

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

EYENOVIA, INC.,
Petitioner,

v.

SYDNEXIS, INC.,
Patent Owner.

Case IPR2022-00964
U.S. Patent No. 9,770,447

DECLARATION OF STEPHEN BYRN, PH. D.

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I. Introduction

1. I, Stephen R. Byrn, Ph.D., have been retained by Mintz, Levin, Cohn, Ferris, Glovsky and Popeo, P.C. on behalf of Eyenovia, Inc. (“Eyenovia”) as an independent expert to opine on the patentability of U.S. Patent No. 9,770,447 (“the ‘447 patent”).

2. I receive \$750 per hour for my services. I am being compensated for the time I spend on this matter, but my compensation is not contingent upon my opinions or the outcome of this or any other proceeding. I do not own any stock in Eyenovia or any other pharmaceutical company (except through mutual funds).

II. Experience and Qualifications

3. I am a Charles B. Jordan Professor of Medicinal Chemistry in the Department of Industrial and Physical Pharmacy at School of Pharmacy, Purdue University. I also consult with numerous pharmaceutical companies on drug development and formulation. I am the Chief Scientific Officer of a small pharmaceutical research and information company named Improved Pharma, LLC.

4. I received my B.A. in Chemistry at DePauw University in 1966, my Ph.D. in Organic and Physical Chemistry at University of Illinois in 1970, and conducted two years of post-doctoral research at University of California, Los Angeles from 1970–1972.

5. In 1972, I became an Assistant Professor of Medicinal Chemistry in the Department of Medicinal Chemistry and Pharmacognosy at the School of Pharmacy and Pharmaceutical Sciences, Purdue University. I have been employed in the same department/school at Purdue University ever since. I became an Associated Professor of Medicinal Chemistry in 1976 and a Professor of Medicinal Chemistry in 1981. I served as the Associate Department Head of Medicinal Chemistry in the Department of Medicinal Chemistry and Pharmacognosy from 1979 to 1988, the Assistant Dean of the Graduate School, Purdue University from 1984 to 1988, and the Head of the Department of Medicinal Chemistry and Pharmacognosy from 1994 to 2009. I founded the Purdue University Center for AIDS Research in 1988 and served as the Director of the center until 1998. I have also been a Co-Director of the Center for Biotechnology Innovation and Regulatory Science in the Discovery Park and Agricultural and Biochemical Engineering Department at Purdue University since 2014. In 2017, I also became the Director of the NIPTE Center of Excellence for Abuse Deterrent Formulations. I am also a co-founder of the Sustainable Medicines in Africa in the Kilimanjaro and Arusha regions of Tanzania in 2007.

6. I have received numerous awards from government agencies, academia, and scientific journals and organizations for my contributions to and expertise in drug formulation. For instance, I was an Elected Member of the United States Pharmacopeia Revision Committee, during 1990–1995, 1995–2000, and

2000–2005. I also served as a member of the Council of Experts and a member of several subcommittees including chemistry, dissolution, excipients and process analytical technologies (PAT) within the United States Pharmacopeia Revision Committee. I also received the FDA Advisory Committee Service Award in 2001. In 2007, I received the AAPS Outstanding Paper Award, 2008. I also received Purdue University's Outstanding Faculty Commercialization Award in 2008 to 2009. Also in 2009, I received the AAPS David Grant Research Achievement Award in Physical Pharmacy. In 2013, I received an FDA Honor Award as a member of FDA/Kilimanjaro School of Pharmacy Regulatory Collaboration. In 2016, I received the AAPS Dale Wurster Award In Pharmaceutics. I also received the AAPS Pharmaceutical Global Health Award in 2018.

7. I also received awards from Purdue University for my dedication to teaching for decades. In 2018, I received LSAMP Faculty Mentor of the Year Award, the Pharmaceutical Sciences Teacher of the Year Award, and Purdue University Morrill Award for the Most Outstanding Faculty Member of Purdue University.

8. I have been on multiple editorial boards for peer-reviewed journals, including the Journal of Pharmaceutical Sciences, AAPS PharmSciTech, Pharmaceutics, the Journal of Validation Technology, the Journal of Drug Targeting, and the Journal of Pharmaceutical and Biomedical Analysis. In addition, I have been

on multiple advisory committees, including the Pharmaceutical Sciences Advisory Committee for the FDA (serving as the Chair from 2000 to 2001), the Drug Substance Technical Committee for the FDA-PQRI, and the Controlled Substances Advisory Committee for the State of Indiana (serving as the chair from 1995 to 1998). I have been a member of the National Academies of Sciences, Engineering, and Medicine, Topical Pain Creams from 2019–2020.

9. I have taught many courses relating to pharmaceuticals and pharmaceutical formulations, including Analytical Medicinal Chemistry, Sterile Products, Industrial Pharmacy, Dosage Forms I, Drug Discovery and Development II, Advanced Medicinal Analysis, Drug Development, Good Regulatory Practices, and Pharmaceutical Manufacturing. I continue to teach many of these courses during the 2021–2022 school year.

10. My laboratory has done extensive research on drug formulations, and I have authored over two hundred book chapters and peer-reviewed journal articles on properties of a wide variety of pharmaceutical compositions. I have also authored three books on the solid state chemistry of drugs. These books address important issues in formulation and drug development. A copy of my curriculum vitae is provided as **Appendix A**.

III. Materials Considered

11. My opinions are based on my education, training, background and experience, the documents I reviewed, and information available to me to date. I have reviewed and considered the documents and materials cited in this declaration. To the extent I am provided with additional documents or information in this proceeding, I reserve the right to modify or expand upon my opinions based on such new information, and in response to any additional reports and testimony.

IV. Legal Standard

12. In preparing this declaration, certain patent law concepts have been explained to me, including the legal standard for interpreting claims, as well as those for assessing written description, enablement, and obviousness.

13. I have been informed by counsel that the Patent Trial and Appeal Board (“PTAB”) applies the same claim construction standard used in district courts, where the claims are given their ordinary meaning as understood by one skilled in the art at the time of effective filing date, informed by the claim language itself, the specification, and the prosecution history. I also understand that “extrinsic evidence”—i.e., evidence other than the patent and prosecution history—can be relevant in determining how a skilled artisan would understand terms of art used in the claims. I have been informed, however, that extrinsic evidence may not be used

to contradict the meaning of the claims as described in the intrinsic evidence—i.e., evidence in the claim language itself, the specification, and the prosecution history.

14. I have been informed by counsel that a patent specification must enable a person of ordinary skill in the art to make and use the full scope of the claimed invention without undue experimentation as of its effective filing date.

15. I have been informed by counsel that, in addition to being required to be enabled, a claim in a granted patent must also be sufficiently supported by the disclosure in the patent's specification, read in the context of what one of skill in the art would have known at the time of the effective filing date. I understand that the basic inquiry for written description is whether the specification provides sufficient information for a skilled artisan to recognize that the named inventors possessed the full scope of the claimed invention.

16. I have further been informed by counsel that a claim is obvious if the differences between the claimed subject matter and the prior art are such that the subject matter as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art ("POSA"). I have been informed that whether the differences between the claimed invention and the prior art are obvious depends on factors including the scope and content of the prior art, the level of ordinary skill in the art, the differences between the claimed invention and the prior art, and secondary considerations of nonobviousness.

17. I also understand that whether a patent claim is obvious is determined from the perspective of a POSA. I further understand that a claimed invention is obvious if a POSA, before the effective filing date, would have been motivated to select, combine, or modify the relevant prior art elements during the normal course of research and development to yield the claimed invention with a reasonable expectation of success. I was also informed that when a claim recites a range, if prior art discloses a portion of the claimed range, the entire claimed range is obvious.

V. Summary of My Opinions

18. Claims 1–19 of the '447 patent recite compositions and methods of treating myopia with atropine at concentrations of about 0.001 wt % to about 0.03 wt %, deuterium oxide, at a pD of 4.2–7.9. In my opinion, claims 1–19 would have

been obvious over the combination of *Chia* (EX1003)¹, *Siegel* (EX1006)², *Kondritzer* (EX1004),³ and *Remington* (EX1005).⁴

¹ *Chia* is a journal article authored by Chia et al. titled “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).” It was published in February 2012 in *Ophthalmology*, a well-known and reputable journal. EX1003, 1–2, 13. Before the earliest possible effective filing date of the ’447 patent, it was cited by researchers and was publicly available to a person of skill in the art. EX1017, 7. *Chia* is relevant to the subject matter of the ’447 patent and would have been considered by one of skill in the art.

² *Siegel* is a journal article authored by *Siegel* et al. titled “Stability of Procaine in Deuterium Oxide.” It was published in August 1964 in the *Journal of Pharmaceutical Sciences*, a well-known and reputable journal. EX1006, 1–3. Before the earliest possible effective filing date of the ’447 patent, it was cited by researchers and was publicly available to a person of skill in the art. EX1052, 2. *Siegel* is relevant to the subject matter of the ’447 patent and would have been considered by one of skill in the art.

³ *Kondritzer* is a journal article authored by *Kondritzer* and Zvirblis titled “Stability of Atropine in Aqueous Solution.” It was published in September 1957 in the

19. *Chia* disclosed a large-scale clinical trial of 0.01% atropine eye drops and demonstrated that this concentration was effective in treating myopia. *Siegel* taught the use of deuterium oxide to improve the stability of ophthalmic procaine solutions. *Kondritzer* disclosed atropine at pH ranges corresponding to pD ranges within those claimed by the '447 patent, and showed that atropine is primarily degraded via base-catalyzed hydrolysis.

Journal of the American Pharmaceutical Association, a well-known and reputable journal. EX1004, 1. Before the earliest possible effective filing date of the '447 patent, it was cited by researchers and was publicly available to a person of skill in the art. EX1020, 7; EX1052, 8; EX1033, 19. *Kondritzer* is relevant to the subject matter of the '447 patent and would have been considered by one of skill in the art.

⁴ *Remington* is excerpted from the nineteenth edition of "Remington: The Science and Practice of Pharmacy," and was published in 1995. EX1005, 4–5. *Remington* is a well-known reference manual for the pharmaceutical sciences. Before the earliest possible effective filing date of the '447 patent, it was cited by researchers and was publicly available to a person of skill in the art. EX1072, 6, 24.

Remington is relevant to the subject matter of the '447 patent and would have been considered by one of skill in the art.

20. There was ample motivation to combine the low-concentration atropine formulations of *Chia* with the deuterium oxide taught by *Siegel*. Modification with deuterium oxide offered the potential to improve the stability of *Chia*'s formulations at pD levels more desirable for clinical administration. Moreover, given the similarities between these two carboxylic esters (atropine and procaine), a POSA would have reasonably expected that the improved stability seen with procaine could also be obtained for atropine. The motivation and reasonable expectation of success in improving atropine was bolstered by the art as a whole, which showed that solvent isotope effects were often seen for carboxylic esters subject to base-catalyzed hydrolysis.

21. Several of the challenged dependent claims of the '447 patent cover well-known components (e.g., buffers, osmolarity adjusting agents) found in many ophthalmic solutions and which had been shown to be effective with atropine specifically. These additional elements were disclosed by *Remington* and do not impart any patentability to the obvious independent claims of the '447 patent.

VI. State of the Art

A. Low-Concentration Atropine for the Treatment of Myopia

1. Myopia

22. Atropine, a nonselective muscarinic antagonist, had been extensively studied for more than a century and was known as "the oldest and most effective

pharmacological treatment to inhibit the development of myopia.” EX1009, 1; EX1003, 13 (“Atropine eyedrops were first proposed as a treatment of myopia in the 1920s.”); EX1013, 2 (“The most widely studied pharmacological agent for the inhibition of myopia progression has been atropine, a nonselective muscarinic antagonist.”).

23. Early clinical trials established that 1.0% and 0.5% atropine solutions were effective in reducing myopia progression. EX1011, 1; EX1003, 13; EX1012, ¶[0006].

24. These high-concentration formulations, however, were found to induce side effects such as photophobia, cycloplegia, and mydriasis in children. EX1003, 13; EX1012, ¶[0006] (explaining “the compliance is poor and dropout rate is correspondingly high” due to photophobia caused by the 1% formulation); EX1015, 1 (“Although 1% atropine effectively slows myopia progression, it is associated with... poor compliance.”).

25. To reduce the undesired side effects, researchers in the field prepared various low-concentration aqueous formulations containing $\leq 0.05\%$ atropine, tested those formulations for myopia treatment, and independently reported satisfactory clinical efficacy and a substantially improved safety profile compared to high dose atropine treatments. EX1003, 13; EX1010, 1; EX1017, 1; EX1014, 1; EX1067, 1; EX1045, 6; EX1012, ¶[0018]; EX1013, 1; EX1016, 4.

26. For instance, Lee 2006 investigated 0.05% atropine for prevention of myopic progression in school-aged children who could not tolerate 0.1% atropine treatment due to side effects. EX1013, 2. Lee 2006 disclosed preparation of 0.05% atropine eye drops by diluting a commercial 1% atropine solution with distilled water and administration to patients by instillation. EX1013, 4. Lee 2006 explains that “[t]his may also have reduced the preservative concentration, thereby decreasing the chance of allergic reaction.” EX1013, 5. Lee 2006 observed that while “0.05% atropine is an effective control agent for myopia progression in school-aged children,” “the instillation of 0.05% atropine at bedtime was relatively more tolerable than other regimens, such as... atropine at concentrations of 0.1% or above.” EX1013, 4.

27. Similarly, a patent application to Wu et al. acknowledged that high concentration (0.5% or 1%) atropine solutions caused side effects, poor patient compliance, and high dropout rate, and described preparing 0.05% atropine solutions by diluting known 1.0% or 0.5% atropine solutions with distilled water or 0.9% sodium chloride solution. EX1012, Abstract, ¶¶[0006], [0012], [0013], [0036]. Wu et al. reported that administration of the lower dose atropine solutions achieved “good efficiency” in myopia prevention and “proved to have excellent accommodation-inhibiting efficiency,” with “significantly reduced [] side-effect of photophobia.” EX1012, ¶¶[0031], [0033].

28. Application No. CN 101049287 also notes the “highly problematic” photophobia side effects associated with high-concentration atropine preparations and described preparing 0.05% atropine solutions by diluting a commercial atropine solution with distilled water or saline. EX1045, 1–3. CN 101049287 reported that the long-term efficacy of its 0.05% atropine solutions is “quite favorable” and that 0.05% atropine solutions had “a much lower incidence of photophobia” compared to higher concentration solutions. EX1045, 3, 6–7.

29. Wen et al. observed that 0.05% atropine sulfate eye drops successfully treated myopia progression in school-age children with minimal adverse effects and recommended using 0.05% atropine sulfate eye drops to treat mild myopia. EX1067, 1, 6–7. Wen disclosed dissolving 0.5 g atropine sulfate, 9.0 g sodium chloride, and 0.3 g ethyl paraben, in water and adding water for injection to 1000 ml. EX1067, 2 (This formulation contains 0.05% atropine sulfate, 0.9% sodium chloride, 0.03% of a preservative, and water.). Wen taught this formulation should have a pH of 4.0 to 6.0. EX1067, 3.

30. By 2014, atropine formulations containing less than 0.05% atropine had also been developed and shown to be clinically effective. For instance, Fang et al., recognizing the side effects of 1% atropine solutions, explained that “[i]n this study, we investigate the effects of very low concentrations of atropine (0.025%) eye drops and hypothesize that these induce fewer photophobia side effects and could prevent

myopia onset in premyopic schoolchildren.” EX1014, 1. Fang prepared topical 0.025% atropine eye drops by diluting a commercially available 0.25% atropine solution and reported that the 0.025% atropine eye drops prevented onset of myopia and myopic shift in premyopic schoolchildren with no systemic side effects. EX1014, 1–4.

31. *Chia* disclosed that their previous clinical trials “showed that atropine 1% eyedrops were effective in controlling myopic progression but with visual side effects resulting from cycloplegia and mydriasis.” EX1003, 13. *Chia* then described its further clinical trial studies, specifically the “Atropine for the Treatment of Myopia 2 (“ATOM2”) trial, which involved administering low-concentration atropine eye drops. EX1003, 13.

32. *Chia* disclosed administering formulations containing 0.5%, 0.1%, or 0.01% atropine sulfate to 400 children with myopic refraction. EX1003, 13. *Chia* taught that these aqueous formulations “consisted of the appropriate dose of atropine sulfate with 0.02% of 50% benzalkonium chloride as a preservative.” EX1003, 14.

33. *Chia* observed that atropine 0.01% “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. *Chia* concluded that among the tested doses, “[t]he lowest concentration of 0.01% atropine thus seems to retain efficacy and is a viable concentration for

reducing myopia progression in children, while attaining a clinically significant improved safety profile” and “exhibit[ing] fewer adverse effects.” EX1003, 19–20. *Chia* recommended 0.01% atropine as “a safe and effective regimen for slowing myopia progression in children.” EX1003, 20.

34. Chia 2014 described follow-up results from the same ATOM2 studies, focusing on the change in spherical equivalent and other ocular parameters one year after stopping the administration of atropine. EX1017, 1. Chia 2014 concluded that whereas “cessation of 0.1% and 0.5% atropine resulted in greater degrees of myopic rebound... the lower dosage of 0.01% atropine appears to result in less myopic rebound, which led to a more sustained effect of myopia retardation and overall reduction of myopia.” EX1017, 6. Chia 2014 concluded that “[c]oupled with the fact that 0.01% atropine also showed the least amount of pupil dilation and accommodative loss, and consequently the fastest recovery from these side effects after cessation, we conclude that atropine eye drops at the lowest dosage of 0.01% results in an optimal balance between efficacy and safety and could represent a clinically viable approach to myopia retardation in children.” EX1017, 6.

35. A patent application to Tan et al. recognized that “[i]t is desirable to provide an atropine composition for reducing and/or preventing myopia progression with negligible or minimal side effects” and described and claims atropine formulations that contain 0.001% to 0.0249% atropine. EX1018, 2:13–14,

4:20–5:2, claims 1–5, 12–18. Tan disclosed that these low-concentration atropine compositions “further comprise at least one pharmaceutically acceptable excipient.” EX1018, 5:2. Tan further disclosed that these atropine formulations could be an eye-drop composition and “may be for use in reducing and/or preventing myopia progression and/or treating myopia.” EX1018, 5:3–4. Tan taught that “0.01% atropine... reduces and/or prevents myopia progression with negligible side effects, such as loss of accommodation, mydriasis, near-vision blur, allergic conjunctivitis and dermatitis.” EX1018, Abstract.

36. Thus, as of 2014, researchers around the world had routinely prepared low dose atropine eye drop formulations, including those containing 0.001% to 0.03% atropine. Those skilled in the art also had shown that those formulations were clinically effective in treating or preventing myopia with a substantially improved safety profile compared to higher-concentration atropine products.

2. Atropine Degradation

37. Atropine is a carboxylic ester. In solution, atropine degrades primarily via cleavage of the acyl-oxygen bond during ester hydrolysis. EX1019, 1 (“Instability of atropine in solution is due mainly to the hydrolytic reaction yielding tropine and tropic acid.”); EX1020, 3 (“Thus, the main pathway of instability in aqueous atropine solution is the hydrolytic reaction yielding tropine and tropic acid.”).

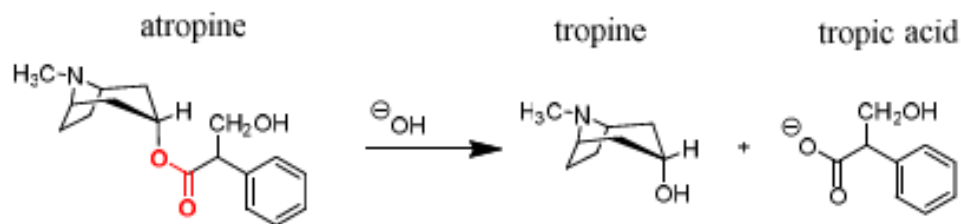


Figure 1. Base-Catalyzed Hydrolysis of Atropine (red denotes ester)

38. Ester hydrolysis reactions are catalyzed by both H^+ ions (“acid-catalyzed hydrolysis”) and OH^- ions (“base-catalyzed hydrolysis”). EX1004, 6 (“Hydrolytic reactions catalyzed by both hydrogen and hydroxyl ions... include hydrolysis of carboxylic esters.”). The total rate of degradation (k) is equal to the sum of the acid-catalyzed and base-catalyzed reactions. EX1004, 6.

39. For atropine, the rate of the acid-catalyzed reaction is much slower than that of the base-catalyzed reaction, and thus, the stability of atropine “is governed by the hydroxyl-ion $[\text{OH}^-]$ concentration....” EX1004, 5. At low OH^- concentrations ($\text{pH} < \sim 3$) the overall rate of reaction is slow, and atropine is stable. EX1004, 8–9. As OH^- concentration increases, however, the overall rate of the reaction increases, and atropine becomes more unstable. EX1004, 8–9.

40. pH is a measure of H^+ concentration. Low pH values represent high H^+ concentrations (and correspondingly low OH^- concentrations); high pH values represent low H^+ concentrations (and correspondingly high OH^- concentrations).

B. Deuterium Oxide Modification

1. Solvent Isotope Effect

41. 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 mass in deuterium, replacing hydrogen with deuterium results in an increase in bond strength. EX1024, 4. This increased bond strength can slow the overall rate of reaction of a deuterated compound compared to its protium analog. EX1022, 3 (“The rate of reaction involving a bond to deuterium is generally slower than that involving a bond to hydrogen.”); EX1023, 5–9; EX1024, 4–5. The difference in the rate of reaction is known as the “kinetic isotope effect” (KIE) or “deuterium isotope effect” (DIE). EX1024, 4.

42. Replacing hydrogen with deuterium in water (H_2O) creates deuterium oxide (“ D_2O ” or “ $^2\text{H}_2\text{O}$ ”), also known as “heavy water.”⁵ EX1025, 19. Similar to the effect of substituting deuterium for regular hydrogen on a compound, substituting D_2O for H_2O can slow the overall rate of reaction. EX1025, 19–20;

⁵ 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 $\text{pD} = \text{metered reading} + 0.4$. EX1025, 37; EX1026, 2; EX1001, 32:20–26. For example, a measurement of pH 4 in pure D_2O is equivalent to pD 4.4.

EX1027, 3; EX1021, 2; EX1028, ¶[0012] (“This generally increased bonding strength occurs both in aqueous solutions of H₂O and D₂O and also during bonding of water to organic molecules, the effect appearing to be even more strongly pronounced in organic molecules.”). The difference in the rate of reaction of a compound in D₂O compared to that in H₂O is known as the kinetic solvent isotope effect (“KSIE” or “SIE”). EX1025, 19; EX1027, 3–4.

43. Several properties of D₂O contribute to the solvent isotope effect, which can be categorized as: (1) “medium effects,” (2) “primary effects,” and (3) “secondary effects.” EX1025, 23.

44. “Medium effects” refer to rate changes caused by the physical differences between D₂O and H₂O, such as viscosity, density, and dielectric constant. EX1025, 23–25. Medium effects alter the rate of reaction per se, not due to any specific interaction between the solvent (D₂O) and the solute (chemical compound in the aqueous solution). EX1025, 24.

45. “Primary effects” refer to the change in rate observed when an isotopically substituted hydrogen is directly involved in the reaction. EX1025, 26. That is, “when an isotopically substituted hydrogen involved in the reaction (that is, one whose bond is being made or broken) is in motion along the reaction coordinate at the transition state.” EX1025, 26.

46. “Secondary effects” refer to the effect caused by isotopically substituted hydrogens not involved in the primary reaction. EX1025, 26. Secondary effects are caused by “an isotopically substituted hydrogen atom undergoes some change in bonding on going from reactant to transition state but is not actually moving or in the process of transfer.” EX1025, 26. Even in the absence of a strong primary effect, secondary effects can have a significant effect on the overall rate of reaction. EX1060, 2.

47. The overall solvent isotope effect observed for a reaction is the net of the rate changes caused by these different effects.

$$\left(\frac{k_{\text{H}_2\text{O}}}{k_{\text{D}_2\text{O}}}\right)_{\text{total}} = \left(\frac{k_{\text{H}}}{k_{\text{D}}}\right)_{\text{pri}} \left(\frac{k_{\text{H}}}{k_{\text{D}}}\right)_{\text{sec}} \left(\frac{k_{\text{H}_2\text{O}}}{k_{\text{D}_2\text{O}}}\right)_{\text{medium}}$$

Figure 2. Solvent Isotope Effect (EX1025, 23)

48. The solvent isotope effect generated by D₂O has long been used to study reaction mechanisms. EX1025, 19–23; EX1027, 3 (noting that “[a] vast amount of chemical and biochemical work has taken advantage of” the properties of D₂O and that “‘deuterium isotope effects’ have been discussed in great detail”); EX1021, 1 (“D₂O and deuterated drugs are widely used in studies of metabolism of drugs and toxic substances in humans and other animals.”).

49. By 2014, the effect of D₂O on a myriad of reactions had been reported, and it was known that the SIE for a compound could be generally predicted by the

SIE observed for similar compounds and reaction types. EX1025, 32 (“As stated in the beginning of Section 4, any method used to predict an isotope effect for a proposed mechanism, including simple analogy with a known reaction, is usually acceptable.”); EX1025, 26, 63–64.

50. The literature showed that D₂O generally slows the base-catalyzed hydrolysis of carboxylic esters, such as atropine. For example, Jencks 1961 studied the effect of D₂O on the degradation of ethyl dichloroacetate, ethyl difluoroacetate, and ethyl chloroacetate, all of which, like atropine, are carboxylic esters subject to base-catalyzed hydrolysis at the acyl carbon. EX1061, 4. Jencks 1961 reported that the rate of reaction for each was slower in D₂O than H₂O across a range of buffers and pH levels. EX1061, 4 (Table III).

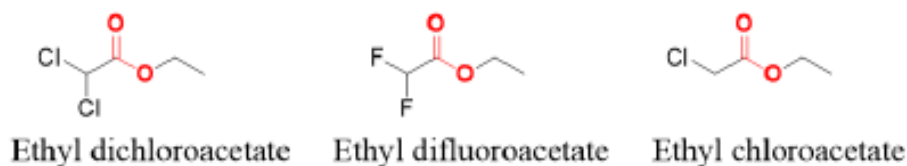


Figure 3. Jencks 1961 Carboxylic Esters

51. Winter 1972 studied the effect of D₂O on the degradation of a series of trifluoroacetates. These compounds, like atropine, are carboxylic esters subject to base catalyzed hydrolysis. EX1060, 2. The authors reported slower rates of degradation for each of these compounds (EX1060, 4 (Table 4)) and noted a similar slowed rate in D₂O with several other carboxylic esters in previous work. (EX1060, 2 (Table 1)).

