

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GENE COMPANY PTY LTD,
Petitioner,

v.

THE TRUSTEES OF COLUMBIA UNIVERSITY
IN THE CITY OF NEW YORK,
Patent Owner.

Patent No. 9,486,432

DECLARATION OF F. PETER GUENGERICH, PH. D.

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I, F. Peter Guengerich, declare as follows:

I. QUALIFICATIONS

1. I have been retained by Counsel on behalf of Gene Company Pty Ltd (Gene Company) to provide opinions in this matter related to my experience and expertise. My opinions are based on my skills, knowledge, training, education, and experience in matters of this nature, and my examination of the materials utilized in preparing this report.

2. I am the Tadashi Inagami Professor of Biochemistry in the Department of Biochemistry at the Vanderbilt University School of Medicine.

3. I received my Bachelor of Science in Agricultural Science from the University of Illinois, Urbana, Illinois in 1970. I then obtained my Ph.D. in Biochemistry from Vanderbilt University in 1973 under the guidance of Professor H.P. Broquist. After that, I was a Postdoctoral Scholar in the laboratory of Professor M.J. Coon in the Department of Biological Chemistry at the University of Michigan Medical School.

4. Subsequent to my postdoctoral work, in 1975 I started as an Assistant Professor of Biochemistry at the Vanderbilt University School of Medicine. In 1980, I was named a tenured Associate Professor of Biochemistry at the Vanderbilt University School of Medicine, and in 1983 I became a (tenured) Professor of Biochemistry at the Vanderbilt University School of Medicine. Since then, I have

held several positions at Vanderbilt University School of Medicine, including: Director, Center in Molecular Toxicology (1981-2011), Harry Pearson Broquist Professor of Biochemistry (2007-2012), Interim Chairman, Department of Biochemistry (2010-2012), Stanford Moore Professor of Biochemistry (2013), and my current position as the Tadashi Inagami Professor of Biochemistry (2013-present).

5. I have extensive experience in the fields of biochemistry and medicinal chemistry with an emphasis on mechanisms of activation and detoxication of drugs, chemical carcinogens, steroids, and toxicants and characterization of enzymes involved in these processes. I also have experience working with deuterated compounds.

6. During my career, I have received numerous honors and distinguished lectureships, which are summarized in my curriculum vitae (CV), which is attached as EX1003. I have published over 750 original peer-reviewed scientific articles and more than 300 invited reviews and chapters during my career.

7. I currently serve on the editorial boards for Chemistry and Biodiversity, Critical Reviews in Toxicology, and Drug Metabolism and Disposition. I served on the Advisory Panel for Nature Reviews in Drug Discovery from 2001-2011. I also served as an Associate Editor of Chemical Research in

Toxicology from 1989-2017, and I served as Associate Editor of The Journal of Biological Chemistry from 2006-2022 and as Deputy Editor from 2013-2021.

8. I am a member of the American Chemical Society, including the Divisions of Biological Chemistry, Medicinal Chemistry, and Chemical Toxicology. I also served as Chair of the latter Division from 2007-2008 and have held several other offices in the Division of Chemical Toxicology. In 2009, I was named as an American Chemical Society Fellow, in the inaugural class for that program.

9. I have served as a scientific consultant for a number of companies including Merck, Sandoz (now Novartis), Schering-Plough (now part of Merck), Oxford Biomedical Research, Otsuka Pharmaceuticals, Orchid Biosciences, Targacept, Aventis, Pfizer, OSI, Novartis, Johnson & Johnson, TEVA, Salix, Vertex, Biogen Idec, Barbeau Pharma/ProCor, BioPure, Resverologix, Medivation, GeminX, Angion Biomedica, Transcept, Purdue Pharma LP, and ZioPharm Oncology. Since 2015 I have been a member of the Expert Panel of the Flavor and Extracts Manufacturers' Association.

10. Under my direction, my laboratory developed the technology for purifying several of the important human liver cytochrome P450 proteins, including those now known as 1A1, 1A2, 2C8, 2C9, 2D6, 2E1, and 3A4. My laboratory also developed useful methods for the heterologous expression of these and other human

cytochrome P450 enzymes in bacteria and their purification and use in assays of the metabolism of drugs and other chemicals.

11. I have experience working with deuterated compounds, as evidenced by my publications, including the following:

- Guengerich, F.P. (1987) *J. Biol. Chem.* 262, 8459-8462. "Oxidative Cleavage of Carboxylic Esters by Cytochrome P-450."
- Peterson, L.A., Harris, T.M., and Guengerich, F.P. (1988) *J. Am. Chem. Soc.* 110, 3284-3291. "Evidence for an Episulfonium Ion Intermediate in the Formation of S-[2-(N⁷-Guanyl)ethyl]glutathione in DNA."
- Guengerich, F.P., and Böcker, R.H. (1988) *J. Biol. Chem.* 263, 8168-8175. "Cytochrome P-450-catalyzed Dehydrogenation of 1,4-Dihydropyridines."
- Guengerich, F.P., Peterson, L.A., and Böcker, R.H. (1988) *J. Biol. Chem.* 263, 8176-8183. "Cytochrome P-450-catalyzed Hydroxylation and Carboxylic Acid Ester Cleavage of Hantzsch Pyridine Esters."
- Funaki, T., Soons, P.A., Guengerich, F.P., and Breimer, D.D. (1989) *Biochem. Pharmacol.* 38, 4213-4216. "In Vivo Oxidative Cleavage of a Pyridine-carboxylic Acid Ester Metabolite of Nifedipine."

- Guengerich, F.P. (1990) *Chem. Res. Toxicol.* 3, 21-26. “Low Kinetic Hydrogen Isotope Effects in the Dehydrogenation of 1,4-Dihydro-2,6-dimethyl-4-(2-nitrophenyl)-3,5-pyridinedicarboxylic Acid Dimethyl Ester (Nifedipine) by Cytochrome P-450 Enzymes are Consistent with an Electron/Proton/Electron Transfer Mechanism.”
- Guengerich, F.P., and Kim, D-H. (1991) *Chem. Res. Toxicol.* 4, 413-421. “Enzymatic Oxidation of Ethyl Carbamate to Vinyl Carbamate and Its Role as an Intermediate in the Formation of 1,*N*⁶-Ethenoadenosine.”
- Okazaki, O., and Guengerich, F.P. (1993) *J. Biol. Chem.* 268, 1546-1552. “Evidence for Specific Base Catalysis in *N*-Dealkylation Reactions Catalyzed by Cytochrome P450 and Chloroperoxidase: Differences in Rates of Deprotonation of Aminium Radicals as an Explanation for High Kinetic Deuterium Isotope Effects Observed with Peroxidases.”
- Guengerich, F.P., Persmark, M., and Humphreys, W.G. (1993) *Chem. Res. Toxicol.* 6, 635-648. “Formation of 1, *N*²- and *N*²,3-Ethenoguanine Derivatives from 1-Halooxiranes: Isotopic Labeling Studies and Formation of a Hemiaminal Derivative of *N*²-(2-Oxoethyl)guanine.”

- Guengerich, F.P., Yun, C-H., and Macdonald, T.L. (1996) *J. Biol. Chem.* 271, 27321-27329. “Evidence for a One-Electron Mechanism in *N*-Dealkylation of *N,N*-Dialkylanilines by Cytochrome P450 2B1. Kinetic Hydrogen Isotope Effects, Linear Free Energy Relationships with Biomimetic Models, Comparisons with Horseradish Peroxidase, and Studies with Oxygen Surrogates.”
- Bell, L.C., and Guengerich, F.P. (1997) *J. Biol. Chem.* 272, 29643-29651. “Oxidation Kinetics of Ethanol by Human Cytochrome P450 2E1. Rate-limiting Product Release Accounts for Effects of Isotopic Hydrogen Substitution and Cytochrome *b*₅ on Steady-state Kinetics.”
- Bell-Parikh, L.C., and Guengerich, F.P. (1999) *J. Biol. Chem.* 274, 23833-23840. “Kinetics of Cytochrome P450 2E1-Catalyzed Oxidation of Ethanol to Acetic Acid via Acetaldehyde.”
- Yun, C-H., Miller, G.P., and Guengerich, F.P. (2000) *Biochemistry* 39, 11319-11329. “Rate-determining Steps in Phenacetin Oxidations by Human Cytochrome P450 1A2 and Selected Mutants.”
- Yun, C-H., Miller, G.P., and Guengerich, F.P. (2001) *Biochemistry* 40, 4521-4530. “Oxidations of *p*-Alkoxyacylanilides by Human Cytochrome P450 1A2. Structure-activity Relationships and Simulation of Individual Rate Constants in Catalysis”

- Guengerich, F. P., Miller, G.P., Hanna, I.H., Sato, H., and Martin, M.V. **(2002)** *J. Biol. Chem.* 277, 33711-33719. “Oxidations of Methoxyphenethylamines by Cytochrome P450 2D6. Analysis of Rate-limiting Steps.”
- Guengerich, F.P., Krauser, J.A., and Johnson, W.W. **(2004)** *Biochemistry* 43, 10775-10788. “Rate-Limiting Steps in Oxidations Catalyzed by Rabbit Cytochrome P450 1A2.”
- Yun, C-H., Kim, K-H., Calcutt, M.W. and Guengerich, F.P. **(2005)** *J. Biol. Chem.* 280, 12279-12291. “Kinetic Analysis of Oxidation of Coumarins by Human Cytochrome P450 2A6.”
- Krauser, J.A., and Guengerich, F.P. **(2005)** *J. Biol. Chem.* 280, 19496-19506. “Cytochrome P450 3A4-Catalyzed Testosterone 6 β -Hydroxylation: Stereochemistry, Kinetic Deuterium Isotope Effects, and Rate-limiting Steps.”
- Kim, K-H., Isin, E.M., Yun, C-H., Kim, D-H., and Guengerich, F.P. **(2006)** *FEBS J.* 273, 2223-2231. “Kinetic Deuterium Isotope Effects for 7-Alkoxy coumarin *O*-Dealkylation Reactions Catalyzed by Human Cytochrome P450s and in Liver Microsomes.”
- Chowdhury, G., Calcutt, M.W., and Guengerich, F.P. **(2010)** *J. Biol. Chem.* 285, 8031-8044. “Oxidation of *N*-Nitrosodimethylamine and

N-Nitrosodiethylamine by Human Cytochrome P450 2A6: Sequential Oxidation to Aldehydes and Carboxylic Acids and Analysis of Reaction Steps.”

- Shinkyo, R., and Guengerich, F.P. (2011) *J. Biol. Chem.* 286, 4632-4643. “Cytochrome P450 7A1 Cholesterol 7 α -Hydroxylation. Individual Reaction Steps in the Catalytic Cycle and Rate-limiting Ferric Iron Reduction.”
- Shinkyo, R., Xu, L., Tallman, K.A., Cheng, Q., Porter, N.A., and Guengerich, F.P. (2011) *J. Biol. Chem.* 286, 33021-33028. “Conversion of 7-Dehydrocholesterol to 7-Ketocholesterol is Catalyzed by Human Cytochrome P450 7A1 and Occurs by Direct Oxidation without an Epoxide Intermediate.”
- Chowdhury, G., Calcutt, M.W., Nagy, L.D., and Guengerich, F.P. (2012) *Biochemistry* 51, 9995-10007. “Oxidation of Methyl and Ethyl Nitrosamines by Cytochromes P450 2E1 and 2B1.”
- Kim, D., Cha, G.-S., Nagy, L.D., Yun, C.-H., and Guengerich, F.P. (2014) *Biochemistry* 53, 6161-6172. “Kinetic Analysis of Lauric Acid Hydroxylation by Human Cytochrome P450 4A11.”
- Yoshimoto, F. K., and Guengerich, F. P. (2014) *J. Am. Chem. Soc.* 136, 15016-15025. “Mechanism of the Third Oxidative Step in the

Conversion of Androgens to Estrogens by Cytochrome P450 19A1
Steroid Aromatase.”

- Pallan, P.S., Wang, C., Lei, L., Yoshimoto, F.K., Auchus, R.J., Waterman, M.R., Guengerich, F.P., and Egli, M. **(2015)** *J. Biol. Chem.* 290, 13128-13143. “Human Cytochrome P450 21A2, the Major Steroid 21-Hydroxylase. Structure of the Enzyme-Progesterone Substrate Complex and Rate-Limiting C-H Bond Cleavage.”
- Yoshimoto, F.K., Gonzalez, E., Auchus, R.J., and Guengerich, F.P. **(2016)** *J. Biol. Chem.* 291, 17143-17164. “Mechanism of 17 α ,20-Lyase and New Hydroxylation Reactions of Human Cytochrome P450 17A1. ¹⁸O-Labeling and Oxygen Surrogate Evidence for a Role of a Perferryl Oxygen.”
- Yoshimoto, F.K., Jung, I.-J., Goyal, S., Gonzalez, E., and Guengerich, F.P. **(2016)** *J. Am. Chem. Soc.* 138, 12124-12141. “Isotope-labeling Studies Support an Electrophilic Compound I Iron Active Species (FeO³⁺) for the Carbon-carbon Bond Cleavage Reaction of the Cholesterol Side Chain Cleavage Enzyme, Cytochrome P450 11A1 (P450_{scc}).”

- Guengerich, F.P. (2013) *J. Labelled Compds. Radiopharmaceuticals* 56, 428-431. “Kinetic Deuterium Isotope Effects in Cytochrome P450 Reactions.”
- Guengerich, F.P. (2017) *Methods Enzymol.* 596, 217-238. “Kinetic Deuterium Isotope Effects in Cytochrome P450 Enzyme Reactions.”
- Johnson, K. M., Phan, T. T. N., Albertolle, M. E., and Guengerich, F. P. (2017) *J. of Biol. Chem.* 292, 13672-13687. “Human Mitochondrial Cytochrome P450 27C1 is Localized in Skin and Preferentially Desaturates *trans*-Retinol to 3,4-Dehydroretinol.”
- Guengerich, F. P., and Fekry, M. I. (2020) *ACS Catalysis* 10, 5008-5022. “Methylene Oxidation of Alkyl Sulfates by Cytochrome P450_{BM-3} and a Role for Conformational Selection in Substrate Recognition.”
- McCarty, K. D., Liu, L., Tateishi, Y., Wapshott-Stehli, H. L., and Guengerich, F. P. (2023) *J. Biol. Chem.*, in press. Nov 23:105495. doi: 10.1016/j.jbc.2023.105495. “The Multi-Step Oxidation of Cholesterol to Pregnenolone by Human Cytochrome P450 11A1 is Highly Processive.”

12. I also have experience working with retinoids, including deuterated retinoids, as evidenced by my publications, including the following:

- Enright, J. M., Toomey, M. B., Sato, S. Y., Temple, S. E., Allen, J. R., Fujiwara, R., Kramlinger, V. M., Nagy, L. D., Johnson, K. M., Xiao, Y., How, M. J., Johnson, S. L., Roberts, N. W., Kefalov, V. J., Guengerich, F. P., and Corbo, J. C. (2015) *Current Biology* 25, 3048-3057 “Cyp27c1 Red-Shifts the Spectral Sensitivity of Photoreceptors by Converting Vitamin A1 into A2.”
- Kramlinger, V. M., Nagy, L. D., Fujiwara, R., Johnson, K. M., Phan, T. T., Xiao, Y., Enright, J. M., Toomey, M. B., Corbo, J. C., and Guengerich, F. P. (2016) *FEBS Letters* 590, 1304-1312. “Human Cytochrome P450 27C1 Catalyzes 3,4-Desaturation of Retinoids.”
- Johnson, K. M., Phan, T. T. N., Albertolle, M. E., and Guengerich, F. P. (2017) *J. Biol. Chem.* 292, 13672-13687 “Human Mitochondrial Cytochrome P450 27C1 is Localized in Skin and Preferentially Desaturates *trans*-Retinol to 3,4-Dehydroretinol.” (also listed in the previous paragraph, as this paper involved deuterated retinoids)
- Glass, S. M., and Guengerich, F. P. (2021) *J. Biol. Chem.* 297, 101142. “Cellular Retinoid-binding Proteins Transfer Retinoids to Human Cytochrome P450 27C1 for Desaturation.”

- Glass, S. M., Webb, S. N., and Guengerich, F. P. (2021) *Arch. Biochem. Biophys.* 714, 109076. “Binding of Cytochrome P450 27C1, a Retinoid Desaturase, to Its Accessory Protein Adrenodoxin.”
- Glass, S. M., Tateishi, Y., Guengerich, F. P., and Wang, H. J. (2023) *Arch. Biochem. Biophys.* 743, 109669. “3,4-Desaturation of Retinoic Acids by Cytochrome P450 27C1 Prevents P450-mediated Catabolism.”

II. SCOPE OF WORK

13. I understand that a petition is being filed with the United States Patent and Trademark Office for Inter Partes Review of U.S. Patent No. 9,486,432 to Ilyas Washington (“the ’432 patent,” attached as EX1001), entitled “Compositions and Methods for Treating Macular Degeneration.” I understand that the ’432 patent is assigned to The Trustees of Columbia University in the City of New York.

14. I have been retained by Gene Company Pty Ltd (“Gene Company”) to offer an expert opinion on the validity of claims 1-28 of the ’432 patent. I receive \$700 per hour for my services. No part of my compensation is dependent on my opinions or on the outcome of this proceeding.

15. I have been specifically asked to provide my opinion on the unpatentability of claims 1-28 of the ’432 patent as of September 12, 2007 (the earliest claimed priority date, sometimes called the critical date). In connection

with this analysis, I have reviewed the '432 patent. I have also reviewed and considered various other documents in arriving at my opinions and cite them in this declaration.

III. LEGAL STANDARDS

16. I understand that the United States Patent Office may cancel issued claims of the '432 patent if the Petitioner (here, Gene Company) demonstrates that the claims fail to satisfy the requirements of patentability that the claims must be novel and non-obvious. I understand that the claims should be understood according to their ordinary and customary meaning as understood by a person of ordinary skill in the art ("POSA") at the time of the invention in light of the language of the claims, the specification, and the prosecution history of record. I have been provided a copy of the prosecution history of the '631 application and the '975 application of record, which are as EX1031 and EX1032, respectively.

A. Anticipation

17. I understand that anticipation requires disclosure in a single reference of every element of a claim. I understand that prior art disclosure of a species anticipates a genus that encompasses the species, that prior art disclosure of a point in a claimed range anticipates the claimed range, and that prior art disclosure of a range overlapping with a claimed range anticipates the claimed range where no criticality has been demonstrated for the claimed range.

B. Obviousness

18. I understand that a claimed invention is unpatentable for obviousness if the differences between the invention and the prior art are such that the subject matter as a whole would have been obvious to a person of ordinary skill in the art at the time the invention was made (i.e., at the critical date).

19. It is further my understanding that a determination of obviousness requires inquiries into: (1) the scope and contents of the prior art when the invention was made; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the pertinent art when the invention was made; and, to the extent they exist, (4) secondary indicia of obviousness.

20. I understand that a claim is obvious if all of the claimed elements were known in the prior art and one skilled in the art would have combined the elements as claimed with a reasonable expectation of success. I understand that obviousness may also be shown by demonstrating that it would have been obvious to modify what is taught in a single piece of prior art to create the patented invention or by combining teachings of two or more prior art references. I understand that in order for a claimed invention to be considered obvious based on a combination of prior art references, there must be some rational underpinning for the proposed combination. I understand that improper hindsight must not be used when determining whether a person of ordinary skill in the art would make the

proposed combination. Thus, a conclusion of obviousness must be firmly based on knowledge and skill of a person of ordinary skill in the art at the time the invention was made without the improper use of post-filing knowledge.

21. In determining whether a particular combination of prior art teachings would have been obvious, I understand that the following are examples of approaches and rationales that may be considered:

- (a) Combining prior art elements according to known methods to yield predictable results;
- (b) Simple substitution of one known element for another to obtain predictable results;
- (c) Use of a known technique to improve similar devices (methods, or products) in the same way;
- (d) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;
- (e) Applying a technique or approach that would have been “obvious to try” (choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success);
- (f) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other

market forces if the variations would have been predictable to one of ordinary skill in the art; or

(g) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

22. I understand that obviousness may be established by showing that all of the claimed elements were known in the prior art and that a person skilled in the art would have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded nothing more than predictable results to one of ordinary skill in the art.

IV. OVERVIEW OF THE '432 PATENT

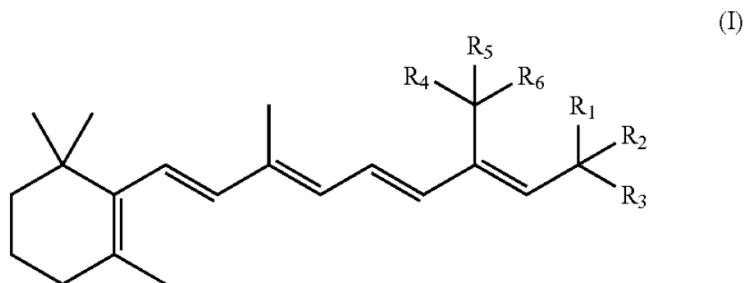
23. I have reviewed the '432 patent in its entirety including the specification, the figures, and the claims. The title of the '432 patent is "Compositions and Methods for Treating Macular Degeneration." The Abstract of the '432 patent states:

Methods of retarding formation of a lipofuscin pigment in the retina and of treating or ameliorating the effects of a disease characterized by an accumulation of a lipofuscin pigment in a retina are provided. These methods include the step of administering to a patient in need thereof a substituted C₂₀-retinoid in an amount sufficient to reduce accumulation of a lipofuscin pigment in the retina. Further provided are methods of retarding formation of A2E and/or ATR-dimer by replacing an all-trans-retinal (ATR) substrate with a C₂₀-D₃-retinal substrate under conditions sufficient to impede the formation of A2E. Compositions for retarding formation of a lipofuscin pigment in the

retina containing a substituted C₂₀-retinoid and a pharmaceutically acceptable carrier are also provided.

EX1001 (the '432 patent), Abstract. For this quote, and throughout my declaration, I have omitted internal citations unless otherwise stated.

24. Among other substituted C₂₀-retinoids, the '432 patent discusses substituting 1-3 of the hydrogens at C₂₀ with fluorine or deuterium. For example, the '432 patent discloses “a composition comprising a pharmaceutically acceptable carrier and a compound according to formula I.” EX1001 (the '432 patent), 5:42-44. Formula I of the '432 patent is reproduced below.



wherein:

R₁ is oxo or H;

R₂ is H or nothing;

R₃ is hydroxy or oxo or CHR₇ where R₇ forms a carotenoid and

R₄, R₅, and R₆ are independently selected from the group consisting of ¹H, ²H, ³H, halogen, and C₁₋₈alkyl.

EX1001 (the '432 patent), 5:42-62.

25. Further, the '432 patent assumes that C₂₀-deuterated retinoids are non-toxic. For example, the '432 patent explains that “[d]euterated vitamin A is widely used in humans and shows no toxicity. Thus, a treatment using a C₂₀-D₁₋₃-

retinoid should be an effective and non-toxic therapy to treat or ameliorate macular degeneration without adverse visual effects.” EX1001 (the ’432 patent), 8:17-21.

26. The ’432 patent notes that effective dosage forms, modes of administration, and dosage amounts are determined “empirically” and that making such determination “is within the skill of the art.”

Effective dosage forms, modes of administration, and dosage amounts, in addition to those disclosed above, *may be determined empirically*, and making such determinations is *within the skill of the art*.

EX1001 (the ’432 patent), 14:31-34. In this quote and throughout my declaration, all bold and italic emphases are added unless stated otherwise.

27. Consistent with its statement that modes of administration will be determined empirically using conventional knowledge within the skill in the art, the ’432 patent lists a variety of administration means, including orally by ingestion or by direct administration to the eyes.

A compound of the present invention *may be administered in any desired and effective manner*: as pharmaceutical compositions for oral ingestion, or as an ointment or drop for local administration to the eyes, or for parenteral or other administration in any appropriate manner such as intraperitoneal, subcutaneous, topical, intradermal, inhalation, intrapulmonary, rectal, vaginal, sublingual, intramuscular, intravenous, intraarterial, intrathecal, or intralymphatic. Further, a compound of the present invention may be administered in conjunction with other treatments. A compound or composition of the present invention maybe encapsulated or otherwise protected against gastric or other secretions, if desired.

EX1001 (the '432 patent), 14:49-56. The '432 provides no data or evaluation of the effects of any kind of local administration of the claimed composition.

28. The '432 patent, citing Remington's Pharmaceutical Sciences (EX1017 "Remington"), further states that the compound may be formulated into pharmaceutically acceptable dosage forms by conventional methods that are known to persons skilled in the art.

Regardless of the route of administration selected, the compounds of the present invention are formulated into pharmaceutically-acceptable dosage forms by *conventional methods known to those of skill in the art*. See, e.g., Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, Pa.).

EX1001 (the '432 patent), 15:3-8.

29. Again citing Remington, the '432 patent further notes that pharmaceutically acceptable carriers are well known in the art, determined using ordinary skill, and include, among other things, water, saline solution, and corn oil.

Pharmaceutically acceptable carriers are well known in the art (see, e.g., Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, Pa.) and The National Formulary (American Pharmaceutical Association, Washington, D.C.)) and include sugars (e.g., lactose, sucrose, mannitol, and sorbitol), starches, cellulose preparations, calcium phosphates (e.g., dicalcium phosphate, tricalcium phosphate and calcium hydrogen phosphate), sodium citrate, *water, aqueous solutions* (e.g., *saline*, sodium chloride injection, Ringer's injection, dextrose injection, dextrose and sodium chloride injection, lactated Ringer's injection), alcohols (e.g., ethyl alcohol, propyl alcohol, and benzyl alcohol), polyols (e.g., glycerol, propylene glycol, and polyethylene glycol), organic esters (e.g., ethyl oleate and triglycerides), biodegradable polymers (e.g., polylactide-polyglycolide, poly(orthoesters), and poly(anhydrides)), elastomeric

matrices, liposomes, microspheres, *oils* (e.g., *corn*, germ, olive, castor, sesame, cottonseed, and groundnut), cocoa butter, waxes (e.g., suppository waxes), paraffins, silicones, talc, silicylate, etc. Each pharmaceutically acceptable carrier used in a pharmaceutical composition of the invention must be “acceptable” in the sense of being compatible with the other ingredients of the formulation and not injurious to the subject. Carriers suitable for a selected dosage form and intended route of administration are *well known in the art*, and acceptable carriers for a chosen dosage form and method of administration can be *determined using ordinary skill in the art*.

EX1001 (the '432 patent), 15:9-27.

30. The '432 patent further discloses additional ingredients and materials known in the art and commonly used with pharmaceutical compositions, vitamin supplements, and nutraceuticals. For example, the '432 patent discloses:

The pharmaceutical compositions or vitamin supplements or nutraceuticals of the invention may, optionally, contain additional ingredients and/or materials commonly used in such pharmaceutical compositions or vitamin supplements or nutraceuticals. These ingredients and materials are well known in the art and include (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and silicic acid; (2) binders, such as carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, hydroxypropylmethyl cellulose, sucrose and acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, sodium starch glycolate, cross-linked sodium carboxymethyl cellulose and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as cetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, and sodium lauryl sulfate; (10) suspending agents, such as ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth; (11) buffering

agents; (12) excipients, such as lactose, milk sugars, polyethylene glycols, animal and vegetable fats, oils, waxes, paraffins, cocoa butter, starches, tragacanth, cellulose derivatives, polyethylene glycol, silicones, bentonites, silicic acid, talc, salicylate, zinc oxide, aluminum hydroxide, calcium silicates, and polyamide powder; (13) inert diluents, such as water or other solvents; (14) preservatives; (15) surface-active agents; (16) dispersing agents; (17) control-release or absorption-delaying agents, such as hydroxypropylmethyl cellulose, other polymer matrices, biodegradable polymers, liposomes, microspheres, aluminum monostearate, gelatin, and waxes; (18) opacifying agents; (19) adjuvants; (20) wetting agents; (21) emulsifying and suspending agents; (22), solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan; (23) propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane; (24) antioxidants; (25) agents which render the formulation isotonic with the blood of the intended recipient, such as sugars and sodium chloride; (26) thickening agents; (27) coating materials, such as lecithin; and (28) sweetening, flavoring, coloring, perfuming and preservative agents.

EX1001 (the '432 patent), 15:37-66 and 16:1-19.

31. The '432 patent broadly claims a pharmaceutical composition comprising any of a group of C₂₀-deuterium enriched retinoids in a pharmaceutically acceptable carrier.

32. For example, claim 1 of the '432 patent recites:

1. A pharmaceutical composition comprising
a substituted C₂₀-D₁₋₃-retinoid and
a pharmaceutically acceptable carrier,

wherein the C₂₀-D₁₋₃-retinoid is selected from the group consisting of C₂₀-D₁₋₃-retinol, C₂₀-D₁₋₃-retinol ester, C₂₀-D₁₋₃ retinal and a C₂₀-D₁₋₃-pro-vitamin A carotenoid.

33. Each of claims 2-28 depends directly or indirectly from claim 1. The text of each of claims 2-28 is provided in Sections XI-XIII below.

V. PROSECUTION HISTORY OF THE '432 PATENT

34. I understand from the face of the '432 patent that it issued from U.S. Application No. 14/510,975 (filed on October 9, 2014), which was a divisional of U.S. Application No. 12/733,631 (filed as PCT/US2008/010676 on September 12, 2008). The '631 application issued as U.S. Patent No. 8,877,809 and reissued as RE47,045. The '432 patent claims priority to U.S. Provisional Patent Application No. 62/993,379, filed on September 12, 2007. For purposes of my opinions, I have assumed that the claims are entitled to a priority date of September 12, 2007.

35. When evaluating whether to issue the '432 patent claims, I understand that the Examiner issued indefiniteness and written description rejections under section 112, as well as a non-statutory obviousness-type double patenting rejection over U.S. Patent Application No. 12/733,631 (the '631 application (now, U.S. Patent No. 8,877,809)). EX1032 (file history of '975 application), 57-60. In response to the section 112 rejections, I read that the patent applicant canceled some claims and amended a claim. EX1032 (file history of '975 application), 40. In response to the double patenting rejection, I read that the patent applicant filed a

terminal disclaimer over the '631 application. EX1032 (file history of '975 application), 40-41. During prosecution of the '432 patent claims, I understand that the Examiner did not assert any prior art-based rejections for anticipation under section 102 or obviousness under section 103. EX1032 (file history of '975 application), 55-61.

36. During prosecution of the '631 application, I read that the Examiner asserted references against the patent applicant. EX1031 (file history of '631 application), 240-242 (asserting obviousness over Radu (EX1035) and Boehm (EX1052); also asserting WO2005/065669 to Lang et al. and US2007/0015827 to Widder et al. (a different application from the Widder reference (EX1009) I discuss in this declaration) to motivate addition of "secondary components").

37. When asserting the Radu reference (EX1035) against the patent applicant, the Examiner stated that "Radu teaches the use of isotretinoin, a C₂₀-retinoid for inhibition of lipofuscin pigment in a retina" and that "Radu also teaches that lipofuscin pigment is A2E." EX1031 (file history of '631 application), 240. The Examiner further noted that "Radu differs from the claimed invention in using substituted C₂₀-D₁₋₃ and the use of the secondary components." EX1031 (file history of '631 application), 240. In response, the patent applicant argued that isotretinoin is a different compound than the compounds claimed in the '631 application and further noted that the claims "specifically exclude isotretinoin, the

pharmacological active agent tested by Radu.” EX1031 (file history of ’631 application), 167. The patent applicant further stated during prosecution that:

Although Radu teaches that 13-*cis*-retinoic acid (also known as isotretinoin), a non-substituted retinoid, inhibits formation of A2E dimers and lipofuscin, isotretinoin however does so by a very different mechanism than retinoids deuterated at the C₂₀ position. Isotretinoin is a retinoid that inhibits lipofuscin accumulation by slowing the visual cycle, which is known to lead to side effects such as night blindness and slowed dark adaptation. Radu specifically writes that “isotretinoin (Accutane) has been shown to slow the synthesis of 11-*cis*-retinaldehyde and regeneration of rhodopsin by inhibiting 11-*cis*-retinol dehydrogenase in the visual cycle.”

EX1031 (file history of ’631 application), 167.

38. The patent applicant further argued that, in contrast to Radu:

Applicant discovered that instead of inhibiting the visual cycle, the described C₂₀-deuterated retinoids (excluding at least isotretinoin and retinylamine, which would inhibit the retinoid pathway), could replace vitamin A with a C₂₀-deuterated vitamin A, which in itself would dimerize in the eye more slowly than non-deuterated vitamin A, because deuterium atoms are lost more slowly from the C₂₀ position than protium during vitamin A dimerization.

EX1031 (file history of ’631 application), 168.

39. Unlike Radu, Olson 1988 (EX1006), which I describe in extensive detail in this declaration (see Section IX.B), discloses a deuterated retinoid at the carbon 20 (C₂₀) position. For example, Olson 1988 discloses the synthesis of “20,20,20-trideutero, 14,20,20,20-tetradeutero, 12,14,20,20,20-pentadeutero, and 10,19,19,19-tetradeutero analogs of retinoic acid ethyl ester and retinyl acetate.”

EX1006 (Olson 1988), 11. Olson 1988 further suggests that use of deuterated

retinol is useful for biological studies regarding metabolism of vitamin A in animals (including humans). EX1006 (Olson 1988), 11. Olson 1989 (EX1007), which is a subsequent publication of Olson 1988, discloses a vitamin A stable isotope dilution assay study in humans using a deuterated retinoid (that was described in Olson 1988) in a pharmaceutically acceptable excipient (e.g., corn oil). EX1007 (Olson 1989), 714.

40. The Examiner also asserted the Boehm reference (EX1052) against the patent applicant during prosecution of the '631 application. Citing Boehm, the Examiner stated that "Boehm discloses a substituted C₂₀ retinoid. Tritium labeled is taught in page 5, line 13-19, formula V, and deuterium labeled is taught on page 6, lines 15-37." EX1031 (file history of '631 application), 240. The Examiner, referring to Boehm, further stated that:

It would have been obvious to a person skilled in the art to use the labeled retinoids instead of retinoid for the inhibition of lipofuscin and treat a disease, such as, [S]targardt's characterized by lipofuscin accumulation and to improve efficacy of treatment, motivated by Boehm, which teaches the advantage of radio labeled retinoid in bind to the retinoid receptors.

EX1031 (file history of '631 application), 240-241.

41. In response, I read that the patent applicant argued that Boehm does not disclose a C₂₀ deuterated retinoid as claimed in the '631 application. EX1031 (file history of '631 application), 168. For example, the patent applicant stated that "[w]hile it is true that Boehm discloses a labeled retinoid, the labeling is not at the

C₂₀ position but at the C₁₁ position, and such labeled retinoids do not fall into the claimed genus, retinoid specifically substituted at the carbon C₂₀ position with deuterium.” EX1031 (file history of ’631 application), 168. The patent applicant further stated that:

In this application, the Applicant discloses retinoids selectively substituted at the retinoid’s carbon number 20, the C₂₀ position. In particular, the claims currently amended focus only on retinoids whereby the protium (¹H or H) at the carbon 20 position have been replaced with deuterium (²H or D).

