UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NEVAKAR, INC.

Petitioner

v.

SYDNEXIS, INC.

Patent Owner

U.S. Patent No. 9,421,199
Filing Date: May 29, 2015
Issue Date: August 23, 2016

Case No. IPR2021-00439

PETITION FOR INTER PARTES REVIEW

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I. Introduction

Petitioner Nevakar Inc. respectfully requests *inter partes* review of U.S. Patent No. 9,421,199 (EX1001), assigned to Patent Owner Sydnexis Inc., and cancellation of claims 1−4 and 7−27.

The challenged claims recite nothing more than conventional low-concentration atropine formulations with deuterium oxide (D_2O) in place of regular water (H_2O) to increase the formulation's stability at pH levels known to be optimal for clinical administration. As of the effective filing date, the use of D_2O to improve stability was well known and was specifically expected to be "of value, for example, in the extemporaneous preparation of ophthalmic solutions, where stability and sterility are important considerations." EX1006, 4. In a later continuation application, the Examiner explained that "increased stability *is the expected property*" of combining D_2O and atropine. EX1042, 3. There was nothing inventive about substituting D_2O for H_2O to achieve the very result—*i.e.*, increased stability—that would have been expected.

II. Technology Background

A. Low-Concentration Atropine Formulations for the Treatment of Myopia

Atropine, a nonselective muscarinic antagonist, has been studied extensively for more than a century and has been described as "the oldest and most effective pharmacological treatment to inhibit the development of myopia." EX1009, 1;

EX1003, 13. Early clinical trials established that 1.0% and 0.5% atropine formulations were effective in reducing the progression of myopia. EX1010, 1; EX1011, 1; EX1003, 13; EX1012 ¶[0006]. At these high concentrations, however, atropine was known to cause side effects, such as photophobia, cycloplegia, and mydriasis, that lead to poor patient compliance. EX1003, 13; EX1012 ¶[0006]; EX1013, 2; EX1014, 3; EX1015, 1. Because treating myopia with atropine requires long-term use, this poor patient compliance resulted in reduced efficacy, especially in adolescent populations. EX1002 ¶¶22−24; EX1016, 3−4.

In an effort to reduce the side effects, researchers studied ≤ 0.03% atropine solutions and reported that clinical efficacy could be maintained with an improved safety profile. EX1003, 13, 15−20; EX1014, 1; EX1017, 1. For instance, Fang reported that 0.025% atropine eye drops prevented myopia onset and myopic shift (EX1014, 1, 3), and Chia observed that 0.01% atropine "had significant clinical effects as evident by its effect on myopia progression, accommodation, and pupil size," and that "atropine-related adverse effects were uncommon at the 0.01% dose." EX1003, 19. A patent application directed to the work of Chia, WO 2012/161655, claimed ophthalmic formulations containing 0.001% to 0.0249% atropine and methods of treating myopia with them. EX1018, 19:12−13, 4:20−5:2; claims 1−5, 12−18.

Thus, as of 2014, it was well established that ≤ 0.03% atropine solutions were clinically effective in treating or preventing myopia and had an improved safety profile compared to high-concentration atropine formulations. EX1002 ¶¶25−36.

B. Stability of Atropine in Aqueous Solution

The stability of atropine is primarily dependent on temperature and pH.[1] *E.g.*, EX1004, 5; EX1019, 1. This was known as early as the 1950s, when Kondritzer and Zvirblis conducted a series of studies demonstrating that the half-life of atropine in solution could be predicted for any temperature and pH. *E.g.*, EX1004, 8; EX1019, 5.

As shown in Figure 1, atropine is a carboxylic ester; in aqueous solution it degrades via classic ester hydrolysis. EX1019, 1; EX1004, 6; EX1020, 5; EX1002 ¶37.

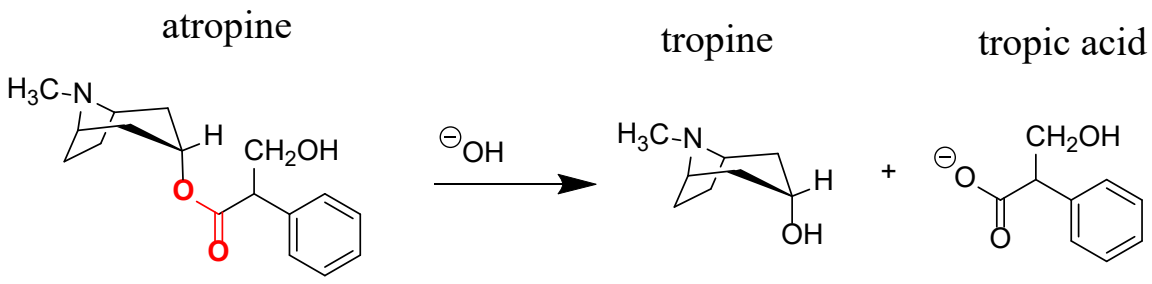


Figure 1. Atropine hydrolysis reaction. Red denotes ester.

[1] pH is a measure of H^+ concentration. Low pH values represent high H^+ concentrations (and low OH^- concentrations). EX1002 ¶40.

Ester hydrolysis reactions are catalyzed by both H^+ ions ("acid-catalyzed hydrolysis") and OH^- ions ("base-catalyzed hydrolysis"). EX1004, 6; EX1002 ¶¶38−39. The rate of degradation (*k*) is equal to the sum of the acid-catalyzed and base-catalyzed reactions. EX1004, 6. For atropine, the rate of the acid-catalyzed reaction is much slower than that of the base-catalyzed reaction, such that the stability of atropine "is governed by the hydroxy-ion [OH^-] concentration…." *Id*., 1, 4. At low OH^- concentrations (*i.e.*, pH < ~3−5) the overall rate of reaction is slow, and atropine is relatively stable. *Id*., 4−5. As OH^- concentration increases, however, the overall rate of the reaction increases, and atropine becomes more unstable (pH > ~5). *Id*.

C. Deuterium Solvent Isotope Effect

Deuterium is a stable isotope of hydrogen that has twice the mass of the regular hydrogen (also known as protium). EX1021, 2. Because of the larger nucleus in deuterium, replacing hydrogen with deuterium results in an increase in bond strength, which often slows the rate of reaction. EX1002 ¶41; EX1022, 3; EX1023, 5−9. The difference in the rate of a reaction between the deuterated compound and its hydrogen analog is known as the "kinetic isotope effect" or KIE. EX1024, 4−5.

Replacing hydrogen with deuterium in regular water (H_2O) results in deuterium oxide (D_2O).[2] EX1025, 19. Similar to the KIE, the degradation of compounds in D_2O will often proceed more slowly than in H_2O. EX1002 ¶42; EX1025, 20−25; EX1027, 3; EX1028 ¶[0012]. The difference in the rate of reaction in D_2O compared to that in H_2O is the sum of medium, primary, and secondary effects and is known as the kinetic solvent isotope effect ("KSIE" or "SIE"). EX1002 ¶¶42−47; EX1025, 19.

Aside from these differences, deuterium is remarkably similar to hydrogen in most other respects. EX1025, 21 ("Certainly it is true that isotopic substitution is the least disturbing structural change that can be made in a system…."); EX1028 ¶[0011]; EX1023, 8−9; EX1002 ¶¶55−56. For nearly a century, this targeted effect—slowing reactions while leaving other properties unchanged—had been extensively studied and had generated a voluminous body of literature. *E.g.*, EX1025, 22−23; EX1027, 3. By 2014, it was well understood that the effect of D_2O

[2] The pH of a solution of deuterium oxide is referred to as "pD." The difference between pH and pD can be calculated by the standard equation pD = metered reading + 0.4. EX1025, 37; EX1026, 1; EX1001, 32:20−26. For example, a measurement of pH 4 in pure D_2O is equivalent to pD 4.4. *Id.*; EX1002 ¶42, n. 5.

on a given compound could be predicted by its effect on analogous compounds and reactions. EX1002 ¶¶48−54; EX1025, 26, 32, 45.

In the years preceding the effective filing date of the '199 patent, there was great interest in using deuterium to improve upon existing pharmaceutical formulations. *See, e.g.*, EX1029, 1[3]; EX1030, 13−14; EX1031, 3−5; EX1032, 14−16; EX1002 ¶¶64−65. Given its predicable KIE and KSIE effects, deuterium offered a simple and relatively inexpensive way to improve the stability of known therapeutics without reducing their clinical efficacy. EX1029, 20; EX1023, 8−9, 16−17; EX1002 ¶¶57−63. Indeed, by 2014, several companies were dedicated exclusively to using deuterium to improve known therapeutics. *E.g.*, EX1031, 3–5.

III. Scope and Content of the Prior Art

A. *Chia*

"Atropine for the Treatment of Childhood Myopia: Safety and Efficacy of 0.5%, 0.1%, and 0.01% Doses (Atropine for the Treatment of Myopia 2)" by Chia et al. (EX1003, "*Chia*") published in 2012, and constitutes prior art under at least 35 U.S.C. § 102(a)(1). *Chia*'s prior art public accessibility is evidenced at least by (1) its date of online publication, October 2, 2011 (EX1003, 20); (2) date stamp

[3] Patent Owner disclosed EX1029 with a date of 1/11/2014 in another application. EX1089, 13.

reporting it was received February 2012 (EX1003, 2); (3) publication in a well-known and reputable journal, *Ophthalmology*; and (4) the fact that it was cited by skilled artisans prior to June 24, 2014 (*e.g.*, EX1017, 7). EX1002 ¶18, n. 1. *Chia* discloses the use of solutions comprising 0.001%−0.03% atropine via eye drops to arrest myopia. *E.g.*, EX1003, 13, 19−20.

As *Chia* recognized, prior treatments with "atropine 1% eyedrops were effective in controlling myopic progression" but caused harmful side effects, such as cycloplegia and mydriasis. EX1003, 13. To address this, *Chia* tested lower concentration formulations and reported that "atropine 0.01% has minimal side effects compared with atropine at 0.1% and 0.5%, and retains comparable efficacy in controlling myopia progression." EX1003, 13. Based on these results, *Chia* concluded that "[t]he lowest concentration of 0.01% atropine… is a viable concentration for reducing myopia progression" and that "the 0.01% formulation exhibited fewer adverse events" than 1%, 0.1%, and 0.5% atropine. EX1003, 19−20.

Chia is analogous art to the '199 patent. It "is from the same field of endeavor"—ophthalmic compositions—and is reasonably pertinent to "one of the particular problems dealt with by the inventor"—reducing atropine side effects in the treatment of myopia. *Unwired Planet, LLC v. Google Inc.*, 841 F.3d 995, 1000–

01 (Fed. Cir. 2016) (citation omitted); EX1002 ¶18, n. 1. *Chia* was neither cited nor considered during prosecution of the '199 patent.

B. *Kondritzer*

"Stability of Atropine in Aqueous Solution" by Kondritzer and Zvirblis (EX1004, "*Kondritzer*") published in 1957, and constitutes prior art under at least 35 U.S.C. § 102(a)(1). *Kondritzer*'s prior art public accessibility is evidenced at least by (1) its date of publication, September 1957 (EX1004, 1−4); (2) publication in a well-known and reputable journal, *Journal of the American Pharmaceutical Association* (EX1004, 1); and (3) the fact that it was cited by skilled artisans prior to June 24, 2014 (EX1020, 7; EX1052, 8; EX1033, 19). EX1002 ¶18, n. 3. *Kondritzer* "evaluate[d] the factors involved in the deterioration of aqueous solutions of atropine and its salts." EX1004, 5. *Kondritzer* reviewed several studies examining the rate of degradation of atropine at different temperatures and pH levels. EX1004, 5−6.

