

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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EYENOVIA, INC.,  
Petitioner,

v.

SYDNEXIS, INC.,  
Patent Owner.

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Case IPR2022-00384  
U.S. Patent No. 10,842,787

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**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. 10,842,787 (the “787 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 contribution 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 the LSAMP Faculty Mentor of the Year Award, the Pharmaceutical Sciences Teacher of the Year Award, and the 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, 2, 4-9, and 12-19 of the '787 patent recite compositions and methods of treating myopia with atropine at concentrations of about 0.001 wt%<sup>1</sup> to about 0.05 wt% at a pH of about 4.8 to 6.4. In my opinion, a POSA would have considered claims 1, 2, 4-9, and 12-19 to be obvious over the combinations of (1) *Chia* (Ex. 1003), *Akorn* (Ex. 1004), and *Kondritzer* (Ex. 1005); (2) *Chia* (Ex. 1003), *Akorn* (Ex. 1004), and *Lund* (Ex. 1007); and (3) *Wu* (Ex. 1006), *Akorn* (Ex. 1004), and *Kondritzer* (Ex. 1005).

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<sup>1</sup> The term “wt %” (also referred to as percent-by-weight or weight-weight or weight-percent) is a common convention in ophthalmic solutions that represents the weight ratio of solute (e.g., atropine) to solution (e.g., water). *See also infra* ¶¶ 27-29.

19. *Chia* discloses a large scale clinical trial of 0.01% atropine eye drops and demonstrates that this concentration was effective in treating myopia. *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. Ex. 1003, 1–2. Before the earliest possible effective filing date of the ’787 patent, it was cited by researchers and was publicly available to a person of skill in the art. Ex. 1016, 7. *Chia* is relevant to the subject matter of the ’787 patent and would have been considered by one of skill in the art.

20. *Akorn* teaches the use of buffering agents to achieve a solution pH range of 3.5 to 6.0 for atropine. *Akorn* is an FDA approved product label titled “Atropine Care™ (atropine sulfate ophthalmic solution).” Ex. 1004, 1. It was published in July 2014 on the FDA approval web page and has an FDA approval date of July, 18, 2014. *Id.*; Ex. 1020; Ex. 1021. Before the earliest possible effective filing date of the ’787 patent, it was publicly available to a person of skill in the art. *Akorn* is relevant to the subject matter of the ’787 patent and would have been considered by one of skill in the art.

21. *Kondritzer* discloses atropine stability data at pH ranges overlapping with those claimed by the ’787 patent and shows that atropine is primarily degraded

via base-catalyzed hydrolysis. *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 *Journal of the American Pharmaceutical Association*, a well-known and reputable journal. Ex. 1005, 1. Before the earliest possible effective filing date of the ’787 patent, it was cited by researchers and was publicly available to a person of skill in the art. Ex. 1024, 6; Ex. 1025, 8; Ex. 1026, 19. *Kondritzer* is relevant to the subject matter of the ’787 patent and would have been considered by one of skill in the art.

22. *Lund* derives an equation to compute the half-life of atropine at various temperatures and pHs and also recognizes, like *Kondritzer*, that atropine degrades primarily via base-catalyzed hydrolysis. *Lund* is a journal article authored by Lund and Waaler titled “The Kinetics of Atropine and Apoatropine in Aqueous Solutions.” Ex. 1007, 1. It was published in 1968 in *Acta Chemica Scandinavica*, a peer reviewed journal. *Id.* Before the earliest possible effective filing date of the ’787 patent, it was cited by researchers and was publicly available to a person of skill in the art. Ex. 1024, 6; Ex. 1027, 234; Ex. 1028, 2; Ex. 1029, 11, Ex. 1030, 36; Ex. 1031, 3. *Lund* is relevant to the subject matter of the ’787 patent and would have been considered by one of skill in the art.

23. *Wu* discloses compositions for treating myopia using concentrations ranging from about 0.001% to 1% by weight atropine, buffering agents, and common

components of ophthalmic solutions. *Wu* is an international application published under the Patent Cooperation Treaty by the World Intellectual Property Organization on November 13, 2014 and titled “Pharmaceutical Composition and Uses Thereof.” Ex. 1006, 1. Before the earliest possible effective filing date of the ’787 patent, it was publicly available to a person of skill in the art. *Wu* is relevant to the subject matter of the ’787 patent and would have been considered by one of skill in the art.

24. There was ample motivation to combine the low-concentration atropine formulations of *Chia* and *Wu* with the buffering agents and pH range taught by *Akorn*. Modification with the buffering agents of *Akorn* offered the potential to improve the stability of *Chia* and *Wu*’s formulations at pH levels more desirable for clinical administration. Moreover, given the well-known pH-dependent stability properties of atropine, as taught by *Kondritzer* and *Lund*, a POSA would have reasonably expected that the low concentration atropine compositions would have improved stability using *Akorn*’s buffering agents to achieve a pH of 3.5 to 6.0.

25. In my opinion, the additional elements recited by the challenged dependent claims of the ’787 patent do not impart any patentability to the obvious independent claims of the ’787 patent.

## **VI. State of the Art**

### **A. Low-Concentration Atropine for the Treatment of Myopia**

#### **1. Myopia Treatment and Prevention**

26. Atropine, a nonselective muscarinic antagonist, has been extensively studied for more than a century and is known as “the oldest and most effective pharmacological treatment to inhibit the development of myopia.” Ex. 1008, 1; Ex. 1003, 1 (“Atropine eyedrops were first proposed as a treatment of myopia in the 1920s.”); Ex. 1012, 2 (“The most widely studied pharmacological agent for the inhibition of myopia progression has been atropine, a nonselective muscarinic antagonist.”).

27. In discussing treating myopia with atropine, many references discuss using specific doses of atropine. These references use the term “%” to characterize the amount of the dose (e.g. “1% atropine”). While many references do not expressly specify that the term “%” means “wt %” (weight-percent or percent-by-weight), “wt %” is a common convention in ophthalmic solutions. Therefore, a person of skill in the art would have readily understood that disclosure of a “1%” solution of atropine or “1% atropine” solution means 1% by weight (or “wt %”). Weight percent is calculated according to the equation below:

$$\text{Weight Percent} = \frac{\text{Mass of Solute (e.g. atropine)}}{\text{Mass of Solution (solute(s) + solvent (e.g. water))}} \quad (100)$$



28. For example, *Akorn* discloses that its “Atropine Sulphate Ophthalmic Solution, *USP 1%*” has approximately 10 milligrams (0.01 grams) of atropine per milliliter of solution. Ex. 1004, 2 (“Dosage Forms and Strengths”). Based on this disclosure, a POSA would understand that *Akorn*’s solution is approximately 1% by weight (wt %) atropine.<sup>2</sup>

29. To calculate the wt % of atropine in *Akorn*’s solution, a POSA would divide the mass of atropine (0.01 grams) by the total mass of the solution and multiply by 100. Because *Akorn* discloses an aqueous solution, *Akorn*’s solvent, which accounts for the bulk of the solution’s mass, is water. *See* Ex. 1004, 3; Ex. 1018, 4-5 (atropine sulfate injection, atropine sulfate solution both comprise water as the solute). Therefore, the mass of one milliliter of the solution is approximately one milliliter of water (1 mL H<sub>2</sub>O = 1 g) plus 0.01 grams of atropine. The masses of the remaining components of *Akorn*’s solution are so insignificant (e.g.  $1 \times 10^{-4}$  g of the preservative benzalkonium chloride) that the mass of those components would

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<sup>2</sup> I note also that within the specification of the ’787 patent, the modifier “wt %” is often not expressly used, even though a POSA would understand that is what is being conveyed by the patent. *See, e.g.*, Ex. 1001, 77:10-30 (Example 5) (discussing 1% Atropine Sulfate solution from Bausch & Lomb and comparing with 0.01% formulations used in the purported invention).

have a negligible effect on the weight percent calculation. The calculation below demonstrates that a POSA would understand that *Akorn*'s solution is approximately 1 wt % atropine.

$$\frac{0.01 \text{ g atropine}}{0.01 \text{ g atropine} + \sim 0.99 \text{ g H}_2\text{O}} (100) = \sim 1 \text{ wt } \%$$

30. Early clinical trials established that 1.0% and 0.5% weight percent atropine solutions were effective in reducing myopia progression. Ex. 1014, 1; Ex. 1003, 1; Ex. 1009, ¶[0006].

31. These high-concentration formulations, however, were found to induce side effects such as photophobia, cycloplegia, and mydriasis in children. Ex. 1003, 1; Ex. 1009, ¶[0006] (explaining “the compliance is poor and dropout rate is correspondingly high” due to photophobia caused by the 1% formulation); Ex. 1014, 1 (“Although 1% atropine effectively slows myopia progression, it is associated with ... poor compliance.”).

32. 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. Ex. 1003, 1; Ex. 1010, 1; Ex. 1016, 1; Ex. 1013, 1; Ex. 1009, ¶[0018]; Ex. 1012, 1; Ex. 1015, 4.

33. For instance, Lee 2006 reports investigating 0.05% atropine for prevention of myopic progression in school-aged children who could not tolerate 0.1% atropine treatment due to side effects. Ex. 1012, 2. Lee 2006 discloses a preparation of 0.05% atropine eye drops by diluting a commercial 1% atropine solution with distilled water and administration to patients by instillation. Ex. 1012, 4. Lee 2006 explains that “[t]his may also have reduced the preservative concentration, thereby decreasing the chance of allergic reaction.” Ex. 1012, 5. Lee 2006 reports observing 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.” Ex. 1012, 4.

34. Similarly, a 2007 patent application to Wu et al. acknowledges that high concentration (0.5% or 1%) atropine solutions cause 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. Ex. 1009, Abstract, ¶¶[0006], [0012], [0013], [0036]. Wu 2007 reports that administration of the lower dose atropine solutions achieved “good efficiency” in myopia prevention and “was proven to have excellent accommodation-inhibiting efficiency,” with “significantly reduced [] side-effect of photophobia.” Ex. 1009, ¶¶[0031], [0033].

35. 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, explains 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.” Ex. 1013, 1. Fang prepared topical 0.025% atropine eye drops by diluting a commercially available 0.25% atropine solution and reports that the 0.025% atropine eye drops prevented onset of myopia and myopic shift in premyopic schoolchildren with no systemic side effects. Ex. 1013, 1–4.

36. *Chia* discloses 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.” Ex. 1003, 1. *Chia* then describes its further clinical trial studies, specifically the “Atropine for the Treatment of Myopia 2” (“ATOM2”) trial, which involved administering low-concentration atropine eye drops. Ex. 1003, 1.

37. *Chia* discloses administering formulations containing 0.5%, 0.1%, or 0.01% atropine sulfate to 400 children with myopic refraction. Ex. 1003, 1. *Chia* teaches that these aqueous formulations “consisted of the appropriate dose of

atropine sulfate with 0.02% of 50% benzalkonium chloride as a preservative.” Ex. 1003, 2.

38. *Chia* observes 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.” Ex. 1003, 7. *Chia* concludes 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.” Ex. 1003, 7-8. *Chia* recommends 0.01% atropine as “a safe and effective regimen for slowing myopia progression in children.” Ex. 1003, 8.

39. *Chia* 2014 describes 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. Ex. 1016, 1. *Chia* 2014 concludes 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.” Ex. 1016, 6. *Chia* 2014 concludes 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.” Ex. 1016, 6.

40. *Wu* teaches that its compositions are useful for treating myopia, and further discloses a composition that includes “about 0.001% to about 1% by weight atropine.” Ex. 1006 ¶[0042]. *Wu* claims methods of treating myopia comprising administering a composition including about 0.001% to about 1% by weight atropine. *Id.* at 24 (claim 4). *Wu* also claims a narrower range of about 0.005% to about 0.05% by weight atropine. *Id.* (claim 5).

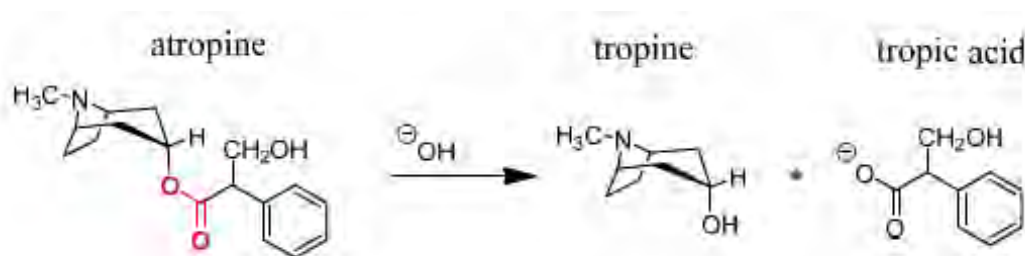
41. *Wu* further discloses that pharmaceutical compositions containing 0.001% to about 0.005% by weight atropine should have a pH of “4.5 to 8.0, e.g. about 6.9.” *Id.* ¶[0044]. To achieve this pH range and stabilize compositions for topical ocular administration, *Wu* discloses the use of buffering agents. *Id.* ¶[0040]. *Wu* further discloses that: “Suitable preservatives for ophthalmic preparations include: benzalkonium chloride, thimerosal, chlorobutanol, methyl paraben, propyl paraben, phenylethyl alcohol, edetate disodium, sorbic acid, Onamer M, or other agents known to those skilled in the art.” *Id.* *Wu* also teaches that the selected preservative should be “employed at a level of from 0.004% to 0.02%.” *Id.* *Wu* discloses that its compositions are for topical ocular administration and explains that

the solution should be “topically applied by placing one drop in the affected eye once a day.” *Id.* ¶[0044].