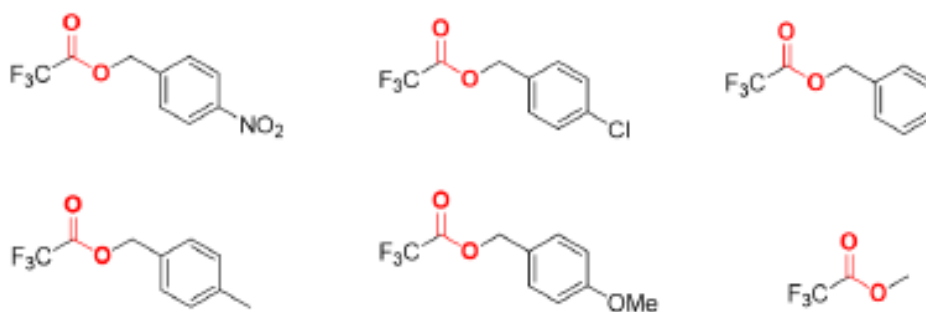


Figure 4. Winter 1972 Carboxylic Esters

52. Minor 1972 studied the effect of D₂O on the degradation of O-Dichloroacetylsalicylate. O-Dichloroacetylsalicylate, like atropine, is a carboxylic ester subject to base-catalyzed hydrolysis. EX1054, 1. The authors reported a solvent isotope effect across a range of pHs and buffer strengths. EX1054, 2 (Table I).

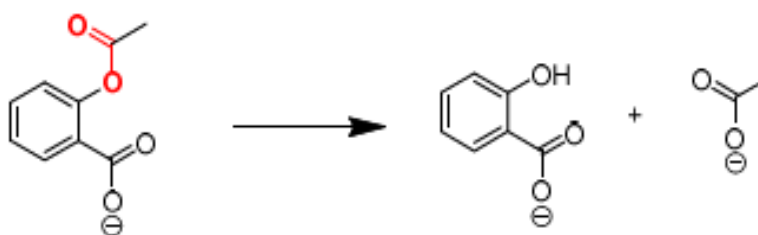


Figure 5. Hydrolysis of O-Dichloroacetylsalicylate

53. Jencks 1993 studied the effect of D₂O on the degradation of a series of phenyl formates and alkyl formates. EX1083, 1. These compounds, like atropine, are carboxylic esters subject to base-catalyzed hydrolysis. The authors reported a solvent isotope effect for each of these compounds across several catalysts. EX1083, 3 (Tables I and II).

54. *Siegel* used D₂O to improve the stability of procaine. EX1006, 4. Procaine is a carboxylic ester subject to base-catalyzed hydrolysis. *Siegel* reported a solvent isotope effect across a range of pHs and observed that at “pH 8 procaine is twice as stable in D₂O as in H₂O.” EX1006, 5.

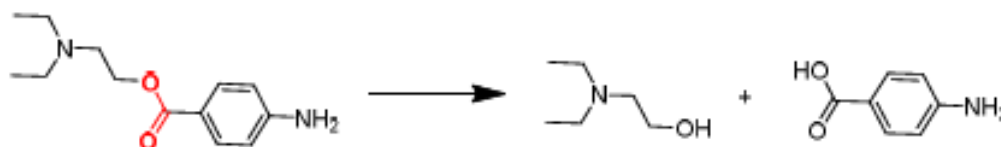


Figure 6. Hydrolysis of Procaine

2. Deuterium Oxide to Improve Known Pharmaceuticals

55. Aside from the differences in the rate of reaction, deuterium oxide is very similar to regular water in most other respects. EX1025, 21; EX1028, ¶[0011] (“Deuterium oxide (D₂O)... is a substance extremely similar to natural water (H₂O).”). As Schowen 1978 explained, “isotopic substitution is the least disturbing structural change that can be made in a system.” EX1025, 21.

Some Physical Properties of Light and Heavy Water ^a		
Property (unit)	H ₂ O	D ₂ O
Molecular weight (¹² C scale)	18.015	20.028
Melting point (°C)	0.00	3.81
Boiling point (°C)	100.00	101.42
Density at 25° (g/cm ³)	0.9970	1.1044
Temperature of maximum density (°C)	3.98	11.23
Dielectric constant, 25°	78.39 ^b	78.06 ^b
Viscosity at 25° (cP)	0.8903	1.107
Viscosity at 20° (cP)	1.005 ^c	1.25 ^c
Ionization constant at 25°	1 × 10 ⁻¹⁴	1.95 × 10 ⁻¹⁵

^a Data taken from more extensive tables in Reference 17, pp. 392–394.

^b Reference 57.

^c Reference 17, p. 347.

Figure 7. Properties of D₂O and H₂O Compared (EX1025, 24)

56. Deuterium generally does not affect the biological properties of a drug, i.e., the manner in which it binds to the target receptor, and it was known that D₂O is safe for use in therapeutics. EX1031, 5 (“[W]e’ve never seen any biologically relevant differences in target selectivity or potency of a drug when we deuterate it.”); EX1027, 5 (“The widespread use of heavy water in clinical studies and treatments without reported adverse effects implies a low toxicity to humans at the doses usually required for treatment.”); EX1029, 10; EX1023, 8–9, 16–17.

57. Due to this targeted effect, i.e., changing the rate of reaction without significantly impacting biological properties, deuterium oxide has been used to improve the properties of a range of therapeutics formulated in aqueous solution. EX1006, 4; EX1052, 2; EX1027, 1–2, 4; EX1029, 1, 6–8, 18–20; EX1030, 7–9; EX1088, 1; EX1058, 1; EX1087, 1; EX1057, 6.

58. For example, *Siegel* used D₂O to improve the stability of procaine, an ophthalmic composition used as local anesthetic. *Siegel* recognized that “since deuterium oxide resembles protium oxide (ordinary water) more closely than any other solvent, it seems appropriate to study the effect of this solvent in pharmaceutical systems.” EX1006, 4; EX1082, 2. The authors further explained that the “stability of [drugs which are liable in aqueous medium] may be prolonged in deuterium oxide” and this may be of value to the “preparation of ophthalmic

solutions, where stability and sterility are important considerations.” EX1006, 4. *Siegel* reported that “the rate of deuteriolysis of procaine is less than the rate of hydrolysis” and that noted any earlier study which showed “activity of procaine, as observed on the cornea of the guinea pig, was greater in D₂O by a factor of 2.” EX1006, 5.

59. Similarly, a patent application to Teva disclosed the use of D₂O to stabilize benactyzine, a carboxylic acid often used in combination with atropine to treat acute exposure to organophosphorus insecticides or nerve gases. EX1052, 2–4. Teva disclosed it was “an object of the present invention to stabilize and thus prolong the long term shelf-life of certain... pharmaceutical compositions by replacing the greater part of the ordinary water normally used therein by deuterium oxide.” EX1052, 2. Consistent with *Siegel*, Teva explained that “deuterium oxide is itself both stable and effectively non-toxic.... It is therefore an ideal solvent medium for the present purposes.” EX1052, 3. Teva further noted that “no new decomposition products due to drug-solvent interactions are to be expected, besides those known from ordinary water” and that D₂O “can be brought to a high uniform standard of chemical and microbiological purity, by adapting the pharmacopoeia standards and tests for ordinary water.” EX1052, 4. In Example II, Teva specifically disclosed that “Benactyzine hydrochloride (40 mg), atropine sulfate (10 mg) and trimedoxime bromide (400 mg) are dissolved in 18 ml of deuterium oxide” and reported that “It

was found that the shelf life at room temperature of the compositions of Examples I and II was considerably enhanced as compared to similar compositions prepared with ordinary water only.” EX1052, 5.

60. By 2014, using deuterium oxide to enhance the stability of known pharmaceuticals was well known in the art. For example, in 2009, Balamurugan et al. described the “widespread use of heavy water in clinical studies and treatments without reported adverse effects” and explained that “D₂O, partly owing to its intrinsic structure, increases the stability of organic molecules, macromolecules, viruses and vaccines.” EX1027, 5. The article further notes that “[e]nough D₂O is now available for exploring its physical, chemical, and biological properties, and subsequent application in biological systems.” EX1027, 3.

61. Similarly, in 2011, Krumbiegel et al. discussed the “[u]se of ²H₂O solvent isotope effects to stabilize chemical compounds.” EX1030, 8. The reference disclosed that “indocyanine green is more stable in ²H₂O and in [1,2-²H²] propandiol than in the non-deuterated solvents by a factor of 1.5” and that “[a] similar solvent isotope effect was observed... with the anti-cancer agent cyclophosphamide.” EX1030, 8. Krumbiegel 2011 clarifies that the concept of deuterium modification is not new, disclosing that “[a]n interesting insight into current activities of pharmaceutical companies to market deuterated drugs is given by an article published in Nature.... 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; *see also* EX1030, 8 (“Over the past decades, several production ways for deuterated organic compounds with names mostly sounding like precursors in pharmacy and pharmacology have been patented.”).

62. In 2014, Nee authored a presentation titled “The use of deuterium oxide to stabilize pharmaceuticals against chemical degradation.” EX1029, 1. The presentation disclosed that D₂O is “readily available with various isotopic purities” (EX1029, 11) and concludes with a slide titled “expected outcomes” that notes “deuterium oxide improve[s] stability of unstable drugs” (EX1029, 20).

63. By the time of the earliest possible effective filing date of the ’447 patent, D₂O had been used to modify other pharmaceuticals prepared in aqueous solution and numerous patents were directed to compositions and methods using D₂O in ophthalmic pharmaceuticals. EX1088, 1 (“This invention relates to a stabilized pharmaceutical composition... characterized in that it comprises one or more a pharmaceutically acceptable vehicle(s)... containing heavy water (D₂O).”); EX1058, 1 (“A deuterated ocular solution is applied to an eye. The deuterated ocular solution includes deuterated water and one or more ocular drugs....”); EX1059, ¶[0047] (“Thus an ‘external’ administration according to the invention can occur, for example, by means of a D₂O -containing ophthalmic ointment (D₂O ophthalmic ointment), D₂O ophthalmic gel, D₂O eye drops....”); EX1087, 1 (using D₂O with

Brilliant Blue, a dye use to stain the eye, and reporting “BBG- D₂O caused no substantial alterations in retinal layers as compared to control eyes”).

64. The increased interest in using D₂O to modify known therapeutics follows the significant increase in the use of deuterium to modify known drugs in general. While the effects of deuterium have been used to study reaction mechanisms for nearly a century, the last several decades have seen a dramatic expansion in its commercial application. EX1031, 3 (“The latest retro rage in the pharmaceutical world is deuterium substitution....”); EX1023, 6 (“But *until recently*, the culture of drug discovery has steadfastly resisted the purposeful incorporation of deuterium into an API despite its extraordinary safety profile, proven capacity to improve drugs, low cost, and the unparalleled predictability of its effects.”) (emphasis added); EX1032, 14–16; EX1055, 50–52. By 2014, several companies were built around using deuterium to improve known therapeutics. EX1031, 3–5.

65. Due to its ability to improve pharmaceuticals without affecting their biological potency, modifying a known drug with deuterium is significantly easier than *de novo* drug design. EX1023, 6, 16–17. As the CEO of a company dedicated to deuterium modification explained “it’s always been difficult to bring drugs to market, and it’s getting harder all the time.” EX1031, 5. Using deuterium modification, pharmaceutical companies can leverage the wealth of data available

for the FDA-approved drug, reducing much of the time and expense associated with traditional drug development. EX1023, 16 (Fig. 11); EX1055, 26–27, 36.

C. Standard Components of Ophthalmic Solutions

66. The importance of stability and sterility in ophthalmic compositions was well understood in the art. Prior art ophthalmic formulations contained routine inactive ingredients, such as buffering agents, viscosity agents, tonicity-adjusting agents, and preservatives, to optimize the properties of those formulations for ophthalmic uses.

1. Ophthalmic Solutions and pH

67. It was well known that ophthalmic solutions should be “formulated to be sterile, isotonic and buffered for stability and comfort.” EX1005, 52. The pH of tear fluid is 7.4. EX1005, 54. Although ophthalmic preparations ideally should be formulated at a pH of the tear fluid for patient comfort, “this [pH] seldom is achieved” in practice, because clinical efficacy must be balanced against stability considerations. EX1005, 52.

68. *Remington*, for example, taught that the proper pH “often represent[s] a compromise between stability of the drug and comfort in the eye,” and that “optimum patient comfort usually is found at the pH of the tear fluid, or about 7.4, while optimum stability for many drugs is generally lower, perhaps as low as 4.0–5.0.” EX1005, 52.

69. *Remington* also provided specific examples that achieved a properly balanced pH. For example, *Remington* discloses that while ophthalmic drugs such as pilocarpine and physostigmine are both active and comfortable in the eye at a pH of 6.8, their chemical stability at such pHs can only be maintained for days or months, with substantial degradation within a year. EX1005, 54. When the pH of solutions containing these drugs is maintained at pH 5, however, “both drugs are stable for a period of several years.” EX1005, 54. *Remington* recommended the use of buffers to maintain the pH at the appropriate level. EX1005, 52–54.

70. Consistent with *Remington*, *Kondritzer* reported that “[t]he half life [of atropine] at any hydrogen ion concentration between pH 3 and 5 is so great that its experimental determination is not practical.” EX1004, 8.

71. For most ophthalmic solutions, including atropine, additional components are often required to adjust the solution to the desired pH. EX1005, 52–54. pH is adjusted by either (1) addition of small amounts of an acid (such as hydrochloric and acetic acid) or a base (sodium hydroxide) or (2) by preparing the buffer solution in specific ratios—e.g., including greater amounts of the weak acid than its conjugate base. EX1076, 2–3, 6.

72. To maintain the pH at the desired level, ophthalmic solutions often include buffer systems. EX1076, 2–3. Buffers are solutions comprised of (1) a weak acid or weak base and (2) their conjugate salt. EX1076, 2–3. For example, the oft-

used citrate buffer, is comprised of citric acid (a weak acid) and sodium citrate (the salt of its conjugate base). EX1077, 32–33. Similarly, other common buffers include acetate buffers (comprised of acetic acid and sodium acetate) and phosphate buffers. EX1076, 6; EX1077, 29, 43–44; EX1005, 52.⁶

73. Buffers differ by the pH ranges at which they are most effective at maintaining the solution at a constant pH. EX1076, 3; EX1080, 23. A buffer's effective range depends on the properties of the weak acid and weak base used to prepare the buffer. EX1080, 23–24. It was known that buffers are most effective within ± 1 pH unit of their pKas. EX1076, 3. For example, acetic acid has a pKa of 4.8 and therefore can maintain the pH of a solution most effectively at pH 3.8–5.8. EX1080, 23; EX1077, 29. Citric acid is a triprotic acid, and thus has a wider buffer range of 2.1–7.4.⁷ EX1080, 23; EX1077, 32–33.

⁶ Dibasic sodium phosphate (disodium hydrogen phosphate) and monobasic sodium phosphate (sodium dihydrogen phosphate) were used in the FDA-approved Akorn 1% atropine sulfate eye drops to maintain a pH of 3.5 to 6.0. EX1066, 3.

⁷ Triprotic acids, such as citric acid, have three hydrogens they can donate during dissociation and thus have three pKas. This contrasts with a monoprotic acid, such as acetic acid, which has a single hydrogen that can be donated.

2. Tonicity-adjusting Agents

74. Tonicity refers to osmotic pressure, e.g., as exerted by salts in ophthalmic solutions relative to tear fluid. EX1005, 54. It was known that “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. 0.9% sodium chloride was often included to provide isotonicity in a variety of known low-concentration atropine solutions. EX1005, 52; EX1067, 2.

3. Preservatives

75. Preservatives had long been used in ophthalmic solutions to “prevent the growth of, or to destroy, microorganisms introduced accidentally when the container is opened during use.” EX1005, 55. Common preservatives include benzalkonium chloride (BAK), methylparaben, and chlorobutanol. EX1005, 55–56; EX1069, 3–8.

76. BAK was long the preservative “used in the large majority of commercial ophthalmic solutions and suspensions.” EX1005, 54. It was known that the concentration of BAK is typically “0.005% to 0.02%” and concentrations of 0.01% were “most common.” EX1005, 54–55. Atropine solutions containing 0.01% BAK were routinely prepared, used in clinical trials, and had been approved by the FDA. EX1003, 14; EX1018, 9:5–7; EX1066, 3.

VII. The '447 Patent

A. Specification

77. The '447 patent discloses ophthalmic compositions to treat myopia. EX1001, Abstract, 1:27–32, 4:26–28. The '447 patent states 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, 6:45–49.

78. The '447 patent discloses that ophthalmic 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, 6:61–7:5. The '447 patent further discloses that these shortcomings can be “prevented or alleviated by formulating muscarinic antagonist (e.g. atropine) compositions at higher pH ranges.” EX1001, 6:65–7:2.

79. The '447 patent states that “deuterated water stabilizes ophthalmic compositions.” EX1001, 7:23–24. The '447 patent discloses that “in some instances compositions comprising deuterated water leads to reduced base catalyzed

hydrolysis when compared to compositions comprising H₂O.” EX1001, 7:29–32. Thus, the use of D₂O can result in “less tear reflex in the eye.” EX1001, 7:34.

80. The ’447 patent also discloses standard formulation components routinely used in ophthalmic compositions. EX1001, 3:1–3; 3:18–21; 32:62–33:1. For example, the ’447 patent notes the use of sodium chloride as an osmolarity (3:1–3) and tonicity (3:18–21) adjusting agent. Similarly, the ’447 patent discloses “useful formulations include one or more pD adjusting agents or buffering agents” including acetate, bicarbonate, ammonium chloride, citrate, and phosphate. EX1001, 32:62–33:1.

81. The ’447 patent discloses standard storage temperatures for atropine solutions. EX1001, 59:10–29. The ’447 patent also discloses a range of pD levels corresponding to pH levels known to be optimum for stability (pH 3–5) up to those known to be optimum for patient comfort (pH 7.4). EX1001, 12:47–13:27.

B. Priority

82. The ’447 patent claims priority to U.S. Provisional Application Nos. 62/016,502 (“the ’502”) and 62/096,433 (“the ’433”). EX1001, cover. All of the claims of the ’447 patent cover atropine formulations in deuterium oxide. EX1001, claims 1–19.

83. In my opinion, neither of these applications provides adequate written description for the claims of the ’447 patent at least because neither the ’502 nor the

'433 application discloses deuterium oxide. EX1043, p. 15–61 and EX1044, p. 15–95.

VIII. Person of Ordinary Skill in the Art

84. As discussed above, the subject matter of the '447 patent is directed to the composition of an FDA-approved drug (atropine) in combination with deuterium oxide and its use to treat myopia, known to be treated by the FDA-approved drug (atropine).

85. Based on my understanding of the technology, education, and experience level of those working in this field, it is my opinion that a POSA working in the field of the '447 patent at the relevant time would have possessed a Ph.D. in Chemistry, Organic Chemistry, Physical Chemistry, or Pharmaceuticals, with several years of experience involving preparation and/or testing of pharmaceutical formulations. A POSA would be familiar with the common inactive ingredients used in aqueous pharmaceutical formulations and the basic characteristics of aqueous formulations, such as stability, and have knowledge about drug degradation kinetics.

IX. Claim Construction

86. In light of the intrinsic record and the state of the art as of the earliest possible effective filing date of the '447 patent, a POSA would have understood the

following claim term as described below. Regardless of how this term is construed, however, the claims would have been obvious.

A. “Extended Period of Time”

87. Claims 2 and 15 recite “after extended period of time under storage condition.” EX1001, claims 2 and 15. As used in the ’447 patent, a POSA would understand an “extended period of time” to mean “at least about 1 week.”

88. The specification repeatedly states that “[i]n some embodiments, the extended period of time is one of: about 1 week.” EX1001, 1:60–65, 5:19–24, 11:37–38, 24:17–23. The ’447 patent also defines the lower bound of other temporal embodiments as “at least one week,” e.g., “In some embodiments, the composition stored in a plastic container has a potency of at least 80% for a period of at least 1 week....” EX1001, 24:46–52.

X. Ground 1: Claims 1–3, 6–7, and 12–19 Would Have Been Obvious Over *Chia* and *Siegel* in view of *Kondritzer*

89. The compositions and their uses of the independent claims of the ’447 patent require three components: (1) “about 0.001 wt % to about 0.03 wt %” of atropine or atropine sulfate, (2) “deuterated water,” and (3) “a pD of from about 4.2 to about 7.9.” EX1001, claims 1, 14, and 17. In my opinion, all these claimed elements were taught in the prior art.

A. Motivation to Combine

90. In 2012, *Chia* reported that 0.01% atropine eye drops were effective for the treatment of myopia and reduced the side effects, and hence, patient compliance issues associated with higher concentration formulations. EX1003, 13, 19–20. This clinical success would have motivated one of skill in the art to make and use low-concentration atropine formulations.

91. D₂O offered the potential to improve on these solutions by allowing for administration at higher pH levels more optimal for patient comfort, and hence, patient compliance, while at the same time enhancing long-term shelf life. Before the earliest possible effective filing date, it was known D₂O could increase the stability of ophthalmic compounds by reducing the rate of base-catalyzed ester hydrolysis, which *Kondritzer* established was the primary mechanism of atropine degradation at the pH levels atropine is administered. *Siegel*—which studied procaine, a carboxylic ester subject to base-catalyzed hydrolysis—specifically taught that stability “may be prolonged in deuterium oxide” and that D₂O “may prove of value, for example, in the extemporaneous preparation of ophthalmic solutions, where stability and sterility are important considerations.” EX1006, 4.

92. *Siegel* and *Kondritzer* provided further motivation to substitute H₂O with D₂O. Given that “deuterium oxide resembles protium oxide (ordinary water) more closely than any other solvent” (EX1006, 4), this relatively simple substitution

offered the potential to improve on *Chia*'s solutions without adversely affecting their clinical efficacy. The motivation was reinforced by the similarities between atropine and procaine as a POSA would have expected that the benefits in stability obtained with D₂O-procaine would likewise be seen in D₂O-atropine formulations.

1. A Person of Skill in the Art Would Have Been Motivated to Formulate Low-Concentration Atropine Formulations

93. Atropine solutions had long been used at concentrations at 1% and 0.5% to treat myopia. EX1003, 13; EX1013, 4; EX1009, 1. These formulations were effective, but caused several important side effects such as photophobia, cycloplegia, and mydriasis that resulted in poor patient compliance. EX1045, 4 (“[T]hese [1% and 0.5%] doses are quite difficult to use in the clinical setting, primarily because of the all-day photophobia occurring after instillation... resulting in poor compliance and a high rate of discontinuation of treatment.”); EX1045, 2; EX1012, ¶[0006]; EX1003, 13; EX1013, 1.

94. Patient compliance refers to the consistency with which a patient actually uses their prescribed medication. EX1048, 4–5. Compliance is particularly important in using atropine to treat myopia because the medication must be used daily over long periods of time. EX1048, 5 (“In instances where long-term medical therapy is necessary to achieve desired outcomes, treatment efficacy can be compromised by suboptimal adherence, compliance, and persistence with the

treatment in general. This occurs both in ophthalmology and in other clinical therapeutic areas.”). The side effects caused by the 1% and 0.5% formulations reduced this compliance and, in turn, the clinical efficacy of atropine. EX1015, 1 (“Although 1% atropine effectively slows myopia progression, it is associated with... poor compliance.”); EX1012, ¶[0006] (explaining “the compliance is poor and dropout rate is correspondingly high” due to photophobia caused by the 1% and 0.5% formulations).

95. To address this issue, *Chia* tested lower concentration formulations and found that “0.01% atropine [] seems to retain efficacy and is a viable concentration for reducing myopia progression in children, while attaining a clinically significant improved safety profile in terms of accommodation, pupil size, and near visual acuity, and subsequently reduced adverse impact on visual function.” EX1003, 19. *Chia* further reported that “The more important aspect of this trial remained the comparison of low dose versus high dose in terms of not only the efficacy but also the visual side effects of atropine” and that the “0.01% formulation exhibited fewer adverse events.” EX1003, 19–20. *Chia* also notes a previous study which found similar results with 0.025% atropine. EX1003, 19.

96. *Chia*’s findings would have motivated one of skill in the art to formulate low-concentration atropine solutions. The authors expressly note that “Atropine 0.01% is currently not commercially available” and that “findings

collectively suggest that a nightly dose of atropine at 0.01% seems to be a safe and effective regimen for slowing myopia progression....” EX1003, 19–20.

97. As atropine requires long-term use, a POSA would have been motivated to formulate ready-to-use solutions that could remain stable over a long period. EX1013, 5 (“[N]o commercial 0.05% atropine solution was available, so the eye drops were prepared by diluting 1% atropine solution.”); EX1048, 4–5.

98. Stability of ophthalmic solutions “is always a primary consideration, both in the bottle and in the tissues” (EX1046, 8) and “pharmaceutical manufacturer[s] strive[] for a shelf-life measured in years.” (EX1046, 15). While a longer shelf life is better for all medications, the stability of low-concentration formulations is particularly important because “the loss of even small amounts of drug... can become significant.” EX1046, 16; EX1047, 1–2; EX1080, 7 (“[S]ince pharmaceutical standards for degradation are very exacting, even relatively slow rates can be problematic.”).

99. As explained above (§ VI.A.2), atropine’s stability largely depends on the pH, which must be balanced against clinical efficacy. EX1005, 54 (explaining 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”); EX1004, 6, 8 (Table III). Optimal patient comfort,

and thus patient compliance, was known to be pH 7.4, the pH of the natural tear fluid of the eye. EX1005, 54.

100. As *Kondritzer* demonstrated, however, atropine is most stable at pH 3–5. EX1004, 6, 8 (Table III). Beyond pH 5, the higher OH[–] concentration leads to an increased rate of base-catalyzed hydrolysis and atropine becomes more unstable; EX1033, 1 (discussing the “instability of atropine solutions... outside the range of pH 3 to 5”); EX1069, 2 (“The effects of temperature and pH are particularly important. Buffering certain drugs in the physiological pH range makes them unstable, particularly at high temperatures.”); *see also* EX1033, 16 (“A 44% loss was found in an isotonic atropine-borax-boric acid solution after storage at room temperature for only one month”); EX1049, 1 (“the stability of atropine is limited.... Upon storage, degradation reactions can take place.”)