Kondritzer explained that "[h]ydrolytic reactions catalyzed by both hydrogen and hydroxyl ions, with no detectable water reaction, include hydrolysis of carboxylic esters." *Id*., 6. *Kondritzer* confirmed that degradation of atropine is primarily due to acid- and base-catalyzed hydrolysis and noted a prior study

reporting that this is also "true for the hydrolysis of procaine."[4] *Id*. *Kondritzer* further disclosed that the effects of both the acid- and base-catalyzed reactions are "governed by the hydroxy-ion concentration and the temperature." *Id*., 5.

Kondritzer derived an equation to predict the pH at which atropine would be most stable for any hydrogen ion concentration. *Id*., 6. To test the validity of their equation, *Kondritzer* measured the rate of hydrolysis (*k*) of atropine at different pHs. *Id*., 6−8. *Kondritzer* found that the half-lives of atropine at various temperatures and pHs determined experimentally matched those predicted by their theoretical equation. *Id*., 8.

Based on this data and a prior study of atropine hydrolysis at higher pHs, *Kondritzer* concluded that, "[a]s expected, the hydrogen ion catalyzed hydrolysis of atropine is slow" and that, "[a]bove pH 4.5, the predominant catalytic reaction involves hydroxyl ion; below pH 3, the predominant catalytic reaction involves hydrogen ion…." *Id*., 8−9.

Kondritzer is analogous art to the '199 patent. It "is from the same field of endeavor"—atropine solutions—and reasonably pertinent to "one of the particular problems dealt with by the inventor"—optimizing pH levels for clinical

[4] Procaine is used as a topical anesthetic in ophthalmic formulations. EX1006, 4. Like atropine, it is a carboxylic ester. EX1033, 1.

administration and long-term stability. *Unwired Planet*, 841 F.3d at 1000–01 (citation omitted); EX1002 ¶18, n. 3. *Kondrtizer* was neither cited nor considered during prosecution of the '199 patent.

C. *Siegel*

"Stability of Procaine in Deuterium Oxide" by Siegel et al. (EX1006, "*Siegel*") published in 1964, and constitutes prior art under at least 35 U.S.C. § 102(a)(1). *Siegel*'s prior art public accessibility is evidenced at least by (1) its date stamp, August 18, 1964 (EX1006, 1); (2) publication in a well-known and reputable journal, *Journal of Pharmaceutical Sciences* (EX1006, 1–3); and (3) the fact that it was cited by skilled artisans prior to June 24, 2014 (*e.g.*, EX1052, 2). EX1002 ¶18, n. 2. *Siegel* discloses the use of D_2O to increase the stability of aqueous ophthalmic solutions. EX1006, 4.

Siegel recognized the potential benefit of substituting D_2O for regular water in ophthalmic solutions, explaining that D_2O resembles ordinary water "more closely than any other solvent" and could be used in ophthalmic solutions. *Id*. The publication explicitly states that deuterium oxide "may prove of value, for example, in the extemporaneous preparation of ophthalmic solutions, where stability and sterility are important considerations." *Id*. *Siegel* further noted that an earlier study found the efficacy of procaine in D_2O was increased "by a factor of 2" and explained

that the increased efficacy is "attributed to a greater stability (*in vivo*) of procaine base in deuterium oxide." *Id*., 5.

Against this backdrop, *Siegel* studied the effect of D_2O on procaine, an ophthalmic compound used as a local anesthetic. *Id*., 4. Based on an earlier study showing that the hydrolysis of procaine "was shown to increase with hydroxide ion concentration," *Siegel* theorized that substituting deuterium oxide—which has a lower hydroxide ion concentration than water at equivalent pHs—would reduce the rate of hydrolysis and produce a more stable solution. *Id*.

Siegel's study showed that "the rate of deuteriolysis of procaine is less than the rate of hydrolysis." *Id*., 5. *Siegel* concluded that "increased stability in D_2O is not simply a pH effect." *Id*.

Siegel is analogous art to the '199 patent. It "is from the same field of endeavor"—ophthalmic solutions—and reasonably pertinent to "one of the particular problems dealt with by the inventor"—improving the clinical efficacy and long-term stability of ophthalmic solutions. *Unwired Planet*, 841 F.3d at 1000–01 (citation omitted); EX1002 ¶18, n. 2. Although the Applicant identified *Siegel* in an Information Disclosure Statement during prosecution, the Examiner never discussed or analyzed *Siegel* in any office action.

D. *Remington*

"Ophthalmic Preparations" and "Pharmaceutical Necessities" in the nineteenth edition of Remington's Pharmaceutical Sciences (EX1005, "*Remington*") published in 1995, and constitutes prior art under at least 35 U.S.C. § 102(a)(1). *Remington*'s prior art public accessibility is evidenced at least by (1) its date of publication, 1995 (EX1005, 4–5); its library stamp (EX1005, 8); and (3) the fact that it was cited by skilled artisans prior to June 24, 2014 (EX1072, 6, 24). EX1002 ¶18, n. 4. *Remington* discloses conventional components of ophthalmic solutions, including a standard solution appropriate for atropine. EX1005, 52.

Regarding components, *Remington* taught "vehicles suitable for salts of Atropine" contain 0.9% sodium chloride (an osmolarity adjusting agent); benzalkonium chloride (a preservative); a buffering agent such as boric acid or a phosphate buffer (sodium acid phosphate anhydrous (a phosphate buffer); and disodium phosphate anhydrous (Na_2HPO_4), and water. *Id*., 1569. *Remington* disclosed a number of other well-known "pharmaceutical necessities" including acetic acid (*id*., 1406−07) and hydrochloric acid (*id*., 1410).

In terms of administration, *Remington* disclosed that ophthalmic solutions are "by far the most common means of administering a drug to the eye" and that "instillation of eyedrops remains… one of the more accepted means of topical drug delivery." *Id*., 1566.

Remington further taught that balancing pH to optimize stability and administration is a key consideration when formulating ophthalmic solutions. *Id*., 1569−71. In this regard, *Remington* disclosed that "optimum patient comfort usually is found at the pH of the tear fluid, or about 7.4." *Id*., 1569. But because most ophthalmic solutions, including atropine, are weak bases, they become unstable at higher pHs. *Id*., 1571. Accordingly, *Remington* explained that "the attainment of optimum stability most often imposes a series of compromises on the formulator" and that "2- to 3-year stability often is achieved only by virtue of compromise." *Id*., 1571.

Remington is analogous art to the '199 patent. It "is from the same field of endeavor"—ophthalmic solutions—and reasonably pertinent to "one of the particular problems dealt with by the inventor"—optimizing ophthalmic solutions for clinical administration and long-term stability. *Unwired Planet*, 841 F.3d at 1000–01 (citation omitted); EX1002 ¶18, n. 4. Although the specification of the '199 patent mentioned *Remington*, it was never cited during prosecution of the '199 patent, and there is no evidence the Examiner considered it.

IV. The '199 Patent

A. The Specification

The '199 patent discloses ophthalmic atropine solutions to treat myopia. EX1001, abstract, 1:15–20, 4:9–11. As disclosed by *Chia*, the '199 patent explains

that "atropine or its pharmaceutically acceptable salts[] prevents or arrests the development of myopia in humans, for example as evidenced by reduction of the rate of increase of myopia in young people." EX1001, 6:28–32; EX1002 ¶¶77−81.

As was also known in the art, the '199 patent discloses that atropine solutions can be "formulated at a relatively lower pH range (*e.g.*, less than 4.5) for stability of muscarinic antagonist (*e.g.*, atropine or its pharmaceutically acceptable salts)" but that "the lower pH range in some instances causes discomfort or other side effects such as pain or burning sensation in the eye" and "elicits a tear response which reduces the absorption of the drug in the eye and therefore the effectiveness." EX1001, 6:44–55. As was known, the '199 patent further explains that these shortcomings can be "prevented or alleviated by formulating muscarinic antagonist (e.g., atropine) compositions at higher pH ranges." EX1001, 6:48–52.

As *Kondritzer* recognized and disclosed, the '199 patent notes that atropine is subject to base-catalyzed hydrolysis. EX1001, 6:67–7:17. As taught by *Siegel* and well understood in the art, the '199 patent discloses that "in some instances compositions comprising deuterated water leads to reduced base catalyzed hydrolysis when compared to compositions comprising H_2O." EX1001, 7:12–14. Thus, the use of D_2O can result in "less tear reflex in the eye." EX1001, 7:16–17.

Aside from replacing H_2O with D_2O, the '199 patent discloses nothing more than standard components well known in the art and specifically disclosed by

Remington. For instance, the '199 patent discloses the use of sodium chloride as an osmolarity (*id*., 2:55–57) and tonicity (*id*., 3:4–6) adjusting agent; a list of standard buffers used in ophthalmic solutions including phosphate, acetate, and citrate buffering agents (*id*., 2:64–3:3); and pH/pD adjusting agents including acetate, bicarbonate, ammonium chloride, citrate, phosphate (*id*., 18:45–64). Likewise, the '199 patent discloses standard storage temperatures for atropine solutions (*id*., 57:38–57) and a range of pD levels corresponding to pH levels known to optimize stability (pH 3–5) up to the optimum clinical efficacy (pH 7.4.) (*id*., 12:25–13:3).

B. Prosecution History

The original claims of the application that led to the '199 patent recited "an ophthalmic composition comprising from about 0.001 wt % to about 0.05 wt % of a muscarinic antagonist and deuterated water." EX1034, 114. These claims were rejected as obvious over U.S. Patent No. 5,716,952 ("WoldeMussie," EX1036), which broadly disclosed numerous muscarinic antagonists in ophthalmic formulations; U.S. Pub. No. 2012/0015035 ("Wildsoet," EX1037), which disclosed standard components of an ophthalmic compositions, *e.g.*, pH adjusting and buffering agents; and U.S. Pub. No. 2012/0203161 ("Herekar," EX1038), which disclosed deuterated water in combination with riboflavin. EX1035, 6−8. None of these references disclosed or otherwise discussed the SIE. EX1035, 6−8.

In response, Applicant amended the claims to specifically recite "wherein the muscarinic antagonist is atropine, or atropine sulfate." EX1039, 2. Applicant argued that the deuterated water in Herekar related to its effect on singlet oxygen and was not intended to increase the shelf life of a therapeutic. *Id*., 7−9. Applicant also presented data disclosed in the '199 patent, allegedly showing the advantages of the formulations with D_2O over those containing H_2O. *Id*., 9−13. Applicant did not discuss, however, the known SIE of D_2O. *Id*., 6−13. For instance, Applicant did not point out that *Siegel* reported a SIE by using D_2O with procaine—a carboxylic ester with the same degradation mechanism as atropine (*i.e.*, base-catalyzed ester hydrolysis). Indeed, *Siegel* was never discussed during prosecution of the '199 patent.

Following Applicant's response, an examiner interview "discussed the advantages of the claimed composition and referred to the portions of the specification to show such advantage." EX1040, 2. The interview summary also mentions discussion of § 112 issues, but there appears to have been no further consideration of WoldeMussie, Wildsoet, Herekar, or any other prior art references. EX1040, 2. The Examiner issued a Notice of Allowance without any further rejections. EX1041, 5−8. The reasons given for allowance were (1) an examiner's amendment addressing various § 112 issues and (2) "the data presented to the

advantages of the combination of atropine and deuterated water in comparison to the combination of atropine and water."[5] EX1041, 6−7.