42. 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. Researchers had also 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

43. Atropine is a carboxylic ester. In solution, it degrades primarily via cleavage of the acyl-oxygen bond during ester hydrolysis. Ex. 1017, 1 (“Instability of atropine in solution is due mainly to the hydrolytic reaction yielding tropine and tropic acid.”); Ex. 1024, 5 (“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)

44. Ester hydrolysis reactions are catalyzed by both  $\text{H}^+$  ions (“acid-catalyzed hydrolysis”) and  $\text{OH}^-$  ions (“base-catalyzed hydrolysis”). Ex. 1005, 2 (“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. *Id.*

45. 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 hydroxy-ion  $[\text{OH}^-]$  concentration....” *Id.* at 1, 4. At low  $\text{OH}^-$  concentrations ( $\text{pH} < \sim 3$ ) the overall rate of reaction is slow, and atropine is extremely stable. *Id.* at 4-5. As  $\text{OH}^-$  concentration increases, however, the overall rate of the reaction increases, and atropine becomes more unstable. *Id.*<sup>3</sup>

#### **B. Standard Components of Ophthalmic Solutions**

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

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<sup>3</sup> pH is a measure of  $\text{H}^+$  concentration. Low pH values represent high  $\text{H}^+$  concentrations (and correspondingly low  $\text{OH}^-$  concentrations); high pH values represent low  $\text{H}^+$  concentrations (and correspondingly high  $\text{OH}^-$  concentrations).



## 1. Ophthalmic Solutions and pH

47. It was well known that ophthalmic solutions should be “formulated to be sterile, isotonic and buffered for stability and comfort.” Ex. 1019, 52. The pH of tear fluid is 7.4. *Id.* at 54.

48. 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. *Id.* at 52.

49. Remington, for example, teaches that the proper pH “often present[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 optimal stability for many drugs is generally lower, perhaps as low as 4.0–5.0.” Ex. 1019 at 52.

50. Remington also provides 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 occurring within a year. *Id.* at 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.” *Id.* at 54. Remington therefore recommends the use of buffers to maintain the pH at the appropriate level. *Id.* at 52–54.

51. To maintain the pH at the desired level, ophthalmic solutions often include buffer systems, which neutralize acid or base present in solution. *See* Ex. 1038, 2–3. Buffers are solutions comprised of (1) a weak acid or weak base and (2) the conjugate salt of that weak acid or base. Ex. 1038, 2–3. For example, citrate buffer is comprised of citric acid (a weak acid) and sodium citrate (the salt of its conjugate base). Ex. 1039, 32–33. Similarly, other common buffers include acetate buffers (comprised of acetic acid and sodium acetate) and phosphate buffers. Ex. 1038, 6; Ex. 1039, 29, 43–44; Ex. 1019, 52. Another common buffer, dibasic sodium phosphate (disodium hydrogen phosphate) and monobasic sodium phosphate (sodium dihydrogen phosphate), was used in the FDA-approved Akorn 1% atropine sulfate eye drops to maintain a pH of 3.5 to 6.0. Ex. 1004, 3.

52. For most ophthalmic solutions, including atropine, additional components are often required to adjust the solution to the desired pH. Ex. 1019, 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. Ex. 1038, 2–3, 6.

53. Buffers differ by the pH ranges at which they are most effective at maintaining the solution at a constant pH. Ex. 1038, 3; Ex. 1040, 23. A buffer's effective range depends on the properties of the weak acid and weak base used to

prepare the buffer. Ex. 1040, 23–24. It was known that buffers are most effective within  $\pm 1$  pH unit of their pKas. Ex. 1038, 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. Ex. 1040, 23; Ex. 1039, 29. Citric acid is a triprotic acid, and thus has a wider buffer range of 2.1–7.4.<sup>4</sup> Ex. 1040, 23; Ex. 1039, 32–33.

## **2. Tonicity-adjusting Agents**

54. Tonicity refers to osmotic pressure, e.g., as exerted by salts in ophthalmic solutions relative to tear fluid. Ex. 1019, 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.” *Id.* at 54. Notably, 0.9% sodium chloride was often included to provide isotonicity in a variety of known low-concentration atropine solutions. *Id.* at 52; Ex. 1041, 2.

## **3. Preservatives**

55. Preservatives had long been used in ophthalmic solutions to “prevent the growth of, or to destroy, microorganisms introduced accidentally when the

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<sup>4</sup> Triprotic acids, such as citric acid, have three hydrogen ions 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.

container is opened during use.” Ex. 1019, 55. Common preservatives include benzalkonium chloride (BAK), methylparaben, and chlorobutanol. *Id.* at 55–56; Ex. 1004, 3; Ex. 1006, ¶[0040]; Ex. 1022, 2-3; Ex. 1023, 2; Ex. 1042, 3–8.

56. BAK was long the preservative “used in the large majority of commercial ophthalmic solutions and suspensions.” Ex. 1019, 54. It was known that the concentration of BAK is typically “0.005%-0.02%” and concentrations of 0.01% were “most common.” *Id.* 54–55. Atropine solutions containing 0.01% BAK were routinely prepared, used in clinical trials, and had been approved by the FDA. Ex. 1003, 2; Ex. 1004, 3; Ex. 1006, ¶[0040]; Ex. 1022, 2-3; Ex. 1023, 2.

## **VII. The '787 Patent**

57. The '787 patent discloses ophthalmic compositions to treat myopia. Ex. 1001, abstract, 5:4–10. The '787 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.” Ex. 1001, 9:55–58.

58. The '787 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.” Ex. 1001, 10:4–14. The ’787 patent further discloses that these shortcomings can be “prevented or alleviated by formulating muscarinic antagonist (e.g., atropine) compositions at higher pH ranges.” Ex. 1001, 10:10–11.

59. The ’787 patent also discloses standard formulation components routinely used in ophthalmic compositions. Ex. 1001, 3:36–38; 3:52–62; 3:47–51. For example, the ’787 patent notes the use of sodium chloride as an osmolarity (3:36–38) and tonicity (3:52–62) adjusting agent. Similarly, the ’787 patent discloses buffering agents including borates, borate-polyol complexes, succinate, phosphate buffering agents, citrate buffering agents, acetate buffering agents, carbonate buffering agents, organic buffering agents, and amino acid buffering agents. Ex. 1001, 3:47–51.

60. The ’787 patent discloses standard storage temperatures for atropine solutions. Ex. 1001, 68:4–23. The ’787 patent also discloses a range of pH levels known to be optimal for stability of atropine (pH 3–5) up to those known to be optimal for patient comfort (pH 7.4). Ex. 1001, 7:9–16.

### **VIII. Person of Ordinary Skill in the Art**

61. As discussed above, the subject matter of the ’787 patent is directed to the composition of an FDA-approved drug (atropine) in combination with buffering agents to achieve a pH range optimum for stability and patient comfort.

62. 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 '787 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 fundamental characteristics of aqueous formulations (such as stability), and would have knowledge about drug degradation kinetics.

**IX. GROUND 1: Claims 1, 2, 4-9, and 12-19 Would Have Been Obvious Over *Chia* and *Akorn* in View of *Kondritzer***

63. The compositions claimed by independent claim 1 and dependent claims 2, 4-9, and 12-19 of the '787 patent require two components: (1) “about 0.001 wt% to about 0.05 wt%” atropine or atropine sulfate and (2) “a buffering agent to provide a pH of from about 4.8 to about 6.4.” Ex. 1001, claim 1. In my opinion, these claimed elements were taught in the prior art by *Chia* and *Akorn* in view of *Konditzer*.

**A. Motivation to Combine**

64. In 2012, *Chia* reported that 0.01% wt% atropine eye drops is effective for the treatment of myopia and reduced the side effects—and hence, patient

compliance issues—associated with higher concentration formulations. Ex. 1003, 1, 7–9. This clinical success would have motivated one of skill in the art to make and use low-concentration atropine formulations.

65. As the stability of atropine was known to be pH-dependent, it was common practice in the art to use buffering agents to regulate pH for pharmaceutical compositions containing atropine. Similarly, it was known that eye comfort was also dependent on pH. *Akorn*, a commercially available FDA-approved atropine sulfate ophthalmic solution, discloses several buffering agents to achieve a solution pH of 3.5 to 6.0 to address both stability and eye comfort.

66. In addition, *Kondritzer* provides further motivation to use *Akorn*'s buffering agents to achieve the claimed pH range. *Kondritzer* discloses that atropine is most stable at pH 3–5, and a POSA would have targeted the higher end of that range for maximum eye comfort. Using an equation derived by *Kondritzer*, a POSA would have been able to confirm that *Akorn*'s buffering agents and pH range would have provided stability under the claimed conditions.

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

67. Atropine solutions had long been used at weight percentages of 1% and 0.5% to treat myopia. Ex. 1003, 1; Ex. 1012, 4; Ex. 1008, 1. These formulations were effective, but caused several significant side effects such as photophobia,

cycloplegia, and mydriasis that resulted in poor patient compliance. Ex. 1043, 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.”); Ex. 1043, 2; Ex. 1009, ¶[0006]; Ex. 1003, 1; Ex. 1012; 1.

68. Patient compliance refers to the consistency with which a patient actually uses their prescribed medication. Ex. 1044, 4–5. Compliance is particularly important when using atropine to treat myopia because the medication must be used daily over long periods of time. Ex. 1044, 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 were known to reduce this compliance and, in turn, the clinical efficacy of atropine. Ex. 1014, 1 (“Although 1% atropine effectively slows myopia progression, it is associated with... poor compliance.”); Ex. 1009, ¶[0006] (explaining “the compliance is poor and dropout rate is correspondingly high” due to photophobia caused by the 1% and 0.5% formulations).

69. To address this issue, *Chia* reported testing 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.”

Ex. 1003, 7. *Chia* further reported that “[t]he 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.” Ex. 1003, 7-8. *Chia* also acknowledged a previous study which found similar results with 0.025% atropine. Ex. 1003, 7.

70. *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....” Ex. 1003, 7–8.

71. 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. Ex. 1012, 5 (“[N]o commercial 0.05% atropine solution was available, so the eye drops were prepared by diluting 1% atropine solution.”); Ex. 1044, 4–5.

72. Stability of ophthalmic solutions “is always a primary consideration, both in the bottle and in the tissues” (Ex. 1045, 8), and “pharmaceutical manufacturer[s] strive[] for a shelf-life measured in years.” (Ex. 1045, 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.” Ex. 1045, 16; Ex. 1035, 1–2; Ex. 1040, 7 (“[S]ince pharmaceutical standards for degradation are very exacting, even relatively slow rates can be problematic.”).

**2. A Person of Skill in the Art Would Have Been Motivated to Modify Low-Concentration Atropine Solutions with Buffering and Stabilizing Agents**

73. To address both stability and eye comfort, *Akorn* would have motivated a POSA to modify *Chia*’s low-concentration solutions with buffering and stabilizing agents.

74. As explained above (§ VI.A.2), atropine’s stability largely depends on the pH, which must be balanced against clinical efficacy. Ex. 1019, 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”); Ex. 1005, 2, 4 (Table III).

75. Optimal patient comfort, and thus patient compliance, was known to be pH 7.4, the pH of the natural tear fluid of the eye. Ex. 1019, 54. As *Kondritzer* demonstrated, however, atropine is most stable at pH 3–5. Ex. 1005, 2, 4 (Table III). Beyond pH 5, the higher OH<sup>−</sup> concentration leads to an increased rate of base-catalyzed hydrolysis and atropine becomes more unstable. *See, e.g.*, Ex. 1026, 1

(discussing the “instability of atropine solutions... outside the range of pH 3 to 5”); Ex. 1042, 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* Ex. 1005, 2 (noting that the art found that “[a]n isotonic atropine-borax-boric acid solution deteriorated 44% in one month”); Ex. 1046, 1 (“[T]he stability of atropine is limited .... Upon storage, degradation reactions can take place.”).