101. Formulating atropine at pH 3–5, i.e., those that provide maximum stability, however, is suboptimal as it causes patient discomfort and irritation. EX1050, 7. As a result, the patient is less willing to use the medication daily, creating the same problem with patient compliance that *Chia* sought to remedy with their low-concentration formulations. EX1015, 1 (“Although 1% atropine effectively slows myopia progression, it is associated with... poor compliance.”); EX1012, ¶[0006] (explaining “the compliance is poor and dropout rate is correspondingly high” due to photophobia caused by the 1% formulation).

102. Formulating atropine at these acidic pHs also reduces the clinical efficacy of individual doses because “[w]hen the therapeutic agents themselves are irritating, excess tearing may occur that may influence bioavailability in affected individuals.” EX1046, 8; *see also* EX1047, 2 (“[T]ears are mainly responsible for the short residence time and low absorption of drugs applied topically to the eye.”); EX1051, 2 (“Poor bioavailability of drugs from ocular dosage forms is mainly due to the precorneal loss factors which include solution drainage, lacrimation, tear dynamics, tear dilution, tear turnover....”).

103. Thus, a POSA would have been motivated to formulate low-concentration atropine solutions that could be administered at pHs closer to those that provided optimal patient compliance and clinical efficacy, but that could also remain stable over long periods of time.

2. A Person of Skill in the Art Would Have Been Motivated to Modify Low-Concentration Atropine Solutions with D₂O

104. In this regard, *Siegel* would have motivated a POSA to modify *Chia*’s low-concentration solutions with D₂O.

105. *Siegel* used D₂O to improve the stability of procaine, an ophthalmic composition used as local anesthetic. EX1006, 4. *Siegel* explicitly stated 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* also noted that an earlier study found the efficacy of procaine in deuterium oxide was greater in D₂O by a factor of two and that the increased activity is “attributed to a greater stability (*in vivo*) of procaine base in deuterium oxide.” EX1006, 5.

106. A POSA would have been further motivated to modify atropine with D₂O because the similarities between procaine and atropine suggested that the increased stability obtained by *Siegel* for procaine could also be obtained for atropine. It was well understood that the solvent isotope effect could be reasonably predicted by the SIE seen for similar compounds and reaction types. EX1025, 32 (“As stated in the beginning of Section 4, any method used to predict an isotope effect for a proposed mechanism, including simple analogy with a known reaction, is usually acceptable.”); *see also* EX1025, 63–64. Thus, not only was D₂O particularly beneficial to low-concentration atropine, a POSA also would have had a high expectation these benefits could be realized.

107. As shown below in Figure 8, atropine and procaine are both carboxylic esters and degrade via the same reaction. *Kondritzer* recognized that, “[h]ydrolytic reactions catalyzed by both hydrogen and hydroxyl ions, with no detectable water reaction, include hydrolysis of carboxylic esters,” a prior study “indicate[d] this to be true for the hydrolysis of procaine,” and *Kondritzer* “assum[ed] that the hydrolytic reactions of atropine are included in this category.” EX1004, 6.

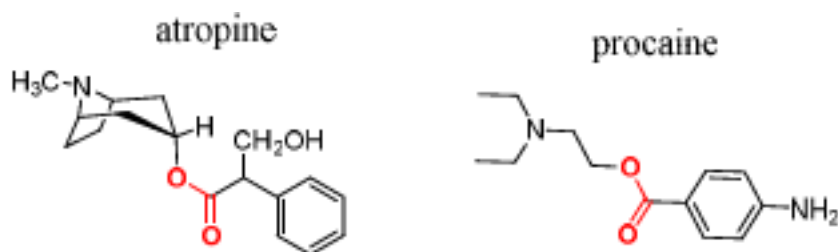


Figure 8. Structures of Atropine and Procaine

108. The stability of procaine and atropine are both “governed by the hydroxyl-ion concentration and the temperature.” EX1004, 5; EX1006, 4 (“The rate of hydrolysis was shown to increase with hydroxide ion concentration.”). Both compounds are primarily degraded via cleavage at the acyl carbon during base-catalyzed hydrolysis.

109. Both procaine and atropine are weak bases. Procaine has a pKa of 8.8, similar to atropine’s pKa of 9.9. EX1053, 41–42; EX1054, 2 (noting that “carboxylic acids of similar strength exhibit similar solvent isotope effects”).

110. Given these similarities, a POSA would have reasonably expected that the solvent isotope effect seen for procaine in D₂O would also be seen for atropine in D₂O. As Schowen 1978 explains, “simple analogy with a known reaction, is usually acceptable” to predict the solvent isotope effect. EX1025, 32; EX1025, 63 (“By analogy with Example I and other base-catalyzed ester hydrolyses where $k_{H_2O}/k_{D_2O} \sim 2-3$ ”).

111. The expectation that atropine would be affected by D₂O in a similar way as procaine was reinforced by the fact that an SIE had been observed for

numerous other carboxylic esters degraded via base-catalyzed hydrolysis. § VI.B; 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*”) (emphasis added); EX1064, 1, 4; EX1063, 2, 4 (Table IV); EX1083, 3.

112. The motivation to modify atropine with D₂O was further bolstered by the fact that, aside from the potential improvements in stability, D₂O is otherwise very similar to H₂O. § VI.B. *Siegel* recognized, “since deuterium oxide resembles protium oxide (ordinary water) more closely than any other solvent, it seems appropriate to study the effect of this solvent in pharmaceutical systems.” EX1006, 4. *Siegel’s* disclosure is consistent with the art as a whole, which showed that “isotopic substitution is the least disturbing structural change that can be made in a system” (EX1025, 21) and that deuterium is the “smallest structural change that can be made” (EX1024, 5). *See also* EX1023, 16 (“[I]t is instructive to consider the great number of discovery and development activities that may be references in full to the protio version with no alteration and possibly no need for repeating.”)

113. Thus, at worst, using D₂O with atropine would be expected to result in an ophthalmic solution at least as effective as the low-concentration H₂O formulation *Chia* demonstrated was clinically effective and had an improved side

effect profile over the higher concentration formulations. § VI.B.2; EX1082, 1–2 (“Since it appears that deuterium oxide is toxic in animals only when the concentration in the body fluids reaches high levels, and since deuterium oxide resembles the common solvent protium oxide more closely than any other, it seems appropriate to explore possible pharmaceutical applications of this solvent.”) As low concentration formulations were not yet commercially available, this alone would have motivated a POSA to formulate low-concentration atropine solutions with D₂O. EX1003, 19–20.

114. Finally, at the same time *Chia*’s work would have motivated a POSA to look to ways of improving the stability of low-concentration atropine, there was an explosion in interest in using deuterium to modify known pharmaceuticals. EX1056, 3; EX1031, 5; EX1032, 14–15; EX1055, 50–52.

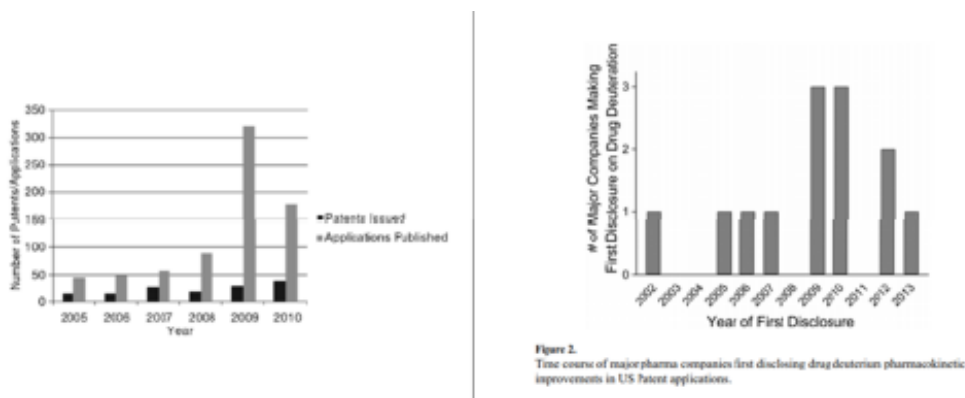


Figure 9. Left: EX1055, 68 (Fig. 10.4); Right: EX1032, 15 (Fig. 2)

115. Unsurprisingly, this trend extended to using D₂O, which, by 2014, had become more widely available, and hence, commercially viable for pharmaceuticals.

EX1023, 16 (“The ultimate source of most reagents for these transformations is the inexpensive, safe, and readily available heavy water (D₂O).”). As Balamurugan et al. noted in their 2009 review, “[e]nough D₂O is now available for exploring its physical, chemical, and biological properties, and subsequent application in biological systems.” EX1027, 3.

116. By 2014, the stabilizing effect of D₂O was widely recognized and had been used to improve a range of different therapeutics. § VI.B; EX1006, 4; EX1052, 2; EX1027, 1–2, 4; EX1029, 1, 6–8, 18–20; EX1030, 7–9; EX1088, 1; EX1058, 1; EX1087, 1; EX1057, 6 (“D₂O itself has an effect in increasing the stability of the compositions of the invention.”). A 2014 presentation titled “The use of deuterium oxide to stabilize pharmaceuticals against chemical degradation” explicitly stated that “Deuterium oxide improve[s] stability of unstable drugs” was an “Expected Outcome[]” of D₂O modification. EX1029, 1, 20. Teva used D₂O 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.

B. Reasonable Expectation of Success

117. A POSA also would have had a reasonable expectation of achieving the compositions recited by the '447 patent.

118. Aside from the substitution of D₂O, the claims of the '447 patent recite standard ophthalmic solutions of atropine proven effective in large scale clinical trials. EX1003, 13; EX1014, 1; § VI.A.1. D₂O presented no unique formulation issues, was widely available at high levels of isotopic purity, would not have been expected to negatively affect efficacy, and had been incorporated into numerous ophthalmic compositions. 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, [0040] (“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 more than reasonable expectation of success in achieving the claimed invention.

119. There was also a reasonable expectation that the claimed formulations would have improved stability compared to solutions containing regular water. *Siegel* taught that at the pD levels closest to those claimed by the '447 patent, D₂O increased the stability of procaine by a factor of at least two. EX1006, 5. As demonstrated by *Kondritzer*, a POSA would have known that, atropine was similar to procaine. EX1006, 4–5; EX1004, 6–8; § X.A.2. As such, a POSA would have reasonably expected that substituting D₂O for H₂O in atropine solutions would have a similar effect as the substitution in procaine solutions. EX1025, 26, 32, 63–64. The expectation of success was bolstered by the art as a whole, which was replete

with literature demonstrating that D₂O increased the stability of these compounds and reactions. § VI.B; EX1060, 4; EX1061, 4; EX1054, 2; EX1062, 3; EX1063, 4; EX1064, 4.

C. Claim-by-Claim Analysis

1. Claim 1

120. Claim 1 of the '447 patent recites “An ophthalmic composition, comprising one and no more than one ophthalmic agent, and deuterated water, at a pD of from about 4.2 to about 7.9, wherein the ophthalmic agent consists of atropine, atropine sulfate, or a combination thereof, at a concentration of from about 0.001 wt % to about 0.03 wt %.” EX1001, claim 1.

a. 1[a] “An ophthalmic composition, comprising...”

121. To the extent that the preamble is limiting, *Chia* renders it obvious.

122. *Chia* disclosed 0.01% atropine formulated as eye drops. EX1003, 13, 14. As was well understood in the art, eye drops are an ophthalmic solution. EX1050, 1 (“The most commonly used dosage form is an aqueous solution of a drug delivered as an eyedrop, which is applied topically to act on the ocular surface or in the interior of the eye.”); EX1005, 48 (“The outflow capacity accommodates the sudden large volume resulting from the instillation of an eyedrop. Most commercial eyedrops range from 50 to 75 µL in volume.”).

123. A POSA would have recognized that ophthalmic solutions are necessarily ophthalmic *compositions*. EX1018, 1:3–5 (“The present invention relates to a composition... for reducing and/or preventing myopia progression. In particular, the invention relates to an ultra-low concentration atropine *solution* for reducing and/or preventing myopia progression.”) (emphasis added); EX1038, ¶[0021]. As such, the atropine eye drops discussed by *Chia* taught “an ophthalmic composition.”

b. 1[b] “one and no more than one ophthalmic agent”

124. Limitation 1[b] is rendered obvious by *Chia*.

125. *Chia* disclosed 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. As explained above, atropine sulfate is an ophthalmic agent. § X.C.b). Aside from atropine, *Chia* does not disclose any other ophthalmic agents included in the trial medications. EX1003, 14. Accordingly, *Chia* discloses an ophthalmic compositions comprised of “one and no more than one ophthalmic agent.”

126. Further, the art showed that administering atropine as a monotherapy, i.e., comprising one and no more one ophthalmic agent, was standard practice in the

use of atropine to treat myopia.⁸ EX1014, 1-2; EX1005, 1569; EX1067, 9. For example, Fang disclosed a clinical trial of atropine for myopia in which patients “received topical 0.025% atropine eye drops.” EX1014, 1–2.

c. 1[c] “and deuterated water”

127. Limitation 1[c] is rendered obvious by *Siegel*.

128. *Siegel* disclosed the replacement of regular water with D₂O in ophthalmic solutions; taught that D₂O could be used to increase the long-term stability and clinical efficacy of procaine; and motivated the use of D₂O in ophthalmic solutions, explaining that D₂O: “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 between atropine and procaine (§ X.A.2), a POSA would have been motivated to apply the teachings of *Siegel* to *Chia*’s low-concentration atropine formulations.

129. D₂O offered a number of potential improvements that were particularly beneficial to *Chia*’s low-concentration atropine solutions.

130. First, increased shelf life is desirable for all medications as it is commercially beneficial to retailers (e.g., pharmacies) and it allows for a medication

⁸ For other indications, such as poisoning due to nerve gas exposure, atropine is administered in combination with other cholinolytic drugs. EX1096, 1–2.

to remain effective for longer periods of time after they are dispensed to the patient. EX1088, 4 (“even in the best of cases, the increase in service life from 50% to 100% (at the temperature of 20° C) of a therapeutic product, will be welcome...”); EX1080, 7; EX1046, 15. The art showed that “pharmaceutical manufacturer[s] strive[] for a shelf-life measured in years.” EX1046, 15. This was particularly beneficial to atropine, which requires long term use to effectively treat myopia. §§ VI.A.1, X.A.1; EX1016, 5.

131. Further, atropine had to be formulated at a pH that balanced stability against clinical efficacy. EX1005, 52–54. While lower pH solutions were more stable, the increased acidity at these lower pHs undermined patient compliance and long-term efficacy; “2- to 3-year stability often [was] achieved only by virtue of compromise.” EX1005, 54. A POSA would have understood that D₂O offered the potential to formulate atropine solutions at pHs closer to the clinically desirable pH of 7.4, while remaining stable enough to enable long-term storage and use. § X.A.

132. This increased stability was especially beneficial to *Chia*’s low-concentration ophthalmic solutions, where “the loss of even small amounts of drug... can become significant.” EX1046, 16; *see also* EX1047, 1–2; EX1051, 2 (“Due to these physiological and anatomical constraints [of ophthalmic administration]... effectively 1% or even less of the instilled dose[] is ocularly absorbed”).

133. The POSA's motivation was bolstered by the fact that substitution of D₂O for H₂O would have been expected to result in a formulation that was at least as effective as that used successfully by *Chia*. §§ VI.B.2, X.A.2; EX1052, 3 (“As [was] well known, deuterium oxide is itself both stable and effectively non-toxic.... It is therefore an ideal solvent medium....”); EX1024, 5; EX1023, 8–9; EX1022, 9. As *Siegel* explained, “since deuterium oxide resembles protium oxide (ordinary water) more closely than any other solvent, it seems appropriate to study the effect of this solvent in pharmaceutical systems.” EX1006, 4. D₂O would not have been expected to affect the biological properties of atropine, and, as such, offered potential improvement with little risk of technical failure. § VI.B.2.

134. In the same vein, the predictability of D₂O meant that substituting it for regular water did not present any unique formulation issues. EX1023, 8–9; EX1028, ¶[0011] (“Deuterium oxide (D₂O)... is a substance extremely similar to natural water (H₂O).”); §§ VI.B.2, X.A.2. Indeed, the ability to leverage the vast amount of information available for known drugs is one of the factors that makes the use of deuterium modification particularly attractive to pharmaceutical manufacturers. EX1023, 15–17.

135. Thus, a POSA would have been motivated to improve the long-term shelf life and clinical efficacy of *Chia*'s low-concentration atropine solutions with

D₂O, and would have had a reasonable expectation of success in achieving such solutions.

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

136. Limitation 1[d] is rendered obvious by *Kondritzer* and *Siegel*.

137. As described above, and acknowledged by the '447 patent, pD equals pH + 0.4. EX1026, 2; EX1001, 33:21–27 (“In some embodiments, the pD is calculated according to the formula disclosed in Glasoe et al.... In some embodiment, the pD is calculated as $pD = pH^* + 0.4$, in which pH* is the measured or observed pH of the ophthalmic composition formulated in a solution comprising deuterated water (e.g., D₂O).”). Thus, the range of pD 4.2–7.9 correlates to a pH of 3.8–7.5. This range covers both the pH at which atropine was known to be most stable (pH 3–5) and the pH that was most desirable for clinical administration (pH 7.4). § VI.C.1.

138. It was well understood that pH is a result-effective variable for stability and patient comfort. *Kondritzer* demonstrated that stability of atropine is “governed by the hydroxyl-ion concentration.” EX1004, 5. Specifically, *Kondritzer* derived an equation “predicting the rate of proton hydrolysis at any particular temperature and hydrogen ion concentration” (EX1004, 6), showed that “[t]he half lives of solutions of atropine at various pH values and temperatures can be calculated for both hydroxyl-ion and hydrogen-ion catalysis,” (EX1004, 8), and disclosed “[c]alculated

half lives of solutions of atropine over the region of pH 2 to 7” (EX1004, 8). *Kondritzer* showed that atropine is most stable at pH 3–5 (pD 3.4–5.4). EX1004, 8 (“The half life at any hydrogen ion concentration between pH 3 and 5 is so great that its experimental determination is not practical.”).

139. A POSA would have known that the natural pH of the eye is pH 7.4 and that “[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. Similarly, it was known that “[t]he proper pH, buffer and buffer capacity often represent a compromise between stability of the drug and comfort in the eye, since optimum patient comfort usually is found at the pH of the tear fluid, or about 7.4, while optimum stability for many drugs is generally lower, perhaps as low as 4.0–5.0.” EX1005, 52.

140. Optimizing pH for atropine solutions for stability and comfort within the known range was routine. For example, *Kondritzer* reviewed the results from numerous prior studies examining the stability of atropine at various pH levels, noting, e.g., “preservation of aqueous atropine solutions by buffering at pH 4-5 has been recommended” and that “no appreciable decomposition was found on sterilization for twenty minutes at 120° until pH 6, or over, was reached, when hydrolysis became very rapid.” EX1004, 6. Similarly, it was text-book knowledge that “[t]he attainment of optimum stability most often imposes a series of compromises on the formulator. The optimum pH may be lower than preferable for

product comfort, although this effect may be minimized by adjusting pH” (EX1005, 54) and that “solution *pH must be selected* for optimum drug stability.” (EX1005, 52) (emphasis added). Accordingly, it would have been obvious to optimize the pD of the compositions recited by claim 1 for stability and comfort.

141. Further, based on the teachings of *Kondritzer* and *Siegel*, it would have been obvious to formulate the claimed atropine solutions at pD 5.4–6.4 (pH 5–6). This range falls within in the claimed ranged of pD 4.2–7.9 and also would have rendered the claimed limitation obvious. Starting from pD 5.4 (pH 5), the top end of the range for which atropine was known to be most stable, a POSA would have been motivated to increase the pD to as close as possible to pD 7.8 (pH 7.4), where patient comfort, and thus, patient compliance and clinical efficacy, was optimal. Based on *Kondritzer*, a POSA would have reasonably expected that pD could be increased until approximately pD 6.4 (pH 6), where “hydrolysis became very rapid.” EX1004, 6.

142. The obviousness of pD 5.4–6.4 was reinforced by *Siegel*, which showed that D₂O would be reasonably expected to increase the stability of atropine, thereby allowing for pD levels beyond those taught by *Kondritzer* to provide optimal stability. EX1006, 4–5. *Siegel* explained that “the rate of deuteriolysis of procaine is less than the rate of hydrolysis” (EX1006, 5) and explicitly stated that the increased stability afford by deuterium oxide “may prove of value, for example, in

the extemporaneous preparation of ophthalmic solutions, where stability and sterility are important considerations.” EX1006, 4.

143. Finally, the POSA’s motivation and reasonable expectation of success for pD 5.4–6.4 was further bolstered by the art as a whole, which showed that this range was bracketed by pH ranges already demonstrated to work for atropine in the treatment of myopia. EX1065, 2 (“The pH value of the product should be 4.0~6.0.”); EX1067, 3 (“The product showed a pH of 4.0–6.0.”). Indeed, the prescribing information for the FDA-approved atropine eye drops instructed that they should be administered at pH “3.5 to 6.0 [i.e., pD 3.9–6.4].” EX1066, 3.

e. 1[e] “wherein the ophthalmic agent consists of atropine, atropine sulfate or a combination thereof”

144. Limitation 1[e] is rendered obvious by *Chia*.

145. As explained above (§ X.C.1.a)), *Chia* disclosed the use of atropine eye drop solutions to treat myopia. EX1003, 13, 19–20.

146. Further, the art showed that the “most widely studied pharmacological agent for the inhibition of myopia progression has been atropine” (EX1013, 2) and numerous references teaching the use of atropine solutions to treat myopia. EX1066, 1; EX1067, 1; EX1014, 1; EX1010, 1; EX1011, 1; EX1012, ¶[0006].

f. 1[f] “at a concentration of from about 0.001 wt % to about 0.03 wt %”

147. Limitation 1[f] is rendered obvious by *Chia*.

148. *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. *Chia*’s concentration falls squarely within the claimed range and rendered this limitation obvious.

149. *Chia*’s disclosure that “0.01% atropine is not commercially available yet” and their conclusion 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” expressly motivated one of skill in the art to formulate low-concentration atropine solutions. EX1003, 20.

150. The obviousness of concentrations of “about 0.001 wt % to about 0.03 wt %” atropine was further underscored by the art as a whole, which showed the efficacy of low-concentration atropine at other concentrations within the claimed range. § VI.A.1. For example, Fang 2010 specifically disclosed that “[r]egular topical administration of 0.025% atropine eye drops can prevent myopia onset and myopic shift in premyopic schoolchildren for a 1-year period.” EX1014, 1; *see also* EX1018, 19:12–13; EX1017, 6.

151. Thus, a POSA would have been motivated towards an ophthalmic composition comprising one and no more than one ophthalmic agent, and deuterated water, at a pD of from about 4.2 to about 7.9, wherein the ophthalmic agent consists of atropine, atropine sulfate, or a combination thereof, at a concentration of from about 0.001 wt % to about 0.03 wt %, and had a reasonable expectation of success achieving the same.

2. Claim 2

152. 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.

153. As explained above (§ X.C.1), claim 1 was obvious. *Chia*, *Siegel*, and *Kondritzer* renders obvious this additional feature of claim 2.

154. As described above (§ X.C.1.d)), based on *Kondritzer* and *Siegel*, it would have been obvious to formulate the claimed atropine solutions at pD 5.4–6.4. As also described above (§ IX), a POSA would understand an “extended period of time” to mean “at least about one week.” A POSA would have reasonably expected

that the atropine solutions recited by claim 1 formulated at least at a pD of 5.4–6.4 would meet the stability limitation of claim 2.

155. A 2004 study “evaluate[d] the pH value of 17 ophthalmic solutions frequently used in ophthalmic practice... to investigate their variation over time.” EX1050, 4. The test period was thirty days and “[a]ll solutions were tested at room temperature, ranging from 19° to 21 C°.” EX1050, 4. The study reported that “we did not find statistically significant differences in pH over time for 10 of 17 solutions analyzed,” including atropine. EX1050, 5. Specifically, the authors reported that atropine had a mean pH of 5.18 (pD 5.58) and ranged from a low of pH 5.13 (pD 5.53) to a high of pH 5.24 (pD 5.64). EX1050, 4 (Table 3). These tested ranges demonstrate that a POSA would reasonably expect a solution at pD of 5.4–6.4 would have a pD of “less than 7.3” for at least thirty days—more than four times as long as the at least about one week required by claim 2.

156. Similarly, a study of atropine done over the course of one year found that “[t]here were slight increases in pH, of 1.08, 0.77, and 0.41 at 35° C, 23° C, and 5° C, respectively.” EX1068, 3. As claim 2 does not recite a temperature limitation, all of these levels of variation are encompassed by claim 2. As such, a POSA would reasonably expect that the atropine solutions of claim 1, formulated at the pD range of 5.4–6.4, would meet the requirement of a pD of “less than 7.3” over at least one

year. During the one-week period required by claim 2, this variation would reasonably be expected to be substantially less, if even measurable.

157. As the prior art demonstrates, even if an “extended period of time” is construed as a period longer than at least about one week, a POSA would still reasonably expect a solution of claim 1 formulated at 5.4–6.4 to meet the stability limitation of claim 2.⁹

158. Thus, a POSA would have been motivated towards an ophthalmic composition as recited by claim 1 which had a pD of less than about 4.8–7.3 after an extended period of storage, and had a reasonable expectation of success in achieving the same.

3. Claim 3

159. Dependent claim 3 recites: “The ophthalmic composition of claim 1, wherein the ophthalmic agent 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

⁹ Indeed, the pD range recited by claim 1, pD 4.2–7.9, is broader than pD 5.4–6.4. As the limitation of claim 2 is dependent on the initial pD of the formulation, i.e., a pD of anywhere from 4.2–7.9, claim 2 allows for a level of variation in pD that exceeds what a POSA would reasonably expect.

about 0.008 wt %, or from about 0.001 wt % to about 0.005 wt %.” EX1001, claim 3.¹⁰

160. As explained above (§ X.C.1), claim 1 was obvious. *Chia* renders obvious this additional feature of claim 3.

161. As explained above (§ X.C.1.f)), *Chia* disclosed administration of 0.01% atropine compositions, a muscarinic agent (EX1003, 18) at a concentration within the ranges recited by claim 1 (“from about 0.001 wt % to about 0.025 wt %”). EX1003, 13. As *Chia*’s therapeutically effective 0.01% atropine concentration falls squarely within the range recited by claim 3, claim 3 would have been obvious for the same reasons explained above for claim 1. § X.C.1.

162. Thus, a POSA would have been motivated towards an ophthalmic composition as recited by claim 1 which had an atropine 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 %, and had a reasonable expectation of success in achieving the same.