During prosecution of a continuation of the '199 patent, U.S. Patent No. 9,770,447, the Examiner stated:

> Applicant in his remarks also argues that Teva does not teach that the addition of D_2O would increase the stability of atropine. [I]t [sic] is the examiner's position that the claims of the instant application are composition claims. The increased stability *is the expected property of such components being used together.*

EX1042, 3.[6]

C. Priority

The '199 patent identifies as "Related U.S. Application Data" U.S. Provisional Application Nos. 62/016,502 ("the '502") and 62/096,433 ("the '433"). EX1001, cover. Neither application, however, discloses "deuterated water," much less deuterated water in a 0.001%−0.03% atropine formulation at a pD of 4.2−7.9. *Compare* EX1043, p. 15−61 and EX1044, p. 15−93 *with* EX1001, claims 1, 22, 25. Accordingly, neither application "contain[s] a written description of the [later-

[5] The claims were also amended from a "0.05%" concentration at the top end of the claimed range to "0.03%." EX1041, 6.

[6] All emphases added unless otherwise noted.

claimed] invention, and of the manner and process of making and using it" as required by 35 U.S.C. § 112. EX1002 ¶¶82−83.

The challenged claims of the '199 patent are therefore not entitled to the filing date of either the '502 or '433 provisional application. *See New Railhead Mfg., L.L.C. v. Vermeer Mfg. Co.*, 298 F.3d 1290, 1293 (Fed. Cir. 2002). Instead, the earliest filing date to which the challenged claims might be entitled is April 23, 2015, the date of the earliest priority application to disclose D_2O.

V. Level of Ordinary Skill in the Art

The level of ordinary skill in the art may be reflected by the prior art of record. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001). A person of ordinary skill in the art ("POSA") at the time of the purported invention would have had a Ph.D. in Chemistry, Organic Chemistry, Physical Chemistry, or Pharmaceutics, with several years of experience involving preparation and/or testing of pharmaceutical formulations. A POSA would have been familiar with the common inactive ingredients used in aqueous pharmaceutical formulations and the basic characteristics of aqueous formulations such as stability, and would have had knowledge about drug degradation kinetics. EX1002 ¶¶84−85.

VI. Claim Construction – "Extended period of time"

Claims 2−4 recite an "extended period of time." As used in the '199 patent, a POSA would understand an "extended period of time" to mean "*at least about 1*

week." Regardless of how the term is construed, however, all the challenged claims would have been obvious for the reasons set forth herein. EX1002 ¶¶86−88.

Claim 5 of the '199 patent specifically contemplates that "about 1 week" is an "extended period of time." EX1001, Claim 5. *See e.g.*, *Integrated Claims Sys., LLC v. Travelers Indem. Co.*, 758 F. App'x 965, 967 (Fed. Cir. 2019) ("'[C]laim terms are normally used consistently throughout the patent' such that the usage of a term in one claim can often illuminate the meaning of the same term in… other claims.") (quoting *Phillips v. AWH Corp.*, 415 F.3d 1303, 1314 (Fed. Cir. 2005) (en banc)); *see also Acromed Corp. v. Sofamor Danek Group, Inc.*, 253 F.3d 1371, 1382 (Fed. Cir. 2001). Likewise, the specification repeatedly states that "In some embodiments, the extended period of time is one of about 1 week." EX1001, 1:46−52, 4:67−5:6, 11:15−16, 23:43−48.

VII. Statement of Precise Relief Requested

Ground	References	Basis	Claims
1	*Chia*, *Siegel*, and *Kondritzer*	§ 103	1−4, 7, 10−11, 14−16, 19−27
2	*Chia*, *Siegel*, *Kondritzer*, and *Remington*	§ 103	1−4, 7−27

VIII. Ground 1: Claims 1−4, 7, 10−11, 14−16, and 19−27 Would Have Been Obvious Over *Chia* and *Siegel* in view of *Kondritzer*

A. Summary of the Combination

The challenged claims recite three elements: (1) *Chia*'s conventional low-concentration atropine formulation with (2) D_2O substituted for H_2O to increase the formulation's stability at (3) pD levels that were well known to be desirable for treating myopia with atropine. EX1002 ¶¶18−21. Before the earliest possible effective filing date, it was known (*e.g.*, from *Siegel*) that D_2O could be used to increase the stability of ophthalmic compounds by reducing the rate of base-catalyzed ester hydrolysis—long understood (*e.g.*, from *Kondritzer*) to be the primary mechanism of atropine degradation. *Siegel* specifically taught that D_2O "may prove of value, for example, in the extemporaneous preparation of ophthalmic solutions, where stability and sterility are important considerations." EX1006, 4. By substituting D_2O for H_2O, *Siegel* observed a solvent isotope effect on procaine—an ophthalmic compound subject to base-catalyzed ester hydrolysis. *Id*., 5.

There was ample motivation to make this substitution. EX1002 ¶¶89−92. In 2012, *Chia* disclosed that low-concentration atropine eye drops effectively treated myopia and reduced the patient compliance issues associated with higher concentration formulations. EX1003, 13, 19−20. This clinical success provided a motivation to make and use low-concentration atropine formulations that could be administered at clinically optimal pH levels—*i.e.*, those approaching the natural pH

of tears (7.4) so as not to exacerbate the compliance problem *Chia* sought to remedy. EX1003, 13. Of course, ensuring stability is always a consideration in ophthalmic formulations, and it was known that stability of atropine decreases as pH increases above 5. EX1004, 6, 8. In this regard, *Siegel* and *Kondritzer* would have motivated a POSA to substitute H_2O with D_2O to increase atropine's stability at higher pHs, and a POSA would have expected success in doing so given the solvent isotope effect and increased stability that *Siegel* reported for procaine. EX1006, 4. As a POSA would readily understand, atropine shares many similarities with procaine and would have reasonably expected the benefits in stability and clinical efficacy obtained with D_2O-procaine would translate to D_2O-atropine formulations. EX1004, 6; EX1006, 4−5.

B. Motivation and Reasonable Expectation of Success

1. A POSA Would Have Been Motivated to Formulate a Low-Concentration Atropine Solution with Long-Term Stability

Atropine eye drops had long been used to treat myopia at concentrations of 0.5% and 1%. *E.g.*, § II.A; EX1002 ¶93. While these solutions were effective in treating myopia, they caused several side effects, such as photophobia, cycloplegia, and mydriasis, which resulted in poor compliance. *E.g.*, EX1012 ¶[0006]; EX1015, 1; EX1014, 3; EX1013, 2; EX1045, 2, 5; EX1002 ¶94.

Recognizing this problem, *Chia* studied the efficacy of lower concentration formulations and demonstrated that 0.01% atropine solutions were clinically

effective to treat myopia, explaining that "atropine 0.01% has minimal side effects compared with atropine at 0.1% and 0.5%, and retains comparable efficacy in controlling myopia progression" compared to higher-concentration solutions. EX1003, 13. *Chia* expressly promoted the use of these lower-concentration solutions, noting that such solutions were not yet commercially available and that their findings "collectively suggest that a nightly dose of atropine at 0.01% seems to be a safe and effective regimen for slowing myopia progression in children, with minimal impact on visual function in children." EX1003, 19−20; *see also* EX1013, 5.

Chia's success with 0.01% atropine and suggestion that it "seems to be a safe and effective regimen for slowing myopia progression in children" (EX1003, 20) provided a motivation to pursue a stable, ready-to-use formulation for that treatment. EX1002 ¶¶95−98. Stability of ophthalmic solutions "is always a primary consideration, both in the bottle and in the tissues," and was particularly important to low-concentration atropine where "the loss of even small amounts of drug… can become significant." EX1046, 16; EX1047, 1−2. Because using atropine for myopia requires long-term treatment, a POSA would have been motivated to increase stability and shelf life of these low-concentration formulations. *E.g.*, EX1048, 5; EX1046, 15 ("[P]harmaceutical manufacturer[s] strive[] for a shelf-life measured in years.").

A POSA would have been further motivated towards a formulation that could maintain long-term stability when formulated at pHs closer to the pH 7.4 optimal for comfort, and thus, patient compliance and adherence. *E.g.*, EX1005, 52; EX1048, 4−5; EX1002 ¶¶99−103. As *Kondritzer* demonstrates, atropine was substantially stable at pH 3−5. EX1004, 6, 8 (Table III); EX1049, 1; EX1033, 1. This acidic pH, however, causes patient discomfort and irritation and leads to the same issue of low compliance that plagued the higher-concentration formulations. EX1050, 7; EX1015, 1; EX1012 ¶[0006]. Moreover, lower pH causes excess tearing that negatively impacts bioavailability and clinical efficacy of individual doses. EX1046, 8; EX1051, 2; EX1047, 2 ("[T]ears are mainly responsible for the short residence time and low absorption of drugs applied topically to the eye.").

Thus, a POSA would have been motivated to increase the long-term stability of *Chia*'s low-concentration atropine at pHs closer to the clinically desirable pH 7.4 EX1002 ¶¶99−103. As discussed below, *Siegel*'s use of D_2O with the structurally similar procaine was an obvious route to improving the stability of *Chia*'s low-concentration atropine for long-term use.

2. A POSA Would Have Been Motivated to Use D_2O to Increase Long-Term Stability of a Low-Concentration Atropine Formulation

Considering *Siegel*, a POSA would have recognized that deuterium oxide could reduce the degradation of atropine at pH levels more optimal for clinical

efficacy and improve long-term shelf life. EX1002 ¶¶104−110. *Siegel* explicitly states that deuterium oxide "may prove of value, for example, in the extemporaneous preparation of ophthalmic solutions, where stability and sterility are important considerations." EX1006, 4. *Siegel* further recognized an earlier study which found the efficacy of procaine in deuterium oxide was greater in D_2O by a factor of two and that the increased activity is "attributed to a greater stability (*in vivo*) of procaine base in deuterium oxide." *Id*., 4−5; *see also* EX1052, 4 (disclosing using D_2O to "stabilize and thus prolong the long term shelf-life"); EX1029, 20. Thus, a POSA would have understood from *Siegel* that D_2O could increase the efficacy and long-term stability of ophthalmic solutions. EX1002 ¶¶58, 104−105.

A POSA would have also known that the SIE seen for procaine in D_2O was attributable to its mechanism of degradation, base-catalyzed hydrolysis and that, in general, carboxylic acids degraded by base-catalyzed hydrolysis exhibited SIEs in D_2O. *See* EX1002 ¶¶50−54, 106−107; EX1006, 4; EX1025, 63; *infra*, § X.A. Likewise, it was understood that the effect of D_2O on the rate of reaction was predicted by the effect seen on structurally related compounds and "by analogy with known reaction mechanisms." EX1025, 26; *see also id*., 45−49; EX1002 ¶¶48−49.

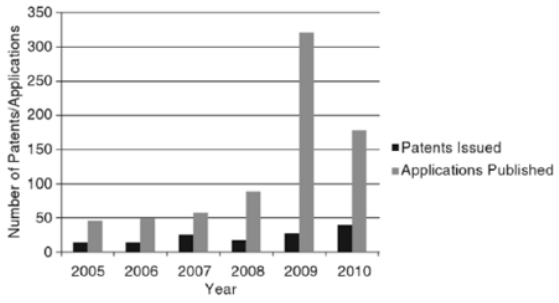
Considering *Kondritzer*, a POSA would have recognized that procaine and atropine share several similarities. EX1002 ¶¶106−111. Atropine, like procaine, is a carboxylic ester, degrades via base catalysis, and its rate of degradation is driven

by OH^- concentration. EX1002 ¶¶107−108; EX1004, 6; EX1006, 4. Also like procaine, atropine is a weak base and its pKa of 9.9 is similar to procaine's pKa of 8.8. EX1002 ¶109; EX1053, 41−42; EX1054, 2. Thus, a POSA would have understood that D_2O reduces the rate of base-catalyzed ester hydrolysis and would therefore be expected to increase the stability of atropine, which likewise degrades via base-catalyzed ester hydrolysis. EX1002 ¶¶106−111.