EX1031 (file history of ’631 application), 156.

42. Boehm is different than the Olson 1988 and Olson 1989 references that are described in Sections IX.A and IX.B, respectively. For example, in contrast to Boehm, Olson 1988 discloses a deuterated retinoid at the carbon 20 (C₂₀) position by disclosing the synthesis of “20,20,20-trideutero, 14,20,20,20-tetradeutero, 12,14,20,20,20-pentadeutero, and 10,19,19,19-tetradeutero analogs of retinoic acid ethyl ester and retinyl acetate.” EX1006 (Olson 1988), 11. Olson 1988 further suggests that use of deuterated retinol is useful for biological studies regarding metabolism of vitamin A in animals (including humans). EX1006 (Olson 1988), 11. Olson 1989 discloses a vitamin A stable isotope dilution assay study in humans using a deuterated retinoid in a pharmaceutically acceptable excipient (e.g., corn oil). EX1007 (Olson 1989), 714.

43. I also read in the prosecution history of the '631 application that the patent applicant argued that Boehm provided no reason to make the C₂₀ substitution. EX1031 (file history of '631 application), 169. For example, the patent applicant stated that “tritium or deuterium in any position other than C₂₀ would not be expected to have any effect on A2E or lipofuscin formation.” EX1031 (file history of '631 application), 169. The patent application further stated that:

Besides, Boehm provides no guidance with respect to how to modify the tritium or deuterium labeled retinoids disclosed therein to obtain a deuterium or tritium labeled retinoid that could slow A2E formation. In particular, Boehm provides no reason to think that substituting deuterium at position 20 would reduce lipofuscin accumulation or lead to any other desirable result. Thus, Boehm provides no motivation to modify Radu's isotretinoin by substituting deuterium at position 20.

EX1031 (file history of '631 application), 169-170.

44. However, Mata (EX1010), which I discuss in great detail in Section IX.E below, provides good reason to believe that lipofuscin is formed by removal of a hydrogen from the C₂₀ of prior art vitamin A analogues and that pharmacologically inhibiting this synthesis pathway will slow lipofuscin formation and may provide an effective treatment for macular degeneration.

45. However, despite repeatedly arguing that the asserted prior art references failed to disclose the claimed C₂₀-deuterated retinoids during prosecution of the '631 application, the patent applicant apparently never informed

the Examiner about prior art references that expressly disclosed the claimed C₂₀-deuterated retinoids. For example, based on my reading of the prosecution history of the '631 application, I found no mention by the patent applicant informing the Examiner that Olson 1988 disclosed the claimed C₂₀-deuterated retinoids that the patent applicant repeatedly stated were missing from the asserted prior art. Nor did I find any mention of the Olson 1989 reference in which the group of individuals (e.g., the group in Olson 1988) that made the C₂₀-deuterated retinoids and other deuterated retinoids demonstrated that it was known to formulate deuterated retinoids in a pharmaceutically-acceptable carrier such as corn oil.

46. Further, despite repeatedly arguing that the asserted prior art failed to disclose that deprotonation of carbon 20 was a prerequisite for lipofuscin formation, the patent applicant apparently never informed the Examiner that the prior art (e.g., Mata) publicly attributed *in vivo* lipofuscin formation to reactions involving removal of a hydrogen from carbon-20 (C₂₀) of vitamin A and its active analogues. As I explain in great detail below, a person of ordinary skill in the art would have understood from Mata's disclosure of the biosynthetic pathway for A2E formation that replacing the C₂₀ hydrogens with deuterium would materially slow the formation of A2E. Accounting for the disclosures of Olson 1988, Olson 1989, and Mata, as well as well-known teachings about the primary kinetic isotope effect (KIE) and the use of selective deuterium substitution of pharmaceutical

compounds to slow reactions involving removal of a hydrogen at a particular position (as even noted by the patent applicant during prosecution), it is my opinion that claims 1-28 in the challenged '432 patent would have been obvious before the critical date of September 2007.

VI. LEVEL OF SKILL IN THE ART

47. I have been advised that “a person of ordinary skill in the art” (POSA) is a hypothetical person to whom one could assign a routine task with reasonable confidence that the task would be successfully carried out. I have been advised further that, in determining the level of ordinary skill in the art that someone would have had at the time the claimed invention was made, I should consider: (1) the levels of education and experience of persons working in the field; (2) the types of problems encountered in the field; and (3) the sophistication of the technology.

48. The '432 patent states that “the present invention relates, inter alia, to compounds, compositions, and methods to slow lipofuscin formation/accumulation in order to treat or ameliorate an ophthalmologic disorder, such as macular degeneration, without or with reduced adverse visual effects.” EX1001 (the '432 patent), 1:18-22. More particularly, the '432 patent states that the compounds “may be used to treat or ameliorate an ophthalmologic disorder, such as e.g., macular degeneration, by slowing or limiting the accumulation of age pigments or lipofuscin in the retinal pigment epithelium (‘RPE’) cells of the retina.” EX1001

(the '432 patent), 1:22-28. As I have explained, the patent claims are directed to deuterated vitamin A compounds (e.g., retinol, retinol acetate, retinal) and deuterated carotenoid vitamin A precursors (e.g., β -carotene). The field of the invention of the '432 patent is thus related to the chemistry and biochemistry of vitamin A compounds and carotenoid vitamin A precursors, and the metabolism and kinetics thereof, especially to the deuteration of such compounds.

49. Based on my specialized education, knowledge, training, and experience, I am familiar with the level of skill of a person of ordinary skill in the art as of the critical date. It is my opinion that a person of ordinary skill in the art of the '432 patent in September 2007 would have had an advanced degree (e.g., Ph.D., M.D., M.S., or equivalent), in a field related to pharmacology, chemistry, biochemistry, ophthalmology, or a related field. It is my opinion that this individual would have worked in consultation with a team including, e.g., a biochemist or a chemist familiar with formulating and deuterating compounds for administration together with a practicing physician who diagnoses and treats ophthalmologic disorders, such as macular degeneration.

50. A person of ordinary skill in the art also would have had practical knowledge and experience about metabolism studies, pharmaceutical formulation, and the deuterium kinetic isotope effect. A person of ordinary skill would have

been familiar with prior art pertaining to the above, including the patents and publications discussed herein.

VII. SUMMARY OF OPINIONS

51. As I will explain in detail below, the teachings of Olson 1988 and Olson 1989 render obvious each of claims 1-6 and 28 of the '432 patent.

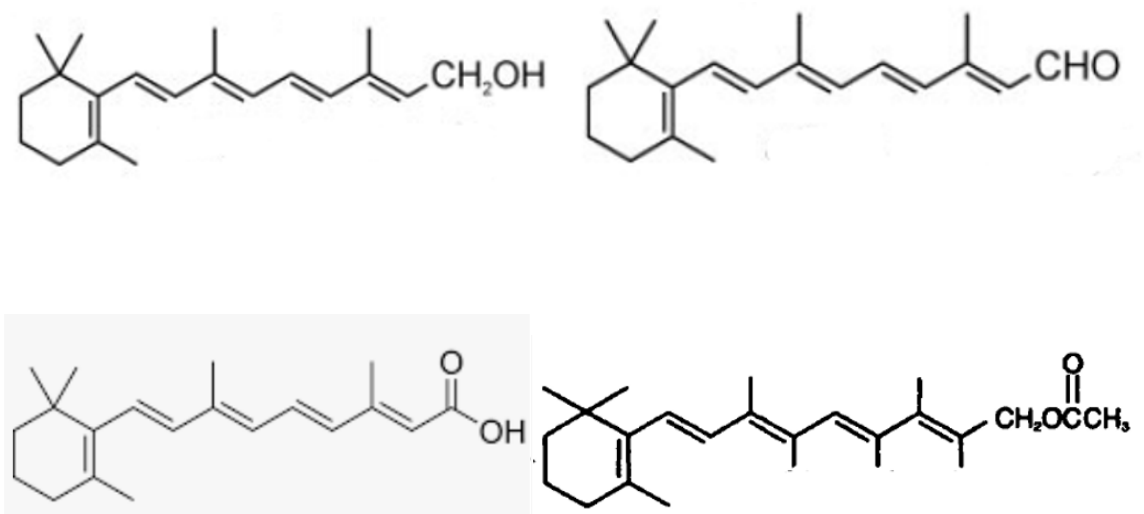
52. The addition of Ortho Pharma (EX1008) also renders each of claims 1-6, 8-23, 25, and 27-28 obvious. The addition of Widder (EX1009) renders each of claims 7, 24, and 26 obvious.

VIII. TECHNICAL BACKGROUND

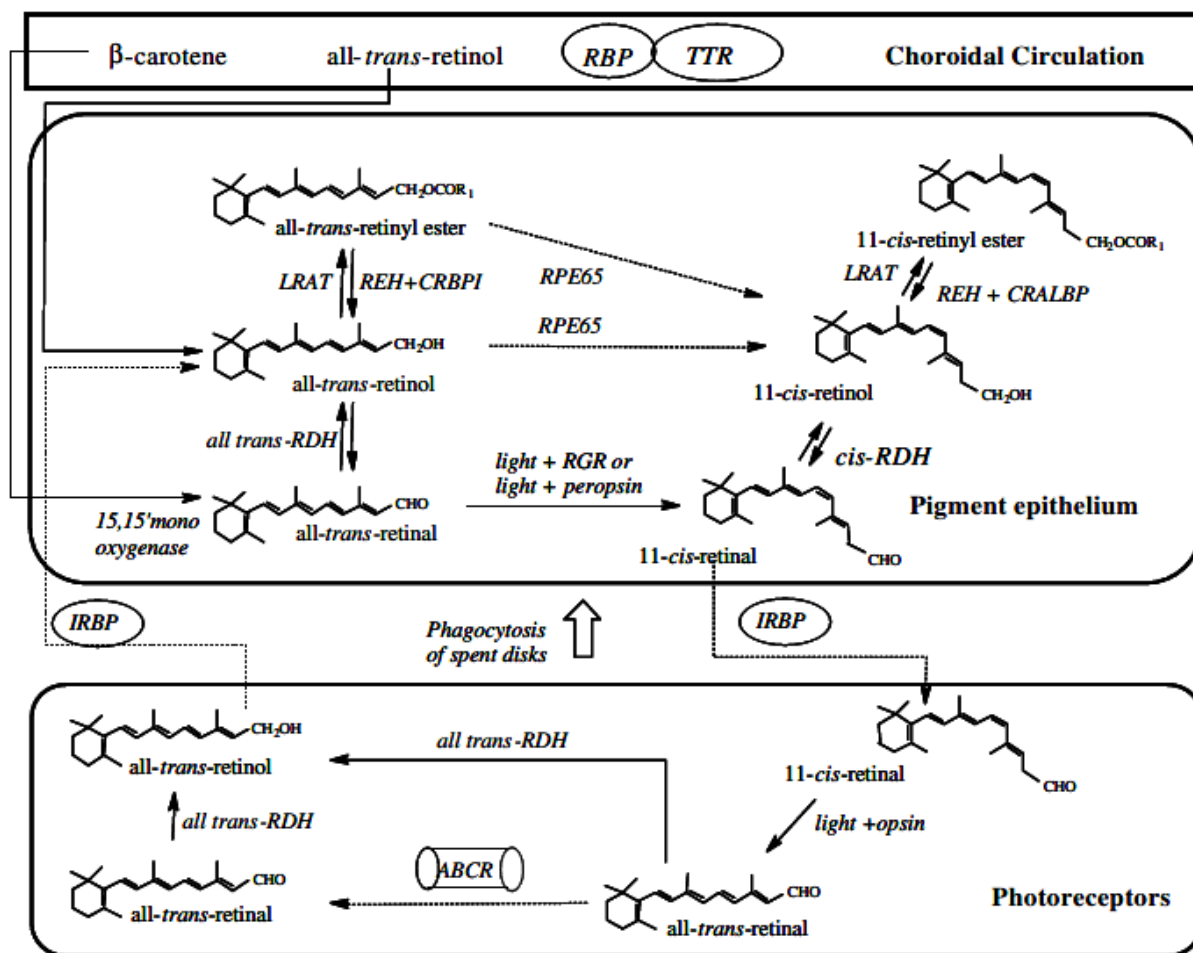
53. As described below, it is my opinion that the '432 patent was not the first to teach: (1) the treatment or prevention of macular degeneration by the administration of vitamin A analogues and by the inhibition of lipofuscin formation; (2) the use of deuterium to slow 1,5-sigmatropic shifts; or (3) the identification of C₂₀ as the site of the 1,5-sigmatropic shift through which undesirable lipofuscin components (e.g., A2E and ATR-dimer) were formed in vivo. It is also my opinion that the '432 patent did not provide the first disclosure of the claimed C₂₀-deuterated retinoids or suggestion to use them in applications that would involve a pharmaceutical composition in a pharmaceutically acceptable carrier.

A. It Was Known to Use Vitamin A Retinoids to Treat and Prevent Ocular Diseases

54. As an initial matter, by 2007, it was well known that vitamin A refers to a group of retinoid compounds. See, e.g., EX1009 (Widder), 15:19-32. I have reproduced below four retinoid compounds of vitamin A, including vitamin A alcohol (retinol, top left), vitamin A aldehyde (retinal, top right), vitamin A acid (retinoic acid, below left), and vitamin A ester (retinyl acetate, below right). See, e.g., EX1009 (Widder), 3-10. Retinoid vitamin A precursor compounds include provitamin A carotenoids such as β -carotene.



55. Vitamin A retinoids were known to be important to eye health because they were known to play an essential role in the “visual cycle.” EX1009 (Widder), 1:12-16. Because the role of vitamin A retinoids in the visual cycle was so prominent and essential, the visual cycle was also referred to as the “retinoid cycle.” EX1009 (Widder), 1:12-16. An illustration of the role of retinoids in the reactions of the visual or retinoid cycle is provided below in a figure reproduced from a 2003 article from Kuska et al.:



EX1050 (Kuska), Fig. 1. Notably, the reactions in the cycle illustrated above do not involve conversion of retinoids at any of carbons 10, 19, or 20. In 2006, inventors Kenneth Widder, Jay Lichter, and Nathan L. Mata published a patent application entitled “Methods and Compositions for Treating Ophthalmic Conditions with Retinyl Derivatives.” The patent application was published on January 19, 2006, under the Patent Cooperation Treaty (PCT) with an international publication number of WO2006/007314A1. I will refer to this PCT patent publication by the last name of the first-listed named inventor, Widder.

56. First, Widder provides an overview of the visual cycle. For example,

Widder states that:

The vertebrate retina contains two types of photoreceptor cells – rods and cones. Rods are specialized for vision under low light conditions. Cones are less sensitive, provide vision at high temporal and spatial resolutions, and afford color perception. Under daylight conditions, the rod response is saturated and vision is mediated entirely by cones. Both cell types contain a structure called the outer segment comprising a stack of membranous discs. The reactions of visual transduction take place on the surfaces of these discs. The first step in vision is absorption of a photon by an opsin-pigment molecule (rhodopsin), which involves 11-*cis* to all-*trans* isomerization of the chromophore. Before light sensitivity can be regained, the resulting all-*trans*-retinal must be converted back 11-*cis*-retinal in a multi-enzyme process which takes place in the retinal pigment epithelium, a monolayer of cells to the retina.

EX1009 (Widder), 16:1-9.

57. Widder further explains that the visual cycle or the retinoid cycle includes a series of enzyme catalyzed reactions that takes place in retinal pigment epithelium and within the outer segment of the rods. EX1009 (Widder), 1:12-16.

Widder teaches that the cycle involves conversion of the retinoid to an all-*trans* isomer and then subsequent regeneration to the *cis* isomer. EX1009 (Widder), 1:12-16. For example, Widder states that:

The *visual cycle or retinoid cycle* is a series of light-driven and enzyme catalyzed reactions in which the active visual chromophore rhodopsin is *converted to an all-trans-isomer that is then subsequently regenerated*. Part of the cycle occurs within the outer segment of the rods and part of the cycle occurs in the retinal pigment epithelium (RPE). Components of this cycle include various

dehydrogenases and isomerases, as well as proteins for transporting intermediates between the photoreceptors and the RPE.

EX1009 (Widder), 1:12-16. Internal citations generally omitted; all bold and italics added as emphasis unless otherwise indicated.

58. Widder explains that vitamin A in the form of retinol, retinal, and retinol (also retinyl) acetate plays a central role in the visual cycle. For example, Widder states that:

Other proteins associated with the visual cycle are responsible for transporting, removing and/or disposing of compounds and toxic products that accumulate from excess production of visual cycle retinoids, such as all-*trans*-retinal (atRAL). For example, *N*-retinylidene-*N*-retinylethanolamine (A2E) arises from the condensation of all-*trans*-retinal with phosphatidylethanolamine. Although certain levels of this orange-emitting fluorophore are tolerated by the photoreceptors and the RPE, excessive quantities can lead to adverse effects, including the production of lipofuscin, and potentially drusen under the macula. In addition, A2E can be cytotoxic to the RPE, which can lead to retinal damage and destruction. Drusen are extracellular deposits that accumulate below the RPE and are risk factors for developing age-related macular degeneration. Thus, removal and disposal of toxic products that arise from side reactions in the visual cycle are important because several lines of evidence indicate that the over-accumulation of toxic products is partially responsible for the symptoms associated with the macular degenerations and retinal dystrophies.

EX1009 (Widder), 1:17-28.

59. Widder further provides that:

Vitamin A in serum is delivered to extra-hepatic target tissues and immediately esterified by the membrane-bound enzyme LRAT. LRAT catalyzes the transfer of a fatty acid from membrane phospholipids to retinol thereby generating all-*trans* retinyl esters, the

principal storage form of vitamin A in all tissues. In the RPE, all-*trans* retinyl esters are the sole substrate for a unique isomerase enzyme which generates a light-sensitive visual chromophore precursor, 11-*cis* retinol. Subsequent oxidation of this retinoid and conjugation to the opsin apoprotein in the retina yields rhodopsin.

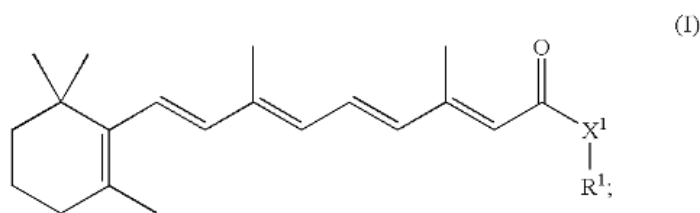
EX1009 (Widder), 15:19-24. Widder thus explains that the body creates visual stimuli by taking all-*trans* retinol ester (also called retinyl ester), converting the all-*trans* retinol ester into 11-*cis* retinal (which is a visual chromophore), and using light exposure to isomerize 11-*cis* retinal into all-*trans* retinal.

60. In addition to teaching that vitamin A is essential to the visual cycle, Widder also teaches that it was desirable to reduce A2E formation, the accumulation of which was known to be associated with eye disorders including macular degeneration. EX1009 (Widder), 1:19-33. For example, Widder teaches that reducing serum retinol levels in the body was one way to treat ophthalmic conditions associated with the overproduction of waste products that accumulate during the course of the visual cycle to treat ophthalmic conditions such as macular degeneration. EX1009 (Widder), 2:35-37. Widder, in its Abstract, states that:

Compounds that cause reversible night blindness may be used to treat ophthalmic conditions associated with the overproduction of waste products that accumulate during the course of the visual cycle. We describe methods and compositions using such compounds and their derivatives to treat, for example, the macular degenerations and dystrophies or to alleviate symptoms associated with such ophthalmic conditions. Such compounds and their derivatives may be used as single agent therapy or in combination with other agents or therapies.

EX1009 (Widder), Abstract. As such, Widder teaches that compounds for treating ophthalmic conditions such as macular degeneration may be used as single agent therapy or in combination with other agents or therapies.

61. To modulate the serum retinol levels in a mammal, Widder describes the administration of a compound having the structure of Formula (I), which I have reproduced below.



wherein X_1 is selected from the group consisting of NR^2 , O, S, CHR^2 ; R^1 is $(CHR^2)_x-L^1-R^3$, wherein x is 0, 1, 2, or 3; L^1 is a single bond or $-C(O)-$; R^2 is a moiety selected from the group consisting of H, (C_1-C_4) alkyl, F, (C_1-C_4) fluoroalkyl, (C_1-C_4) alkoxy, $-C(O)OH$, $-C(O)-NH_2$, $-(C_1-C_4)$ alkylamine, $-C(O)-(C_1-C_4)$ alkyl, $-C(O)-(C_1-C_4)$ fluoroalkyl, $-C(O)-(C_1-C_4)$ alkylamine, and $-C(O)-(C_1-C_4)$ alkoxy; and R^3 is H or a moiety, optionally substituted with 1-3 independently selected substituents, selected from the group consisting of (C_2-C_7) alkenyl, (C_2-C_7) alkynyl, aryl, (C_3-C_7) cycloalkyl, (C_5-C_7) cycloalkenyl, and a heterocycle, provided that R^3 is not H when both x is 0 and L^1 is a single bond; or an active metabolite, or a pharmaceutically acceptable prodrug or solvate thereof.

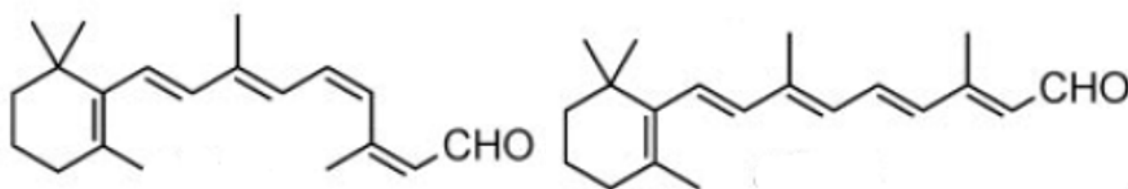
EX1009 (Widder), 3:1-12. Widder thus provides an example of administering altered retinoid compounds for the treatment of macular degeneration.

62. For obvious reasons, Widder teaches that it is preferable to reduce A2E/lipofuscin formation without directly inhibiting a visual cycle protein. For example, Widder states that:

In addition, (a) administration of an agent or agents that lower the levels of serum retinol in a patient ***without modulating at least one enzyme of the visual cycle*** or (b) administration of an agent that modulate at least one enzyme of the visual cycle without lowering levels of serum retinol in a patient, by themselves, may also provide a treatment for such dystrophies and degenerations or the symptoms associated thereof. Assays, such as those described herein, may be used to select further agents possessing this dual action, including agents selected from compounds having the structure of Formula (I) as well as other agents. Putative lead compounds include other agents known or demonstrated to effect the serum level of retinol.

63. EX1009 (Widder), 46:39-47:6. Widder explains that the administration of an agent that lowers the levels of serum retinol in a patient but does not modulate an enzyme of the visual cycle can provide treatment for macular degeneration. Widder thereby reflects that it was known in the art that it was desirable to inhibit the undesirable lipofuscin-associated side effects of the visual cycle without interfering with the visual cycle itself. I have reproduced images of the structures of 11-*cis* retinal below (left) and all-*trans* retinal below (right).

EX1009 (Widder), 47:30-31.



64. Widder's solution for reducing lipofuscin associated A2E formation to treat macular degeneration and other ophthalmic disorders was to reduce serum retinoid levels to avoid more drastically inhibiting the visual cycle. Given that the body carefully regulates serum retinoid levels, a person of ordinary skill in the art would have recognized that it was desirable to reduce lipofuscin associated A2E formation more directly without altering the body's regulation of serum retinoid levels.

65. In 2004, for example, Harold C Furr, Michael H Green, Marjorie Haskell, Najat Mokhtar, Penelope Nestel, Sam Newton, Judy D Ribaya-Mercado, Guangwen Tang, Sherry Tanumihardjo, and Emorn Wasantwisut published an article in the periodical publication *Public Health Nutrition* entitled "Stable isotope dilution techniques for assessing vitamin A status and bioefficiency of provitamin A carotenoids in humans." For convenience, I will refer to this article by the last name of the first-listed author, Furr.

66. Furr discloses that the body regulates the plasma concentration of vitamin A because vitamin A, in addition to being essential for the visual cycle, also was known to be potentially toxic. For example, Furr states that:

The *plasma concentration of retinol* in the nutritionally adequate individual is *tightly regulated by homeostatic mechanisms*. Mathematical modelling indicates that vitamin A is extensively recirculated from extrahepatic tissues to the liver, and this system of storage and recirculation elegantly accommodates excess of a

potentially *toxic nutrient while ensuring adequate amounts* of retinol to all tissues during dietary insufficiency.

EX1019 (Furr), 596. Furr teaches that inadequate levels of vitamin A can lead to night blindness: “[n]ight blindness is a response to pronounced vitamin A deficiency.” EX1019 (Furr), 596. In addition, Furr teaches that it was known that inadequate levels of vitamin A can lead to corneal damage. EX1019 (Furr), 596.

67. Furr discloses that one way the body controls vitamin A concentrations in vulnerable tissues is to store excess vitamin A in the liver. For example, Furr notes that “Vitamin A in excess of immediate requirements is stored as retinyl esters predominantly in the liver, although other tissues contain some stores. Vitamin A is released from the liver as retinol and transported in plasma by retinol-binding protein.” EX1019 (Furr), 596. Accordingly, a person having ordinary skill in the art would have recognized before 2007 that it was desirable to more directly reduce lipofuscin formation, including A2E formation, without altering the body’s regulation of serum retinol concentrations.

68. By 2007, vitamin A deficiency also was known to be a major global public health problem. Furr explained in 2004 that vitamin A deficiency is a global health problem. Furr states, for example, that:

Vitamin A deficiency is a major public health problem in many parts of the world: over 131 million children of pre-school age are vitamin A-deficient, and 4.4 million pre-school children are afflicted with xerophthalmia.

EX1019 (Furr), 596.

69. Furr explains that “[v]itamin A is obtained from the diet as provitamin A carotenoids from fruit and vegetables, or as pre-formed retinyl esters from liver, eggs, dairy products or fortified foods.” EX1019 (Furr), 596. Retinyl acetate (also called retinol acetate) was thus the form of vitamin A in which the body naturally obtained and stored the vitamin. The body then naturally draws on this form of the vitamin to form the 11-*cis* retinal that will be converted into all-*trans* retinal to generate visual signals in the brain as part of the visual cycle, as I explained above.

70. Furr further discloses that β -carotene (famously found in carrots) was a well-known example of the 50 known pro-vitamin A carotenoids and that the *in vivo* provitamin A value of these carotenoids from foods can be determined. For example, Furr states that:

Of the over 600 *carotenoids* that have been identified in nature, only about **50 are precursors of vitamin A**. Of these, the major provitamin A carotenoids in the human diet are **β -carotene, α -carotene and β -cryptoxanthin**. The *in vivo* provitamin A value of these carotenoids from foods is dependent on a number of factors that have been characterized as bioaccessibility, bioavailability, bioconversion and bioefficiency. Bioaccessibility is defined as the fraction of total dietary carotenoid made available for absorption in the gut. Bioavailability is defined as the fraction of dietary carotenoid absorbed from food. Bioconversion is defined as the ratio of retinol formed to total provitamin A carotenoid absorbed. Bioefficiency is defined as the ratio of retinol formed to the total provitamin A carotenoid in the diet.

EX1019 (Furr), 601. Accordingly, a person of ordinary skill in the art was well aware before 2007 to treat ophthalmic disorders by administering any of retinol, retinal, retinal acetate or other retinol esters, or pro-vitamin A carotenoids such as β -carotene.

71. Furr further explains that various techniques have been employed to assess the body's stores and deployment of vitamin A. Furr discloses that vitamin A status can be assessed through various approaches, including physiological indicators such as night blindness, clinical signs such as corneal damage, and biochemical indicators such as plasma or liver concentrations or isotope dilution assays. For example, Furr states:

Human vitamin A status can be assessed by a variety of approaches: estimates of dietary intake; physiological indicators (night blindness); clinical signs (Bitot's spots, corneal damage); and biochemical indicators (plasma retinol concentration, liver vitamin A concentration, relative dose response (RDR), modified relative dose response (MRDR) and isotope dilution)

EX1019 (Furr), 596-97.

72. As such, it is my opinion that essential role of retinol, retinal, retinal esters (including retinal acetate), and pro-vitamin A carotenoids such as β -carotene in the visual cycle was known by the critical date and that a person of ordinary skill in the art had good reason to reduce A2E formed from these retinoids while minimizing interference with the visual cycle.

B. It Was Known That a Byproduct of All-*trans* Retinal (ATR) Produced in the Visual Cycle Was Toxic A2E Lipofuscin Associated With Macular Degeneration

73. By 2007, it was known that undesirable lipofuscin fluorophores associated with ophthalmic disorders including macular degeneration arise from A2E and all-*trans* retinal (ATR)-dimers that are formed as side effects of the visual cycle. In 2005, Nathan E. Fishkin, Janet R. Sparrow, Rando Allikmets, and Koji Nakanishi published “Isolation and characterization of a retinal pigment epithelial cell fluorophore: An all-*trans*-retinal dimer conjugate” in the periodical publication *Proceedings of the National Academy of Science USA*. For convenience, I will refer to this article by the last named of the first-listed author, Fishkin.

74. Fishkin explained in 2005 that lipofuscin fluorophores of the retinal pigment epithelium originate mainly as retinoid byproducts from the visual cycle. For example, Fishkin states that:

Whereas the lipofuscin that is amassed by most nonproliferating cells is derived from autophagy, ***lipofuscin fluorophores of the retinal pigment epithelium (RPE) originate, in large part, from photoreceptor cells, with >90% of the fluorescent material being generated from conjugates formed by retinoids of the visual cycle.***

EX1011 (Fishkin), 7091.

75. Fishkin further explains that retinal pigment epithelium lipofuscin fluorophore accumulation increases with age, is abundant in individuals with Stargardt’s macular degeneration, and contributes to the death of retinal pigment

epithelium cells, thereby causing macular degeneration. For example, Fishkin states:

RPE *lipofuscin fluorophores accumulate with age*, the greatest accretion is in RPE cells underling the central retina, and the retinoid-derived fluorophores are *particularly abundant in Stargardt's disease*, a macular degeneration of juvenile onset. Indeed several lines of evidence indicate that the lipofuscin fluorophores that accumulate in RPE *contribute to the death of these cells in some forms of macular degeneration*. The *loss of RPE is a critical event* because it is thought that it *leads to bystander-like degeneration of photoreceptors that culminates in visual impairment*.

EX1011 (Fishkin), 7091. As such, Fishkin teaches not only that the association between lipofuscin fluorophore accumulation and macular degeneration was known by 2005, but also that lipofuscin formation was believed to play a causal role in macular degeneration. Indeed, Fishkin states that “the nondegradable fluorophores that accumulate as lipofuscin in retinal pigment epithelium (RPE) cells contribute to the etiology of macular degeneration.” EX1011 (Fishkin), Abstract, 7091.

76. Fishkin identifies two lipofuscin chromophores, *N*-retinylidene-*N*-retinylethanolamine (A2E) and all-*trans* retinal (ATR) dimer. EX1011 (Fishkin), 7091. For example, Fishkin states: “[h]ere, we report the isolation and structural characterization of an additional RPE lipofuscin fluorophore that originates as a condensation product of two molecules of all-*trans*-retinal (ATR) dimer.” EX1011 (Fishkin), 7091. Fishkin further states that:

We have isolated and structurally characterized ATR dimer-PE conjugate, an RPE lipofuscin fluorophore. Based on the experiments with isolated ROS, we suggest that synthesis of this chromophore begins in the outer segment membrane with the formation of ATR dimer, a condensation product of two molecules of ATR. Evidence also is provided that ATR dimer readily forms a SB conjugate with PE, although reactions between the aldehyde group of ATR dimer and other amines also may occur. The ATR dimer-PE conjugate exhibits a red-shifted UV-visible spectrum, and its UV profile and HPLC retention time are the same as a pigment isolated from extracts obtained from RPE eyecups and neutral retinæ of *Abcr*-null mutant mice. Pigments with UV-visible absorbances corresponding to that of ATR dimer-PE conjugate also were detected in RPE isolated from human eyes.

EX1011 (Fishkin), 7094.

77. In addition to identifying ATR-dimer, Fishkin identifies *N*-retinylidene-*N*-retinylethanolamine (A2E) as the more well-known of the problematic lipofuscin-forming compounds created as an undesirable byproduct of the visual cycle. Fishkin teaches that A2E's amphiphilic properties disrupt cell membranes and responds to blue-light irradiation by becoming oxidized. For example, Fishkin states:

Since A2E was characterized, several consequences of its accumulation have been reported. Because of its amphiphilic properties, *A2E can exert detergent-like effect on cell membranes*, perturb lysosomal function, and mediate blue-light damage. *Blue-light irradiation of A2E leads to the photooxidation of A2E* such that oxygens are added to carbon-carbon double bonds along the side arms of the molecule.

EX1011 (Fishkin), 7091.

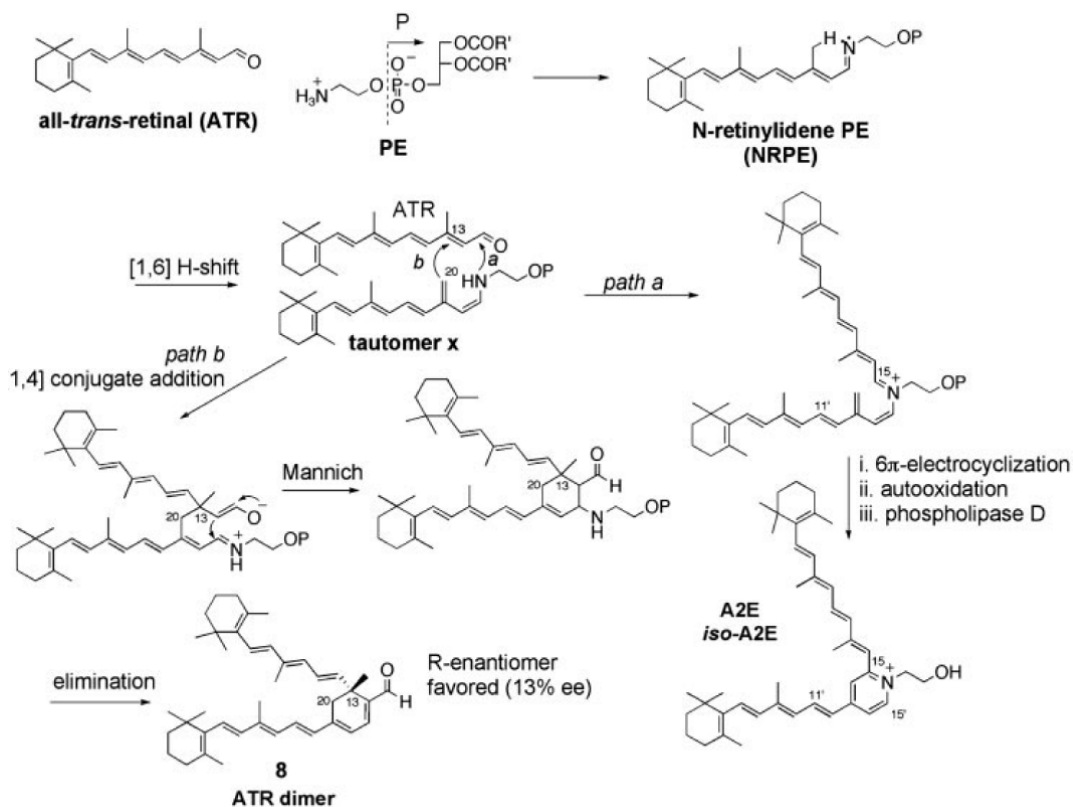
78. Fishkin further explains that A2E/lipofuscin makes retinal pigment epithelial cells susceptible to blue light damage and that all-*trans* retinal (ATR)-dimer accumulation may similarly cause retinal pigment epithelium cell death by making them sensitive to blue-light damage. For example, Fishkin states:

Although **A2E** is the most studied of the lipofuscin fluorophores, it is not expected to be the only **photosensitizer** in RPE lipofuscin. Because the **lipofuscin of RPE is considered to be responsible for the sensitivity of the cell to blue-light damages**, it will be important to determine the extent to which ATR dimer-PE conjugate contributes to the photoreactivity of RPE lipofuscin.