¹⁰ I understand a certificate of correction was filed for the ’447 patent that changed “muscarinic antagonist” to “ophthalmic agent.” EX1098.

4. Claims 6 and 7

163. Dependent claim 6 recites: “The ophthalmic composition of claim 1, wherein the ophthalmic composition further comprises a preservative.” EX1001, claim 6.

164. Dependent claim 7 recites: “The ophthalmic composition of claim 6, 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.” EX1001, claim 7.

165. As explained above (§ X.C.1), claim 1 was obvious. *Chia* renders obvious these additional features of claims 6 and 7.

166. Claim 7 recites a list of well-known, traditional preservatives used in atropine and other ophthalmic compositions. EX1005, 54–56. *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 (emphasis added).

167. *Chia*’s disclosure reflected standard practice in the art. EX1005, 54–56; EX1069, 20 (disclosing 0.02% benzalkonium chloride as preservative for atropine formulations); EX1066, 3 (“benzalkonium chloride 0.1 mg (0.01%)”);

EX1049, 2 (“standard solution preparation” comprising “0.2 mg benzalkonium chloride”).

168. For example, *Remington* disclosed atropine formulations comprising benzalkonium chloride and taught that it is “*by far, the most common preservative used in ophthalmic preparations.*” EX1005, 55. Remington also disclosed that chlorobutanol is an effective anti-microbial and recommends that “ophthalmic solutions that contain chlorobutanol should be buffered between pH 5.0 and 5.5.” EX1005, 56; EX1069, 8 (disclosing chlorobutanol to preserve eyedrops).

169. As the specific preservatives recited by claim 7 were obvious, claim 6, which recites all preservatives, was likewise obvious.

170. Thus, a POSA would have been motivated towards an ophthalmic composition as recited by claim 1 which included a preservative, including benzalkonium chloride, cetrimonium, sodium perborate, stabilized oxychloro complex, SofZia, polyquaternium-1, chlorobutanol, edetate disodium, polyhexamethylene biguanide, and had a reasonable expectation of success in achieving the same.

5. Claim 12

171. Dependent claim 12 recites: “The ophthalmic composition of claim 1, wherein the ophthalmic composition comprises one of: less than 5% of H₂O, less

than 4% of H₂O, less than 3% of H₂O, less than 2% of H₂O, less than 1% of H₂O, less than 0.5% of H₂O, less than 0.1% of H₂O, or 0% of H₂O.” EX1001, claim 12.

172. As explained above (§ X.C.1), claim 1 was obvious. *Siegel* renders obvious this additional feature of claim 12.

173. As explained above for claim 1 (§ X.C.1.c)), substituting deuterium oxide for regular water in 0.01% atropine solutions was obvious. Using high concentrations of deuterium oxide in these solutions was also obvious.

174. *Siegel* disclosed that “[a]nalysis of the deuterium oxide buffers indicated that the deuterium oxide content was at least 99%.” EX1006, 4. As *Siegel* explained, the D₂O -procaine solutions were prepared by adding procaine to these buffer solutions, and, as such, taught that the D₂O-procaine solutions contained at least 95% deuterium oxide as recited by claim 12. EX1006, 4. It would have been obvious to use the same levels of D₂O effective in increasing the stability of procaine to increase the stability of atropine. EX1006, 4–5.

175. Even without this explicit teaching, however, the use of at least 95% deuterium oxide in the formulations of claim 1 would have been obvious. The purpose of using D₂O in place of H₂O was to increase the stability of the formation. §§ VI.B, X.A.2. A POSA would have understood that higher levels of deuterium oxide would lead to a greater solvent isotope effect, and thus greater increases in stability compared to atropine solutions with larger amounts of regular water.

EX1022, 10–11; EX1070, 2; EX1064, 7 (Fig. 3). For example, Blake 1975 reported that “[t]he rate of hydrolysis [of acetylcholine bromide] was decreased 10.6% in 20% D₂O, 23% in 50% D₂O, and about 33% in 75% D₂O” compared to regular water. EX1022, 10–11. Similarly, Kresge 1964 disclosed that “[t]he isotope effect... showed a linear dependence on solvent deuterium content.” EX1070, 2. A POSA would have known that using lower concentrations of D₂O, which would just mean a greater proportion of the solution was regular water, would result in a smaller solvent isotope effect.

176. Thus, a POSA would have been motivated to use >95% D₂O to maximize the solvent isotope effect to increase the stability of the formulation. As >95% D₂O was readily available, and had been shown to work with procaine by *Siegel*, there was ample motivation and a more than reasonable expectation of success in using solutions that contained 5% or less H₂O. EX1006, 4–5; EX1052, 3 (“[P]harmaceutical compositions may contain, say, about 98% or 99% deuterium oxide, the balance being ordinary water.”); EX1063, 2 (“the hydrogen content of the solvent ... did not exceed 0.5 %”); EX1057, 10 (“D₂O was from Sigma, product no. D-4501, stated to be 99.9% D.”) EX1062, 2 (99.5% D₂O); EX1061, 1 (99.8% D₂O); EX1064, 2 (99.9% D₂O).

177. Thus, a POSA would have been motivated towards an ophthalmic composition as recited by claim 1 that comprised 0–5% H₂O and had a reasonable expectation of success in achieving the same.

6. Claim 13

178. Dependent claim 13 recites: “The ophthalmic composition of claim 1, wherein the ophthalmic composition is not formulated as an injectable formulation.” EX1001, claim 13.

179. As explained above (§ X.C.1), claim 1 was obvious. *Chia* renders obvious this additional feature of claim 13.

180. *Chia* disclosed an atropine solution formulated for administration as “eye drops” and does not mention atropine formulated as an injectable. EX1003, 13–14 (discussing a prior study of “atropine 1% *eyedrops*”). Thus, the eye-drop formulations used by *Chia* for the treatment of myopia disclose an “ophthalmic composition... not formulated as an injectable formulation” as recited by claim 13. It would have been obvious to formulate the compositions of claim 1 in the same manner shown to be effective for the treatment of myopia, i.e., a non-injectable solution.

181. Moreover, to treat myopia, the art showed that *Chia*'s use of atropine eye drops was standard practice in the art.¹¹ § VI.A.1. For example, *Remington* taught "instillation of eyedrops remains... one of the more accepted means of topical drug delivery," and guided the administration of eye drops. EX1005, 49. *See also* EX1018, 18:2–4 ("[R]eduction in myopia progression with atropine *eye drops* observed in both studies....") (emphasis added); EX1014, 1 (Patients "received 0.025% atropine *eye drops* at bedtime every night.") (emphasis added); EX1013, 1 ("The results of this study demonstrate that, with regular *instillation, topical 0.05% atropine* is an effective agent for controlling myopia progression....") (emphasis added).

182. Thus, a POSA would have been motivated towards the ophthalmic composition of claim 1 that was not formulated as an injectable formulation, and had a reasonable expectation of success in achieving the same.

7. Claim 14

183. Dependent claim 14 recites: "An ophthalmic solution, comprising one and no more than one ophthalmic agent, and deuterated water, at a pD of from about

¹¹ Atropine is formulated as an injectable solution for the treatment of nerve gas exposure. EX1068, 1 ("Atropine is one of the preferred antidotes [for injection] for nerve gas exposure"); EX1052, 2

4.2 to about 7.9, wherein the ophthalmic agent consists of atropine, atropine sulfate, or a combination thereof, at a concentration of from about 0.001 wt % to about 0.03 wt %.” EX1001, claim 14.

184. As explained above (§ X.C.1), claim 1 was obvious. Claim 14 is identical to claim 1 except it recites an “ophthalmic solution” instead of an “ophthalmic composition.” EX1001, claims 1, 14.

185. *Chia* disclosed 0.01% atropine formulated as eye drops. EX1003, 13, 14. As was well understood in the art, eye drops are an ophthalmic solution. EX1050, 1 (“The most commonly used dosage form is an aqueous solution of a drug delivered as an eyedrop, which is applied topically to act on the ocular surface or in the interior of the eye.”); EX1005, 48 (“The outflow capacity accommodates the sudden large volume resulting from the instillation of an eyedrop. Most commercial eyedrops range from 50 to 75 μ L in volume.”).

186. Thus claim 14 is obvious for all the reasons described for claim 1. § X.C.1.

8. Claim 15

187. Claim 15 recites: “The ophthalmic solution of claim 14, wherein the ophthalmic solution 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 15.

188. As explained above (§ X.C.2), claim 2 was obvious. Claim 15 is identical to claim 2 except it recites an “ophthalmic solution,” instead of an “ophthalmic composition.” EX1001, claims 2, 15.

189. As explained above for claim 14 (§ X.C.7), *Chia* disclosed an ophthalmic solution. EX1003, 13. Accordingly, claim 15 is obvious for all the same reasons described for claim 2. § X.C.2.

9. Claim 16

190. Claim 16 recites: “The ophthalmic solution of claim 14, wherein the ophthalmic solution comprises one of: less than 5% of H₂O, less than 4% of H₂O, less than 3% of H₂O, less than 2% of H₂O, less than 1% of H₂O, less than 0.5% of H₂O less than 0.1% of H₂O, or 0% of H₂O.” EX1001, claim 16.

191. As explained above (§ X.C.5), claim 12 was obvious. Claim 16 is identical to claim 12 except it recites an “ophthalmic solution,” instead of an “ophthalmic composition.” EX1001, claims 12, 16.

192. As explained above for claim 14 (§ X.C.7), *Chia* disclosed an ophthalmic solution. EX1003, 13. Accordingly, claim 16 is obvious for all the same reasons described for claim 12. § X.C.5.

10. Claim 17

193. Claim 17 recites: “A method of arresting myopia progression, comprising administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition comprising one and no more than one ophthalmic agent, and deuterated water, at a pD of from about 4.2 to about 7.9, wherein the ophthalmic agent consists of atropine, atropine sulfate, or a combination thereof, at a concentration of from about 0.001 wt % to about 0.03 wt %.” EX1001, claim 17.

194. As explained above (§ X.C.1), claim 1 was obvious. Claim 17 recites a method of treating myopia with ophthalmic compositions identical to those recited in claim 1. As *Chia* taught 0.01% atropine solutions were effective to arrest the progression of myopia, it was obvious to use the compositions of claim 1 to arrest the progression of myopia. EX1003, 13, 19–20.

195. *Chia* taught 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 solutions. EX1003, 19–20. Specifically, *Chia* disclosed that “[t]he primary end point was myopia progression” (EX1003, 14) and that “[t]he mean myopia progression at 2 years was -0.30 ± 0.60 ... in the atropine... 0.01% group[.]” (EX1003, 13).

196. As of the earliest possible effective filing date of the '447 patent, the efficacy of atropine compositions (including within the range of concentrations recited by claim 17) in slowing the progression of myopia had been established by multiple large scale clinical trials. EX1003, 19–20; EX1014, 1; EX1017, 1; EX1018, 19:12–13.

197. Claim 17 recites nothing more than the obvious substitution of D₂O for H₂O in the treatment of a disease clinically established to be treated by atropine within the claimed ranges. § VI.A.1. As explained above (§§ X.A.2, X.C.1.c)), a POSA would have been motivated to formulate *Chia*'s low-concentration atropine solutions with D₂O to increase the long term shelf life and clinical efficacy of the formulations to treat myopia.

198. The substitution of D₂O for regular water would not have been expected to negatively affect the clinical efficacy of atropine and D₂O had been successfully used in place of regular water in numerous ophthalmic therapeutics. §§ VI.B.2, X.A.2, X.B. Therefore, a POSA would have reasonably expected that atropine solutions, already shown to be effective in slowing the progression of myopia when used with regular water, would be at least as effective in slowing the progression of myopia when combined with D₂O. §§ VI.B.2, X.A.2, X.B.

199. Thus, a POSA would have been motivated towards a method of arresting myopia progression with an ophthalmic composition as recited by claim 1 and had a reasonable expectation of success in achieving the same.

11. Claim 18

200. Dependent claim 18 recites: “The method of claim 17, wherein the ophthalmic composition is stored at between about 2° C. to about 10° C. prior to first use.” EX1001, claim 18.

201. As explained above (§ X.C.10), claim 17 was obvious. *Kondritzer* renders obvious this additional feature of claim 18.

202. *Kondritzer* specifically disclosed atropine solutions at 10° C and pH 3.97 (pD 4.37). EX1004, 8 (Table II). These solutions fall within the ranges of claim 18. EX1001, claim 18. Moreover, *Kondritzer* taught that the stability of atropine, including at the pD levels recited by claim 18, is dependent on temperature, with stability increasing as temperature decreases. EX1004, 5 (“The effect of each reaction is governed by the hydroxyl-ion concentration and the temperature.”); EX1004, 8 (Table III).

203. As explained above (§§ VI.C.1, X.A), stability was a key consideration for the formulation, storage, and administration of atropine. As clinical efficacy depends on the amount of atropine in solution at the time of administration, it would have been obvious to store the compositions of claim 18 at between about 2° C to

about 10° C prior to first use to reduce degradation and thereby increase the amount of atropine remaining in the composition at the time of first use.

204. Moreover, the art showed that storing therapeutics at lower temperatures was a well-known technique for enhancing stability. EX1047, 7 (“[T]he formulation was not stable at room temperature necessitating storage at 5° C”); EX1057, 3 (“[S]olutions or dispersions may be stored at a reduced temperature such as in a refrigerator in order to reduce degradation.”). This practice extended to ophthalmic compositions, including atropine, which were often stored at between about 2° C and about 10° C prior to administration. EX1050, 4 (storing several ophthalmic drug solutions “in a refrigerator”); EX1068, 1 (disclosing storage of atropine formulations at 5° C).

205. Thus, a POSA would have been motivated towards the method of claim 17, wherein the composition was stored at between about 2° C to about 10° C prior to first use, and had a reasonable expectation of success in achieving the same.

12. Claim 19

206. Dependent claim 19 recites: “The method of claim 17, wherein the ophthalmic composition is stored at between about 16° C. to about 26° C. after first use.” EX1001, claim 19.

207. As explained above (§ X.C.10), claim 17 was obvious. *Kondritzer* renders obvious this additional feature of claim 19.

208. *Kondritzer* specifically disclosed atropine solutions at 20° C and pH 3.84 (pD 4.24). EX1004, 8 (Table II). These solutions fall within the ranges of claim 19. Moreover, as discussed above (§§ VI.A.2, X.C.3), *Kondritzer* taught that the stability of atropine, including at the pD levels recited by claim 19, is dependent on temperature, with stability increasing as temperature decreases. EX1004, 5, 8 (Table III). *Kondritzer* shows that atropine is more stable at 20° C than at higher temperatures. EX1004, 8 (Table III).

209. Moreover, the temperatures recited by claim 19, 16°–26° C, encompass room temperature, 20°–22° C. It was standard practice to store ophthalmic medications, including atropine, at room temperature between administrations—i.e., “after first use.” EX1066, 5; EX1071, 1; EX1068, 1. The FDA-approved atropine prescribing information directs the patient to store “at 20° to 25 °C.” EX1066, 5. It would have been obvious to store the formulations recited by claim 19 at the same temperatures ophthalmic solutions, including atropine, were usually stored.

210. Thus, a POSA would have been motivated towards the method of claim 19, wherein the ophthalmic composition is stored at between about 16° C to about 26° C after first use, and had a reasonable expectation of success in achieving the same.

XI. Ground 2: Claims 1–19 Would Have Been Obvious over *Chia*, *Siegel*, *Kondritzer*, and *Remington*

A. Summary of the Combination

211. As discussed above (§ X.C.1), claim 1 would have been obvious over *Chia*, *Siegel*, and *Kondritzer*.

212. Claims 4–5 and 8–11 (which all ultimately depend from claim 1) recite nothing more than standard components long used in atropine solutions for the treatment of myopia and would have been obvious over *Remington*.

213. *Chia* disclosed that its study used 0.01% atropine solution with 0.01% BAK preservative, but it does not provide a list of all of the components (e.g., buffers, osmolarity adjusting agents) that may have been used in the solutions. EX1003, 13. These components, however, were taught by *Remington*, which disclosed common components used in ophthalmic solutions, and specifically disclosed a standard ophthalmic formulation that was suitable for use with atropine. EX1005, 49–56.

214. *Remington* is a classic and authoritative pharmacy textbook that was recognized by and relied on by the FDA in its guidance on drug stability. EX1072, 6, 24; EX1037, ¶[0073] (“Pharmaceutically acceptable excipients have been amply described in a variety of publications, including, for example, A. Gennaro (2000)

‘Remington: The Science and Practice of Pharmacy.’”).¹² *Remington*, excerpted from the 19th edition, published in 1995, describes suitable and routine components for ophthalmic solutions, appropriate characteristics of ophthalmic solutions, and routine methods of administering ophthalmic solutions. EX1005, 49–56.

215. Further, *Remington* expressly motivated combining atropine formulations such as *Chia*’s with the standard formulations it disclosed, noting “[t]he following solutions are *suggested*” and explaining “[t]hese vehicles are suitable for salts of... atropine.” EX1005, 52. A POSA would have been motivated to use the same components already shown to work for atropine solutions.

216. As explained above (§§ VI.B.2, X.A.2, X.C.1.c)), deuterium would not have been expected to change the biological properties of atropine or present any unique formulation challenges in switching from regular water to D₂O. EX1023, 8–9. As such, in modifying *Chia*’s low-concentration atropine with the D₂O from *Sigel*, a POSA would have simply used the same types of components that were established to work in atropine solutions containing regular water. EX1005, 52; EX1066, 3. Thus, there was ample motivation to combine the components disclosed

¹² The ’447 patent itself relies on *Remington* for standard practices in the art, explaining “detailed descriptions of many methods of sterilization are given in Chapter 40 of Remington.” EX1001, 42:7–11.

by *Remington* with the atropine solutions of *Chia* as modified by *Siegel* to arrive at the claimed atropine formulations with a reasonable expectation of success.

B. Claim-by-Claim Analysis

1. Claims 1–3, 6–7, and 12–19

217. As explained above, the pD limitation recited by claims 1–3, 6–7, and 12–19 would have been obvious over *Chia*, *Siegel*, and *Kondritzer* given that it was well-known that a pH of 7.4 (pD 7.8) was optimal for patient comfort.

218. In my opinion, claims 1–3, 6–7, and 12–19 also would have been obvious over *Chia*, *Siegel*, *Kondritzer*, and *Remington*. *Remington* explicitly disclosed that “[i]deally, ophthalmic preparations should be formulated at a pH equivalent to the tear fluid value of 7.4.” EX1005, 54.

219. Further, *Remington* expressly motivated the optimization of pD levels between the levels of maximum stability and those of optimal comfort, explaining: “The proper pH, buffer and buffer capacity often represent a compromise between stability of the drug and comfort in the eye, since optimum patient comfort usually is found at the pH of the tear fluid, or about 7.4, while optimum stability for many drugs is generally lower, perhaps as low as 4.0–5.0.” EX1005, 52. *Remington* provided a real-world example of this optimization, disclosing that “[d]rugs such as pilocarpine and physostigmine are both active and comfortable in the eye at a pH of 6.8; however, at this pH chemical stability (or instability) can be measured in days

or months... On the other hand, at pH 5 both drugs are stable for a period of several years.” EX1005, 54.

220. Thus, for the same reasons discussed above in Ground 1 as well as these additional reasons, claims 1–3, 6–7, and 12–19 would also have been obvious over *Chia, Siegel, Kondritzer, and Remington*. § X.

2. Claims 4 and 5

221. Dependent claim 4 recites: “The ophthalmic composition of claim 1, wherein the ophthalmic composition further comprises an osmolarity adjusting agent.” EX1001, claim 4.

222. Dependent claim 5 recites: “The ophthalmic composition of claim 4, wherein the osmolarity adjusting agent is sodium chloride.” EX1001, claim 5.

223. As discussed above (§ X.C.1), claim 1 was obvious. *Remington* renders obvious these additional features of claims 4 and 5.

224. *Remington* explicitly disclosed an ophthalmic formulation “suitable for salts of... atropine” containing sodium chloride. EX1005, 52.

225. Further, *Remington* further taught “isotonicity always is desirable and particularly is important in intraocular solutions,” (EX1005, 54) that “[a]n ophthalmic solution is considered isotonic when its tonicity is equal to that of an 0.9% sodium chloride solution,” (EX1005, 54) and that the lacrimal system is

“unaffected by the addition of concentrations of up to 2% sodium chloride” (EX1005, 48).

226. A POSA would have understood that a tonicity adjusting agent is necessarily an osmolarity adjusting agent. Tonicity is a measure of the effective osmotic pressure gradient exerted by salts in aqueous solution. EX1005, 54 (“Tonicity refers to the osmotic pressure exerted by salts in aqueous solution.”). An agent that adjusts tonicity, for example, sodium chloride, will necessarily adjust osmolarity. EX1085, 16–19; *see also* EX1085, 17 (disclosing adjustment of osmolarity with “a typical electrolyte like sodium chloride”). As such, *Remington’s* further disclosure of sodium chloride to adjust tonicity would have been understood as necessarily teaching its use to adjust osmolarity.

227. Further, sodium chloride is one of the most commonly used components in ophthalmic solutions. EX1069, 2 (“[O]phthalmic solution may safely range from the equivalent of 0.7% to 1.5% sodium chloride.”); EX1068, 2 (“A stock solution of atropine sulfate was prepared [with]... sodium chloride 0.9% solution....”); EX1065, 1; EX1067, 2.

228. Sodium chloride had been shown to work with numerous atropine formulations, including those at lower concentrations. For example, Li et al. disclosed formulations of “Atropine sulfate 0.4g” with “sodium chloride 9.0g”, in

“water for injection added to 1,000ml.” EX1065, 1.¹³ Similarly, Wen et al. disclosed formulations of “0.05% atropine sulfate eye drops” that included “sodium chloride 9.0g.” EX1067, 2.

229. As these examples demonstrate, *Remington's* inclusion of sodium chloride in formulations suitable for atropine reflected standard practice and would have been obvious to include in the compositions of claims 4 and 5. As the sodium chloride of claim 5 was obvious, claim 4, which recites all osmolarity adjusting agents, was likewise obvious.

230. Thus, a POSA would have been motivated to formulate an ophthalmic composition of claim 1, wherein the ophthalmic composition further comprises an osmolarity adjusting agent, including sodium chloride, and had a reasonable expectation of success in achieving the same.

3. Claims 8 and 9

231. Dependent claim 8 recites: “The ophthalmic composition of claim 1, wherein the ophthalmic composition further comprises a buffer agent.” EX1001, claim 8.

232. Dependent claim 9 recites: “The ophthalmic composition of claim 8, wherein the buffer agent is selected from borates, borate-polyol complexes,

¹³ Li 2006's formulation is a 0.04% atropine solution with 0.9% sodium chloride.

phosphate buffering agents, citrate buffering agents, acetate buffering agents, carbonate buffering agents, organic buffering agents, amino acid buffering agents, or combinations thereof.” EX1001, claim 9.

233. As discussed above (§ X.C.1), claim 1 was obvious. *Remington* renders obvious these additional features of claims 8 and 9.

234. Claim 9 recites a list of well-known, traditional types of buffers used with ophthalmic compositions, including atropine. EX1005, 35–36, 41–43, 52. *Remington* explicitly disclosed a standard formulation, appropriate for use with atropine, comprising “phosphate buffering agents” encompassed by claim 9. EX1005, 52.

235. In particular, *Remington* disclosed a formulation “suitable for salts of Atropine” containing sodium acid phosphate anhydrous (NaH_2PO_4) and disodium phosphate anhydrous (Na_2HPO_4), both of which are phosphate buffering agents. EX1005, 52. It was known that sodium acid phosphate anhydrous (NaH_2PO_4) is also called “sodium dihydrogen phosphate” and disodium phosphate anhydrous (Na_2HPO_4) is also called “disodium hydrogen phosphate.” EX1073, 133; EX1074, 1; EX1075, 1.

236. Further, the art showed that *Remington's* disclosure was standard practice, further highlighting the obviousness of including these buffers in the compositions of claim 1. EX1069, 2 (“The United States Pharmacopoeia XVI

recommends an isotonic phosphate buffer as an ophthalmic vehicle....”); EX1069, 20 (disclosing “Phosphate buffer solution pH 6.45” for atropine formulations); EX1033, 4–5 (disclosing “acetic acid, acetate, citric acid, citrate, phosphoric acid, phosphate” are “commonly used as buffering agents”). The FDA-approved atropine formulation contains dibasic sodium phosphate (disodium hydrogen phosphate) and monobasic sodium phosphate (sodium dihydrogen phosphate) as buffering agents. EX1066, 3.

237. As the specific buffer agents recited by claim 9 were obvious, claim 8, which recites all buffer agents, was likewise obvious.

238. Thus, a POSA would have been motivated to formulate an ophthalmic composition of claim 1, wherein the ophthalmic composition further comprises a buffer agent, including, 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, and had a reasonable expectation of success in achieving the same.

4. Claim 10

239. Dependent claim 10 recites: “The ophthalmic composition of claim 1, wherein the ophthalmic composition further comprises a pD adjusting agent.” EX1001, claim 10.

240. As discussed above (§ X.C.1), claim 1 was obvious. *Remington* renders obvious this additional feature of claim 10.

241. *Remington* taught that adjusting the pH of ophthalmic solutions was routine in the art. For example, *Remington* explains that “optimum pH may be lower than preferable for product comfort, although this effect may be minimized by adjusting pH with a buffer of minimum capacity.” EX1005, 54. *Remington* further explains 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).

242. The standard formulation “suitable for salts of atropine” disclosed by *Remington* uses a greater amount of the acid component of the buffer (sodium acid phosphate). EX1005, 52. A POSA would have understood that these components would adjust the formulation’s pH.¹⁴

¹⁴ The ’447 patent uses “pD adjusting” and “buffering” agents interchangeably, explaining “the pD adjusting agents or buffers include deuterated hydrochloric acid (DCI), deuterated sodium hydroxide (NaOD), deuterated acetic acid (CD₃COOD), or deuterated citric acid (C₆D₈O₇).” (EX1001, 33:2–5). EX1001, 77:51–52 (“The A & C indicate the buffer species used, acetic acid and citric acid respectively.”).

243. Additionally, pH may be adjusted independent of the buffer via the addition of small amounts of acids or bases. § VI.C.1. Such components were well known in the art and were used across a variety of different pharmaceuticals to adjust pH. Specifically, *Remington* discloses that 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,” i.e., a compound used to increase the H⁺ concentration of a solution, is a pH adjusting agent. EX1077, 10 (defining an “Acidifying Agent” as an “Agent added to make a system more acid, decreasing the value of pH”); see also EX1078, 9; EX1079, [0174]; EX1028, [0069].

