2% vs. 100.9%), but Example 7 used methylparaben and ethylparaben instead of BAC as the preservative. (EX2094 at 142-43.) None of the art of record indicates that these parabens form an insoluble salt with acidic NSAIDs, [redacted]

96. Given BAC's significant risks, as well as the art's solutions to successfully eliminate these risks, Dr. Laskar's focus on Ogawa Example 6 suggests that his proposed solution is premised on knowing the end result, *i.e.*, the subject matter claimed in the '431 patent, and working backwards to define a problem that will lead him back to the claimed subject matter.

B. At the Time of Invention, A Person of Ordinary Skill in the Art Would Not Have Combined Ogawa's Teachings With Those of Sallmann

1. Ogawa and the problem it identifies with bromfenac

97. Ogawa discloses ophthalmic formulations of benzoylphenylacetic acids, such as bromfenac. Ogawa teaches that bromfenac chemically degrades, producing red insoluble matters, and Ogawa sought to stabilize bromfenac from that degradation. (EX1004 at 2:32-36; EX2095 at Exp. Exs. 4-6.) Ogawa's solution involved using a water soluble polymer, *e.g.*, PVP, and a sulfite, *i.e.*, sodium sulfite. (EX1004 at 3:7-15; EX2095 at 101.) Sodium sulfite is a well-known antioxidant. (EX2014 at 3:51-55.) Applying common sense and logic, a person of ordinary skill in the art would have understood that the sodium sulfite in Ogawa was used to prevent the oxidative degradation of bromfenac. (EX2105 at ¶ 37.) Indeed, InnoPharma acknowledges as much, indicating that sodium sulfite is added "to prevent oxidation reactions." (Petition at 49.)

98. The formation of red insoluble matters provides further support that bromfenac oxidizes when it degrades. When a drug product chemically degrades, it undergoes a reaction typically reflected by the production of colored insoluble degradants, and colored insoluble degradants are typical of an oxidation reaction. (EX2105 at ¶ 37.) [redacted]

[redacted]

99. The red insoluble particles do not constitute, therefore, a precipitate of bromfenac and BAC. In fact, none of the art of record specifically states that bromfenac forms a precipitate with BAC, and nowhere in Ogawa is such a precipitate ever mentioned. [redacted] Given the complexities and intricacies of ophthalmic formulation systems, a person of ordinary skill in the art cannot predict whether an individual NSAID will form an insoluble salt with BAC in a given system. (EX2105 at ¶ 77.)

100. Polysorbate 80, moreover, does not stabilize the bromfenac in Ogawa's formulations. This would have been clear to a person of ordinary skill in the art from Ogawa's description itself. First, Ogawa is completely silent on the function of polysorbate 80, ascribing no expressed role to it. (EX1004; EX2095.) A person of ordinary skill in the art would have known, however, that polysorbate 80 was not used as a solubilizer, for that person knew that bromfenac sodium was freely soluble in water (EX2039 at 29; EX2140 at 156:20-157:6; EX2105 at ¶ 47) and Ogawa does not disclose any NSAID/BAC precipitation issue. Second, the sole stability issue disclosed by Ogawa is the oxidative degradation of bromfenac,

which a person of ordinary skill in the art would have understood from Ogawa was addressed using PVP and sodium sulfite (EX1004 at 3:7-15), not polysorbate 80. Indeed, the sodium sulfite supplied the antioxidant properties that led Ogawa to state that solutions containing it had "remarkably enhanced" stability. (*Id.* at Exp. Ex. 6.)

101. I note that Dr. Laskar incorrectly characterizes Ogawa and the excipients responsible for bromfenac's stability. Dr. Laskar states that Ogawa discloses that polysorbate 80, along with PVP and a sulfite, stabilizes bromfenac. (EX1003 at ¶ 50.) This is wrong, and no passage in Ogawa states this, nor do any of the examples support it. The passage from Ogawa that Dr. Laskar cites for his proposition that polysorbate 80 allegedly stabilizes bromfenac is at column 3, lines 49-53. This passage does not refer to polysorbate 80, explicitly or implicitly. Moreover, the data from the formulations of Experimental Examples 4-6 in Ogawa actually confirm that polysorbate 80 does not stabilize bromfenac. (EX2095 at Exp. Exs. 4-6.)

102. The bromfenac formulations in Experimental Example 4 of Ogawa contain polysorbate 80, but not PVP or sodium sulfite. All of these formulations formed red insoluble matter. (EX1004 at 8:4-22; EX2095 at 107.) Experimental Example 5 tests two formulations: B-1, which contains PVP but not sodium sulfite, and B-2, which contains polysorbate 80 but not PVP or sodium sulfite. (EX1004

at 8:23-45; EX2095 at 107.) Red insoluble matters formed in B-2, and even with the addition of PVP in B-1, some red insoluble matter was still observed at four weeks. (EX1004 at 8:23-45; EX2095 at 107.) Experimental Example 6 tested formulation "B" (which is actually B-1)[4] and B-3, both containing PVP and polysorbate 80. (EX1004 at Exp. Ex. 6; EX2095 at Exp. Ex. 6.) Formulation B-1, which did not contain any sodium sulfite, produced red insoluble matter at four weeks. (*Id.*) But adding sodium sulfite to Formulation B-1 prevented the formation of red insoluble matter in Formulation B-3, leading Ogawa to comment that bromfenac decomposition was not observed and bromfenac's stability was remarkably enhanced. (EX1004 at Exp. Ex. 6 & Table 10; EX2095 at Table 10.)

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[4] Experimental Example 6 of Ogawa does not mention polysorbate 80, yet this reflects a printing error as polysorbate 80 actually was present. The corresponding Japanese publication of Ogawa contains the same three Experimental Examples (Experimental Examples 4-6), and Experimental Example 6 is reported as containing 0.15 g of polysorbate 80 and 2.0 g of PVP, consistent with their amounts in Experimental Examples 4 and 5. (Certified translation of Japanese publication of Ogawa, EX2095 at 107.) The counterpart Japanese Ogawa confirms that Experimental Example 6 of the U.S. Ogawa had a printing error, and that Formulation "B" in Experimental Example 6 is actually "B-1."

Thus, polysorbate 80 has no effect on the stability of bromfenac, one way or the other.

103. Dr. Laskar's statement that polysorbate 80 stabilizes bromfenac (EX1003 at ¶ 50) is fundamental to InnoPharma's position that a person of ordinary skill in the art would have "swapped" tyloxapol for polysorbate 80 with a reasonable expectation of success. (Petition at 51-52; EX1003 at ¶¶ 98-99.) The data in Ogawa's Experimental Examples 4-6 completely undermine that premise, ultimately establishing that polysorbate does not stabilize bromfenac, let alone prevent the oxidative degradation of bromfenac or otherwise maintain bromfenac's chemical stability.

2. A person of ordinary skill in the art would not have looked to Sallmann or combined its teachings with those of Ogawa

104. The only reason why InnoPharma and Dr. Laskar have considered Sallman for combination with Ogawa is because they know from the '431 patent that tyloxapol unexpectedly stabilizes bromfenac. [redacted]

([redacted]; *see also*, EX2140 at 86:1-8 (Dr. Lawrence testifying that "[t]here's a plethora of stable – of surfactants in water.").) A person of ordinary skill in the art, however, would not have selectively chosen Sallmann's tyloxapol, for Ogawa tells a person of ordinary skill in the art to pursue antioxidants, like sodium sulfite, to stabilize bromfenac. Also, Sallmann uses tyloxapol as a solubilizer, but because bromfenac sodium was known to be freely soluble in water (EX2039 at 29; EX2140 at 156:20-157:6; EX2105 at ¶ 47), there would not have been any reason to even consider it. In addition, a person of ordinary skill in the art would not have been motivated to pursue tyloxapol because tyloxapol is known to generate hydroperoxides, which would degrade bromfenac. (EX2105 at ¶¶ 71-72.)

105. More specifically, Sallmann is directed to formulations of the potassium salt of diclofenac. Sallmann's invention is the use of diclofenac potassium as superior to diclofenac sodium for treating ocular inflammation, with improved ocular penetration, ocular tolerance, onset of action and duration of action in the eye. (EX1009 at 1:48-59.) Sallmann obtained this patent despite the known existence of diclofenac sodium for treating ocular inflammation.

106. Sallmann formulates diclofenac potassium with a number of additional inactive components, including separate categories of solubilizers, chelating agents, and stabilizers. Sallmann lists tyloxapol as one of a number of

solubilizers, but its most preferred solubilizer is not tyloxapol but the Cremophor® excipients, identified as "especially preferred," for they are "tolerated extremely well by the eye." (*Id.* at 4:58-64.)

107. [redacted]

108. I disagree with Dr. Laskar for a number of reasons. The unequivocal teachings of Sallmann elevate Cremophor® over tyloxapol. Sallmann describes only Cremophor® as "especially preferred" (EX1009 at 4:58-64) and never mentions any problems formulating with it. Nor would a person of ordinary skill in the art have understood there to have been any problems because many of Sallmann's eye drop formulations, such as Examples 1, 8, and 11, contain Cremophor®, and Sallmann exclusively uses the formulation of Example 8 to demonstrate his invention's superior anti-inflammatory efficacy and ocular penetration. (*Id.* at 10:25-12:37.) Tellingly, Sallmann provides no such data for Example 2, which contains tyloxapol. Additionally, commercialized diclofenac is

formulated with Cremophor®, not tyloxapol. (EX2057 at 1.) [redacted] A person of ordinary skill in the art would expect that the commercialized diclofenac formulation was optimized, part of which included the selection of Cremophor® as its optimal solubilizer. This undermines Dr. Laskar's argument that Cremophor®'s viscosity would have been expected to cause formulation problems and in fact confirms Sallmann's preference for Cremophor® over all other solubilizers, including tyloxapol.

109. Sallmann, furthermore, separately teaches using stabilizers, such as cyclodextrins. (EX1009 at 5:56-6:21.) In fact, Sallmann's Example 2 includes both a solubilizer (tyloxapol) and a stabilizer (γ-cyclodextrin). (*Id.* at 8:1-15.) Dr. Laskar contends the tyloxapol is used as a stabilizer (EX1003 at ¶ 98), but Sallmann only discloses its use as a solubilizer.

110. Dr. Laskar asserts that it would have been obvious to substitute polysorbate 80 from Ogawa Example 6 with tyloxapol from Sallmann Example 2. Regarding this substitution theory, I understand that 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 No. 15 at 11.) In my view, a person of

ordinary skill in the art would not have made this substitution for a number of reasons.

111. First, the objective of Ogawa was to develop a formulation in which bromfenac is chemically stabilized against oxidative degradation. (*See supra* at ¶¶ 97-99.) Ogawa Example 6, in fact, is described as "stable, excellent for a long period of time." (EX1004 at 10:49-57.) A person of ordinary skill in the art conducting rational ophthalmic drug formulation research and development would not have blindly substituted polysorbate 80 in Ogawa Example 6 without considering how it might impact the chemical stability of a formulation already touted as excellent. The goal behind any substitution or modification of Ogawa Example 6 would have been to improve upon the formulation's stability. A person of ordinary skill in the art would not have pursued excipients that would not be expected to have any effect on or would lessen the stability benchmark set by Ogawa Example 6. None of the art InnoPharma or Dr. Laskar has identified discloses tyloxapol as a stabilizer for an NSAID in an aqueous formulation, and certainly not to chemically stabilize the NSAID.