EX1011 (Fishkin), 7096.

79. Fishkin discloses a biosynthetic pathway in Figure 10, which I have reproduced below, of all-*trans* retinal (ATR) dimer and *N*-retinylidene-*N*-retinyldethanolamine (A2E) formation. Fishkin explains that the proposed biosynthetic pathway was based on previous reported mechanisms known in the art.

Base-catalyzed condensation of α,β -unsaturated aldehydes containing a β -methyl substituent have been previously reported to produce cyclohexa-1,3-diene-carbaldehydes similar to ATR dimer. Based on the reported mechanism for this type of transformation, **a pathway for biogenesis of ATR dimer is proposed in Fig. 10**. Within the context of this postulated scheme, ATR dimer could form in outer segments under ostensibly neutral conditions with **ATR dimer and A2-PE, the precursor of A2E, both forming from the same tautomer** that was previously hypothesized to arise from a [1,6] H-shift of *N*-retinylphosphatidylethanolamine (NRPE).



EX1011 (Fishkin), 7095. Fishkin thus discloses that the same reaction step, which involves a [1,6] H-shift and which Fishkin describes as converting *N*-retinylidene PE (NRPE) into “tautomer x,” results in the formation of both ATR dimer and A2E.

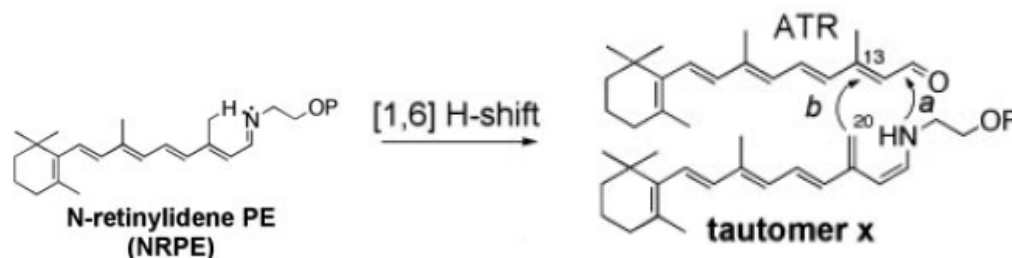
80. Fishkin, referring to Figure 10 which I have reproduced above, further discloses that “[b]oth ATR dimer and A2-PE may form from the same tautomer x arising from a [1,6] H-shift of NRPE” and that “in path b, C₂₀ of NRPE reacts with C₁₃ of free ATR in a Michael-type addition, followed by a Mannich reaction to close the ring, and elimination of the amino group of PE, yielding the ATR dimer.”

EX1011 (Fishkin), 7095. Still referring to Figure 10 reproduced above, Fishkin further explains that:

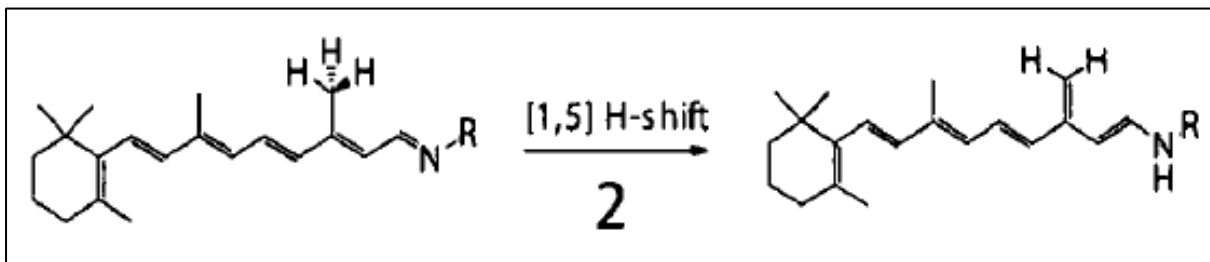
Indeed, that ATR dimer forms in ROS lends support to the proposed existence of this tautomer, as this intermediate would account for the nucleophilicity of C₂₀ and its participation in the [1,4] conjugate addition. According to the scheme in Fig. 10, C₂₀ of NRPE would react with C₁₃ of free ATR in a Michael-type addition, and after ring closure and elimination of the amino group of PE, ATR dimer would be formed.

EX1011 (Fishkin), 7095. A person of ordinary skill in the art would have recognized that inhibiting the [1,6] H-shift in Figure 10 of Fishkin was a desirable location for inhibiting the biogenesis of the undesirable lipofuscin because it is upstream of the pathway branch (so will slow both A2E formation and ATR-dimer formation) but is downstream of ATR formation so that it will not interfere with the visual cycle.

81. I have reproduced below the portion of Figure 10 that discloses the [1-6] hydrogen-shift in Fishkin in the reaction step between NRPE and tautomer x.



EX1011 (Fishkin), 7095. Chemically, this is the exact same reaction that the patent describes as a [1,5] hydrogen-shift, which I have also reproduced below. The difference in nomenclature does not reflect any difference in the chemical reaction. In each case, the H-shift requires breaking a C₂₀-bond with hydrogen.



EX1001 (the '432 patent), Figure 2.

82. The method of quantifying *N*-retinylidene-*N*-retinyldethanolamine (A2E) in lipofuscin in patients with age-related macular degeneration was known by 2007. For example, in 1998, Craig A. Parish, Masaru Hashimoto, Koji Nakanishi, James Dillion, and Janet Sparrow published “Isolation and one-step preparation of A2E and iso-A2E, fluorophores from human retinal pigment epithelium” in the periodical publication *Proceedings of the National Academy of Science of the United States of America*. For convenience, I will refer to this article by the last name of the first-listed named author, Parish.

83. Parish was published years before Fishkin, when the relationship between A2E and age-related macular degeneration (AMD) was not yet confirmed. Parish isolated A2E from RPE lipofuscin extracted from a human eye and

explained that its protocols permitted the amount of A2E to be easily quantified.

For example, Parish states:

This work describes the optimization of conditions for the single-step preparation of A2E in high yield providing large (>50 mg) quantities of material. An efficient ***HPLC protocol allows for the identification of the fluorophores present in RPE lipofuscin by using extracts from a single human eye.*** This procedure has resulted in the identification of one ***novel pigment (iso-A2E) present in aged eye RPE lipofuscin.*** The presence of all-trans- and 13-cis-retinol in most extracts also has been confirmed. While the role of A2E in AMD remains unclear, the ***amount of this natural product in each eye can be easily quantified by this procedure.*** The ability to determine the amount of A2E in the RPE of an individual is of special interest for epidemiological studies. A substantial source of A2E and iso-A2E will enable the further clarification of the role of these fluorophores in AMD.

EX1018 (Parish), 14613.

84. Parish further discloses in Figure 2 a proposed pathway for conversion of all-*trans* retinal (ATR) to *N*-retinylidene-*N*-retinylethanolamine (A2E), which I have reproduced below.

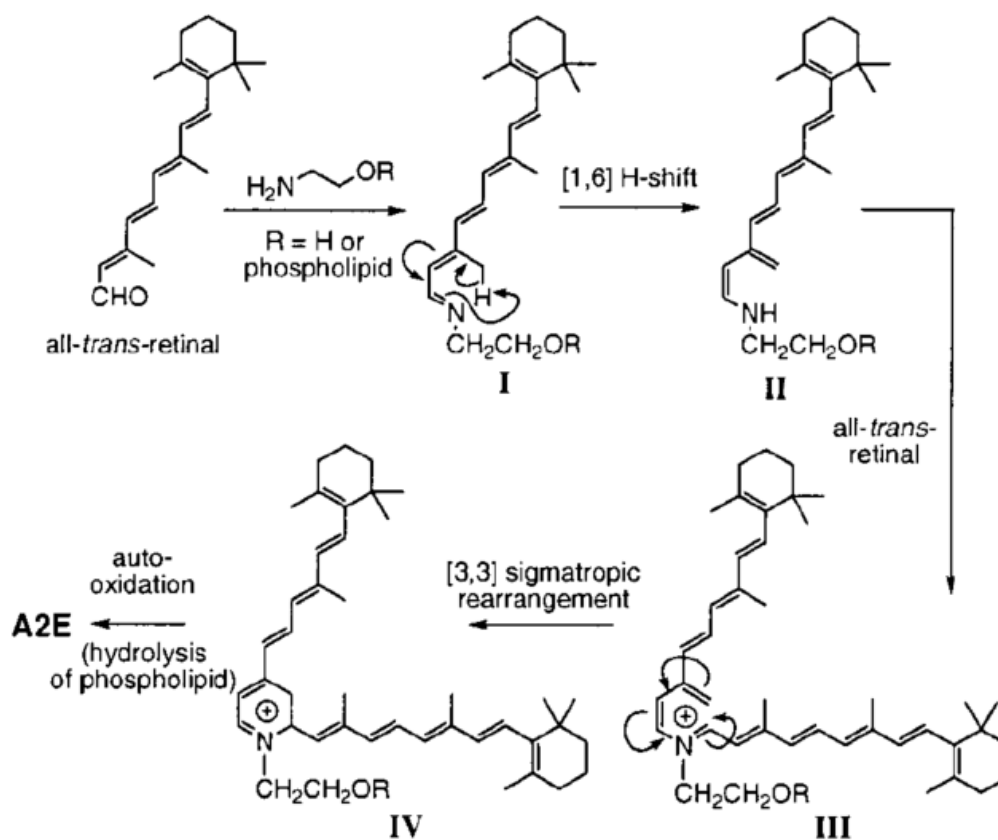
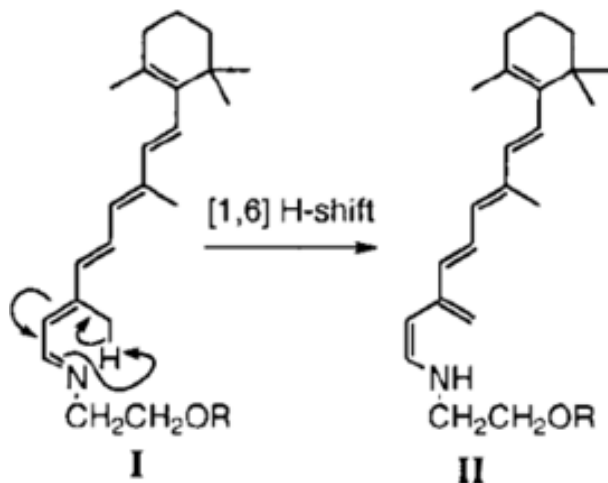


FIG. 2. Biogenesis of A2E from retinal and (phosphatidyl)ethanolamine.

EX1018 (Parish), 14611.

85. Parish, referring to Figure 2, further discloses, “[t]he genesis of A2E although speculative, could involve initial Schiff base formation between *all-trans*-retinal and ethanolamine or phosphatidylethanolamine to give (I), a [1,6]-proton tautomerization to enamine (II) followed by Schiff base generation with a second molecule of retinal to (III).” EX1018 (Parish), 14609. I have reproduced below the [1,6] hydrogen-shift described in Figure 2 of Parish.



EX1018 (Parish), 14611.

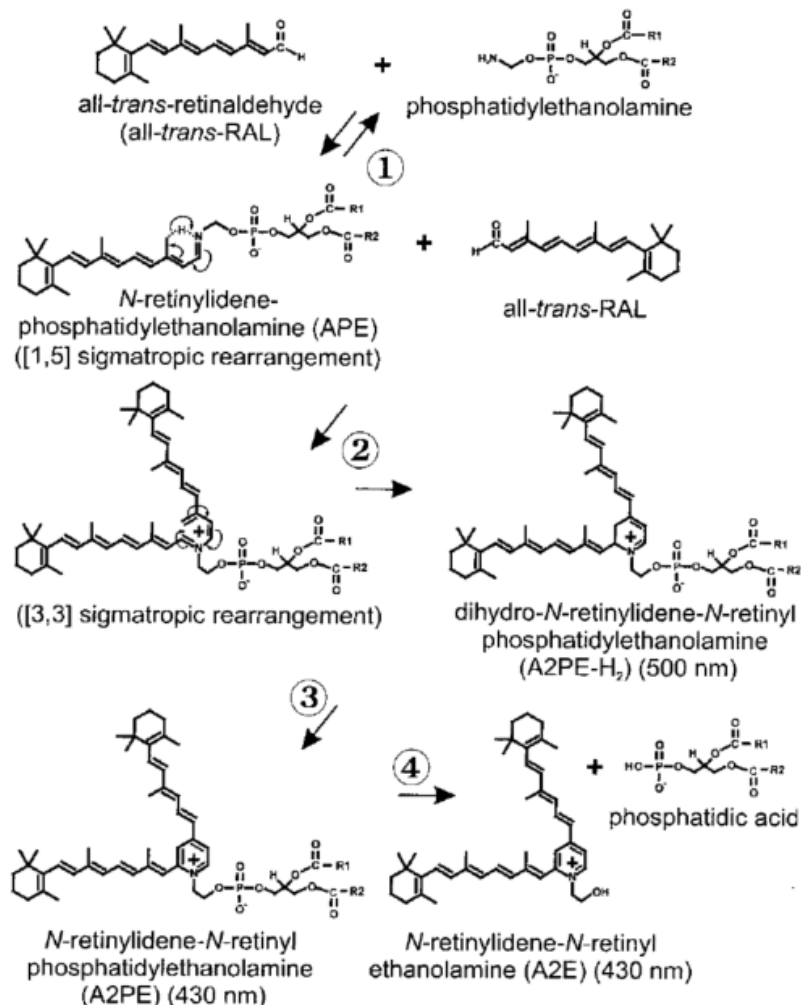
86. As I explain below, Parish’s speculation of a [1,6]-proton shift would subsequently be substantiated.

87. As part of my review of the knowledge of the art prior to 2007, I reviewed an article by Nathan L. Mata, Jian Weng, and Gabriel H. Travis published in the periodical publication *Proceedings of the National Academy of Science USA* on June 20, 2000 entitled “Biosynthesis of a major lipofuscin fluorophore in mice and humans with ABCR-mediated retinal and macular degeneration.” For convenience, I will refer to this article by the last name of the first-listed inventor, Mata.

88. Mata builds on Parish by substantiating the hypothetical biosynthetic pathway that is present in Mata Figure 5, which I have reproduced below, of *N*-retinylidene-*N*-retinyethanolamine (A2E) from all-*trans* RAL (ATR). Mata

explains that a [1,5]-sigmatropic rearrangement occurs in reaction 1 of the hypothetical biosynthetic pathway shown in Mata Figure 5 below.

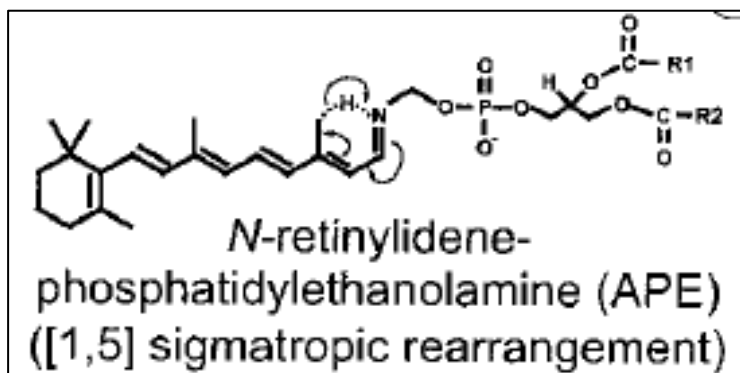
Hypothetical biosynthetic pathway for A2E in mice and humans lacking the RmP transporter. This model is ***based on the proposed scheme for A2E biogenesis by Parish*** et al. In outer segments after a photobleach, phosphatidylethanolamine and all-*trans*-RAL are transiently in equilibrium with APE (reaction 1). After ***a (1,5) sigmatropic rearrangement***, the resulting secondary amine may condense with another molecule of all-*trans*-RAL. Subsequent (3,3) sigmatropic rearrangement of the bis-retinoid product results in the formation of A2PE-H₂ (reaction 2), an irreversible step at neutral pH. Oxidation of A2PE-H₂ to A2PE (reaction 3) occurs within RPE phagolysosomes and is accompanied by a shift in the visible Y_{max} from 500 to 430 nm. This blue shift is expected, because the two tetraene side chains are oriented meta on the pyridinium ring, hence resonance delocalization occurs at a higher energy in the oxidized form because of loss of aromaticity. Finally, ***A2E is formed*** within RPE phagolysosomes on acid hydrolysis of the phosphate ester and release of phosphatidic acid (reaction 4).



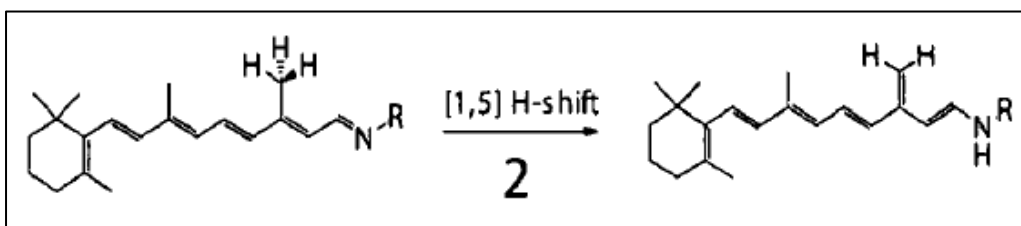
EX1010 (Mata), 7158.

89. The biosynthetic pathway provided in Mata is the same mechanism that the '432 patent would later adopt. Specifically, the [1,5]-sigmatropic rearrangement in reaction 1 of Mata, which I have reproduced below (top), is the same as the [1,5] hydrogen-shift described in the '432 patent, which I have also reproduced below (bottom). Despite the visual differences between the mechanisms of Figure 2 in the '432 patent and Figure 5 of Mata, it is my opinion that Mata describes the same mechanism disclosed in the '432 patent, indicating

that the mechanism of ATR transformation into A2E was well known in the art prior to the critical date.



EX1010 (Mata), 7158.



EX1001 (the '432 patent), Figure 2.

90. Further, Mata substantiated this proposed biosynthetic pathway. For example, referring to Figure 5, Mata states that:

We confirmed our identification of the A2E and phosphatidic acid products after incubation in HCl by MS and HPLC, respectively. The major form of A2PE-H2 had the identical fatty acid composition as the phosphatidic-acid product of its hydrolysis and the predominant form of phosphatidylethanolamine in outer segments (29). These data suggest that A2PE-H2 is the source of phosphatidic acid after incubation in HCl and that phosphatidylethanolamine from outer segments is the starting material for A2PE-H2 formation. The stability of A2PE-H2 in a nonoxidizing environment suggests that reaction 2 in Fig. 5 is effectively irreversible. A2PE-H2 was present in both retina and RPE of *abcr*^{-/-} mice. A2PE and A2E, however, were exclusively present in RPE. These observations suggest that the final two

reactions in Fig. 5 occur only within the oxidizing and acidic environment of RPE phagolysosomes.

EX1010 (Mata), 7158.

91. To further substantiate the proposed biosynthetic pathway, Mata states that:

The biochemical abnormalities in outer segments and RPE from *abcr*^{-/-} mice were similar to those observed in postmortem tissues from two patients with STGD1 and FFM. In particular, phosphatidylethanolamine was 2- to 3-fold more abundant in retina, and A2E 6- to 12-fold more abundant in RPE from patients vs. controls. A2PE-H₂ was abundantly present in retina and RPE from both patients but was undetectable in control tissues. The specific molecular defects in the patients presented here have not yet been defined. However, because FFM and STGD1 are both recessive diseases caused by mutations in *ABCR*, these patients presumably have partial or complete loss of RmP function. The similarity of phenotypes between *abcr*^{-/-} mice and humans with *ABCR*-mediated diseases was surprising, given that FFM and STGF1 are predominantly macular degenerations and that mouse retina does not contain a macula. In humans, greater vulnerability of the macula to the *ABCR*-mediated disease process may be secondary to the higher ratio of outer segments to RPE cells in this area.

EX1010 (Mata), 7159.

92. Mata, still referring to the biosynthetic pathway, explains that:

One prediction of the pathway proposed in Fig. 5 is that A2E accumulation should depend on the availability of all-*trans*-RAL and hence on light exposure. To test this hypothesis, we blocked any increase above basal levels of all-*trans*-RAL by raising *abcr*^{-/-} mice under total darkness. The level of A2E in these animals was approximately equal to that of wild-type mice. Thus, the increased formation of A2E in *abcr*^{-/-} mice is completely light dependent, which supports the proposed pathway. Interestingly, when mice raised under cyclic light for 12 weeks were transferred to the dark, no

reduction in the level of A2E was observed, even after 16 weeks in total darkness. These data indicate that A2E is not cleared by the RPE in *abcr*^{-/-} mutants, in contrast to the transient accumulation of lipofuscin reported in rats after intravitreal leupeptin injection. The observed inhibition of A2E accumulation in *abcr*^{-/-} mice raised under total darkness suggests that limiting light exposure may reduce the rate of disease progression in humans with recessive ABCR-mediated diseases. Although the mechanism of A2PE-H₂ formation undoubtedly varies with genetic etiology, the final pathway of A2E accumulation may be similar in other forms of lipofuscin-mediated macular or retinal degeneration. Pharmacologic inhibition of one or more steps in the A2E synthetic pathway may thus be an effective treatment strategy for other macular degenerations associated with lipofuscin accumulation.

EX1010 (Mata), 7159.

93. A person of ordinary skill in the art would thus have had good reason to inhibit the [1,5]-sigmatropic shift disclosed in the '432 patent to reduce lipofuscin formation associated with ophthalmic disorders including macular degeneration. First, the [1,5]-sigmatropic shift step in the pathway is just upstream of the intermediate that results in both A2E and ATR-dimer but sufficiently downstream of ATR formation, thus reducing the formation of undesirable lipofuscin without interfering with the visual cycle. Second, a person of ordinary skill in the art with the perspective of a chemist would have recognized that the [1,5]-sigmatropic rearrangement was likely a rate-limiting step due to the requirement that the bond between the hydrogen and Carbon 20 will break so that the hydrogen can shift to the nitrogen. A person of ordinary skill in the art would have recognized that cleavage of this carbon-hydrogen bond would already have

been relatively slow under physiological conditions absent enzymatic catalysis (especially on the C-20 methyl moiety, even as compared to a methylene moiety), and that enzymatic catalysis was very unlikely because lipofuscin formation was undesirable. Accordingly, further slowing the cleavage of this carbon-hydrogen bond at Carbon 20 would have been likely to slow the formation of A2E and ATR-dimer lipofuscin pigments that were understood to contribute to ophthalmic disorders including macular degeneration.

C. Deuterium's Kinetic Isotope Effect (KIE) Was Known to Make Reactions Requiring Cleavage of Carbon-Hydrogen Bonds 5-10 Times Slower.

94. A person of ordinary skill in the art before 2007 would have had good reason to replace the hydrogens on Carbon 20 of retinol, retinal, retinal acetate (and other retinol esters), and pro-vitamin A carotenoids to slow the [1,5]-sigmatropic rearrangement of reaction of all-*trans* retinal (ATR) and thereby reduce lipofuscin formation without interfering with the visual cycle. As I explain in detail below, it was well-known before 2007 that replacing hydrogens with deuteriums in carbon-hydrogen bonds slowed reactions such as the [1,5]-sigmatropic shift that required cleavage of the carbon-hydrogen bond. This reasonable expectation would have been reasonably confirmed even using in vitro experiments and then subsequently using in vivo experiments.

95. Using deuteration to slow undesirable reactions was one of several known uses of deuteration by 2007. For example, it was known that: (i) deuteration of a compound was useful for tracking compounds in vivo; (ii) the deuteration of a compound was useful for the identification of metabolites and sites of metabolic action; and (iii) the deuteration of a compound was useful for the inhibition (e.g., slowing) of reactions that involve cleavage of a carbon-hydrogen bond.

96. As an initial matter, the use of stable isotopes such as deuterium was known and understood by 2007. For example, in 1982, N.J. Haskins published an article entitled “The Application of Stable Isotopes in Biomedical Research” in the periodical publication *Biomedical Mass Spectrometry*. For convenience, I will refer to this article by the last name of the author, Haskins. Haskins explains that stable isotopes were useful for a variety of purposes. For example, Haskins states:

This review will cover the application of stable isotopes in the following areas: (1) stable isotope dilution assays; (2) metabolite identification (stable isotope signature); (3) absolute bioavailability by co-administration; (4) determining pharmacokinetics during chronic administration studies; (5) bioequivalence measurements; (6) metabolic ‘switching’ and stable isotope effects; (7) toxic effects of stable isotopes.

EX1012 (Haskins), 269; *see also* EX1051 (Miwa), 1 (article in periodical publication observing that “[k]inetic isotope effects have traditionally been employed to extract the mechanistic details of chemical and enzymatic reactions”). As I will explain in further detail below, some of these applications (e.g., stable

isotope dilution assay) benefit from placing the stable isotope (e.g., deuterium) at a locus of chemical stability (e.g., Carbons 10 and 19 of retinol) whereas other applications (e.g., slowing undesirable reactions) benefit from placing the stable isotope (e.g., deuterium) at a locus where a chemical reaction is known to take place (e.g., Carbon 20).

97. Haskins explains that deuterium is a “stable isotope” of hydrogen and that deuterium is routinely used for biological studies. Haskins further explains that a stable isotope (sometimes called a “heavy isotope”) is a non-radioactive isotope of an element. For example, Haskins states:

STABLE ISOTOPE. Generally an isotope of an element which is non-radioactive (i.e. does not decay by emission of alpha, beta, or gamma radiation). However, in this context the most common isotopes (that is ^1H (protium), ^{12}C , ^{16}O , ^{14}N , ^{32}S) of hydrogen, carbon, nitrogen, oxygen and sulfur are excluded, although they are stable isotopes. The most commonly used are as follows:

Isotope	Natural abundance (%)
^2H (deuterium)	0.0148
^{13}C	1.11
^{15}N	0.365
^{17}O	0.037
^{18}O	0.204
^{33}S	0.760
^{34}S	4.22

These are also referred to as HEAVY ISOTOPES.

EX1012 (Haskins), 269.

98. Haskins further discloses that stable isotope dilution assays were known and that these assays commonly use deuterium to diagnose the amount of a given compound in an organism. For example, Haskins states that:

The requirement for a labelled internal standard is that it should be isotopically as pure as possible, and for this reason deuterium (99.9% atom %) is the best heavy isotope for this work. It also happens to be cheap and useful when using relatively large quantities of internal standards.

EX1012 (Haskins), 270. As such, Haskins teaches that deuterium is an ideal heavy isotope due to its high isotopic purity and availability.

99. The first step in using deuterium in any compound is to evaluate whether the deuterated compound is chemically equivalent to the original compound for the purposes being evaluated. Generally, deuterated compounds are chemically equivalent to their reference compounds except to the extent the site of deuteration is subject to a material chemical reaction where the kinetic isotope effect affects the reaction (e.g., one involving cleavage of a carbon-hydrogen bond). For example, Haskins states:

(1) Because the internal standard is chemically equivalent (as a first approximation) a stable isotope analogue of a compound is going to have similar extraction, chromatographic and ionization characteristics to the parent. Thus, a labelled standard can be added as the first step in an extraction sequence, minimizing errors due to procedural losses.

EX1012 (Haskins), 270. Haskins thus teaches that stable isotope analogues (e.g., deuterated versions of reference compounds) are “chemically equivalent (as a first approximation)” to the reference compound and thus have similar extraction, chromatographic, and ionization characteristics as the reference compound.

EX1012 (Haskins), 270.

100. Haskins, citing to the work of other researchers in the field, discloses that an ideal isotopically labelled standard should contain three or more heavy atoms and high purity. For example, Haskins states that:

More recently still, Bush and Trager have taken up the work of Pickup and McPherson, modified by Colby and McCaman and have produced a more generalized model suitable for multivariant analysis. All of these models suggest the *optimum stable isotopically labelled standard should contain three or more heavy atoms and have a high degree of purity to obtain good precision.*

EX1012 (Haskins), 270-271. It was thus well known and conventional to replace multiple hydrogens on a particular carbon of an organic compound (e.g., all three hydrogens on a methyl moiety) with deuterium.

101. Haskins further discloses that deuterium was known to be used to identify and/or track metabolites. For example, in addition to deuterium being used to diagnose compound concentrations in vivo, Haskins discloses that labeling a compound with “deuterium clusters” was a method that was well-known to a person of ordinary skill in the art.

Deuterium, due to its ready availability and low costs, has been used extensively to form artificial isotope clusters for metabolite identification.

EX1012 (Haskins), 272. A conventional example of a deuterium cluster is replacing all three hydrogens on a methyl moiety with deuterium.

102. Haskins discloses that the primary isotope effect means that reactions requiring cleavage of a carbon-hydrogen bond will take place much slower when the hydrogen is replaced with the larger and heavier deuterium atom. Haskins further explains that the slowing of deuterium cleavage from carbon as compared to cleavage of hydrogen from carbon results because the carbon-deuterium bond is more stable and requires greater energy of activation than the carbon-hydrogen bond. Each of these aspects of deuteration of organic compounds was well known in the art before 2007.

103. Haskins provides a conventional description of the deuterium kinetic isotope effect (KIE) as a change in the rate of reaction caused by substituting the common hydrogen isotope with a stable isotope. Haskins also explains that there is “large” kinetic effect (i.e., significant slowing of the reaction) of up to 14-fold expected for cleavage of the bond with hydrogen. For example, Haskins states:

ISOTOPE EFFECT. Changes in rates of reaction caused by substitution of the common isotope by a stable or radioactive isotope. ***Large kinetic effects are found especially when substitution of deuterium for protium is carried out.*** The rate of cleavage of C-(²H) bonds can be ***up to 14 times slower*** than similar cleavage of C-(¹H) bonds.

EX1012 (Haskins), 270. Haskins explains that this slowing in reaction kinetics results from the greater mass (2x) of deuterium as compared to protium (e.g., the conventional hydrogen isomer) and the greater energy of action required to cleave the lower vibrational frequency of the deuterium-carbon bonds. For example, Haskins states:

The difference in mass between deuterium and protium causes the vibrational frequencies of C – D, O – D and N – D bonds to be lower than for corresponding C – H, O – H and N – H bonds. The more stable deuterium bond requires greater energy of activation and substitution of deuterium for protium can have *a profound effect on the rate of chemical reactions involving bond cleavage*.

EX1012 (Haskins), 273. Haskins thus explains that deuterium substitution can have a profound effect on the rate of chemical reactions involving bond cleavage.

104. Haskins further discloses that the rate of bond cleavage for a deuterium is generally 2-5 times slower than for the hydrogen, but can be as high as 7- to 10-fold slower. For example, Haskins states that “[g]enerally values k_H/k_D are in the range of 2-5, but the maximum effect can be as high as 7-10.” EX1012 (Haskins), 273. Reducing the speed by 2-10 times of a reaction requiring cleavage of a carbon-hydrogen bond was thus an expected result.

105. The strong kinetic effects discussed above are “PRIMARY isotope effects” that occur when the deuterium is directly involved in the bond at issue.

EX1012 (Haskins), 273. Haskins further explains that deuterium can have secondary isotope effects when it affects the rates of reactions not directly

involving cleavage of a deuterium bond. EX1012 (Haskins), 273. These effects are generally much smaller than the primary kinetic isotope effects seen with deuterium. For example, Haskins states:

Deuterium can also affect rates of reaction not directly involving cleavage of a deuterium bond, (e.g., hydrolysis of trideuteromethyl esters) and these are known as SECONDARY isotope effects. The ratio k_H/k_D is usually 1-2 for these. Isotope effects occur for ^{13}C , ^{15}N , ^{18}O , etc., but in general these are negligible compared with the large effects seen for deuterium.

106. Haskins further explains that labeling a compound with deuterium in a position where primary isotope effects could occur is a useful way to determine where cleavage occurs and to identify the recovered drug and its metabolites. For example, Haskins states:

If the object is to label recovered drug and metabolites to prove them to be drug derived, then even deuterium in a position where primary isotope effect could occur may be suitable. Indeed, ***distortion of the ($^2\text{H}_0$)/($^2\text{H}_X$) ratio away from the theoretical can give information about any isotope effects.***

EX1012 (Haskins), 273. Haskins thus teaches that deuteration of a compound at a given position is useful to identify any isotope effects so that one can determine based on a significant isotope effect that cleavage of a hydrogen from the labeled carbon is involved in the metabolic or synthetic pathway.

107. Once a chemist evaluates whether there is any primary kinetic isotope effect, they then know which types of assays for which a particular deuterated compound is suitable. When the goal is to avoid impacting the rate of metabolism

(e.g., in a stable isotope dilution assay), a person of ordinary skill in the art would know to avoid the strong primary isotope effect of deuterium by identifying sites of desired carbon-hydrogen bond cleavage and avoiding deuteration at those sites.

EX1012 (Haskins). Haskins discloses that when a deuterium “label is [located] away from any obvious site of metabolism, only secondary isotope effects will be observed, and these are usually sufficiently small to be neglected.” EX1012 (Haskins), 271. In contrast, when a primary kinetic isotope effect is measured, this indicates that cleavage of hydrogen from that deuterated carbon is a prerequisite to the involved reaction.

108. Accordingly, by 2007, persons of ordinary skill in the art were well aware that replacing the carbon-hydrogen bonds at a particular carbon with carbon-deuterium bonds was not only useful for identifying metabolites, but also for identifying and confirming the locus and mechanism of metabolism.