76. Formulating atropine at pH 3–5, however, was known to be suboptimal as it causes patient discomfort and irritation. Ex. 1034, 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 its low-concentration formulations. Ex. 1014, 1 (“Although 1% atropine effectively slows myopia progression, it is associated with... poor compliance.”); Ex. 1009, ¶[0006] (explaining “the compliance is poor and dropout rate is correspondingly high” due to photophobia caused by the 1% formulation).

77. Formulating atropine at these acidic pHs was also known to reduce 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.” Ex. 1045, 8; *see also* Ex. 1035, 2 (“[T]ears are mainly responsible for the short residence time and low absorption of drugs applied topically

to the eye.”); Ex. 1047, 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....”).

78. 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.

**B. Reasonable Expectation of Success**

79. A POSA also would have had a reasonable expectation of achieving the compositions and treatment methods recited by claims 1, 2, 4-9, and 12-19 of the '787 patent.

80. Buffering agents are common components in ophthalmic compositions to stabilize and increase patient comfort. *See* § VI.B.1. In view of this common practice, a POSA would have had a considerable expectation of success using *Akorn's* buffering agents to achieve a pH range of 3.5-6.0 to stabilize *Chia's* low concentration atropine formulations. This would have required nothing more than routine experimentation, given all that was known in the art regarding how atropine stability correlates with the extent of ester hydrolysis and thus is dependent on both pH and temperature.

81. Moreover, in view of *Kondritzer*'s disclosure that optimum atropine stability in aqueous solutions is at pH 3-5, *Kondritzer* would have confirmed this expectation of success. Ex. 1005, 4 (showing decreasing atropine stability as pH increases to 7.0). A POSA would have understood that the composition would remain stable at the higher end of the range while increasing patient comfort. By targeting the higher end of *Akorn*'s pH range in order to optimize stability in view of patient comfort, a POSA would have had a reasonable expectation of success in combining the teachings of *Chia* and *Akorn* to achieve the claimed atropine formulations. Ex. 1019, 1569 (ophthalmic preparations should be formulated at a pH equivalent to the tear fluid value of 7.4).

### **C. Claim-by-Claim Analysis**

#### **1. Claim 1**

82. Claim 1 of the '787 patent recites: "A stabilized ophthalmic composition for treating pre-myopia, myopia, or progression of myopia, comprising from about 0.001 wt % to about 0.05 wt % of atropine or atropine sulfate and water, wherein the stabilized ophthalmic composition further comprises a buffering agent to provide a pH of from about 4.8 to about 6.4, wherein the stabilized ophthalmic composition is a liquid, and wherein the stabilized ophthalmic composition comprises less than about 10% of a degradant formed from degradation of the atropine or atropine sulfate after an extended period of time of at least 2 weeks under

a storage temperature of from about 20° C. to about 70° C. and relative humidity from about 50% to about 80%.” Ex. 1001, claim 1.

a. **1[a] “A stabilized ophthalmic composition for treating pre-myopia, myopia, or progression of myopia, comprising...”**

83. To the extent that the preamble is limiting, *Chia* and/or *Akorn* renders it obvious.

84. *Chia* discloses 0.01% atropine formulated as eye drops. Ex. 1003, 1-2. As was well understood in the art, eye drops are an ophthalmic solution. Ex. 1034, 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.”); Ex. 1019, 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.”).

85. A POSA would have recognized that ophthalmic solutions are necessarily ophthalmic compositions. Ex. 1048, 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); Ex. 1049, ¶[0021]. As such, the atropine eye drops discussed by *Chia* teach “an ophthalmic composition.”

86. Further, a POSA would have recognized that *Chia*'s "prepackaged" composition, administered over the course of a multi-year study, would almost certainly have included components to reduce degradation of atropine—i.e., a POSA would have recognized that the formulation in *Chia* was stabilized. Ex. 1003 at 2. Given the well-understood stability characteristics of atropine, a POSA would have recognized that the authors of the *Chia* study would not have used an unstable composition. Compositions that are not stable would render the results of the study meaningless and risk patient safety. Thus, *Chia* renders obvious claim 1's "stabilized ophthalmic composition for treating pre-myopia, myopia, or progression of myopia."

87. In addition to this understanding of *Chia*'s composition, *Akorn* discloses an FDA-approved, commercially available atropine sulfate ophthalmic solution. Ex. 1004 at 3. A POSA would have understood that *Akorn* discloses a stabilized ophthalmic composition via its disclosure of several buffering agents to adjust pH to a range of 3.5-6.0, including monobasic sodium phosphate, hydrochloric acid and/or sodium hydroxide. Ex. 1004 at 3. This understanding would have been reinforced by a POSA's knowledge of FDA requirements to assess the stability characteristics of drug products and because atropine has been used to control myopia for decades. *See* Ex. 1003; Ex. 1008). Accordingly, *Chia* and/or *Akorn* disclose a "stabilized" ophthalmic composition.

**b. 1[b] “from about 0.001 wt % to about 0.05 wt % of atropine or atropine sulfate and water, wherein...”**

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

89. *Chia* discloses that atropine is a muscarinic antagonist (Ex. 1003, 6), 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 Ex. 1003, 7–8. *Chia*’s concentration falls squarely within the claimed range and renders this limitation obvious.

90. *Chia*’s disclosure that “0.01% atropine is not commercially available yet,” and the 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,” would have motivated one of skill in the art to formulate low-concentration atropine solutions. Ex. 1003, 8.

91. The obviousness of concentrations of “about 0.001 wt % to about 0.05 wt %” atropine is further underscored by the art as a whole, which shows the efficacy of low-concentration atropine at concentrations within the claimed range. § VI.A.1. For example, Fang 2010 specifically discloses 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.” Ex. 1013, 1; *see also* Ex. 1006 ¶[0042], claim 5; Ex. 1016, 6.

**c. 1[c] “the stabilized ophthalmic composition further comprises a buffering agent to provide a pH of from about 4.8 to about 6.4, wherein”**

92. Limitation 1[c] is rendered obvious by *Akorn* in view of *Kondritzer*.

93. This claimed range overlaps with the pH range at which atropine was known to be most stable (pH 3–5), and is near the pH that was known to be most desirable for clinical administration (pH 7.4). § VI.A-B. *Akorn* discloses a stabilized ophthalmic composition, as discussed above. *Akorn* further discloses that dibasic sodium phosphate, monobasic sodium phosphate, hydrochloric acid and/or sodium hydroxide “may be added to adjust pH (3.5 to 6.0).” Ex. 1004, 3; *see also* Ex. 1022 (same); Ex. 1023 (same). Therefore, *Akorn*’s composition significantly overlaps with and renders obvious the claimed pH range and discloses several buffering agents to “provide a pH of from about 4.8 to 6.4,” as in claim 1.

94. In teaching ingredients to adjust pH, *Akorn* explicitly discloses buffering agents, including dibasic sodium phosphate (disodium hydrogen phosphate) and monobasic sodium phosphate (sodium dihydrogen phosphate), which are also encompassed by dependent claims 6 and 7. Ex. 1004, 3. *Id.*

95. The art shows that *Akorn* discloses standard buffering agents, further highlighting the obviousness of using a buffering agent. Ex. 1019, 52 (disclosing a

formulation “suitable for salts of Atropine” containing sodium acid phosphate anhydrous ( $\text{NaH}_2\text{PO}_4$ ) and disodium phosphate anhydrous ( $\text{Na}_2\text{HPO}_4$ )); Ex. 1026, 4–5 (disclosing that “acetic acid, acetate, citric acid, citrate, phosphoric acid, phosphate” are “commonly used as buffering agents”). As *Akorn* identifies several specific buffering agents, it renders the broader claim 1 “buffering agent” obvious.

96. It was also well understood that pH is a result-effective variable for stability and patient comfort in atropine ophthalmic formulations. *Kondritzer* demonstrates that the stability of atropine is “governed by the hydroxyl-ion concentration.” Ex. 1005, 1. Specifically, *Kondritzer* derived an equation “predicting the rate of proton hydrolysis at any particular temperature and hydrogen ion concentration” (*Id.* at 2), which shows 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,” (*Id.* at 2), and further discloses “[c]alculated half lives of solutions of atropine over the region of pH 2 to 7” (*Id.* at 4). *Kondritzer* shows that atropine is most stable at pH 3–5. *Id.* at 4 (The half life at any hydrogen ion concentration between pH 3 and 5 is so great that its experimental determination is not practical.”).

97. 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.” Ex. 1019, 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.” Ex. 1019, 52.

98. 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° C until pH 6, or over, was reached, when hydrolysis became very rapid.” Ex. 1005, 2. Similarly, it was textbook 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” (Ex. 1019, 54) and that “solution *pH must be selected* for optimum drug stability.” (Ex. 1019, 52) (emphasis added). Accordingly, it would have been obvious to optimize the pH of the compositions recited by claim 1 for stability and comfort.

99. Further, based on the teachings of *Akorn* and *Kondritzer*, it would have been obvious to formulate the claimed atropine solutions at pH 5–6. Starting from 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 pH to as close as possible to 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 pH could be increased until around pH 6, where “hydrolysis became very rapid.” Ex. 1005, 2. The obviousness of the claimed pH was reinforced by *Akorn*’s disclosure of buffering agents to provide a pH range of 3.5 to 6.0 for an atropine ophthalmic formulation.

100. Finally, a POSA’s motivation and reasonable expectation of success for the pH range of about 4.8 to about 6.4 was further bolstered by the art as a whole, which shows that this range was bracketed by pH ranges already demonstrated to work for atropine in the treatment of myopia. Ex. 1050, 2 (“The pH value of the product should be 4.0~6.0.”); Ex. 1041, 3 (“The product showed a pH of 4.0–6.0.”).

**d. 1[d] “the stabilized ophthalmic composition is a liquid, and wherein”**

101. Limitation 1[d] is rendered obvious by *Chia* and/or *Akorn*.

102. *Chia* discloses 0.01% atropine formulated as eye drops. Ex. 1003, 1-2. As was well understood in the art, eye drops are a liquid ophthalmic solution. *E.g.*, Ex. 1034, 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.”) (emphasis added). A POSA would have understood

that *Chia*'s eye drops, which were an aqueous solution (i.e. a solution where the solvent is water), were liquids.

103. Likewise, *Akorn* discloses an aqueous liquid solution that is administered in the form of eyedrops. Ex. 1004. Further confirming that *Akorn*'s solution is a liquid, *Akorn* discloses its atropine sulfate concentration in the form of milligram (mg) per milliliter (mL) and explains that the solution is supplied in dropper bottles with 2, 5, and 15 mL fills.

- e. **1[e] “the stabilized ophthalmic composition comprises less than about 10% of a degradant formed from degradation of the atropine or atropine sulfate after an extended period of time of at least 2 weeks under a storage temperature of from about 20° C. to about 70° C. and relative humidity from about 50% to about 80%.”**

104. Limitation 1[e] is rendered obvious by *Chia* and *Akorn* in view of *Kondritzer*.

105. The percentage of “a degradant” under a particular set of conditions is an inherent property of the claimed ophthalmic composition. Accordingly, a POSA would have understood the teachings of *Chia*, *Akorn*, and *Kondritzer* to necessarily disclose limitation 1[e], and would have confirmed this understanding using *Kondritzer*.

106. *Kondritzer* shows that atropine degradation was a predictable function of pH and temperature. Ex. 1005, 1, 4-5. *Kondritzer* derives an equation to predict

the pH at which atropine would be most stable for any hydrogen ion concentration. Ex. 1005, 2. To test the validity of the equation, *Kondritzer* measures the rate of hydrolysis ( $k$ ) of atropine at different pHs. Ex. 1005, 2–5. *Kondritzer* reports that the half-lives of atropine at various temperatures and pHs calculated from the experimental data matched those predicted by the theoretical equations. Ex. 1005, 4 (Table I). In short, *Kondritzer* shows that by modulating pH and/or temperature, varying levels of atropine stability (and thus varying levels of atropine “degradant”) can be achieved for various time intervals. This is a recipe for routine experimentation.

107. In addition to being determinable by routine experimentation, *Kondritzer* shows that atropine stability (and thus atropine “degradants”) is also theoretically predictable. For example, *Kondritzer* discloses the predicted half-lives of atropine at pH levels falling within the range recited by limitation 1[e] and encompassing the pH range of 4.8 to 6.4. Ex. 1005, 4 (Table III). As shown in Figure 10, below, *Kondritzer* teaches that at 20° C and pH 5, the half-life of atropine is 266 years; and at 20° C and pH 6, the half-life of atropine is 27 years.