112. Second, that polysorbate 80 and tyloxapol are both non-ionic surfactants would not be determinative for a person of ordinary skill in the art, contrary to Dr. Laskar's suggestion. Non-ionic surfactants constitute an enormous category of surfactants, differing greatly in structure and function. Indeed, Dr.

Lawrence has testified that the number of possible different non-ionic surfactants is effectively limitless. (EX2140 at 75:1-3.) Even among polysorbates themselves, significant differences in properties exist, such as solubilizing ability. (EX2105 at ¶ 81.) I am aware that non-ionic surfactants differ among each other and are not freely substitutable, as was confirmed by the Northern District of California in a patent case in which that Court upheld the non-obviousness of patent claims covering the ophthalmic drug Acular®, which the Federal Circuit affirmed on appeal. (EX2138 at ¶ 74 ("Such a wide variation in the ability to solubilize demonstrates that all water-soluble, micelle-forming, non-ionic surfacntats do not perform alike.") and at 1 ("Affirmed by *Syntex (U.S.A.) LLC v. Apotex, Inc.*, 221 Fed. Appx. 1002, 2007 U.S. App. LEXIS 9276 (Fed. Cir. 2007)").)

113. Moreover, the subject matter of the '431 patent pertains to ophthalmic formulation chemistry, which is inherently complex and where small modifications to compositional components can yield substantial changes in the properties of the resultant composition, unpredictably impacting chemical stability, efficacy, preservative efficacy and safety. [redacted] Given the vast structural

differences between polysorbate 80 and tyloxapol (EX2105 at ¶¶ 79-84), a person of ordinary skill in the art would not have simply substituted polysorbate 80 with tyloxapol. Instead, a person of ordinary skill in the art would have used common sense and, following rational formulation research and development, would have been guided by the teachings of the art.

114. Furthermore, to the extent a person of ordinary skill in the art would have even focused on Ogawa, which InnoPharma and Dr. Laskar admittedly have not established (*supra* at ¶¶ 58, 91; EX1003 at ¶ 111), a person of ordinary skill in the art would have been guided by what Ogawa teaches as a solution to bromfenac's oxidative degradation problem: the use of antioxidants. A person of ordinary skill in the art considering the teachings of Ogawa—said by Dr. Laskar to constitute the closest prior art—would have been led to consider other antioxidants, other than those in Ogawa, to even further improve bromfenac's chemical stability. For example, U.S. Patent No. 5,856,345 to Doi discloses antioxidants to stabilize aqueous solutions of pranoprofen, also an NSAID. (EX2025 at abstract.)

115. In addition, a person of ordinary skill in the art would not have just substituted polysorbate 80 with tyloxapol merely because they are surfactants. I understand that there must be some reason or incentive to make a substitution, judged in context of the prior art and what it reasonably suggests to a person of ordinary skill in the art. As an initial matter, a person of ordinary skill in the art

would have noticed that Ogawa is completely silent on the function of polysorbate 80, ascribing no expressed role to it. Tyloxapol is expressly disclosed as a solubilizer in Sallmann. (EX1009 at 4:52-62.) A person of ordinary skill in the art, however, would have known that Ogawa did not use polysorbate 80 as a solubilizer, because bromfenac sodium was known to be freely soluble in water. (EX2039 at 29; EX2140 at 156:20-157:6; EX2105 at ¶ 47.) There would have been no logical basis to substitute tyloxapol for polysorbate 80, other than knowing from the '431 patent that tyloxapol worked to stabilize bromfenac.

116. Moreover, a person of ordinary skill in the art would not have expected a solubilizer would address bromfenac's oxidative degradation. Solubilizers typically solubilize poorly soluble drugs. (EX2105 at ¶ 54.) [redacted] A person of ordinary skill in the art would have determined from Ogawa's specification and examples that polysorbate 80 had no effect, one way or the other, on bromfenac's stability, chemically or otherwise. (EX1004 at 8:3-9:5; EX2095 at Exp. Exs. 4-6.) Furthermore, a person of ordinary skill in the art would have understood that both polysorbate 80 and tyloxapol can degrade to generate hydroperoxides, which would be expected to increase bromfenac's chemical degradation. (EX2105 at ¶¶ 71-72.) As such, a person of

ordinary skill in the art would not have reasonably expected to improve bromfenac's chemical stability by using Sallmann's tyloxapol in Ogawa's formulations.

117. For all these reasons, a person of ordinary skill in the art objectively reading Ogawa would not have substituted one non-ionic surfactant (polysorbate 80) with another (tyloxapol) with the reasonable expectation of positively impacting bromfenac's chemical stability. Instead, what Ogawa very clearly suggests to a person of ordinary skill in the art, as discussed, is the use of antioxidants to address bromfenac's oxidative degradation problem. If anything, to the extent a person of ordinary skill in the art would have considered Ogawa at all, which InnoPharma has not established, this person would have used known antioxidants to impact stability. (*See supra* at ¶ 114.) This is completely divergent from the path the inventors of the '431 patent took in arriving at the claimed subject matter. In fact, the inventors proceeded contrary to the conventional wisdom in inventing the subject matter claimed.

3. Dr. Laskar's alleged motivation and expectation of success in fact would not have made the combination of Ogawa and Sallmann obvious to make

118. I understand that InnoPharma alleges that it would have been obvious to try "swapping" tyloxapol for polysorbate 80 in Ogawa Example 6 (Petition at 22), contending there were a finite number of surfactants and that tyloxapol, said to

be one of three preferred surfactants, was "used to stabilize diclofenac." (*Id.* at 25-26.) I disagree completely.

119. For the reasons discussed above, it is my opinion that a person of ordinary skill in the art would not have "swapped" these compounds as InnoPharma proposes. Additionally, I note that InnoPharma completely mischaracterizes Sallmann. Sallmann does not describe tyloxapol as a stabilizer for diclofenac. Rather, Sallmann describes tyloxapol as a solubilizer, and it is one of many solubilizers. (EX1009 at 4:52-67.) Significantly, Sallmann separately teaches using non-surfactant stabilizers, particularly cyclodextrins. (*Id.* at 5:59-6:17.)

120. Moreover, being from an enormous category of surfactants, differing substantially in structure and function, tyloxapol would not have been substituted for polysorbate 80 in a complex ophthalmic formulation system simply because both are surfactants. (EX2105 at ¶¶ 79-84; *see also* EX2140 at 86:1-8 (Dr. Lawrence testifying that "[t]here's a plethora of stable – of surfactants in water.").) As discussed above, I am aware that the Northern District of California squarely addressed this issue in its opinion in connection with the ophthalmic drug product Acular®, which was affirmed by the Federal Circuit, stating "[s]uch a wide variation in the ability to solubilize demonstrates that all water-soluble, micelle-forming, non-ionic surfactants do not perform alike." (EX2138 at ¶ 74.) Moreover,

Dr. Lawrence testified that the number of possible non-ionic surfactants is effectively limitless (EX2140 at 75:1-3).

121. Furthermore, as discussed above, a person of ordinary skill in the art would necessarily consider a proposed substitution's impact on the stability of Ogawa Example 6, touted as excellent. (EX1004 at 8:50-57.) Knowing from Ogawa that polysorbate 80 does not stabilize bromfenac from oxidative degradation, a person of ordinary skill in the art would not have substituted tyloxapol for polysorbate 80 merely because both are surfactants. Knowing also that both polysorbate 80 and tyloxapol are solubilizers would not have motivated the substitution because no information or data demonstrated a solubility concern for bromfenac, actually known to be freely water-soluble. (EX2039 at 29; EX2140 at 156:20-157:6; EX2105 at ¶ 47.) Instead, a person of ordinary skill in the art would have realized that tyloxapol generates hydroperoxides in solution, which would be expected to increase bromfenac's oxidative degradation. (EX2105 at ¶¶ 71-72.) This would have further discouraged the substitution of polysorbate 80 with tyloxapol.

122. InnoPharma further alleges that Sallmann teaches that tyloxapol is a better surfactant than polysorbate 80. (Petition at 24.) I do not understand how InnoPharma reaches this conclusion, for Sallmann never mentions polysorbate 80. InnoPharma also argues that polysorbate 80 and tyloxapol are interchangeable,

citing to Aviv (EX1026). But Aviv is directed to emulsions, not aqueous solutions. (*Id.* at abstract.) As discussed above, an emulsion is a biphasic system made up of droplets dispersed within a continuous phase. The non-ionic surfactants in Aviv prevent the droplets from coalescing into the continuous phase and destabilizing the emulsion. (*Id.*) A person of ordinary skill in the art would have gleaned nothing about the ability of Aviv's non-ionic surfactants to prevent oxidative degradation of bromfenac.

123. InnoPharma further argues that tyloxapol is a better solubilizer than polysorbate 80, citing to Yasueda (EX1012; Petition at 25), as a basis for both motivation and expectation of success. I disagree, for Yasueda contradicts this argument and undermines InnoPharma's positions. Yasueda discloses pranlukast, a cysteinyl leukotriene receptor-1 antagonist that is not an NSAID and is completely structurally different from any of the NSAIDs referenced by InnoPharma or Dr. Laskar. (EX2105 at ¶¶ 63-68.) Yasueda, moreover, actually teaches in Table 1 that polysorbate 80 (719.6 μg/ml) is clearly superior to tyloxapol (551.0 μg/ml) for solubilizing pranlukast. (EX1012 at Table 1.) Dr. Laskar's reliance on Tables 4 of Yasueda is similarly misplaced. (*Id.* at 6:47-7:45.) Nothing can be gleaned from these tables regarding the relative solubilizing effect of polysorbate 80 versus tyloxapol. None of the polysorbate 80 formulations contains BAC. Without BAC, no alleged NSAID/BAC precipitation—the

cornerstone of InnoPharma's and Dr. Laskar's motivation position—could occur, and a person of ordinary skill in the art would not have drawn any conclusions regarding how well polysorbate 80 solubilizes a precipitate that could never form. Thus, Yasueda neither motivates nor leads a person of ordinary skill in the art to reasonably expect that tyloxapol would have chemically stabilized bromfenac from oxidative degradation.

124. Moreover, the Handbook of Pharmaceutical Excipients, which [redacted] Dr. Lawrence considered as an important reference to a person of ordinary skill in the art formulating an aqueous liquid preparation in 2003, does not disclose tyloxapol. ([redacted]; EX2140 at 188:9-189:6.) This further undermines Dr. Laskar's position because a person of ordinary skill in the art would not have considered tyloxapol as a candidate when consulting the Handbook of Pharmaceutical Excipients to formulate an aqueous liquid preparation.

125. [redacted] A person of ordinary skill in the art would not have expected that substituting tyloxapol for polysorbate 80 in Ogawa's Example 6 would work when there is no reliable way of predicting the influence of salts, such as BAC or EDTA sodium, on other components and, in turn, their effect on the

stability of the aqueous preparations of bromfenac. This provides further support for my opinion that Dr. Laskar's proposed combination here would not have been obvious.

4. A person of ordinary skill in the art would not have modified Sallmann with the teachings of Ogawa

126. A person of ordinary skill in the art also would not have started with Sallmann and replaced Sallmann's diclofenac with Ogawa's bromfenac. As discussed above, Sallmann focuses uniquely on formulations of diclofenac potassium, which Sallmann distinguishes from diclofenac sodium because of its superior properties, including ocular penetration, ocular tolerance, onset of action and duration of action in the eye. (EX1009 at 1:48-59.) A person of ordinary skill in the art would not have replaced diclofenac potassium with bromfenac sodium, for doing so would have been contrary to the entire purpose and essence of Sallmann's invention.