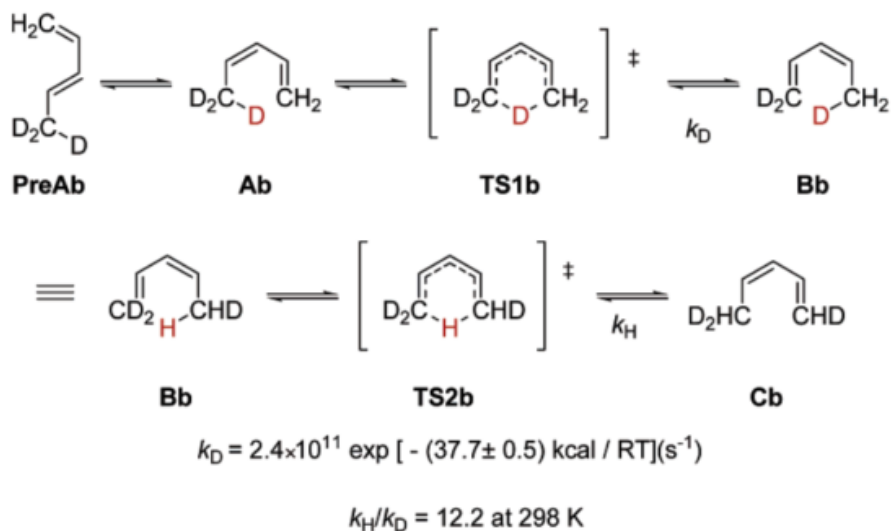
109. In 1981, Thomas A. Baillie published “The Use of Stable Isotopes in Pharmacological Research,” a review article, in the periodical publication *Pharmacological Reviews*. For convenience, I will refer to this article by the first named author, Baillie.

110. Baillie discloses use of deuterium labelling in defining sites of metabolic attack. For example, Baillie states that “Loss or retention of deuterium substituents at specific positions in a molecule can afford valuable information on

sites of metabolic attack and is a technique that has been used in studies of drug metabolism for some years.” EX1013 (Baillie), 106.

111. In addition, by 2007, it was known that there is a strong kinetic isotope effect (KIE) associated with a 1,5-sigmatropic shift. In 2006, researchers Yasuaki Itou, Seiji Mori, Taro Udagawa, Masanori Tachikawa, Takayoshi Ishimoto, and Umpei Nagashima published an article entitled “Quantum Treatment of Hydrogen Nuclei in Primary Kinetic Isotope Effects in a Thermal [1,5]-Sigmatropic Hydrogen (or Deuterium) Shift from (Z)-1,3-Pentadiene” in the periodical publication *The Journal of Physical Chemistry*. For convenience, I will refer to this article by the last name of the first listed inventor, Itou.

112. Itou, referring to an article by Roth and König, provides that “[t]he experimental hydrogen/deuterium (H/D) in the kinetic isotope effects (KIE) of the homogeneous gas-phase reaction for (Z)-1,3-pentadiene was examined by Roth and König, and is illustrated in Figure 2.” EX1016 (Itou), 262. I have reproduced Figure 2 from Itou below.



113. Itou further discloses that the authors in the Roth article experimentally determined a large kinetic isotope effect value of 12.2 in a 1,5-sigmatropic shift of a deuterated 1,3-pentadiene. For example, Itou states that:

The large KIE value of $k_H/k_D = 12.2$ (k_H and k_D refer to the rate constant of the reaction for H and D compounds, respectively) at 298 K, which is derived from the extrapolation from the values in the temperature ranging 463.4-478.5 K and modified intermediate neglect of differential overlap (MINDO)/2 calculations, suggests that the reaction proceeds according to a mechanism that includes a transition structure with CS symmetry

EX1016 (Itou), 261.

114. Authors Wolfgang R. Roth and Joachim König published “Kinetic Isotope Effect of the 1.5-Hydrogen Displacement in *cis*-Pentadiene-(1.3)” (*Kinetischer Isotopeneffekt der 1.5-Wasserstoffverschiebung im cis-Pentadien-(1.3)*) in the periodical publication *Justus Liebigs Annalen der Chemie* in 1966. For

convenience, I will refer to this reference by the last name of the first-listed author, Roth.

115. Roth discloses measuring and comparing the gas-phase reaction of (Z)-1,3-pentadiene and deuterated (Z)-1,3-pentadiene. The mechanism proposed in Roth is outlined in Figure 2 of Itou, which I have reproduced above.

116. Roth disclosed that there is a large kinetic isotope effect value (e.g., 12.2) associated with the 1,5-sigmatropic shift in diene systems. Specifically, Roth determined experimentally that the 1,5-sigmatropic shift of a deuterated 1,3-pentadiene (with a CD₃) would proceed 12.2 times slower than the protiated 1,3-pentadiene.

117. As such, a person having ordinary skill in the art would expect that the substitution of the C₂₀ methyl (CH₃) with CD₃ would similarly observe a large kinetic isotope effect associated with the 1,5-sigmatropic shift at the C₂₀ position. Further, it is my opinion that deuteration of the C₂₀ methyl would have a similar kinetic profile as the well-studied 1,3-pentadiene system outlined in both Roth and Itou because C₂₀ forms a similar diene system as in 1,3-pentadiene.

118. In sum, by 2007, it was known (1) to treat or prevent ocular disorders such as macular degeneration by administering vitamin A and by inhibiting lipofuscin formation; (2) that the undesirable lipofuscin pigment was formed by a

deprotonation reaction at C₂₀; and (3) that deuterium substitution could be used to slow such undesirable reactions.

IX. ANALYSIS OF ASSERTED REFERENCES

A. Olson 1988 (EX1006)

119. In 1988, H. Robert Bergen, Harold C. Furr, and James A. Olson, researchers at the Iowa State University Department of Biochemistry and Biophysics, published an article entitled “Synthesis of Tri-, Tetra-, and Penta-Deuterated Forms of Vitamin A” in the periodical publication *Journal of Labelled Compounds and Radiopharmaceuticals*. I will refer to this article as Olson 1988.

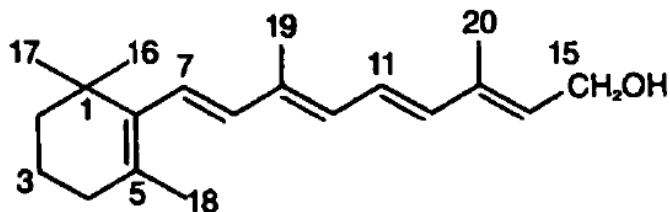
120. Olson 1988 discloses that making and purifying deuterated forms of vitamin A was known. EX1006, (Olson 1988), 11. Specifically, Olson 1988 discloses the synthesis of “20,20,20-trideutero, 14,20,20,20-tetradeutero, 12,14,20,20,20-pentadeutero, and 10,19,19,19-tetradeutero analogs of retinoic acid ethyl ester and retinyl acetate.” EX1006 (Olson 1988), 11.

121. Olson 1988 explains that use of deuterated retinol is useful for studying metabolism of vitamin A in humans. For example, Olson 1988 states that:

For studying the metabolism of vitamin A in humans, nonradioactive deuterated or ¹³C labeled compounds of high purity are desired. Because the natural abundance of ¹³C in retinol, a C-20 compound, is 22% at M+1 and 4.8% at M+2, deuterated compounds should contain three or more deuteriums in metabolically and chemically stable positions to provide adequate analytical sensitivity.

EX1006 (Olson 1988), 11.

122. As an initial matter, Olson 1988 provides a labeled structure in Scheme 1, which I have reproduced below, of retinol that contains a carbon numbering system. In Scheme 1, retinol carbons 1, 3, 5, 7, 11, and 15-20 are labeled.



Scheme 1. Numbering system for retinol (vitamin A alcohol).

EX1006 (Olson 1988), 12. Olson 1988 uses this numbering system to characterize the deuterated forms of vitamin A in Olson 1988's synthesis of "20,20,20-trideutero, 14,20,20,20-tetradeutero, 12,14,20,20,20-pentadeutero, and 10,19,19,19-tetradeutero analogs of retinoic acid ethyl ester and retinyl acetate."

EX1006 (Olson 1988), 11.

123. Olson 1988 further explains that retinoids are typically synthesized using a Wittig reaction or a modification of it. For example, Olson 1988 states that:

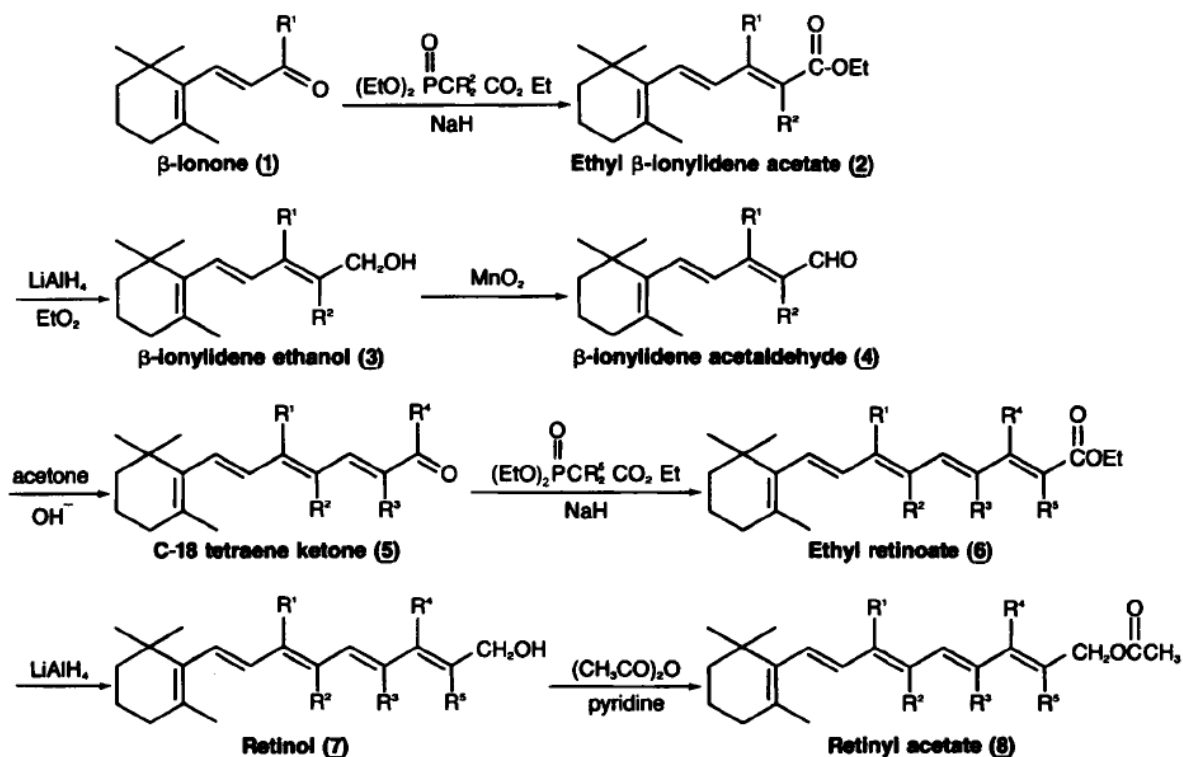
Retinoids and carotenoids are primarily synthesized by the Wittig reaction or some modification of it. We have used a modified Wittig-Horner procedure in association with the base-catalyzed incorporation of deuterium from $^2\text{H}_2\text{O}$ or perdeuteroacetone to synthesize four deuterated retinols with 3 to 5 deuterium atoms. The most useful for biological studies is the 10,19,19,19- $^2\text{H}_4$ labeled compound.

As such, Olson 1988 provides that:

The synthesis of 20,20,20-trideutero, 14,20,20,20-tetradeutero, 12,14,20,20,20-pentadeutero, and 10,19,19,19-tetradeutero analogs of retinoic acid ethyl ester and retinyl acetate, by a modified Wittig-Horner synthesis, is described. Deuterium was introduced by base-catalyzed exchange into appropriate intermediates.

EX1006 (Olson 1988), 11-12.

124. The route of synthesis disclosed in Olson 1988 is provided below.



Scheme 2. Synthesis of deuterated forms of vitamin A.

20,20,20- $^2\text{H}_3$ -Retinoic acid ethyl ester ($\text{R}^1 = \text{CH}_3$; $\text{R}^4 = \text{C}^2\text{H}_3$);

14,20,20,20- $^2\text{H}_4$ -Retinoic acid ethyl ester ($\text{R}^1 = \text{CH}_3$; $\text{R}^4 = \text{C}^2\text{H}_3$; $\text{R}^5 = ^2\text{H}$);

12,14,20,20,20- $^2\text{H}_5$ -Retinyl acetate ($\text{R}^1 = \text{CH}_3$; $\text{R}^3 = ^2\text{H}$; $\text{R}^4 = \text{C}^2\text{H}_3$; $\text{R}^5 = ^2\text{H}$);

10,19,19,19- $^2\text{H}_4$ -Retinyl acetate ($\text{R}^1 = \text{C}^2\text{H}_3$; $\text{R}^2 = ^2\text{H}$; $\text{R}^4 = \text{CH}_3$).

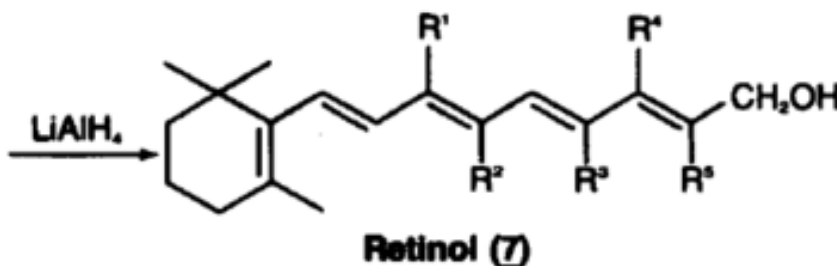
EX1006 (Olson 1988), 13.

125. Referring to the route of synthesis, Olson 1988 provides that the crude product from one reaction can be used in succeeding reactions. For example. Olson 1988 states that:

The advantage of this route for *synthesis of 20,20,20-trideuteroretinol* (Scheme 2, $R^4=C^2H_3$) are the preferential formation of the all-trans isomer in the Wittig-Horner reactions (essentially 100% in the first reaction), the high yields (>60%) at each step, and the very low quantities of reaction side products. Thus the crude product from one reaction can be used in succeeding reactions without further purification. The overall yield from β -ionone for the sum of cis and trans isomers of 20,20,20- $^2H_3$ -retinyl acetate is 15%. For the trans isomer alone, the yield is approximately 5%.

EX1006 (Olson 1988), 12. It is my opinion that 20,20,20-trideuteroretinol is C_{20} - D_3 -retinol, which is one of the retinoids within the scope of the claims of the '432 patent.

126. In addition to the forgoing quote, Olson 1988 repeatedly discloses making and purifying C_{20} - D_{1-3} -retinol (e.g., 20,20,20-trideuteroretinol). For example, compound 7 in the route of synthesis, which is also reproduced below and labeled "Retinol (7)", is the same C_{20} - D_3 -retinol encompassed by claim 1 of the '432 patent.



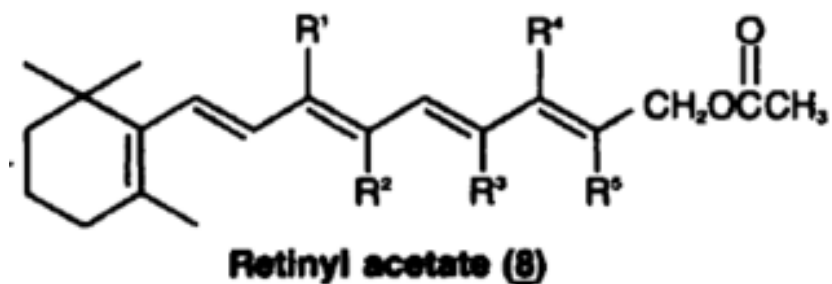
EX1006 (Olson 1988), 13.

127. To prepare and make the C₂₀-D₃-retinol (e.g., “Retinol (7)”), Olson 1988 discloses that:

20,20,20-²H₃-Retinol was prepared by adding 20,20,20-²H₃-retinoic acid ethyl ester (5 g, 0.015 mol, in 100 ml diethyl ether) dropwise to 0.57 (0.015 mol) LiAlH₄ in 250 ml anhydrous diethyl ether at -70°, with stirring. After being stirred 30 min at -70°, the solution was allowed to warm to room temperature; if reduction was not complete as judged by TLC, the solution was cooled, and more LiAlH₄ added. The reaction was quenched by careful addition of 1 N H₂SO₄ to the cooled solution. The mixture was warmed to room temperature, washed with 1 N H₂SO₄ (2 x 200 ml) and then with water (3 x 200 ml), dried (MgSO₄), and rotary evaporated to give 3.65 g (85% yield) of crude product.

EX1006 (Olson 1988), 18.

128. In addition, Olson 1988 discloses making and purifying C₂₀-D₃-retinol acetate (e.g., 20,20,20-²H₃-retinyl acetate). Compound 8 in the route of synthesis, which is also reproduced below and labeled “Retinyl acetate (8)”, is the C₂₀-D₃-retinol ester used in the '432 patent and is the compound claimed in claim 3 of the '432 patent.



EX1006 (Olson 1988), 13.

129. Olson 1988 discloses the synthesis of C₂₀-D₃-retinol acetate from C₂₀-D₃-retinol. For example, to prepare and make the C₂₀-D₃-retinol acetate, Olson 1988 states that:

20,20,20-²H₃-Retinol (1 g, 0.003 mol) was dissolved in 10 ml pyridine and cooled in an ice bath. Acetic anhydride (0.28 ml, 0.003 mol) was added dropwise. After being stirred 15 min, the solution was allowed to warm to room temperature and checked by TLC; if acetylation was not complete, the solution was cooled, and more acetic anhydride was added. Ice was then added to destroy residual acetic anhydride. The solution was poured into 250 ml hexane and washed with water (6 x 250 ml) to remove pyridine. The organic layer was dried (MgSO₄) and rotary evaporated to give an overall crude yield of 60% (40% *cis*, 60% all-*trans*) 20,20,20-²H₃-retinyl acetate. The isomers were separated by HPLC (hexane:ethyl acetate, 98:2).

EX1006 (Olson 1988), 18.

130. Olson 1988 further states that all-*trans* ²H₃-retinyl acetate could be prepared from the *cis* isomers. For example, Olson 1988 states that

All-*trans* ²H₃-retinyl acetate could be prepared from the *cis* isomers by dissolving up to 1 g of the *cis* isomers in 100 ml hexane and adding a small crystal of iodine. After being stirred 1 hr, the organic layer was washed with 100 ml 5% NaHSO₃, then with water (2 x 100 ml), and was then dried (MgSO₄). The all-*trans* ester was purified from the equilibrium mixture (55% all-*trans*, 35% 13-*cis*, 10% other *cis* forms) by HPLC.

EX1006 (Olson 1988), 18-19.

131. Olson 1988 further discloses that nearly 94% of the retinyl acetate was deuterated and the majority was trideuterated (C₂₀-D₃). EX1006 (Olson 1988), 18.

132. Olson 1988 further teaches performing preparative-scale purification of these products using HPLC. EX1006 (Olson 1988), 15. For example, Olson 1988 states that:

All synthetic and chromatographic procedures were carried out under yellow fluorescent lights (F40 Gold). Preparative-scale purifications of products were performed by high-pressure liquid chromatography (HPLC) on a Whatman M-20 silica column (22 mm ID x 50 cm L) with hexane:ethyl acetate eluents. Thin-layer chromatography (TLC) was performed on Machery-Nagel Polygram-Sil G/UV₂₅₄ TLC plates using ethyl acetate:hexane (20:80) as the developing solvent. Plates were visualized by using ultraviolet illumination (254 nm and 366 nm). Mass spectrometry was performed on either a Finnegan Model 400 or an Extranuclear SpectrEL quadrupole mass spectrometer. Trimethylsilyl derivatives of deuterated retinols for GC-MS analyses were prepared by reaction with tri-methylsilyldiethylamine.

EX1006 (Olson 1988), 15.

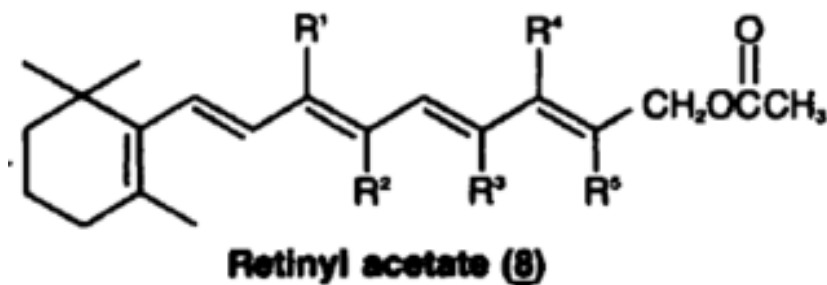
133. Further, Olson 1988 identified deuteration of vitamin A at carbons 10 and 19 (e.g., 10,19,19,19-²H₄-vitamin A) as the preferred analog for isotope dilution assays of vitamin A in vivo because of its high isotopic integrity and chemical stability at those carbons. EX1006 (Olson 1988), 11. For example, Olson 1988 explains that the synthesis of 10,19,19,19-²H₄-retinyl acetate “can be attributed to the greater stability of β-ionone relative to the C-18 ketone and to the essential absence of nondeuterated side products in this first reaction step.”

EX1006 (Olson 1988), 15. Further, Olson 1988 states that:

The 10,19,19,19-²H₄-vitamin A, because of its high isotopic integrity (>98% ²H₄), is the preferred analog for biological studies of vitamin A metabolism.

EX1006 (Olson 1988), 11.

134. The structure of the 10,19,19,19-²H₄-retinyl acetate disclosed in Olson 1988 is reproduced below.



EX1006 (Olson 1988), 13.

135. To prepare and make the 10,19,19,19-²H₄-retinyl acetate, Olson 1988 discloses that:

Trideuterated β -ionone was synthesized according to the procedure of Johansen and Liaaen-Jensen. Briefly, 50g (0.26 mol) β -ionone was stirred with 156 g (7.8 mol) deuterium oxide. The emulsion that formed was dispersed by adding freshly distilled pyridine until the solution cleared. Then, 50 drops of 40% NaO²H were added, and the solution was stirred for 3 hr. The solution was poured into 500 ml hexane, and the aqueous layer was removed. The organic layer was washed repeatedly (6 x 400 ml water) to remove pyridine, then was dried (MgSO₄), filtered, and rotoevaporated. The deuteration reaction was repeated once. The yield was 45 g (90% yield) of 13,13,13 trideutero beta-ionone, with deuterium incorporation of >98% ²H₃, as measured by NMR.

The tri-deuterated β -ionone was used in a Wittig-Horner reaction with deuterated phosphonate to give tetradeuterated ethyl β -ionylidene acetate. The methods for synthesis of 20,20,20-²H₃-retinyl acetate were used to complete the synthesis, except that nondeuterated reactants were employed for the remaining addition reactions.

Deuterium incorporation, as determined by NMR and GLC-MS, was >98% $^2\text{H}_4$ in the final product, 10,19,19,19- $^2\text{H}_4$ -retinyl acetate.

EX1006 (Olson 1988), 20.

136. Olson 1988's selection of the $\text{C}_{10,19}$ -tetradeuterated vitamin A for biological assays that required chemical stability at the positions of deuterated makes sense because, in 1988, neither carbon 10 nor carbon 19 of vitamin A was known to be involved in the visual cycle or in known biological reactions. Olson 1988 does not explicitly state that carbon 20 was thought to be uninvolved with biological reactions. As I explained above, however, Mata subsequently demonstrated that deprotonation of carbon 20 was a prerequisite for undesirable lipofuscin formation. In light of Mata's disclosures, a person of ordinary skill in the art would thus have understood Olson 1988's C_{20}D_3 -vitamin A compounds in a new light as a promising means to confirm Mata's synthesis pathway and to reduce lipofuscin formation.

B. Olson 1989 (EX1007)

137. In 1989, researchers Oliver Amedee-Manesme, Andrew J. Clifford, A Daniel Jones, and Dale P. Anderson, as well as the researchers listed in Olson 1988 (e.g., Harold C. Furr, H. Robert Bergen, and James A. Olson), published "Vitamin A concentrations in liver determined by isotope dilution assay with tetradeuterated vitamin A and by biopsy in generally healthy adult humans" in the periodical

publication *The American Journal of Clinical Nutrition*. For convenience, I will refer to this article as Olson 1989.

138. Olson 1989 discloses a vitamin A stable isotope dilution assay study in 11 humans using the 10,19,19,19-tetradeuterated retinyl acetate (99% pure) that was described in Olson 1988 (see Section IX.A above). EX1007 (Olson 1989), 713-14 & Abstract. For example, Olson 1989 discloses:

The vitamin A status of 11 generally healthy surgical patients was estimated by measuring the dilution of a 45-mg oral dose of tetradeuterated retinyl acetate (99% pure). After purification of retinol by high-performance liquid chromatography, the ratio of $^2\text{H}_4$ -retinol: ^1H -retinol in plasma was measured by gas chromatography-mass spectrometry. On the basis of the observed ratios of $[\text{H}_4]\text{retinol}:[\text{H}]\text{retinol}$ over 19-47 d, the total body reserves and liver concentrations of vitamin A were calculated. Liver biopsy samples taken at surgery were directly analyzed for vitamin A. The correlation coefficient between calculated and measured liver vitamin A concentrations for 10 of the subjects was 0.88, and the Spearman's rank correlation coefficient was 0.95 ($p < 0.002$). Thus, total body reserves of vitamin A in humans can be estimated validly in the marginal and satisfactory ranges by a benign, relatively noninvasive procedure.

EX1007 (Olson 1989), Abstract.

139. To conduct this study, Olson 1989 further describes that:

Eleven hospitalized patients (aged 22-87 y) scheduled for cholecystectomy ($n = 6$) were admitted into the study. In all except subject 7 (Table 1), who had viral hepatitis A, liver function tests as well as concentrations of serum albumin and total plasma protein were normal. As judged by dietary interview, nine subjects routinely ingested normal amounts (900-2100 mg) of carotenoids and vitamin A whereas subjects 1 and 2 ate foods containing very small quantities of carotenoids and vitamin A.

EX1007 (Olson 1989), 713.

140. Table 1 of Olson 1989, which is reproduced below, shows the calculated and measured liver concentrations of vitamin A of each human patient. Referring to table 1, Olson 1989 states that it shows “[i]nformation about the subjects, the H-D ratio of plasma retinol after extensive equilibration, and the calculated (means of two or three determinations) and measured liver vitamin A levels.”

TABLE 1
Calculated and measured liver concentrations of vitamin A and related variables in generally healthy surgical patients

Subject	Sex	Age	Weight	Serum retinol	H-D ratio	Calculated TLR*	Vitamin A in liver		
							Calculated	Measured	Calculated:measured
		<i>y</i>	<i>kg</i>	$\mu\text{mol/L}$		<i>mmol</i>		$\mu\text{mol/g}$	
1	F	23	129	1.40	5.78	0.16	0.065	0.049	1.32
2	M	52	70	1.61	5.03	0.13	0.068	0.105	0.65
3	F	22	73	1.96	5.85	0.16	0.093	0.20	0.47
4	F	38	92	1.29	19.2	0.72	0.30	0.30	1.00
5	F	54	127	2.69	17.5	0.63	0.23	0.33	0.69
6	F	25	132	1.36	25.6	1.09	0.53	0.37	1.42
7	F	29	84	2.52	24.4	0.88	0.38	0.39	0.98
8	F	87	76	2.06	4.74	0.12	0.080†	0.40	0.20
9	F	32	145	1.64	26.3	0.99	0.37	0.40	0.94
10	F	31	128	1.85	38.5	1.60	0.72	0.48	1.49
11	F	69	59	1.33	50.0	2.02	1.12	0.56	2.01

* Total liver reserve of vitamin A.

† Excluded from analysis.

EX1007 (Olson 1989), 714-715.

141. Olson 1989 explains that the tetradeuterated retinyl acetate was administered orally to the human patients, after being formulated in corn oil (e.g., a pharmaceutically-acceptable excipient). For example, Olson 1989 states that:

Four to 6 d after surgery, a relative dose response (RDR) test was conducted in the conventional manner *with an oral dose of 450 μg retinyl acetate in corn oil*. The results of these studies already have been reported. Shortly thereafter each subject *was given a 45 mg all-*

trans 10, 19, 19, 19, 19-[²H₄]retinol as retinyl acetate in corn oil. The [²H₄]retinyl acetate (99% isotopic purity) was synthesized, characterized, and purified as described previously.

EX1007 (Olson 1989), 714. Olson 1989's formulation was a pure, pharmaceutical formulation being used for pharmaceutical diagnostic purposes.

142. Regarding the results of its study, Olson 1989 explains:

Information about the subjects, the H-D ratio of plasma retinol after extensive equilibration, and the calculated (means of two or three determinations) and measured liver vitamin A levels are presented in Table 1, and the latter as well in Figure 1. The correlation coefficient between calculated and measured vitamin A values, except for subject 8, is 0.88. The spearman rank correlation coefficient, except for subject 8, is 0.95 ($p < 0.002$).

The H-D ratios alone reflect relative total body reserves with values <6 at the lower end, 17-26 in the middle, and >38 at the higher end under these conditions of measurement. In the two to three plasma samples taken from each patient over the course of the experiment, the H-D ratio of plasma retinol expectedly increased with time (data not shown). As indicated earlier plasma values showed no relationship with liver reserves over the range studied (0.05-0.56) $\mu\text{mol/g}$. Similarly, liver reserves were not age-related in this small sample of adults (Table 1).

EX1007 (Olson 1989), 714.

143. Figure 1 in Olson 1989, which shows the "Relationship between calculated and measured amounts of vitamin A ($\mu\text{mol/g}$ wet wt) in the livers of 11 generally healthy human adults. The solid line is the line of identity (1:1 correspondence)," is reproduced below.

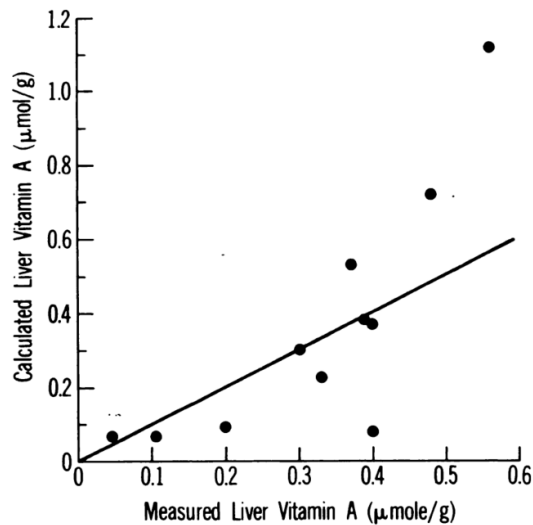


FIG 1. Relationship between calculated and measured amounts of vitamin A ($\mu\text{mol/g}$ wet wt) in the livers of 11 generally healthy human adults. The solid line is the line of identity (1:1 correspondence).

EX1006 (Olson 1989), 715.

C. Ortho Pharma (EX1008)

144. On January 18, 2007, a patent application entitled “Carotenoid-containing product” was published in the *Patent Gazette* with German patent application publication number 20-2006-014-588.5. The published patent is owned by Orthomol Pharmazeutische Vertiebs GmbH. For convenience, I will refer to this patent application publication as Ortho Pharma.

145. Ortho Pharma discloses compositions comprising carotenoids with vitamins, antioxidants, flavonoids, minerals, and other excipients in a solid and liquid form for promoting eye health in patients with age-related eye diseases, such as age-related macular degeneration. EX1008 (Ortho Pharma), ¶[0002], Abstract.

146. Ortho Pharma discloses that age-related eye diseases like macular degeneration are increasing. For example, Ortho Pharma states that “It is well known that age-related eye diseases such as age-related macular degeneration or senile cataract have greatly increased and will continue to increase due to the rising average age of the population.” EX1008 (Ortho Pharma), ¶[0002], Abstract.

147. Ortho Pharma provides that there is a need for “an agent that provides a comprehensive supply of antioxidant substances, vitamins, trace elements, and nutrients to the eye. Furthermore, there is a need to provide a product that is improved in terms of its composition and that improves the absorption of the ingredients.” EX1008 (Ortho Pharma), ¶[0006].

148. Ortho Pharma further discloses “a carotenoid-containing product that is particularly suitable for balanced nutritive supplementation of the diet in age-related eye diseases such as age-related macular degeneration or senile cataract.” EX1008 (Ortho Pharma), ¶[0001].

149. Ortho Pharma discloses making and using compositions, such as solutions, comprising vitamin A in a pharmaceutically acceptable carrier, such as water or oil. EX1008 (Ortho Pharma), ¶¶[0099], [0103]-[0106]. For example, Ortho Pharma discloses formulating vitamin A together with other vitamins and minerals in a liquid dosage form for ingestion. EX1008 (Ortho Pharma), ¶[0008].

150. Ortho Pharma teaches that administering the vitamins and minerals in liquid dosage form is well-tolerated and more available to an organism than when administered in solid dosage forms. EX1008 (Ortho Pharma), ¶¶[0012]-[0015]. For example, Ortho Pharma provides at paragraphs [0012] to [0015] that:

A major advantage of the carotenoid-containing product is realized by the use according to the invention of at least two separately present dosage forms, wherein a first dosage form is present in solid form, and a second dosage form is present in liquid form. It has been shown, for example, that administration in a liquid dosage form is a particularly well-tolerated form of administration for some ingredients, in particular flavonoids from citrus fruits, vitamins, and trace elements.

It is particularly advantageous that the ingredients contained are in a matrix more typical of foodstuffs. The ingredients are thus more available for the organism. Vitamins in particular can be absorbed more effectively. Without being committed to any particular theory, it is believed that this may result in significantly improved bioavailability of the active ingredients.

Advantageously, the liquid dosage form can also provide increased solubility of the components. Intake in the form of tablets, for example, can lead to delayed release and delayed dissolution of the ingredients in the stomach and intestines, resulting in poorer absorption.

Advantageously, the flavonoids obtainable from citrus fruits, vitamins, and trace elements contained in the liquid dosage form can be absorbed by the body much better compared to a usual dosage form as tablet or capsule.

EX1008 (Ortho Pharma), ¶¶[0012]-[0015].

151. Ortho Pharma identifies water as a preferred solvent for the vitamins and minerals disclosed. For example, Ortho Pharma states that:

The term “solution” as used in the present invention means a mixture of a solvent and substances dissolved, suspended and/or emulsified therein, preferably solids or liquids. Preferred solutions are those that form a mixture of a solvent and substances dissolved therein, in particular active ingredients. *A particularly preferred solvent is water.*

EX1008 (Ortho Pharma), ¶[0038].

152. Ortho Pharma further discloses that the carotenoid-containing product may be in the form of solutions. For example, Ortho Pharma discloses that “the carotenoid-containing product may be in the form of 1 to 3 capsules and/or 1 to 3 tablets and 1 to 3 solutions.” EX1009 (Ortho Pharma), ¶[0039]. Ortho Pharma further provides that:

Preferably, the carotenoid-containing product comprises at least a first solid dosage form in the form of a capsule and a second liquid dosage form in the form of a solution. Usable capsules are preferably soft gelatin capsules.

In preferred embodiments, the carotenoid-containing product comprises...at least one solution containing flavonoids, in particular bioflavonoids obtainable from citrus fruits, vitamins selected from the group comprising vitamin C, vitamin A, vitamin E, vitamin B₁, vitamin B₂, nicotinamide, vitamin B₆, vitamin B₁₂, vitamin D₃, and/or biotin, trace elements selected from the group comprising zinc, selenium, and/or chromium, and active ingredients selected from the group comprising beta-carotene and/or taurine...at least one capsule containing omega-3 fatty acids, L-cystine, and carotenoids selected from the group comprising lutein, zeaxanthin, and lycopene, and active ingredients selected from the group comprising folic acid, pantothenic acid, and/or flavonoids, in particular bioflavonoids obtainable from red grapes and/or elderberries.