Moreover, as *Siegel* recognized, "since deuterium oxide resembles protium oxide (ordinary water) more closely than any other solvent" (EX1006, 4), the substitution of D_2O would not be expected to negatively influence the stability of atropine or otherwise detract from its clinical efficacy. EX1002 ¶112; EX1052, 4 ("[N]o new decomposition products… to be expected, besides those which are known from ordinary water…."); EX1023, 16. The simple substitution of D_2O for H_2O held the potential to improve the shelf-life and clinical efficacy without affecting any of the other beneficial properties. EX1002 ¶113; EX1029, 1, 6−8, 18−20; EX1030, 7−9; EX1023, 7−9. Thus, a POSA would have been motivated to make this substitution since it offered a desired improvement without an adverse effect on clinical efficacy. *Incyte Corp. v. Concert Pharms. Inc.*, IPR2017-01256, Paper 119, at 27 (PTAB Apr. 8, 2019) (finding motivation to modify known pharmaceutical with deuterium based on "the potential to improve the safety, tolerability, and efficacy of those compounds"); *Daiichi Sankyo Co. v. Matrix Labs.,*

Ltd., 619 F.3d 1346, 1352 (Fed. Cir. 2010) (motivation based on expectation of "similar or improved properties compared with the old").

Finally, between *Siegel*'s publication and the priority date of the '199 patent, D_2O had become more widely available. *E.g.*, *compare* EX1029, 11 and EX1027, 3 ("Enough D_2O is now available for exploring its physical, chemical, and biological properties, and subsequent application in biological systems") *with* EX1006, 4 (disclosing price of D_2O reasonable to "study" its effect on procaine); *see also* EX1002 ¶115; EX1023, 16. As shown below in Figure 2, the decade preceding the priority date of the '199 patent saw an explosion in the use of deuterium to improve upon known pharmaceuticals. EX1002 ¶114; *see also* EX1056, 3; EX1031, 5. As a 2011 article noted, "It is remarkable that these activities have their roots more than 40 years ago when in the 1960s first corresponding results were published." EX1030, 14.



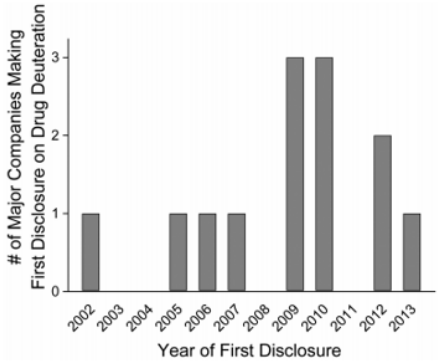


Figure 2.
Time course of major pharma companies first disclosing drug deuterium pharmacokinetic improvements in US Patent applications.

Figure 2. Left: EX1055, 68 (Fig. 10.4) Right: EX1032, 15 (Fig. 2)

Since *Siegel*'s publication, numerous researchers had recognized D_2O's potential to improve known pharmaceuticals. *E.g.*, EX1002 ¶¶60−63, 115−116; EX1029, 1, 6−8, 18−20; EX1030, 7−9, 13−14; EX1027, 1−2; EX1057, 6 ("D_2O itself has an effect in increasing the stability of the compositions of the invention."). For example, Teva used D_2O to reduce hydrolysis of carboxylic acid derivatives in aqueous solution and explained that "stability… for long-term storage can be enhanced by replacing at least a major part of the ordinary water in such compositions by deuterium oxide." EX1052, 2. A 2014 presentation titled "The use of deuterium oxide to stabilize pharmaceuticals against chemical degradation" explicitly taught that "Deuterium oxide improve[s] stability of unstable drugs" was an "Expected Outcome" of D_2O modification. EX1029, 1, 20.

3. A POSA Would Have Had a Reasonable Expectation of Success in Substituting D_2O for H_2O in a Low-Concentration Atropine Formulation

A POSA would have had a "reasonable expectation of success in deriving *the claimed invention* in light of the teachings of the prior art." *See Amgen, Inc. v. F. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1362 (Fed. Cir. 2009). Aside from the substitution of D_2O, the claims of the '199 patent recite standard ophthalmic solutions of 0.001%−0.03% atropine proven effective against myopia in large scale clinical trials. *E.g.*, EX1003, 13, 15−20; EX1014, 1; EX1017, 1; EX1002 ¶¶25−36, 118. D_2O did not present any unique formulation issues and had been incorporated into numerous ophthalmic therapeutics. *E.g.*, EX1002 ¶118; EX1006, 4−5; EX1058, Abstract ("A deuterated ocular solution is applied to an eye. The deuterated ocular solution includes deuterated water and one or more ocular drugs."); EX1059, 8 ("The invention relates… to the use of deuterium oxide for the production of a drug for the prevention and/or treatment of virus-based diseases of the eye."); EX1087, 1. Accordingly, there was a reasonable expectation of success in achieving the claimed invention. EX1002 ¶¶117−118.

There was also a reasonable expectation that the claimed formulations would have improved stability compared to solutions containing regular water. EX1002 ¶119. *Siegel* taught that at pD levels close to those of the '199 claims, D_2O increased the stability of procaine by a factor of 2−3. EX1006, 5. Owing to the

similarities in structure and degradation reactions between procaine and atropine, a POSA would have reasonably expected that a similar SIE would be seen for atropine as was seen for procaine. EX1002 ¶¶107−111; EX1025, 26, 32, 63. The expectation of success was bolstered by the art as a whole, which was replete with literature demonstrating that D_2O increased the stability of carboxylic acids subject to base-catalyzed ester hydrolysis. EX1002 ¶¶49−54, 119; EX1060, 4; EX1061, 4; EX1054, 2; EX1062, 3; EX1063, 4; EX1064, 4.

C. Claim-by-Claim Analysis

1. Claim 1

a. 1[a] "An ophthalmic composition, comprising…"

Should the preamble be construed as limiting, *Chia* renders it obvious. *Chia* disclosed administration of an atropine eye drop solution for the treatment of myopia. EX1003, 13, 19−20. Atropine is a known ophthalmic compound, (EX1003, 13), and atropine solutions such as those disclosed in *Chia* are a species of ophthalmic compositions. EX1002 ¶¶120−123; *Atlas Powder Co. v. IRECO, Inc*., 190 F.3d 1342, 1346 (Fed. Cir. 1999) ("[A] single prior art species within the patent's claimed genus reads on the generic claim….").

b. 1[b] "from about 0.001 wt % to about 0.03 wt % of a muscarinic antagonist…"

Chia renders this limitation obvious. EX1002 ¶¶124−126. *Chia* disclosed that atropine is a muscarinic antagonist (EX1003, 18), that "[t]he lowest

concentration of 0.01% atropine… is a viable concentration for reducing myopia progression," and that "the 0.01% formulation exhibited fewer adverse events" than 1%, 0.1%, and 0.5% atropine. EX1003, 19−20; *see also id*., 13−14. Moreover, *Chia* provides express motivation, disclosing that 0.01% atropine was not yet commercially available and concluding that their "findings collectively suggest that a nightly dose of atropine at 0.01% seems to be a safe and effective regimen for slowing myopia progression in children, with minimal impact on visual function in children." EX1003, 20; EX1002 ¶126. The efficacy of low concentration atropine was well established in the art. *See, e.g.*, EX1018, 19:12−13; EX1014, 1; EX1002 ¶127.

c. 1[c] "and deuterated water"

Siegel renders this limitation obvious. EX1002 ¶¶128−136. *Siegel* disclosed ophthalmic solutions comprising D_2O, taught that D_2O increased the long-term stability and clinical efficacy of procaine, and expressly motivated its use, stating that D_2O: "may prove of value, for example, in the extemporaneous preparation of ophthalmic solutions, where stability and sterility are important considerations." EX1006, 4−5. Given the similarities of atropine and procaine discussed above, a POSA would have been motivated to apply the teachings of *Siegel* to the low-concentration formulations championed by *Chia*. EX1002 ¶129.

As *Siegel* demonstrated, D_2O offered the potential to improve the stability of low-concentration atropine solutions without negatively affecting their beneficial properties—*i.e.*, the efficacy in treating myopia established by *Chia*. EX1002 ¶¶134−135. As a POSA would have understood, this increased stability would have been particularly desirable for *Chia*'s atropine solutions, which required long-term use, had to balance pH against stability for optimal clinical efficacy, and were of low concentration such that the loss of small amounts to degradation could negate efficacy. EX1002 ¶¶132−133.

First, long-term shelf life is unquestionably beneficial, as it allows the solutions to remain effective for longer periods than comparable H_2O formulations. EX1002 ¶131; EX1088, 4; EX1080, 7; EX1046, 15. This was particularly beneficial to atropine, which requires long term use to effectively treat myopia. *E.g.*, EX1002 ¶131; §§ VIII.B.1−2. *Siegel*'s use of D_2O followed the art: "As [was] well known, deuterium oxide is itself both stable and effectively non-toxic…. It is therefore an ideal solvent medium for [increasing long-term stability]."). EX1052, 3.

Low-concentration atropine also had to be formulated at a pH that balanced long-term stability against clinical efficacy. EX1002 ¶132. While lower pH solutions were more stable, the increased acidity at these lower pHs undermined patient compliance and long-term efficacy; indeed "2- to 3-year stability often [was]

achieved only by virtue of compromise." EX1005, 54. Further, increased stability was especially beneficial to low-concentration atropine formulations, where "the loss of even small amounts of drug… can become significant." EX1046, 16; EX1047, 1−2; EX1051, 2. D_2O offered the potential to improve upon the long-term stability of the low-concentration formulations, while increasing the pH levels to those more optimal for clinical efficacy. §§ VIII.B.1−2.

The POSA's motivation was bolstered by the "utterly predicable" nature of deuterium modification (EX1023, 17)—the simple substitution of D_2O would have been expected to result in a product *at least* as effective as the H_2O formulation used successfully by *Chia*. EX1002 ¶¶134−135; EX1052, 4. Aside from being heavier, deuterium oxide is nearly identical to water in most other respects. EX1002 ¶¶55−57; EX1028 ¶[0011]; EX1023, 8−9; EX1022, 9; *see Conopco, Inc. v. The Proctor & Gamble Company*, IPR2013-00505, Paper 69, at 21 (PTAB Feb. 10, 2015) ("Where two known alternatives are interchangeable for a desired function, an express suggestion to substitute one for the other is not needed to render a substitution obvious.") (citing *In re Fout*, 675 F.2d 297, 301 (CCPA 1982)).

Finally, motivation may be based on "common knowledge [or] the prior art as a whole." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1362 (Fed. Cir. 2007). While *Siegel* disclosed the benefits of D_2O with a close structural analog of atropine, the targeted effect of deuterium—*i.e.*, its ability to increase stability while leaving

all other properties unchanged—was textbook science. *E.g.*, EX1002 ¶¶57−64; EX1023, 5−9. Because motivation may be based on an expectation of "similar or improved properties," this alone provided the POSA sufficient motivation to modify *Chia*'s low-concentration atropine with D_2O. *Daiichi*, 619 F.3d at 1352; *see also Incyte*, IPR2017-01256, Paper 119 at 27.

d. 1[d] "at a pD of from about 4.2 to about 7.9"

Kondritzer and *Siegel* render this limitation obvious. EX1002 ¶¶137−144.

It was well known that pH is a result-effective variable for stability and patient comfort. EX1002 ¶¶139−140. *Kondritzer* taught that the rate of degradation is dependent on OH^- concentration, (*i.e.*, pH) (EX1004, 5−6, 8) and it was well understood that "comfort in the eye" is dependent on pH (EX1005, 52). Optimization of pH was routine in ophthalmic solutions where selection of the "proper pH… often represent[s] a compromise between stability of the drug and comfort in the eye." EX1005, 52. *Kondritzer* explicitly supported such optimization, disclosing atropine's stability is optimum at pH 3−5 (pD 3.4−5.4) (EX1004, 8), stability predictions between pH 2 and pH 7 (*id*., 4), and referencing prior studies at pH 4–5 (pD 4.4–5.4) and pH 2.8–6 (pD 3.2–6.4) (*id*., 2). EX1002 ¶141. As pH was a well-known result-effective variable, and these ranges overlap with and/or are encompassed by the pD 4.2–7.9 range of claim 1, the claimed range was obvious. *E.I. DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996,

1010 (Fed. Cir. 2018) ("[D]iscovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art.") (quoting *In re Boesch*, 617 F.2d 272, 276 (CCPA 1980)).