127. Even if Dr. Laskar were correct that Sallmann's formulations would have been selected for modification, which he is not, a person of ordinary skill in the art would have used bromfenac potassium instead of bromfenac sodium in Sallmann's formulations. Sallmann extolls the benefits of diclofenac potassium over the corresponding sodium salt. (EX1009 at 1:48-59, Ex. 12.) Given Sallmann's indisputable preference for potassium salts, a modification of Sallmann

with Ogawa, if anything, would have led a person of ordinary skill in the art to a bromfenac potassium formulation.

128. Furthermore, as discussed above, Dr. Laskar testified at the Combigan® trial that there is no reliable way of predicting the influence of a particular salt species on the behavior of another compound in a given dosage form. ([redacted]; EX2137 at 123:2-7.) Accordingly, a person of ordinary skill in the art would not have had any expectation that substituting bromfenac for the structurally dissimilar diclofenac potassium in Sallmann's Example 2 would have resulted in a stable formulation, particularly given cyclodextrin's ability to interact with bromfenac and negatively impact its stability. (EX2105 at ¶ 96.)

129. There are additional reasons why a person of ordinary skill in the art would not have been motivated to modify Sallmann Example 2 with Ogawa's bromfenac. As discussed above, the only reason why InnoPharma and Dr. Laskar focus on Sallmann Example 2, which contains tyloxapol, is because they know from the '431 patent that tyloxapol works unexpectedly to stabilize bromfenac. [redacted]

But InnoPharma and Dr. Laskar ignore the many other examples in Sallmann containing solubilizers more preferred than tyloxapol.

130. Sallmann's Examples 8 and 11 contain Sallmann's "especially preferred" solubilizer Cremophor®, a reaction product of castor oil and ethylene oxide, identified as well tolerated by the eye. (EX1009 at 4:56-62.) Sallmann, moreover, provides experimental data for the formulation of Example 8 that demonstrates its superior anti-inflammatory efficacy and ocular penetration. (*Id.* at 10:25-12:37.) Sallmann provides no such data for Example 2. If a person of ordinary skill in the art were to have even looked at Sallmann, which Dr. Laskar has not established, he/she would have focused on Example 8 and, if a solubilizer were desired, used a Cremophor® solubilizer.

131. Moreover, a person of ordinary skill in the art would have appreciated from Ogawa that bromfenac degraded via oxidation. (*See supra* ¶¶ 97-99.) Sallmann's Example 2 contains neither PVP nor sodium sulfite, the two excipients taught by Ogawa for chemically stabilizing bromfenac against oxidative degradation. A person of ordinary skill in the art would have therefore expected the oxidative degradation to persist because Example 2 contains no excipient not already in Ogawa's formulations that would have prevented the bromfenac's degradation. There would have been no expectation of producing a chemically stable bromfenac formulation. Indeed, modifying Sallmann Example 2 with Ogawa's bromfenac would have been a step backwards from Ogawa. Simply put, a person of ordinary skill in the art would have not have made this combination.

C. Dr. Laskar's Reliance on Fu is Similarly Scientifically Unsupportable and Does Not Remedy the Deficiencies in his Reliance on Ogawa and Sallmann

132. Fu is directed to ophthalmic formulations of ketorolac with BAC and other inactive ingredients, particularly Octoxynol 40. (EX1011 at *e.g.*, 3, 6, 7-9.) Octoxynol 40 is taught to solubilize a precipitate[5] formed between ketorolac and BAC, maintaining the physical stability of the solution and eliminating its turbidity or cloudiness. (*Id.* at 9:20-24.) Fu teaches physical stability and contains no information regarding the chemical stability or degradation of ketorolac or any NSAID. Fu also does not disclose bromfenac or tyloxapol. And contrary to InnoPharma's and Dr. Laskar's contention (Petition at 19, 51; EX1003 at ¶¶ 33, 96-97), none of the art specifically indicates that bromfenac and BAC form any precipitate that leads to cloudiness or turbidity. [redacted]

[5] Relying on Fu, Dr. Laskar states that ketorolac forms a "complex" with BAC and that Octoxynol 40 either prevents this "complex" from forming or that it solubilizes it. (EX1003 at ¶ 96, n.30) I understand from the declaration of Dr. Stephen Davies that Fu does not actually substantiate that such a complex forms and that it would not be a "complex" that forms but, if anything, a salt that precipitates out of solution. (EX2105 at ¶ 76.)

[redacted]

133. InnoPharma confuses chemical stability with physical stability, blending them together as if they were one and the same. (Petition at 31-32.) But they constitute different problems necessitating different solutions, which would have been readily recognized by a person of ordinary skill in the art. Dr. Lawrence has testified that chemical stability and physical stability are "generally considered as different types of stability." (EX2140 at 225:12-15.) Even Dr. Laskar seems to recognize these stability differences (EX1003 at ¶¶ 32, n.5, 33, n.6), but then still conflates them in arguing that tyloxapol would have been expected to stabilize bromfenac. (*Id.* at ¶ 40.) Having hypothesized an obviousness position based on Ogawa, which Dr. Laskar admits constitutes the closest prior art (Petition at 55; EX1003 at ¶ 95) and which teaches the use of an antioxidant to address the oxidative chemical degradation of bromfenac, Dr. Laskar improperly looks to Fu, which actually addresses physical stability of an entirely different NSAID using a solubilizer. Given these important fundamental differences between Ogawa and Fu, a person of ordinary skill in the art would not have considered Fu to address bromfenac's chemical stability.

134. Additionally, based on Fu, a person of ordinary skill in the art would not have combined Fu with Ogawa because Fu's nonionic surfactant, taught as a

solubilizer, would not have been expected to impede the oxidative degradation of bromfenac. Nor would attempting to solubilize the oxidized degradation products have helped, for the chemical degradation products are no longer bromfenac and would be inactive. Were a person of ordinary skill in the art to have considered modifying Ogawa, which, as discussed above, I do not believe he/she would have done, that person would have looked to other antioxidants, besides those in Ogawa. (*See supra* ¶ 114.)

135. [redacted] Example 5 of Fu is directed exclusively to physical stability, as the first sentence in the example indicates. (EX1011 at 18:11-14.) Fu provides no information or data regarding the chemical stability or degradation of ketorolac or any indication that ketorolac had a chemical stability issue. [redacted]

1. Dr. Laskar's reliance on Fu for tyloxapol is unsupported

136. As discussed above, Fu does not disclose or ever allude to tyloxapol. The ethoxylated octylphenols broadly referred to by Fu do not include tyloxapol and constitute an enormous class of compounds, from which tyloxapol would not

be envisioned or, based on Fu's clear teaching, even suggested. Properly and objectively viewed, a person of ordinary skill in the art would not have relied on Fu to formulate an aqueous liquid preparation containing tyloxapol. [redacted]

137. Fu's Example 5 specifically compares the ability of Octoxynol 40, Fu's most preferred surfactant and the only one for which it provides data, to physically stabilize formulations containing ketorolac and BAC with polysorbate 80 (Tween 80), and Myrj 52. (EX1011 at 10, 18-19.) Under certain conditions, Octoxynol 40 physically stabilized these formulations to a greater extent than did polysorbate 80. (*Id.*) Despite Fu's clear preference for Octoxynol 40, InnoPharma focuses on Octoxynol 9, relying on a broad grouping of Octoxynol 9 with Octoxynol 12, Octoxynol 13 and Octoxynol 40. (Petition at 52.) Significantly, however, Fu provides no data for Octoxynol 9, and for a person of ordinary skill in the art, who would naturally be influenced by experimental data, there would have

been no reason to choose Octoxynol 9 over any of Octoxynol 12, Octoxynol 13 or Octoxynol 40, particularly Octoxynol 40.

138. Nonetheless, from Octoxynol 9, Dr. Laskar jumps to tyloxapol, which is not disclosed in Fu, and attempts to substantiate this jump by alleging that tyloxapol is in the same enormous class of compounds as Fu's Octoxynols. According to Dr. Laskar, "[s]tructurally, tyloxapol is an oligomeric form of Octoxynol 9 (Triton X-100)." (EX1003 at ¶ 34.) As discussed below, Dr. Laskar is wrong. Relying on Ali (EX1052), Dr. Laskar also contends that tyloxapol and Octoxynol 9 have been used interchangeably "in manufacturing ophthalmic preparations." (EX1003 at ¶ 64.) This is also wrong.

139. First, Dr. Laskar's reliance on Ali is entirely misplaced. Ali actually teaches that tyloxapol and Octoxynol 9 can be used as surfactants for milling bulk crystalline materials used in making ophthalmic suspensions. (EX1052 at 2:1-20.) Tyloxapol functions to keep active ingredients from re-agglomerating once micronized by milling. Its use in Ali is the antithesis of Fu's use of solubilizers, because a person of ordinary skill in the art, reading Ali, would know that the active ingredients need to stay as suspended particles and not go into solution. To be sure, Ali has nothing to do with using surfactants as components in a formulation for a chemical stabilization effect. (*Id.*)

140. Additionally, each of Octoxynol 40, Octoxynol 9 and tyloxapol are significantly structurally and functionally different. Their disparate molecular weights highlight their structural differences: Octoxynol 9's molecular weight is 625, Octoxynol 40's molecular weight is 1966, and tyloxapol's molecular weight is 4500. (EX2105 at ¶ 90.) Further, contrary to Dr. Laskar's contention, tyloxapol is ***not*** an oligomer of Octoxynol 9.[6] Tyloxapol has an extra methylene group in its monomeric form as compared to Octoxynol 9. (EX2105 at ¶¶ 87-88.) [redacted]

141. Indeed, Octoxynol 9, Octoxynol 40 and tyloxapol will have different three-dimensional shapes. From these differences, a person of ordinary skill in the art would understand that these compounds will exhibit significantly different

[6] Dr. Laskar cites Schott (EX1024) for this proposition. (EX1003 at ¶ 64.) Schott actually states that "[t]yloxapol is ***essentially*** an oligomer of octoxynol 9." (EX1024 at 496, emphasis added.) Dr. Laskar further cites Regev (EX1025) for this proposition. (EX1003 at ¶ 64.) Similarly, Regev actually states that tyloxapol has "a repeating unit ***close to*** Triton X-100," which is one manufacturer's version of Octoxynol 9. (EX1025 at 8, emphasis added.) These statements thus confirm that tyloxapol is not an oligomer of Octoxynol 9.

functional and chemical properties, making their interaction with other components in ophthalmic solutions uncertain and unpredictable. (EX2105 at ¶¶ 87, 91.) These unpredictable interactions further undermine Dr. Laskar's suggestion that Octoxynol 9, Octoxynol 40 and tyloxapol are somehow interchangeable.

142. Furthermore, nowhere in the Handbook of Pharmaceutical Excipients, which [redacted] Dr. Lawrence considered an important reference to an ophthalmic formulator in 2003, is tyloxapol or any Octoxynol disclosed. ([redacted]; EX2140 at 188:9-189:6.) Their omission from this Handbook reference clearly suggests that a person of ordinary skill in the art would not have, without knowledge of the '431 patent, so readily chosen tyloxapol, let alone when formulating an aqueous liquid preparation of bromfenac.