EX1008 (Ortho Pharma), ¶[0040]-[0041].

153. Ortho Pharma further provides that the carotenoid-containing product can comprise:

at least one solution containing citrus extract, vitamins selected from the group comprising vitamin C, vitamin A, vitamin E, vitamin B₁, vitamin B₂, nicotinamide, vitamin B₆, vitamin B₁₂, vitamin D₃, and/or biotin, trace elements selected from the group comprising zinc, selenium, and/or chromium, and active ingredients selected from the group comprising beta-carotene and/or taurine...at least one capsule containing fish oil, L-cystine, and carotenoids selected from the group comprising lutein, zeaxanthin, and lycopene, and active ingredients selected from the group comprising folic acid, pantothenic acid, red grape extract, and/or elderberry extract.

EX1008 (Ortho Pharma), ¶[0042].

154. Ortho Pharma further provides a solution in the carotenoid-containing product with various ranges of vitamins and minerals. For example, Ortho Pharma discloses a carotenoid-containing product that may comprise:

at least one solution containing: 200 mg of vitamin C, 600 µg of vitamin A, 73 mg of vitamin E, 2 mg of vitamin B₁, 2.5 mg of vitamin B₂, 20 mg of nicotinamide, 2.5 mg of vitamin B₆, 9 µg of vitamin B₁₂, 2.5 µg of vitamin D₃, 150 µg of biotin, 15 mg of zinc, 60 µg of selenium, 60 µg of chromium, 50 mg of taurine, 2 mg of beta-carotene, and/or 36 mg of flavonoids, in particular bioflavonoids obtainable from citrus fruits, in particular hesperidin...at least one capsule containing: 400 µg of folic acid, 15 mg of pantothenic acid, 16 mg of carotenoids, thereof 12 mg of lutein, 840 µg of zeaxanthin, 1 mg of lycopene, 10 mg of flavonoids, in particular bioflavonoids obtainable from red grapes, and 4 mg of flavonoids, in particular bioflavonoids obtainable from elderberries, 258 mg of omega-3 fatty acids, thereof preferably 185 mg of docosahexaenoic acid, and/or 50 mg of L-cystine

EX1008 (Ortho Pharma), ¶[0044].

155. As another example, Ortho Pharma provides a carotenoid-containing product that may comprise:

At least one solution containing: 200 mg of vitamin C, 600 µg of vitamin A, 73 mg of vitamin E, 2 mg of vitamin B₁, 2.5 mg of vitamin B₂, 20 mg of nicotinamide, 2.5 mg of vitamin B₆, 9 µg of vitamin B₁₂, 2.5 µg of vitamin D₃, 150 µg of biotin, 15 mg of zinc, 60 µg of selenium, 60 µg of chromium, 50 mg of taurine, 2 mg of beta-carotene, and/or 4.1 g of citrus extract...At least one capsule containing: 400 µg of folic acid, 15 mg of pantothenic acid, 16 mg of carotenoids, including 12 mg of lutein, 840 µg of zeaxanthin, 1 mg of lycopene, 20 mg of red grape extract and 13.3 mg of elderberry extract, 370 mg of fish oil and/or 50 mg of L-cystine

EX1008 (Ortho Pharma), ¶[0046].

156. Ortho Pharma also discloses additional excipients that can be employed for formulations, including fillers, starch, vegetable oil, carriers such as silicon dioxide, and others. EX1008 (Ortho Pharma), ¶¶[0050]-[0051]. For example, Ortho Pharma discloses that:

Usual additives and/or auxiliaries known to the person skilled in the art are suitable. Particularly preferred are additives selected from the group comprising *humectants such as glycerol, starch, preferably modified starch, in particular from wheat and/or corn, vegetable oil, gelatin, maltodextrin, stabilizers such as gum arabic, preservatives such as potassium sorbate, sweeteners such as acesulfame K, sodium cyclamate, and/or saccharin sodium, carriers such as silicon dioxide, flavors, and/or colorants such as iron oxide,*

EX1008 (Ortho Pharma), ¶[0051].

157. Ortho Pharma teaches administering the formulation to individuals to treat or prevent eye diseases such as macular degeneration, including as a

nutritional supplement. EX1008 (Ortho Pharma), ¶¶[0001]-[0003], [0008], [0010]-[0011], [0052]-[0054]. Ortho Pharma teaches that it was known that “age-related eye diseases such as age-related macular degeneration or senile cataract have greatly increased and will continue to increase due to the rising average age of the population” and it was also known that “the complaints can be aggravated, especially in old age, by an incorrect diet or an inadequate supply of the necessary vitamins and nutrients...supportive care, especially for elderly patients, is known to prevent deficiencies in the supply of vitamins and nutrients to the eye.” EX1008 (Ortho Pharma), ¶[0002]-[0003]. As such, Ortho Pharma discloses “a carotenoid-containing product that is particularly suitable for balanced nutritive supplementation of the diet in age-related eye diseases such as age-related macular degeneration or senile cataract.” EX1008 (Ortho Pharma), ¶[0001].

158. Ortho Pharma further provides that the carotenoid-containing product can comprise, among other things, vitamin E, zinc, and vitamin D. For example, Ortho Pharma discloses:

a carotenoid-containing product, in particular suitable for nutritive balanced supplementation of the diet in age-related eye diseases, which comprises, based on a daily dose of the carotenoid-containing product, as active ingredients the substances: 50 mg to 500 mg of vitamin C; 0.1 mg to 2 mg of vitamin A; 10 mg to 400 mg of vitamin E; 0.2 mg to 5 mg of vitamin B₁; 0.2 mg to 5 mg of vitamin B₂; 5 mg to 50 mg of nicotinamide; 0.2 mg to 5 mg of vitamin B₆; 0.1 mg to 1 mg of folic acid; 5 µg to 50 µg of vitamin B₁₂; 0.1 µg to 10 µg of vitamin D₃; 50 µg to 300 µg of biotin; 3 mg to 30 mg of pantothenic acid; 2 mg to 30 mg of zinc; 20 µg to 100 µg of selenium; 20 µg to

100 µg of chromium; secondary plant compounds selected from the group comprising 6 mg to 32 mg of carotenoids comprising carotenoids selected from the group comprising beta-carotene, lutein, zeaxanthin, and lycopene, and 20 mg to 1000 mg of flavonoids comprising flavonoids obtainable from citrus fruits, red grapes, and elderberries; 20 mg to 200 mg of sulfur-containing amino acids selected from the group comprising L-cystine and/or N-acetylcysteine; 20 mg to 200 mg of taurine; 50 mg to 1000 mg of omega-3 fatty acids, wherein the product is in the form of at least two separately present dosage forms of different composition of active ingredients, wherein a first solid dosage form comprises substances selected from the group comprising omega-3 fatty acids and carotenoids selected from the group comprising lutein, zeaxanthin, and lycopene, and wherein a second liquid dosage form comprises substances selected from the group comprising flavonoids obtainable from citrus fruits, vitamins, and trace elements.

EX1008 (Ortho Pharma), ¶[0008].

159. Ortho Pharma discloses that “it has been shown that the product according to the invention and the formulation of the components of the carotenoid-containing product according to the invention can provide *comprehensive nutritional support to the eye*, in particular to the eye of elderly persons” EX1008 (Ortho Pharma), ¶[0010].

160. Ortho Pharma further discloses “[e]xamples of carotenoid-containing products.” EX1008 (Ortho Pharma), ¶[0055]. For example, Ortho Pharma provides Example 1, which discloses a “[c]arotenoid-containing product comprising 1 capsule and 1 solution.” Ortho Pharma discloses that the 1 solution contains:

200 mg of vitamin C, 600 µg of vitamin A, 73 mg of vitamin E, 2 mg of vitamin B₁, 2.5 mg of vitamin B₂, 20 mg of nicotinamide, 2.5 mg of vitamin B₆, 9 µg of vitamin B₁₂, 2.5 µg of vitamin D₃, 150 µg of

biotin, 15 mg of zinc, 60 µg of selenium, 60 µg of chromium, 50 mg of taurine, 2 mg of beta-carotene, 36 mg of hesperidin available from citrus fruits

EX1008 (Ortho Pharma), ¶[0056].

161. Ortho Pharma further discloses that the 1 capsule contains:

400 µg of folic acid, 15 mg of pantothenic acid, 16 mg of carotenoids, thereof 12 mg of lutein, 840 µg of zeaxanthin, 1 mg of lycopene, 10 mg of bioflavonoids available from red grapes, 4 mg of bioflavonoids available from elderberries, 258 mg of omega-3 fatty acids, thereof preferably 185 mg of docosahexaenoic acid, 50 mg of L-cystine.

EX1008 (Ortho Pharma), ¶[0056].

D. Widder (EX1009)

162. On January 19, 2006, a patent application entitled “Methods and Compositions for Treating Ophthalmic Conditions with Retinyl Derivatives” was published under the Patent Cooperation Treaty (PCT) with International Publication Number WO 2006/007314 A1. The inventors listed on this PCT patent publication are Kenneth Widder, Jay Lichter, and Nathan L. Mata. For convenience, I will refer to this patent publication by the last name of the first listed inventor, Widder.

163. Widder generally discloses compounds used to treat macular degeneration. For example, in the Abstract, Widder states that:

Compounds that cause reversible night blindness may be used to treat ophthalmic conditions associated with the overproduction of waste products that accumulate during the course of the visual cycle. We describe methods and compositions using such compounds and their derivatives to treat, for example, the macular degenerations and

dystrophies or to alleviate symptoms associated with such ophthalmic conditions. Such compounds and their derivatives may be used as single agent therapy or in combination with other agents or therapies.

EX1009 (Widder), Abstract.

164. Widder further discloses that:

In any of the aforementioned aspects are further embodiments comprising administering at least one additional agent selected from the group consisting of an inducer of nitric oxide production, an anti-inflammatory agent, a physiologically acceptable antioxidant, a physiologically acceptable mineral, a negatively charged phospholipid, a carotenoid, a statin, an anti-angiogenic drug, a matrix metalloproteinase inhibitor, 13-*cis*-retinoic acid (including derivatives of 13-*cis*-retinoic acid), 11-*cis*-retinoic acid (including derivatives of 11-*cis*-retinoic acid), 9-*cis*-retinoic acid (including derivatives of 9-*cis*-retinoic acid), and retinylamine derivatives.

165. EX1009 (Widder), 5:21-26. Referring to the negatively charged phospholipids above, Widder at page 6, lines 7-8 discloses that “the additional agent is a negatively charged phospholipid, including embodiments in which the negatively charged phospholipid is phosphatidylglycerol.” EX1009 (Widder), 6:7-8.

166. Widder further discloses that the pharmaceutical composition may comprise 13-*cis* retinoic acid. For example, Widder discloses that:

In further embodiment of the pharmaceutical composition aspect, the pharmaceutical composition further comprising an effective amount of at least one additional agent selected from the group consisting of an inducer of nitric oxide production, an anti-inflammatory agent, a physiologically acceptable antioxidant, a physiologically acceptable mineral, a negatively charged phospholipid, a carotenoid, a statin, an anti-angiogenic drug, a matrix metalloproteinase inhibitor, **13-*cis*-**

retinoic acid (including derivatives of 13-cis-retinoic acid), 11-cis-retinoic acid (including derivatives of 11-cis-retinoic acid), 9-cis-retinoic acid (including derivatives of 9-cis-retinoic acid), and retinylamine derivatives

167. EX1009 (Widder), 8:10-16. Widder discloses that the compounds can be administered in a variety of ways. For example, Widder states that:

The compounds of Formula (I) can be administered in a variety of ways, including all forms of local delivery to the eye. Additionally, the compounds of Formula (I) can be administered systemically, such as orally or intravenously. The compounds of Formula (I) can be administered topically to the eye and can be formulated into a variety of topically administrable ophthalmic compositions, such as solutions, suspensions, gels or ointments.

EX1009 (Widder), 25:16-20.

168. Further regarding routes of administration, Widder discloses that:

In any of the aforementioned aspects are further embodiments in which (a) the effective amount of the compound is systemically administered to the mammal; (b) the effective amount of the compound is administered orally to the mammal; (c) the effective amount of the compound is intravenously administered to the mammal; (d) the effective amount of the compound is ophthalmically administered to the mammal; (e) the effective amount of the compound is administered by iontophoresis; or (f) the effective amount of the compound is administered by injection to the mammal.

EX1009 (Widder), 4:33-35, 5:1-3.

169. Widder further discloses administering vitamin A with fenretinide to reduce lipofuscin formation to thereby treat macular degeneration. For example, in Example 15 entitled “Combination Therapy Involving Fenretinide, Vitamins and Minerals,” Widder provides that:

Administration of fenretinide in combination with vitamins and minerals can be either orally or parenterally administered at amounts effective to inhibit the development or reoccurrence of macular degeneration. Test dosages are initially in the range of about 20 mg/kg per day of fenretinide with 100-1000 mg vitamin C, 100-600 mg vitamin E, 10,000-40,000 IU vitamin A, 50-200 mg zinc and 1-5 mg copper for 15 to 20 weeks.

EX1009 (Widder), 47:21-27.

E. Mata (EX1010)

170. As part of my review of the knowledge of the art prior to 2007, I reviewed an article by Nathan L. Mata, Jian Weng, and Gabriel H. Travis published in the periodical publication *Proceedings of the National Academy of Science United States of America* (PNAS) on June 20, 2000 entitled “Biosynthesis of a major lipofuscin fluorophore in mice and humans with *ABCR*-mediated retinal and macular degeneration.” For convenience, I will refer to this article by the last name of the first-listed author, Mata.

171. As an initial matter, Mata discloses that it was known that age-related macular degeneration is common in the elderly and is characterized by the accumulation of fluorescent extracellular deposits and fluorescent lipofuscin granules in cells of the retinal pigment epithelium. For example, Mata states:

Age-related macular degeneration (AMD) is a common cause of blindness in the elderly. It is characterized by the accumulation of fluorescent extracellular deposits called drusen and fluorescent lipofuscin granules in cells of the retinal pigment epithelium (RPE).

EX1010 (Mata), 7154.

172. Mata further discloses that lipofuscin accumulation in the retinal pigment epithelium was known to be associated with several diseases, including forms of macular degeneration (including Stargardt's disease). Mata states that:

Lipofuscin accumulation in the RPE is also associated with Stargardt's disease (STGD1) and fundus flavimaculatus (FFM), recessive forms of macular degeneration that affect children.

EX1010 (Mata), 7154.

173. Mata further explains that certain genes appear to cause A2E accumulation in retinal pigment epithelium (RPE) cells:

ABCR encodes rim protein (RmP), an ATP-binding cassette transporter located in the rims of outer-segment discs. Rim protein (RmP) reconstituted in phospholipid vesicles containing phosphatidylethanolamine exhibits increased ATPase activity on addition of all-*trans*-retinaldehyde (RAL). Mice with a knockout mutation in the *abcr* gene have a complex ocular phenotype including elevated phosphatidylethanolamine in photoreceptor outer segments, elevated all-*trans*-RAL after light exposure, and ***accumulation of N-retinylidene-N-retinylethanolamine (A2E) in RPE cells***. Based on these observations, it has been suggested that RmP may function as an outwardly directed flippase for phosphatidylethanolamine conjugated to all-*trans* RAL.

EX1010 (Mata), 7154.

174. Mata provides that *N*-retinylidene-*N*-retinylethanolamine (A2E) was known to be a major fluorophore of lipofuscin that is toxic to retinal pigment epithelium cells. For example, Mata states that “[a] major fluorophore of lipofuscin is the toxic *bis*-retinoid, *N*-retinylidene-*N*-retinylethanolamine (A2E)” and

“[a]ccumulation of A2E, the major fluorophore of lipofuscin, is toxic to RPE cells.” EX1010 (Mata), 7154.

175. As I explained in Section VIII.B above, Mata substantiates Parish’s speculation of a [1,6]-proton shift. As such, Mata builds on and confirmed Parish’s hypothetical biosynthetic pathway, which Mata depicts in Figure 5 (which I have reproduced below) where *N*-retinylidene-*N*-retinylethanolamine (A2E) is formed by condensation of phosphatidylethanolamine and all-*trans* retinaldehyde (all-*trans* RAL). For example, Mata, citing Parish et al, states that:

Parish *et al.* hypothesized that A2E forms by condensation of phosphatidylethanolamine with all-*trans*-RAL, followed by oxidation and hydrolysis of the phosphate ester.

EX1010 (Mata), 7154.

176. Mata, referring to Parish, states that “we corroborate this hypothesis by identifying three critical intermediates in the biosynthesis of A2E in ocular tissues from *abcr*^{-/-} mice and humans with *ABCR*-mediates recessive macular degeneration.” EX1010 (Mata), 7154. Mata further states:

Our results corroborate the scheme proposed by C.A. Parish, M. Hashimoto, K. Nakanishi, J. Dillion & J. Sparrow [Proc. Natl. Acad. Sci. USA (1998) 95, 14609-14613], ***for the biosynthesis of A2E***: (i) condensation of all-*trans*-retinaldehyde (all-*trans*-RAL) with phosphatidylethanolamine to form a Schiff base; (ii) condensation of the amine product with a second all-*trans*-RAL to form a bis-retinoid; (iii) oxidation to yield a pyridinium salt; and (iv) hydrolysis of the phosphate ester to yield A2E.

EX1010 (Mata), 7154.

177. To identify the three intermediates (referenced in the paragraph above) in the biosynthesis of A2E, Mata describes that:

APE is the Schiff-base conjugate of phosphatidylethanolamine and all-trans-RAL. A2PE-H₂ and A2PE were proposed as intermediates in the synthesis of A2E but have not been previously identified.

Immediately after light exposure, we observed significantly elevated APE in *abcr* ^{-/-} compared with wild-type outer segments (Table 1). This difference is probably due to increased phosphatidylethanolamine in the mutants, because the levels of all-*trans*-RAL were similar in mice of both genotypes (Table 1). Most of the excess APE in *abcr* ^{-/-} outer segments was unprotonated (Table 1), possibly indicating higher intradiscal pH immediately after a photobleach. ***This form, in contrast to protonated APE, is capable of sigmatropic rearrangement and subsequent condensation with a second molecule of all-trans-RAL to yield A2PE-H₂ (Fig. 5).*** A2PE-H₂ was abundantly present in *abcr* ^{-/-} outer segments and RPE and accumulated dramatically with age (Fig. 1). Unexpectedly, A2PE-H₂ was undetectable in wild-type outer segments despite the presence, albeit at a lower level, of APE. This suggests that clearance of APE in wild-type outer segments is significantly faster than the rate of A2PE-H₂ formation.

EX1010 (Mata), 7157.

178. I have reproduced Table 1 in Mata below.

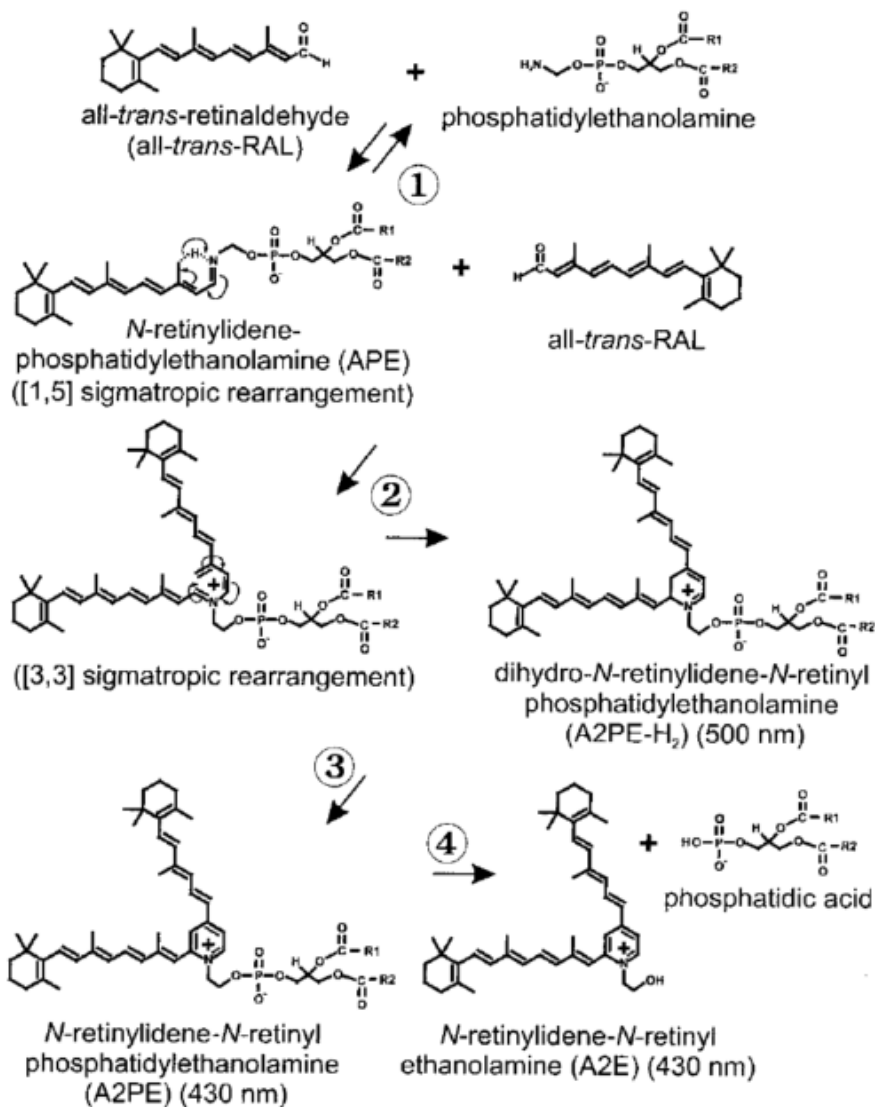
Table 1. Phosphatidylethanolamine, all-*trans*-RAL, and APE in outer segments

Genotype	PE, pmol/eye	All- <i>trans</i> -RAL, pmol/eye	APE, pmol/eye	[H ⁺]APE, pmol/eye	% all- <i>trans</i> -RAL as APE
Wild type	17,200 ± 1,930	72.2 ± 1.87	13.8 ± 1.37	3.48 ± 1.31	24%
<i>abcr</i> ^{-/-}	33,300 ± 4,680	74.1 ± 2.87	40.8 ± 3.56	4.43 ± 0.59	61%

HPLC analysis for phosphatidylethanolamine (PE), all-*trans*-RAL, APE, and protonated APE ([H⁺]APE) were performed on the same samples (*n* = 3) from wild-type and *abcr* ^{-/-} outer segments immediately after a 45% photobleach. All values are expressed as pmol per eye ± standard deviations. The last column shows the percent of total all-*trans*-RAL as APE (nonprotonated plus protonated) in wild-type and *abcr* ^{-/-} outer segments.

EX1010 (Mata), 7155.

179. Mata Figure 5 illustrates the “biosynthetic pathway for A2E in mice and humans lacking the RmP transporter,” which I have reproduced below.



EX1010 (Mata), 7158.

180. Referring to the pathway above, Mata identifies a critical (1,5)-sigmatropic rearrangement, which is the same [1,5]-hydrogen shift identified in the

'432 patent. Mata substantiates this pathway and the (1,5)-sigmatropic shift in the pathway. For example, Mata states:

This model is based on the proposed scheme for A2E biogenesis by Parish et al. In outer segments after a photobleach, phosphatidylethanolamine and all-*trans*-RAL are transiently in equilibrium with APE (reaction 1). ***After a (1,5) sigmatropic rearrangement***, the resulting secondary amine may condense with another molecule of all-*trans*-RAL. Subsequent (3,3) sigmatropic rearrangement of the bis-retinoid product results in the formation of A2PE-H₂ (reaction 2), an irreversible step at neutral pH. Oxidation of A2PE-H₂ to A2PE (reaction 3) occurs within RPE phagolysosomes and is accompanied by a shift in the visible Y_{max} from 500 to 430 nm. This blue shift is expected, because the two tetraene side chains are oriented meta on the pyridinium ring, hence resonance delocalization occurs at a higher energy in the oxidized form because of loss of aromaticity. Finally, ***A2E is formed within RPE*** phagolysosomes on acid hydrolysis of the phosphate ester and release of phosphatidic acid (reaction 4).

EX1010 (Mata), 7158. Though Mata's synthetic scheme identifies two sigmatropic rearrangements (e.g., (3,3)-sigmatropic rearrangement and (1,5)-sigmatropic rearrangement), the site of the (1,5)-sigmatropic rearrangement is the preferred location for deuteration to slow A2E formation because, as I explain in Section VIII.C above, it was known that there is a large kinetic isotope effect (e.g., 12.2) associated with a 1,5-sigmatropic shift in a 1,3-pentadiene system (see EX1016 (Itou), citing to Roth (EX1015)). It is readily apparent to a person of ordinary skill that the (1,5)-sigmatropic rearrangement is likely to be the rate-limiting step in the pathway because the kinetics of the (3,3)-sigmatropic rearrangement are significantly faster than that of the (1,5)-sigmatropic rearrangement, since the

(3,3)-sigmatropic rearrangement does not involve cleavage of a carbon-hydrogen bond. As such, based at least on the teachings of Itou and Roth, it is my opinion that the kinetics of the (1,5)-sigmatropic rearrangement would be significantly slower than the (3,3)-sigmatropic rearrangement in Mata and thus likely the rate limiting step in the mechanism.

181. Mata identifies two avenues for slowing progression of disease in humans with macular degeneration associated with lipofuscin formation. One method (e.g., the same identified in Widder) is to reduce all-*trans* retinal formation. Mata addresses this avenue for slowing disease progression by discussing limiting exposure to light. For the second avenue, which is a more targeted avenue, Mata expressly suggests targeting the A2E synthetic pathways Mata identified. For example, Mata states that:

These data suggest that humans with retinal or macular degeneration caused by loss of RmP function may slow progression of their disease by limiting exposure to light. The precursors of A2E identified in this study may represent pharmacological targets for the treatment of ABCR-mediated macular degeneration.

EX1010 (Mata), 7154. A person of ordinary skill in the art would understand that the second avenue (e.g., recognizing A2E synthesis precursors as pharmacological targets of inhibition) had the advantage of being narrowly tailored to address undesirable lipofuscin formation without inhibiting the visual cycle.

182. Mata teaches that its disclosed A2E synthesis pathway is not strictly limited to A2E accumulation due to the absence of the *abcr* gene because the final pathway of A2E accumulation reported in Mata may be similar in other forms of lipofuscin-mediated ophthalmic disease. For example, Mata states:

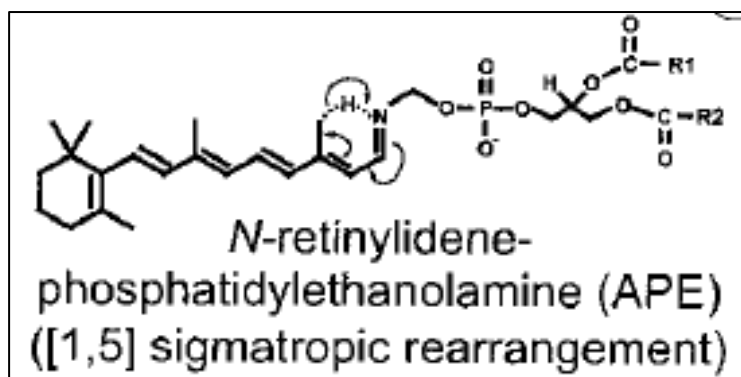
Although the mechanism of A2PE-H₂ formation undoubtedly varies with genetic etiology, ***the final pathway of A2E accumulation may be similar in other forms of lipofuscin-mediated macular or retinal degeneration.***

EX1010 (Mata), 7159.

183. Importantly, Mata teaches that “[p]harmacologic inhibition of one or more steps in the A2E synthetic pathway may thus be an effective treatment strategy for other macular degenerations associated with lipofuscin accumulation.”

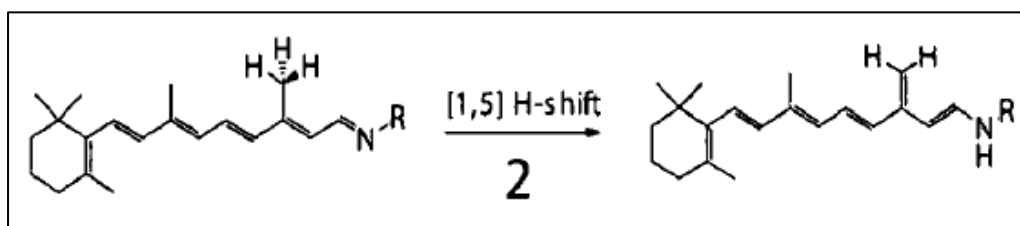
EX1010 (Mata), 7159. This provides a person of ordinary skill in the art with very good reason to inhibit the rate-limiting step in Mata’s pathways, which, as I explained above, is the [1,5]-sigmatropic rearrangement. A person of ordinary skill in the art would have recognized that C-20 deuteration was a promising avenue that would have been expected to reduce A2E/lipofuscin formation.

184. As I explained above, the prior art biosynthetic pathway that Mata corroborated is the same pathway that the ’432 patent later identified as the reason that C-20 deuteration slows lipofuscin formation. Specifically, step 1 of the biosynthetic pathway in Mata (which is provided below), features *N*-retinylidene-*N*-retinylethanolamine (A2E) and a [1,5]-sigmatropic rearrangement.



EX1010 (Mata), 7158.

185. This [1,5]-sigmatropic rearrangement requires breaking the C₂₀-bond with its hydrogen. Despite the visual and nomenclature differences, this is the same [1,5]-sigmatropic rearrangement later identified in the '432 patent (which I have reproduced below).



EX1001 (the '432 patent), Figure 2.

186. A person of ordinary skill in the art would thus have had good reason to inhibit the [1,5]-sigmatropic shift that was disclosed in Mata to reduce lipofuscin formation associated with ophthalmic disorders including macular degeneration. The [1,5]-sigmatropic shift step in the pathway in the '432 patent is just upstream of the intermediate that results in both A2E and ATR-dimer but sufficiently downstream of ATR formation, thus reducing the formation of undesirable

lipofuscin without interfering with the visual cycle. Further, a person of ordinary skill in the art with the perspective of a chemist would have recognized that the [1,5]-sigmatropic rearrangement in Mata was likely the rate-limiting step due to the requirement that the bond between the hydrogen and carbon-20 will break so that the hydrogen can shift to the nitrogen.

X. CLAIM CONSTRUCTION

187. I have been advised that the claims should be understood according to their ordinary and customary meaning as understood by a person of ordinary skill in the art at the time of the invention in light of the language of the claims, the specification, and the prosecution history of record. I have applied the plain and ordinary meaning of the claims in my analysis below.

XI. [GROUND 1] CLAIMS 1-6 AND 28 ARE OBVIOUS OVER OLSON 1988 AND OLSON 1989

188. For the reasons discussed in detail below, it is my opinion that each of claims 1-6 and 28 of the '432 patent is obvious as a whole. The obviousness of claims 1-6 and 28 is exemplified by disclosures in the Olson 1988 and Olson 1989 references.

189. I have evaluated below whether the combination of Olson 1988 and Olson 1989 discloses each and every element of each of claims 1-6 and 28 of the '432 patent. I have also analyzed whether a person of ordinary skill in the art before the critical date would have had good reason to combine these references in

a manner that satisfies each claim as a whole with a reasonable expectation of success. As I explain in detail below, the answer to each of these questions is yes.

190. As a high-level summary: (1) Olson 1988 discloses making and purifying C₂₀-D₁₋₃-retinoids, including C₂₀-D₃-retinol and a C₂₀-D₁₋₃-retinol ester (e.g., C₂₀-D₃-retinol acetate). EX1006, Abstract; *id.*, 12-13, 15-19. Olson 1988 further teaches that its deuterated forms of vitamin A are useful for biological studies. EX1006, 11. Olson 1989, a subsequent publication by the same research group as Olson 1988, teaches that one aspect of performing biological studies using their purified deuterated forms of vitamin A is making a pharmaceutical composition including the deuterated vitamin A and a pharmaceutically acceptable carrier (such as corn oil, for example). EX1007, 713-14 & Abstract. The sections below explain in more detail how Olson 1988 and Olson 1989 disclose each and every element of claims 1-6 and 28.

A. Claim 1

A pharmaceutical composition comprising...a
a pharmaceutically acceptable carrier...

191. I have reproduced above the preamble along with the element “a pharmaceutically acceptable carrier” of claim 1 in the challenged ’432 patent.

192. First, it is my opinion that Olson 1989 teaches a pharmaceutical composition comprising a purified deuterated vitamin A analogue in a pharmaceutically acceptable carrier. EX1007 (Olson 1989), 713-14 & Abstract.

193. For example, Olson 1989 discloses that “[t]he vitamin A status of 11 generally healthy surgical patients was estimated by measuring the dilution of a 45-mg oral dose of tetradeuterated retinyl acetate (99% pure).” EX1007 (Olson 1989), 713. Olson 1989 further discloses that, in its study, “*each subject was given 45 mg all-trans 10,19,19,19,19-[²H₄]retinol as retinyl acetate in corn oil*. The [²H₄]retinyl acetate (99% isotopic purity) was synthesized, characterized, and purified as described previously.” EX1007 (Olson 1989), 714. As such, Olson 1989 discloses a pharmaceutical composition (e.g., all-*trans* 10,19,19,19-[²H₄]retinol as retinyl acetate) in a pharmaceutically acceptable carrier (e.g., corn oil).

194. I have also reviewed the 19th edition of “Remington: The Science and Practice of Pharmacy” which was published in 1995 by *Mack Publishing Company* and authored by Alfonso R. Gennaro. For convenience, I will refer to this reference as Remington. Remington provides that corn oil is a pharmaceutically acceptable carrier that was well known in the art before 2007.

195. Remington, for example, states that corn oil is a “[c]lear, light yellow, oily liquid with a faint characteristic odor and taste; specific gravity 0.914 to 0.921” and is “[s]lightly soluble in alcohol; miscible with ether, chloroform, benzene or solvent hexane.” EX1017 (Remington), 1394. Remington, regarding the use of corn oil, further notes that:

Uses—Main official use is a *solvent* and *vehicle for injections*. It is used as an edible oil substitute for solid fats in the management of hypercholesterolemia. Other uses include making soaps and for burning. It is a semidrying oil and therefore unsuitable for lubricating or mixing paint.

EX1017 (Remington), 1394. As such, Remington provides that corn oil is a pharmaceutically acceptable carrier well known in the art, and it is my opinion that corn oil a pharmaceutically acceptable carrier was well known more than a decade before September 2007. This is consistent with my own experience for nearly the past 50 years, as I personally used corn oil as a pharmaceutical carrier for administration to rat subjects as early as 1975.