244. The obviousness of including a pH adjusting agent is underscored by the art as a whole, which showed that the inclusion of such components in aqueous formulations, including atropine solutions, was routine practice. For example, Garcia-Valdecabres explained that “[t]he adjustment of an ophthalmic solution’s pH by the appropriate choice of a buffer is one of the most important considerations in its formulation.” EX1050, 2; *see also* EX1076, 2–3, 6. This practice extended to D₂O formulations: Teva disclosed that “[t]he pH is adjusted by known methods to 2.7 with *strong acid*, and the volume is brought to 20 ml with more deuterium oxide.” EX1052, 5 (emphasis added).

245. Thus, a POSA would have been motivated to formulate an ophthalmic composition of claim 1, wherein the ophthalmic composition further comprises a pD adjusting agent, and would have had a reasonable expectation of success in doing so.

5. Claim 11

246. Dependent claim 11 recites: “The ophthalmic composition of claim 10, wherein the pD adjusting agent comprises deuterated hydrochloric acid, deuterated sodium hydroxide, deuterated acetic acid, or deuterated citric acid.” EX1001, claim 11.

247. As discussed above (§ XI.B.4), claim 10 was obvious. *Siegel* and *Remington* render obvious this additional feature of claim 11.

248. As discussed above for claim 10, *Remington* taught that adjusting the pH of ophthalmic solutions was routine (EX1005, 52–54) and disclosed specific examples of common agents used to adjust pH. EX1005, 36, 39. Hydrochloric acid, sodium hydroxide, acetic acid, and citric acid are four common agents used to adjust the pH of solutions; *Remington* specifically disclosed acetic acid is “used primarily as an acidifying agent” (EX1005, 36) and that hydrochloric acid is “[o]fficially classified as pharmaceutical aid that is used as an acidifying agent” (EX1005, 39). § XI.B.4. As explained above, POSA would have understood that an “acidifying agent” is a pH adjusting agent. § XI.B.4.

249. The obviousness of these four components is further highlighted by their ubiquity throughout the art as a whole. The Handbook of Pharmaceutical Excipients, a seminal reference text in the field, specifically disclosed all four agents and explains that they are primarily used for adjustment of pH. EX1077, 29 (“[A]cetic acid solutions are widely used as *acidulants* in a variety of pharmaceutical formulations.”), 32 (“Citric acid... is widely used in pharmaceutical formulations and food products, *primarily to adjust the pH of solutions.*”), 39 (“Hydrochloric acid is widely used as an *acidulant*, in a variety of pharmaceutical and food preparations.”), 41 (“Sodium hydroxide is widely used in pharmaceutical formulations to adjust the pH of solutions.”); *see also* EX1077 10, 43–44.

250. The FDA-approved atropine formulation used “hydrochloric acid and/or sodium hydroxide” as “pH adjusting agents.” EX1066, 3. Similarly, a patent application to Purandare disclosed that “in the case of an ophthalmic composition, the pH of the composition is suitably adjusted between about pH 4 to 7” and that “[e]xamples of suitable pharmaceutically acceptable pH adjusting agents include, but are not limited to, sodium hydroxide, citric acid, hydrochloric acid, boric acid, acetic acid.” EX1078, 9; *see also* EX1079, ¶[0174]; EX1028, ¶[0069].

251. Garcia-Valdecabres et al. studied seventeen commercial eye drops and disclosed that “[t]he buffer agents present in the studies of ophthalmic solutions are phosphate, citrate... [and] acetate.” EX1050, 6. Moreover, a POSA would have

been motivated to use acetic acid and citric acid specifically as it was known that these agents were optimal for use at pHs of 2.1–7.4 (pD 2.5–7.9) and 3.8–5.8 (pD 4.2–6.2), respectively—i.e., at overlapping pD ranges recited by the claims of the '477 patent. EX1080, 23; EX1081, 6 (“Therefore, acetic acid was added to create an acetic acid-acetate buffer system. To prepare a solution with a pH value near 6, we adjusted the concentrations of acetic acid and sodium acetate....”).

252. It would have been obvious to use deuterated analogs of the same common components used to adjust pH in regular water. *Siegel* specifically disclosed “deuterium oxide buffers” were used to adjust the pH of their procaine-D₂O formulations. EX1006, 4. Moreover, *Siegel* referenced a prior study of procaine in D₂O (EX1006, 5), which 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.

253. *Siegel*’s disclosure of the use of deuterated pD adjusting agents with D₂O formulations was consistent with the art as a whole. For example, Nee 2014 specifically contemplated using deuterated buffers in D₂O pharmaceutical products to correct for the pD-pH difference. EX1029, 18; *see also* EX1089, 13.

254. Thus, a POSA would have been motivated towards an ophthalmic composition of claim 10, wherein the pD adjusting agent comprises deuterated

hydrochloric acid, deuterated sodium hydroxide, deuterated acetic acid, or deuterated citric acid, and had a reasonable expectation of success in achieving the same.

XII. Secondary Indicia

255. I understand that during prosecution of the application that led to the '447 patent, the Applicant presented data from the specification of the '447 patent and asserted that the data was unexpected. EX1094, 9–13. In my opinion, these results would not have been unexpected.

256. The data presented shows the expected effect of replacing H₂O with D₂O in the atropine formulations. The three examples presented during prosecution, “better stability,” “lower main degradant,” and “longer shelf life,” are simply alternative ways of expressing the same expected effect of D₂O.

257. Moreover, the results are based solely on three highly specific formulations that are not commensurate with or otherwise representative of the broad claims of the '447 patent.

A. Solvent Isotope Effect Was Not Unexpected

258. Patent Owner argued during prosecution that the D₂O formulations were unexpectedly more stable than their H₂O counterparts. EX1094, 9–13. I note that Patent Owner did not reference any prior art relating to stabilization due to the

solvent isotope effect or otherwise provide any explanation for why a POSA would have found the data “unexpected.” EX1094, 9–13.

259. Contrary to Patent Owner’s assertions, a slowed rate of reaction for atropine in D₂O compared to atropine in H₂O would not have been unexpected. It was known that the solvent isotope effect could be predicted based on those seen for analogous compounds and reaction types. § VI.B. As discussed above (§ VI.B.1), a solvent isotope effect was expected for carboxylic esters subject to base-catalyzed hydrolysis.¹⁵

260. In addition to a slowed reaction rate not being unexpected, the magnitude of the effect in the ’447 patent, which shows an approximately two-fold difference in the H₂O vs. D₂O formulations, was in line with “other base-catalyzed ester hydrolyses where $k_{H2O}/k_{D2O} \sim 2-3$.” EX1025, 63. That is, the magnitude of the SIE reported in the ’447 patent was also not unexpected.

¹⁵ I understand that during prosecution, the Examiner stated: “The increased stability is the expected property of such components being used together.... [T]he arguments regarding the unexpected results have been noted. It is the examiner’s position that such results are obtained by combination of atropine and D₂O, which is the expected property of Teva’s composition as well.” EX1042, 3.

261. For example, Jencks et al.'s 1961 study of carboxylic esters showed solvent isotope effects similar to those in the '477 patent. § VI.B.1. As shown below in Figure 10, "[t]he rates of neutral and base-catalyzed hydrolysis [were] two- to threefold lower in deuterium oxide solution." EX1061, 3.

Ester	Reactant	k_0 , min. ⁻¹	k_0^D , l. mole ⁻¹ min. ⁻¹	k_0^D/k_0
Ethyl difluoroacetate	Water	0.0034	6.1×10^{-5}	2.1
	D ₂ O	0.0016	2.9×10^{-4}	
	Aniline		0.0092	
	K acetate		.037	2.7
	In D ₂ O		.014	
	Imidazole		.62	2.8
	In D ₂ O		.22	
Ethyl dichloroacetate	OH ⁻		2.7×10^3	
	Water	00030	5.3×10^{-3}	5 ^b
	D ₂ O	00006 ^b	1.1×10^{-3}	
	Na formate		0.0019	
	Aniline		.0010	
	K acetate		.0030	2.2
	In D ₂ O	.0014		
	Pyridine		.012	
	Na succinate ^a		.014	
	4-Picoline		.017	
	K phosphate ^a		.044	
	Imidazole		.082	3.0
Ethyl chloroacetate	In D ₂ O		.027	
	Tris-(hydroxymethyl)-aminomethane ^f		.71	
	OH ⁻		5.3×10^3	
	Water	6.5×10^{-4}	1.2×10^{-3}	
	K acetate		4.4×10^{-3}	
	Imidazole		0.0022	3.0
	In D ₂ O		.0007	
Ethyl trichloroacetate ^a	Ammonia ^f		.18	
	OH ⁻		2.2×10^3	
Ethyl oxamide	Solvent ^g	0.0017		
	K acetate		0.013	
Glycine ethyl ester HCl	Imidazole		0.015	
	OH ⁻		2.5×10^3	
	Imidazole		0.00038	
	OH ⁻		1200 ^b	

Figure 10. Solvent Isotope Effects Reported by Jencks 1961

262. As shown below in Figure 11, Winter 1972 reported an SIE of between 1.8 and 3.9 across several carboxylic esters degraded by base-catalyzed hydrolysis. EX1060, 4 (Table 4); § VI.B.1.

Ester (CF ₃ COOR)	k_{H_2O} ($\times 10^3 s^{-1}$)*	k_{D_2O} ($\times 10^3 s^{-1}$)*	k_{H_2O}/k_{D_2O}
4-Nitrobenzyl	7.996(7) ± 0.065	2.030(4) ± 0.029	3.9
4-Chlorobenzyl	3.305(9) ± 0.065	0.8731(4) ± 0.0112	3.8
Benzyl	2.448(10) ± 0.035	0.6563(4) ± 0.0109	3.7
4-Methylbenzyl	1.939(5) ± 0.028	0.5356(4) ± 0.0058	3.6
4-Methoxybenzyl	3.212(8) ± 0.038	1.794(4) ± 0.013	1.8
Methyl	1.934(4) ± 0.026	0.5644(4) ± 0.0024	3.4

Figure 11. Solvent Isotope Effects Reported by Winter 1972.

263. Minor et al.'s 1972 study of O-Dichloroacetylsalicylate reported an average solvent isotope effect of 2.17 across a range of pHs and buffer strengths. EX1054, 1 (Abstract), 2 (Table I); § VI.B.1.

$R = [NaO_2CCH_2]/[HO_2CCH_2]$	$[NaO_2CCH_2] + [HO_2CCH_2], M$	$10^4 k_{\text{cat}}, \text{sec}^{-1}$		
		H ₂ O	D ₂ O	$\mu \approx 0.5$
1.874 (pH 4.88) ^a	0.5007	751, 744, 740	395, 357, 376	537, 533, 533, 549
	0.4006	740, 774, 747	365, 380, 384	
	0.3004	732, 781, 732	376, 357	
	0.2003	735, 770, 739	388, 368	
	0.1001	747, 740, 766	380, 376, 372	
	Av for R = 1.874:	751 \pm 12	375 \pm 9	
4.747 (pH 5.21) ^a	0.5011	759, 778, 751	361, 388	538 \pm 6 ^b 595, 572, 547, 568
	0.4009	766, 747, 751	388, 395	
	0.3007	728, 781, 785	380	
	0.2004	774, 740, 774	384, 361, 372	
	0.1002	778, 766, 729	392, 384, 372	
	Av for R = 4.747:	759 \pm 15	376 \pm 11	
10.506 (pH 5.56) ^a	0.5013	755, 788, 766	384, 365, 392	571 \pm 13 ^b 549, 584, 580
	0.4010	736, 781, 766	376, 384	
	0.3008	751, 743, 751	388, 384	
	0.2005	751, 751, 755	384	
	0.1003	747, 785, 785	388, 384, 392	
	Av for R = 10.506:	760 \pm 14	385 \pm 5	

Figure 12. Solvent Isotope Effects Reported by Minor 1972¹⁶

¹⁶ Solvent isotope effect is shown by the faster rate in H₂O (column 3) than D₂O (column 4).

264. Jencks 1993's study of a series of alkyl formates and phenyl formates reported similar SIEs across a range of catalysts. EX1083, 3 (Tables I and II); § VI.B.1.

catalyst	10 ³ k _s (M ⁻¹ min ⁻¹), R (pH ₀)				
	p-methoxy-phenyl (10.2)	p-methyl-phenyl (10.2)	phenyl (9.9)	m-nitro-phenyl (8.2)	p-nitro-phenyl (7.2)
cacodylate		35	81	6600	17000
k _{cat}		42			
acetate	1.1	1.3	1.4	15	78
k _{cat}	0.46		0.65	11	67
k _{cat} /k _{no}	2.5		2.2	1.4	1.2
3-chloro-propionate		0.72	0.65	7.4	34
methoxycarbonate		0.62	0.62	3.0	8.0
k _{cat}		0.24			4.1
k _{cat} /k _{no}		2.8			2.0
chloroacetate			0.47	2.7	6.1
cyanacetate		0.46	0.42	1.8	3.3
k _{cat}					1.70
dichloroacetate				1.5	
H ₂ O ⁺	0.0039	0.0032	0.0036	0.0217	0.063
D ₂ O ⁺	0.00047	0.0006	0.00085	0.0074	0.017
k _{H2O} /k _{D2O}	4.2	5.3	4.2	3.6	3.7

catalyst	10 ³ k _s (M ⁻¹ min ⁻¹), R					
	CH ₃ -C ₂ H ₅	CH ₃ -CF ₃	CH ₃ -CHCl ₂	CH ₃ -C≡CH	CH ₃ -CH ₂ Cl	CH ₃ -CH ₃
cacodylate		43		9.2		1.2
acetate	4.8	5.5	2.1	1.2	0.95	0.16
in D ₂ O	1.7		0.81			0.065
k _{H2O} /k _{D2O}	2.8		2.6			2.5
methoxyacetate	2.6	2.1	0.64	0.29	0.19	
cyanacetate	0.71	0.72	0.22	0.08		
H ₂ O ⁺	0.0045	0.008	0.0073	0.0014	0.0020	0.00023
D ₂ O ⁺	0.0036		0.0045			0.000075
k _{H2O} /k _{D2O}	1.3		1.6			3.0

Figure 13. Solvent Isotope Effects Reported by Jencks 1993

265. As discussed above (§§ VI.B.1, X.A.2), *Siegel* studied the solvent isotope effect for procaine. At pH 8, i.e., the pH closest to that recited by the claims of the '447 patent, *Siegel* found a solvent isotope effect of 3. EX1006, 5 (Table I).

266. As of the earliest possible effective filing date of the '447 patent, solvent isotope effects of similar magnitude had been reported for a large number of other carboxylic esters degraded by base-catalyzed hydrolysis. 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”) (emphasis added); EX1064, 4 (Table I); EX1063, 4 (Table IV); EX1062, 3 (Table II); EX1060, 2 (Table 1).

B. Data Presented in the '447 Specification

267. Patent Owner presented data from the '447 patent supposedly showing three advantages of the D₂O formulations: (1) “better stability,” (2) “lower main degradant,” and (3) “longer-shelf life.” EX1094, 9–13. All three of these examples are simply different ways of expressing the expected effect of D₂O. All that Patent Owner did was preform the same routine experiments carried out in the references above, obtained the comparable results as the references above, then extrapolated these expected effects to produce a predicted shelf-life.

1. Better Stability

268. “Better Stability” refers to the rate at which atropine degrades in H₂O compared to D₂O, i.e., the rate at which atropine is lost from solution as it breaks down to tropine, tropic acid, and other minor products. EX1094, 10–11.

269. This data was generated by measuring the atropine remaining in solution at 0, 2, and 4 weeks at 25° C, 40° C, and 60° C. EX1001, 76:32-78:58. The amount of atropine remaining at the different time points and temperatures is shown in Tables 24(A) and 24(B) of the '447 patent. EX1001, 77:55-78:58.

270. From this data, I calculated the rate constant (k) of the reaction for each formulation at the different pHs and temperatures tested.¹⁷ Rate constant is

¹⁷ Rate constant (k) is also referred to as the “velocity constant” of the reaction.

calculated via first order kinetics in Equation 1, where $P(t)$ is purity as a function of time; $P(0)$ the initial purity at time 0; and k the rate constant.¹⁸

$$P(t) = P(0) \cdot \exp(-k \cdot t) \quad \text{or} \quad \ln(P(t)) = \ln(P(0)) - k \cdot t$$

Equation 1

271. The rate constant for the H₂O formulation is then divided by the rate constant for the same formulation in D₂O to obtain the solvent isotope effect for each pair-wise comparison at the tested pHs and temperatures. EX1025, 19. This is shown in Table 1, below.

Table 1. Rate Constants and Solvent Isotope Effects '447 Patent Table 24

Formulation	pH	T = 0	T = 2	T = 4	K	K _{H2O} / K _{D2O}
3 at 25° C	4.8	98.16	98.16	98.45	0.000	
7 at 25° C	4.8	98.93	99.07	98.39	0.001	
3 at 40° C	4.8	98.16	97.98	97.35	0.002	
7 at 40° C	4.8	98.93	98.51	97.55	0.004	
						0.50
3 at 60° C	4.8	98.16	95.94	94.65	0.009	
7 at 60° C	4.8	98.93	96.7	94.01	0.013	
						0.69
5 at 25° C	5.8	98.16	97.92	97.54	0.002	
8 at 25° C	5.8	98.93	98.95	98.51	0.001	
						2.00
5 at 40° C	5.8	98.16	95.88	93.51	0.012	
8 at 40° C	5.8	98.93	98.53	97.44	0.004	
						3.00
5 at 60° C	5.8	98.16	80.94	66.83	0.096	
8 at 60° C	5.8	98.93	95.97	92.72	0.016	
						6.00

¹⁸ See, e.g., EX1108, 89 (First-order Reactions).

Formulation	pH	T = 0	T = 2	T = 4	K	K _{H2O} / K _{D2O}
10 at 25° C	6.4	98.66	96.67	95.81	0.007	
9 at 25° C	6.4	99.29	98.42	98.07	0.003	
						2.33
10 at 40° C	6.4	98.66	91.07	85.27	0.036	
9 at 40° C	6.4	99.29	95.2	93.22	0.016	
						2.25
10 at 60° C	6.4	98.66	59.77	42.87	0.208	
9 at 60° C	6.4	99.29	75.17	65.97	0.102	
						2.04
11 at 25° C	6.4	99.47	97.87	96.69	0.007	
9 at 25° C	6.4	99.29	98.42	98.07	0.003	
						2.33
11 at 40° C	6.4	99.47	90.97	84.26	0.041	
9 at 40° C	6.4	99.29	95.2	93.22	0.016	
						2.56
11 at 60° C	6.4	99.47	54.96	34.4	0.265	
9 at 60° C	6.4	99.29	75.17	65.97	0.102	
						2.60
13 at 25° C	6.8	97.21	95.42	93.24	0.010	
12 at 25° C	6.8	98.53	97.17	95.99	0.007	
						1.43
13 at 40° C	6.8	97.21	83.05	73.00	0.072	
12 at 40° C	6.8	98.53	90.75	84.64	0.038	
						1.89
13 at 60° C	6.8	97.21	43.99	27.5	0.316	
12 at 60° C	6.8	98.53	56.78	46.05	0.190	
						1.66

272. The solvent isotope effects are summarized in Table 2, below. As expected, the SIE for each pair-wise comparisons is in line with those seen for the numerous carboxylic acids reviewed above. § XII.A.

Table 2. Summary of Solvent Isotope Effects '447 Patent Table 24

Pair-Wise Comparisons ('447 patent Table 24)	Solvent Isotope Effect k _(H2O) /k _(D2O)		
	25° C	40° C	60° C
Formulations 3 & 7 (pH 4.8/pD 5.2)	n.d.	0.50	0.69

Pair-Wise Comparisons (‘447 patent Table 24)	Solvent Isotope Effect $k_{(H_2O)}/k_{(D_2O)}$		
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

273. The lack of effect for the comparison of formulations 3 and 7 was also not unexpected. These formulations are at pH 4.8; at this pH, base-catalyzed hydrolysis plays a smaller role in the overall rate of reaction. Moreover, at these pHs, the slower rate of the overall reaction makes experimental determination impractical.¹⁹ EX1004, 8 (“The half-life at any hydrogen ion concentration between pH 3 and 5 is so great that its experimental determination is not practical.”).

274. It is important to note that given the limitations of the experimental data, these rates should be interpreted qualitatively. That is, while general trends (e.g., the expected increased rate of reaction at higher temperatures, higher pHs, and

¹⁹ As shown in the ‘447 patent, the error in these runs is large. EX1001, 74:56–58 (“FIGS. 6 and 7 illustrate the poor correlation between RS and tropic acid with Formulation 4 and Formulation 7, respectively.”). For example, in several runs, the atropine remaining in solution actually increases at later time points for both the H₂O and D₂O formulations. EX1001, 77:55–78:40 (Table 24A), 78:44–58 (Table 24B).

in the H₂O formulations) can be observed, individual numerical variations are of little, if any, significance.

275. All of the data and resulting predications are based on single-run experiments. These experiments are measuring the degradation of a material that makes up 0.01% of the solution, and, as such, are prone to experimental error. EX1001, cl. 77 (Table 23A). Usually, experiments of these type are re-run 3–5 times and the data is averaged to account for this issue. EX1084, 10 (Figure 4); EX1060, 4 (Table 4).

276. Moreover, the data generated from these experiments show large standard deviations (e.g., EX1001, 75:21–22, 81:6–19 (Table 28)) and appear to have been conducted under inconsistent experimental conditions. EX1001, 74:37–41 (“In some instances, the observed differences are due to the probe differences or additional variables such as for example, the age of the standard buffers or temperature gradients within the laboratory environment.”); Cl. 66–67 (Table 11), n. 1, 2 (“The 25°C. and the 60° C. samples were pulled at 15 days, the 40°C. samples were pulled at 11 days.... The 25° C. and the 60° C. samples were pulled at 28 days, the 40°C. samples were pulled at 24 days.”); 69:43–45 (“concentration w[as] analyzed using the RP-*UPLC* method”), 70:66–67 (“A RP-*HPLC* method was used to carry out the analysis.”) (emphasis added). In a footnote to the week 4 data—that is the basis for the “better stability” example—the ’447

patent states: “Some chromatographic interference[s] were observed to occur late in the run (~27-32 minutes) for many of the t = 4 week stability samples and in some instances is proposed to be system related.” EX1001, 72:26–28 (Table 15, n.1).²⁰

277. Thus, while the data is indicative of a qualitative increase in stability in the D₂O formulations, individual numerical variations should not be interpreted as representing significant differences. For example, while the SIE of 6.00 for formula 8 at 60° C would not have been unexpected (e.g., EX1061, 4 (Table III), EX1083, 3 (Table I)), the variation between this run and all the other data is likely due in part, if not entirely, to experimental error.²¹²²

2. Lower Main Degradant

278. “Lower main degradant” refers to the rate at which the main degradant of atropine, tropic acid, is formed. EX1094, 11–12. This data is generated in a

²⁰ The data presented in Table 15 matches the data presented in Table 24. EX1001, 71:45–72:28, 77:55–78:58. Table 24 does not include this footnote.

²¹ Table 29 shows no calculation for tropic acid formation for formulation 5 due to poor correlation, yet Table 30 still produces a shelf-life estimate based on tropic acid formation for formulation 5. EX1001, 81:21–82:28.

²² EX1001, 73:58–63 (“with the exception of Formulations 5 and 6 at 60° C.... these potency values are within the error of the HPLC method”).

similar manner as that in the “better stability” example, but instead of measuring atropine remaining in solution, it measures the product formed by the degradation reaction. EX1001, 78:60–79:41. Lower main degradant is not a distinct “unexpected result” from “better stability”; the two tests are simply different methods of measuring the same expected effect of replacing H₂O with D₂O.

279. The data showing tropic acid in solution at each of the different time points and temperatures is shown in Tables 25A and 25B of the ’447 patent. I calculated the rate of tropic acid formation (*k*) and the solvent isotope effect (K_{H_2O}/K_{D_2O}) using the same methodology described above for the “better stability.” § XII.B.1. The solvent isotope effects calculated from the data in the ’447 patent are summarized in Table 3, below.

Table 3. Summary of Solvent Isotope Effects ’447 Patent Table 25

Pair-Wise Comparisons (’447 patent Table 25)	Solvent Isotope Effect $k_{(H_2O)}/k_{(D_2O)}$		
	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

280. As would have been expected, the relative rates for “lower main degradant” are very similar to those seen for “better stability.” The slightly higher solvent isotope effect seen in the “lower main degradant” example is because this example measures the effect of D₂O on the specific reaction producing tropic acid—i.e., the base-catalyzed reaction known to be slowed by D₂O. But the “better stability” example measures the total loss of atropine in solution, and thus accounts for all other means by which atropine is lost, e.g., dehydration, absorption, oxidation, etc. Thus, because the “lower main degradant” measures the effect of D₂O more directly, the differences between the H₂O and D₂O formulations appear slightly larger than those in the “better stability” example.

281. As a practical matter, this has no effect. Tropic acid formation is just a proxy for the overall stability of atropine; reducing the levels of a particular degradant is of no consequence. As the '447 patent recognizes: “This related substance is likely to be the first parameter to fail specification.” EX1001, 68:44–45. This point is also illustrated by the data in Table 30, where the shelf-life of the formulations is limited by the total related substances—i.e., the limit for related substances is reached before the limit for tropic acid. EX1001, 81:56–82:28 (Table 30).

3. Longer Shelf Life

282. The '447 patent then takes the data generated in the “better stability” and “lower main degradant” and uses it to calculate shelf-life based on specific limits for each. EX1094, 12–13. Shelf-life for related substances is based on the data from the “better stability” example; shelf-life based on tropic acid is based on the “lower main degradant” example. EX1001, 80:59–82:28.

283. This is simply another way of expressing the same expected effect of D₂O slowing the rate of reaction. These allegedly distinct results are not based on any new experimental data and show nothing different than the “better stability” and “lower main degradant” examples.

284. The shelf-life data is calculated by a less precise version of the predications done by *Kondritzer* in 1957.²³ The '447 patent calculates the activation energy for 40° and 60° C. This is done via the same equation used to calculate rate constant (k), described above (§ XII.B.1).

²³ The '447 patent uses “two-point” calculations. EX1001, 80:63–81:1. This means that the rate constant is calculated from two time points (presumably weeks 2 and 4). Predications of this kind are generally based on more time points. For example, *Kondritzer* used five points to calculate the rate constant for atropine hydrolysis. EX1004, 7.