2. Fu does not suggest an amount of tyloxapol that could be used to stabilize bromfenac

143. Each of claims 6, 15 and 20 of the '431 patent is generally directed to an aqueous liquid preparation consisting essentially of bromfenac sodium salt and tyloxapol and commonly recites a concentration of tyloxapol of about 0.02 w/v %. Remaining claims 16, 17, 21 and 22 depend directly or indirectly from claims 6, 15 and 20.

144. Citing Fu, InnoPharma argues the specified tyloxapol concentration of "about 0.02 w/v %" in these claims would have been obvious. (Petition at 44.) Alleging that Octoxynol 40 and tyloxapol belong to the same class of ethoxylated

octylphenols, and alleging that Fu used 0.02 w/v % Octoxynol 40 to stabilize formulations containing ketorolac and BAC, InnoPharma concludes that this amount would have been sufficient to stabilize bromfenac. (*Id.*) I disagree entirely.

145. In making this argument, InnoPharma initially relies on Octoxynol 9. But with no data in Fu for Octoxynol 9, InnoPharma drops its reliance Octoxynol 9, pointing instead to amounts used for Octoxynol 40 and contending that these amounts should work. The structural differences among Octoxynol 9, Octoxynol 40 and tyloxapol are such that a person of ordinary skill in the art would have expected significantly different functional and physicochemical properties between Octoxynol 40 and tyloxapol. (EX2105 at ¶¶ 85-92.) Indeed, the critical micellar concentration ("CMC") of Octoxynol 40 is 0.810 mM, whereas the CMC of tyloxapol is 0.018 mM. (EX2105 at ¶ 90; EX2047 at Table 3; EX2048 at 770.) This difference in CMC between Octoxynol 40 and tyloxapol indicates they will form micelles at different molar concentrations and vastly different weight per volume concentrations, leading a person of ordinary skill in the art to conclude that any amounts of Octoxynol 40 would not have translated to tyloxapol. (*Id.* at ¶¶ 90-93.)

146. Fu and Ogawa also use different formulations, including different active ingredients and excipients. Ogawa's formulations contain chemical stabilizers, including water-soluble polymers such as PVP and antioxidants such as

sodium sulfite. (EX1004 at *e.g.*, Example 6.) Fu's compositions do not contain any similar chemical stabilizers. (EX1011.) That none of Fu's compositions contains chemical stabilizers, and that Fu never mentions any chemical stability problems for ketorolac, would have signaled to a person of ordinary skill in the art that ketorolac does not undergo oxidative degradation like bromfenac. Fu's compositions also contain NaCl, whereas Ogawa's do not. (*Id.* at *e.g.*, 12:1-13:15; [redacted]; EX2137 at 123:2-7.) From the structurally different NSAIDs to the different excipients used by Fu and Ogawa, a person of ordinary skill in the art would have recognized that Fu's and Ogawa's formulations contain many different ions in solution capable of interacting such that the amounts of Octoxynol 40 used in Fu would not have translated in any way to an amount of tyloxapol to be used with bromfenac. (EX2105 at ¶ 93.)

147. Dr. Laskar argues that 0.02% Octoxynol 40, used in Fu to allegedly physically stabilize formulations containing ketorolac and BAC, would have been sufficient to stabilize bromfenac. (EX1003 at ¶ 75.) I disagree. There is no evidence of record establishing that bromfenac precipitates with BAC, [redacted], and there is no evidence in the prior art that using tyloxapol could effectively result in chemically stabilizing an aqueous solution containing an NSAID, including bromfenac. Moreover, Fu suggests that ketorolac does not undergo oxidative degradation (EX1011, all Examples lack

antioxidants). As such, a person of ordinary skill in the art would not have even looked to Fu's amount of Octoxynol 40 to physically stabilize ketorolac and would not have expected it to work to chemical stabilize bromfenac against oxidative degradation.

148. Moreover, even if Dr. Laskar's focus on tyloxapol were proper, which it is not, the art Dr. Laskar cites teaches away from using 0.02 w/v% tyloxapol. Sallmann's Example 2 uses five times as much tyloxapol at 0.1 w/v%, and as a solubilizer, not a stabilizer. (EX1009 at 8:1-15.) In fact, five out of six of the eye drop formulations disclosed in Sallmann that contain tyloxapol use 0.1 w/v% tyloxapol. (EX1009 at Exs. 2, 15, 17.) Indeed, in its Institution Opinion, citing InnoPharma's Petition and Dr. Laskar's declaration, the Board has stated that "we accept 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 at 16 (citing Pet. 19-22, EX1003 at ¶¶ 50-51).) The only example using less tyloxapol, Example 3, does not contain BAC and would not have been expected to have a physical stability issue—InnoPharma's motivation for selecting tyloxapol. Although Sallmann generally states that the concentration of solubilizers can broadly range from 0.1 to 5000 times the concentration of the active ingredient (EX1009 at 4:65-67), this statement is not specific to tyloxapol and has no applicability at all to bromfenac,

which is not mentioned in Sallmann. Indeed, a person of ordinary skill in the art would have understood that what may work for one component in an ophthalmic formulation may not work for another.

149. Yasueda likewise does not support Dr. Laskar's position. Indeed, even Dr. Laskar states that Yasueda "teach[es] an ophthalmic preparation of an acidic drug formulated with 0.5-8 w/v% of tyloxapol." (EX1003 at ¶¶ 73, 88.) In fact, Yasueda's examples, including those cited by Dr. Laskar (formulations in Table 4) consistently use 4.0 g (4.0 w/v %) of tyloxapol. (EX1012 at Tables 4 & 5.)

150. Thus, the art of record specifically relating to tyloxapol teaches amounts that are many times higher than the amount recited in claims 6, 15-17 and 20-22 of the '431 patent. A person of ordinary skill in the art would not have been led to use tyloxapol, and certainly would not have been led to use the much lower amount at 0.02 w/v% of tyloxapol recited in these claims.

IX. OBJECTIVE EVIDENCE OF NON-OBVIOUSNESS OF THE '431 PATENT CLAIMS

A. A Unique, Non-Prior Art, Aspect of the '431 Patent Claims: The Use of Tyloxapol with Bromfenac

151. The aqueous liquid preparations claimed in the '431 patent require at least bromfenac and tyloxapol. This unique aspect of the '431 patent claims is neither taught nor suggested by the prior art, making the claimed subject matter

novel and non-obvious for all the reasons I have explained above. Another unique aspect of the '431 patent is the use of 0.02 w/v % tyloxapol with bromfenac, as recited in claims 6, 15-17 and 20-22 of the '431 patent.[7] As discussed below, the use of tyloxapol in formulation with bromfenac, including of 0.02 w/v % of tyloxapol, unexpectedly leads to improved chemical stability for bromfenac and improved preservative efficacy of the formulation compared to bromfenac formulations with polysorbate 80 at about 0.15 w/v %, conceded by Dr. Laskar to constitute the closest prior art.

152. [redacted]

(*See infra* Section XI. claim chart demonstrating that Prolensa® falls within the scope of certain claims of the '431 patent.) Dr. Laskar similarly acknowledges that

[7] The '431 patent identifies this amount of tyloxapol as preferred and demonstrates its unexpected superior chemical stabilizing effect in the examples of the patent. (EX1001 at Tables 1 & 2.) Even the Examiner's reasons for allowance recognized that the tested concentrations of tyloxapol in the examples showed unexpected and remarkable stabilizing effect compared with the polysorbate 80. (EX2033 at 7-8.)

Prolensa® falls within the scope of claims of the '431 patent. (EX1003 at ¶ 42.) As discussed below, the unexpected superior results and other objective evidence of non-obviousness observed for compositions falling within the scope of the claims, like Prolensa®, is directly attributed to formulating bromfenac with tyloxapol in preparations for ophthalmic use.

B. The Unexpectedly Superior Chemical Stabilizing Benefits of Tyloxapol Compared to Polysorbate 80

153. A person of ordinary skill in the art reading the '431 patent specification would have understood that the inventors sought to provide aqueous liquid preparations containing bromfenac and tyloxapol that are chemically stable, with controlled microbial growth, and can be safely and effectively administered for ophthalmic use at a pH that does not cause eye irritation. (EX1001 at 2:34-47.) A person of ordinary skill in the art would also understand that the '431 patent inventors succeeded in that regard by using tyloxapol with bromfenac. And as discussed below, Prolensa® embodies that success. Administered at pH 7.8, close to the pH of natural tears (7.4) (EX2088 at ¶ 66b; [redacted]), Prolensa® is chemically stable, has excellent preservative efficacy, and effectively treats ocular inflammation without causing eye irritation. (*See* [redacted]; [redacted]; EX2026 at 1; EX2027 at 1; EX2013 at 1.)

1. The '431 patent compares against the closest prior art for purposes of showing unexpected results

154. Dr. Laskar states that the closest prior art to the '431 patent, Ogawa, discloses "stable aqueous compositions of bromfenac containing BAC and the non-ionic surfactant, polysorbate 80." (EX1003 at ¶ 95.) Dr. Laskar further states that additional formulation ingredients, including boric acid, borax, sodium edetate, BAC, PVP and sodium sulfite, would be understood by a person of ordinary skill in the art not to affect a formulation's stability. (EX1003 at ¶ 52.) Therefore, a formulation that contains at least bromfenac, BAC and polysorbate 80, would be considered proper for comparison purposes in evaluating unexpected results commensurate with the full scope of the claimed subject matter.

155. Some of the comparative experiments that I discuss below, including comparative examples from the '431 patent specification, compare the chemical stability of a formulation containing bromfenac, BAC and polysorbate 80 to a formulation containing bromfenac, BAC and tyloxapol. They use the same stability test as used in Ogawa (EX1004 at *e.g.*, 8:39-45; 10:50-52) to evaluate the relative abilities of tyloxapol and polysorbate 80 to stabilize bromfenac from chemical degradation under the highly stressed conditions of 60 °C. for four weeks. Some of these experiments were conducted at pH 7, which, as I will explain, severely challenges the formulations to effectively delineate the relative stabilization capabilities of the tested compounds. In those experiments, only the

use of the non-ionic surfactant, polysorbate 80 or tyloxapol, is varied, making the comparison a proper head-to-head test.

156. Testing at the low pH of 7 accelerates bromfenac's degradation and serves to clearly delineate the relative stabilization capability of the tested compounds. 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 at Exp. Ex. 4, Table 8; EX2088 at ¶ 66b; [redacted] [redacted].) Ogawa confirms the effect of lowering pH on accelerating the degradation of bromfenac. (EX1004 at Exp. Ex. 4.)

157. Ogawa Experimental Example 4, the results of which are shown in Table 8, shows that as the pH drops from 9.0-8.0 to 7.0-6.0, the percentage (%) of remaining bromfenac after 3 weeks at 60°C. drops from the upper 90s to the mid-50s and even as low as 19%. (*Id.* at Exp. Ex. 4, Table 8.) Thus, testing at highly stressed conditions, 60°C for four weeks at the harsh pH of 7, allows a person of ordinary skill in the art to clearly observe the relative stabilization capability of polysorbate 80 and tyloxapol.