196. During my review of the challenged '432 patent, I noticed that the specification cites Remington as authority to show that Remington provides pharmaceutically acceptable dosage forms that were well known in the art. For example, the '432 patent states that:

Regardless of the route of administration selected, ***the compounds of the present invention are formulated into pharmaceutically-acceptable dosage forms by conventional methods known to those of skill in the art.*** See, e.g., Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, Pa.).

EX1001 (the '432 patent), 15:3-8.

197. The '432 patent, still citing Remington, then lists several pharmaceutically acceptable carriers provided in Remington that were well known in the art, including corn oil. The '432 patent, for example, states that:

Pharmaceutically acceptable carriers are well known in the art (see, e.g., Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, Pa.) and The National Formulary (American Pharmaceutical Association, Washington, D.C.)) and include sugars (e.g., lactose, sucrose, mannitol, and sorbitol), starches, cellulose preparations, calcium phosphates (e.g., dicalcium phosphate, tricalcium phosphate and calcium hydrogen phosphate), sodium citrate, water, aqueous solutions (e.g., saline, sodium chloride injection, Ringer's injection, dextrose injection, dextrose and sodium chloride injection, lactated Ringer's injection), alcohols (e.g., ethyl alcohol, propyl alcohol, and benzyl alcohol), polyols (e.g., glycerol, propylene glycol, and polyethylene glycol), organic esters (e.g., ethyl oleate and triglycerides), biodegradable polymers (e.g., polylactide-polyglycolide, poly(orthoesters), and poly(anhydrides)), elastomeric matrices, liposomes, microspheres, ***oils (e.g., corn, germ, olive, castor, sesame, cottonseed, and groundnut), cocoa butter, waxes (e.g., suppository waxes), paraffins, silicones, talc, silicylate, etc.*** Each pharmaceutically acceptable carrier used in a pharmaceutical composition of the invention must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the subject. Carriers suitable for a selected dosage form and intended route of administration are well known in the art, and acceptable carriers for a chosen dosage form and method of administration can be determined using ordinary skill in the art.

EX1001 (the '432 patent), 15:9-27.

198. Therefore, Olson 1989 teaches use of corn oil as a pharmaceutically acceptable carrier, and Remington provides that corn oil is a pharmaceutically acceptable carrier that was well known in the art. Further, the '432 patent cites Remington as authority that corn oil is a well-known pharmaceutically acceptable carrier.

199. Claim 1 further recites the retinoid element, which I have reproduced below.

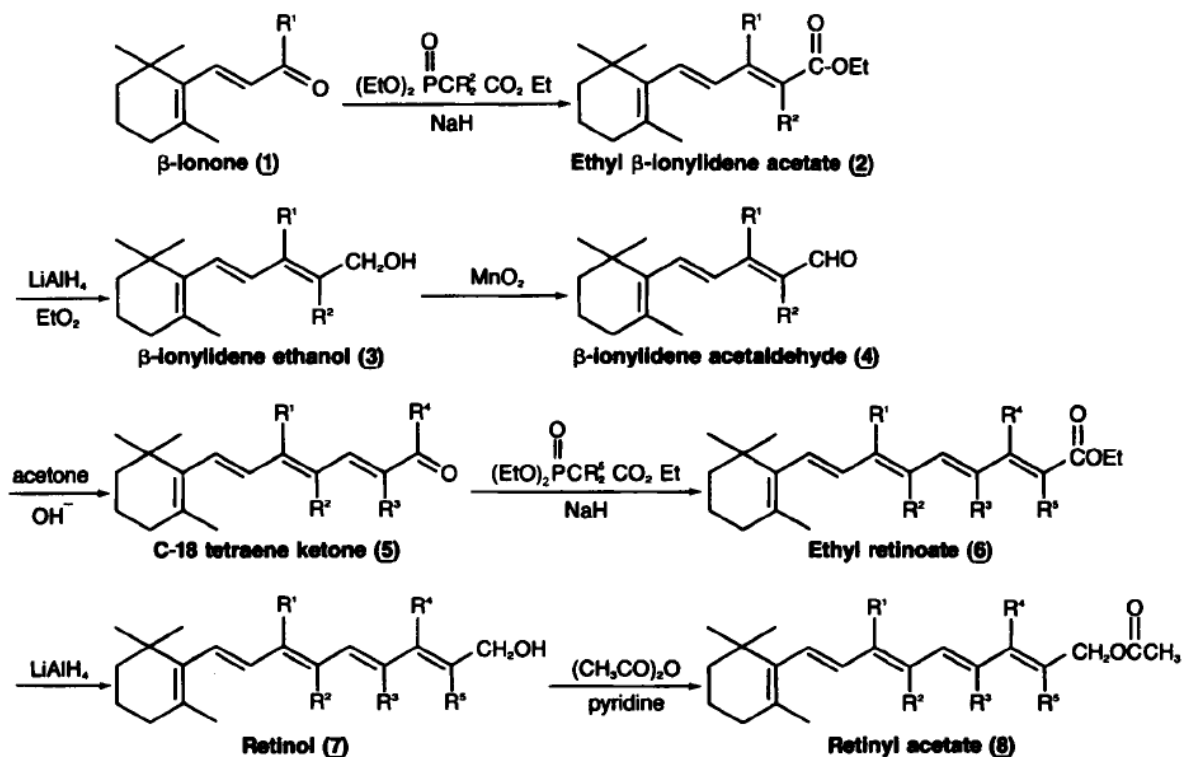
...a substituted C₂₀-D₁₋₃-retinoid...

wherein the C₂₀-D₁₋₃-retinoid is selected from the group consisting of C₂₀-D₁₋₃-retinol, C₂₀-D₁₋₃-retinol ester, C₂₀-D₁₋₃ retinal and a C₂₀-D₁₋₃-pro-vitamin A carotenoid.

Other than specifying deuteration at carbon 20, the claim elements reproduced above merely recite known forms and precursors of vitamin A that had long been administered to individuals with ophthalmic conditions including macular degeneration.

200. Olson 1988 discloses making and purifying substituted C₂₀-D₁₋₃-retinoids, including C₂₀-D₃-retinol and a C₂₀-D₃-retinol ester (e.g., C₂₀-D₃-retinol acetate) as recited in claim 1 of the challenged '432 patent. EX1006 (Olson 1988), Abstract; 12-13, 14, 15-19.

201. For example, Olson 1988 discloses the “synthesis of tri-, tetra-, and penta-deuterated forms of vitamin A” and provides a route of synthesis, which I have reproduced below.



Scheme 2. Synthesis of deuterated forms of vitamin A.

20,20,20- $^2\text{H}_3$ -Retinoic acid ethyl ester ($\text{R}^1 = \text{CH}_3$; $\text{R}^4 = \text{C}^2\text{H}_3$);

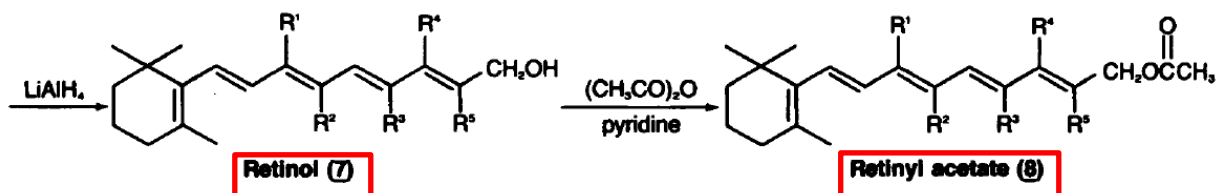
14,20,20,20- $^2\text{H}_4$ -Retinoic acid ethyl ester ($\text{R}^1 = \text{CH}_3$; $\text{R}^4 = \text{C}^2\text{H}_3$; $\text{R}^5 = ^2\text{H}$);

12,14,20,20,20- $^2\text{H}_5$ -Retinyl acetate ($\text{R}^1 = \text{CH}_3$; $\text{R}^3 = ^2\text{H}$; $\text{R}^4 = \text{C}^2\text{H}_3$; $\text{R}^5 = ^2\text{H}$);

10,19,19,19- $^2\text{H}_4$ -Retinyl acetate ($\text{R}^1 = \text{C}^2\text{H}_3$; $\text{R}^2 = ^2\text{H}$; $\text{R}^4 = \text{CH}_3$).

EX1006 (Olson 1988), 13.

202. Within the route of synthesis provided above, Olson 1988 discloses the synthesis “of 20,20,20-trideuteroretinol (Scheme 2, $\text{R}^4\text{-C}^2\text{H}_3$)” and 20,20,20- $^2\text{H}_3$ -retinyl acetate. EX1006 (Olson 1988), 12. I have reproduced below specifically the synthesis of 20,20,20-trideuteroretinol and 20,20,20- $^2\text{H}_3$ -retinyl acetate, and have boxed in red the relevant deuterated compounds (e.g., Retinol (7) = 20,20,20-trideuteroretinol, and Retinyl acetate (8) = 20,20,20- $^2\text{H}_3$ -retinyl acetate).



Scheme 2. Synthesis of deuterated forms of vitamin A.

20,20,20-²H₃-Retinoic acid ethyl ester (R¹ = CH₃; R⁴ = C²H₃);

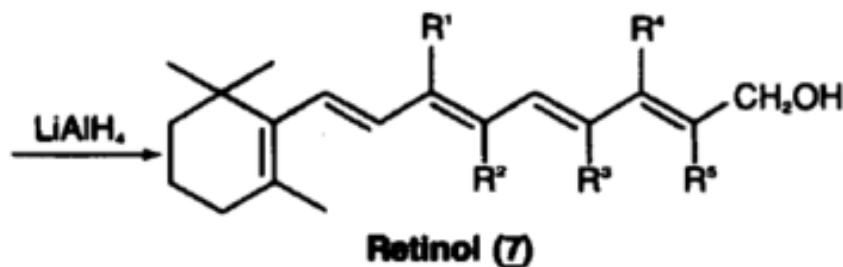
14,20,20,20-²H₄-Retinoic acid ethyl ester (R¹ = CH₃; R⁴ = C²H₃; R⁵ = ²H);

12,14,20,20,20-²H₅-Retinyl acetate (R¹ = CH₃; R³ = ²H; R⁴ = C²H₃; R⁵ = ²H);

10,19,19,19-²H₄-Retinyl acetate (R¹ = C²H₃; R² = ²H; R⁴ = CH₃).

EX1006 (Olson 1988), 13. Each of these compounds is a claimed retinoid as in claim 1.

203. Olson 1988 further discloses a procedure to prepare and make the 20,20,20-trideuteroretinol, which is further reproduced below for convenience.



EX1006 (Olson 1988), 13.

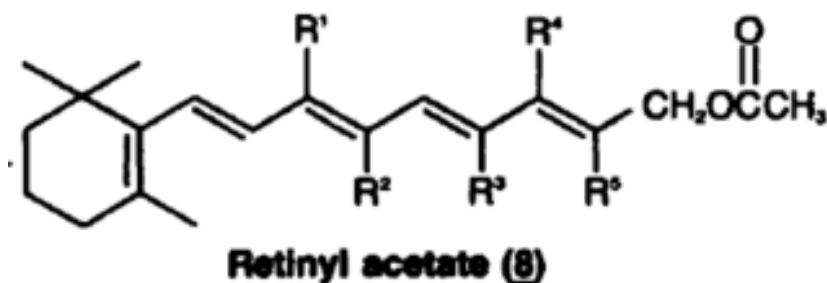
204. To make the 20,20,20-trideuteroretinol, for example, Olson 1988 explains that the:

20,20,20-²H₃-Retinol was prepared by adding 20,20,20-²H₃-retinoic acid ethyl ester (5 g, 0.015 mol, in 100 ml diethyl ether) dropwise to 0.57 (0.015 mol) LiAlH₄ in 250 ml anhydrous diethyl ether at -70°, with stirring. After being stirred 30 min at -70°, the solution was allowed to warm to room temperature; if reduction was not complete as judged by TLC, the solution was cooled, and more

LiAlH₄ added. The reaction was quenched by careful addition of 1 N H₂SO₄ to the cooled solution. The mixture was warmed to room temperature, washed with 1 N H₂SO₄ (2 x 200 ml) and then with water (3 x 200 ml), dried (MgSO₄), and rotary evaporated to give 3.65 g (85% yield) of crude product.

EX1006 (Olson 1988), 18.

205. Olson further discloses a procedure to prepare and make the 20,20,20-²H₃-retinyl acetate, which is reproduced below for convenience.



EX1006 (Olson 1988), 13.

206. To make the 20,20,20-²H₃-retinyl acetate from C₂₀-D₁₋₃-retinol, for example, Olson 1988 states that:

20,20,20-²H₃-Retinol (1 g, 0.003 mol) was dissolved in 10 ml pyridine and cooled in an ice bath. Acetic anhydride (0.28 ml, 0.003 mol) was added dropwise. After being stirred 15 min, the solution was allowed to warm to room temperature and checked by TLC; if acetylation was not complete, the solution was cooled, and more acetic anhydride was added. Ice was then added to destroy residual acetic anhydride. The solution was poured into 250 ml hexane and washed with water (6 x 250 ml) to remove pyridine. The organic layer was dried (MgSO₄) and rotary evaporated to give an overall crude yield of 60% (40% cis, 60% all-trans) 20,20,20-²H₃-retinyl acetate. The isomers were separated by HPLC (hexane:ethyl acetate, 98:2).

EX1006 (Olson 1988), 18.

207. Olson 1988 further states that:

All-trans ²H₃-retinyl acetate could be prepared from the cis isomers by dissolving up to 1 g of the cis isomers in 100 ml hexane and adding a small crystal of iodine. After being stirred 1 hr, the organic layer was washed with 100 ml 5% NaHSO₃, then with water (2 x 100 ml), and was then dried (MgSO₄). The all-trans ester was purified from the equilibrium mixture (55% all-trans, 35% 13-cis, 10% other cis forms) by HPLC.

EX1006 (Olson 1988), 19.

208. Therefore, Olson 1988 discloses the claimed retinoid and Olson 1989 discloses a pharmaceutically acceptable carrier. Accordingly, it is my opinion that claim 1 as a whole was obvious over Olson 1988 and Olson 1989.

B. Claims 2-3: Tri-deutero Vitamin A

2. The pharmaceutical composition according to claim 1, wherein the substituted C₂₀-D₁₋₃-retinoid is selected from the group consisting of C₂₀-D₃-retinol, C₂₀-D₃-retinol ester, C₂₀-D₃-retinal and a C₂₀-D₃-pro-vitamin A carotenoid.

3. The pharmaceutical composition according to claim 2, wherein the substituted C₂₀-D₁₋₃-retinoid is C₂₀-D₃-retinol acetate.

209. Claims 2 and 3 are both directed to a pharmaceutical composition of claim 1 wherein the C₂₀-D₁₋₃-retinoid is C₂₀-D₃-retinol acetate.

210. As I have previously addressed above, claim 1 is obvious over Olson 1988 and Olson 1989.

211. As I have discussed above for claim 1, Olson 1988 discloses making and purifying substituted C₂₀-D₁₋₃-retinoids, including C₂₀-D₃-retinol and a C₂₀-D₃-

retinol ester (e.g., C₂₀-D₃-retinol acetate). For example, Olson 1988 specifically discloses a C₂₀-D₃ retinol and C₂₀-D₃ retinol acetate (also known as retinyl acetate and retinoic acid ethyl ester) in Scheme 2. EX1006 (Olson 1988), 12-13.

212. Accordingly, it is my opinion that each of claims 2 and 3 as a whole is also obvious over Olson 1988 and Olson 1989.

C. Claims 4: Dosage Forms

4. The pharmaceutical composition according to claim 1, wherein the pharmaceutical composition is in unit dosage form.

213. Claim 4 is directed to forms of administration of a pharmaceutical composition of claim 1.

214. As I have previously addressed above, claim 1 is obvious over Olson 1988 and Olson 1989.

215. Olson 1989 discloses administering a pharmaceutical composition in a unit dose form. For example, Olson 1989 discloses administering an oral dose of 45 mg of deuterated retinyl acetate in corn oil.

Four to 6 d after surgery, a relative dose response (RDR) test was conducted in the conventional manner with an oral dose of 450 µg retinyl acetate in corn oil. The results of these studies already have been reported. Shortly thereafter each subject was given *a 45 mg all-trans 10,19,19,19,19-[²H₄]retinol as retinyl acetate in corn oil.*

EX1007 (Olson 1989), 714.

216. Accordingly, it is my opinion that claim 4 as a whole is obvious over Olson 1988 and Olson 1989.

D. Claims 5-6 and 28: Reduced A2E Formation

5. The pharmaceutical composition according to claim 1, wherein the C₂₀-D₁₋₃-retinoid, corresponding to the aldehyde of the C₂₀-D₁₋₃-retinol acetate, forms A2E in vitro about 7 times slower than non-deuterium-enriched retinoid.

6. The pharmaceutical composition according to claim 1, wherein the substituted C₂₀-D₁₋₃-retinoid inhibits the formation of A2E and/or ATR-dimer compared with the corresponding non-deuterium enriched retinoid.

28. The pharmaceutical composition according to claim 3, wherein the C₂₀-D₁₋₃-retinoid corresponding to the aldehyde of the C₂₀-D₁₋₃-retinol acetate, forms A2E in vitro about 7 times slower than non-deuterium-enriched retinoid.

217. As I have previously addressed above, claim 1 is obvious over Olson 1988 and Olson 1989.

218. The additional limitations of claims 5, 6, and 28 are all directed to slowing the formation of A2E and/or all-*trans* retinal (ATR)-dimer compared to a corresponding non-deuterium enriched retinoid. The additional limitation of these claims all encompasses the natural property of C₂₀-D₃-all-*trans* retinal that it inhibits the formation of A2E (claim 6) or forms A2E 7 times slower (claims 5 and 28) as compared to the non-deuterium-enriched all-*trans* retinal. This property flows naturally from the C-20 deuterium substitution and the kinetic isotope effect that naturally results from it. As I explained in Section VIII.C above, this effect is a result of the increased size, lower bond frequency, high energy of activation for

bond cleavage, and thus slower bond cleavage of the carbon deuterium bond as compared to the carbon hydrogen bond.

219. I note that, consistent with the knowledge of a person of ordinary skill in the art before 2007, the '432 patent acknowledges that the 7-fold slower formation of A2E and the slower formation of ATR-dimer as compared to the non-deuterium-enriched retinoid is an inherent property of C₂₀-D₃-retinal. For example, the '432 patent states that "C₂₀-D₃-all-trans-retinal forms A2E about 7-times slower than all-trans-retinal." EX1001 (the '432 patent), 8:13-17. The '432 patent further states that "When C₂₀ hydrogens are replaced by deuteriums, A2E formation is about seven times slower (FIG. 3) and ATR-dimer formation is about 15 times slower (FIG. 4)." EX1001 (the '432 patent), 18:10-58. As yet another example, the '432 patent states that "Replacing the C₂₀ Hydrogens of all-*trans*-Retinal with Deuteriums Slows the Formation of A2E [and ATR-Dimer] In Vitro." EX1001 (the '432 patent), 18:10-15 and 18:40-43.

220. As discussed above for claim 1, Olson 1988 discloses C₂₀-D₃-all-*trans* retinal and it was obvious in view of Olson 1988 and Olson 1989 to formulate it in a pharmaceutically-acceptable carrier for metabolic studies.

221. Further supporting the analysis I have provided above, Mata suggests pharmacological inhibition of the A2E biosynthetic pathway that requires deprotonation of Carbon 20 through a 1,5-sigmatropic shift. EX1010 (Mata), 7158-

59 & FIG. 5. As I have explained in Section VIII.C above, a person having ordinary skill in the art would have been well aware of the deuterium kinetic isotope effect and that the C₂₀-D₃-retinoid, including C₂₀-D₃-retinol acetate, would have been reasonably expected to slow elimination of the C₂₀-deuterium bond as compared to the C₂₀-protium bond, and therefore slow the formation of A2E. As explained above in Section VIII.C above, it was common for deuteration to slow a reaction by 5-10 times.

222. Accordingly, it is my opinion that each of claims 5, 6, and 28 is obvious over Olson 1988 and Olson 1989.

E. Rational Underpinnings for the Combination

223. By September 2007, a person having ordinary skill in the art would have had good reason to formulate the C₂₀-deuterated vitamin A analogues provided in Olson 1988 in a pharmaceutically acceptable carrier as claimed.

224. As an initial matter, persons having ordinary skill in the art would have had good reason to formulate the C₂₀-deuterated vitamin A analogues provided in Olson 1988 in a pharmaceutically acceptable carrier for administration to an animal (including humans) for biological studies. Indeed, doing so would have been readily apparent.

225. Olson 1988 provides that its deuterated vitamin A analogues are useful for performing biological studies. EX1006 (Olson 1988), 11. For example,

Olson 1988 discloses that “[f]or studying the metabolism of vitamin A in humans, nonradioactive deuterated or ^{13}C labeled compounds of high purity are desired.”

EX1006 (Olson 1988), 11. Olson 1988 further discloses the synthesis of “20,20,20-trideutero, 14,20,20,20-tetradeutero, 12,14,20,20,20-pentadeutero, and 10,19,19,19-tetradeutero analogs of retinoic acid ethyl ester and retinyl acetate.”

EX1006 (Olson 1988), 11. A person of ordinary skill in the art would have understood that to make use of such compounds, especially in biological studies, they would conventionally be formulated in a pharmaceutically acceptable carrier. *See, e.g.*, EX1007 (Olson 1989), 713-14 & Abstract (vitamin A analogues in corn oil), EX1022 (AREDS), Abstract (study published in periodical publication *Archives of Ophthalmology* teaching administration of beta carotene in tablet form).

226. This conventional understanding is exemplified in Olson 1989, which is a subsequent publication by a similar research group as Olson 1988. Olson 1989 provides a biological study that formulated deuterated vitamin A analogues in a pharmaceutically acceptable carrier for administration to humans. EX1007 (Olson 1989), 713-14 & Abstract. For example, Olson 1989 provides that “each subject was given a 45 mg all-trans 10,19,19,19,19- $^{2}\text{H}_4$ retinol as retinyl acetate in corn oil.” EX1007 (Olson 1989), 713-14 & Abstract. Therefore, at least based on the teachings of the Olson 1988 and Olson 1989 references, it is my opinion that a

person having ordinary skill in the art would have had good reason to formulate the C₂₀-D₃-retinol acetate in a pharmaceutically-acceptable carrier for administration to animals (including humans) for biological studies.

227. Relying on teachings of Olson 1988, Olson 1989 employed the 10,19,19,19-[²H₄] retinol acetate disclosed in 1988 for isotope dilution assays. EX1007 (Olson 1989), 713-714 (citing EX1006). Olson 1988 provides that 10,19,19,19-[²H₄] retinol acetate has high isotopic integrity. EX1006 (Olson 1988), 11. For example, Olson 1988 provides that “[t]he 10,19,19,19-²H₄-vitamin A, because of its high isotopic integrity (>98% ²H₄), is the preferred analog for biological studies of vitamin A metabolism.” EX1006 (Olson 1988), 11. Olson 1988 further provides that 10,19,19,19-[²H₄] retinol acetate contains three or more deuterium atoms in metabolically and chemically stable positions. For example, Olson 1988 states that the synthesis of 10,19,19,19-²H₄-retinyl acetate “can be attributed to the greater stability of β-ionone relative to the C-18 ketone and to the essential absence of nondeuterated side products in this first reaction step.” EX1006 (Olson 1988), 15.

228. In addition, although some biological studies (e.g., isotope dilution assays) were best served by deuteration at locations that would not induce a strong kinetic isotope effect, other biological assays (e.g., mechanistic studies or studies

identifying sites of metabolic degradation) favored deuteration in locations where primary kinetic isotope effects do occur. EX1012 (Haskins), 270-73.

229. Referring to the use of deuterium labeling in finding sites of metabolic attack, Baillie states that “Loss or retention of deuterium substituents at specific positions in a molecule can afford valuable information on sites of metabolic attack and is a technique that has been used in studies of drug metabolism for some years.” EX1013 (Baillie), 106.

230. In 1986, Agnes Van Langenhove published “Isotope Effects: Definitions and Consequences for Pharmacologic Studies” in the periodical publication *The Journal of Clinical Pharmacology*. For convenience, I will refer to this published paper by the last name of the author, Langenhove. Langenhove states that:

On the other hand, when stable isotope-labeled compounds are used for mechanistic studies, isotope effects can be used to their advantage: they provide detailed information about the nature of the enzymatic or drug action mechanism. Although this information can then be used to modify a drug’s action or its toxicity, it is also extremely useful when selecting stable isotope-labeled compounds for pharmacokinetic studies.

EX1014 (Langenhove), 383.

231. As I have explained in Sections VIII.B and IX.E above, references that became known to persons of ordinary skill in the art well after Olson 1988 and Olson 1989 provided good reason to formulate the C₂₀-D₃-retinol acetate provided

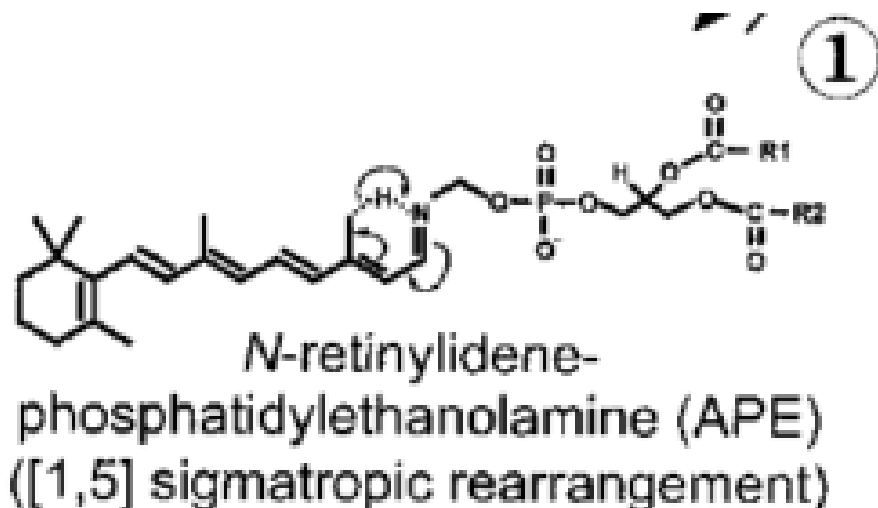
in Olson 1988 in a pharmaceutically acceptable carrier for biological studies. For example, Mata taught that deprotonation at C-20 of retinal was a pre-requisite for undesirable A2E formation. EX1010 (Mata), 7154 & Abstract, 7157-7158, Fig. 5 & Caption. As such, a person having ordinary skill in the art would have recognized that this deprotonation likely was a rate-limiting step in A2E formation and that substituting deuterium in place of the hydrogens at C-20 would slow A2E formation due to the powerful primary kinetic isotope effect expected from this substitution. A person having ordinary skill in the art thus had good reason to formulate the C₂₀-D₃-retinol or retinol acetate disclosed in Olson 1988 in a pharmaceutically-acceptable carrier (e.g., corn oil) disclosed in Olson 1989 at least for biological studies for (1) tracking compounds in vivo; (2) identifying metabolites and sites of metabolic action; or (3) inhibiting (e.g., slowing) reactions that involve cleavage of a hydrogen to C-20. Biological assays of such a deuterated analogue would be best suited to address the threshold inquiry of measuring the impact of the analogue's specifically located deuteration.

232. Mata further provides good reason to prepare and administer a pharmaceutical composition comprising a deuterated vitamin A analogue in a pharmaceutically acceptable carrier to reduce lipofuscin formation and thereby treat or prevent macular degeneration. For example, Mata discloses C₂₀ as a site of action for the metabolic pathway creating lipofuscin pigments associated with

macular degeneration. EX1010 (Mata), 7154 & Abstract, 7157-7158, Fig. 5 & Caption. Mata further discloses that this metabolic pathway depends on removing a hydrogen atom from C₂₀ through a 1,5-sigmatropic shift. EX1010 (Mata), 7158, FIG. 5. Mata expressly suggests inhibiting this metabolic pathway to reduce lipofuscin formation as a means for treating or preventing macular degeneration. EX1010 (Mata), 7154 & Abstract, 7159. As such, a person having ordinary skill in the art would have been well aware that the 1,5-sigmatropic shift disclosed in Mata was likely a rate-limiting step in A2E-formation and that inhibiting this step in the pathway would reduce A2E formation.

233. Further, persons of ordinary skill in the art would have understood that deuterating C₂₀ would slow A2E formation because 1,5-sigmatropic shifts were known to be subject to strong primary deuterium kinetic isotope effects. EX1015 (Roth and König, *Justus Liebigs Annalen Chemie*, **1966**) 24-32; EX1016 (Itou, et al. *J. Phys. Chem. A.*, **2006**) *111*, 261-67 (left column). For example, as explained in Section VIII.C. above, Itou, citing Roth, provides an analysis of the kinetic isotope effect of a 1,5-sigmatropic shift in a 1,3-pentadiene system. Roth further discloses that there is a large kinetic isotope effect associated with the 1,5-sigmatropic shift. Roth experimentally determined that the 1,5-sigmatropic shift of a deuterated 1,3-pentadiene with C-D₃ would proceed 12.2 times slower than the proteated 1,3-pentadiene. It is therefore my opinion that the mechanism of the

[1,5]H-shift at C-20, which is disclosed in Mata as reproduced below (and which was subsequently depicted in Figure 2 of the '045 patent) would similarly have a large kinetic isotope effect as experimentally determined in Roth.



EX1010, (Mata), Fig. 5 (excerpted). As such, a person having ordinary skill in the art would expect that the substitution of the C₂₀ methyl (CH₃) with CD₃ would similarly observe a large kinetic isotope effect associated with the 1,5-sigmatropic shift at the C₂₀ position.

234. Accordingly, persons having ordinary skill in the art would have had good reason to formulate the C₂₀-D₃-retinol acetate disclosed in Olson 1988 in a pharmaceutically-acceptable carrier (e.g., corn oil) for administration to an animal (including a human) to confirm and record the reduction in lipofuscin formation.

F. Reasonable Expectation of Success

235. Persons having ordinary skill in the art before 2007 would have had a reasonable expectation of success for making a pharmaceutical composition

comprising a claimed C₂₀-deuterated retinoid and a pharmaceutically-acceptable carrier. As discussed above in Sections IX.A and XI.i, Olson 1988 teaches that persons having ordinary skill in the art already had created claimed C₂₀-deuterated retinoids and had synthesized “20,20,20-trideutero, 14,20,20,20-tetradeutero, 12,14,20,20,20-pentadeutero, and 10,19,19,19-tetradeutero analogs of retinoic acid ethyl ester and retinyl acetate.” EX1006 (Olson 1988), 11. Further, as discussed in Section IX.B, Olson 1989 teaches that persons having ordinary skill in the art already had formulated deuterated retinoids in a pharmaceutical composition comprising a pharmaceutically-acceptable carrier such as corn oil. EX1007 (Olson 1989), 713-14 & Abstract. Accordingly, a person having ordinary skill in the art before 2007 would have had a reasonable expectation of success for making C₂₀-retinoids in a pharmaceutically-acceptable carrier as in claim 1 of the challenged ’432 patent.

236. That there would have been a reasonable expectation of success is not realistically in doubt. Indeed, the ’432 patent notes that formulation of the claimed compounds was conventional and within the skill of the art. For example, and as discussed in Section IV above, the ’432 patent notes that “[e]ffective dosage forms, modes of administration, and dosage amounts, in addition to those disclosed above, may be determined empirically, and making such determinations is within the skill of the art.” EX1001 (the ’432 patent), 14:31-34.

237. The '432 patent further states that the pharmaceutical composition may be administered by a variety of means, including orally by ingestion or locally to the eye. EX1001 (the '432 patent), 14:49-56. For example, citing to Remington, the '432 patent states that “[r]egardless of the route of administration selected, the compounds of the present invention are formulated into pharmaceutically-acceptable dosage forms by conventional methods known to those of skill in the art.” EX1001 (the '432 patent), 15:3-8, 15:32-36 (citing Remington’s).

238. Further citing to Remington the '432 patent notes that “[p]harmaceutically acceptable carriers are well known in the art” and include, *inter alia*, water, saline solution, or corn oil. EX1001 (the '432 patent), 15:9-27 (citing Remington’s). The '432 patent’s broad description of pharmaceutically acceptable carriers and its concession that they were well known in the art confirms my conclusions above regarding rationale to combine with a reasonable expectation of success in formulating the compounds of Olson 1988 in pharmaceutical carriers such as those taught by Olson 1989. Therefore, persons having ordinary skill in the art would have had a reasonable expectation of success for making the C₂₀-retinoid compounds and a pharmaceutically acceptable carrier as claimed in the challenged patent.

XII. [GROUND 2] CLAIMS 1-6, 8-23, 25 AND 27-28 ARE OBVIOUS OVER OLSON 1988 AND ORTHO PHARMA 2006

239. For the reasons discussed in detail below, it is my opinion that each of claims 1-6, 8-23, 25 and 27-28 of the '432 patent is obvious as a whole. The obviousness of claims 1-6, 8-23, 25 and 27-28 is exemplified by disclosures in the Olson 1988 and Ortho Pharma references.

240. I have evaluated below whether the combination of Olson 1988 and Ortho Pharma discloses each and every element of each of claims 1-6, 8-23, 25 and 27-28 of the '432 patent. I have also analyzed whether a person of ordinary skill in the art before the critical date would have had good reason to combine these references in a manner that satisfies each claim as a whole with a reasonable expectation of success. As I explain in detail below, the answer to each of these questions is yes.

241. My analysis in Ground 2 incorporates the statements regarding Olson 1988 from Ground 1 above in Section XI, which demonstrates that Olson 1988 suggests making and purifying the claimed C₂₀-D₁₋₃-retinoids. Further, my analysis of the present Ground 2 replaces the teachings of Olson 1989 with the teachings of Ortho Pharma.

242. As an initial matter, Ortho Pharma, which is discussed in detail in Section IX.C above, discloses formulating vitamin A in a pharmaceutically-acceptable carrier, including in combination with, *inter alia*, additional vitamins

(e.g., vitamin C, vitamin D, and vitamin E) and minerals (e.g., zinc). EX1008 (Ortho Pharma), ¶[0041]. For example, Ortho Pharma discloses a carotenoid-containing product comprising a solution with, among other things, vitamin C, vitamin A, vitamin E, vitamin D, and zinc:

at least one solution containing flavonoids, in particular bioflavonoids obtainable from citrus fruits, vitamins selected from the group comprising *vitamin C*, *vitamin A*, *vitamin E*, vitamin B₁, vitamin B₂, nicotinamide, vitamin B₆, vitamin B₁₂, *vitamin D₃*, and/or biotin, trace elements selected from the group comprising *zinc*, selenium, and/or chromium, and active ingredients selected from the group comprising beta-carotene and/or taurine

EX1008 (Ortho Pharma), ¶[0041].