Further, it would have been obvious to formulate the claimed atropine solution at pD 5.4–6.4 (pH 5–6) based on the teachings of *Kondritzer* and *Siegel*. EX1002 ¶¶142−143. Such a composition falls squarely within and renders obvious the claimed range. *See Alcon Res., Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1368 (Fed. Cir. 2012) ("[I]f prior art discloses a portion of the claimed range, the entire claim is invalid"); *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311 (Fed. Cir. 2006); *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003).

To balance long term stability with clinical considerations, a POSA would have been motivated towards a pH between pD 5.4 (pH 5)—the high end of optimum stability according to *Kondritzer*—and pD 7.8 since "[i]deally, ophthalmic preparations should be formulated at a pH equivalent to the tear fluid value of 7.4 [*i.e.*, pD of 7.8]." EX1005, 54. A POSA would have been motivated to get close to pD 7.8, but would have recognized that above pD 6.4 "hydrolysis became very rapid." EX1004, 6. Thus, a POSA would have recognized that pD 5.4−6.4 was optimal. EX1002 ¶142.

The motivation and reasonable expectation of success for these higher pD levels was further bolstered by *Siegel*, which demonstrated that D_2O-atropine

solutions would be expected to have increased stability compared to H_2O solutions. EX1006, 5; EX1002 ¶143. And the obviousness of pD 5.4–6.4 is underscored by it being bracketed by the pH ranges already shown to work for atropine in the treatment of myopia. EX1065, 2 ("The pH value of the product should be 4.0~6.0 [pD 4.4–6.4]."); EX1066, 3 (pH 3.5–6 [pD 3.9–6.4]); EX1086; EX1067, 3 (pH 4–6 [pD 4.4–6.4]); EX1002 ¶144.

e. 1[e] "wherein the muscarinic antagonist is atropine, or atropine sulfate"

Chia renders this limitation obvious. EX1002 ¶¶145–148. As discussed above, *Chia* disclosed the use of atropine solutions to treat myopia. EX1003, 13, 19−20. Moreover, the art showed that the "most widely studied pharmacological agent for the inhibition of myopia progression has been atropine" (EX1013, 2) and was replete with references teaching the use of atropine solutions to treat myopia. *E.g.*, § VIII.B.1; EX1002 ¶¶25−36, 147.

2. Claim 2

Dependent claim 2 recites: "The ophthalmic composition of claim 1, wherein the ophthalmic composition has a pD of one of: less than about 7.3, less than about 7.2, less than about 7.1, less than about 7, less than about 6.8, less than about 6.5, less than about 6.4, less than about 6.3, less than about 6.2, less than about 6.1, less than about 6, less than about 5.9, less than about 5.8, less than about 5.2, or less than about 4.8 after extended period of time under storage condition." EX1001, claim 2.

The combination of *Chia*, *Siegel*, and *Kondritzer* renders this additional feature obvious. EX1002 ¶¶149−155.

As discussed above, an "extended period of time" should be construed as at least one week. There was a reasonable expectation of success that the formulations of claim 1 at least at the obvious pD of 5.4−6.4 (§ VIII.C.1.d) would meet the stability limitation of claim 2. *See Santarus, Inc. v. Par Pharms., Inc*., 694 F.3d 1344, 1354 (Fed. Cir. 2012) ("an obvious formulation cannot become nonobvious" by claiming its properties); *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991).

A prior study of atropine eye drops at pH 5 (pD 5.4) showed no statistically significant variation in pH over thirty days. EX1050, 5. Similarly, the art showed that over the course of one year, "[t]here were slight increases in pH [of an atropine formulation], of 1.08, 0.77, and 0.41 at 35°C, 23°C, and 5°C, respectively." EX1068, 3. A formulation with an initial pD of 5.4 would be expected to increase by, at most, 1.08 over the course of one year and would be well within the bounds set by claim 2—*e.g.*, "less than 7.3." Over the course of a one-week period, this variation would be substantially less, even if measurable. EX1002 ¶¶152−153. And, as demonstrated by this example, if the Board construes an "extended period of time" as a period longer than at least one week, claim 2 would still be obvious. EX1002 ¶154.

3. Claim 3

Dependent claim 3 recites: "The ophthalmic composition of claim 1, wherein the ophthalmic composition comprises one of: at least about 80%, at least about 85%, at least about 90%, at least about 93%, at least about 95%, at least about 97%, at least about 98%, or at least about 99% of the muscarinic antagonist based on initial concentration after extended period of time under storage condition." EX1001, claim 3. The combination of *Chia*, *Siegel*, and *Kondritzer* renders this additional feature obvious. EX1002 ¶¶156−165.

As discussed above, an "extended period of time" should be construed as at least one week. There was a reasonable expectation that the formulations of claim 1 at least at the obvious pD 5.4–6.4 (§ VIII.C.1.d) would retain at least 80% atropine after at least one week. *See Santarus*, 694 F.3d at 1354; *In re Baxter*, 952 F.2d at 392.

Kondritzer disclosed the predicted half-lives of atropine at pH levels falling within the range of 5.4–6.4. EX1004, 8 (Table III). The data shows that at room temperature (20° C) and pH 5 (pD 5.4) atropine has a half-life of 266 years. *Ibid*. As Dr. Byrn explains, this means that at these conditions, atropine would retain 80% of the initial concentration for 85.6 years. EX1002 ¶¶159−162. This readily meets the stability limitation of claim 3, which allows for up to 80% degradation after at least one week. EX1002 ¶162. As *Siegel* taught that the claimed D_2O formulations

would be expected to be more stable (§§ VIII.B.2−3), the expectation of success for the compositions of claim 3 would be even higher than the H_2O formulations disclosed by *Kondritzer*. EX1002 ¶163.

As this example demonstrates, if the Board construes an "extended period of time" as a period longer than at least one week, claim 3 would still be obvious. EX1002 ¶162. Moreover, neither claim 1 nor claim 3 recites a temperature limitation and both allow for pD levels down to 4.2 (pH 3.8). *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 419 (2007) ("What matters is the objective reach of the claim. If the claim extends to what is obvious, it is invalid under § 103."); *Atlas Powder*, 190 F.3d at 1346. At a storage condition of pH 3.8 and 2° C, which also reads on claim 3, a POSA would reasonably expect 80% of the initial concentration for an even longer period of time than the pH 5/20° C example. EX1004, 8; EX1002 ¶164.

4. Claim 4

Dependent claim 4 recites: "The ophthalmic composition of claim 1, wherein the ophthalmic composition further has a potency of one of: at least 80%, at least 85%, at least 90%, at least 93%, at least 95%, at least 97%, at least 98%, or at least 99% after extended period of time under storage condition." EX1001, claim 4. The combination of *Chia* and *Kondritzer* renders this additional feature obvious. EX1002 ¶¶166−173.

There was a reasonable expectation that the formulations of claim 1 at the obvious pD 5.4–6.4 (§ VIII.C.1.d) would retain at least 80% potency after at least one week. *See Santarus*, 694 F.3d at 1354; *In re Baxter*, 952 F.2d at 392. Potency is a function of concentration; the retained potency mirrors the retained concentration level, discussed above for claim 3. EX1002 ¶169; EX1072, 6; EX1001, 1:29−46. As explained for claim 3, *Kondritzer* demonstrates that a POSA would expect the compositions of claim 1 at the obvious pD 5.4–6.4 to retain at least 80% for longer than at least one week. § VIII.C.3. As potency tracks concentration, a POSA would likewise expect the compositions of claim 1 to readily exceed the limitations of claim 4. EX1002 ¶170; *see KSR*, 550 U.S. at 419; *Atlas Powder*, 190 F.3d at 1346.

If the Board construes "an extended period of time" as a longer period than "at least one week," claim 4 still would have been obvious. As described above for claim 3, a POSA would have expected the solution to retain 80% concentration for significantly longer than one week, and likewise, would have expected 80% potency after significantly longer than at least one week. EX1002 ¶171. Moreover, as with claim 3, claim 4 recites no limitations on temperature and allows for pD levels down to 4.2 (pH 3.8); formulations stored at low temperatures and/or low pDs would retain at least 80% potency even longer. *See* § VIII.C.3; EX1002 ¶172.

5. Claim 7

Dependent claim 7 recites: "The ophthalmic composition of claim 1, wherein the muscarinic antagonist is present in the composition at a concentration of one of: from about 0.001 wt % to about 0.025 wt %, from about 0.001 wt % to about 0.02 wt %, from about 0.001 wt % to about 0.01 wt %, from about 0.001 wt % to about 0.008 wt %, or from about 0.001 wt % to about 0.005 wt %." EX1001, claim 7. *Chia* renders this additional feature obvious. EX1002 ¶¶174−177.

As explained above, *Chia* disclosed administration of 0.01% atropine compositions, a muscarinic agent at a concentration within the ranges recited by claim 7 (*e.g.*, "from about 0.001 wt % to about 0.025 wt %"). § VIII.C.1.b; EX1003, 13; *see KSR*, 550 U.S. at 419; *Atlas Powder*, 190 F.3d at 1346. Claim 7 imparts no patentability over claim 1 and would have been obvious for all the reasons discussed above. *See* § VIII.C.1.

6. Claims 10 and 11

Dependent claim 10 recites: "The ophthalmic composition of claim 1, wherein the ophthalmic composition further comprises a preservative." EX1001, claim 10. Dependent claim 11 recites: "The ophthalmic composition of claim 10, wherein the preservative is selected from benzalkonium chloride, cetrimonium, sodium perborate, stabilized oxychloro complex, SofZia, polyquaternium-1, chlorobutanol,

edetate disodium, polyhexamethylene biguanide, or combinations thereof." *Id.*, claim 11. *Chia* renders these additional features obvious. EX1002 ¶¶178−185.

Claim 11 recites a list of well-known, traditional preservatives used in atropine and other ophthalmic compositions. EX1002 ¶¶75−76, 181. *Chia* explicitly discloses that its "[t]rial medication consisted of the appropriate dose of atropine sulfate with 0.02% of 50% *benzalkonium chloride as a preservative*." EX1003, 14. *Chia*'s disclosure reflected standard practice in the art. *E.g.*, EX1002 ¶¶182−183 EX1005, 55−56; EX1066, 3; EX1049, 2; *see also* EX1069, 8 (disclosing chlorobutanol to preserve eyedrops).

Because "[a] broader independent claim cannot be nonobvious where a dependent claim stemming from that independent claim is invalid for obviousness," the obviousness of benzalkonium chloride as recited by claim 11 renders claim 10 obvious. *Comaper Corp. v. Antec, Inc*., 596 F.3d 1343, 1350 (Fed. Cir. 2010); *Atlas Powder*, 190 F.3d at 1346.

7. Claim 14

Dependent claim 14 recites: "The ophthalmic composition of claim 1, wherein the ophthalmic composition is essentially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof." EX1001, claim 14. *Chia* renders this additional feature obvious. EX1002 ¶¶186−191.

Chia discloses arresting myopia with atropine formulations free of procaine and benactyzine. EX1003, 13. The art demonstrates that atropine is generally not administered with procaine or benactyzine to treat myopia. *E.g.*, EX1002 ¶189; EX1005, 52 (disclosing standard formulations suitable for use with atropine that do not contain procaine or benactyzine); EX1067, 2 (disclosing process of preparing atropine formulation that does not include the addition of procaine or benactyzine.); EX1014, 1−2. It would have been obvious to formulate atropine compositions in the same manner shown to be effective to treat myopia—"essentially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof." EX1002 ¶190.