158. At a higher pH, a person of ordinary skill in the art would expect the differences in chemical stabilization between surfactants to be smaller and less observable. This can be also seen from Ogawa's Experimental Example 4 and Table 8, where the stability increases toward 100% bromfenac remaining at a pH

of 8 and 9. (*Id.* at Exp. Ex. 4, Table 8.) In fact, a person of ordinary skill in the art would expect that increasing the pH above 8 would only minimally impact chemical stability, in contrast to the significant decrease in chemical stability observed when the pH is lowered from 8 to 7. Thus, testing at a pH lower than pH 8, such as pH 7, allows a person of ordinary skill in the art to effectively compare the different effect of surfactants on chemical stability, while testing at a higher pH than 8 would not expose these differences.

2. A person of ordinary skill in the art would have had no expectation, based on polysorbate 80, of tyloxapol's effect on the chemical stability of bromfenac formulations

159. Dr. Laskar argues that, because polysorbate 80 and tyloxapol are both non-ionic surfactants, they are interchangeable and should behave similarly as surfactants. (EX1003 at ¶¶ 38, 56.) I understand that the Board in its Institution Opinion preliminarily stated that "[a]t this stage of the proceeding, absent evidence to the contrary, it would have been well within the level of ordinary skill in the art to replace one non-ionic surfactant (polysorbate 80) with another non-ionic surfactant (tyloxapol) in Ogawa's Example 6, because both were known to be useful as surfactants in ophthalmic preparations." (Paper No. 15 at 12:17-21.)

160. As discussed above, a person of ordinary skill in the art reading Ogawa would have understood that polysorbate 80 does not stabilize bromfenac. Not only does Ogawa ascribe no role to polysorbate 80, not as a solubilizer and

certainly not as a stabilizer, but the data in Ogawa's Experimental Examples 4-6 confirm that polysorbate 80 does not stabilize bromfenac. (*See supra* ¶¶ 100-103.) Accordingly, a person of ordinary skill in the art would not have expected that substituting tyloxapol for polysorbate 80 would have had any impact on bromfenac's chemical stability.

161. Dr. Laskar's reliance on Fu and Yasueda to argue that tyloxapol's stabilizing effect was expected is misplaced. The stability test in Fu is a physical stability test, not a chemical stability test that measures oxidative degradation. Physical stability and chemical stability constitute different problems necessitating different solutions, which would have been readily recognized by a person of ordinary skill in the art. Dr. Lawrence has testified that chemical stability and physical stability are "generally considered as different types of stability." (EX2140 at 225:12-15.) Even Dr. Laskar seems to recognize these stability differences (EX1003 at ¶¶ 32, n.5, 33, n.6). Moreover, there is no evidence that Fu's ketorolac undergoes oxidative degradation. There would have thus been no basis from Fu for a person of ordinary skill in the art to predict what would have been expected regarding the relative chemical stability effects of polysorbate 80 and tyloxapol on bromfenac.

162. Regarding Yasueda, Dr. Laskar argues that Yasueda teaches that tyloxapol solubilizes better than polysorbate 80 and would be expected to be a

better stabilizer. (EX1003 at ¶ 59.) Table 1 of Yasueda, however, clearly indicates that polysorbate 80 (719.6 μg/mL) is a much better solubilizer than tyloxapol (551.0 μg/mL). (EX1012 at Table 1.) Even if solubilizing ability has something to do with chemical stability, which Dr. Laskar has not established, polysorbate 80 would have been expected to outperform tyloxapol. Moreover, because the degradation pathway of pranlukast and bromfenac are different (EX2105 at ¶¶ 67, 71), any conclusions drawn from Table 5 of Yasueda regarding the chemical stability of pranlukast formulations would not have been applicable to bromfenac. (*Id.* at ¶ 71.)

3. Tyloxapol's unexpectedly superior chemical stabilizing effect

163. The following table comes from the declaration of Mr. Shirou Sawa (EX2098 at Section A; *see also*, EX1004 at Exp. Ex. 4 & Table 8 for formulation A-2.) It provides the results from a chemical stability test, run 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. The table below also includes an additional test formulation from Ogawa, namely, Formulation A-2 from Experimental Example 4 and Table 8, which contains bromfenac, BAC and polysorbate 80. Formulations A-28 and A-29 contain the same components as

Formulations A-21 and A-27, but with different amounts of tyloxapol. (EX2098 at Section A.)

Formulation code	A-20	A-21	A-27	A-28	A-29	A-2 in Ogawa
Designated code in Table 1 of the '431 patent	**Comparison Ex. 1**	**A-02**	**A-03**	**N/A**	**N/A**	**N/A**
Bromfenac sodium hydrate	0.1 g	0.1 g	0.1 g	0.1 g	0.1 g	0.1 g
Boric acid	1.5 g	1.5 g	1.6 g	1.6 g	1.6 g	q.s.
Borax	-	-	-	-	-	1.0 g
Benzalkonium chloride	0.005 g	0.005 g	0.005 g	0.005 g	0.005 g	0.005 g
Polysorbate 80	0.17 g	-	-	-	-	0.3 g
Tyloxapol	-	0.15 g	0.02 g	0.05 g	0.1 g	-
Disodium edetate	-	-	-	-	-	0.002 g
Sodium hydroxide	q.s.	q.s.	q.s.	q.s.	q.s.	-
Distilled water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Total amount	100 mL	100 mL	100 mL	100 mL	100 mL	100 mL
pH	7	7	7	7	7	7
Residual bromfenac 60 °C - 4 weeks	51.27%	73.81%	89.64%	85.96%	82.01%	54.2 % (60°C, 3 weeks)

164. The table above shows that bromfenac's chemical stability was 44% better with tyloxapol at 15 g (73.81% bromfenac remaining) compared to with polysorbate 80 at 0.17 g (51.27% bromfenac remaining).[8] Furthermore, in an

[8] The percent increase in stability of the bromfenac formulation is calculated as the difference in the residual amount (%) of bromfenac for the tyloxapol-containing formulation and polysorbate 80-containing formulation, divided by the residual

unexpected and counterintuitive manner, the chemical stability of bromfenac was 75% better using tyloxapol in the amount of 0.02 g (89.64% bromfenac remaining), which is less than 1/8 the amount of polysorbate 80 in the formulation containing 0.17 g (51.27% bromfenac remaining). Also, using tyloxapol in amounts of 0.1 g (82.01% bromfenac remaining) and 0.05 g (85.96% bromfenac remaining), bromfenac's chemical stability improved by 60% (formulation A-29) and 68% (formulation A-28), respectively compared with using polysorbate 80 at 0.17 g (51.27% bromfenac remaining).[9]

165. These vastly superior chemical stability results for tyloxapol were entirely unexpected because, based on Ogawa, substituting one non-ionic surfactant for another would not have been expected to impact chemical stability at

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amount (%) of bromfenac for the polysorbate 80-containing formulation, multiplied by 100.

[9] To the extent these compared compositions from the table contain ingredients other than just bromfenac and tyloxapol (i.e., boric acid, BAC, and sodium hydroxide), they would be understood by a person of ordinary skill in the art not to affect bromfenac's chemical stability and were, in any event, present in each of the tested compositions, making the comparison a proper head-to-head comparison that isolated the relative stabilizing effect of polysorbate 80 and tyloxapol.

all. Moreover, tyloxapol's ability to dramatically improve bromfenac's chemical stability at significantly lower amounts than polysorbate 80 formulations in Ogawa was completely unexpected and much more than a mere difference in degree.

[redacted] Considering the harsh condition of pH 7, and the significantly reduced amount of tyloxapol as compared with polysorbate 80, these results are remarkable. And given Dr. Laskar's statement that the basic and novel properties of the claimed preparations of the '431 patent "would not be adversely affected by the inclusion of borax, sodium borate, sodium chloride, PVP, sodium sulfite, and disodium edetate," I would also expect that tyloxapol's unexpected superior chemical stabilization effect would be present in the formulations of the claims containing tyloxapol even including other excipients not present in the compositions evaluated above. (EX1003 at ¶ 52.)

166. Indeed, the results reported for Ogawa's Formulation A-2 corroborate the unexpected superior results observed from comparing formulations A-20 through A-29. Referring, for example, to formulations A-21 (73.81% bromfenac remaining) and A-27 (89.64% bromfenac remaining), at 1/2 and 1/15 the amount

of polysorbate 80 used in Ogawa's Formulation A-2 (54.2% bromfenac remaining), and at four weeks instead of three weeks, tyloxapol unexpectedly stabilized bromfenac from degradation 36% and 65% better, respectively, than polysorbate 80.

167. The next comparative test was conducted at a higher pH of about 8.2 to 8.3 (EX2098 at Section C), one less conducive to degrading bromfenac (EX1004 at Exp. Ex. 4, Table 8) and one where the difference in stabilizing effect is not as clearly discernable. Formulations containing bromfenac sodium, boric acid, borax, BAC, polyvinylpyrrolidone, disodium edetate, sodium sulfite, sodium hydroxide and either polysorbate 80 or tyloxapol were tested at a pH of about 8.2-8.3 at 60° C. for 4 weeks. (*Id.*) Formulation BF (PE) in the following table corresponds to Bronuck. (EX2098 at Section C.) Dr. Laskar has stated that Bronuck is an embodiment of Ogawa. (EX1003 at ¶ 42.)

Formulation code	**BF (PE) (Bronuck)**	**A-01 (PE)**	**A-03 (PE)**
Bromfenac sodium hydrate	0.1 g	0.1 g	0.1 g
Boric acid	1.1 g	1.1 g	1.1 g
Borax	1.1 g	1.1 g	1.1 g
Benzalkonium chloride	0.005 g	0.005 g	0.005 g
Polysorbate 80	0.15 g	-	-
Tyloxapol	-	0.02 g	0.03 g
Polyvinylpyrrolidone	2.0 g	2.0 g	2.0 g
Disodium edetate	0.02 g	0.02 g	0.02 g
Sodium sulfite	0.2 g	-	-
Sodium hydroxide	q.s	q.s	q.s.
Distilled water	q.s.	q.s.	q.s.
Total amount	100 mL	100 mL	100 mL
pH	8.3	8.2	8.2
Residual bromfenac 60 °C - 4 weeks	91.45%	93.61%	95.07%

168. The Bronuck formulation (BF (PE)) containing 0.15 g of polysorbate 80 had 91.45% residual bromfenac, whereas the formulations containing 0.02 g and 0.03 g of tyloxapol had 93.61% and 95.07% residual bromfenac, respectively. (EX2098 at Section C.) Significantly, Formulations A-01 (PE) and A-03 (PE), using substantially less surfactant, did not include the antioxidant sodium sulfite that Ogawa touted as instrumental in achieving "remarkably enhanced" stability results. (EX1004 at 8:66-9:3.) In view of Ogawa, these results are completely unexpected and suggest the possibility of eliminating a chemical component from a formulation to be instilled on surgically compromised ocular tissue, another substantial and material benefit attributable to the use of tyloxapol. [redacted]

[redacted]

169. The data in Table 2 of the '431 patent, also taken from the Sawa Declaration (EX2098 at Section B), confirm these results at a pH of higher than 8.0. Although these formulations used significantly lower amounts of tyloxapol than the amount of polysorbate 80 used in Ogawa (about 1/3, 1/5, and 1/8 the amount), these tyloxapol-containing formulations achieved comparable stabilization results to Ogawa's Example 6, which was reported to be 100.9%.[10] 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% residual amount of bromfenac, as shown in the table below.

[10] Because the residual amount cannot exceed 100%, the reported value of 100.9% likely reflects measurement error or a slight amount of water that evaporated. A person of ordinary skill in the art would expect the actual percentage to be at or below 100%.