TABLE III.—PREDICTED STABILITY OF ATROPINE IN AQUEOUS SOLUTIONS  $t_{1/2}$  IN YEARS

Temp., °C.	7.0	6.0	5.0	pH 4.5	4.0	3.0	2.0
20	2.7	27	266	811	1800	548	56
30	0.61	6.1	61	194	473	203	21
40	0.16	1.6	16	49	135	80.7	8.5
50	..	0.44	4.4	13.8	39.2	33.3	3.6
60	..	0.14	1.4	4.3	12.9	14.4	1.6
70	..	..	0.46	1.39	4.34	6.52	0.76
80	..	..	0.17	0.5	1.63	3.04	0.37
90	..	..	..	0.21	0.65	1.48	0.19
100	..	..	..	0.1	0.31	0.76	0.10

Figure 10. Atropine Stability Predictions from *Kondritzer*

Based on this chart, I calculated the time it would take for “10%” of atropine to degrade (as claimed in claim 1 of the ’787 patent) at pH 5 and 20° C. This is done utilizing a degradation ratio of 0.9 (90%) based on the data from *Kondritzer*, as shown in Equation 1, below.

$$\text{Stability (years)} = \left( \frac{\ln(0.9) (266)}{\ln(0.5)} \right) = 40.4$$

108. As shown above, at 20° C and pH 5, a POSA would reasonably expect the compositions of claim 1 to comprise 90% atropine for approximately 40.4 years. At these parameters, which fall within the limitations of claim 1, *Kondritzer* shows that atropine would readily exceed the stability requirements of limitation 1[e], which allows for up to 10% degradation after at least two weeks. A POSA would have understood how to perform this and other, similar stability calculations based on *Kondritzer* (i.e., at other pHs and temperatures). Even at 70° C and pH 5, for example, *Kondritzer*’s theoretical numbers suggest that approximately 90% atropine

would persists for approximately 3-4 weeks, still above the claimed “2 weeks” required by claim 1.

109. A relative humidity from about 50% to about 80% would not affect the stability of the claimed aqueous atropine composition. The claimed atropine composition is an aqueous solution. As an aqueous solution, the relative humidity in solution would be 100%. Therefore the relative humidity of the ambient air, whether it is 50%, 60%, or even 90%, would not be expected to affect the stability of atropine molecules that are in solution. Those molecules are already dissolved in, and interacting with, the water molecules in solution.

## **2. Claims 2, 4, and 5**

110. Dependent claims 2, 4, and 5 all recite stabilized ophthalmic compositions with narrower ranges of atropine or atropine sulfate concentrations. Dependent claim 2 recites: “The stabilized ophthalmic composition of claim 1, wherein the atropine or atropine sulfate is present in the composition at a concentration of from about 0.001 wt % to about 0.03 wt %.” Ex. 1001, claim 2. Similarly, dependent claim 4 recites: “The stabilized ophthalmic composition of claim 1, wherein the atropine or atropine sulfate is present in the composition at a concentration of from about 0.01 wt % to about 0.02 wt %.” *Id.* at claim 4. Last, dependent claim 5 recites: “The stabilized ophthalmic composition of claim 1,



wherein the atropine or atropine sulfate is present in the composition at a concentration of about 0.01 wt %.” *Id.* at claim 5.

111. As explained above (§ IX.C.1), claim 1 is rendered obvious by *Chia* and *Akorn* in View of *Kondritzer*. *Chia* discloses these additional limitations of claims 2, 4, and 5 as well.

112. As explained above (§ IX.C.1), *Chia* discloses administration of 0.01% atropine compositions, a muscarinic agent at a concentration within the ranges recited by claim 1. Ex. 1003, 1. As *Chia*’s therapeutically effective 0.01% atropine concentration falls squarely within the ranges and values recited by claims 2, 4, and 5, those claims would have been obvious for the same reasons explained above for claim 1. § IX.C.1.

113. Thus, a POSA would have been motivated to make an ophthalmic composition as recited by claim 1 which had an atropine concentration of one of: about 0.001 wt % to about 0.03 wt %, about 0.01 wt % to about 0.02 wt %, or about 0.01 wt %, and would have had a reasonable expectation of success in achieving the same.

### **3. Claims 6 and 7**

114. Dependent claim 6 recites: “The stabilized ophthalmic composition of claim 1, wherein the buffering agent comprises a borate, a boratepolyol complex, a phosphate buffering agent, a citrate buffering agent, an acetate buffering agent, a

carbonate buffering agent, an organic buffering agent, an amino acid buffering agent, or a combination thereof.” Ex. 1001, claim 6. Dependent claim 7 recites: “The stabilized ophthalmic composition of claim 1, wherein the buffering agent comprises sodium dihydrogen phosphate, disodium hydrogen phosphate, or a combination thereof.” *Id.* at claim 7.

115. As discussed above (§ IX.C.1), claim 1 is rendered obvious by *Chia* and *Akorn* in View of *Kondritzer*. *Akorn* discloses the additional limitations of claims 6 and 7 as well.

116. *Akorn* explicitly discloses two phosphate buffering agents encompassed by claims 6 and 7. Ex. 1004, 3. Specifically, *Akorn* discloses dibasic sodium phosphate (disodium hydrogen phosphate) and monobasic sodium phosphate (sodium dihydrogen phosphate). *Id.* Accordingly, *Akorn* discloses the additional limitations of claims 6 and 7 and renders them obvious.

117. The art confirms that *Akorn* discloses standard buffering agents, further highlighting the obviousness of using these buffers in claim 1’s compositions. Ex. 1019, 52 (disclosing a formulation “suitable for salts of Atropine” containing sodium acid phosphate anhydrous ( $\text{NaH}_2\text{PO}_4$ ) and disodium phosphate anhydrous ( $\text{Na}_2\text{HPO}_4$ )); Ex. 1026, 4–5 (disclosing that “acetic acid, acetate, citric acid, citrate, phosphoric acid, phosphate” are “commonly used as buffering agents”).

118. As the specific buffer agents recited by claim 7 were obvious, claim 6, which recites general categories of buffer agents, was likewise obvious.

119. Thus, a POSA would have been motivated to formulate a stabilized ophthalmic composition of claim 1, wherein the buffering agent comprises a borate, a boratepolyol complex, a phosphate buffering agent, a citrate buffering agent, an acetate buffering agent, a carbonate buffering agent, an organic buffering agent, an amino acid buffering agent, or a combination thereof and would have had a reasonable expectation of success in achieving the same.

#### **4. Claims 8 and 9**

120. Dependent claim 8 recites: “The stabilized ophthalmic composition of claim 1, wherein the stabilized ophthalmic composition further comprises a tonicity adjusting agent.” Ex. 1001, claim 8. Dependent claim 9 recites: “The stabilized ophthalmic composition of claim 8, wherein the tonicity adjusting agent comprises a halide salt of a monovalent cation.” *Id.* at claim 9.

121. As discussed above (§ IX.C.1), claim 1 is rendered obvious by *Chia* and *Akorn* in View of *Kondritzer*. *Chia* and *Akorn* in view of the knowledge of a POSA render these additional limitations obvious.

122. Tonicity is a measure of the effective osmotic pressure gradient exerted by salts in aqueous solution. Ex. 1019, 54 (“Tonicity refers to the osmotic pressure exerted by salts in aqueous solution.”). It was textbook knowledge that “isotonicity

always is desirable and particularly is important in intraocular solutions.” Ex. 1019, 54. A POSA would have recognized that decreasing the concentration of atropine sulfate (a salt) from *Akorn*’s 1% atropine sulfate solution to *Chia*’s 0.01% atropine sulfate solution would require the addition of a tonicity adjusting agent to maintain eye comfort.

123. In addition, “[a]n ophthalmic solution is considered isotonic when its tonicity is equal to that of an 0.9% sodium chloride solution.” *Id.* An agent that adjusts tonicity, for example, sodium chloride, will necessarily adjust osmolarity. Ex. 1051, 16–19; *see also* Ex. 1051, 17 (disclosing adjustment of osmolarity with “a typical electrolyte like sodium chloride”).

124. As these examples demonstrate, the inclusion of sodium chloride in formulations suitable for atropine reflected standard practice, and it would have been obvious to include in the compositions of claims 8 and 9. As sodium chloride is a halide salt of a monovalent cation (salt comprising one halide anion,  $\text{Cl}^-$ , and one monovalent cation,  $\text{Na}^+$ ), it renders claim 9 was obvious. Likewise, claim 8, which recites all tonicity adjusting agents, was obvious.

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

## 5. Claims 12, 13, and 14

126. Dependent claim 12 recites: “The stabilized ophthalmic composition of claim 1, wherein the stabilized ophthalmic composition further comprises a preservative.” Ex. 1001, claim 12. Dependent claim 13 recites: “The stabilized ophthalmic composition of claim 12, wherein a concentration of the preservative is from about 0.0001% to about 1%.” *Id.* at claim 13. Dependent claim 14 recites: “The stabilized ophthalmic composition of claim 12, wherein the preservative is selected from benzalkonium chloride, cetrimonium, sodium perborate, stabilized oxychloro complex, polyquaternium-1, chlorobutanol, edetate disodium, polyhexamethylene biguanide, or combinations thereof.” *Id.* at claim 14.

127. As explained above (§ IX.C.1), claim 1 is rendered obvious by *Chia* and *Akorn* in View of *Kondritzer*. *Chia* and/or *Akorn* disclose these additional limitations of claims 12, 13, and 14 as well.

128. Claim 14 recites a list of well-known, traditional preservatives used in atropine and other ophthalmic compositions. Ex. 1019, 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.**” Ex. 1003, 2 (emphasis added).

129. *Chia*’s disclosure reflected standard practice in the art. Ex. 1019, 54–56 (disclosing atropine formulations comprising benzalkonium chloride and teaching

that it is “by far, the most common preservative used in ophthalmic preparations.”); Ex. 1042, 20 (disclosing 0.02% benzalkonium chloride as preservative for atropine formulations); Ex. 1004, 3 (“benzalkonium chloride 0.1 mg (0.01%)”); Ex. 1046, 2 (“standard solution preparation” comprising “0.2 mg benzalkonium chloride”). *Akorn* confirms this standard practice and discloses “benzalkonium chloride 0.1 mg (0.01%)” as an inactive ingredient. Ex. 1004, 3. Previous publications from *Akorn* regarding its atropine sulfate solution confirm that *Akorn*’s benzalkonium chloride is used as a preservative. *See, e.g.*, Ex. 1022, 1-2 (“Preservative: Benzalkonium Chloride 0.1 mg (0.01%)”); Ex. 1023, 2 (same).

130. Based on these disclosures, claim 13 recites a well-known concentration range for traditional preservatives used in ophthalmic solutions containing atropine. The concentrations of benzalkonium chloride disclosed in *Chia* (0.02% of 50% benzalkonium chloride) and *Akorn* (benzalkonium chloride 0.1 mg (0.01%)) are squarely within the claimed range (from about 0.0001% to about 1%).

131. As the specific preservatives recited by claim 14 were obvious, claim 12, which recites all preservatives, was likewise obvious. Similarly, as the specific concentration range recited by claim 13 were obvious, claim 12, which recites preservatives at any concentration, is likewise obvious.

132. 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, polyquaternium-1, chlorobutanol, edetate disodium, polyhexamethylene biguanide, or combinations thereof, and would have had a reasonable expectation of success in achieving the same at the claimed concentration ranges.

## **6. Claim 15**

133. Dependent claim 15 recites: “The stabilized ophthalmic composition of claim 1, wherein the stabilized ophthalmic composition is essentially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof.” Ex. 1001, claim 15.

134. As explained above (§ IX.C.1), claim 1 is rendered obvious by *Chia* and *Akorn* in View of *Kondritzer*. *Chia* and *Akorn* disclose the additional limitation of claim 15 as well.

135. *Chia* discloses slowing the progression of myopia with atropine formulations that do not contain procaine and benactyzine. Ex. 1003, 1. Similarly, *Akorn* discloses an atropine sulfate ophthalmic solution that does not list procaine or benactyzine as ingredients. Ex. 1004, 3.

136. The art demonstrates that atropine is rarely, if ever, administered with procaine or benactyzine to treat myopia. Ex. 1013, 1–2 (disclosing treatment of myopia with low-concentration atropine free of procaine and benactyzine); Ex. 1016, 13–14 (same); Ex. 1041, 2 (disclosing a process of preparing atropine

formulation that does not include procaine or benactyzine.); Ex. 1019, 52 (disclosing a standard atropine formulation that does not include procaine or benactyzine).

137. It would have been obvious to formulate atropine compositions in the same way shown to be effective to treat myopia—“essentially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof.”

138. Thus, a POSA would have been motivated towards an ophthalmic composition as recited by claim 1 that was essentially free of procaine, benactyzine, and their pharmaceutically acceptable salts, and would have had a reasonable expectation of success in achieving the same.