8. Claims 15 and 16

Dependent claim 15 recites: "The ophthalmic composition of claim 1, wherein the ophthalmic composition has a dose-to-dose muscarinic antagonist concentration variation of one of: less than 50%, less than 40%, less than 30%, less than 20%, less than 10%, or less than 5%." EX1001, claim 15. Dependent claim 16 recites: "The ophthalmic composition of claim 15, wherein the dose-to-dose muscarinic antagonist concentration variation is based on one of: 10 consecutive doses, 8 consecutive doses, 5 consecutive doses, 3 consecutive doses, or 2 consecutive doses." *Id.*, claim 16. The combination of *Chia* and *Kondritzer* renders these additional features obvious. EX1002 ¶¶192−200.

"Dose-to-dose muscarinic antagonist concentration variation" refers to the difference in the concentration of a muscarinic antagonist between sequentially administered doses.[7] EX1001, 9:1−9, 37:50−38:48; EX1002 ¶195. That is, claims 15 and 16 would read on an atropine solution in which the atropine concentration of a second dose was at least 50% of the concentration of the first dose.

Chia discloses that "0.01% atropine [is] to be administered once nightly"—*i.e.*, a period of approximately twenty-four hours between doses. EX1003, 13. Administration of atropine nightly was standard practice in the art. *E.g.*, EX1011, 2; EX1014, 1−2; EX1017, 1−2; EX1002 ¶196.

Variation in the amount of the active ingredient between doses is driven by the stability of the of the active ingredient in solution. EX1002 ¶197. As discussed above for claim 3, *Kondritzer* shows that a POSA would expect the compositions

[7] To the extent Patent Owner asserts that "dose-to-dose uniformity" refers to ophthalmic agent distribution, claims 15 and 16 are obvious. As discussed above for claim 1[a], *Chia* taught ophthalmic *solutions*. § VIII.C.1.a. "By definition, all-ingredients are completely in solution, uniformity is not a problem…." EX1005, 49. Moreover, any minor issues with dose-to-dose uniformity that are not related issues such as whether the patient shakes the bottle prior to use (EX1001, 38:20−35); claims 15 and 16 do not recite any limitations on these. EX1002 ¶198.

recited by claim 1 to retain at least 80% concentration for longer than at least one week. § VIII.C.3; EX1004, 8. Claims 15 and 16 recite a far lower concentration (50%) for a shorter period of time (twenty four hours), and thus would have been obvious. EX1002 ¶199; *see also KSR*, 550 U.S. at 419; *Atlas Powder*, 190 F.3d at 1346; *Comaper*, 596 F.3d 1350 (Fed. Cir. 2010).

9. Claim 19

Dependent claim 19 recites: "The ophthalmic composition of claim 1, wherein the ophthalmic composition comprises one of: less than 5% of H_2O, less than 4% of H_2O, less than 3% of H_2O, less than 2% of H_2O, less than 1% of H_2O, less than 0.5% of H_2O, less than 0.1% of H_2O, or 0% of H_2O." EX1001, claim 19. *Siegel* renders this additional feature obvious. EX1002 ¶¶201−207.

As explained above for claim 1, substituting deuterium oxide for regular water in 0.01% atropine solutions was obvious. § VIII.C.1.d. *Siegel* disclosed that the D_2O solutions used to stabilize procaine consisted of 99% deuterium oxide. EX1006, 4. It would have been obvious to use the same levels of D_2O effective in increasing the stability of procaine to increase the stability of atropine. EX1006, 4−5; EX1002 ¶204.

Moreover, a POSA would have understood that higher levels of deuterium oxide—*i.e.*, the 95% or more recited by claim 19—would lead to a greater solvent isotope effect, and, in turn, larger increases in stability compared to atropine

solutions with greater amounts of regular water. EX1022, 10−11 (reporting prior study finding "[t]he rate of hydrolysis [of acetylcholine bromide] was decreased 10.6% in 20% D_2O, 23% in 50% D_2O, and about 33% in 75% D_2O" compared to regular water); EX1070, 2; EX1064, 7 (Fig. 3). Conversely, lower concentrations of D_2O would simply mean that a greater proportion of the solution was regular water, and thus, would be less stable than the solutions containing >95% D_2O. EX1002 ¶¶205−206.

Consistent with this intuitive concept, the art as a whole demonstrated that use of high levels of deuterium oxide were standard practice in the art. *E.g.*, EX1052, 3 ("[P]harmaceutical compositions may contain, say, about 98% or 99% deuterium oxide, the balance being ordinary water."); EX1063, 2 ("[T]he hydrogen content of the solvent… did not exceed 0.5 %"); EX1062, 2 (99.5% D_2O); EX1061, 1 (99.8% D_2O); EX1064, 2 (99.9% D_2O); EX1057, 10 (99.9% D_2O).

10. Claim 20

Dependent claim 20 recites: "The ophthalmic composition of claim 1, wherein the ophthalmic composition is not formulated as an injectable formulation." EX1001, claim 20. *Chia* renders this additional feature obvious. EX1002 ¶¶208−212.

Chia disclosed an atropine composition formulated for administration as "eye drops" (EX1003, 13−14) that a POSA would have understood was "not formulated

as an injectable solution." EX1002 ¶210. To treat myopia, formulating atropine as topical solutions for instillation was standard practice (EX1002 ¶211); the art taught "instillation of eyedrops remains… one of the more accepted means of topical drug delivery." EX1005, 49; *see also* EX1018, 18:2−4; EX1014, 1; EX1013, 1.

11. Claim 21

Dependent claim 21 recites: "The ophthalmic composition of claim 1, wherein the ophthalmic composition is formulated as an ophthalmic solution for the treatment of pre-myopia, myopia, or progression of myopia." EX1001, claim 21. *Chia* renders this additional feature obvious. EX1002 ¶¶213−217.

As explained above, the atropine solutions recited by claim 1 were obvious. § VIII.C.1. *Chia* disclosed that 0.01% atropine solutions were effective to treat myopia. EX1003, 13, 19−20. Thus, it would have been obvious to formulate *Chia*'s atropine solutions, modified with the D_2O of *Siegel* at the pD levels of *Kondritzer*, to treat pre-myopia, myopia, or progression of myopia. EX1002 ¶¶215−217; *see also*, § VIII.C.15.

12. Claim 22

Claim 22 is identical to claim 1 except it recites an "ophthalmic solution" instead of an "ophthalmic composition." *Chia* discloses an ophthalmic solution. EX1003, 13. Accordingly, claim 22 is obvious for all the reasons described for claim 1. § VIII.C.1; EX1002 ¶¶218−221.

13. Claim 23

With the exception of "ophthalmic solution," claim 23 is identical to claim 2. *Chia* discloses an ophthalmic solution. EX1003, 13. Accordingly, claim 23 is obvious for all the reasons described for claim 2. § VIII.C.2; EX1002 ¶¶222−224.

14. Claim 24

With the exception of "ophthalmic solution," claim 24 is identical to claim 19. *Chia* discloses an ophthalmic solution. EX1003, 13. Accordingly, claim 24 is obvious for all the reasons described for claim 19. § VIII.C.9; EX1002 ¶¶225−227.

15. Claim 25

Claim 25 recites "A method of arresting myopia progression, comprising administering to an eye of an individual in need thereof an effective amount" of the ophthalmic compositions recited in claim 1. EX1001, claim 25.[8] As discussed above, *Chia* and *Siegel* in view of *Kondritzer* rendered claim 1 obvious. § VIII.C.1. As *Chia* taught that its 0.01% atropine solutions were effective to treat myopia, a POSA would have found it obvious to use the solutions of claim 1 to treat myopia. EX1003, 13, 19−20; EX1002 ¶¶228−234.

Chia tested 0.01% atropine solutions in a clinical trial of 400 subjects. EX1003, 13. *Chia* taught that "[t]he lowest concentration of 0.01% atropine… is a viable concentration for reducing myopia progression" and that "the 0.01%

[8] "B-" in claim 25 appears to be a typo which should be "pD."

formulation exhibited fewer adverse events" than 1%, 0.1%, and 0.5% atropine solutions. EX1003, 19−20.

There was also a reasonable expectation of success that the method of claim 25 would arrest myopia. EX1002 ¶¶231−234. Consistent with the art as a whole, *Chia* demonstrated that 0.01% atropine sulfate solutions significantly decreased the progression of myopia. EX1003, 13, 15−19; EX1014, 1, 3; EX1017, 1; EX1018, 19:12−13. D_2O substitution would not be expected to change the biological properties of the formulation compared to the solution formulated with regular water, and thus would be expected to be at least as effective in treating myopia. EX1002 ¶¶55−63, 233; §§ VIII.B.2−3.

16. Claim 26

Dependent claim 26 recites: "The method of claim 25, wherein the ophthalmic composition is stored at between about 2° C. to about 10° C. prior to first use." EX1001, claim 26. *Kondritzer* renders this additional feature obvious. EX1002 ¶¶235−240.

Kondritzer specifically disclosed atropine solutions at 10° C and pH 3.97 (pD 4.37)—*i.e.*, solutions within the ranges of claim 26—and taught that the stability of atropine increases as storage temperature decreases at pHs within the ranges of claim 26 (*e.g.*, pH 4.5, 5). EX1004, 8; EX1002 ¶237. Stability was a key consideration for formulation, storage, and administration of atropine. § VIII.B.1; EX1002 ¶238.

Thus, it would have been obvious to store the formulations recited by claim 1 at the low temperatures of claim 26 prior to first use for treating myopia, at least because those temperatures would enhance long-term stability. EX1002 ¶¶238−239; EX1050, 4; EX1068, 1 (disclosing storage of atropine formulations at 5° C); EX1047, 7; EX1057, 3; *see KSR*, 550 U.S. at 419; *Atlas Powder*, 190 F.3d at 1346.

17. Claim 27

Dependent claim 27 recites: "The method of claim 25, wherein the ophthalmic composition is stored at between about 16° C. to about 26° C. after first use." EX1001, claim 27. *Kondritzer* renders this additional feature obvious. EX1002 ¶¶241−245.

Kondritzer specifically disclosed atropine solutions at 20° C and pH 3.84 (pD 4.24)—*i.e.*, solutions within the ranges of claim 27—and taught that atropine is more stable at 20° C than at higher temperatures. EX1004, 8; EX1002 ¶243. Moreover, room temperature—*i.e.*, the temperature at which atropine would be stored under normal conditions—is 20°−22° C, encompassed by the range of claim 27. *See, e.g.*, EX1066, 5; EX1071, 1; EX1068, 1. It would have been obvious to store the formulations recited by claim 1 after first use for treating myopia at the same temperatures that H_2O-atropine formulations were stored. EX1002 ¶¶244−245; *see KSR*, 550 U.S. at 419; *Atlas Powder*, 190 F.3d at 1346.

IX. Ground 2: Claims 1−4 and 7−27 Would Have Been Obvious over *Chia*, *Siegel*, *Kondritzer*, and *Remington*

A. Summary of the Combination

As discussed above, claim 1 would have been obvious over *Chia*, *Siegel*, and *Kondritzer*. §§ VIII.A−C. Claims 8−13 and 17−18 recite nothing more than standard components long used in atropine solutions for the treatment of myopia. EX1002 ¶¶66−74, 247−251. *Chia* discloses that it used 0.01% aqueous atropine solution with 0.01% BAK preservative, but it does not provide a full accounting of the components of the solutions. EX1003, 13. This is cured by *Remington*, which discloses standard ophthalmic formulations suitable for use in the atropine solutions. EX1005, 49−54.