Formulation code	A-01	A-02	A-03	Example 6 (Ogawa)
Designated code in Table 2 of the '431patent	A-04	A-05	A-06	N/A
Bromfenac sodium hydrate	0.1 g	0.1 g	0.1 g	0.1 g
Boric acid	1.1 g	1.1 g	1.1 g	1.25 g
Borax	1.1 g	1.1 g	1.1 g	1.0 g
Benzalkonium chloride	0.005 g	0.005 g	0.005 g	0.005 g
Tyloxapol	0.02 g	0.05 g	0.03 g	-
Polyvinylpyrrolidone	2.0 g	2.0 g	2.0 g	2.0 g
Disodium edetate	0.02 g	0.02 g	0.02 g	0.02 g
Sodium sulfite	-	-	-	0.2 g
Sodium hydroxide	q.s	q.s	q.s.	-
Distilled water	q.s.	q.s.	q.s.	q.s.
Total amount	100 mL	100 mL	100 mL	100 mL
pH	8.15	8.15	8.15	8
60 °C - 4 weeks	92.57%	90.93%	91.97%	100.9%

170. The inventors of the '431 patent consistently achieved these results using tyloxapol and without using the antioxidant sodium sulfite that Ogawa used. Again, in light of what Ogawa teaches persons of ordinary skill in the art, these results are highly unexpected and meaningfully and materially contribute to the art as a whole in potentially eliminating sodium sulfite from being administered to a patient's surgically compromised eye.

171. The results in the previous two tables, which demonstrate tyloxapol's unexpected superior chemical stabilization effect to potentially eliminate an excipient in the formulation, would be applicable to all formulations of the claims

containing tyloxapol, whether they recite sodium sulfite or not. The presence of tyloxapol would necessarily bring the demonstrated benefit to all claimed formulations containing it.

172. I disagree with Dr. Laskar's opinion that "the purported unexpected stability of the claimed preparations is not observed across the entire claimed pH range." (EX1003 at ¶ 102.) In these experiments, tyloxapol was tested at both the harsher pH (with respect to bromfenac degradation) of 7 and the milder pH of more than 8 and showed unexpectedly superior stabilizing effects compared to polysorbate 80 at these different pH ranges, which are representative of the usable pH range. The test results effectively demonstrate tyloxapol's unexpectedly superior stabilizing effect commensurate with the scope of the claims.

173. Furthermore, I disagree with Dr. Laskar's statement that "Senju has also not demonstrated, and is unlikely to be able to demonstrate, that the stability of aqueous bromfenac preparations is increased over the entire range of BAC homologues, as claimed in the '431 patent" and that "[a] POSA would have presumed that the stability of an aqueous bromfenac liquid preparation would depend in part on the type of BAC used." (EX1003 at ¶¶ 103-04.) The National Formulary of the U.S. Pharmacopeia sets forth guidelines for manufacturers to follow to ensure uniformity of BAC batches, which the article that Dr. Laskar cites actually confirms. (EX1018 at 878:19-32.) As such, Dr. Laskar's argument is

undermined by the art he cites. In any event, as I stated previously, a person of ordinary skill in the art would not have expected that BAC would affect the results of a chemical stability test involving bromfenac. Even Dr. Laskar would appear to agree with me, having indicated that BAC, by referring to its use in Ogawa, would not have been expected to affect bromfenac's chemical stability. (EX1003 at ¶ 52.)

C. Tyloxapol is Unexpectedly Better than Polysorbate 80 at Maintaining Preservative Efficacy

174. With respect to preservative efficacy, none of the art of record discloses or suggests that tyloxapol would have a more favorable effect on preservative efficacy than would polysorbate 80. Dr. Laskar contends that, because polysorbate 80 and tyloxapol are both non-ionic surfactants, they should behave similarly. (EX1003 at ¶¶ 38, 56.) On that basis then, a person of ordinary skill in the art would not have expected that tyloxapol would have had a superior effect on a given formulation's preservative efficacy as compared to polysorbate 80.

175. Data in Section D of Mr. Sawa's Declaration (EX2098), which includes Tables 3-1 and 3-2 of the '431 patent and is reproduced below, demonstrate that tyloxapol unexpectedly improves preservative efficacy of bromfenac formulations as compared to polysorbate 80.

Formulation Code	**Bronuck**	**A-01**	**A-02**
Designated code in Tables 2, 3-1 and 3-2 showing results in the '431 patent	**N/A**	**A-04 & Table 3-1**	**A-05 & Table 3-2**
Bromfenac sodium hydrate	0.1 g	0.1 g	0.1 g
Boric acid	1.1 g	1.1 g	1.1 g
Borax	1.1 g	1.1 g	1.1 g
Benzalkonium chloride	0.005 g	0.005 g	0.005 g
Polysorbate 80	0.15 g	-	-
Tyloxapol	-	0.02 g	0.05 g
Polyvinylpyrrolidone	2.0 g	2.0 g	2.0 g
Disodium sulfite	0.02 g	0.02 g	0.02 g
Sodium sulfite	0. 2 g	-	-
Sodium hydroxide	q.s.	q.s	q.s
Distilled water	q.s.	q.s.	q.s.
Total Amount	100 mL	100 mL	100 mL
pH	8.3	8.19	8.20

176. The Bronuck formulation identified in Mr. Sawa's Declaration, which contains 0.15 g of polysorbate 80, did not satisfy either of the European Pharmacopoeia A or B standards. (EX2098 at Section D.) The formulations containing tyloxapol, however, surprisingly satisfied the European Pharmacopoeia standards. (*Id.*) The A-04 formulation, which contains 0.02 g of tyloxapol, satisfied both the European Pharmacopoeia A and B standards. I understand that Criteria A of the European Pharmacopeia is more stringent, [redacted] The A-05 formulation, which contains 0.05 g of tyloxapol, satisfied the European Pharmacopoeia B standard.

(*Id.*) I also understand that the European Pharmacopeia A and B standards are more stringent than the US Pharmacopeia standard. (EX2124 at 129.)

177. That the Ogawa formulation did not satisfy either of the European Pharmacopoeia standards, and that the formulations containing tyloxapol satisfied the European Pharmacopoeia standards as discussed, is unexpected for surfactants that Dr. Laskar argues should behave similarly (EX1003 at ¶ 56). Again, this is not merely a difference in degree. [redacted]

D. Tyloxapol's Unexpectedly Superior Stabilizing Effect Led to Actual Benefits for Patients

178. The unexpected stabilization effects of tyloxapol translated into actual benefits, manifested in Prolensa®, which were similarly unexpected. Tyloxapol's

superior stabilization ability permitted formulating Prolensa® [redacted] and at pH 7.8 (*supra* at ¶¶ 163-73; [redacted].) This represents a significant reduction on a logarithmic scale from a pH of 8.3 used in the non-prior art commercially available bromfenac formulations Xibrom® and Bromday®, which both contained polysorbate 80. (EX2026 at 5; EX2027 at 4.) In fact, I am aware that Dr. Laskar testified in a patent infringement case that the pH of an ophthalmic formulation is important to the "stability, comfort, and bioavailability." (EX2136 at 59:13-18.) [redacted] as compared to the amount of polysorbate 80 at 0.15 w/v% in Xibrom® and Bromday®. (EX2026 at 5; EX2027 at 4.) Thus, Prolensa® [redacted] has a pH closer to that of natural tears (7.4), making it more comfortable and less irritating to the patient. (EX2088 at ¶ 66b; [redacted] Unlike Xibrom® and Bromday®, which have the adverse effect of eye irritation, including burning/stinging, Prolensa® is non-irritating. (*Compare* EX2026 at 1 (Xibrom® Prescribing Information) & EX2027 at 1 (Bromday® Prescribing Information) *with* EX2013 at 1 (Prolensa® Prescribing Information), which demonstrates that there are no burning/stinging indicated for Prolensa®.) Because tyloxapol's stabilization effect on bromfenac was unexpected, the achievements of lowered pH, [redacted] and no burning or stinging were similarly unexpected.

179. In addition, at a lower pH, the intraocular penetration of bromfenac is improved, such that less bromfenac can be administered to achieve the same therapeutic effect. (EX2030 at 1 ("Bromfenac ophthalmic solution 0.07%, pH 7.8 readily penetrated ocular tissues with levels similar to those of bromfenac ophthalmic solution 0.09%, pH 8.3.").) Compared to Bromday® at 0.09% bromfenac, the concentration of bromfenac in Prolensa® is 0.07%, advantageously placing 22% less drug in contact with surgically compromised ocular tissue without a reduction in efficacy. (*Id.* at 2 ("Prolensa® was reformulated from bromfenac 0.09% (Bromday®; Bausch + Lomb) to achieve similar ocular bioavailability with a lower concentration of active drug, thereby ensuring similar clinical efficacy to Bromday® but with reduced exposure of the surgically compromised ocular surface to the drug.").) Compared to Ogawa Example 6 at 0.1% bromfenac, moreover, Prolensa® contains 30% less bromfenac. It would not have been expected that tyloxapol's surprising stabilizing effect could also have produced such a reduction in the amount of bromfenac without a corresponding reduction in ocular penetration and efficacy.

180. [redacted], compared to 0.15 w/v% polysorbate 80 in Xibrom® and Bromday®. (EX2026 at 5; EX2027 at 4.)

E. Copying of Prolensa® by Generic Drug Companies

181. I understand that six separate generic drug companies, including InnoPharma, have sought FDA approval to market Prolensa®. (EX2006; EX2016; EX2017; EX2018; EX2019; EX2108.) In their Paragraph IV letters, most of the generic companies did not allege any non-infringement position, or they only alleged non-infringement positions based on alleged invalidity of the claims that cover Prolensa®, indicating that their generic bromfenac products copy Prolensa®. (EX2006 at 164; EX2016 at 11-13; EX2017 at 14; EX2018 at 16-17; EX2019 at 17; EX2108 at 41.) [redacted]

182. That six separate generic drug companies have sought to market exact copies of Prolensa® supports the successful and non-obvious nature of the formulation. (*Accord* [redacted]; EX2136 at 133:12-15 (In the Combigan® patent infringement case, Dr. Laskar conceded that it is a lot easier to be able to just copy an innovator's formulation than to have to start from scratch.).) Indeed, several researchers who are ophthalmologists and leading cataract surgeons have acknowledged the significant benefits of Prolensa® in peer-reviewed

articles. (EX2113 at 965; EX2118 at 31; EX2119 at 929.) Furthermore, Lupin, which I understand is the first generic company among the six generic companies seeking to market a copy of Prolensa®, filed its ANDA a mere three months after Prolensa® was approved. (EX2015 at 1; EX2106 at 5.) Lupin, moreover, publicly forecasted that Prolensa®'s revenues would reach $100 million in two to three years, despite the expected generic competition from Bromday®. (EX2022 at 4.) These reasons support my opinion that tyloxapol's unexpected stabilizing ability led to Prolensa®'s significant and recognized benefits, which led InnoPharma, Lupin and many other generics to copy Prolensa®.

X. CONCLUSION

183. In view of the foregoing, and as summarized below, it is my opinion that a person of ordinary skill in the art as of January 21, 2003, would have had no reason to combine the disclosures of Ogawa and Sallmann and thus would not have arrived at the claimed subject matter recited in claims 1-5, 7-14 and 18-19 of the '431 patent.