## **7. Claims 16 and 17**

139. Dependent claim 16 recites: “The stabilized ophthalmic composition of claim 1, wherein the stabilized ophthalmic composition is topically administered.” Ex. 1001, claim 16. Dependent claim 17 recites: “The stabilized ophthalmic composition of claim 1, wherein the stabilized ophthalmic composition is administered by instillation.” *Id.* at claim 17.

140. As explained above (§ IX.C.1), claim 1 is rendered obvious by *Chia* and *Akorn* in View of *Kondritzer*. *Chia* and/or *Akorn* disclose these additional limitations of claims 16 and 17 as well.

141. *Chia* discloses an atropine composition formulated for administration as “eyedrops.” Ex. 1003. Likewise, *Akorn* advises that its solution should be



“topically” administered to the eye in the form of drops. Ex. 1004. *Akorn* characterizes this topical administration as “instillation” of its atropine sulfate ophthalmic solution. *Id.*

142. The art shows that *Chia* and/or *Akorn*’s use of atropine eye drops was standard practice in the art. Specifically, topically administering ophthalmic solutions by instillation, including solutions containing atropine, was common practice in the art. Ex. 1019 (“The instillation of eyedrops remains ... one of the more accepted means of topical drug delivery.”); Ex. 1048, 18:2–4 (“[R]eduction in myopia progression with atropine eye drops observed in both studies....”); Ex. 1013, 1 (Patients “received 0.025% atropine eye drops at bedtime every night.”); Ex. 1012, 1 (“The results of this study demonstrate that, with regular instillation, topical 0.05% atropine is an effective agent for controlling myopia progression....”).

143. Thus, a POSA would have been motivated towards the ophthalmic composition of claim 1 that was topically “topically administered” “by instillation,” and would have had a reasonable expectation of success in achieving the same.

## **8. Claim 18**

144. Dependent claim 18 recites: “The stabilized ophthalmic composition of claim 1, wherein the stabilized ophthalmic composition is administered through an eye drop bottle containing the stabilized ophthalmic composition.” Ex. 1001, claim 18.

145. As explained above (§ IX.C.1), claim 1 is rendered obvious by *Chia* and *Akorn* in View of *Kondritzer*. *Akorn* discloses this additional limitation of claim 18 as well.

146. As discussed above, *Akorn* discloses that its solution should be “topically” administered to the eye via eyedrop instillation. Ex. 1004, 4. *Akorn* further discloses that its atropine sulfate ophthalmic composition “is supplied in a plastic **dropper bottle** with a red cap.” *Id.* (emphasis added).

147. Moreover, as explained above, administering atropine solutions via eye drops was standard practice in the art. *See* § IX.C.1. Correspondingly, A POSA would have understood that using a dropper bottle to deliver the eye drops was also common practice. *See, e.g.*, Ex. 1019, 49 (explaining “How to Use Eyedrops” and instructing how to use various types of eye drop bottles).

148. Thus, a POSA would have been motivated towards the stabilized ophthalmic composition of claim 1 that is administered through an eye drop bottle containing the stabilized ophthalmic composition, and would have had a reasonable expectation of success in achieving the same.

## 9. Claim 19

149. Dependent claim 19 recites: “A method of treating the pre-myopia, myopia, or progression of myopia in an individual in need thereof, comprising

administering to an eye of the individual an effective amount of the stabilized ophthalmic composition of claim 1.” Ex. 1001, claim 19.

150. As discussed above (§ IX.C.1), claim 1 is rendered obvious by *Chia* and *Akorn* in View of *Kondritzer*. *Chia* and *Akorn* in view of *Kondritzer* disclose this additional limitation of claim 19 as well.

151. *Chia* teaches that administration of its 0.01% atropine solution, via eyedrops, was effective to treat myopia and progression of myopia. Ex. 1003, 1 (determining 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.). Thus, a POSA would have found it obvious to use the solutions of claim 1 to treat pre-myopia, myopia, or progression of myopia.

152. Thus, a POSA would have been motivated towards a method of treating pre-myopia, myopia, or progression of myopia in an individual in need thereof, comprising administering to an eye of the individual an effective amount the stabilized ophthalmic composition of claim 1, and would have had a reasonable expectation of success in achieving the same.

**X. GROUND 2: Claims 1, 2, 4-9, and 12-19 Would Have Been Obvious Over *Chia* and *Akorn* in View of *Lund***

153. As discussed above, the compositions and their uses of independent claim 1 of the '787 patent require two components: (1) “about 0.001 wt% to about 0.05 wt%” atropine or atropine sulfate and (2) “a buffering agent to provide a pH of from about 4.8 to about 6.4.” Ex. 1001, claim 1. In my opinion, these claimed elements were taught in the prior art by *Chia* and *Akorn* in view of *Lund*.

**A. Motivation to Combine**

154. *Chia* discloses low-concentration atropine compositions within the claimed concentration range. *See infra*, §§ IX.A, IX.C.1. *Akorn* explicitly discloses several buffering agents to achieve a solution pH that significantly overlaps with the claimed pH range. *Id.*

155. Like *Kondritzer*, *Lund* provides further motivation to use *Akorn*’s buffering agents to achieve the claimed pH range. *Lund* discloses that atropine is most stable at pH 2–5.4 within a broader range of pH 1.0–6.0 (Ex. 1007, 1, 10), and a POSA would have targeted the higher end of those ranges for maximum eye comfort. Using the information and equations derived by *Lund*, a POSA would have confirmed that *Akorn*’s buffering agents and pH range would have provided stability under the claimed conditions.

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

156. *Chia* would have provided a POSA the motivation to formulate low-concentration atropine formulations. *See infra*, §§ IX.A, IX.C.1.

**2. A Person of Skill in the Art Would Have Been Motivated to Modify Low-Concentration Atropine Solutions with Buffering and Stabilizing Agents**

157. To address the twin goals of stability and eye comfort, *Akorn* would have motivated a POSA to modify *Chia*'s low-concentration solutions with buffering and stabilizing agents. *See infra*, §§ IX.A, IX.C.1.

158. Moreover, *Lund* demonstrates that atropine is most stable at pH 2–5.4. Ex. 1007, 10. As explained above, beyond a pH of about 5, the higher OH<sup>−</sup> concentration leads to an increased rate of base-catalyzed hydrolysis and atropine becomes more unstable. § IX.A. Further, formulating atropine compositions at the low end of pH 2-5.4 is suboptimal for patient comfort and reduces patient compliance. *Id.* Accordingly, using *Akorn*'s buffering agents, a POSA would have targeted the higher end of the known pH range, according to *Lund*, for maximum stability and patient comfort.

159. 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.

**B. Reasonable Expectation of Success**

160. A POSA also would have had a reasonable expectation of achieving the compositions recited by the '787 patent.

161. As explained above, buffering agents are common components in ophthalmic compositions to stabilize and increase patient comfort, and a POSA would have had a considerable expectation of success using *Akorn's* buffering agents to stabilize *Chia's* low concentration atropine formulations. § IX.A. This could have been achieved simply by using the formulation and pH range disclosed in *Akorn*, or else via routine experimentation given the known chemistry of atropine hydrolysis at varying pHs and temperatures.

162. Further, in view of *Lund's* disclosure that optimum atropine stability in aqueous solutions is at pH 2-5.4, *Lund* would have confirmed this expectation of success. Ex. 1007, 10. A POSA also would have understood that the composition would remain stable at the higher end of the range while increasing patient comfort. By targeting the higher end of *Akorn's* disclosed pH range in order to optimize stability in view of patient comfort, a POSA would have had a reasonable expectation of success in combining the teachings of *Chia* and *Akorn* to achieve the

claimed atropine formulations. Ex. 1019, 1569 (ophthalmic preparations should be formulated at a pH equivalent to the tear fluid value of 7.4).

### **C. Claim-by-Claim Analysis**

#### **1. Claim 1**

163. Claim 1 of the '787 patent recites “A stabilized ophthalmic composition for treating pre-myopia, myopia, or progression of myopia, comprising from about 0.001 wt % to about 0.05 wt % of atropine or atropine sulfate and water, wherein the stabilized ophthalmic composition further comprises a buffering agent to provide a pH of from about 4.8 to about 6.4, wherein the stabilized ophthalmic composition is a liquid, and wherein the stabilized ophthalmic composition comprises less than about 10% of a degradant formed from degradation of the atropine or atropine sulfate after an extended period of time of at least 2 weeks under a storage temperature of from about 20° C. to about 70° C. and relative humidity from about 50% to about 80%.” Ex. 1001, claim 1.

#### **a. 1[a] “A stabilized ophthalmic composition for treating pre-myopia, myopia, or progression of myopia, comprising...”**

164. As discussed above, to the extent that the preamble is limiting, *Chia* and/or *Akorn* renders it obvious. § IX.C.1.a.

**b. 1[b] “from about 0.001 wt % to about 0.05 wt % of atropine or atropine sulfate and water, wherein...”**

165. As discussed above, limitation 1[b] is rendered obvious by *Chia*.

§ IX.C.1.b.

**c. 1[c] “the stabilized ophthalmic composition further comprises a buffering agent to provide a pH of from about 4.8 to about 6.4, wherein”**

166. Limitation 1[c] is rendered obvious by *Akorn* in view of *Lund*.

167. This claimed range overlaps with the pH at which atropine was known to be most stable (pH 2–5.4) and is near the pH that was most desirable for clinical administration (pH 7.4). § VI.A-B. As discussed above, *Akorn* discloses a stabilized ophthalmic composition that comprises buffering agents to achieve a solution pH of 3.5 to 6.0. § IX.C.1.c.

168. It was also well understood that pH is a result-effective variable for stability and patient comfort. *Lund* teaches that atropine has maximum stability in the pH range 1-6 (more specifically, pH 2.0-5.4) and that the stability is influenced by pH and temperature *See e.g.*, Ex. 1007, 7 (Table 2). Specifically, *Lund* teaches that “[i]n the ranges pH < 2 and pH > 6... the stability of atropine could be computed from [equation] 12,” and explains that “[a]s the hydrolysis of atropine was a first-order reaction, the half life of atropine could be computed[.]” *Id.* at 11-12.



169. 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.” Ex. 1019, 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.” Ex. 1019, 52.

170. Optimizing pH for atropine solutions for stability and comfort within the known range was routine. For example, *Lund* reviewed the results from numerous prior studies examining the stability of atropine at various pH levels, noting, e.g., “[f]rom the results it is seen that the decrease in atropine in the pH range 2-4 is due to both hydrolysis and dehydration” while providing calculated values for atropine  $t_{1/2}$  “in the pH range where atropine has its maximum stability... in Table 6.” Ex. 1007, 6, 12. Similarly, it was textbook 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” (Ex. 1019, 54) and that “solution **pH must be selected** for optimum drug stability.” (Ex. 1019, 52) (emphasis added). Accordingly, it would have been obvious to optimize the pH of the compositions recited by claim 1 for stability and comfort.

171. Further, based on the teachings of *Akorn* and *Lund*, it would have been obvious to formulate the claimed atropine solutions at pH 5–6. This range falls within in the claimed pH range of about 4.8 to about 6.4, and also would have rendered the claimed limitation obvious. A POSA would have been motivated to increase the pH to as close as possible to pH 7.4, where patient comfort, and thus, patient compliance and clinical efficacy, was optimal. Based on *Lund*, a POSA would have reasonably expected that pH could be increased until around pH 6, which is the high end of the range within which “atropine has the maximum stability.” Ex. 1007, 3 (citing *Kondritzer*). The obviousness of the claimed pH was reinforced by *Akorn*’s disclosure of buffering agents to provide a pH range of 3.5 to 6.0.

172. Finally, a POSA’s motivation and reasonable expectation of success for the pH range of about 4.8 to about 6.4 was further bolstered by the art as a whole, which shows that this range was bracketed by pH ranges already demonstrated to work for atropine in the treatment of myopia. Ex. 1050, 2 (“The pH value of the product should be 4.0~6.0.”); Ex. 1041, 3 (“The product showed a pH of 4.0–6.0.”).

**d. 1[d] “the stabilized ophthalmic composition is a liquid, and wherein”**

173. As discussed above, limitation 1[d] is rendered obvious by *Chia* and/or *Akorn*. § IX.C.1.d

- e. **1[e] “the stabilized ophthalmic composition comprises less than about 10% of a degradant formed from degradation of the atropine or atropine sulfate after an extended period of time of at least 2 weeks under a storage temperature of from about 20° C. to about 70° C. and relative humidity from about 50% to about 80%.”**

174. Limitation 1[e] is rendered obvious by *Chia* and *Akorn* in view of *Lund*.

175. The percentage of “a degradant” under a particular set of conditions is an inherent property of the claimed ophthalmic composition. Accordingly, a POSA would have understood the teachings of *Chia*, *Akorn*, and *Lund* to necessarily disclose limitation 1[e], and would have confirmed this understanding using *Lund*.