285. The activation energies calculated for the two temperatures are then averaged to obtain a single activation energy for related substances and tropic acid. EX1001, 80:63–81:5. These single activation energies are used in the Arrhenius Equation to predict the half-lives of the formulations at different pHs and temperatures and to predict the time it would take for atropine to degrade to 8% (RS) and 5% (tropic acid) in weeks and months. EX1001, 80:63–81:5; EX1004, 6–8.

286. These results are not unexpected. It is textbook science that reducing the rate of reaction will reduce the amount of product formed. EX1085, 36–37; EX1004, 6–8. These further “longer-shelf life” calculations are nothing more than an extrapolation of the expected effect over a greater time period.

C. Any Differences Between the Alleged Unexpected Results and the Closest Prior Art Are Insignificant Differences in Degree

287. Patent owner did not provide any evidence of why a POSA would have found the data presented during prosecution “unexpected.” EX1094, 9–13. Similarly, Patent Owner did not compare the data in the ’447 patent to the stabilizing effect of D₂O on any prior-art compounds. EX1094, 9–13.

288. The art showed that deuterium oxide increased the stability of procaine by approximately two to three-fold at the pD ranges closest to those recited by the claims of the ’447 patent. EX1006, 5. And, as described above, this magnitude of

effect had been seen for numerous other carboxylic esters subject to base-catalyzed hydrolysis. §§ VI.B, XII.A.

289. In my opinion, if the small variations seen in the data from the '447 patent are anything more than experimental error, they are, at best, an insignificant difference in degree. That is, if any of the data represent actual differences between the formulations in the '447 patent and the prior art, such differences are nothing more than incremental variations in the stabilizing effect of D₂O, not a difference in kind.

D. The Data Presented Is Not Commensurate in Scope With the Claims of the '447 Patent

290. The data in the '447 patent are not representative of the broad scope of the claims. The claims of the '447 patent cover (1) atropine at 0.001% to 0.03%, (2) deuterated water, and (3) pD from 4.2 to 7.9. EX1001, claims 1–19.

291. The formulations presented in the '447 patent are formulated at specific pH levels and contain high levels of D₂O. These factors have a significant impact on the stability of the formulations.

a. pD of 4.2–7.9

292. The claims of the '447 patent include a broad pD of 4.2–7.9 (pH 3.8–7.5). As discussed above (§§ VI.C.1, X.C.1.d)), this broad range simply encompasses all of the known pD levels for maximum atropine stability and optimal clinical administration.

293. As pD is a logarithmic scale, there is more than a 5,000-fold difference in the OD^- concentration between pD 4.2 and pD 7.9. As explained (§§ VI.A.2, X.C.2), *Kondritzer*, and numerous subsequent papers, demonstrated that the stability of atropine varies significantly with OH^- concentration.

294. Accordingly, the results presented for formulations at specific pDs are not representative of atropine formulations at all of the pDs claimed by the '447 patent. For example, the claims of the '447 patent would include atropine formulations at a pD 4.2 (pH 3.8). At these pHs, base-catalyzed hydrolysis plays a smaller role in the overall rate of degradation, and hence, D_2O may impart a smaller SIE.

b. Levels of D_2O

295. None of the claims of the '447 patent except for claims 12 and 16 recite a specific level of deuterium oxide content. Claims 1–11, 13–15, and 17–19 of the '447 patent thus cover atropine formulations containing any amount of D_2O .

296. It was known that the solvent isotope effect varies significantly with D_2O content. EX1022, 10–11 (“The rate of hydrolysis was decreased 10.6% in 20% D_2O , 23% in 50% D_2O , and about 33% in 75% D_2O ”); EX1070, 2 (“The isotope effect on this reaction showed a linear dependence on solvent deuterium content.”); EX1064, 7 (Fig. 3) (showing solvent isotope effect dependent on D_2O concentration); § X.C.5.

297. The formulations presented for the alleged unexpected results were formulated in pure D₂O, with no regular water added to the solutions. EX1001, 64:24–46. These formulations are not representative of claims that would read on a formulation comprising 1% deuterium oxide, where a POSA would expect that a solvent isotope effect would be negligible at best.

XIII. Applicant's Arguments During Prosecution

298. I understand that during prosecution of the application that lead to the '447 patent, the Examiner issued a rejection over *Teva* (EX1052; "*Teva*"), Wildsoet (EX1037) and WoldeMussie (EX1036). EX1093, 4; EX1090, 3.²⁴ I understand that the Examiner relied on *Teva* to teach the use of D₂O with atropine. EX1093, 4; EX1092.

299. *Teva* is a patent application directed to “improved pharmaceutical compositions having long term shelf life” for certain water-hydrolysable active ingredients based on the use D₂O in place of ordinary water. EX1052, 1. It focuses on compositions comprising D₂O and benactyzine and specifically discloses and claims a combination therapy of benactyzine and atropine in D₂O. EX1052, 5–6 (e.g., Example II, claim 15). As discussed above (§ VI.B.2), *Teva* taught that H₂O

²⁴ I understand a first rejection was issued over the '199 patent. EX1091, 3–4.

could readily be replaced with D₂O and that D₂O extended the benactyzine formulation's shelf-life. EX1052, 2–5.

300. I understand that during prosecution, Applicant attempted to distinguish *Teva* based on (1) structural differences between atropine and benactyzine, and (2) *Teva*'s disclosure that atropine is “relatively more stable” than benactyzine. EX1094, 5–9; EX1095, 7–10. As the Examiner recognized, these arguments do not distinguish *Teva* from Applicant's claimed subject matter. EX1042, 3; EX1097, 6. Contrary to Applicant's assertions, *Teva* would not have dissuaded a POSA from combining atropine and D₂O; rather, *Teva* further underscores the POSA's motivation and reasonable expectation of success for the D₂O-atropine compositions claimed in the '447 patent.

301. First, Applicant asserted that *Teva* does not teach the use of D₂O with atropine because *Teva* was directed to “ α -amino or α -hydroxy carboxylic acid derivatives,” whereas atropine is a “ β -hydroxy carboxylic ester.” EX1094, 6; EX1095, 7–8. As of the earliest possible effective filing date of the '447 patent, however, D₂O had been used to stabilize a wide range of compounds, including carboxylic esters not limited to α -amino and α -hydroxy groups. §§ VI.B, X.A.2.²⁵

²⁵ For example, procaine, disclosed by *Siegel*, is not a α -amino or α -hydroxy carboxylic acid. § X.A.2.

That *Teva* was focused on stabilizing one specific type of carboxylic ester (benactyzine) would not have dissuaded a POSA from combining D₂O with another carboxylic ester (atropine).

302. Second, Applicant asserted that *Teva* taught “actively teaches that atropine is stable in regular water.” EX1094, 7; EX1095, 8 (emphasis omitted). Applicant omitted, however, that *Teva* is directed to formulations of benactyzine and atropine at a pH of 2.7 for the treatment of acute exposure to organophosphorus insecticides or nerve gases, not ophthalmic compositions for the treatment of myopia. EX1052, 4–5. *Teva* does not teach that ophthalmic compositions of atropine are stable in regular water.

303. Unlike ophthalmic solutions of atropine, which are formulated as near as possible to the pH of the eye, 7.4, atropine used for *Teva*’s indication may be administered at significantly lower pHs, where atropine is relatively stable. § VI.A.2. Indeed, in the Example II disclosing atropine and benactyzine, *Teva* specifically discloses that the pH of the solutions “is adjusted by known methods to 2.7.” EX1052, 5. As a POSA would have understood, at pH 2.7, atropine is degraded by the slow acid-catalyzed hydrolysis reaction, and, as such, is relatively stable as *Teva* stated. §§ VI.A.2, X.A; *see also* EX1096, 2 (“A mixture of the three drugs (trimedoxime bromide, atropine sulfate, and benactyzine hydrochloride) was

prepared at pH 2.8 to maximize the overall stability of the active ingredients of the multicomponent formulation.”).

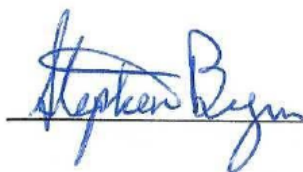
304. As explained throughout this declaration, however, at higher pHs—i.e., those at which atropine is formulated for the treatment of myopia—a POSA would have known that atropine is significantly less stable due to the faster rate of base-catalyzed hydrolysis. §§ VI.A.2, X.A.1. As detailed above (§ X.A), a POSA would have been motivated to combine D₂O with atropine to enhance long term stability while enabling administration of atropine at pHs closer to those optimal for patient comfort. In the context of treating myopia, it is irrelevant that atropine is more stable than benactyzine at pH 2.7.

305. Moreover, Teva disclosed that atropine is “*relatively* more stable” (EX1052, 5) than benactyzine, not that “atropine is stable in ordinary water” as represented by Applicant (EX1094, 7; EX1095, 8). *Teva* is correct that benactyzine is unstable in water and taught that its rate of degradation determines the shelf life in a combination product with atropine. EX1096, 5 (“Benactyzine is the least stable of the active ingredients in the antidote formulation [benactyzine, atropine, and trimedoxime]”).

306. Thus, at most, *Teva* discloses that at pH 2.7, atropine is “relatively more stable” than the unstable benactyzine—it does not teach that atropine is stable in regular water, much less that ophthalmic solutions of atropine formulated at higher

pHs would not stand to benefit from the substitution of D₂O for H₂O. *Teva* demonstrates that a POSA would have been well aware that D₂O could be used to stabilize known pharmaceuticals, including carboxylic acids, and (2) that atropine itself could be readily combined with D₂O. These disclosures only serve to underscore the obviousness of the compositions claimed in the '447 patent.

I declare under the pains and penalties of perjury under the laws of the United States of America that all statements made are true and correct.

A handwritten signature in blue ink, reading "Stephen Byrn", is written over a horizontal line.

Stephen Byrn

Dated: March 7, 2022

Appendix A

CURRICULUM VITAE - DR. STEPHEN R. BYRN

Professional Title: Charles B. Jordan Professor of Medicinal Chemistry; School of Pharmacy and Pharmaceutical Sciences, Department of Industrial and Physical Pharmacy, Purdue University, West Lafayette, Indiana 47907

Home Address: 824 Barlow Street, West Lafayette, Indiana 47906

Marital Status: Married, ten children

Education: DePauw University, Greencastle, Indiana, B.A., 1962-1966, Chemistry

University of Illinois, Urbana, Illinois, Ph.D., 1966-1970, Organic and Physical Chemistry

University of California, Los Angeles, California, Postdoctoral, 1970-1972, Physical Chemistry

Professional Experience: Assistant Professor of Medicinal Chemistry, Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, Indiana, July 1, 1972 to June 30, 1976

Associate Professor of Medicinal Chemistry, Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, Indiana, July 1, 1976 to June 30, 1981

Professor of Medicinal Chemistry, Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, Indiana, July 1, 1981 to present

Associate Department Head of Medicinal Chemistry, Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, Indiana, 1979 to 1988

Assistant Dean of the Graduate School, Purdue University, West Lafayette, Indiana, 1984 to 1988

Head, Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, Indiana, 1988 to 1994

Founder and Director, Purdue University Center for AIDS Research, September 30, 1988 to March 1, 1998

Head, Department of Industrial and Physical Pharmacy, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, Indiana, September 1, 1994 to June 30, 2009

Charles B. Jordan Professor of Medicinal Chemistry, 1992 to present.

Co-Director, Center for Biotechnology Innovation and Regulatory Science, Discovery Park and Agricultural and Biochemical Engineering Department, 2014-present

Director, NIPTE Center of Excellence for Abuse Deterrent Formulations,
March, 2017-present

Memberships:

Phi Eta Sigma, Rho Chi, Phi Lambda Upsilon, Phi Kappa Phi, Sigma Xi
American Chemical Society
American Crystallographic Association
American Association of Pharmaceutical Scientists

Awards, Honors:

Rector Scholar, DePauw University, 1962-1966
Sinclair Oil Company Fellow, University of Illinois, 1967-1968
National Science Foundation Graduate Fellow, University of Illinois, 1968-1971
National Institutes of Health Postdoctoral Fellow, University of California, 1971-1972
Elected Fellow, American Association of Pharmaceutical Scientists, 1989
Elected Member, United States Pharmacopeia Revision Committee, 1990-1995 & 1995-2000 & 2000-2005.
Council of Experts 2000-2005, Member of several subcommittees including chemistry, dissolution, excipients and PAT.
Purdue University Representative to the USP, 2000, 2005, 2010.
Alumni Citation, DePauw University, 1991
Thomas W. Binford Memorial Award for Outstanding Contributions to Entrepreneurial Development, World of Difference Award, State of Indiana, 2000
FDA Advisory Committee Service Award, October 31, 2001
AAPS Outstanding Paper Award, 2008, APQ Section (With L. Taylor)
Purdue University, Outstanding Faculty Commercialization Award, 2008-09
AAPS David Grant Research Achievement Award in Physical Pharmacy, 2009
Special Issue (September 2010) of the Journal of Pharmaceutical Sciences was dedicated to Stephen R. Byrn, based on his contributions to the field of solid state pharmaceuticals.
FDA Honor Award. Stephen Byrn as Member of FDA/Kilimanjaro School of Pharmacy Regulatory Collaboration, 2013
AAPS Dale Wurster Award In Pharmaceuticals, November 16, 2016.
LSAMP Faculty Mentor of the Year Award, Purdue University, 2018
Pharmaceutical Sciences Teacher of the Year Award, Purdue University, 2018
Purdue University Morrill Award, Most Outstanding Faculty Member, 2018
AAPS Pharmaceutical Global Health Award, November 2018

Memberships, Editorial Boards and Major Committees:

Journal of Pharmaceutical Sciences Editorial Advisory Board - 1994-present.
AAPS Pharm. Sci. Tech. Editorial Advisory Board – 2007 – present.
Pharmaceutics Editorial Advisory Board - 2009 – 2014
Journal of Validation Technology, Editorial Advisory board – 2010 – 2012
Crystal Growth and Design Editorial Advisory Board – 2002 to 2007
Journal of Drug Targeting, 1993-1995.
Journal of Pharmaceutical and Biomedical Analysis, 1998-2002
Pharmaceutical Sciences Advisory Committee, FDA 1997-2001, Chair 2000-2001
Controlled Substances Advisory Committee, State of Indiana 1982-1998 (Chair 1995-8)
Drug Substance Technical Committee, FDA-PQRI, 1997-present (Chair 1997-2001)
National Academies of Sciences, Engineering, and Medicine, Topical Pain Creams, March 1, 2019 - present

Professional Service:

American Chemical Society, Secretary-Treasurer, Vice-Chairman and Chairman Purdue Section, 1976-1982

Controlled Substances Advisory Committee, 1982-1998, Secretary, 1987-1994, Chair, 1994-1998

American Society of Pharmacognosy, Program Committee, 1977

Symposium Organizer American Chemical Society, Division of Medicinal Chemistry, 1987

Organizer, First and Third Midwest Organic Solid State Chemistry Symposia, 1988 (University of Illinois), 1990 (Purdue University), 2005 (Purdue University, with Ken Morris). Co-organizer, 2016 (Purdue University)

Organizer of a Short Course, entitled "Polymorphs and Solvates of Drugs," 1988 (Bradford, England), 1990 (Purdue University), 1992 (Bradford, England)

Reviewer numerous journals including JACS, J. Org. Chem., Acc. Chem. Res., J. Pharm. Sci., Pharm. Res., Crystal Growth and Design

Chair, NIPTE Abuse Deterrent Center of Excellence 2017 - present

University Committees:

Athletic Affairs Committee, 1979-1984

Computer Center Policy Committee, 1983-1988

Commencement Committee, 1984-1989

Development Committee, 1991-2

Vision (Long Range Planning) Committee, 1993

University Promotions Committee 1995-1998.

Purdue University Faculty Senate 2007-2010 and 2012-2016.

Global Academic Committee, 2018-Present

Departmental Committees:

As Chair of two departments I have served on numerous departmental committees.

Graduate School Committees:

M.D.-Ph.D., 1984-1988

Area Committee, 1984-1988

Computer Committee, 1984-1988

Residency Review Committee, 1984-1988

David Ross Fellowship Committee, 1984

Teaching Effort:**Courses Taught – Pharmacy and Doctor of Pharmacy Curriculum**

Pharmaceutical Solids, 1998-2001.

Regulatory Affairs, 1998-present.

MDCH 310 - Analytical Medicinal Chemistry, 1972-1997

MDCH 418 - Computers in Pharmacy, 1978-1988

IPPH 471 – Sterile Products – Instructor in Charge 2004-05, 2014

IPPH 363 – Industrial Pharmacy - 2008-2012 (Instructor in charge, 2010)

PHRM 898 – Dosage Forms I – Solid state, Tablets, Capsules – 2012-present, course coordinator 2017

PHRM 461 – Drug Discovery and Development II – 2014-present

Courses Taught - Graduate Curriculum

MDCH 614 - Advanced Medicinal Analysis, 1972-1997

IPPH 590/587 - Pharmaceutical Solids 2004 – 2018

MDCH 698, 699 - Directed research for M.S. and Ph.D. graduate students and post-doctoral associates. 1972
- Present

IPPH 521– Drug Development 2004 - 2014

IPPH 522 – Good Regulatory Practices 2004 – 2014

IPPH 562 – Pharmaceutical Manufacturing 2010

PHRM 46100 – Drug Discovery and Development II, 2013-present

ABE 52100 – Drug Development

ABE 52200 – Good Regulatory Practices

IT 50800 - Quality and Productivity in Industry and Technology

IT 57100 Project Management in Industry and Technology

Teaching Programs Co-Founded – MS Degree in Biotechnology Innovation and Regulatory Sciences in the US and Africa (Joint with Professor Kari Clase, Ph. D.) originally Program in Regulatory and Quality Compliance, cofounded jointly with M. Schmidt, Ph. D.:

This new area of specialization in the Agricultural and Biochemical Engineering Department focuses on creating leaders in biotechnology innovation and regulatory science, especially relating to pharmaceuticals. The curricula also addresses topics of innovation and integrates emerging technologies.

The program consists of 10 courses and a special project for a total of 30 credit hours. The array of courses will provide:

- an understanding of all aspects of quality
- an understanding of biotechnology innovation and regulatory science
- in-depth knowledge related to biotechnology and pharma
- knowledge on how to lead and manage operations within the industry

The degree format is tailored to student needs:

- Traditional, on-campus degree program in West Lafayette
- Blended online and weekend program

- In Africa in collaboration with Kilimanjaro School of Pharmacy, Moshi, Tanzania and Nelson Mandela, African Institute of Science and Technology, Arusha, Tanzania

Sustainable Medicines in Africa (Joint with Sr. Zita Ekeocha, M.S. and Professor Kari Clase)

The sustainable medicine program in Africa is aimed at addressing the problem of lack of access to high quality medicines in Africa. This program consists of: (1) Master's degree in Biotechnology Innovation and Regulatory Science (Sr. Zita Ekeocha)); (2) an actual GMP-level pharmaceutical manufacturing facility, and (3) a quality medicines laboratory equipped with HPLCs. The educational programs are aimed at providing source of well-trained manufacturing scientists for pharmaceutical industry in Tanzania and Africa. The GMP-level facility is used to teach manufacturing under strict quality control. The GMP facility will serve as a model for other such facilities throughout Sub-Saharan Africa. The feasibility of establishing a sustainable medicine program in Tanzania is supported by the experience of the former Infusion Units Project in Tanzania, now known as Saint Luke Foundation (SLF). This program has manufactured and distributed infusion solutions throughout Tanzania since 1983. Additionally, the availability of trained personnel and a model facility will combat several current problems especially those related to counterfeited/poor quality medicines.

This Master's degree in Biotechnology Innovation and Regulatory Science is supported by Bill and Melinda Gates Foundation as an ANDi (African National Drug Innovation) Center for Pharmaceutical Manufacturing and Regulatory Training. This center is one of less than 50 centers in Africa.

Graduate Students and Postdoctoral Associates:

M.S. (thesis) - E. Kreutzer (1976), S. VanEss (1977), B. Stewart (1978), G. Migliaccio (1979), G. Gibson-Clay (1979), J. Gomes (1979), P. Hoyos (1982), L. Morales (1991), H. Tat (1998), R. Alajlouni

Ph.D. - G. Dolch (1976), M.D. Tsai (1978), R. Clay (1979), J. Gomes (1981), H. Martinez (1983), I. Lassalle (1984), P. Sutton (1984), P. Toren (1985), J. Chaber (1986), D. Kessler (1986), P. Hoyos (1986), E. Kolodziej (1986), D. Carlson (1989), C. Chan (1990), P. Saindon (1991), K. Ray (1992), N. Sipahimalani (1992), Wu-Po Ma (1993), D. Nugyen (1993), P. Toma (1993), G. Stephenson (1994), M. Wahle (1997), W. Xu (1997), T. Borchardt (1997), V. Joshi (1998), X. He (1999), R. Te (2000), X. Chen (2000), Y. Hu (2000), Zhihui Qui (2001); Hui Li (2002); T. Davis (2003), A Gupta (2005), Chen Mao (2007), Faraj Atassi (2007), EunHee Lee (2007), Yuerong Hu (With L. Taylor) (2008); Niraj Trasi (2011), Ziyang Su (2011); Sumana Penumetcha (2011); Xin Chen (2012); Y. Song (2015), H. Nie (2017); Salma Salem (2019)

Postdoctoral Associates - P.Y. Siew (1976), C.T. Lin (1980), P. Perrier (1981), J. Stowell (1984), B. Tobias (1988), C. Chan (1990), C. Cox (1990), Kin-shan Huang (1995), R. Schlam (1999); N. Poendaev (2001-2003), D. Smith (2003-2006), Eun Hee Lee (2007-2010)

Current Graduate Students - Amrinder Singh

Current Senior Research Associate – Daniel Smith, Ph. D.

Undergraduate Student Activities:

Counselor for Pharmacy Students, 1978-1996.
Faculty Fellow (Shreve Hall & Hillenbrand Hall), 1982-1997.
Senior Faculty Fellow (Shreve Hall), 1986-1990.
Senior Faculty Fellow (Hillenbrand Hall) 1993-1995
Adopt a Student Program, College of Pharmacy, 2009-10

Research Interests:

Solid State Chemistry of Drugs/Pharmaceutical Solids

Investigators: S. Byrn, Amrinder Singh

The overall goal of our research is to develop the field of Solid State Chemistry of Drugs so that all of the principles and factors governing solid state chemistry are understood. This knowledge is then used to predict and analyze all behaviors of solids observed during the drug development process and in formulations. Thus, the solid state chemistry of drugs is being studied to improve knowledge of the factors which affect this chemistry and to develop new methods of studying these reactions. At present, our group is focusing solid state acid base reactions and stability. We are also interested solid state desolvation reactions, solid state decarboxylation reactions, solid-solid reactions, and solid state rearrangements. These studies are important in that they will lead to better understanding of the mechanism of drug degradation and eventually to new approaches to stabilizing drugs. By carrying out research on the solid state chemistry of drugs it is hoped that new approaches and ideas for drug analysis including solid state NMR spectroscopy and X-ray diffraction will be developed. In addition, this research is aimed at providing new insight into drug stability and at developing methods for predicting drug stability. Furthermore, approaches to the production via crystallization of the desired drug form are an important component of these studies.

Processing and Manufacturing of Pharmaceuticals

Investigators: S. Byrn, Amrinder Singh

Approaches to understanding the molecular basis of pharmaceutical manufacturing are being developed. These approaches which include Raman mapping and EDS can in favorable cases provide information on the spatial location of all components in tablets and capsules. The effect of processing on the solid state chemistry of drugs and the stability of formulations is also being investigated. Particular emphasis is placed on the wet granulation and coating. Continuous manufacturing and manufacturing design are also being investigated especially for protease inhibitors and fixed dose combination drugs. The regulatory aspects of processing and manufacturing are also being emphasized.

Analysis of Amorphous Pharmaceuticals

Investigators: Amrinder Singh

The structure of amorphous pharmaceuticals is not known and poorly understood. Pair distribution functions derived from X-ray powder diffraction measurements made at Argonne National Laboratories Synchrotron as well as solid state NMR measurements along with more conventional studies can provide phase diagrams and information on the functional groups and atom-atom distances involved in drug-drug and drug-polymer interactions present in amorphous materials. These methods will lead to the establishment of a rational design method for amorphous compositions. This bottom-up design approach focuses on amorphous protease inhibitors since these are the most bioavailable compositions. This new method will determine structural details of amorphous compositions by providing atom-atom distances and other structural parameters. We will use the atomic distances, and other parameters determined, to predict properties of these compositions including stability (failure to crystallize), dissolution rate, and bioavailability. This method is particularly important since amorphous drugs are now being used to cure HCV and as potential treatments for a range of other viral diseases besides HIV.

Abuse Deterrent Formulations of Opioids

Investigators: Dan Smith

The goal of the abuser is to alter the opioid dosage from such that it provides a plasma concentration that is sufficient to induce euphoria. The abuse-deterrent dosage form is designed to minimize the feeling of euphoria when taken as prescribed by a patient, i.e. when using the medication as intended. However, a prescription drug abuser would try to modify the dosage form in a manner to increase the plasma concentration to a level that would induce euphoria. They can achieve this by increasing the rate of drug uptake. For example, they could crush a controlled release tablet, which would induce dose dumping when swallowed. They could change the route of administration. For example the abuser could crush a tablet and then try and inject or snort the contents of the crushed tablet. Thus, abuse deterrent formulations are investigated to identify the failure modes. This knowledge will lead to second generation formulations that are even more difficult to abuse than those currently on the market.

Engagement Program Co-Founded – Chao Center now Purdue GMP Center:

The Chao Center is a self-supporting manufacturing facility located in the Purdue Research Park. A major donor, Dr. Allan Chao, established the Center with a very substantial gift of \$5.0 million. The Chao Center is involved in contract research and manufactures the anti-tuberculosis drug Seromycin for Lilly.

Publications (Books):

Byrn, S.R., "Solid State Chemistry of Drugs," Academic Press, New York, New York, 1982.

Knevel, A.M., DiGangi, F.E., and Byrn, S.R., "Quantitative Pharmaceutical Chemistry," 7th Edition, Waveland Press, Inc., Prospect Heights, Illinois, 1983.