- Ogawa teaches that sodium sulfite, an antioxidant, prevents oxidative degradation of bromfenac. (EX1004 at Exp. Ex. 6.) Ogawa does not teach polysorbate 80 as a stabilizer, contrary to Dr. Laskar's characterization. (*Id.* at Exp. Exs. 4-6.) Moreover, there is no teaching in Ogawa, nor in any art of record, that bromfenac would form a precipitate with BAC (*id.*), which is Dr. Laskar's alleged motivation to substitute tyloxapol in Sallmann's Example 2 for polysorbate 80 in Ogawa's Example 6. [redacted]

[redacted]

- Sallmann teaches formulations of diclofenac potassium, distinguished over diclofenac sodium in the prior art. (EX1009 at 1:48-59.) Sallmann teaches a number of inactive components, including separate categories of solubilizers, chelating agents and stabilizers, and Sallmann discloses tyloxapol as a solubilizer. (*Id.* at 4:58-64.) A person of ordinary skill in the art would have understood that solubilizers are unnecessary for formulations of bromfenac as bromfenac is freely water soluble. (EX2039 at 29; EX2140 at 156:20-157:6; EX2105 at 47.) Even if there were a need for a solubilizer, which Dr. Laskar has not established, Sallmann teaches Cremophor® as the "especially preferred" solubilizer, further supporting that a person of ordinary skill in the art would not have chosen tyloxapol. (EX1009 at 4:58-64.) Sallmann, furthermore, separately teaches using non-surfactant stabilizers, such as cyclodextrins. (*Id.* at 5:56-6:21.)

- Ogawa and Sallmann, therefore, are directed to compositions of different active ingredients and to solving different problems. A person of ordinary skill in the art would not have combined these references in order to formulate a bromfenac ophthalmic solution.

- Polysorbate 80 and tyloxapol are not interchangeable because of their different chemical structures and properties. A person of ordinary skill in the art would not have concluded that tyloxapol and polysorbate 80 are interchangeable from the disclosure of Yasueda, which is directed to pranlukast formulations. Pranlukast is structurally and chemically different from bromfenac and degrades by a completely different mechanism than does bromfenac. Instead, a person of ordinary skill in the art would have understood that tyloxapol generates hydroperoxides in solution, which would be expected to increase bromfenac's oxidative degradation. A person of ordinary skill in the art would not have expected that substituting tyloxapol for polysorbate 80 in Ogawa's Example 6, which is touted as having excellent stability, would increase

stability when there is no reliable way of predicting the influence of tyloxapol and other components on the stability of bromfenac formulations.

- Nowhere in the Handbook of Pharmaceutical Excipients, which [redacted] Dr. Lawrence considered an important reference to an ophthalmic formulator in 2003, is tyloxapol disclosed. ([redacted]; EX2140 at 188:9-189:6.) The omission of tyloxapol from the Handbook of Pharmaceutical Excipients clearly suggests that a person of ordinary skill in the art would not have used tyloxapol with an aqueous liquid preparation of bromfenac, absent knowledge of the '431 patent working backward from the claims.

- A person of ordinary skill in the art would not have substituted bromfenac in Ogawa for diclofenac potassium in Sallmann's Example 2 as that would have been contrary to Sallmann's teaching directed to the use of diclofenac potassium. (EX1009 at 1:48-59.) Moreover, a person of ordinary skill in the art would have predicted, if anything, that the oxidative degradation of bromfenac would persist because neither PVP nor sodium sulfite would be included if bromfenac were substituted for diclofenac potassium in Sallmann's Example 2. Furthermore, Dr. Laskar has not established that additional ingredients in Sallmann's Example 2, particularly cyclodextrin, would not materially affect the basic and novel properties of the claimed bromfenac formulations.

184. It is further my opinion, which is summarized below, that a person of ordinary skill would have had no reason to further combine Ogawa, Sallmann and Fu, or any other prior art references identified by InnoPharma, to arrive at the claimed subject matter recited in claims 6, 15-17 and 20-22 of the '431 patent.

- Ogawa teaches that sodium sulfite, an antioxidant, prevents oxidative degradation of bromfenac. (EX1004 at Exp. Ex. 6.) Ogawa does not teach that bromfenac and BAC form a complex,

[redacted] (*Id.*; [redacted].) Sallmann teaches formulations of diclofenac potassium, distinguished over diclofenac sodium in the prior art. (EX1009 at 1:48-59.) Sallmann, moreover, contains no teaching that diclofenac is susceptible to chemical degradation. (*Id.* at 1:1 - 3:26.) Fu teaches the use of Octoxynol 40 to prevent the formation of a precipitate in ketorolac and BAC formulations, and therefore Fu addresses physical stability as opposed to chemical stability of ketorolac formulations. (*See, e.g.*, EX1011 at Ex. 5.) Nowhere does Fu disclose that ketorolac is susceptible to chemical degradation, including oxidative degradation. And nowhere does Fu disclose tyloxapol or bromfenac. (EX1011 at 11-19.)

- Ogawa, Sallmann and Fu therefore are directed to compositions of different active ingredients and to solving different problems. A person of ordinary skill in the art would not have combined the teachings of these references, particularly when Ogawa, which InnoPharma states is the closest prior art, teaches that bromfenac is susceptible to oxidative degradation and when neither Sallmann nor Fu addresses oxidative degradation.

- Tyloxapol, Octoxynol 9 and Octoxynol 40 are not interchangeable because of their different chemical structures and properties. The structural differences among Octoxynol 9, Octoxynol 40 and tyloxapol are such that a person of ordinary skill in the art would have expected significantly different functional and physicochemical properties between these Octoxynols and tyloxapol, as demonstrated, for example, by the different CMC values for each surfactant. A person of ordinary skill in the art would have recognized that Fu's and Ogawa's formulations contain many different ions in solution capable of interacting such that the 0.02 % Octoxynol 40 used in Fu for ketorolac formulations would not have translated in any way to any amount of tyloxapol to be used with bromfenac. Moreover, Sallmann's Example 2 and most of the other diclofenac potassium eye drops disclosed in Sallmann disclose 0.1 w/v % tyloxapol, which further undermines Dr. Laskar's contention that a person of ordinary skill in the art would have relied on Fu

to make a formulation containing 0.02 w/v % tyloxapol. Indeed, in its Institution Opinion, citing InnoPharma's Petition and Dr. Laskar's declaration, the Board has stated that "we accept 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 at 16 (citing Pet. 19-22, EX1003 at ¶¶ 50-51).)

- Nowhere in the Handbook of Pharmaceutical Excipients, which [redacted] Dr. Lawrence considered an important reference to an ophthalmic formulator in 2003, is tyloxapol or any Octoxynol disclosed. ([redacted]; EX2140 at 188:9-189:6.) The omission of tyloxapol and Octoxynols from the Handbook of Pharmaceutical Excipients clearly suggests that a person of ordinary skill in the art would not have used tyloxapol with an aqueous liquid preparation of bromfenac, absent knowledge of the '431 patent working backward from the claims.

- A person of ordinary skill in the art would not have substituted bromfenac in Ogawa for diclofenac potassium in Sallmann's Example 2 as that would have been contrary to Sallmann's teaching directed to the use of diclofenac potassium. (EX1009 at 1:48-59.) Moreover, a person of ordinary skill in the art would have predicted, if anything, that the oxidative degradation of bromfenac would persist because neither PVP nor sodium sulfite would be included if bromfenac were substituted for diclofenac potassium in Sallmann's Example 2. Furthermore, Dr. Laskar has not established that additional ingredients in Sallmann's Example 2, particularly cyclodextrin, would not materially affect the basic and novel properties of the claimed bromfenac formulations.

185. It is further my opinion, which is summarized below, that various secondary considerations of nonobviousness, including unexpected results and

other objective evidence confirm the nonobviousness of the subject matter of the '431 patent claims.

- The aqueous liquid preparations claimed in the '431 patent require at least bromfenac and tyloxapol, which is a unique aspect neither taught nor suggested by the prior art. Another unique aspect of the '431 patent is the use of 0.02 w/v % tyloxapol with bromfenac, as recited in claims 6, 15-17 and 20-22 of the '431 patent. The unexpected superior results and other objective evidence of non-obviousness observed for compositions falling within the scope of its claims, like Prolensa®, is directly attributed to formulating bromfenac with tyloxapol in preparations for ophthalmic use.

- As demonstrated in Section IX.B., the use of tyloxapol in bromfenac formulations, including 0.02 w/v % of tyloxapol, unexpectedly improves the chemical stability compared to bromfenac formulations with polysorbate 80 at about 0.15 w/v %, conceded by Dr. Laskar to constitute the closest prior art. At the harsh condition of pH of 7, tyloxapol at 0.02 w/v% performed unexpectedly better compared to polysorbate 80 at 0.15 w/v%. And at a pH higher than 8, tyloxapol at significantly lower concentrations than 0.15 w/v% achieved comparable results to Ogawa's Example 6 without using Ogawa's highly touted sodium sulfite.

- As demonstrated in Section IX.C., the use of tyloxapol in bromfenac formulations unexpectedly improves preservative efficacy. Dr. Laskar contends that because polysorbate 80 and tyloxapol are both non-ionic surfactants, they should behave similarly (EX1003 at ¶¶ 38, 56), and none of the art of record discloses or suggests that tyloxapol would have a more favorable effect on preservative efficacy than polysorbate 80. The Bronuck formulation containing polysorbate 80, however, failed the European Pharmacopoeia A and B standards known to be more stringent than the US Pharmacopoeia, while the tyloxapol formulations discussed in section IX.C. satisfied either of the European Pharmacopoeia standards.

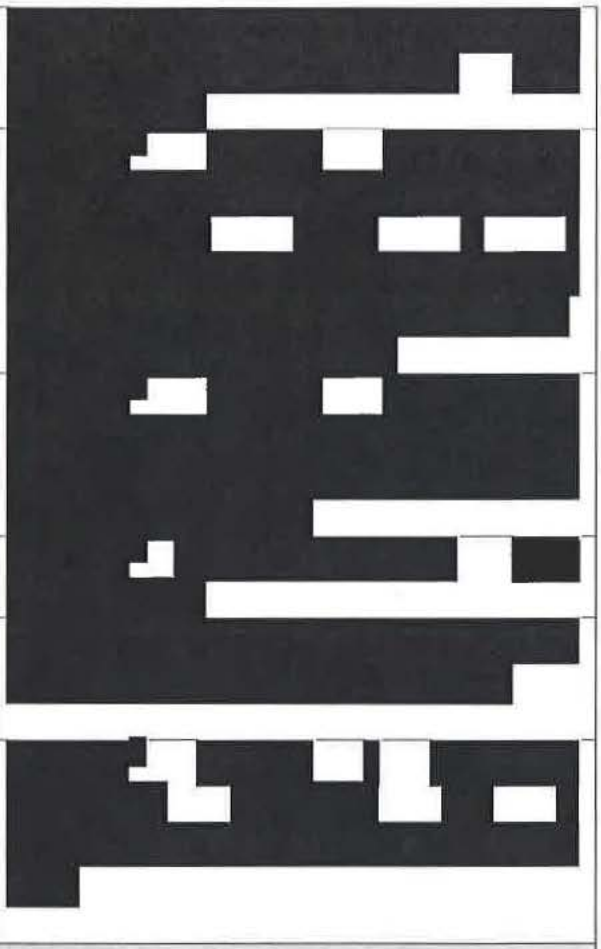
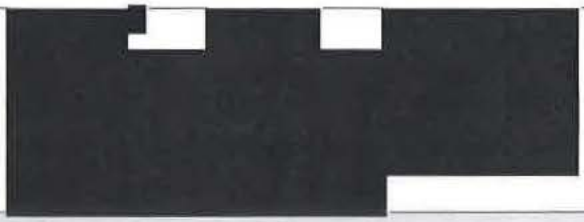
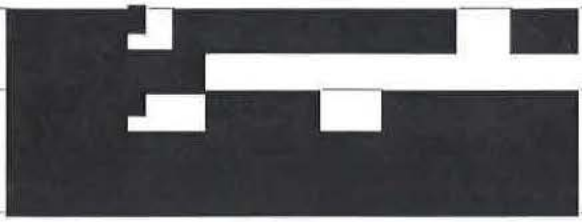
- As demonstrated in Section IX.D., tyloxapol's superior stabilization ability permitted [redacted] at pH 7.8. The pH of Prolensa® is closer to the pH of natural tears, [redacted], together making it more comfortable and less irritating to the patient. Unlike Xibrom® and Bromday®, which have the adverse effect of burning/stinging, Prolensa® is non-irritating. Because tyloxapol's stabilization effect on bromfenac was unexpected, the achievements of lowered pH, [redacted] and no burning or stinging were similarly unexpected. Several researchers have acknowledged the significant benefits of Prolensa® in peer-reviewed articles. (EX2113 at 965; EX2118 at 31; EX2119 at 929.)