176. *Lund* also shows that atropine degradation was a predictable function of pH and temperature. Ex. 1007, 6-12. Specifically, *Lund* derived an equation to predict the pH at which atropine would be most stable for any hydrogen ion concentration. *Id.* *Lund* measured the rate of hydrolysis ( $k$ ) of atropine at different pHs and temperatures and teaches that the half-life of atropine can be computed from  $t_{1/2} = \ln 2 / k_1$  where  $k_1$  is the velocity constant for the hydrolysis of atropine, which changes at different pH values and temperatures. *Id.* at 6-10.  $k_1$  can be determined using the formula below:

$$k_1 = A_{H,1} \exp(-E_{H,1}/RT)[H^+] + A_{OH,1} \exp(-E_{OH,1}/RT)[OH^-]$$

177. Furthermore, in the pH range 2.0-6.0,  $k_1 + k_2 \approx k$ , and thus the  $k_1 + k_2$  values from Table 2 of *Lund* can be used for varying pH values at 80° C. And since

*Lund* discloses that the temperature dependence of the system was found to obey the Arrhenius equation, a POSA would have known how to extrapolate outside of the given temperature ranges (i.e., reaction rate doubling for every 10° C increase in temperature, and being halved for every 10° C decrease in temperature). *See* Ex. 1007, 12.

178. Based on the disclosures in *Lund*, I calculated the time it would take for 10% of atropine to degrade at 40° C and pH 5.3. I used the equation  $T_{90} = -\ln(0.9)/(k_1+k_2)$  and the  $(k_1+k_2)$  figures from Table 2, then multiplied by 16 (4 doublings) to account for 40° C instead of 80° C. This gives a value of **45.5 days**.

$$\text{Stability} = \left( \frac{-\ln(0.9)}{1.54 \cdot 10^{-3}} \right) * 16 = 1094.65 \text{ hours} \\ (45.5 \text{ days})$$

179. Using the equation above, at 40° C and pH 5.3, a POSA would reasonably expect the compositions of claim 1 to comprise 96.8% atropine at approximately 2 weeks. At these parameters, which fall within the limitations of claim 1, *Lund* shows that atropine would readily exceed the stability requirements of limitation 1[e], which allows for up to 10% degradation after at least two weeks.

$$\text{Percent Atropine at} \\ \text{2 Weeks/14 days/336 Hours} = -\ln(x) = \frac{336}{16} * (1.54 \cdot 10^{-3})$$

$$\ln(x) = -21 * (1.54 \cdot 10^{-3})$$

$$\begin{aligned} \ln(x) &= -0.03234 \\ \downarrow \\ x &= e^{-0.03234} = 0.9681773458 \\ \downarrow \\ \text{Percent Atropine at} \\ \text{2 Weeks/14 days/336 Hours} &= 100 * x = \quad \quad \quad \mathbf{96.8\%} \end{aligned}$$

## 2. Claims 2, 4, and 5

180. Dependent claims 2, 4, and 5 all recite stabilized ophthalmic compositions with narrow ranges of atropine or atropine sulfate concentrations. Dependent claim 2 recites: “The stabilized ophthalmic composition of claim 1, wherein the atropine or atropine sulfate is present in the composition at a concentration of from about 0.001 wt % to about 0.03 wt %.” Ex. 1001, claim 2. Similarly, dependent claim 4 recites: “The stabilized ophthalmic composition of claim 1, wherein the atropine or atropine sulfate is present in the composition at a concentration of from about 0.01 wt % to about 0.02 wt %.” *Id.* at claim 4. Last, dependent claim 5 recites: “The stabilized ophthalmic composition of claim 1, wherein the atropine or atropine sulfate is present in the composition at a concentration of about 0.01 wt %.” *Id.* at claim 5.

181. As explained above (§ X.C.1), claim 1 is rendered obvious by *Chia* and *Akorn* in View of *Lund*. *Chia* discloses the additional limitations of claims 2, 4, and 5 as well. See § IX.C.2.

### 3. Claims 6 and 7

182. Dependent claim 6 recites: “The stabilized ophthalmic composition of claim 1, wherein the buffering agent comprises a borate, a boratepolyol complex, a phosphate buffering agent, a citrate buffering agent, an acetate buffering agent, a carbonate buffering agent, an organic buffering agent, an amino acid buffering agent, or a combination thereof.” Ex. 1001, claim 6. Dependent claim 7 recites: “The stabilized ophthalmic composition of claim 1, wherein the buffering agent comprises sodium dihydrogen phosphate, disodium hydrogen phosphate, or a combination thereof.” *Id.* at claim 7.

183. As discussed above (§ X.C.1), claim 1 is rendered obvious by *Chia* and *Akorn* in View of *Lund*. As discussed in ground 1, *Akorn* also discloses these additional limitations of claims 6 and 7 as well. *See* § IX.C.3.

### 4. Claims 8 and 9

184. Dependent claim 8 recites: “The stabilized ophthalmic composition of claim 1, wherein the stabilized ophthalmic composition further comprises a tonicity adjusting agent.” Ex. 1001, claim 8. Dependent claim 9 recites: “The stabilized ophthalmic composition of claim 8, wherein the tonicity adjusting agent comprises a halide salt of a monovalent cation.” *Id.* at claim 9.

185. As discussed above (§ X.C.1), claim 1 is rendered obvious by *Chia* and *Akorn* in View of *Lund*. As explained regarding ground 1, *Chia* and *Akorn* in view

of the knowledge of a POSA render these additional limitations obvious as well. *See* § IX.C.4.

### **5. Claims 12, 13, and 14**

186. Dependent claim 12 recites: “The stabilized ophthalmic composition of claim 1, wherein the stabilized ophthalmic composition further comprises a preservative.” Ex. 1001, claim 12. Dependent claim 13 recites: “The stabilized ophthalmic composition of claim 12, wherein a concentration of the preservative is from about 0.0001% to about 1%.” *Id.* at claim 13. Dependent claim 14 recites: “The stabilized ophthalmic composition of claim 12, wherein the preservative is selected from benzalkonium chloride, cetrimonium, sodium perborate, stabilized oxychloro complex, polyquaternium-1, chlorobutanol, edetate disodium, polyhexamethylene biguanide, or combinations thereof.” *Id.* at claim 14.

187. As explained above (§ X.C.1), claim 1 is rendered obvious by *Chia* and *Akorn* in View of *Lund*. As discussed regarding ground 1, *Chia* and/or *Akorn* disclose these additional limitations of claims 12, 13, and 14 as well. *See* § IX.C.5.

### **6. Claim 15**

188. Dependent claim 15 recites: “The stabilized ophthalmic composition of claim 1, wherein the stabilized ophthalmic composition is essentially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof.” Ex. 1001, claim 15.

189. As explained above (§ X.C.1), claim 1 was obvious. As discussed regarding ground 1, *Chia* and *Akorn* disclose this additional feature of claim 15 as well. *See* § IX.C.6.

## **7. Claims 16 and 17**

190. Dependent claim 16 recites: “The stabilized ophthalmic composition of claim 1, wherein the stabilized ophthalmic composition is topically administered.” Ex. 1001, claim 16. Dependent claim 17 recites: “The stabilized ophthalmic composition of claim 1, wherein the stabilized ophthalmic composition is administered by instillation.” *Id.* at claim 17.

191. As explained above (§ X.C.1), claim 1 is rendered obvious by *Chia* and *Akorn* in View of *Lund*. As discussed regarding ground 1, *Chia* and/or *Akorn* disclose these additional limitations of claims 16 and 17 as well. *See* § IX.C.7.

## **8. Claim 18**

192. Dependent claim 18 recites: “The stabilized ophthalmic composition of claim 1, wherein the stabilized ophthalmic composition is administered through an eye drop bottle containing the stabilized ophthalmic composition.” Ex. 1001, claim 18.

193. As explained above (§ X.C.1), claim 1 is rendered obvious by *Chia* and *Akorn* in View of *Lund*. As explained regarding ground 1, *Akorn* discloses this additional feature of claim 18 as well. *See* § IX.C.8.



## 9. Claim 19

194. Dependent claim 19 recites: “A method of treating the pre-myopia, myopia, or progression of myopia in an individual in need thereof, comprising administering to an eye of the individual an effective amount of the stabilized ophthalmic composition of claim 1.” Ex. 1001, claim 19.

195. As discussed above (§ X.C.1), claim 1 is rendered obvious by *Chia* and *Akorn* in View of *Lund*. *Chia* and *Akorn* in view of *Lund* also disclose the additional limitation of claim 19.

196. *Chia* teaches that administration of its 0.01% atropine solution, via eyedrops, was effective to treat myopia and progression of myopia. Ex. 1003, 1 (determining 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.). Thus, a POSA would have found it obvious to use the solutions of claim 1 to treat pre-myopia, myopia, or progression of myopia.

197. Thus, a POSA would have been motivated towards a method of treating pre-myopia, myopia, or progression of myopia in an individual in need thereof, comprising administering to an eye of the individual an effective amount the stabilized ophthalmic composition of claim 1, and had a reasonable expectation of success in achieving the same.

**XI. GROUND 3: Claims 1, 2, 4-9, and 12-19 Would Have Been Obvious Over *Akorn* and *Wu* in view of *Kondritzer***

198. The compositions and their uses of independent claim 1 of the '787 patent require two components: (1) “about 0.001 wt% to about 0.05 wt%” atropine or atropine sulfate and (2) “a buffering agent to provide a pH of from about 4.8 to about 6.4.” Ex. 1001, claim 1. In my opinion, these claimed elements were taught in the prior art by *Akorn* and *Wu* in view of *Kondritzer*.

**A. Motivation to Combine**

199. *Wu* discloses low concentration atropine solutions comprising 0.001% to about 1% by weight atropine. Ex. 1006, ¶¶[0042]-[0044], claim 17. *Wu* further discloses a method of treating myopia comprising administering a “0.005% to about 0.05% by weight atropine.” *Id.* at claim 18. *Wu* teaches that these solutions should have a pH of “4.5-8.0, e.g. about 6.9.” *Id.* ¶[0044]. This explicit disclosure of atropine concentrations overlapping with the claimed range, and a pH range overlapping with the claimed range, would have motivated one of skill in the art to make and use the claimed low-concentration atropine formulations.

200. Moreover, because the stability of atropine, and similar active ingredients, was known to be pH-dependent, it was common practice in the art to use buffering agents to regulate pH. It was also known that eye comfort was dependent on pH. *Akorn*, a commercially available FDA-approved atropine sulfate

ophthalmic solution, discloses several buffering agents to achieve a solution pH, 3.5 to 6.0, to address both stability and eye comfort.

201. In addition, *Kondritzer* provides further motivation to use *Akorn's* buffering agents to achieve the claimed pH range. *Kondritzer* discloses that atropine is most stable at pH 3–5, and a POSA would have targeted the higher end of that range for maximum eye comfort. Using an equation derived by *Kondritzer*, a POSA would have confirmed that *Akorn's* buffering agents and pH range would have provided stability under the claimed conditions.

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

202. As discussed above, atropine solutions had long been used at concentrations at 1% and 0.5% to treat myopia, but these concentrations had several drawbacks. *See* § IX.A.1. *Wu* explicitly acknowledges these drawbacks, noting that “anti-muscarinic agents may cause side effects of blurred vision and photophobia. These side effects maybe overcome by administering lower dosage of anti-muscarinic agents . . . to achieve the desired therapeutic effect.” Ex. 1006, ¶[0038].

203. Although *Wu* suggests also trying atropine with NSAIDs to reduce the side effects to an even greater extent, *Wu* expressly claims a composition comprising a single anti-chondrogenesis agent, which is the anti-muscarinic agent atropine. *Id.*

at claims 10, 15-18. Thus, *Wu*'s disclosure and claims would have expressly motivated one of skill in the art to formulate low-concentration atropine solutions.

204. Further, as explained above, atropine treatments require long-term use, and the long-term stability of ready-to-use atropine solutions would have been a primary consideration for a POSA. § IX.A.1.

**2. A Person of Skill in the Art Would Have Been Motivated to Modify Low-Concentration Atropine Solutions with Buffering and Stabilizing Agents**

205. To address stability, and eye comfort, *Akorn* would have motivated a POSA to modify *Wu*'s low-concentration solutions with buffering and stabilizing agents.

206. As explained above, in light of *Akorn* and *Kondritzer*, 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. § IX.A.2.