Byrn, S.R., Stowell, J.G., and Pfeiffer, R.R., Solid State Chemistry of Drugs," 2nd Edition, SSCI Press, West Lafayette, IN, 1999

Byrn, S.R., Zografi, G., Chen, Xiaoming (Sean), "Solid State Properties of Pharmaceutical Materials," John Wiley and Co., Hoboken, NJ, 2017

Publications (Book Co-Edited)

Templeton, Allen; Byrn, Stephen R.; Haskell, Roy J.; Prisinzano, Thomas E., "Discovering and Developing Molecules with Optimum Drug-Like Properties", AAPS Press, Springer, NY, NY 2016

Publications:

1. Weingarten, H., Miles, M.G., Byrn, S.R., and Hobbs, C.F., *J. Am. Chem. Soc.*, 1967, **89**, 5874, "Amination of β -Dicarbonyl Compounds with Tetrakis (dimethylamino) Titanium."
2. Curtin, D.Y. and Byrn, S.R., *J. Am. Chem. Soc.*, 1969, **91**, 1865, "Stereoisomerism at the Oxygen:Carbon Single Bond Due to Hydrogen Bonding. Structures of the Yellow and White Crystalline Forms of Dimethyl 3,6- Dichloro-2,5-Dihydroxy-terephthalate."
3. Curtin, D.Y. and Byrn, S.R., *J. Am. Chem. Soc.*, 1969, **91**, 6102, "Structures in Solution of the Yellow and White Forms of Dimethyl 3,6-Dichloro-2,5-Dihydroxyterephthalate."
4. Curtin, D.Y., Byrn, S.R., and Pendergrass, D.B., Jr., *J. Org. Chem.*, 1969, **34**, 3345, "Thermal Rearrangement of Arylazotribenzoyl-methanes in the Solid State. Examination with Differential Thermal Analysis."

5. Byrn, S.R., Maverick, E., Muscio, O.J., Trueblood, K.N., and Jacobs, T.L., *J. Am. Chem. Soc.*, 1971, **93**, 6680, "The Structure of Two Head to Head Allene Dimers."
6. Byrn, S.R., Curtin, D.Y., and Paul, I.C., *J. Am. Chem. Soc.*, 1972, **94**, 890, "The X-Ray Crystal Structure of the Yellow and White Forms of Dimethyl 3,6-Dichloro-2,5-Dihydroxyterephthalate and a Study of the Conversion of the Yellow Form to the White Form in the Solid State."
7. Wang, A.H.J., Misavage, R.J., Byrn, S.R., and Paul, I.C., *J. Am. Chem. Soc.*, 1972, **94**, 7100, "The Crystal and Molecular Structure of 1-Azabicyclo (3.3.3) Undecane Hydrochloride. Correlation of Molecular Dimensions with Spectroscopic Properties."
8. Byrn, S.R., *Biochemistry*, 1974, **13**, 5186, "The Cation-Binding Properties of Gramicidin."
9. Byrn, S.R., *Indiana Pharmacist*, 1974, **79**, "Caution Advised in Handling Neutral Red Dye."
10. Byrn, Stephen R., *Amer. Jour. Pharm. Ed.*, 1975, **40**, 295, "Combined BS:MS Programs: Alternatives for Pharmacy Students."
11. Byrn, S.R., *J. Pharm. Sci.*, 1976, **65**, 1-22, "Mechanisms of Solid-State Reactions of Drugs."
12. Byrn, S.R. and Lin, C.T., *J. Am. Chem. Soc.*, 1976, **98**, 4004, "The Effect of Crystal Packing and Defects on the Desolvation of Hydrate Crystals of Caffeine and L(-)-1,4-cyclohexadiene-1-alanine."
13. Byrn, S.R., Graber, C.W., and Midland, S.L., *J. Org. Chem.*, 1976, **41**, 2283, "Comparison of the Solid State and Solution Conformation of Methapyriline, Tripeleminamine, Diphenhydramine, Histamine and Choline. The IR-X-Ray Method for Determination of Solution Conformation."
14. Byrn, S.R. and Siew, P.Y., *J. Chem. Soc.*, 1977, Perkin II, 144, "The Structure and Conformation of β -Thiodan in the Solid State and in Solution. Application of the IR-X-Ray Method."
15. Weintraub, H.J.R., Tsai, M.D., Byrn, S.R., Chang, C.-j., and Floss, H.G., *Int. J. Quantum Chem., Quantum Biology Symp.*, 1976, **3**, 99, "Conformational Analysis of Some Pyridoxal Amino Acid Schiff Bases."
16. Stamos, I.K., Howie, G.A., Manni, P.E., Haws, W.J., Byrn, S.R., and Cassady, J.M., *J. Org. Chem.*, 1977, **42**, 1703, "Synthesis and Structures of Dilactones Related to Anemonin."
17. Otten, J.G., Yeh, C.S., Byrn, S.R., and Morrison, H.A., *J. Amer. Chem. Soc.*, 1977, **99**, 6353, "Solution Phase Photodimerization of Tetramethyl Uracil. Further Studies of Ground-State Aggregates."
18. Byrn, S.R. and Dolch, G.D., *J. Pharm. Sci.*, 1978, **67**, 688, "Analysis of the Binding of Daunomycin and Doxorubicin to DNA Using Computerized Curve Fitting Procedures."
19. Lin, C.T., Siew, P.Y., and Byrn, S.R., *J. Chem. Soc.*, 1978, Perkin II, 957, "Solid State Dehydrochlorination and Decarboxylation Reactions I. Reactions of *p*-Aminosalicylic Acid Hydrochloride and *p*-Aminosalicylic Acid and the Crystal Structure of *p*-Aminosalicylic Acid."
20. Lin, C.T., Siew, P.Y., and Byrn, S.R., *J. Chem. Soc.*, 1978, Perkin II, 963, "Solid State Dehydrochlorination and Decarboxylation Reactions II. Reactions of Three Crystal Habits of *p*-Aminosalicylic Acid Hydrochloride and the Crystal Structure of *p*-Aminosalicylic Acid Hydrochloride."
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Patents

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Papers Presented or Co-Authored:

A large number of papers have been presented at various conferences since 1974.

Invited Lectures, Seminars, and Courses:

"The Mechanisms of Action of Ion Transporting Antibiotics," DePauw Univ., Greencastle, Indiana, October, 1974.

"The Solid State and Solution Conformational Isomerism of Drugs," Commercial Solvents Corporation, Terre Haute, Indiana, May, 1975.

"Solid State Reactions of Drugs," Indiana State University, Terre Haute, Indiana, April, 1975.

"Desolvations of Organic Molecular Crystals and their Pharmaceutical Applications," Chemistry Department, University of Illinois, Urbana Illinois, November, 1977.

"Desolvations of Organic Molecular Crystals and their Pharmaceutical Applications," Department of Medicinal Chemistry, University of Illinois at the Medical Center, Chicago, Illinois, March, 1978.

"Solid State Reactions of Drugs," Eli Lilly and Co., Indianapolis, Indiana, June, 1979.

"Relationship between the Solid State and Solution Conformation of Drugs," Youngstown State University, Youngstown, Ohio, Oct., 1980.

"Solid State Reactions in Medicinal Chemistry," Rose Polytechnical Institute, March, 1980.

"Solid State NMR Spectra of Drugs," Eli Lilly and Co., June, 1982.

"Solid State Chemistry of Drugs," DePauw University, Greencastle, Indiana, October, 1983.

"Polymorphism and the Solid State Chemistry of Drugs," McNeil Laboratories, Fort Washington, Pennsylvania, January, 1984.

"Structure Elucidation of Natural Products Using X-Ray Crystallography," King Saud University, Riyadh, Saudi Arabia, A series of 4 lectures presented in February, 1984.

"Mode of Action of AMSA," Drug Dynamics Institute, School of Pharmacy, University of Texas, Austin, Texas, May, 1984.

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"Methods for the Analysis of Drugs," Hewlett Packard Short Course, Purdue University, West Lafayette, Indiana, June 19, 1985.

"Solid State Chemistry of Drugs," Chemistry Department, University of Kentucky, Lexington, Kentucky, October, 1984.

"Chemistry of Drug-DNA Interactions," Phi Lambda Upsilon Lecture, DePauw-Wabash Chapter, DePauw University, Greencastle, Indiana, March 20, 1986.

"Desolvation of Drug Crystal Forms" and "Crystallographic Study and Solid State NMR Spectra of Crystalline Drugs," both Seminars presented at Merck-Frosst Pharmaceuticals, Montreal, Canada, May 4-6, 1986.

"Solid State Chemistry of Drugs, Desolvation, Oxidation, and Solid State NMR Spectra of Steroid Crystal Forms," Merck Sharp and Dohme Research Laboratories, West Point, Pennsylvania, June 10, 1986.

"Solid State Stability of Drug Substances," Burroughs Wellcome Company, Research Triangle Park, North Carolina, October 1, 1986.

"Solid State Oxidation Reactions," Merck Sharpe and Dohme Research Laboratories, West Point, Pennsylvania, May 8, 1987

"Polymorphs and Solvates of Drugs," Ortho Lecture Series, Ortho Pharmaceutical, Raritan, New Jersey, April 22, 1987.

"Solid State Chemistry of Drugs," K. N. Trueblood Retirement Symposium, University of California, Los Angeles, California, March 18, 1989.

"Residential School: Polymorphs and Solvates of Drugs," Short Course, Royal Society of Chemistry, University of Bradford, London, June 24-26, 1989.

"Solid State Oxidation Reactions," University of Wisconsin, Madison, Wisconsin, June 12, 1989.

"Solid State Chemistry of Drugs," Land-of-Lakes Conference, Madison, Wisconsin, June 13, 1989.

"Solid State Chemistry of Steroids," Upjohn Company, Kalamazoo, Michigan, November 6, 1989.

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"Powder Diffraction Analysis of Pharmaceuticals," Parke-Davis/Warner Lambert, Holland, Michigan, May 3, 1991.

"Anticancer Drug Design," American Cancer Society, Indianapolis, Indiana, February 25, 1989.

"Polymorphs and Solvates of Drugs," Short Course, Purdue University, June 5-7, 1990.

"Crystal Hydrates and Water in Crystalline Pharmaceuticals," Eino Nelson Conference, Phoenix, Arizona, November 27, 1990.

"Polymorphs and Solvates of Drugs," Burroughs-Wellcome, Inc., Greenville, North Carolina, April 9, 1991.

"Pharmaceutical Solids Short Course," Rhone-Poulenc Rorer, Collegeville, Pennsylvania, January 22-23, 1992.

"Pharmaceutical Solids Short Course," Eli Lilly and Company, Indianapolis, Indiana, February 13-14, 1992.

"Regulatory Issues for Pharmaceutical Solids," Merck Research Laboratories, West Point, Pennsylvania, February 28, 1992.

"Pharmaceutical Solids Short Course," Sandoz Pharmaceutical, East Hanover, New Jersey, March 2-3, 1992.

"Pharmaceutical Solids Short Course," Meadowlands Hilton, Seacacus, New Jersey, April 21-22, 1992.

"Pharmaceutical Solids Short Course," UNIGOV, University of Puerto Rico, San Juan, Puerto Rico, April 30-May 1, 1992.

"Pharmaceutical Solids Short Course," Abbott Laboratories, Chicago, Illinois, May 15, 1992

"Pharmaceutical Solids Short Course," Sterling, Inc., Renseleer, NY, June 4-5, 1992

"Residential School: Polymorphs and Solvates of Drugs," Short Course, Royal Society of Chemistry, University of Bradford, London, July, 27-29, 1992.

"Pharmaceutical Solids Short Course," Burroughs Wellcome, Greenville, NC, August 11-12, 1992

"Pharmaceutical Solids Short Course," Washington Marriott, Washington, DC, October 27-28, 1992

"Polymorphs and Solvates Short Course," AAPS Short Course, San Antonio, TX, November 15, 1992

"Drug-Excipient Interactions in the Solid State," UNIGOV Conference on Excipients, San Juan, PR, Jan. 28, 1993

"Pharmaceutical Solids Short Course," Rhône-Poulenc Rorer, Paris, France, Feb. 9-10, 1993

"Pharmaceutical Solids Short Course," Meadowlands Hilton, Secaucus, NJ, April 27-30, 1993

"Pharmaceutical Solids Short Course," Syntex, Inc., Palo Alto, CA, May 6-7, 1993

"Mobility in Pharmaceutical Solids," G.D. Searle, Chicago, Illinois, May 12, 1993

"Solid State Chemistry of Drugs," Parke-Davis Warner/Lambert, Morris Plains, NJ, June 21, 1993

"Pharmaceutical Solids Short Course," Washington Marriott, Washington D.C., September 30, 1993

"Solid-State Pharmaceutical Chemistry," PR&D Building Dedication, Merck Research Laboratories, West Point, PA, October 8, 1993

"AIDS Research at Purdue University," Northeast Missouri State University, Kirksville, MO December 7, 1993.

"Mobility in Pharmaceutical Solids," Hoffmann-LaRoche, Nutley, NJ December 9, 1993.

"Solid State Chemistry of Drugs," Parke-Davis Warner/Lambert, Holland, MI, February 24, 1994.

"Mobility in Pharmaceutical Solids," Pfizer Central Research, Groton, CT, February 9, 1994.

"Solid State Pharmaceutical Chemistry," University of Minnesota, Minneapolis, MN, April 4, 1994.

"Pharmaceutical Solids Short Course," Pfizer, Inc., Groton, CT, April 11-12, 1994.

"Pharmaceutical Solids Short Course," Meadowlands Hilton, Secaucus, NJ, April 27-30, 1994.

"Pharmaceutical Solids Short Course," Geneva, Pharmaceuticals, Broomfield, CO, May 4-5, 1994.

"Pharmaceutical Solids Short Course," Crystal City Marriott, Washington, D.C., October 5-7, 1994.

"Instrumental Methods of Characterizing Bulk Drug Substances" Pharmaceutical Seminars, Wilmington, N.C., June, 1994

"Pharmaceutical Solids," R.W. Johnson, August 10, 1995.

"Pharmaceutical Solids," Upjohn Co., December 7, 1995.

"Pharmaceutical Solids Short Course," Crystal City Marriott, Washington, D.C., April, 1995.

"Solid State Chemistry of Drugs," Syntex Chemicals, Inc., Boulder, CO, February 2, 1996

"Intersection of Laws, Regulations, and Scientific Principles," Burkett Lectures, DePauw University, Greencastle, IN April 2, 1996.

"Organic Solid State Chemistry and Pharmaceutical Materials Science," Burkett Lectures, DePauw University, Greencastle, IN April 2, 1996.

"Pharmaceutical Solids Short Course," Crystal City Marriott, Washington, D.C., April 30-May 2, 1996.

"Practical Consequences of Polymorphism," McNeil Consumer Products, Ft. Washington, PA May 7, 1996.

"Practical Consequences of Polymorphism," Biogen, Cambridge MA, June 12, 1996.

"Practical Consequences of Polymorphism," Genentech, S. San Francisco, CA, June 19, 1996.

"Pharmaceutical Solids Short Course," Crystal City Marriott, Washington, D.C., April 28 -May 1, 1998.

"Pharmaceutical Solids," Short Course at the DuPont-Merck, June 12-13, 1997.

"Pharmaceutical Solids," Short Course at the FDA, September 29, 1997.

"Pharmaceutical Solids Short Course," Crystal City Marriott, Washington, D.C., April 29-May 1, 1998.

"Pharmaceutical Solids," Proctor and Gamble Pharmaceuticals, Norwich, N.Y., July 27-28, 1998

"Pharmaceutical Solids Short Course," Sanofi Pharma, September 21-23, 1998

"Pharmaceutical Solids Short Course," Novartis, Feb. 4-5, 1999

"CAMP Technologies, J&J, Spring House," PA April 13-15, 1999

"Pharmaceutical Solids, SSCI Course," Washington, DC, April 28-30, 1999

"Solid-state Chemistry of Drugs and Analysis," University of Michigan, College of Pharmacy and Engineering, Ann Arbor, MI 2-10-00.

"Solid-state Chemistry of Drugs," University of Minnesota, College of Pharmacy, 3-30-00.

"Polymorphism and Solid-state Chemistry of Drugs," Ball State University, Chemistry Department, Muncie, IN 11-11-99.

"Particle Formation and Crystallization of Pharmaceuticals," London, England and Crystal City, VA, June and Sept 9-10. 1999

"Pharmaceutical Solids Short Course," Roche, August 12-13, 1999

"Pharmaceutical Solids Short Course," Searle, October 10-13, 1999

"Pharmaceutical Solids Short Course," Warner-Lambert, November 1-3, 1999

"Pharmaceutical Solids Short Course," Warner-Lambert, Feb. 23-25, 2000

"Pharmaceutical Solids Short Course," Pfizer, March 20-22, 2000

"Pharmaceutical Solids," SSCI Course, Washington, DC, May 9-11, 2000

"Pharmaceutical Solids," SSCI Course, Fremont, CA, May 23-25, 2000

"Pharmaceutical Solids," SSCI Course, J&J, July 29-31, 2000.

“Pharmaceutical Materials Science and Research,” AAPS Head’s Meeting, Indianapolis, IN, October 27, 2000.

“Dimensions of Pharmaceutical Solids,” IIT Seminar, November, 2000.

“Pharmaceutical Solids,” SSCI Course, Schering, May, 2001.

“Pharmaceutical Solids,” SSCI Course, Washington, DC, May 2001.

“Pharmaceutical Solids,” SSCI Course, Pfizer, May, 2001.

“Six Dimensions of Pharmaceutical Solids,” Wyeth Ayerst, January 2001.

“Polymorphism and Stability of Drugs,” Univ. of Kentucky, February 7, 2001.

“Pharmaceutical Solids, SSCI Course,” Washington, DC, May 8-10, 2001

“New Technologies for Process Analytical Technologies,” FDA, Washington, DC, April 1, 2002.

“PAT,” Watson Pharmaceuticals, Corona, CA, March 3-4, 2003

“Pharmaceutical Solids, SSCI Course,” Washington, DC, May 9-11, 2002

“Pharmaceutical Solids, SSCI Course,” Washington, DC, May 10-12, 2003

“Solid State Chemistry of Biologicals,” SSCI Course, South San Francisco, Nov. 16-17, 2003

“Pharmaceutical Solids, SSCI Course,” Washington, DC, May 5-7, 2004

“PAT: Achieving Mechanistic Understanding through Solid State Chemistry,” SSCI Short Course, Princeton, NJ, September, 2004

“Midwest Organic Solid State Chemistry Symposium” June 2-4, 2005, Purdue University.

“Pharmaceutical Solids, SSCI Course,” Washington, DC, May 9-11, 2005

“Biological Solids,” South San Francisco, CA, February 15-16, 2005

“Pharmaceutical Solids, SSCI Course,” Washington, DC, March 29-31, 2006.

“Pharmaceutical Solids, SSCI Course,” Merck and Co., West Point, PA, September 16-17, 2006.

“Biopharmaceutical Solids, Aptuit/SSCI Course,” San Francisco, CA, February, 27-28, 2007.

“Pharmaceutical Solids, SSCI Course,” Washington, DC, April 10-12, 2007.

“Pharmaceutical Solids, SSCI Course,” Washington, DC, April 8-10, 2008.

“Pharmaceutical Solids, SSCI Course,” San Francisco, CA, May 14-15, 2008.

“Processing and Formulation Approaches for Improving the Apparent Solubility Controlled Release, Glatt Controlled Release Symposium, Sept. 18-20, 2007, Mahwah, NJ.

“Solid State Properties in Drug Development,” Howard University, Washington, DC, Sept. 10, 2007.

“Pharmaceutical Solids, SSCI Course,” Washington, DC, April 22-24, 2008.

“Forced Degradation Testing To Improve Stability Prediction and Reduce Time to Market”, Forced Degradation of Small Molecules Conference, Philadelphia, PA, February 25-27, 2008

“Solid Phase Characterization Short Course,” EAS, Nov. 11, 2008

“Pharmaceutical Solids, SSCI Course,” Washington, DC, April 21-23, 2009.

“Pharmaceutical Solids, SSCI Course,” San Francisco, CA, May 13-14, 2009.

“Drug Discovery”, Kilimanjaro School of Pharmacy/St. Luke Foundation Course, Moshi, Tanzania, March 17 - 28, 2008

“Drug Development”, Kilimanjaro School of Pharmacy/St. Luke Foundation Course, Moshi, Tanzania, December 1-12, 2008

“Drug Development”, Kilimanjaro School of Pharmacy/St. Luke Foundation Course, Moshi, Tanzania, May 18-29, 2009

“Pharmaceutical Manufacturing,” Kilimanjaro School of Pharmacy/St. Luke Foundation Course, Moshi, Tanzania, August 3-14, 2009.

“Drug Discovery”, Kilimanjaro School of Pharmacy/St. Luke Foundation Course, Moshi, Tanzania, March 17 - 28, 2010

“Pharmaceutical Solids, SSCI Course,” Washington, DC, April 13-15, 2010.

“Drug Development”, Kilimanjaro School of Pharmacy/St. Luke Foundation Course, Moshi, Tanzania, March 10-19, 2010

“Physical Characterization and Methods of Analysis”, Short Course,” EAS, Nov. 14, 2010

“Drug Development”, Kilimanjaro School of Pharmacy/St. Luke Foundation Course, Moshi, Tanzania, March 14-25, 2011

“Physical Characterization and Methods of Analysis”, Short Course,” EAS, Nov. 12-13, 2011

“Sustainable Medicines in Africa,” University of Kansas, Oct. 10, 2011

“Drug Development”, Kilimanjaro School of Pharmacy/St. Luke Foundation Course, Moshi, Tanzania, March 14-25, 2011

“Manufacturing”, Kilimanjaro School of Pharmacy/St. Luke Foundation Course, Moshi, Tanzania, August 8-19, 2011

“Documents”, Kilimanjaro School of Pharmacy/St. Luke Foundation Course, Moshi, Tanzania, March 5-16, 2012

“Drug Development”, Kilimanjaro School of Pharmacy/St. Luke Foundation Course, Moshi, Tanzania, August 6-17, 2012

“Drug Registration: US FDA Approaches to Reviewing Generic Drug Applications and PEPFAR Reviews.” Short course taught by US FDA, Kilimanjaro School of Pharmacy, Purdue University, and Howard University, Moshi, Tanzania , Sept. 24-28, 2012.

“Pharmaceutical Solids,” SSCI Short Course, Chicago, IL, Oct. 18-19, 2012

“Pharmaceutical Solids,” EAS Short Course, Somerset, NJ, November 4, 2013

“Solid State Properties of Pharmaceutical Materials”, Eastern Analytical Symposium, Sommerset, NJ, Nov. 12 and 13, 2015

"Molecular Structure of Medicines," Wagner Lecture, University of Michigan, Sept. 26, 2016.

“Solid State Chemistry of Drugs Impact and Regulatory Awareness,” Short Course, Bangkok, Thailand, August 11, 2017.

“Pharmaceutical Solids,” EAS Short Course, Somerset, NJ, November 11, 2018

Invited Symposium Talks at National or International Meetings:

"The Purdue BS-MS Program," AACP Meeting, Boston, Massachusetts, July, 1980.

"Polymorphism and the Solid State Chemistry of Drugs," FACSS Meeting, Philadelphia, Pennsylvania, September, 1983.

"CP/MAS Spectra of Drugs, A New Method for the Investigation of Polymorphs and Solvates," 25th Annual Medicinal Chemistry Symposium, SUNY Buffalo, Buffalo, New York, June 11-14, 1984.

"Polymorphism and the Solid State Chemistry of Drugs," Eastern Analytical Symposium, New York, New York, November 15, 1984.

"Structure-Reactivity Correlations in Crystalline Solids," 132nd Annual A.Ph.A. Meeting, San Antonio, Texas, February 19, 1985.

"Solid State Chemistry of Drugs," A.Ph.A. Acad. Pharm. Sci., Short Course on Materials Characterization, San Francisco, California, March 16, 1986.

"Solid State Chemistry of Polymorphs, Solvates, and Metastable Crystal Forms of Drugs," North Eastern Regional Pharmaceuticals Association Seventh Annual Meeting, New Haven, Connecticut, June 27, 1986.

"Correlation of Crystal Structure and Solid State NMR Spectra of Steroid Polymorphs," 44th Pittsburgh Diffraction Conference, Pittsburgh, Pennsylvania, October 29-31, 1986.

"Polymorphism of Drugs," Annual Meeting of the American Crystallographic Association, University of Texas, Austin, Texas, March 15-20, 1987.

"Overview - Current Status of Basic Research in Pharmaceutical Solids," Second Annual Meeting, American Association of Pharmaceutical Sciences, Boston, Massachusetts, June 7-12, 1987.

"X-ray Crystallography and Solid-State NMR," American Crystallographic Association Symposium, Philadelphia, Pennsylvania, June 1988.

"Hepa Filtration and Biosafety Training of Pharmacy Students," Biomedical Safety Conference, Indianapolis, Indiana, June 1989.

"Design of Anti-AIDS Drugs," 17th International Symposium of the Controlled Release Society, Reno, Nevada, July 22-25, 1990.

"Structure and Stability of Crystal Solvates," American Association of Pharmaceutical Scientists, Las Vegas, Nevada, November 6, 1990.

"Structure and Behavior of Crystal Hydrates," Eino Nelson Conference, Phoenix, Arizona, November 27, 1990.

"Structure and Mobility of Polymorphs and Solvates of Pharmaceuticals," 4th Computational Methods in Chemical Design, Kloster Irsee, Germany, May 15-20, 1994.

"Solid State Chemical Instability: Mechanistic and Kinetic Issues" 36th Annual International Industrial Pharmaceutical Research Conference, Merrimac, Wisconsin, June 6-10, 1994.

"Solid State Pharmaceutical Chemistry: Applications of Solid State NMR," PharmAnalysis Conference, Atlantic City, NJ, June 21, 1994.

"Solid State Pharmaceutical Chemistry," 25th Meeting, Fine Particle Society and Second International Conference, New Brunswick, NJ, July 26, 1994.

"Solid State Pharmaceutical Chemistry," Am. Cryst. Assoc., July, 27, 1995, Montreal, Canada

"Chemical Reactions in Amorphous or Disordered Pharmaceutical Solids," Fine Particle Society, Chicago, IL, August 23, 1995

“Color Dimorphism from 1905 To 1995,” COGM International Meeting, Washington, DC, August 30, 1995

“Practical Consequences of Polymorphism,” FDA-AAPS Workshop on Polymorphism, Washington, D.C., February 26-28, 1996

“New Developments in Solid State NMR,” AAPS-USP Meeting, Washington, D.C., April 25-6, 1996.

“Solid State NMR Spectra of Drugs, Eastern Analytical Symposium, Somerset, N.J., Nov. 8, 1996

“Solid-state Chemical Reactions of Drugs,” Higuchi Conference, Lake of the Ozarks, Mo., March 9-11, 1997.