Remington is a seminal text in the pharmaceutical sciences, which taught the standard practices for ophthalmic formulations. *See, e.g.*, EX1002 ¶¶248−249; EX1005, 46, 49−54; EX1037 ¶[0073]; EX1072, 6, 24; EX1001, 40:55−61. A POSA would have been motivated to combine the well-known components disclosed by *Remington* with the atropine solutions of *Chia* at least because these components were known to provide safe and effective treatment. *E.g.*, EX1005, 51−52; EX1066, 3; EX1002 ¶250. Moreover, *Remington* expressly motivates the combination with atropine formulations such as *Chia*'s, disclosing a standard formulation, noting "[t]he following solutions are *suggested*" and explaining "[t]hese vehicles are suitable for salts of… atropine." EX1005, 52; EX1002 ¶250.

As D_2O would not have been expected to change the biological properties of atropine or present any unique formulation issues (§§ VIII.B.2−3), a POSA would have been motivated to use the same types of components that were established to work in atropine solutions containing regular water with a reasonable expectation of success. EX1002 ¶251.

B. Claim-by-Claim Analysis

1. Claims 1−4, 7, 10−11, 14−16, and 19−27

As explained above, the pD limitation recited by claims 1−4, 7, 10−11, 14−16, and 19−27 would have been obvious over *Chia*, *Siegel*, *Kondritzer* given the well-known fact that a pH of 7.4 (pD 7.8) was optimal for patient comfort. To the extent that the Board finds an explicit disclosure of this teaching necessary, *Remington* disclosed it. EX1005, 54. EX1002 ¶253. Likewise, if the motivation to optimize pD is not sufficiently clear from *Kondritzer*, *Remington* explicitly disclosed "ophthalmic solutions are formulated to be… buffered for stability and comfort" (EX1005, 52), that "optimum pH [for stability] may be lower than preferable for product comfort, although this effect may be minimized by adjusting pH," and provides a specific example of balancing pH for stability and comfort (EX1005, 54). EX1002 ¶254. Thus, for the same reasons discussed in Ground 1 and these additional reasons, claims 1−4, 7, 10−11, 14−16, and 19−27 would also have been

obvious over *Chia*, *Siegel*, *Kondritzer*, and *Remington*. §§ VIII.A−C; EX1002 ¶¶252−255.

2. Claims 8 and 9

Dependent claim 8 recites: "The ophthalmic composition of claim 1, wherein the ophthalmic composition further comprises an osmolarity adjusting agent." EX1001, claim 8. Dependent claim 9 recites: "The ophthalmic composition of claim 8, wherein the osmolarity adjusting agent is sodium chloride." *Id*., claim 9. *Remington* renders these additional features obvious. EX1002 ¶¶256−265.

Remington discloses an ophthalmic formulation suitable for atropine containing sodium chloride. EX1005, 52. *Remington* further taught "isotonicity always is desirable and particularly is important in intraocular solutions" and that "[a]n ophthalmic solution is considered isotonic when its tonicity is equal to that of an 0.9% sodium chloride solution." EX1005, 54. As Dr. Byrn explains, a tonicity adjusting agent is necessarily an osmolarity adjusting agent. EX1002 ¶261; EX1085, 16−19. The '199 patent specifically discloses sodium chloride as a "tonicity adjusting agent" (EX1001, 3:4−14) and *Remington*'s disclosure reflected standard practice in the art. *E.g.*, EX1002 ¶¶262−264; EX1068, 2; EX1069, 2; EX1067, 2; EX1065, 1.

The obviousness of sodium chloride as recited by claim 9 renders claim 8 obvious. *Atlas Powder*, 190 F.3d at 1346; *Comaper*, 596 F.3d at 1350.

3. Claims 12 and 13

Dependent claim 12 recites: "The ophthalmic composition of claim 1, wherein the ophthalmic composition further comprises a buffer agent." EX1001, claim 12. Dependent claim 13 recites: "The ophthalmic composition of claim 12, wherein the buffer agent is selected from borates, borate-polyol complexes, phosphate buffering agents, citrate buffering agents, acetate buffering agents, carbonate buffering agents, organic buffering agents, amino acid buffering agents, or combinations thereof." *Id*., claim 13. *Remington* renders these additional features obvious. EX1002 ¶¶266−273.

Claim 13 recites a list of well-known, traditional types of buffers used in atropine and other ophthalmic compositions. *E.g.*, EX1002 ¶269; EX1005, 35−36, 41−43, 52. For example, *Remington* discloses a standard atropine formulation comprising sodium acid phosphate anhydrous and disodium phosphate anhydrous. EX1005, 52. As Dr. Byrn explains, a POSA would have understood that sodium acid phosphate anhydrous and disodium phosphate anhydrous are both "phosphate buffering agents" as recited by claim 13. EX1002 ¶270; EX1073, 133; EX1074, 1; EX1075, 1.

The art shows that *Remington*'s disclosure was standard practice and further demonstrates that it would have been obvious to include buffers in the atropine compositions recited by claim 1. EX1002 ¶271; EX1069, 2, 20; EX1033, 4−5. For

example, the FDA-approved atropine formulation contains dibasic sodium phosphate (disodium hydrogen phosphate) and monobasic sodium phosphate (sodium dihydrogen phosphate) as buffering agents. EX1066, 3.

The obviousness of phosphate buffers as recited by claim 13 renders claim 12 obvious. *Atlas Powder*, 190 F.3d at 1346; *Comaper*, 596 F.3d at 1350.

4. Claim 17

Dependent claim 17 recites: "The ophthalmic composition of claim 1, wherein the ophthalmic composition further comprises a pD adjusting agent." EX1001, claim 17. *Remington* renders this additional feature obvious. EX1002 ¶¶274−280.

Remington taught that adjusting the pH of ophthalmic compositions was routine, explaining that "optimum *pH adjustment* usually requires compromise on the part of the formulator" (EX1005, 54) and instructs that the "solution *pH must be selected* for optimum drug stability." (EX1005, 52). *Remington* discloses a standard formulation suitable for atropine which includes buffering agents (§ IX.B.3). A POSA would have understood that this disclosure is necessarily a "pD adjusting agent" (EX1002 ¶277)—indeed, *Remington* explicitly contemplates "adjusting pH with a buffer" (EX1005, 54).

Moreover, it was well known that pH could be adjusted independent of the buffer with acids and bases. EX1002 ¶¶68−72, 278; EX1076, 2−3, 6; EX1052, 5. Under "Pharmaceutical Necessities" *Remington* discloses standard components for

such adjustment, including acetic acid and hydrochloric acid. EX1005, 36, 39. Specifically, *Remington* disclosed acetic acid is "used primarily as an acidifying agent" (EX1005, 36) and that hydrochloric acid is "[o]fficially classified as pharmaceutic aid that is used as an acidifying agent." (EX1005, 39). A POSA would have understood that an "acidifying agent," is a "pD adjusting agent." EX1002 ¶278; EX1077, 10; *see also* EX1078, 9; EX1079 ¶[0174]; EX1028 ¶[0069].

5. Claim 18

Dependent claim 18 recites: "The ophthalmic composition of claim 17, wherein the pD adjusting agent comprises deuterated hydrochloric acid, deuterated sodium hydroxide, deuterated acetic acid, or deuterated citric acid." EX1001, claim 18. *Remington* and *Siegel* render this additional limitation obvious. EX1002 ¶¶281−289.

Claim 18 depends from claim 17 and further recites deuterated analogs of four standard pD adjusting agents. As explained (§ IX.B.4), *Remington* specifically notes that acetic acid and hydrochloric acid were "acidifying"—i.e., pD adjusting—agents. EX1005, 36, 39; EX1002 ¶283. Indeed, these four agents were ubiquitous in the formulation of pharmaceuticals (EX1077, 29, 32, 39, 41) and had been used as pD adjusting agents in D_2O (EX1028 ¶[0069]), ophthalmic compositions (EX1078, 9; EX1050, 6), and the FDA-approved atropine eyedrops (EX1066, 3). EX1002 ¶¶284−286. Moreover, both citric and acetic acid were known to be

optimal within the claimed pD range (EX1080, 23; EX1081, 6) and the FDA-approved atropine formulation used "hydrochloric acid and/or sodium hydroxide" as "pH adjusting agents." (EX1066, 3). EX1002 ¶¶285−286.

It would have been obvious to use deuterated analogs of the same common pD adjusting agents with atropine-D_2O compositions. EX1002 ¶¶287−288. *Siegel* discloses the use of deuterium oxide to increase the stability and clinical efficacy of ophthalmic solutions and specifically notes the use of "deuterium oxide buffers." EX1006, 4. Moreover, *Siegel* references a prior study of procaine in D_2O by the same authors (EX1006, 5), which specifically used "*sodium hydroxide* for pH values 5.0 to 8.0" and explained that "[t]he deuterium oxide buffer systems were prepared from the same reagents except that all replaceable hydrogen was exchanged with deuterium." EX1082, 2. The art specifically contemplated using deuterated buffers in D_2O pharmaceutical products to correct for the pD-pH difference. EX1029, 18.

X. Alleged Unexpected Results

The alleged unexpected results—the reason given for allowance of the '199 patent—are nothing more than the expected stabilization of atropine due to D_2O, followed by basic arithmetic. EX1002 ¶¶290−292. Presented over thirty charts, "better stability," "lower main degradant," and "longer shelf life" are simply different ways of expressing the same expected effect of D_2O. In a continuation application addressing the same data, the Examiner recognized that "[t]he increased

stability is the expected property of [atropine and D_2O] being used together." EX1042, 3. To the extent they are relevant at all, the results are sourced from three highly specific formulations that are not remotely probative of the broad claims of the '199 patent.

A. A Solvent Isotope Effect Was Not Unexpected

Patent owner failed to provide any explanation or prior art showing why increased stability in D_2O would have been "unexpected." EX1039, 9−13; *see In re Baxter*, 952 F.2d at 392. As of the earliest possible effective filing date, an extensive body of literature showed that a slowed rate of reaction for carboxylic esters subject to base-catalyzed hydrolysis in D_2O would not be unexpected. EX1002 ¶¶293−301.

For example, Jencks 1961 reported that reaction rates were "decreased approximately two-fold" (EX1061, 2); Winter 1972 reported a SIE of 1.8−3.9 across a series of five carboxylic esters (EX1060, 4 (Table 4); and Minor 1972 reported "solvent isotope effect of k_{H2O}/k_{D2O} = 2.17" for O-dichloroacetylsalicylic (EX1054, 1). EX1002 ¶¶296−300. These examples represent a fraction of carboxylic acids subject to base-catalyzed hydrolysis for which SIEs of similar magnitude had been reported. *See, e.g.*, EX1061, 6−7 (reporting "*the two- to threefold decrease in deuterium oxide solution of the rates of the reactions with water of these esters* and of a number of other acyl compounds, including acetylimidazole, acetylimidazolium, acetic anhydride, acetyl phenyl phosphate and possibly

acetylpyrazole and ethyl benzoate."); EX1064, 4 (Table I); EX1063, 4 (Table IV); EX1083, 3 (Tables I and II); EX1062, 3 (Table II) EX1060, 2 (Table 1). The data presented by Patent Owner for atropine would not have been unexpected to a POSA. EX1002 ¶294−295.

B. Data Presented to Obtain Allowance

During prosecution, Patent Owner alleged that the D_2O formulations showed three advantages over their H_2O counterparts: (1) better stability; (2) lower main degradant; and (3) longer-shelf life. EX1039, 9−13. Obscured in myriad charts and figures (EX1001, p. 3−12, 69:40−80:65), this data amounts to nothing more than extrapolation from the same experiments, showing the same slowed reaction rate in D_2O, as reported by the numerous references above. EX1002 ¶302.