243. Ortho Pharma further discloses a carotenoid-containing product comprising a solution with various doses of vitamins and minerals. For example, Ortho Pharma discloses a carotenoid-containing product comprising:

at least one solution containing: 200 mg of vitamin C, 600 µg of vitamin A, 73 mg of vitamin E, 2 mg of vitamin B₁, 2.5 mg of vitamin B₂, 20 mg of nicotinamide, 2.5 mg of vitamin B₆, 9 µg of vitamin B₁₂, 2.5 µg of vitamin D₃, 150 µg of biotin, 15 mg of zinc, 60 µg of selenium, 60 µg of chromium, 50 mg of taurine, 2 mg of beta-carotene, and/or 36 mg of flavonoids, in particular bioflavonoids obtainable from citrus fruits, in particular hesperidin

At least one solution containing: 200 mg of vitamin C, 600 µg of vitamin A, 73 mg of vitamin E, 2 mg of vitamin B₁, 2.5 mg of vitamin B₂, 20 mg of nicotinamide, 2.5 mg of vitamin B₆, 9 µg of vitamin B₁₂, 2.5 µg of vitamin D₃, 150 µg of biotin, 15 mg of zinc, 60 µg of selenium, 60 µg of chromium, 50 mg of taurine, 2 mg of beta-carotene, and/or 4.1 g of citrus extract EX1008 (Ortho Pharma), ¶[0044], [0046].

244. Ortho Pharma further discloses active ingredients, including, *inter alia*, vitamin A acetate, vitamin E, vitamin D, ascorbic acid, and zinc:

the carotenoid-containing product may contain active ingredients in the form of substances selected from the group consisting of orange juice concentrate, fish oil, sodium L-ascorbate, vitamin E, ascorbic acid, citrus extract, taurine, L-cystine, zinc (II) chloride, nicotinamide, calcium D-pantothenate, red grape extract, carotenoids comprising lutein, lycopene, and zeaxanthin, elderberry extract, vitamin B6 hydrochloride, vitamin B1 hydrochloride, vitamin B2, beta-carotene, vitamin A acetate, folic acid, chromium (III) chloride, biotin, sodium selenate, vitamin B12, and/or vitamin D3

EX1008 (Ortho Pharma), ¶[0049].

245. Ortho Pharma teaches that “administration in liquid dosage form is a particularly well-tolerated form of administration for some ingredients, in particular flavonoids from citrus fruits, vitamins, and trace elements.” EX1008 (Ortho Pharma), ¶[0012]. Ortho Pharma further teaches that “It is particularly advantageous that the ingredients contained are in a matrix more typical of foodstuffs. The ingredients are thus more available for the organism.” EX1008 (Ortho Pharma), ¶[0013].

246. Ortho Pharma identifies water as a preferred solvent for the vitamins and minerals mentioned in Ortho Pharma. EX1008 (Ortho Pharma), ¶[0038]-[0042], [0044], [0046]. For example, Ortho Pharma states that “Preferred solutions are those that form a mixture of a solvent and substances dissolved therein, in

particular active ingredients. *A particularly preferred solvent is water.*” EX1008 (Ortho Pharma), ¶[0038].

247. Ortho Pharma also discloses additional excipients that can be employed for formulations, including fillers, starch, vegetable oil, carriers such as silicon dioxide, and others. EX1008 (Ortho Pharma), ¶¶[0050]-[0051]. For example, Ortho Pharma provides that:

In preferred embodiments, the carotenoid-containing product may comprise at least one additive, preferably several additives, for improving bioavailability, improving texture, improving solubility and/or improving dissolution rate, disintegrants, shelf-life improving substances, taste-masking substances, taste-improving substances, substances for increasing or decreasing the viscosity, stabilizers, colorants, fillers, mold release agents, and/or disintegration accelerators.

Usual additives and/or auxiliaries known to the person skilled in the art are suitable. Particularly preferred are additives selected from the group comprising *humectants such as glycerol, starch, preferably modified starch, in particular from wheat and/or corn, vegetable oil*, gelatin, maltodextrin, stabilizers such as gum arabic, preservatives such as potassium sorbate, sweeteners such as acesulfame K, sodium cyclamate, and/or saccharin sodium, carriers such as silicon dioxide, flavors, and/or colorants such as iron oxide.

EX1008 (Ortho Pharma), ¶¶[0050]-[0051].

248. Ortho Pharma further teaches administering the formulation to individuals to treat or prevent eye diseases such as macular degeneration, including administration as a nutritional supplement. EX1008 (Ortho Pharma), ¶¶[0001]-[0003], [0008], [0010]-[0011], [0052]-[0054]. For example, Ortho Pharma discloses that:

Advantageously, a supplementary diet and/or a supportive dietary treatment with the carotenoid-containing product according to the invention can, for example, show positive effects on the health of the eye in the case of an existing macular degeneration or senile cataract, as well as counteract a macular degeneration or senile cataract.

EX1008 (Ortho Pharma), ¶[0011].

249. Ortho Pharma, discussing the use of the carotenoid-containing product for age-related eye diseases, further states that:

The carotenoid-containing product can be used for *dietary treatment of age-related eye diseases*. Furthermore, the carotenoid-containing product can be used for the *preparation of an agent for the dietary treatment of age-related eye diseases such as age-related macular degeneration or senile cataract*. The carotenoid-containing product according to the invention is also suitable as a balanced dietary supplement for patients with age-related eye diseases such as age-related macular degeneration or senile cataract. The carotenoid-containing product according to the invention is particularly suitable *as a supplementary balanced diet*.

EX1008 (Ortho Pharma), ¶[0052].

250. As shown by my analysis below, the combination of the Olson 1988 and Ortho Pharma references would make obvious each of claims 1-6, 8-23, 25 and 27-28.

A. Claim 1

1. A pharmaceutical composition comprising...a
a pharmaceutically acceptable carrier...

251. I have reproduced above the preamble along with the element “a pharmaceutically acceptable carrier” of claim 1 in the challenged ’432 patent.

252. Ortho Pharma discloses making and using compositions, such as solutions, comprising vitamin A in a pharmaceutically acceptable carrier, such as water or oil. EX1008 (Ortho Pharma), ¶¶[0099], [0103]-[0106]. For example, Ortho Pharma discloses formulating vitamin A together with other vitamins (such as vitamins C, D, and E) and minerals (such as zinc) in a liquid dosage form for ingestion. EX1008 (Ortho Pharma), ¶[0008].

253. Ortho Pharma teaches that administering the vitamins and minerals in liquid dosage form is well-tolerated and more available to an organism than when administered in solid dosage forms. EX1008 (Ortho Pharma), ¶¶[0012]-[0015]. For example, Ortho Pharma provides at paragraphs [0012] to [0015] that:

A major advantage of the carotenoid-containing product is realized by the use according to the invention of at least two separately present dosage forms, wherein a first dosage form is present in solid form, and a second dosage form is present in liquid form. It has been shown, for example, that administration in a liquid dosage form is a particularly well-tolerated form of administration for some ingredients, in particular flavonoids from citrus fruits, vitamins, and trace elements.

It is particularly advantageous that the ingredients contained are in a matrix more typical of foodstuffs. The ingredients are thus more available for the organism. Vitamins in particular can be absorbed more effectively. Without being committed to any particular theory, it is believed that this may result in significantly improved bioavailability of the active ingredients.

Advantageously, the liquid dosage form can also provide increased solubility of the components. Intake in the form of tablets, for example, can lead to delayed release and delayed dissolution of the ingredients in the stomach and intestines, resulting in poorer absorption.

Advantageously, the flavonoids obtainable from citrus fruits, vitamins, and trace elements contained in the liquid dosage form can be absorbed by the body much better compared to a usual dosage form as tablet or capsule.

EX1008 (Ortho Pharma), ¶¶[0012]-[0015].

254. Ortho Pharma identifies water as a preferred solvent for the vitamins and minerals disclosed. For example, Ortho Pharma states that “[a] *particularly preferred solvent is water.*” EX1008 (Ortho Pharma), ¶[0038].

255. Ortho Pharma also discloses additional excipients that can be employed for formulations, including fillers, starch, vegetable oil, carriers such as silicon dioxide, and others. EX1008 (Ortho Pharma), ¶¶[0050]-[0051]. For example, Ortho Pharma discloses that:

Usual additives and/or auxiliaries known to the person skilled in the art are suitable. Particularly preferred are additives selected from the group comprising *humectants such as glycerol, starch, preferably modified starch, in particular from wheat and/or corn, vegetable oil, gelatin, maltodextrin, stabilizers such as gum arabic, preservatives such as potassium sorbate, sweeteners such as acesulfame K, sodium cyclamate, and/or saccharin sodium, carriers such as silicon dioxide, flavors, and/or colorants such as iron oxide.*

EX1008 (Ortho Pharma), ¶[0051].

256. Ortho Pharma teaches administering the formulation to individuals to treat or prevent eye diseases such as macular degeneration, including as a nutritional supplement. EX1008 (Ortho Pharma), ¶¶[0001]-[0003], [0008], [0010]-[0011], [0052]-[0054]. For example, Ortho Pharma discloses that “it has been shown that the product according to the invention and the formulation of the

components of the carotenoid-containing product according to the invention can provide *comprehensive nutritional support to the eye*, in particular to the eye of elderly persons” EX1008 (Ortho Pharma), ¶[0010].

257. It is my opinion that Ortho Pharma clearly discloses a pharmaceutical composition comprising a pharmaceutically acceptable carrier as described in claim 1 of the challenged ’432 patent.

258. The ’432 patent, citing Remington, notes that water is a pharmaceutically acceptable carrier that was known in the art. EX1001 (the ’432 patent), 15:9-26. For example, the ’432 patent states that “Pharmaceutically acceptable carriers are well known in the art...include...*water*, aqueous solutions (e.g., saline, sodium chloride injection, Ringer’s injection, dextrose injection, dextrose and sodium chloride injection, lactated Ringer’s injection)...oils (e.g., corn, germ, olive, castor, sesame, cottonseed, and groundnut)”. EX1001 (the ’432 patent), 15:9-27.

259. The ’432 patent further notes that “Carriers suitable for a selected dosage form and intended route of administration are well known in the art” and formulation of the claimed compounds in the challenged ’432 patent is done “by conventional methods known to those of skill in the art” and that “acceptable carriers for a chosen dosage form and method of administration can be determined using ordinary skill in the art.” EX1001 (the ’432 patent), 15:9-27.

260. Further, Remington teaches a short list of pharmaceutically acceptable carriers that includes water. EX1017 (Remington), 21. For example, Remington discloses that:

Diluting agents (vehicles or carriers) are indifferent substances which are used as solvents for active medicinals. They are of primary importance for diluting and flavoring drugs which are intended for oral administration, but a few such agents are designed specifically for diluting parenteral injections...The best diluting agent is usually the best solvent for the drug. Water-soluble substances, for example, should be flavored and diluted with an aqueous agent and alcohol-soluble drugs with an alcoholic vehicle.

EX1017 (Remington), 21.

261. Remington further discloses that among the list of diluting agents include aqueous diluting agents, which include orange flower water, peppermint water, water, and purified water. EX1017 (Remington), 21. For example Remington states that:

Aqueous diluting agents include aromatic waters, syrups and mucilages. Aromatic waters are used as diluting agents for water-soluble substances and salts, but cannot mask the taste of very disagreeable drugs. Some of the more common flavored aqueous agents and the official forms of water are listed below.

EX1017 (Remington), 21-22.

262. Accordingly, Ortho Pharma discloses a pharmaceutical composition comprising a pharmaceutically acceptable carrier (e.g., water).

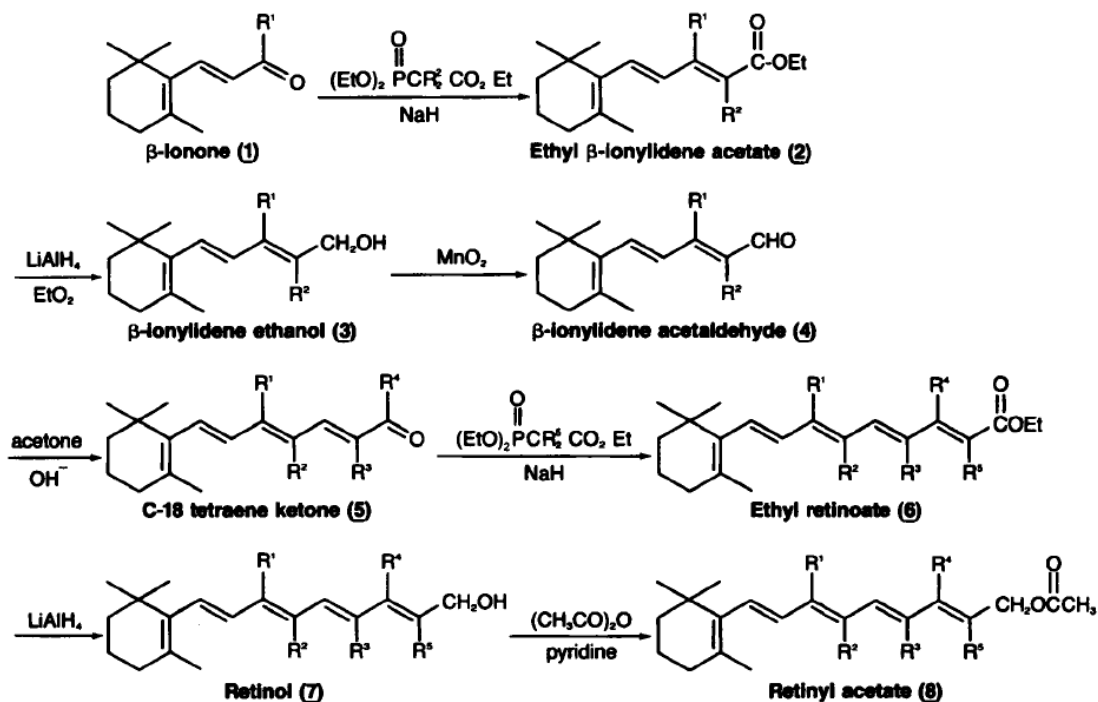
263. Claim 1 further recites the retinoid element, which I have reproduced below.

...a substituted C₂₀-D₁₋₃-retinoid...

wherein the C₂₀-D₁₋₃-retinoid is selected from the group consisting of C₂₀-D₁₋₃-retinol, C₂₀-D₁₋₃-retinol ester, C₂₀-D₁₋₃ retinal and a C₂₀-D₁₋₃-pro-vitamin A carotenoid.

264. As described in great detail in Section XI.i. in Ground 1 above, Olson 1988 discloses making and purifying substituted C₂₀-D₁₋₃-retinoids, including C₂₀-D₃-retinol and a C₂₀-D₃-retinol ester (e.g., C₂₀-D₃-retinol acetate) as recited in claim 1 of the challenged '432 patent. EX1006 (Olson 1988), Abstract; 12-13, 14, 15-19.

265. For example, Olson 1988 discloses the “synthesis of tri-,tetra-, and penta-deuterated forms of vitamin A” and provides a route of synthesis, which I have reproduced below. EX1006 (Olson 1988), 11.



Scheme 2. Synthesis of deuterated forms of vitamin A.

20,20,20- $^2\text{H}_3$ -Retinoic acid ethyl ester ($\text{R}^1 = \text{CH}_3$; $\text{R}^4 = \text{C}^2\text{H}_3$);

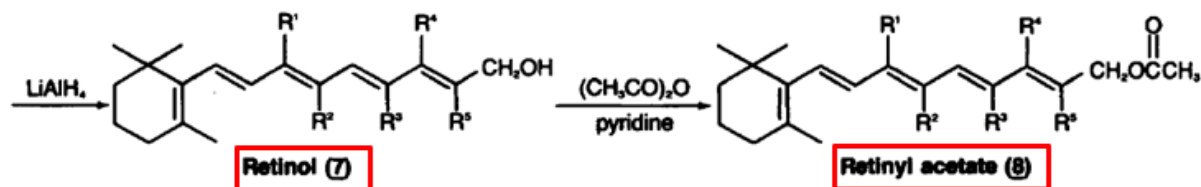
14,20,20,20- $^2\text{H}_4$ -Retinoic acid ethyl ester ($\text{R}^1 = \text{CH}_3$; $\text{R}^4 = \text{C}^2\text{H}_3$; $\text{R}^5 = ^2\text{H}$);

12,14,20,20,20- $^2\text{H}_5$ -Retinyl acetate ($\text{R}^1 = \text{CH}_3$; $\text{R}^3 = ^2\text{H}$; $\text{R}^4 = \text{C}^2\text{H}_3$; $\text{R}^5 = ^2\text{H}$);

10,19,19,19- $^2\text{H}_4$ -Retinyl acetate ($\text{R}^1 = \text{C}^2\text{H}_3$; $\text{R}^2 = ^2\text{H}$; $\text{R}^4 = \text{CH}_3$).

EX1006 (Olson 1988), 13.

266. In particular, within the route of synthesis provided above, Olson 1988 discloses the synthesis “of 20,20,20-trideuteroretinol (Scheme 2, $\text{R}^4\text{-C}^2\text{H}_3$)” and 20,20,20- $^2\text{H}_3$ -retinyl acetate. EX1006 (Olson 1988), 12. I have reproduced below specifically the synthesis of 20,20,20-trideuteroretinol and 20,20,20- $^2\text{H}_3$ -retinyl acetate, and have boxed in red the relevant deuterated compounds (e.g., Retinol (7) = 20,20,20-trideuteroretinol and Retinyl acetate (8) = 20,20,20- $^2\text{H}_3$ -retinyl acetate). EX1006 (Olson 1988), 13.



Scheme 2. Synthesis of deuterated forms of vitamin A.

20,20,20- $^2\text{H}_3$ -Retinoic acid ethyl ester ($\text{R}^1 = \text{CH}_3$; $\text{R}^4 = \text{C}^2\text{H}_3$);

14,20,20,20- $^2\text{H}_4$ -Retinoic acid ethyl ester ($\text{R}^1 = \text{CH}_3$; $\text{R}^4 = \text{C}^2\text{H}_3$; $\text{R}^5 = ^2\text{H}$);

12,14,20,20,20- $^2\text{H}_5$ -Retinyl acetate ($\text{R}^1 = \text{CH}_3$; $\text{R}^3 = ^2\text{H}$; $\text{R}^4 = \text{C}^2\text{H}_3$; $\text{R}^5 = ^2\text{H}$);

10,19,19,19- $^2\text{H}_4$ -Retinyl acetate ($\text{R}^1 = \text{C}^2\text{H}_3$; $\text{R}^2 = ^2\text{H}$; $\text{R}^4 = \text{CH}_3$).

EX1006 (Olson 1988), 13. Each of these compounds is a claimed retinoid as in claim 1.

267. Thus, Olson 1988 discloses a pharmaceutical composition comprising a claimed deuterated vitamin A analog and Ortho Pharma teaches a composition comprising a pharmaceutically acceptable carrier.

268. Accordingly, it is my opinion that claim 1 as a whole is obvious over the Olson 1988 and Ortho Pharma references.

B. Claims 2-3: Tri-Deutero Vitamin A

2. The pharmaceutical composition according to claim 1, wherein the substituted $\text{C}_{20}\text{-D}_{1-3}$ -retinoid is selected from the group consisting of $\text{C}_{20}\text{-D}_3$ -retinol, $\text{C}_{20}\text{-D}_3$ -retinol ester, $\text{C}_{20}\text{-D}_3$ -retinal and a $\text{C}_{20}\text{-D}_3$ -pro-vitamin A carotenoid.

3. The pharmaceutical composition according to claim 2, wherein the substituted $\text{C}_{20}\text{-D}_{1-3}$ -retinoid is $\text{C}_{20}\text{-D}_3$ -retinol acetate.

269. Claims 2 and 3 are both directed to a pharmaceutical composition of claim 1 wherein the $\text{C}_{20}\text{-D}_{1-3}$ -retinoid is $\text{C}_{20}\text{-D}_3$ -retinol acetate.

270. As I have previously addressed above, claim 1 is obvious over Olson 1988 and Ortho Pharma. As I have discussed above for claim 1, Olson 1988 discloses making and purifying substituted C₂₀-D₁₋₃-retinoids, including C₂₀-D₃-retinol and a C₂₀-D₃-retinol ester (e.g., C₂₀-D₃-retinol acetate). For example, Olson 1988 specifically discloses a C₂₀-D₃ retinol and C₂₀-D₃ retinol acetate (also known as retinyl acetate and retinoic acid ethyl ester) in Scheme 2.

271. Accordingly, it is my opinion that each of claims 2 and 3 as a whole is also obvious over Olson 1988 and Ortho Pharma.

C. Claim 4: Dosage Forms

4. The pharmaceutical composition according to claim 1, wherein the pharmaceutical composition is in unit dosage form.

272. Claims 4 is directed to forms of administration of a pharmaceutical composition of claim 1.

273. As I have previously addressed above, claim 1 is obvious over Olson 1988 and Ortho Pharma. As discussed above, Ortho Pharma discloses daily doses of the liquid dosage form since Ortho Pharma provides for: “a carotenoid-containing product, in particular suitable for nutritive balanced supplementation of the diet in age-related eye diseases, which comprises, based on a *daily dose* of the carotenoid-containing product... a second *liquid dosage form*.” EX1008 (Ortho Pharma), ¶[0008]. Ortho Pharma also discloses various doses of vitamins and minerals:

200 mg to 2300 mg, preferably 440 mg to 1600 mg, preferred 700 mg to 1400 mg of vitamin C...0.4 mg to 9 mg, preferably 1.3 mg to 6.7 mg, preferred 1.7 mg to 5 mg of vitamin A...40 mg to 1800 mg, preferably 85 mg to 900 mg, preferred 240 mg to 350 mg of vitamin E...0.4 µg to 45 µg, preferably 4.4 µg to 23 µg, preferred 8.5 µg to 14 µg of vitamin D₃...8 mg to 140 mg, preferably 22 mg to 115 mg, preferred 44 mg to 90 mg of zinc

EX1008 (Ortho Pharma), ¶[0036].

274. Ortho Pharma further discloses doses of vitamins and minerals in solution in a drinking vial. EX1008 (Ortho Pharma), ¶¶[0056]-[0058]. For example, at paragraph [0056], Ortho Pharma discloses a:

Carotenoid-containing product comprising 1 capsule and...1 solution containing...200 mg of vitamin C, 600 µg of vitamin A, 73 mg of vitamin E, 2 mg of vitamin B₁, 2.5 mg of vitamin B₂, 20 mg of nicotinamide, 2.5 mg of vitamin B₆, 9 µg of vitamin B₁₂, 2.5 µg of vitamin D₃, 150 µg of biotin, 15 mg of zinc, 60 µg of selenium, 60 µg of chromium, 50 mg of taurine, 2 mg of beta-carotene, 36 mg of hesperidin available from citrus fruits; 1 capsule containing...400 µg of folic acid, 15 mg of pantothenic acid, 16 mg of carotenoids, thereof 12 mg of lutein, 840 µg of zeaxanthin, 1 mg of lycopene, 10 mg of bioflavonoids available from red grapes, 4 mg of bioflavonoids available from elderberries, 258 mg of omega-3 fatty acids, thereof preferably 185 mg of docosahexaenoic acid, 50 mg of L-cystine.

EX1008 (Ortho Pharma), ¶[0056].

275. Accordingly, it is my opinion that claim 4 as a whole is obvious over Olson 1988 and Ortho Pharma.

D. Claims 5-6 and 28: Reduced A2E Formation

5. The pharmaceutical composition according to claim 1, wherein the C₂₀-D₁₋₃-retinoid, corresponding to the aldehyde of the C₂₀-D₁₋₃-retinol acetate, forms A2E in vitro about 7 times slower than non-deuterium-enriched retinoid.

6. The pharmaceutical composition according to claim 1, wherein the substituted C₂₀-D₁₋₃-retinoid inhibits the formation of A2E and/or ATR-dimer compared with the corresponding non-deuterium enriched retinoid.

28. The pharmaceutical composition according to claim 3, wherein the C₂₀-D₁₋₃-retinoid corresponding to the aldehyde of the C₂₀-D₁₋₃-retinol acetate, forms A2E in vitro about 7 times slower than non-deuterium-enriched retinoid.

276. As I have previously addressed above, claim 1 is obvious over Olson 1988 and Ortho Pharma.

277. The additional limitations of claims 5, 6, and 28 are all directed to slowing the formation of A2E and/or all-*trans* retinal (ATR)-dimer compared to a corresponding non-deuterium-enriched retinoid. The additional limitation of these claims all encompasses the natural property of C₂₀-D₃-all-*trans* retinal that it inhibits the formation of A2E (claim 6) or forms A2E 7 times slower (claims 5 and 28) as compared to the non-deuterium-enriched all-*trans* retinal. This property flows naturally from the C-20 deuterium substitution and the kinetic isotope effect that naturally results from it. As I explained in Section VIII.C above, this kinetic isotope effect is a result of the increased size, lower bond frequency, high energy of activation for bond cleavage, and thus slower bond cleavage of the carbon deuterium bond as compared to the carbon hydrogen bond.

278. Accordingly, it is my opinion that each of claims 5-6 and 28 as a whole is obvious over Olson 1988 and Ortho Pharma.

E. Claims 8-9: Additives

8. The pharmaceutical composition according to claim 1, further comprising one or more additives.

9. The pharmaceutical composition according to claim 8, wherein the additives are selected from the group consisting of zinc, vitamin E, vitamin D, and combinations thereof.

279. Claims 8 and 9 are both directed to a pharmaceutical composition of claim 1 that further comprise an additive selected from zinc, vitamin E, vitamin D, and combinations thereof.

280. As I have previously addressed above, claim 1 is obvious over Olson 1988 and Ortho Pharma. Ortho Pharma discloses a carotenoid containing product comprising, *inter alia*, vitamin E, vitamin D, and zinc. For example, Ortho Pharma provides for:

a carotenoid-containing product, in particular suitable for nutritive balanced supplementation of the diet in age-related eye diseases, which comprises, based on a daily dose of the carotenoid-containing product, as active ingredients the substances: 50 mg to 500 mg of vitamin C; 0.1 mg to 2 mg of vitamin A; **10 mg to 400 mg of vitamin E**; 0.2 mg to 5 mg of vitamin B₁; 0.2 mg to 5 mg of vitamin B₂; 5 mg to 50 mg of nicotinamide; 0.2 mg to 5 mg of vitamin B₆; 0.1 mg to 1 mg of folic acid; 5 µg to 50 µg of vitamin B₁₂; **0.1 µg to 10 µg of vitamin D₃**; 50 µg to 300 µg of biotin; 3 mg to 30 mg of pantothenic acid; **2 mg to 30 mg of zinc**

EX1008 (Ortho Pharma), ¶[0008].

281. Accordingly, it is my opinion that each of claims 8 and 9 is obvious over Olson 1988 and Ortho Pharma.

F. Claims 10-12: Zinc Additives

10. The pharmaceutical composition according to claim 9, wherein the zinc is present in the pharmaceutical composition at between about 3 to about 80 mg.

11. The pharmaceutical composition according to claim 9, wherein the zinc is present in the pharmaceutical composition at between about 3 to about 10 mg.

12. The pharmaceutical composition according to claim 9, wherein the zinc is present in the pharmaceutical composition at between about 10 to about 80 mg.

282. Claims 10-12 are all directed to a pharmaceutical composition of claim 1 that further comprises between about 3 mg to about 10 mg of zinc.

283. As I have previously addressed above, claim 1 is obvious over Olson 1988 and Ortho Pharma. Ortho Pharma discloses “a carotenoid-containing product, in particular suitable for nutritive balanced supplementation of the diet in age-related eye diseases, which comprises, based on a daily dose of the carotenoid-containing product, as active ingredients the substances...**2 mg to 30 mg of zinc.**” EX1008 (Ortho Pharma), ¶[0008].

284. The 2 mg to 30 mg of zinc range disclosed in Ortho Pharma overlaps with the ranges of zinc present in claims 10-12 of the '432 patent (e.g., between about 3 to about 80 mg, between about 3 to about 10 mg, and between about 10 to about 80 mg).

285. Accordingly, it is my opinion that each of claims 10-12 is obvious over Olson 1988 and Ortho Pharma.

G. Claims 13-15: Vitamin E Additives

13. The pharmaceutical composition according to claim 9, wherein the vitamin E is present in the pharmaceutical composition at between about 3 to about 3,000 mg.

14. The pharmaceutical composition according to claim 9, wherein the vitamin E is present in the pharmaceutical composition at between about 3 to about 15 mg.

15. The pharmaceutical composition according to claim 9, wherein the vitamin E is present in the pharmaceutical composition at between about 15 to about 3,000 mg.

286. Claims 13-15 are all directed to a pharmaceutical composition of claim 1 that further comprises between about 3 mg to about 15 mg of vitamin E.

287. As I have previously addressed above, claim 1 is obvious over Olson 1988 and Ortho Pharma. Ortho Pharma discloses “a carotenoid-containing product, in particular suitable for nutritive balanced supplementation of the diet in age-related eye diseases, which comprises, based on a daily dose of the carotenoid-containing product, as active ingredients the substances...*10 mg to 400 mg of vitamin E.*” EX1008 (Ortho Pharma), ¶[0008].

288. The 10 mg to 400 mg of vitamin E range disclosed in Ortho Pharma overlaps with the ranges of vitamin E present in claims 13-15 of the '432 patent (e.g., between about 3 to about 3,000 mg, between about 3 to about 15 mg, and between about 15 to about 3,000 mg).

289. Accordingly, it is my opinion that each of claims 13-15 is obvious over Olson 1988 and Ortho Pharma.

H. Claims 16-18: Vitamin D Additives

16. The pharmaceutical composition according to claim 9, wherein the vitamin D is present in the pharmaceutical composition at between about 0.005 to about 0.1 mg.

17. The pharmaceutical composition according to claim 9, wherein the vitamin D is present in the pharmaceutical composition at between about 0.005 to about 0.015 mg

18. The pharmaceutical composition according to claim 9, wherein the vitamin D is present in the pharmaceutical composition at between about 0.015 to about 0.1 mg

290. Claims 16-18 are all directed to a pharmaceutical composition of claim 1 that further comprises between about 0.005 mg to about 0.015 mg of vitamin D.

291. As I have previously addressed above, claim 1 is obvious over Olson 1988 and Ortho Pharma. Ortho Pharma discloses “a carotenoid-containing product, in particular suitable for nutritive balanced supplementation of the diet in age-related eye diseases, which comprises, based on a daily dose of the carotenoid-containing product, as active ingredients the substances...*0.1 µg to 10 µg of vitamin D₃*.” EX1008 (Ortho Pharma), ¶[0008].

292. The 0.1 µg to 10 µg (e.g., 0.0001 mg to 0.01 mg) of vitamin D₃ range disclosed in Ortho Pharma overlaps with the ranges of vitamin D present in claims 16-18 of the '432 patent (e.g., between about 0.005 to about 0.1 mg, between about 0.005 to about 0.015 mg, and between about 0.015 to about 0.1 mg).

293. Accordingly, it is my opinion that each of claims 16-18 is obvious over Olson 1988 and Ortho Pharma.

I. Claims 19: Retinoid Concentrations

19. The pharmaceutical composition according to claim 1, wherein the C₂₀-D₁₋₃-retinoid is present in the pharmaceutical composition at a level sufficient to deliver on average about 0.1 to about 90 mg/day to a patient.

294. Claim 19 is directed to a pharmaceutical composition of claim 1 wherein the C₂₀-D₁₋₃ retinoid is present in the pharmaceutical composition at a level sufficient to deliver about 0.1 mg/day to about 90 mg/day on average to a patient.

295. As I have previously addressed above, claim 1 is obvious over Olson 1988 and Ortho Pharma. Ortho Pharma discloses “a carotenoid-containing product, in particular suitable for nutritive balanced supplementation of the diet in age-related eye diseases, which comprises, based on a daily dose of the carotenoid-containing product, as active ingredients the substances...*0.1 mg to 2 mg of vitamin A.*” EX1008 (Ortho Pharma), ¶[0008].

296. The 0.1 mg to 2 mg of vitamin A range disclosed in Ortho Pharma overlaps with range present in the limitation “wherein the C₂₀-D₁₋₃-retinoid is present in the pharmaceutical composition at a level sufficient to deliver on average about 0.1 to about 90 mg/day to a patient” in claims 19 of the '432 patent.

297. Accordingly, it is my opinion that claim 19 as a whole is obvious over Olson 1988 and Ortho Pharma.

J. Claims 20-23: Additional Actives

20. The pharmaceutical composition according to claim 1, wherein the pharmaceutical composition comprises an additional active.

21. The pharmaceutical composition according to claim 20, wherein the additional active is selected from the group consisting of eye antioxidants, minerals, negatively-charged phospholipids, carotenoids, and combinations thereof.

22. The pharmaceutical composition according to claim 21, wherein the eye antioxidant is selected from the group consisting of vitamin C, vitamin E, beta-carotene, coenzyme Q, OT-551, 4-hydroxy-2,2,6,6-tetramethylpiperidine-N-oxyl, butylated hydroxytoluene, resveratrol, a Trolox analog (PNU-83836-E), bilberry extract, and combinations thereof.

23. The pharmaceutical composition according to claim 21, wherein the mineral is selected from the group consisting of cupric oxide, zinc oxide; selenium-containing compounds, and combinations thereof.

298. Claims 20-23 are all directed to a pharmaceutical composition of claim 1 that further comprises an additional active. Claim 21 is directed to an additional active from the group consisting of eye antioxidants, minerals, negatively-charged phospholipids, carotenoids, and combinations thereof. Claim 22 is directed to an eye antioxidant from the group consisting of vitamin C, vitamin E, beta-carotene, coenzyme Q, OT-551, 4-hydroxy-2,2,6,6-tetramethylpiperidine-N-oxyl, butylated hydroxytoluene, resveratrol, a Trolox analog (PNU-83836-E), bilberry extract, and combinations thereof. Claim 23 is directed to a mineral from the group consisting of cupric oxide, zinc oxide; selenium-containing compounds, and combinations thereof.

299. As I have previously addressed above, claim 1 is obvious over Olson 1988 and Ortho Pharma. Ortho Pharma discloses a carotenoid containing product that comprises active ingredients such as vitamin C, vitamin E, selenium, carotenoids, beta-carotene, and zinc. For example, Ortho Pharma provides for:

a carotenoid-containing product, in particular suitable for nutritive balanced supplementation of the diet in age-related eye diseases, which comprises, based on a daily dose of the carotenoid-containing product, *as active ingredients* the substances: 50 mg to 500 mg of *vitamin C*; 0.1 mg to 2 mg of vitamin A; 10 mg to 400 mg of *vitamin E*; 0.2 mg to 5 mg of vitamin B₁; 0.2 mg to 5 mg of vitamin B₂; 5 mg to 50 mg of nicotinamide; 0.2 mg to 5 mg of vitamin B₆; 0.1 mg to 1 mg of folic acid; 5 µg to 50 µg of vitamin B₁₂; 0.1 µg to 10 µg of vitamin D₃; 50 µg to 300 µg of biotin; 3 mg to 30 mg of pantothenic acid; 2 mg to 30 mg of *zinc*; 20 µg to 100 µg of *selenium*; 20 µg to 100 µg of chromium; secondary plant compounds selected from the group comprising 6 mg to 32 mg of *carotenoids* comprising carotenoids selected from the group comprising *beta-carotene*, lutein, zeaxanthin, and lycopene, and 20 mg to 1000 mg of flavonoids comprising flavonoids obtainable from citrus fruits, red grapes, and elderberries; 20 mg to 200 mg of sulfur-containing amino acids selected from the group comprising L-cystine and/or N-acetylcysteine; 20 mg to 200 mg of taurine; 50 mg to 1000 mg of omega-3 fatty acids, wherein the product is in the form of at least two separately present dosage forms of different composition of active ingredients, wherein a first solid dosage form comprises substances selected from the group comprising omega-3 fatty acids and carotenoids selected from the group comprising lutein, zeaxanthin, and lycopene, and wherein a second liquid dosage form comprises substances selected from the group comprising flavonoids obtainable from citrus fruits, vitamins, and trace elements.