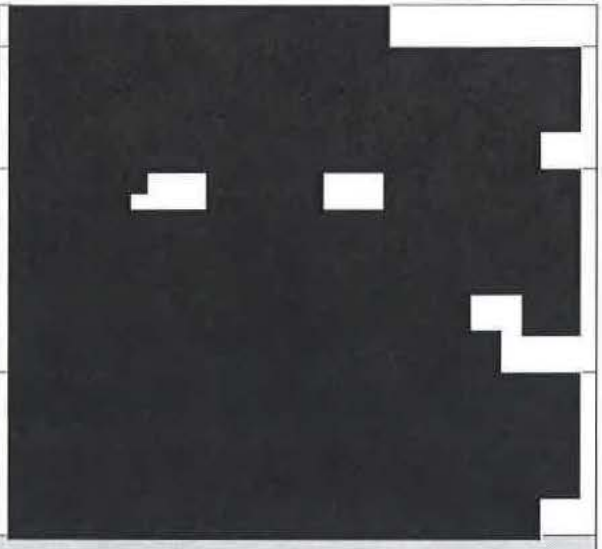
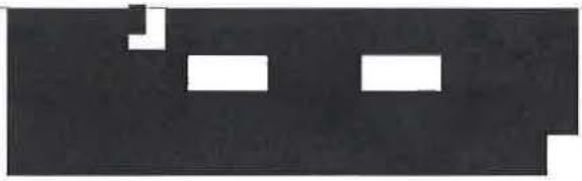
- Six generic drug companies have sought FDA approval to market exact copies of Prolensa®, which is demonstrated from their Paragraph IV letters, supporting the successful and non-obvious nature of the formulation. [redacted] Lupin, the first ANDA filer among the six generic companies seeking to market generic copies of Prolensa®, filed its ANDA a mere three months after Prolensa® was approved. (EX2015 at 1; EX2106 at 5.) Lupin, moreover, publicly forecasted that Prolensa®'s revenues would reach $100 million in two to three years, despite the expected generic competition from Bromday®. (EX2022 at 4.)

XI. CLAIM CHART DEMONSTRATING THAT PROLENSA® FALLS WITHIN THE SCOPE OF CERTAIN CLAIMS OF THE '431 PATENT

186. [redacted].

Claims of the '431 Patent	[redacted]
1. An aqueous liquid preparation	

consisting essentially of the following two components, wherein	
the first component is 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein	
the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and 3/2 hydrate;	
the second component is tyloxapol, wherein	
said liquid preparation is formulated for ophthalmic administration, and wherein	
when a quaternary ammonium compound is included in said liquid preparation, the quaternary ammonium compound is benzalkonium chloride.	
2. The aqueous liquid preparation according to claim 1, wherein	See claim 1.
the first component is 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt.	
3. The aqueous liquid preparation according to claim 1, wherein	See claim 1.
the second component is tyloxapol and	
the pharmacologically acceptable salt of 2-amino-3-(4-bromobenzoyl)phenylacetic acid	

is a sodium salt, wherein	
the concentration of the tyloxapol is from about 0.01 w/v % to about 0.5 w/v %; and wherein	
the first component is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt, wherein	
the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.01 to about 0.5 w/v %.	
4. The aqueous liquid preparation according to claim 3, wherein	See claim 3.
the concentration of the tyloxapol is from about 0.01 w/v% to about 0.3 w/v % and	
the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt is from about 0.05 to about 0.2 w/v %.	
6. The aqueous liquid preparation of claim 4, wherein	See claim 4.
the concentration of the tyloxapol is about 0.02 w/v%.	
7. The aqueous liquid preparation according to claim 1, wherein	See claim 1.
the formulation further includes one or more additives selected from the group consisting of a preservative, buffer, thickener, stabilizer, chelating agent, and pH controlling agent.	

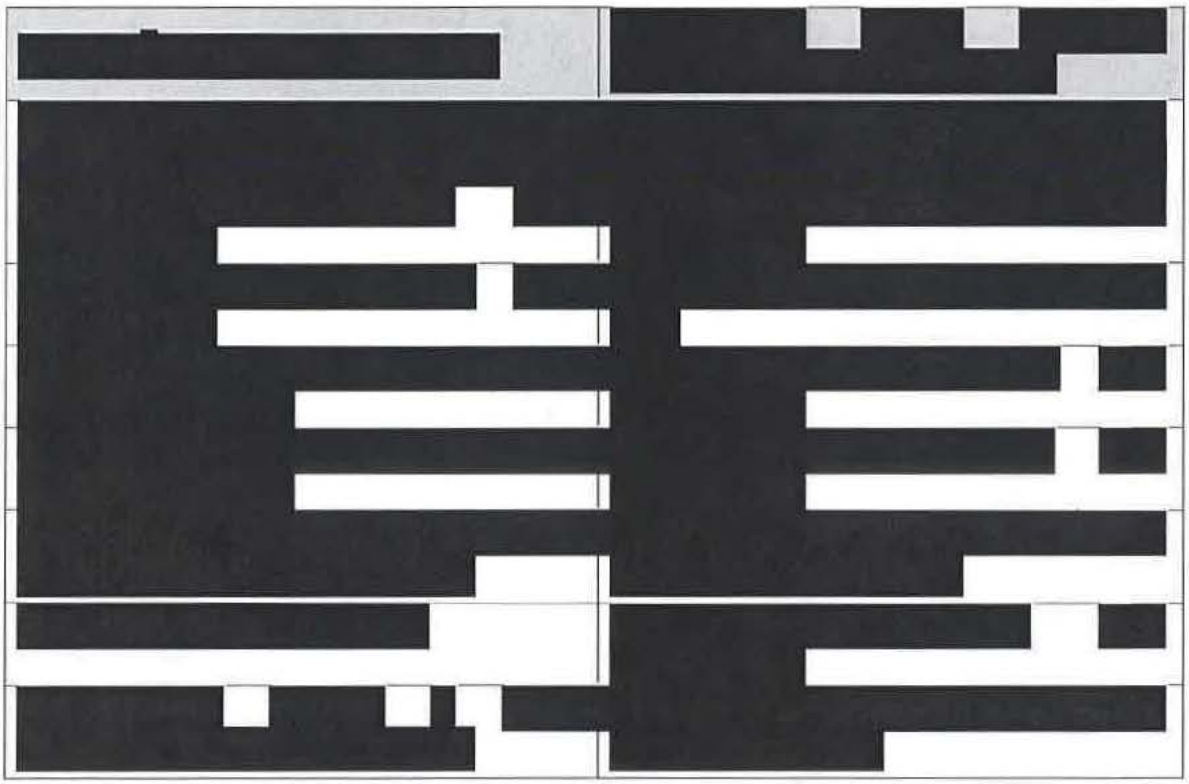
8. The aqueous liquid preparation according to claim 7, wherein	See claim 7.
said preservative is benzalkonium chloride; wherein	
said buffer is boric acid and/or sodium borate; wherein	
said thickener is polyvinylpyrrolidone; wherein	
said stabilizer is sodium sulfite; wherein	
said chelating agent is sodium edetate; and wherein	
said pH controlling agent is sodium hydroxide.	
9. The aqueous liquid preparation according to claim 8, wherein	See claim 8.
the pH is from about 7 to about 9.	
10. The aqueous liquid preparation according to claim 8, wherein	See claim 8.
the pH is from about 7.5 to about 8.5.	
18. An aqueous liquid preparation consists essentially of:	
(a) 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, wherein	
the hydrate is at least one selected from a 1/2 hydrate, 1 hydrate, and	

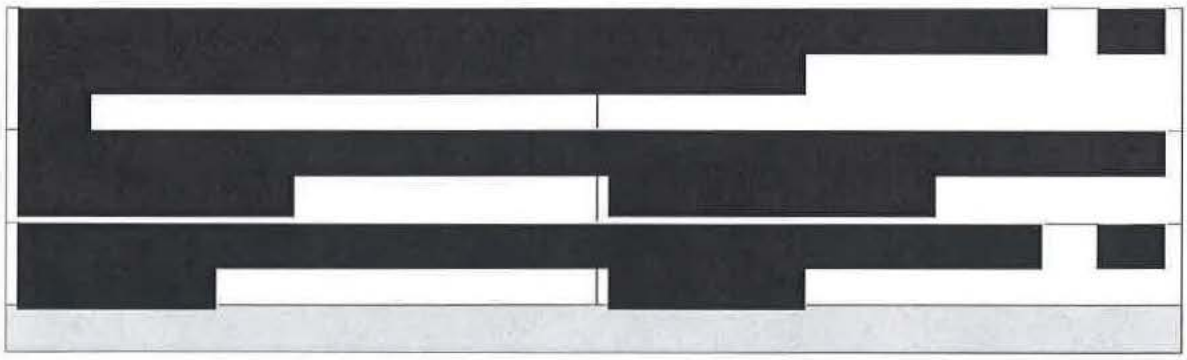
3/2 hydrate,	[redacted]
(b) tyloxapol,	
(c) boric acid,	
(d) sodium tetraborate,	
(e) EDTA sodium salt,	
(f) benzalkonium chloride,	
(g) polyvinylpyrrolidone, and	
(h) sodium sulfite, wherein	
said liquid preparation is formulated for ophthalmic administration, and wherein	
benzalkonium chloride is the only quaternary ammonium compound which is included in said liquid preparation.	[redacted]
19. The aqueous liquid preparation according to claim 18, wherein	See claim 18.
(a) is a 2-amino-3-(4-bromobenzoyl)phenylacetic acid sodium salt.	[redacted]
20. The aqueous liquid preparation according to claim 19, wherein	See claim 19.
the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic	[redacted]

acid sodium salt is from about 0.01 to about 0.5 w/v % and the concentration of the tyloxapol is about 0.02 w/v%.	[redacted]

XII. [redacted]

187. [redacted]





I declare under penalty of perjury that the foregoing is true and correct to the best of my knowledge and belief.

Executed 12/22/2015.

Robert O. Williams III

Dr. Robert O. Williams, III, Ph.D.