**B. Reasonable Expectation of Success**

207. A POSA also would have had a reasonable expectation of achieving the compositions recited by the '787 patent.

208. Buffering agents are common components in ophthalmic compositions to stabilize and increase patient comfort. *See* § VI.B.1. In view of this common

practice, a POSA would have had a considerable expectation of success using *Akorn's* buffering agents, to achieve a pH range of 3.5-6.0, to stabilize *Wu's* low concentration atropine formulations.

209. Moreover, in view of *Kondritzer's* disclosure that optimum atropine stability in aqueous solutions is at pH 3-5, *Kondritzer* would have confirmed this expectation of success. Ex. 1005, 4 (showing decreasing atropine stability as pH increases to 7.0). A POSA thus would have understood that the composition would remain stable at the higher end of the range while increasing patient comfort. By targeting the higher end of *Akorn's* disclosed pH range in order to optimize stability in view of patient comfort, a POSA would have had a reasonable expectation of success in combining the teachings of *Wu* and *Akorn* to achieve the claimed atropine formulations. Ex. 1019, 1569 (ophthalmic preparations should be formulated at a pH equivalent to the tear fluid value of 7.4).

### **C. Claim-by-Claim Analysis**

#### **1. Claim 1**

210. Claim 1 of the '787 patent recites "A stabilized ophthalmic composition for treating pre-myopia, myopia, or progression of myopia, comprising from about 0.001 wt % to about 0.05 wt % of atropine or atropine sulfate and water, wherein the stabilized ophthalmic composition further comprises a buffering agent to provide a pH of from about 4.8 to about 6.4, wherein the stabilized ophthalmic composition is

a liquid, and wherein the stabilized ophthalmic composition comprises less than about 10% of a degradant formed from degradation of the atropine or atropine sulfate after an extended period of time of at least 2 weeks under a storage temperature of from about 20° C. to about 70° C. and relative humidity from about 50% to about 80%.” Ex. 1001, claim 1.

**a. 1[a] “A stabilized ophthalmic composition for treating pre-myopia, myopia, or progression of myopia, comprising...”**

211. To the extent that the preamble is limiting, *Wu* and/or *Akorn* renders it obvious.

212. *Wu* discloses low concentration atropine solutions comprising 0.001% to about 1% by weight atropine and 0.005% to about 0.05% by weight atropine formulated as eye drops. Ex. 1006, ¶¶[0042]-[0044]. As was well understood in the art, eye drops are an ophthalmic solution. Ex. 1034, 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.”); Ex. 1019, 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.”).

213. A POSA would have recognized that ophthalmic solutions are necessarily ophthalmic compositions. Ex. 1048, 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); Ex. 1049, ¶[0021]. As such, the atropine eye drops discussed by *Wu* teaches “an ophthalmic composition.” *Wu*’s composition is also stabilized, as it suggests the use of buffers and recommends a pH range of 4.5 to 8.0. Ex. 1006, ¶¶[0042]-[0044].

214. In addition to this understanding of *Wu*’s composition, *Akorn* discloses an FDA-approved, commercially available atropine sulfate ophthalmic solution. Ex. 1004 at 3. A POSA would have understood that *Akorn* discloses a stabilized ophthalmic composition via its disclosure of several buffering agents to adjust pH to a range of 3.5-6.0, including monobasic sodium phosphate, hydrochloric acid and/or sodium hydroxide. Ex. 1004 at 3. This understanding would have been reinforced by a POSA’s knowledge of FDA requirements to assess the stability characteristics of drug products and because atropine has been used to control myopia for decades. *See* Ex. 1003; Ex. 1008). Accordingly, *Wu* and/or *Akorn* discloses a “stabilized” ophthalmic composition.

**b. 1[b] “from about 0.001 wt % to about 0.05 wt % of atropine or atropine sulfate and water, wherein...”**

215. Limitation 1[b] is rendered obvious by *Wu*.

216. *Wu* discloses that atropine is an anti-muscarinic agent (Ex. 1006, ¶[0037]) and claims a method of treating atropine comprising administering “0.001% to about 1% by weight atropine” solution. Ex. 1006, claim 17. *Wu* further claims a method of treating myopia comprising administering a “0.005% to about 0.05% by weight atropine” solution. *Id.* at claim 18. Accordingly, *Wu*’s claimed atropine concentrations fall squarely within the claimed range and would have rendered this limitation obvious.

217. *Wu* further recognizes that: “[A]nti-muscarnic agents may cause side effects of blurred vision and photophobia. These side effects maybe overcome by administering lower dosage of anti-muscarinic agents . . . to achieve the desired therapeutic effect.” This disclosure would have motivated one of skill in the art to formulate low-concentration atropine solutions. Ex. 1006, ¶[0038].

218. The obviousness of concentrations of “about 0.001 wt % to about 0.05 wt %” atropine was further underscored by the art as a whole, which shows the efficacy of low-concentration atropine at concentrations within the claimed range. § VI.A.1. For example, Fang 2010 specifically discloses 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.” Ex. 1013, 1; *see also* Ex. 1006 ¶[0042], claim 5; Ex. 1016, 6.



- c. **1[c] “the stabilized ophthalmic composition further comprises a buffering agent to provide a pH of from about 4.8 to about 6.4, wherein”**

219. Limitation 1[c] is rendered obvious by *Akorn* and *Wu* in view of *Kondritzer*.

220. As discussed above, the claimed range covers the pH at which atropine was known to be most stable (pH 3–5) and is near the pH that was most desirable for clinical administration (pH 7.4). §§ VI.A-B; IX.C.1.c. Further, *Akorn* discloses a stabilized ophthalmic composition comprising several standard buffering agents to adjust pH to 3.5 to 6.0. § IX.C.1.c. As with *Akorn*, *Wu* discloses a pH range of 4.5 to 8.0, which significantly overlaps with the claimed range and renders it obvious.

221. As explained above, it was also well understood that pH is a result-effective variable for stability and patient comfort, and optimizing pH for atropine solutions for stability and comfort within the known range was routine. § IX.C.1.c. In sum, based on the teachings of *Akorn*, *Wu*, and *Kondritzer*, it would have been obvious to formulate the claimed atropine solutions at the claimed pH range of about 4.8 to about 6.4.

- d. **1[d] “the stabilized ophthalmic composition is a liquid, and wherein”**

222. Limitation 1[d] is rendered obvious by *Wu* and/or *Akorn*.

223. *Wu* discloses low concentration atropine solutions comprising 0.001% to about 1% by weight atropine and 0.005% to about 0.05% by weight atropine formulated as eye drops. Ex. 1006, ¶¶[0042]-[0044]. As was well understood in the art, eye drops are a liquid ophthalmic solution. *See, e.g.*, Ex. 1034, 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.”) (emphasis added). A POSA would have understood that *Wu*’s eye drops, which were an aqueous solution (i.e. a solution where the solvent is water), were liquids.

224. Likewise, *Akorn* discloses an aqueous liquid solution that is administered in the form of eyedrops. Ex. 1004. Further confirming that *Akorn*’s solution is a liquid, *Akorn* discloses its atropine sulfate concentration in the form of milligram (mg) per milliliter (mL) and explains that the solution is supplied in dropper bottles with 2, 5, and 15 mL fills.

- e. **1[e] “the stabilized ophthalmic composition comprises less than about 10% of a degradant formed from degradation of the atropine or atropine sulfate after an extended period of time of at least 2 weeks under a storage temperature of from about 20° C. to about 70° C. and relative humidity from about 50% to about 80%.”**

225. Limitation 1[e] is rendered obvious by *Wu* and *Akorn* in view of *Kondritzer*.

226. The percentage of “a degradant” under a particular set of conditions is an inherent property of the claimed ophthalmic composition. Accordingly, a POSA would have understood the teachings of *Wu*, *Akorn*, and *Kondritzer* to necessarily disclose limitation 1[e], and would have confirmed this understanding using *Kondritzer*.

227. As discussed above, *Kondritzer* provides a roadmap for routine experimentation with atropine stability at varying pHs and temperatures. Moreover, *Kondritzer* shows that atropine degradation was a predictable function of pH and temperature. § IX.C.1.c. For example, at 20° C and pH 5, a POSA would have reasonably expect the compositions of claim 1 to comprise 90% atropine for approximately 40.4 years. § IX.C.1.e. At these parameters, which fall within the limitations of claim 1, *Kondritzer* shows that atropine would readily exceed the stability requirements of limitation 1[e], which allows for up to 10% degradation after at least two weeks.

## **2. Claims 2, 4, and 5**

228. Dependent claims 2, 4, and 5 all recite stabilized ophthalmic compositions with narrow ranges of atropine or atropine sulfate concentrations. Dependent claim 2 recites: “The stabilized ophthalmic composition of claim 1, wherein the atropine or atropine sulfate is present in the composition at a concentration of from about 0.001 wt % to about 0.03 wt %.” Ex. 1001, claim 2.

Similarly, dependent claim 4 recites: “The stabilized ophthalmic composition of claim 1, wherein the atropine or atropine sulfate is present in the composition at a concentration of from about 0.01 wt % to about 0.02 wt %.” *Id.* at claim 4. Last, dependent claim 5 recites: “The stabilized ophthalmic composition of claim 1, wherein the atropine or atropine sulfate is present in the composition at a concentration of about 0.01 wt %.” *Id.* at claim 5.

229. As explained above (§ XI.C.1), claim 1 is rendered obvious over *Akorn* and *Wu* in view of *Kondritzer*. *Wu* discloses these additional limitations of claims 2, 4, and 5 as well.

230. As explained above (§ XI.C.1), *Wu* claims a method of administering “0.001% to about 1% by weight atropine” to treat myopia. Ex. 1006, claims 10, 15-17. *Wu* further claims a method of treating myopia comprising administering a “0.005% to about 0.05% by weight atropine” solution. *Id.* at claims 10, 15, 18. As *Wu*’s “effective amount[s]” of atropine fall squarely within the ranges and values recited by claims 2, 4, and 5, those claims would have been obvious for the same reasons explained above for claim 1. § XI.C.1.

231. Thus, a POSA would have been motivated to make an ophthalmic composition as recited by claim 1 which had an atropine concentration of one of: about 0.001 wt % to about 0.03 wt %, about 0.01 wt % to about 0.02 wt %, or about 0.01 wt %, and had a reasonable expectation of success in achieving the same.

### **3. Claims 6 and 7**

232. Dependent claim 6 recites: “The stabilized ophthalmic composition of claim 1, wherein the buffering agent comprises a borate, a boratepolyol complex, a phosphate buffering agent, a citrate buffering agent, an acetate buffering agent, a carbonate buffering agent, an organic buffering agent, an amino acid buffering agent, or a combination thereof.” Ex. 1001, claim 6. Dependent claim 7 recites: “The stabilized ophthalmic composition of claim 1, wherein the buffering agent comprises sodium dihydrogen phosphate, disodium hydrogen phosphate, or a combination thereof.” *Id.* at claim 7.

233. As discussed above (§ XI.C.1), claim 1 is rendered obvious over *Akorn* and *Wu* in view of *Kondritzer*. Further, as explained in § IX.C.3, *Akorn* discloses these additional limitations of claims 6 and 7 as well.

### **4. Claims 8 and 9**

234. Dependent claim 8 recites: “The stabilized ophthalmic composition of claim 1, wherein the stabilized ophthalmic composition further comprises a tonicity adjusting agent.” Ex. 1001, claim 8. Dependent claim 9 recites: “The stabilized ophthalmic composition of claim 8, wherein the tonicity adjusting agent comprises a halide salt of a monovalent cation.” *Id.* at claim 9.

235. As discussed above (§ XI.C.1), claim 1 is rendered obvious over *Akorn* and *Wu* in view of *Kondritzer*. *Wu* and *Akorn* in view of the knowledge of a POSA render these additional limitations obvious.

236. Tonicity is a measure of the effective osmotic pressure gradient exerted by salts in aqueous solution. Ex. 1019, 54 (“Tonicity refers to the osmotic pressure exerted by salts in aqueous solution.”). It was text-book knowledge that “isotonicity always is desirable and particularly is important in intraocular solutions.” Ex. 1019, 54. A POSA would have recognized that decreasing the concentration of atropine sulfate (a salt) from *Akorn*’s 1% atropine sulfate solution to *Wu*’s 0.001% to about 1% by weight atropine and/or 0.005% to about 0.05% by weight atropine solution would require the addition of a tonicity adjusting agent to maintain eye comfort.