“Assessment: Impact of Bulk Drug Manufacturing Changes on Physical Properties”, AAPS-FDA BACPAC Conference, Washington D.C., March 25, 1997

“Practical Consequences of Polymorphism,” ACT Meeting, St. Louis, Mo., April 7-9, 1997.

“Characterization of Polymorphic Behavior: Research and Regulatory Perspective,” AAPS Eastern Regional Meeting, New Brunswick, N.J., June 9-10, 1997.

“Overview - What is Polymorphism and How Important is it?” British Pharmaceutical Conference, Scarborough England, September 18, 1997.

“Chemical Reactivity in the Solid State,” AAPS National Meeting, Boston, Mass., Nov. 2-6, 1997

“Solid State Chemistry – Regulations and Reactions” MSI International Symposium, San Diego, CA, February 18-20, 1998

“Physical Transformations of Solvated Pharmaceuticals,” Royal Society of Chemistry National Meeting, Polymorphism Symposium, Durham, England, April 7, 1998

“Stability of Solid Pharmaceuticals,” AAPS Western Regional Meeting, South San Francisco, CA. June 1, 1998

“Crystallization and Polymorphism Issues in Controlled Release Dosage Forms,” Organized and presented at a one day short course, Controlled Release Society International Meeting, Las Vegas, NV., June 25, 1998.

“BACPAC,” World Pharm Conference, Philadelphia, PA, Sept 22, 1998

“BACPAC and PQRI,” DIA Conference, Washington, D.C., Nov. 9, 1998

“PQRI”, AAPS National Meeting, San Francisco, CA, Nov. 17, 1999

“Energy-temperature Diagrams,” PhaTA4, Karlsruhe, Germany, March 24, 1999

“BACPAC, An Update, SUPAC Conference, Washington, DC, 5-4-99

“BACPAC, Bulk Active Post Approval Changes,” World Pharm., Philadelphia, PA, 10-28-00.

“Transformation During Processing,” AAPS National Meeting, New Orleans, LA 11-15-99

“PQRI, Drug Substances Technical Committee,” AAPS National Meeting, New Orleans, LA 11-15-99

“Impurities and Stability of Pharmaceuticals,” GMP-API Course, Univ. of Wisconsin Continuing Ed., Jan 20, 2000 and May 19, 2000.

“Crystallization of Pharmaceuticals,” Alun Bowen Lecture, British Crystallographic Association Meeting, April 4, 2000, Edinburgh, Scotland

“Computational Approaches to Solid State Chemistry,” Millennium Pharmaceutical Sciences Meeting, San Francisco, CA April 18, 2000

“Chemical Stability of Pharmaceuticals,” Land of Lakes Conference, Devils Lake, WI, June, 2000.

“Solid State NMR of Pharmaceuticals,” SMASH NMR Conference, Argonne, IL July 16, 2000.

“Polymorphism,” Land of Lakes Analytical Conference, Devils Lake, WI, July 31, 2000.

“Fundamentals of Solid State Reactions,” AAPS National Meeting, Indianapolis, IN, Oct. 26, 2000.

“NIR and LIF Methods of Monitoring Blend Homogeneity,” AAPS National Meeting, Indianapolis, IN 2000.

“Strategies for Metastable Phases,” AAPS Congress of Americas Short Course, March 2000.

“Implications of Solid State Chemistry for Process Development,” Rhodia International Conference on Process Development, Amelia Island, FL, April 2001

“Raman Mapping and Physical Transformations,” EAS, September 2001, Atlantic City, NJ

“Using Crystal Engineering to Predict Stability and Reduce Time to Market,” Higuchi Research Seminar, May 2001, Lawrence, KA.

Polymorphism & Crystallization Conference, Chairperson and Presenter on Regulatory Aspects, Philadelphia, PA June 20-21, 2002.

“Crystallization and Solid State Chemistry of Pharmaceuticals”, Aminoff Symposium, Royal Academy of Sciences, Stockholm, Sweden, September 12, 2002.

“Validation of Process Analytical Technologies”, IVT PAT Conference, Gaithersburg, MD, Oct. 24, 2002

“Engineering Sameness: Polymorphism, Crystallization, and Stability of Solid Pharmaceuticals”, AICHE Plenary Lecture, AICHE National Meeting, Indianapolis, IN, November 4, 2002

“Solid State Analysis of API in Drug Product,” AAPS National Meeting, November 6, 2002

“Validation of NIR Methods for the Pharmaceutical Industry,” AAPS National Meeting, November 6, 2002

“Achieving Sameness, USP, Washington, DC, December 18, 2002.

“Strategies for Incorporating NIR into PAT, “ IIR Conference, Washington, DC, Feb 4-6, 2003.

“Overview of Particle Manufacture and Blending,” Particle Size analysis Workshop, AAPS, April 30, 2003.

“Reactivity of Polymorphs, Predicting Stability,” ACS Prospectives Conference, Tampa, FL Feb 23, 2003

“Regulatory Aspects of Polymorphism,” APV Course, Bonn, Germany, May 12, 2003

“Approaches to PAT using In-line Sensors,” PAT Summit, Washington, DC, September 29, 2003

“Solid State Characterization Technologies for Online Analysis,” AAPS National Meeting, Salt Lake City, UT, October 30, 2003

“National GMP Curriculum, “AAPS National Meeting, Salt Lake City, UT, October 28, 2003

Enz Lectures, University of Kansas, August, 2004

“Solid State Chemistry of Amorphous Materials,” ACS Prospectives Symposium, Feb 8-11, 2004

“Polymorphism and Pharmaceuticals,” Stephen R. Byrn, IUCR Intl. School of Crystallography, Diversity Amidst Similarity, Erice, Italy

“Strategies to Improve Solubility Using Amorphous Materials and Co-crystals,” Barnett Improving Solubility Conference, Philadelphia, PA, June 3, 2005.

“Polymorphs of API and Implications in Drug Development,” CVG Conference, Toronto, CA, Sept. 27, 2004

“Implementing Quality by Design,” IIR PAT Conference, Princeton, NJ, Dec. 13, 2004.

“Novel Approaches to Characterization,” AAPS National Meeting, Baltimore, MD, November 2005.

“Busse Lectures” (1. Solid State Pharmaceutical Chemistry; 2. Regulated Pharmaceutical Industry in 2010), University of Wisconsin, Madison, Wisconsin.

“Achieving Mechanistic Understanding through Solid State Chemistry,” PAT Workshop, J. Liang and S. Byrn, PAT Conference, June 14-17, 2005, Philadelphia, PA.

“Regulatory Applications of Patent-Derived Analytical Methods,” PITTCON, March 4, 2005, Orlando FL,

“Using PAT to Reduce Time to Market” Academic and Industrial Research in PAT, Wyeth Scientific Symposium, Pearl River, NY, Feb. 27, 2005.

“PAT Process Understanding and Control of APIs” PAT Workshop, J. Liang and S. Byrn, PAT Conference, June 14-17, 2005, Philadelphia, PA.

“Novel Approaches to Characterization. Accelerating the Drug Development Process” AAPS National Meeting, November 11 2004, Baltimore, MD.

“Polymorphs in API, Implications for Drug Development”, CVG Meeting, Toronto, CA, Sept. 27-28, 2005.

“Building a Start-up Knowledge Based Company” ACS National Meeting, August 2004, Philadelphia, PA.

“Design and Characterization of Pharmaceutical Solids for Quality Product Development, Strategies for the 21st Century,” Keynote Lecture, Stephen R. Byrn, Ph. D., Department of Industrial and Physical Pharmacy, Purdue University and SSCI, Inc. West Lafayette, Indiana, Land of Lakes 48th Conference, Merrimac Wisconsin, June 2006.

“Physical Characterization of Pharmaceutical Solids,” NIST Meeting on Organic Materials, NIST, Rockville, MD, April 5-7, 2006.

“What does this all mean to a Formulator,” AAPS National Meeting, Nashville, TN, Nov. 6-11, 2006.

“New Opportunities in Solid State Characterization”, British Pharmaceutical Conference, Manchester, England, September 24-28, 2005.

“Using PAT to Understand Process and Reduce Time to Market and Speed Drug Development while Avoiding Regulatory Problems,” Bioanalytical Testing World Congress, Philadelphia, PA, and September 19-21, 2006.

“Science-Based Product Management and PAT”, Global Manufacturing Summit, September 7-9, 2005, Atlanta, GA.

“Solid State Strategies for Improving Solubility”, Water-Insoluble Drug Delivery Course, Park Hyatt Hotel, Philadelphia, PA, July 18, 2005.

“Implication of Polymorphism for Formulation Design”, Formulation Development Meeting, Philadelphia, PA, July 26-27, 2006

“Improving Drug Development Via Crystallization And Crystal Growth.” Edinburg, Scotland, Sept 10-12, 2006.

“Physical Stability in the Solid State”, Stephen R. Byrn, AAPS Workshop on Pharmaceutical Stability, September 10-12, Bethesda, MD, 2006.

“Quality by “Design and PAT”, AICHE National Meeting, Salt Lake City Utah, November 5, 2007.

Chairman Polymorphism and Crystallization Scientific Forum, IQPC, December 3-5, Philadelphia, PA. Presented Lead-off Talk entitled: “Designing Optimized Formulations Utilizing Polymorphs/Cocrystals/Amorphous Forms within a Preclinical Timeframe.”

“Leverage Forced Degradation Testing To Improve Stability Prediction and Reduce Time to Market”, Forced Degradation of Small Molecules, February 25-27, 2008

“Strategies for Preparation and Manufacture of Polymer-based Nanoparticulate Formulations”, Bio-Nano Conference, Hyderabad India, March 13-14, 2008.

“Quality by design and Process Analytical Technology for Pharmaceutical Manufacturing in the 21st Century”, Bio-Nano Conference, Hyderabad India, March 13-14, 2008.

“Molecules to Medicines: Bringing Drugs to Market Following GMP. Green Chemistry and Production of Essential Medicines in Developing Countries”, March 18-20, 2008, Abuja Nigeria

“A Model for Education and Pharmaceutical Manufacturing in Africa, Green Chemistry and Production of Essential Medicines in Developing Countries”, March 18-20, 2008, Abuja Nigeria

“Understanding Additive Effects on Crystallization, Polymorphic Transformation and Solubility” ACS Award in Separations Science and Technology Symposium, ACS National Meeting, New Orleans, LA, April 7, 2008

“Fast to IND with Quality by Design”, ISPE International Conference, Boca Raton, FL, Oct. 28, 2008.

“Utilizing Amorphous Dispersions to Reduce Time to IND”, AAPS International Meeting, Atlanta, GA, Nov. 23, 2008.

“A QbD Solubility Enhancement Platforms for Fast Drug Development Abstract”, Keynote lecture at the Indo-US Bilateral Workshop on Pharmaceutical Cocrystals and Polymorphs, Mysore, India, February 8 to 11, 2009

“Accelerating Proof of Concept Using Solid State Chemistry”, PGSRM Conference, Purdue University, June 25-27,

“Sustainable Medicines in Africa”, Swintowsky Distinguished Lecture, University of Kentucky, Lexington, KY, Sept. 24, 2009

“Accelerating Proof of Concept”, Swintowsky Distinguished Lecture, University of Kentucky, Lexington, KY, Sept. 25, 2009

“Accelerating Proof of Concept Using Solid State Chemistry,” David Grant Award Lecture, AAPS, Sept 11, 2009, Los Angeles, CA.

“Accelerating Translational/Clinical Research using Solid State Chemistry”, David Grant Symposium, University of Minnesota, June 2, 2010.

“Strategies for Novel Pediatric Formulations,” Peck Symposium, Purdue University, October 14, 2010.

“Solid-state Chemistry of Biopharmaceuticals: Fundamental Issues and Study Approaches”, Arden House AAPS Conference, West Point, NY, March 10, 2011

“Sustainable Medicine Program in Tanzania and East Africa” AAPS Indianapolis-Cincinnati Discussion Group, January 27, 2011

Sustainable Medicines in Africa, AAPS National Meeting, New Orleans, LA, Nov. 15, 2011

Sustainable Medicines in Africa FACCS National Meeting, Reno, NV, Oct. 5, 2011

Design and Characterization of Drug Substance Solid Form for Quality Formulation Development, Strategies for the 21st Century, Land of Lakes Conference, Devil’s Lake, Wisconsin, June 11-15, 2012.

Accelerating Proof of Concept Using Solid State Chemistry, Aptuit Conference on Early Drug Development, Florence, Italy, May 15, 2012.

Enhancing Drug Bioavailability and Solubility, Stephen Byrn, Boston Solubility and Bioavailability Conference, January 22, 2013

Sustainable Medicines in Africa, Pittcon, Philadelphia, PA, March 19, 2013

Business and Clinical Rationale for Development of Fixed Dose Combination Products, Land of Lakes Conference on FDC Drugs, Madison, WI, June 3, 2014

Enhancing Drug Bioavailability and Solubility, Stephen Byrn, California Solubility and Bioavailability Conference, June 18, 2013

Framing the Key Properties that Must be Optimized in Drug Molecules in Order to have a Drug Product, AAPS National Meeting, San Antonio, November 12, 2013

Winning the Race: Using the Right Strategies for Phase and Formulation to Rapidly Achieve Clinical Entry, AAPS National Meeting, San Antonio, November 13, 2014

Introducing Levitation Technology for the Production of Amorphous Drugs, Boston Solubility Project, ex Pharma, Boston Mass. Jan. 27-28, 2014.

Structure and Analysis of Amorphous Solids, ICDD Meeting, Hyderabad, India, August, 18, 2017

Regulatory Science of Solid State Chemistry, IUCr Crystallography Meeting, Hyderabad, India, August, 19, 2017.

Pharmaceutical Synchrotron XRPD Workshop, 6-8 May, 2018, Purdue University, Co-organizer. International Synchrotron meeting.

Structure and Analysis of Amorphous Dispersions, Stephen Byrn, Chris Benmore, Gabriel deAraujo, Amrinder Rai, Purdue University, West Lafayette, IN and Argonne National Laboratory, Chicago, IL. Presentation at Pharmaceutical Synchrotron XRPD Workshop, 6-8 May, 2018, Purdue University.

Synchrotron X-Ray Diffraction and Pair Distribution Function Analysis of Drug/Polymer Dispersions: A Comparison of Subtraction Techniques to Isolate Intra-and Intermolecular Interactions, Pamela Smith^a, Stephen R. Byrn^a, Gabriel L.B. de Araujo^b, Chris J. Benmore^ca) Improved Pharma, b) Department of Pharmacy, University of Sao Paulo, c) X-ray Science Division, Advanced Photon Source, Argonne National Laboratory PPXRD-16 and SS-XRPD-2 at the Swiss National Light Source, Villagen, Switzerland, 9 May 2019 to 12 May 2019.

Co-organized and chaired several sessions of the PPXRD-16 and SS-XRPD-2 at the Swiss National Light Source, Villagen, Switzerland, 9 May 2019 to 12 May 2019.

Continuity of Solids between Amorphous and Crystalline States, Stephen Byrn and Gabriel De Araujo, Purdue University, Chris Benmore, Argonne Laboratories, American Crystallographic Association, National Meeting, American Crystallographic Association Meeting, Cincinnati, Ohio, July 2019.

Principal Investigator on Grants:

"Conformational Isomerism in the Solid State and in Solution," Stephen R. Byrn, Am. Chem. Soc. Starter Grant #2687-G1, \$7,500, 7-1-72 to 6-30-76.

"The Structures of Ion Transporting Antibiotics in the Solid State and in Solution," Stephen R. Byrn, Cottrell Research Grant from the Research Corporation, \$5,345, 1-1-73 to 12-31-75.

"The Interaction of Intercalating Agents with Dideoxynucleotides-Daunomycin," Stephen R. Byrn, Purdue Cancer Committee Grant, \$6,000, 1-1-74 to 12-31-75.

"Structural Studies of Physiologically Active Agents," Stephen R. Byrn, NIH Grant #ES00929, \$91,076 Direct Costs, 5-1-74 to 4-30-77.

"Solid State Reactions in Medicinal Chemistry," Stephen R. Byrn, NIH Grant #GM21174, \$75,000 Direct Costs, 6-1-74 to 5-31-77.

"Structural Studies of Physiologically Active Agents," Stephen R. Byrn, NIH Grant #ES00929, \$127,500 Direct Costs, 5-1-77 to 4-30-80.

"Conformational of Pyridoxal Schiff's Bases in the Presence and Absence of Enzymes," Stephen R. Byrn and M.D. Tsai, David Ross Grant, \$8,400, 3-1-76 to 2-28-78.

"Solid State Reactions in Medicinal Chemistry," Stephen R. Byrn, NIH Grant #GM21174, \$126,000 Direct Costs, 9-1-78 to 8-31-81.

"Molecular Pharmacology of 9-Aminoacridine Antitumor Agents," Purdue Cancer Committee, \$5,000, 7-1-80 to 12-31-82.

"Mechanism of Degradation of Moxalactam and Related Compounds," Eli Lilly and Company, 1-1-81 to 12-31-81, \$50,000 Total Costs.

"Acridine-DNA Interactions," Part of a Program Project Grant from the National Cancer Institute, W.M. Baird Project Director, ca. \$100,000 Direct Costs for 9-1-81 to 6-30-84.

"Solid State Chemistry of Drugs," Eli Lilly and Company, 1-1-82 to 12-31-82, \$46,000 Direct Costs.

"Mode of Action of Mutagenic Drugs," NIH Grant #GM29175, 3-1-83 to 2-28- 86, \$181,000 Direct Costs.

"Solid State Chemistry of Insulin, Nabilone and Cefaclor," Eli Lilly and Company, 1-1-83 to 12-31-83, \$34,000 Direct Costs.

"Solid State Chemistry of Insulin and Ceftazidine," Eli Lilly and Company, 5-1-85 to 4-30-86, \$5,000 Total Costs, (0593-57-13335), D.L. Smith Co-PI.

"Polymorphism and the Bioavailability of Drugs," NIH Grant #GM34520, 12-1-84 to 11-30-85, \$180,000 Direct Costs.

"National Cooperative Drug Discovery Group for the Treatment of AIDS - Synthetic Approach," NIH U01 AI25712, 9-1-87 to 8-31-90, \$1,046,000 Direct Costs for three years.

"Anti-HIV (AIDS) Agents Targeted to the RNA Template," NIH Grant #GM24289, 4-1-88 to 3-31-91, \$228,000 for three years.

"Solid State Chemistry of Drugs," Grant from Merck and Company, 1988-1990, \$50,000.

"Center for AIDS Research," \$3,100,000 direct cost, approximately \$4,600,000 total costs. September 30, 1988 - March 1, 1994.

"Chemical Pharmacology Training Grant," 7-1-90 to 6-30-95, approximately \$900,000 Direct Costs for 5 years.

"Chemical Pharmacology Training Grant," 7-1-95 to 6-30-97, approximately \$1,200,000 Direct Costs for 5 years.

"Effect of Water on the Molecular Mobility of Pharmaceuticals," Purdue-Wisconsin Joint Project, S. R. Byrn and G. Zografi. Supported by Merck, Pfizer, Sandoz, Glaxo, Upjohn, Boehringer, Bristol-Myers Squibb, and Syntex 1991-1997, approximately \$115,000 per year.

"Crystal Growth and Nucleation During Drying," 9-1-95 to 8-31-97, \$50,000. NSF Pharmaceutical Processing Center, Purdue University, West Lafayette, IN

"CAMP - Consortium for the Advancement of Manufacturing in Pharmacy" 12-1-96 to 12-31-97, about \$380,000, Drying end Point Detection and Blending Detection, CAMP, Narabeth, PA

"CAMP - Consortium for the Advancement of Manufacturing in Pharmacy" 1-1-98 to 12-31-98, about \$400,000, Blending Detection, Parametric Release, Crystallization, (PI or Co-PI) CAMP, Narabeth, PA.

"CAMP - Consortium for the Advancement of Manufacturing in Pharmacy" 1-1-99 to 12-31-99, about \$467,000, Blending Detection, Parametric Release, Crystallization, Dye Lasers(PI or Co-PI) CAMP, Narabeth, PA.

NSF "Crystallization During Wet Granulation" ca. \$30,000 7/1/97 – 12-31-01

NSF "Solid State Acid Base Reactions" ca. \$35,000 7/1/97-12/31/00

"CAMP - Consortium for the Advancement of Manufacturing in Pharmacy" Founder of CAMP along with Professor C. Cooney, MIT, G.K. Raju, and W. Leishear. Funding for 1-1-99 to 12-31-07 about \$450,000 per year. Projects include: Blending Detection, PAT, Crystallization.

"Effect of Water on the Stability of Solid Pharmaceuticals," Purdue-Wisconsin Joint Project. Founder along with Professor G. Zografi, University of Wisconsin. Program now includes Professors K. Morris, L. Taylor, R. Pinal, and T. Carvajal at Purdue and Professor N. Rodriguez-Hornedo, Univ. of Michigan. Current supporters are Pfizer, Boehringer, Bristol-Myers Squibb, Roche, Inhale, and Abbott. Funding for 1997-present, approximately \$100,000 per year.

"Concretion," NSF, 1-1-00 to 12-31-02, \$54,000.

"PTCC – Particle Technology and Crystallization Consortium" Founder of PTCC along with Professors A. Myerson, IIT, K. Morris, Purdue and C. Cooney, MIT. Funding for 1-1-03 to 12-31-07 about \$400,000 total costs. Projects include: Crystallization monitoring, crystallization inhibition, PAT, and sensors.

"Discovering Once-a-Day Specialty Pharmaceutical Products" A.E. Mann Institute, Purdue University, 12-1-2008 to 5-31-2009, \$98,150 DC.

"Mapping base technologies for detecting counterfeit medications" Lilly Endowment, Purdue University, \$100,000, Jan. 1, 2008 through Dec. 31, 2010.

“Indiana Clinical Translational Institute,” A. Shekhar, PI, Stephen Byrn, Program Leader Regulatory, 2% Effort, UL1RR025761, KL2RR025760, TL1RR025759, 5/1/08 to 4/30/13. Total Award \$24,765,925.

“Drug Reformulation”, Mann Institute, Purdue University, \$265,000, 11/1/08 to 9/30/10.

“In-vitro, In-vivo Correlations for Dissolution Tests”, FDA, \$62,000, 9/1/09 to 9/30/10

Formulation of SMA Compound, DHHA-SAIC, August 2010 through July 31, 2011, ~ \$180,000.

“Industrial Pharmacy Services Laboratory, IPPH Department, Purdue University, July 2012-present, about \$200,000 per year

“Evaluation of Drug Product Formulations of Abuse Deterrent Drugs”, NIPTE and FDA, HHSF2232013011189P, Sept. 16, 2013 – Sept. 12, 2015. Total Award \$500,000.

“Master’s Scholarships for Students Studying in Kilimanjaro School of Pharmacy for Purdue MS Degree, Merck Foundation, \$600,000. Sept 2014 to June 30, 2016.

“Investigations of Active Coating End Point Determination”, Astra Zeneca, Nov. 1, 2015 through April 30, 2016, \$134,000.

“Evaluation of Drug Product Formulations of Abuse Deterrent Drugs”, NIPTE and FDA, April 1, 2017 – August 31, 2017. Total Award \$100,000.

“Pharmaceutical Quality Scorecard Development,” NIPTE and FDA, 2U01FD004275, December 1, 2017 – November 30, 2018, \$329,635 and Dec. 1, 2018 to March 31, 2020, \$329,635.

“Methods of Evaluating Drug Abuse by Smoking,” National Institute of Pharmaceutical Technology and Education/ FDA, 2U01FD004275, March 1, 2018, \$94,000.

“Highly Bioavailable Compositions of URM-099,” University of Rochester, May 1, 2018, \$40,000.

“New Salts of Bedaquiline”, S.R. Byrn, PI, Bill and Melinda Gates Foundation, June 1, 2020 to July 31, 2021, \$180,000.

“Formulation Studies of Mitragynine”, S. R. Byrn, PI, V. Gurvich and S. Hoag, Co-PI, Sept 30, 2020 to August 31, 2024, \$695,000.

Co-Principal Investigator on Grants:

"Chemical-Antitumor Activity of Lactones and Epoxides," J.M. Cassady and S.R. Byrn, NIH Grant, #CA \$114,906 Direct Costs, 9-1-75 to 8-31-78.

Member of the Cancer Center of Purdue University. This Cancer Center has received two core grants and a building grant from the National Cancer Institute. 1978 to 1994.

RR025759-61NIH/NCRR (A. Shekhar (PI), 07/01/08 - 06/30/13, Indiana Clinical and Translational Science Institute. Description: Multi-institutional project to support translational research in Indiana. Role: Program Leader, Regulatory Knowledge and Support, Member Pediatric Research Team. 2012 to present.

“Sustainable Medicines in Africa,” Bill and Melinda Gates Foundation, July 1, 2018-June 30, 2020, \$650,612.

“Sustainable Medicines for Africa”, Merck Foundation, July 1, 2018 through June 30, 2020 – Two fellowship grants for \$94,000, K. Clase, PI.

“NIPTE FDA Certification Program in Pharmaceutical Technology”, Sept. 1, 2018 – Oct. 31, 2019, co-PI, \$294,722, K Clase, PI.

“Amorphous Pharmaceutical Product Development using Containerless Methods.” Oct 1, 2018-December 31, 2020. Phase 2 SBIR, Materials Development, Inc., Evanston, IL. \$50,000.

“Assessment of Smoking and Vaping risk of opioids and commercial products, and standardization of methods to asses these properties” Sept. 1, 2019 to August 31, 2021, \$226,993, Vadim Gurvich, PI, BAA, Contract No., 5F40119C10112.

“Sustainable Medicines in Africa”, S.R. Byrn Co-PI, Bill and Melinda Gates Foundation, August 1, 2018 to July 31, 2024, \$1,700,000.

Consultantships and Companies Founded:

Numerous consultantships with many pharmaceutical companies (including Novartis, Pfizer, BMS, J&J, Wyeth, Lilly, Roche, Abbott, Watson, and Merck) and many others over the years 1975 to present.

Co-Founder and Study Director, SSCI, a research and information GMP contract research firm in West Lafayette, IN employing about 90 people, 1991-2006. SSCI was sold to Aptuit in 2006. Consultant to Aptuit Nov. 2009-present

Consulting for several legal firms on major solid state chemistry, formulation, polymorphism, and salt litigations including the Zantac cases, the Paxil cases, the Norvasc cases, the Plavix cases, the Prevacid cases, the Elan nanoparticle patents 1990-present.

Co-Founder and Chief Scientific Officer (as a consultant), Improved Pharma, West Lafayette, Indiana, 2006 – present.

Last Update: February 2021.