1. Better Stability Was Not Unexpected

During prosecution, Patent Owner compared the rate of degradation for the D_2O formulations to that of the corresponding H_2O formulations. EX1039, 10−11; EX1002 ¶¶303−304. Unsurprisingly, as shown below in Table 1, the SIE for atropine is directly in line with the litany of prior art references that studied the effect of D_2O on the base-catalyzed hydrolysis of carboxylic esters. EX1002 ¶¶305−308; § X.A.

Table 1

Pair-Wise Comparisons ('199 patent Table 24)	**Solvent Isotope Effect $k_{(H2O)}/k_{(D2O)}$**		
	25° C	40° C	60° C
Formulations 3 & 7[9] (pH 4.8/pD 5.2)	n.d.	0.50	0.69
Formulations 5 & 8 (pH 5.8/pD 6.2)	2.00	3.00	6.00
Formulations 10 & 9 (pH 6.4/pD 6.8)	2.33	2.25	2.04
Formulations 11 & 9 (pH 6.4/pD 6.8)	2.33	2.56	2.60
Formulations 13 & 12 (pH 6.8/pD 7.2)	1.43	1.89	1.66

[9] At these lower pHs other degradation pathways are involved, and, in any event "The half life [of atropine]… between pH 3 and 5 is so great that its experimental determination is not practical." EX1004, 8; EX1002 ¶308.

Moreover, as Dr. Byrn explains, the data in the '199 patent are based on single-run experiments, show large standard deviations, and appear to compare data generated with different experimental methods. EX1002 ¶¶309−311; *cf*. EX1084, 2, 5−10. Thus, while indicative of the expected qualitative increase in stability of the D_2O formulations, individual numerical variations are of little, if any, significance. EX1002 ¶312. For example, while the SIE of 6 for formulation 8 at 60° C would not have been unexpected (*e.g.*, EX1061, 4, EX1083, 3), the variation between this run and all the other data is likely due in part, if not entirely, to experimental error. EX1002 ¶312.

2. Lower Main Degradant Was Not Unexpected

"Lower main degradant" (EX1039, 11−12) is nothing more than a different way of measuring the same expected effect of D_2O discussed above (§ X.B.1). EX1002 ¶313. In the "better stability" example, the rate of substrate (atropine) breakdown is measured, whereas this example measures the rate at which the resulting product (tropic acid) is formed. EX1001, 75:34−78:20; EX1002 ¶314. Unsurprisingly, as shown in Table 2, the SIEs observed for the pair-wise comparisons largely match those of the "better stability" example. EX1002 ¶¶314−315.

Table 2

Pair-Wise Comparisons ('199 patent Table 25)	**Solvent Isotope Effect $k_{(H2O)}/k_{(D2O)}$**		
	25° C	40° C	60° C
Formulations 3 & 7 (pH 4.8/pD 5.2)	0.62	1.13	1.48
Formulations 5 & 8 (pH 5.8/pD 6.2)	5.09	6.82	8.37
Formulations 10 & 9 (pH 6.4/pD 6.8)	2.51	2.14	2.23
Formulations 11 & 9 (pH 6.4/pD 6.8)	2.57	2.45	2.82
Formulations 13 & 12 (pH 6.8/pD 7.2)	1.82	1.96	1.78

As Dr. Byrn explains, the slight increase in the effect of D_2O seen in these measurements compared to those in "better stability" was also expected because the "lower main degradant" example measures the SIE more directly. EX1002 ¶315. This small difference is of no moment. As the '199 patent acknowledges, "[t]his related substance is likely to be the first parameter to fail specification." EX1001,

67:35−37. That is, as shown in the '199 patent's data, the shelf life of all of the formulations is governed by the rate of related substances, measured in the "better stability" example. EX1001, 80:36−65 (Table 30); EX1002 ¶¶315−316.

3. Longer Shelf Life Was Not Unexpected

Patent Owner then takes the data from these first two results and converts them into predicted shelf life based on the rate of degradation (formation of all related substances, *i.e.*, the total degradation of atropine measured in "better stability") and product formation (tropic acid, *i.e.*, "lower main degradant"). EX1039, 12−13; EX1001, 79:40−80:65; EX1002 ¶317. This is yet another manner of expressing the same expected effect of D_2O. EX1002 ¶¶318.

It is textbook science that reducing the rate of reaction will increase the shelf life of the drug. EX1085, 36−37; EX1004, 6−8. Even accepting Patent Owner's calculations the results are not unexpected. EX1002 ¶¶318−321. Indeed, these are not even results—they are merely predications done via simple arithmetic that produce superficially large distinctions (EX1039, 12−13), from the small, expected changes in stability caused by the SIE. EX1002 ¶¶318−321.

C. The Alleged Unexpected Results Are Neither Significant Nor Commensurate With the Scope of the Claims

Finally, to be probative of non-obviousness, differences must have been "unexpected *and significant*," *Eli Lilly & Co. v. Zenith Goldline*, 471 F.3d 1369, 1378 (Fed. Cir. 2006)—the reported SIE is at best, an insignificant difference in

degree. EX1002 ¶¶322−324. *See Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013); *Accord Healthcare Inc. v. Daiichi Sankyo Co., Ltd.*, IPR2015-00864, Paper 104, at 29−30 (PTAB Sept. 12, 2016). Moreover, to the extent that they are relevant at all, Patent Owner's data—which is sourced from formulations with specific pH levels and essentially free of regular water—are not probative of the '199 patent's broad claims; "objective evidence of non-obviousness must be commensurate in scope with the claims which the evidence is offered to support." *In re Grasselli*, 713 F.2d 731, 743 (Fed. Cir. 1983); EX1002 ¶¶325−332.

All of the claims of the '199 patent recite a broad range of pD 4.2−7.9 (pH 3.8−7.5). As pD is a logarithmic scale, this range spans a more than 5,000-fold difference in OH^- concentration. EX1002 ¶¶327−328. As explained (*e.g.*, § VIII.C.3), the stability of atropine varies with OH^- concentration. EX1002 ¶328. The alleged unexpected results are limited to four specific pD levels that are not probative of the broad range claimed. EX1002 ¶329; EX1039, 10−13; *see E.I. DuPont*, 904 F.3d at 1012.

Further, with the exception of claims 19 and 24, none of the claims of the '199 patent recite a specific level of deuterium oxide content. §§ VIII.C, IX.B. As such, these claims would read on atropine formulations containing *any* amount of D_2O. EX1002 ¶330. It was well known that the SIE varies significantly with D_2O content. *E.g.*, EX1002 ¶331; EX1022, 10−11; EX1064, 7 (Fig. 3); EX1070, 2; *see also*

§ VIII.C.9. All of the formulations presented for the alleged unexpected results were formulated in D_2O free of regular water. EX1001, 63:50−64:53. To the extent these results are relevant at all, they cannot be probative of claims that would read on a formulation comprising 1% or less D_2O. EX1002 ¶332.

XI. Non-Institution Under 35 U.S.C. § 325 Would be Improper

Non-institution under § 325 would be improper based on weighing the factors in *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8, at 17−18 (PTAB Dec. 15, 2017).

Regarding factors (a) and (b), the asserted combinations are materially different than and not cumulative of the prior art involved during examination of the challenged claims, WoldeMussie, Wildsoet, and Herekar. *See* § IV.B. The base reference in prosecution was WoldeMussie, which generically disclosed muscarinic antagonists in ophthalmic formulations but did not disclose atropine. EX1035, 7. In contrast, *Chia* discloses atropine, at concentrations within the ranges recited by the claims of the '199 patent, to treat myopia. EX1003, 13, 19−20.

For D_2O, the Examiner relied on Herekar, which taught the use of deuterium oxide to "extend lifetimes of UV A/Rf photogenerated intra-stromal singlet oxygen" and did not disclose the kinetic effects of D_2O. EX1038 ¶[0011]; EX1035, 7−8. In contrast, *Siegel* disclosed D_2O to stabilize an ophthalmic composition of procaine. EX1006, 4−5. The Examiner did not consider any reference analogous to

Kondritzer, which taught specific pHs within the ranges recited by the claims of the '199 patent, and demonstrated atropine would be expected to be subject to SIEs when combined with D_2O. §§VIII.A−C.

Regarding factors (c) and (d), there is little to no overlap because the Examiner did not use any of the ground references to reject any claim and did not make any arguments regarding them. EX1035, 3−10. *Siegel* was the only reference listed in a considered IDS, and it is not assumed that a reference was substantively evaluated when "the prior art was simply listed in an IDS during prosecution." *Becton*, Paper 8 at 23; *see Netflix Inc. v. Hulu LLC*, IPR2020-00558, Paper 10 at 40 (PTAB Aug. 26, 2020) (granting institution and explaining "[b]ecause the combination… was not considered by the examiner, we find consideration of the references and arguments based thereon to be materially different than the examiner's previous consideration…").

Regarding factor (e), the Examiner erred in allowing the asserted claims to issue at least because "the Examiner was simply not aware" of the teachings of the most pertinent art and "[t]he Petition… presents different prior art than the Office was aware of." *Oticon Med. AB v. Cochlear Ltd.*, IPR2019-00975, Paper 15, at 19−20 (PTAB Oct. 16, 2019) (precedential) (granting institution). Additionally, as discussed (§ IV.B), the '199 patent would not have been allowed but for the alleged unexpected results presented by Applicant during prosecution. *See* EX1040, 2;

EX1041, 6−7. The Examiner, however, was not aware of the litany of prior art references in the Petition that establish that these results were neither unexpected nor significant, and would not be probative of non-obviousness of the alleged invention. *See Prollenium US Inc., v. Allergan Industrie, SAS*, IPR2019-01617, Paper 17, at 53−56 (PTAB Mar. 20, 2020).

XII. Mandatory Notices Under 37 C.F.R. § 42.8

A. Real Parties-in-Interest

The real party-in-interest is Nevakar, Inc.

B. Related Matters

Sydnexis is the owner of the following U.S. applications and patents related to the ’199 patent. U.S. Application No. 17/097,930 is pending and claims benefit of priority to U.S. Application No. 16/224,286, filed December 18, 2018, and issued as U.S. Patent No. 10,864,208, which is a continuation of U.S. Application No. 15/895,933, filed February 13, 2018, and issued as U.S. Patent No. 10,201,534, which is a continuation of U.S. Application No. 15/661,816, filed July 27, 2017, and issued as U.S. Patent No. 10,076,515, which is a continuation of U.S. Application No. 15/208,537, filed July 12, 2016, and issued as U.S. Patent No. 9,770,447, which is a continuation of U.S. Application No. 14/726,139, filed May 29, 2015, and issued as the ’199 patent.

C. Lead and Back-Up Counsel, and Service Information

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XIII. Grounds for Standing

Nevakar certifies the '199 patent is available for IPR and Nevakar is not barred or estopped from requesting IPR challenging the patent claims on the grounds identified herein.

XIV. Conclusion

Nevakar has established a reasonable likelihood of prevailing with respect to each of the challenged claims, so the Board should institute IPR2021-00439 and cancel the claims. The Office may charge any required fees to Deposit Account No. 06-0916.

Dated: February 3, 2021

Respectfully submitted,

/James R. Barney/
James R. Barney (Reg. No. 46,539)

CERTIFICATION OF COMPLIANCE

The undersigned hereby certifies that the foregoing Petition contains 13,959 words, excluding those portions identified in 37 C.F.R. § 42.24(a), as measured by the word-processing system used to prepare this paper.

By: /James R. Barney/
James R. Barney (Reg. No. 46,539)

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a), the undersigned certifies that on February 3, 2021, a copy of the foregoing **Petition for *Inter Parties* Review** and **the associated Power of Attorney** were served by FedEx on the correspondence address of record indicated in the Patent Office's public PAIR system for U.S. Patent No. 9,421,199:

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