237. As discussed above regarding ground 1, in view of the reduced amount of salt in solution, it was well known that a tonicity agent, such as sodium chloride, would be needed to increase osmolarity and comfort. § IX.C.4. As *Akorn* discloses sodium chloride, a halide salt of a monovalent cation, claim 9 was obvious. *Id.* Likewise, claim 8, which recites all tonicity adjusting agents, was obvious. *Id.*

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

## 5. Claims 12, 13, and 14

239. Dependent claim 12 recites: “The stabilized ophthalmic composition of claim 1, wherein the stabilized ophthalmic composition further comprises a preservative.” Ex. 1001, claim 12. Dependent claim 13 recites: “The stabilized ophthalmic composition of claim 12, wherein a concentration of the preservative is from about 0.0001% to about 1%.” *Id.* at claim 13. Dependent claim 14 recites: “The stabilized ophthalmic composition of claim 12, wherein the preservative is selected from benzalkonium chloride, cetrimonium, sodium perborate, stabilized oxychloro complex, polyquaternium-1, chlorobutanol, edetate disodium, polyhexamethylene biguanide, or combinations thereof.” *Id.* at claim 14.

240. As explained above (§ XI.C.1), claim 1 is rendered obvious over *Akorn* and *Wu* in view of *Kondritzer*. *Wu* and/or *Akorn* disclose these additional limitations of claims 12, 13, and 14 as well.

241. Claim 14 recites a list of well-known, traditional preservatives used in atropine and other ophthalmic compositions. Ex. 1019, 54–56. *Wu* explicitly discloses that “[s]uitable preservatives for ophthalmic preparations include: ***benzalkonium chloride***, thimerosal, ***chlorobutanol***, methyl paraben, propyl paraben, phenylethyl alcohol, ***edetate disodium***, sorbic acid, Onamer M, or other agents known to those skilled in the art. In one embodiment, the preservative is employed ***at a level of from 0.004% to 0.02%***.” Ex. 1006, ¶[0040] (emphasis added).

As explained above, *Akorn* discloses the preservative benzalkonium chloride 0.1 mg (0.01%). § IX.C.5.

242. As discussed regarding ground 1, these disclosures reflected standard practice in the art, and claim 13 recites a well-known concentration range for traditional preservatives used for ophthalmic compositions containing atropine. § IX.C.5. As the specific preservatives recited by claim 14 were obvious, claim 12, which recites all preservatives, was likewise obvious. Similarly, as the specific concentration range recited by claim 13 were obvious, claim 12, which recites preservatives at any concentration, is likewise obvious.

243. 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, polyquaternium-1, chlorobutanol, edetate disodium, polyhexamethylene biguanide, or combinations thereof, and had a reasonable expectation of success in achieving the same at the claimed concentration ranges.

## **6. Claim 15**

244. Dependent claim 15 recites: “The stabilized ophthalmic composition of claim 1, wherein the stabilized ophthalmic composition is essentially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof.” Ex. 1001, claim 15.



245. As explained above (§ XI.C.1), claim 1 is rendered obvious over *Akorn* and *Wu* in view of *Kondritzer*. *Wu* and *Akorn* disclose this additional limitation of claim 15 as well.

246. While *Wu* mentions procaine, it only discloses procaine as a potential organic ion in one of many illustrative salts of the disclosed therapeutic agents. *See* Ex. 1006, ¶[0026]. Procaine is just one of approximately 25 ions for potential use with therapeutic agents. *See id.* Importantly, *Wu* does not claim an ophthalmic composition including procaine and does not otherwise discuss procaine. *See generally id.* Further, *Wu* makes no mention of benactyzine in its ophthalmic atropine solutions. *See generally* Ex. 1006. Thus, *Wu*'s claimed compositions that render claim 1 obvious are “essentially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof.”

247. Similarly, *Akorn* discloses an atropine sulfate ophthalmic solution that does not list procaine or benactyzine as ingredients. Ex. 1004, 3. As explained regarding ground 1, the art demonstrates that atropine is rarely, if ever, administered with procaine or benactyzine to treat myopia. §IX.C.6. Therefore, it would have been obvious to formulate atropine compositions in the same way shown to be effective to treat myopia—“essentially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof.”

248. Thus, a POSA would have been motivated to make an ophthalmic composition as recited by claim 1 that was essentially free of procaine, benactyzine, and their pharmaceutically acceptable salts, and had a reasonable expectation of success in achieving the same.

## **7. Claims 16 and 17**

249. Dependent claim 16 recites: “The stabilized ophthalmic composition of claim 1, wherein the stabilized ophthalmic composition is topically administered.” Ex. 1001, claim 16. Dependent claim 17 recites: “The stabilized ophthalmic composition of claim 1, wherein the stabilized ophthalmic composition is administered by instillation.” *Id.* at claim 17.

250. As explained above (§ XI.C.1), claim 1 is rendered obvious over *Akorn* and *Wu* in view of *Kondritzer*. *Wu* and/or *Akorn* disclose these additional limitations of claims 16 and 17 as well.

251. *Wu* teaches atropine compositions for “topical ocular administration” and recommends that “the solution be topically applied by placing one drop in the affected eye once a day.” Ex. 1006, ¶[0044]. Likewise, *Akorn* advises that its solution should be “topically” administered to the eye in the form of drops. Ex. 1004. *Akorn* characterizes this topical administration as “instillation” of its atropine sulfate ophthalmic solution. *Id.*

252. As discussed regarding claim 1, the art shows that *Wu* and/or *Akorn*'s use of atropine eye drops was standard practice in the art. § IX.C.7.

253. Thus, a POSA would have been motivated to make the ophthalmic composition of claim 1 that was topically “topically administered” “by instillation.”

## **8. Claim 18**

254. Dependent claim 18 recites: “The stabilized ophthalmic composition of claim 1, wherein the stabilized ophthalmic composition is administered through an eye drop bottle containing the stabilized ophthalmic composition.” Ex. 1001, claim 18.

255. As explained above (§ XI.C.1), claim 1 is rendered obvious over *Akorn* and *Wu* in view of *Kondritzer*. Further, as discussed regarding ground 1, *Akorn* discloses this additional limitation of claim 18. *See* § IX.C.8.

## **9. Claim 19**

256. Dependent claim 19 recites: “A method of treating the pre-myopia, myopia, or progression of myopia in an individual in need thereof, comprising administering to an eye of the individual an effective amount of the stabilized ophthalmic composition of claim 1.” Ex. 1001, claim 19.

257. As discussed above (§ XI.C.1), claim 1 is rendered obvious over *Akorn* and *Wu* in view of *Kondritzer* was obvious. *Wu* and *Akorn* in view of *Kondritzer* disclose the additional limitations of claim 19 as well.

258. *Wu* teaches the administration of its low-concentration atropine solutions via eyedrops to treat myopia. Ex. 1006, ¶[0044]. *Wu* further characterized its low-concentration atropine solutions as containing an “effective amount” of atropine. *Id.* at claims 10, 15-18.

259. Thus, a POSA would have been motivated towards a method of treating pre-myopia, myopia, or progression of myopia in an individual in need thereof, comprising administering to an eye of the individual an effective amount the stabilized ophthalmic composition of claim 1, and had a reasonable expectation of success in achieving the same.

## **XII. Secondary Indicia**

260. I understand that during prosecution of the application that issued as the ’787 patent, Applicant presented data from the specification and asserted that the data was unexpected. Ex. 1037, 1593. In my opinion, these results would not have been unexpected to a POSA.

261. The data presented shows the expected outcome of using a known pH range for stable, ophthalmically-acceptable atropine solutions. Applicant asserted that (1) the pH range of about 4.8 to about 6.4 was “critical” to the stability of H<sub>2</sub>O-based dilute atropine formulations, and (2) stability problems of such formulations were not known in the art, so “there [was] no reason to target that pH [range].” However, as discussed above, atropine’s pH and temperature dependent stability was

well-known in the art, and the claimed pH range substantially overlapped with the prior art's pH ranges for atropine solutions. In view of this knowledge, a POSA would have recognized the benefits of targeting the higher end of the known pH stability range for atropine.

262. As shown by *Kondritzer* and *Lund*, “stability problems” of atropine had been recognized over fifty years before the priority date of the '787 patent. Although Applicant argued that atropine sulfate formulations suffered from an “unexpected stability problem” at a pH of 6.8, this problem was not “unexpected” at all, because it had already been recognized by both *Kondritzer* and *Lund*. See Ex. 1005, 2-5 (noting that a prior art study found that “hydrolysis became very rapid” around pH 6 or over); Ex. 1007, 7-12.

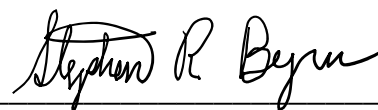
263. Indeed, *Kondritzer* shows a sharp decrease in predicted stability above a pH of 6.0. See Ex. 1005, Table III. Similarly, using the data and equation from *Lund*, a POSA would have recognized that atropine in aqueous solution experiences a sharp decrease in stability above a pH of 6.0. See § X.C.1.e. Had the Examiner substantively evaluated *Kondritzer* and/or *Lund*, they would have recognized that the stability “problems” of atropine at pH 6.8 were not just expected, but known.

264. Regardless of the existence of pH or atropine stability problems, Applicant's claimed pH range was already known in the art for atropine ophthalmic solutions. For example, *Akorn* expressly teaches a pH range of 3.5-6.0 for its

atropine sulfate solution, and *Wu* suggests a pH range of 4.5-8.0 for its ophthalmic solutions. Ex. 1004, 3; Ex. 1006, ¶[0044]. Further supplementing this knowledge, *Kondritzer* and *Lund* collectively teach that atropine had optimal stability around pH 3.5-6. *See generally* Ex. 1005; Ex. 1007.

265. Applicant's claimed pH range of 4.8-6.4 substantially overlaps with all of these well-known pH ranges disclosed in the art for atropine. In my opinion, a POSA would have considered Applicant's pH range to be neither unexpected nor significant. Put another way, any differences between the alleged unexpected results and the pH ranges of *Akorn*, *Wu*, *Kondritzer*, and *Lund* are insignificant differences in degree.

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 black ink, reading "Stephen R. Byrn", is positioned above a horizontal line.

Stephen Byrn  
December 29, 2021

# 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," 2<sup>nd</sup> 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.; Prinszano, 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  $\beta$ -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  $\beta$ -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**

1. Pyridines for treating injured mammalian nerve tissue, Borgens; Richard B. (Delphi, IN), Shi; Riyi (West Lafayette, IN), Byrn; Stephen R. (West Lafayette, IN), Smith; Daniel T. (Lafayette, IN), US Patent 8,729,107, Sept. 9, 2010.
2. Pyridines for treating injured mammalian nerve tissue, Borgens; Richard B. (Delphi, IN), Shi; Riyi (West Lafayette, IN), Byrn; Stephen R. (West Lafayette, IN), Smith; Daniel T. (Lafayette, IN), US 8,097,638, July 16, 2007.
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4. Crystalline forms of [R-(R\*,R\*)]-2-(4-fluorophenyl)-.beta.,.delta.-dihydroxy-5-(1-methylethyl)- -3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1), Byrn; Stephen Robert (West Lafayette, IN), Coates; David Andrew (West Lafayette, IN), Gushurst; Karen Sue (Lafayette, IN), Krzyzaniak; Joseph Francis (Pawcatuck, CT), Li; Zheng Jane (Quaker Hill, CT), Morrison, II; Henry Grant (Lafayette, IN), Park; Aeri (West Lafayette, IN), Vlahova; Petinka Ivanova (Lafayette, IN), US 7,144,915, June 6, 2003.
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### **Book Chapters**

Solid State Structure of Chiral Organic Pharmaceuticals, Stahly, G.P.; and Byrn, S. R., in Molecular Modeling Applications in Crystallization, 313-345, Allan Myerson, Ed., Cambridge Univ., Press

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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.

"Solid State Chemistry of Drugs," Eli Lilly-Tippecanoe Labs, May 10, 1985.

"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.

"Solid State Chemistry of Drugs," Wyeth-Ayerst Pharmaceuticals, Rouses Point, New York, February 20, 1990.

"Solid State Chemistry of Drugs," Smith Kline Beecham, King of Prussia, Pennsylvania, April 11, 1990.

X-Ray Crystallographic Analysis of Pharmaceuticals," Land of Lakes Conference, Madison, Wisconsin, August 1, 1990.

"Solid State Oxidation Reactions," Pfizer Central Research, Groton, Connecticut, August 18, 1989.

"Solid State Chemistry of Drugs," Glaxo, Inc., Research Triangle Park, North Carolina, August 22, 1990.

"Polymorphs and Solvates of Drugs," Short Course presented to Hoffmann LaRoche, Nutley, New Jersey, September 11 and 12, 1990.

"Stability of Solvated Crystals," Abbott Laboratories, Abbott Park, Illinois, April 17, 1991.

"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 21<sup>st</sup> 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 48<sup>th</sup> 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 21<sup>st</sup> 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 21<sup>st</sup> 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<sup>a</sup>, Stephen R. Byrn<sup>a</sup>, Gabriel L.B. de Araujo<sup>b</sup>, Chris J. Benmore<sup>c</sup>a) 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, Villigen, 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, Villigen, 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.