EX1008 (Ortho Pharma), ¶[0008].

300. Ortho Pharma also discloses administration of zinc (II) chloride, β -carotene, and selenium-containing compounds as additional actives. EX1008

(Ortho Pharma), ¶¶[0043], [0049]. For example, Ortho Pharma discloses:

In preferred embodiments, the carotenoid-containing product may contain active ingredients in the form of substances selected from the group consisting of orange juice concentrate, fish oil, sodium L-ascorbate, vitamin E, ascorbic acid, citrus extract, taurine, L-cystine, ***zinc (II) chloride***, nicotinamide, calcium D-pantothenate, red grape extract, carotenoids comprising lutein, lycopene, and zeaxanthin, elderberry extract, vitamin B6 hydrochloride, vitamin B₁ hydrochloride, vitamin B₂, ***beta-carotene***, vitamin A acetate, folic acid, chromium (III) chloride, biotin, ***sodium selenate***, vitamin B₁₂, and/or vitamin D₃.

EX1008 (Ortho Pharma), ¶[0049].

301. Ortho Pharma thus discloses an additional active within the scope of each of claims 20-23. Accordingly, it is my opinion that each of claims 20-23 is obvious over Olson 1988 and Ortho Pharma.

K. Claim 25: Carotenoid

25. The pharmaceutical composition according to claim 1, wherein the carotenoid is selected from the group consisting of zeaxanthin, lutein, and combinations thereof.

302. Claim 25 is directed to a pharmaceutical composition of claim 1 that further comprises a carotenoid from the group consisting of zeaxanthin, lutein, and combinations thereof.

303. As I have previously addressed above, claim 1 is obvious over Olson 1988 and Ortho Pharma. Ortho Pharma discloses “the carotenoid-containing

product comprises, based on a daily dose of the carotenoid-containing product, as active ingredients the substances...16 mg *of carotenoids*, thereof preferably 12 mg of *lutein*, and/or 840 µg of *zeaxanthin*” EX1008 (Ortho Pharma), ¶[0043].

304. Accordingly, it is my opinion that claim 25 is obvious over Olson 1988 and Ortho Pharma.

L. Claim 27: Nutraceuticals

27. The pharmaceutical composition according to claim 1, wherein the pharmaceutical composition is suitable for use as nutraceutical composition.

305. Claim 27 is directed to a pharmaceutical composition of claim 1 that is suitable for use as a nutraceutical composition.

306. As I have previously addressed above, claim 1 is obvious over Olson 1988 and Ortho Pharma.

307. Ortho Pharma teaches administering its vitamin A composition to individuals to treat or prevent eye diseases such as macular degeneration, including administration as a nutritional supplement. EX1008 (Ortho Pharma), ¶¶[0001]-[0003], [0008], [0010]-[0011], [0052]-[0054]. For example, Ortho Pharma discloses that “it has been shown that the product according to the invention and the formulation of the components of the carotenoid-containing product according to the invention *can provide comprehensive nutritional support to the eye*, in particular to the eye of elderly persons.” EX1008 (Ortho Pharma), ¶[0010].

308. Accordingly, it is my opinion that claim 27 is obvious over Olson 1988 and Ortho Pharma.

M. Rational Underpinnings for the Combination

309. The rationale to combine analysis from Ground 1 in Section XI.v above applies equally to Ground 2.

310. As I have discussed above, Olson 1988 discloses making and purifying C₂₀-D₃-vitmain A (e.g., retinol and retinol acetate), and specifically discloses the synthesis of “20,20,20-trideutero, 14,20,20,20-tetradeutero, 12,14,20,20,20-pentadeutero, and 10,19,19,19-tetradeutero analogs of retinoic acid ethyl ester and retinyl acetate.” EX1006 (Olson 1988), Abstract; 11-13, 14, 15-19. Ortho Pharma teaches administration of vitamin A in combination with other vitamins and additives to treat and prevent age-related eye diseases, including macular degeneration. EX1008 (Ortho Pharma), ¶¶[0001]-[0003], [0008], [0010]-[0011], [0052]-[0054]. Ortho Pharma also identifies water as a pharmaceutically acceptable carrier and states that “[a] particularly preferred solvent is water.” EX1008 (Ortho Pharma), ¶[0038]. As such, it is my opinion that a person having ordinary skill in the art would have had a good reason to employ the C₂₀-D₃-vitamin A retinol or retinol acetate, as disclosed in Olson 1988, in a pharmaceutical composition such as water in place of the non-deuterated forms of vitamin A, as discussed in Ortho Pharma.

311. As an initial matter, there was good reason to replace non-deuterated forms of vitamin A being used to treat or prevent macular degeneration with the C₂₀-deuterated vitamin A disclosed in Olson 1988. For example, Mata taught that deprotonation at C-20 of retinal was a pre-requisite for undesirable A2E formation. EX1010 (Mata), 7154 & Abstract, 7157-7158, Fig. 5 & Caption. As I have explained above in Sections VIII.C and IX.E, a person of ordinary skill in the art would have recognized that this deprotonation was likely a rate-limiting step in A2E formation and that substituting deuterium in place of the hydrogens at C-20 would slow A2E formation due to the high primary kinetic isotope effect expected from this substitution. It is thus my opinion that a person of ordinary skill in the art had good reason to replace non-deuterated vitamin A being used to treat or prevent macular degeneration, as in Ortho Pharma, with Olson 1988's C₂₀-D₃-retinol or retinol acetate to inhibit (e.g., slow) reactions that involve cleavage of a hydrogen from C-20 (e.g., A2E formation).

312. Mata provides good reason to employ Olson 1988's C₂₀-deuterated vitamin A to reduce lipofuscin formation and thereby treat or prevent macular degeneration. For example, Mata discloses C₂₀ as a site of action for the synthetic pathway creating lipofuscin pigments associated with macular degeneration. EX1010 (Mata), 7154 & Abstract, 7157-7158, Fig. 5 & Caption. Mata further discloses that this synthetic pathway depends on removing a hydrogen atom from

C₂₀ through a 1,5-sigmatropic shift. EX1010 (Mata), 7158, FIG. 5. Mata expressly suggests inhibiting this synthetic pathway to reduce lipofuscin formation as a means for treating or preventing macular degeneration. EX1010 (Mata), 7154 & Abstract, 7159. As I have discussed above, the 1,5-sigmatropic shift disclosed in Mata is the same 1,5-sigmatropic shift described in Figure 2 of the '432 patent. Therefore, a person of ordinary skill in the art would have been well aware that the 1,5-sigmatropic shift disclosed in Mata (as well as the 1,5-sigmatropic shift described in Figure 2 of the '432 patent) was likely a rate-limiting step in A2E-formation and that inhibiting that step in the pathway would reduce A2E formation.

313. As I have explained in Section VIII.C above, a person of ordinary skill in the art would have understood that deuterating C₂₀ would slow A2E formation because 1,5-sigmatropic shifts were known to be subject to strong primary deuterium kinetic isotope effects. For example, Itou discloses that the authors in the Roth experimentally determined a large kinetic isotope effect value of 12.2 in a 1,5-sigmatropic shift of a deuterated 1,3-pentadiene system. EX1016 (Itou), 261. As such, a person having ordinary skill in the art would expect that the substitution of the C₂₀ methyl (CH₃) with CD₃ would similarly observe a large kinetic isotope effect associated with the 1,5-sigmatropic shift at the C₂₀ position.

314. Accordingly, persons having ordinary skill in the art had good reason to employ C₂₀-D₃-retinol or retinol acetate in a pharmaceutical and/or nutraceutical composition for administration to patients experiencing age-related eye disorders including macular degeneration.

N. Reasonable Expectation of Success

315. The reasonable expectation of success analysis from Ground 1 in Section XI.vi applies equally to Ground 2.

316. Persons having ordinary skill in the art before 2007 would have had a reasonable expectation of success for making a pharmaceutical composition comprising a claimed C₂₀-deuterated retinoid and a pharmaceutically acceptable carrier. This is because compositions comprising vitamin A and pharmaceutically acceptable carriers were known and disclosed in prior art references. For example, and as discussed above in Section IX.A, Olson 1988 teaches that persons having ordinary skill in the art already had created claimed C₂₀-deuterated retinoids and had synthesized “20,20,20-trideutero, 14,20,20,20-tetradeutero, 12,14,20,20,20-pentadeutero, and 10,19,19,19-tetradeutero analogs of retinoic acid ethyl ester and retinyl acetate.” EX1006 (Olson 1988), 11. Further, as discussed in Section IX.C, Ortho Pharma identifies water as an ideal solvent for the vitamins and minerals in solution and states that “[a] particularly preferred solvent is water.” EX1008 (Ortho Pharma), ¶[0038]-[0042]. In addition, Ortho Pharma teaches that additional

excipients can be employed for formulations, such as fillers, starch, vegetable oil, carriers such as silicon dioxide and others since Ortho Pharma discloses that “[p]articularly preferred are additives selected from the group comprising humectants such as glycerol, starch, preferably modified starch, in particular from wheat and/or corn, vegetable oil.” EX1008 (Ortho Pharma), ¶[0051]. Ortho Pharma further teaches that the same pharmaceutically-acceptable carrier used to formulate non-deuterated forms of vitamin A can be used to formulate deuterated forms of vitamin A. Accordingly, it is my opinion that a person having ordinary skill in the art before 2007 would have had a reasonable expectation of success for making C₂₀-retinoids in a pharmaceutically acceptable carrier as claimed.

317. Furthermore, and as noted above under Ground 1 in Section XI.vi, the reasonable expectation of success is confirmed by the '432 patent, which notes that formulation of the claimed compounds was conventional and within the skill of the art. For example, the '432 patent notes that “Effective dosage forms, modes of administration, and dosage amounts, in addition to those disclosed above, may be determined empirically, and making such determinations is within the skill of the art.” EX1001 (the '432 patent), 14:31-34.

318. The '432 patent further states that the pharmaceutical composition may be administered by a variety of means, including orally by ingestion or locally to the eye. EX1001 (the '432 patent), 14:49-56. For example, citing to Remington,

the '432 patent states that “[r]egardless of the route of administration selected, the compounds of the present invention are formulated into pharmaceutically-acceptable dosage forms by conventional methods known to those of skill in the art.” EX1001 (the '432 patent), 15:3-8 and 15:32-36 (citing Remington).

319. Further citing Remington, the '432 patent further notes that “[p]harmaceutically acceptable carriers are well known in the art” and include, *inter alia*, water, saline solution, or corn oil. EX1001 (the '432 patent), 15:9-27 (citing Remington). Accordingly, it is my opinion that persons having ordinary skill in the art may not now take a contradictory position than persons before 2007 having ordinary skill in the art did. Therefore, persons having ordinary skill in the art would have had a reasonable expectation of success for making the C₂₀-retinoid compounds and a pharmaceutically acceptable carrier as claimed.

XIII. [GROUND 3] CLAIMS 7, 24 AND 26 ARE OBVIOUS OVER OLSON 1988 IN VIEW OF ORTHO PHARMA AND FURTHER IN VIEW OF WIDDER

320. For the reasons discussed in detail below, it is my opinion that each of claims 7, 24 and 26 of the '432 patent is obvious as a whole. The obviousness of claims 7, 24 and 26 is exemplified by disclosures in the Olson 1988, Ortho Pharma, and Widder references.

321. I have evaluated below whether the combination of Olson 1988, Ortho Pharma, and Widder discloses each and every element of each of claims 7, 24, and

26 of the '432 patent. I have also analyzed whether a person of ordinary skill in the art before the critical date would have had good reason to combine these references in a manner that satisfies each claim as a whole with a reasonable expectation of success. As I explain in detail below, the answer to each of these questions is yes.

322. My analysis in Ground 3 incorporates the statements regarding Olson 1988 from Grounds 1 and 2 above in Sections XI and XII, respectively, which demonstrates that Olson 1988 suggests making and purifying the claimed C₂₀-D₁₋₃-retinoids. My analysis in Ground 3 also incorporates the statements regarding Ortho Pharma from Ground 2 above in Section XII, which demonstrates that Ortho Pharma discloses treating eye disorders, such as age-related macular degeneration, by administering a composition comprising vitamins (e.g., vitamins A, E, and D), and minerals (e.g., zinc) and a pharmaceutically-acceptable carrier (e.g., water).

323. Ground 3 adds the teachings of Widder, which discloses teachings of additional supplements and routes of administration for delivering retinoids for the treatment of eye diseases, including macular degeneration.

324. Widder, in Example 15 entitled “Combination Therapy Involving Fenretinide, Vitamins and Minerals,” which I have discussed in Section IX.D above, teaches combining vitamin A with fenretinide for the purpose of reducing lipofuscin formation to treat or prevent macular degeneration. EX1009 (Widder), 47:21-27.

325. Widder further teaches that fenretinide decreases the amount of A2E in the retinal pigment epithelium by lowering the amount of retinol delivered to the eye and also by lowering the steady state levels of all-*trans* retinal in the eye.

EX1009 (Widder), 46:25-47:6. For example, Widder discloses that:

In addition, (a) administration of an agent or agents that lower the levels of serum retinol in a patient without modulating at least one enzyme of the visual cycle or (b) administration of an agent that modulate at least one enzyme of the visual cycle without lowering levels of serum retinol in a patient, by themselves, may also provide a treatment for such dystrophies and degenerations or the symptoms associated thereof. Assays, such as those described herein, may be used to select further agents possessing this dual action, including agents selected from compounds having the structure of Formula (I) as well as other agents. Putative lead compounds include other agents known or demonstrated to effect the serum level of retinol.

EX1009 (Widder), 46:39-47:6.

326. Widder further discloses “methods for reducing the formation of lipofuscin in an eye of a mammal comprising administering to the mammal an effective amount of a first compound having the structure of Formula (I).” EX1009 (Widder), 3:18-20. Widder further discloses that “the compounds of Formula (I) can be used to...provide at least some of the following benefits...reduction in the amount of all-*trans* retinal (atRAL), reduction in the formation of A2E, reduction in the formation of ipofuscin, reduction in the formation of drusen, and reduction in light sensitivity.” EX1009 (Widder), 14:34-39.

327. Widder also teaches co-administering negatively-charged phospholipids to treat macular degeneration and administering macular degeneration treatment directly to the eye. EX1009 (Widder), 33:1-7, 25:16-26:2.

For example, Widder discloses that:

The use of certain negatively-charged phospholipids has also been shown to benefit patients with macular degenerations and dystrophies...Examples of suitable negatively charged phospholipids that could be used in combination with at least one compound having the structure of Formula (I) include cardiolipin and phosphatidylglycerol. Positively-charged and/or neutral phospholipids may also provide benefit for patients with macular degenerations and dystrophies when used in combination with compounds having the structure of Formula (I).

EX1009 (Widder), 33:1-7.

328. Widder further discloses that:

The compound of Formula (I) can be administered in a variety of ways, including all forms of local delivery to the eye. Additionally, the compounds of Formula (I) can be administered systemically, such as orally or intravenously. The compounds of Formula (I) can be administered topically to the eye and can be formulated into a variety of topically administrable ophthalmic compositions, such as solutions, suspensions, gels or ointments. Thus, "ophthalmic administration" encompasses, but is not limited to, intraocular injection, subretinal injection, intravitreal injection, periocular administration, subconjunctival injections, retrobulbar injections, intracameral injections (including into the anterior or vitreous chamber), sub-Tenon's injections or implants, ophthalmic solutions, ophthalmic suspensions, ophthalmic ointments, ocular implants and ocular inserts, intraocular solutions, use of iontophoresis, incorporation in surgical irrigating solutions, and packs (by way of example only, a saturated cotton pledget inserted in the fornix).

Administration of a composition to the eye generally results in direct contact of the agents with the cornea, through which at least a portion of the administered agents pass. Often, the composition has an effective residence time in the eye of about 2 to about 24 hours, more typically about 4 to about 24 hours and most typically about 6 to about 24 hours.

A composition comprising a compound of Formula (I) can illustratively take the form of a liquid where the agents are present in solution, in suspension or both. Typically when the composition is administered as a solution or suspension a first portion of the agent is present in solution and a second portion of the agent is present in particulate form, in suspension in a liquid matrix. In some embodiments, a liquid composition may include a gel formulation. In other embodiments, the liquid composition is aqueous. Alternatively, the composition can take the form of an ointment.

EX1009 (Widder), 25:16-35.

329. As shown by my analysis below, the Olson 1988, Ortho Pharma, and Widder references would make obvious each of claims 7, 24, and 26.

A. Claim 7: Supplement

7. The pharmaceutical composition according to claim 1, further comprising an effective amount of a supplement selected from the group consisting of (2E,6E)-N-hexadecyl-3,7,11-trimethyldodeca-2,6,10-trienamine, (12E,16E)-13,17,21-trimethyldocosa-12,16,20-trien-11-one, 13-cis-retinoic acid, all-trans-retinylamine, and fenretinide, and combinations thereof.

330. Claim 7 is directed to a pharmaceutical composition of claim 1 that further comprises an effective amount of a supplement from the group consisting of (2E,6E)-N-hexadecyl-3,7,11-trimethyldodeca-2,6,10-trienamine, (12E,16E)-

13,17,21-trimethyldocosa-12,16,20-trien-11-one, 13-*cis* retinoic acid, all-*trans* retinylamine, and fenretinide, and combinations thereof.

331. As I have previously addressed above in Ground 2, claim 1 is obvious over Olson 1988 and Ortho Pharma.

332. Widder discloses a pharmaceutical composition comprising an effective amount of fenretinide co-administered with vitamin A. Widder discloses a combination therapy to inhibit the development or reoccurrence of macular degeneration that includes an effective amount of fenretinide in combination with vitamin A. EX1009 (Widder), 47:21-27. For example, Widder, at Example 15, states that:

Administration of fenretinide in combination with vitamins and minerals can be either orally or parenterally administered at amounts effective to inhibit the development or reoccurrence of macular degeneration. Test dosages are initially in the range of about 20 mg/kg per day of fenretinide with 100-1000 mg vitamin C, 100-600 mg vitamin E, 10,000-40,000 IU vitamin A, 50-200 mg zinc and 1-5 mg copper for 15 to 20 weeks.

EX1009 (Widder), 47:21-27.

333. Widder further discloses that “Because A2E itself is cytotoxic to the RPE (which can lead to retina cell death), administration of compounds having the structure of Formula (I) (alone, or in combination with other agents, as described herein) reduces the rate of accumulation of A2E, a cytotoxic agent, thus providing patient benefit.” EX1009 (Widder), 14:40-15:1-3. Widder further discloses that:

Administration of fenretinide or placebo to a patient can be either orally or parenterally administered at amounts effective to inhibit the development or reoccurrence of macular degeneration. Effective dosage amounts are in the range of from about 1-4000 mg/m² up to three times a day.

EX1009 (Widder), 40:3-5.

334. Accordingly, it is my opinion that claim 7 is obvious over Olson 1988, Ortho Pharma, and Widder.

335. A person having ordinary skill in the art would have had good reason to make a pharmaceutical composition comprising an effective amount of fenretinide and C₂₀-deuterated vitamin A within the scope of claim 7. As I have discussed above in Ground 2 (see Section XII above) and in Section IX.D, a person of ordinary skill in the art would have expected that substituting C₂₀-deuterated vitamin A for non-deuterated vitamin A would reduce undesirable lipofuscin formation associated with macular degeneration without interfering with the visual cycle. EX1009 (Widder), Abstract, 1:17-28, 3:18-20, 14:34-15:10.

336. Widder discloses that fenretinide treats macular degeneration by reducing the overproduction of lipofuscin waste products that accumulate in the eye during the course of the visual cycle. For example, Widder teaches that “[c]ompounds that cause reversible night blindness may be used to treat ophthalmic conditions associated with the overproduction of waste products that accumulate during the course of the visual cycle.” EX1009 (Widder), Abstract.

Widder further discloses that fenretinide decreases the amount of A2E in the retinal pigment epithelium cells by lowering the amount of retinol delivered to the eye and by lowering the steady state levels of all-*trans* retinal (ATR). EX1009 (Widder), 46:25-47:6; *see also id.*, 15:14-32

337. Thus, a person having ordinary skill in the art would have understood that replacing the vitamin A in the combination therapy disclosed in Widder with C₂₀-deuterated vitamin A would reduce lipofuscin formation while ameliorating or avoiding undue inhibition of the visual cycle, including by permitting reduction in the dose of fenretinide.

338. Further it is my opinion that a person having ordinary skill in the art would have had a reasonable expectation of success for making a pharmaceutical composition comprising an effective amount of fenretinide and C₂₀-deuterated vitamin A, within the scope of claim 7. First, as I have discussed above, Widder at Example 15 discloses making a combination therapy comprising vitamin A and fenretinide. EX1009 (Widder), 47:21-27 (Example 15). Second, Widder discloses that a variety of conventional means was available for successfully formulating its compositions. EX1009 (Widder), 4:33-5:12, 23:7-11, 25:1-6, 25:16-26:40, 27:9-29:10, 29:32-30:19. Third, as I have discussed above in Ground 1, Olson 1989 discloses that vitamin A and deuterated vitamin A can be formulated successfully in the same pharmaceutically-acceptable carriers (e.g., corn oil). EX1007 (Olson

1989). Fourth, as I have discussed above in Ground 2, Ortho Pharma discloses that vitamin A also can be formulated in aqueous solutions (e.g., water). EX1008 (Ortho Pharma).

339. Consistent with the prior art references that I have mentioned herein, the challenged '432 patent clearly notes that formulating C₂₀-deuterated vitamin A was conventional and within the ordinary skill of the art in view of Remington. EX1001 (the '432 patent), 14:31-34, 14:49-56, 15:3-36. This statement is consistent with my conclusion that a person having ordinary skill in the art would have had a reasonable expectation of success for making what is claimed.

340. Accordingly, it is my opinion that claim 7 is obvious over Olson 1988, Ortho Pharma, and Widder.

B. Claim 24: Phospholipids

24. The pharmaceutical composition according to claim 21, wherein the negatively-charged phospholipid is selected from the group consisting of cardiolipin, phosphatidylglycerol, and combinations thereof.

341. Claim 24 is directed to a pharmaceutical composition of claim 1 that further comprises a negatively-charged phospholipid selected from the group consisting of cardiolipin, phosphatidylglycerol, and combinations thereof.

342. As I have previously addressed above in Ground 2 above, claims 1 and 21 are obvious over: Olson 1988 and Ortho Pharma.

343. Widder discloses that “[t]he use of certain negatively-charged phospholipids has also been shown to benefit patients with macular degenerations and dystrophies.” EX1009 (Widder), 33:1-2. Widder further identifies that cardiolipin and phosphatidylglycerol are suitable examples of negatively charged phospholipids that can be combined with the compounds disclosed in Widder. For example, Widder states that:

Examples of suitable negatively charged phospholipids that could be used in combination with at least one compound having the structure of Formula (I) include *cardiolipin and phosphatidylglycerol*. Positively-charged and/or neutral phospholipids may also provide benefit for patients with macular degenerations and dystrophies when used in combination with compounds having the structure of Formula (I).

EX1009 (Widder), 33:3-7.

344. A person having ordinary skill in the art would have had good reason to include each or both of cardiolipin and phosphatidylglycerol as additional actives in the pharmaceutical composition of claim 1 because Widder, citing Shaban, teaches that these negatively charged phospholipids have “been shown to benefit patients with macular degeneration.” EX1004 (Widder), 33:1-2.

345. In 2002, Hamdy Shaban, Consuelo Borrás, Jose Vina, and Christoph Richter published “Phosphatidylglycerol Potently Protects Human Retinal Pigment Epithelial Cells Against Apoptosis Induced by A2E, a Compound Suspected to Cause Age-related Macula Degeneration” in the periodical publication

Experimental Eye Research. For convenience, I will refer to this paper by the last name of the first-listed author, Shaban. The Shaban reference teaches that these particular negatively-charged phospholipids are useful for ameliorating existing lipofuscin components (e.g., A2E). For example, Shaban teaches that:

A2E induces apoptosis in several cell types including porcine retinal pigment epithelial cells, detaches pro-apoptotic proteins from mitochondria, and inhibits cytochrome c oxidase. A2E acts primarily at the level of cardiolipin/cytochrome c oxidase, which in the light becomes permanently inactivated by A2E...A2E at low concentrations causes apoptosis in cultured human retinal pigment epithelial cells. These cells are more sensitive to A2E in light than in the dark. Phosphatidylglycerol, a negatively charged phospholipid and immediate biosynthetic precursor of cardiolipin readily inhibits apoptosis.

EX1021 (Shaban), Abstract.

346. As such, a person having ordinary skill in the art would have had good reason to include one or both of cardiolipin and phosphatidylglycerol as an additional active in the pharmaceutical composition to inhibit apoptosis caused by existing A2E even while inhibiting the formation of additional A2E by the use of the C₂₀-deuterated vitamin A.

347. A person having ordinary skill in the art would have had a reasonable expectation of success for making the pharmaceutical composition of claim 1 comprising one or both of cardiolipin and phosphatidylglycerol as an additional active.

348. First, Widder already discloses making a combination therapy comprising vitamin A and fenretinide and teaches cardiolipin and phosphatidylglycerol can be used in combination with fenretinide. EX1009 (Widder), 47:21-27, 33:3-5. For example, Widder teaches in Example 15, which is entitled Combination Therapy Involving Fenretinide, Vitamins and Minerals, that:

Administration of fenretinide in combination with vitamins and minerals can be either orally or parenterally administered at amounts effective to inhibit the development or reoccurrence of macular degeneration. Test dosages are initially in the range of about 20 mg/kg per day of fenretinide with 100-1000 mg vitamin C, 100-600 mg vitamin E, 10,000-40,000 IU vitamin A, 50-200 mg zinc and 1-5 mg copper for 15 to 20 weeks.

EX1009 (Widder), 47:21-27. Widder further teaches that “suitable negatively charged phospholipids that could be used in combination with at least one compound having the structure of Formula (I) include cardiolipin and phosphatidylglycerol.” EX1009 (Widder), 33:3-5.

349. Second, Widder discloses that a variety of conventional means were available for successfully formulating its compositions. EX1009 (Widder), 25:8-15, 27:30-40, 28:1-2. For example, Widder discloses that:

Pharmaceutical compositions comprising a compound of Formula (I) may be manufactured in a manner that is itself known, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or compression processes. Pharmaceutical compositions may be formulated in conventional manner using one or more physiological acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be

used pharmaceutically. Any of the well-known techniques, carriers, and excipients may be used as suitable and as understood in the art.

EX1009 (Widder), 25:8-15.

350. Widder further discloses that:

For oral administration, compounds of Formula (I) can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers or excipients well known in the art. Such carriers enable the compounds described herein to be formulated as tablets, powders, pills, dragees, capsules, liquids, gels, syrups, elixirs, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained by mixing one or more solid excipient with one or more of the compounds described herein, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as: for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methylcellulose, microcrystalline cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose; or others such as: polyvinylpyrrolidone (PVP or povidone) or calcium phosphate. If desired, disintegrating agents may be added, such as the cross-linked croscarmellose sodium, polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

EX1009 (Widder), 27:30-40 and 28:1-2.

351. Third, as discussed above in Ground 1, Olson 1989 discloses that vitamin A and deuterated vitamin A can be formulated in the same pharmaceutically-acceptable carrier (e.g., corn oil). EX1007 (Olson 1989).

352. Fourth, as discussed above in Ground 2, Ortho Pharma discloses that vitamin A also can be formulated in aqueous solutions such as water. EX1008

(Ortho Pharma). Further, consistent with the prior art references, the challenged '432 patent readily notes that formulating C₂₀-deuterated vitamin A was conventional and within the ordinary skill of the art in view of Remington. EX1001 (the '432 patent), 14:31-34, 14:49-56, 15:3-36. This statement is consistent with my conclusion that a person having ordinary skill in the art would have had a reasonable expectation of success for making what is claimed.

353. Accordingly, it is my opinion that claim 24 is obvious over Olson 1988, Ortho Pharma, and Widder.

C. Claim 26: Ocular Administration

26. The pharmaceutical composition according to claim 1, wherein the pharmaceutical composition is suitable for administration directly to the eye.

354. Claim 26 is directed to a pharmaceutical composition of claim 1 that is suitable for administration directly to the eye. Based on my review of the '432 patent, "suitable for administration directly to the eye" includes administration as "eye drops, ointment, or injection." EX1001 (the '432 patent), 9:55-58.

355. As I have previously addressed above in Ground 2, claim 1 is obvious over: Olson 1988 and Ortho Pharma.

356. Widder discloses that ophthalmic conditions, which include macular degeneration and Stargardt's disease, can be treated by the administration of an active agent locally to the eye (e.g., by ophthalmic delivery). Widder further

discloses that the administration to the eye can be through a variety of routes of administration including using aqueous eye drops and other aqueous ophthalmic solutions, ophthalmic suspensions, ophthalmic ointments, and ophthalmic injections. EX1009 (Widder), 25:16-26:40 (aqueous eye drops), 4:33-5:12, 23:7-11, 25:1-6 (routes of administration); *see also id.*, 27:9-29:10, 29:32-30:19 (various formulations). For example, Widder states that “Useful compositions can be an aqueous solution, suspension or solution/suspension, which can be presented in the form of eye drops.” EX1009 (Widder), 25:36-37. Widder further discloses that “The compounds of Formula (I) can be administered in a variety of ways, including all forms of local delivery to the eye...can be administered systemically, such as orally or intravenously.” EX1009 (Widder), 25:16-17.

357. Widder further discloses that a pharmaceutical composition for treating ophthalmic conditions comprises a pharmaceutically-acceptable carrier that is suitable for ophthalmic administration. EX1009 (Widder), 8:1-9. Widder teaches that pharmaceutical compositions may be formulated in the conventional manner and directs the reader to Remington’s for appropriate formulations for the particular route of administration. EX1009 (Widder), 24:32-35, 25:11-15. For example, Widder provides that:

The compounds described herein can be administered to a human patient *per se*, or in pharmaceutical compositions where they are mixed with other active ingredients, as in combination therapy, or suitable carrier(s) or excipient(s). Techniques for formulation and

administration of the compounds of the instant application may be found in “Remington: The Science and Practice of Pharmacy,” 20th ed. (2000).

EX1009 (Widder), 24:32-35.

358. A person having ordinary skill in the art would have had good reason to make the pharmaceutical composition claimed suitable for administration directly to the eye. For example, a person having ordinary skill in the art would have recognized, as provided by Widder, that local administration directly to the eye was a desirable route of administration for an active ingredient being administered for the purpose of acting in the eye. The purpose of administering the C₂₀-deuterated vitamin A as explained above in Ground 2 was to supply to the eye C₂₀-deuterated vitamin A that would function normally in the visual cycle therein while reducing undesirable lipofuscin formation therein. Accordingly, a person having ordinary skill in the art had good reason to make the composition suitable for administration directly to the eye to evaluate, confirm, and demonstrate that (1) administration directly to the eye delivered the active ingredient to the targeted tissue; and (2) administration of the active ingredient to the targeted tissue reduced lipofuscin formation. There also was good reason to formulate the pharmaceutical composition for local administration directly to the eye to concentrate the active ingredient in the targeted tissue more specifically than systemic administration.

Local administration of C₂₀-deuterated vitamin A directly to the eye would be particularly indicated in circumstances where an additional active agent (e.g., fenretinide as disclosed in Widder) is used to lower the amount of retinol delivered to the eye.

359. A person having ordinary skill in the art also had a reasonable expectation of success for making the pharmaceutical composition of claim 1 wherein the pharmaceutical composition is suitable for administration directly to the eye. As explained above, Widder, relying on Remington, teaches that it was routine and conventional to formulate an active ingredient (including hydrophobic actives) designed for treating ocular disorders including macular degeneration in a pharmaceutical composition that is suitable for administration directly to the eye. EX1009 (Widder), 24:32-35, 25:11-15, 27:9-29:10. For example, Widder, citing Remington, states that:

Pharmaceutical compositions may be formulated in conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be use pharmaceutically. Proper formulation is dependent upon the route of administration chosen. Any of the well-known techniques, carriers, and excipients may be used as suitable and as understood in the art; *e.g.*, in Remington's Pharmaceutical Sciences, above.

EX1009 (Widder), 25:11-15.

360. Remington teaches formulations for administering active ingredients directly to the eye. EX1017 (Remington), 46-56 (ophthalmic preparations). Similar

to Widder, the challenged '432 patent notes that local administration to the eye of an active ingredient was known in the art and that formulating the active ingredient for administration was conventional and within the ordinary skill of the art in view of Remington. EX1001 (the '432 patent), 14:31-34, 14:49-56, 15:3-36. This statement is consistent with my conclusion that a person of ordinary skill in the art would have had a reasonable expectation of success for making what is claimed.

361. Accordingly, it is my opinion that claim 26 is obvious over Olson 1988, Ortho Pharma, and Widder.

XIV. NO UNEXPECTED RESULTS

362. In light of the prior art, it is my opinion that nothing that was presented in the '432 patent or during the prosecution of the '432 patent or its parent patent application that presented unexpected results.

363. I have reviewed the '432 patent in its entirety. I have also reviewed the prosecution history of the '432 patent (EX1031 (file history of '631 application); EX1032 (file history of '975 application)).

364. The '432 patent discusses some *in vitro* and murine experiments, including several “massive dosing” experiments. The '432 patent also notes that administering C₂₀-fully deuterated all-*trans* retinal (ATR) slowed the formation of A2E *in vitro* by a factor of 7 and slowed the formation of ATR-dimer *in vitro* to an unspecified degree. EX1001 (the '432 patent), 18:9-59 (Examples 1-2).

365. The '432 patent further notes that administering C₂₀-fully deuterated all-*trans* retinal (ATR) or feeding C₂₀-fully deuterated all-*trans* retinol acetate to mice resulted in 35-68% less A2E-lipofuscin as compared to mice receiving the non-deuterated retinoids. EX1001 (the '432 patent), 18:60-19:57, 20:21-52 (Examples 3-4, and 6). The '432 patent also notes that when four *abcr*^{-/-} mice were raised exclusively on C₂₀-fully deuterated all-*trans* retinol acetate, lipofuscin pigments were not detected by HPLC at 5.5-6 months of age but lipofuscin deposits were detected using electron microscopy. EX1001 (the '432 patent), 19:58-20:20 (Example 5).

366. Indeed, various references described herein explain that the deuterium kinetic isotope effect can slow a chemical reaction by replacing hydrogen in a carbon-hydrogen bond with a deuterium to create a carbon-deuterium bond. For example, Haskins expressly suggests that the rate of cleavage of carbon-deuterium bonds can be up to 14 times slower than similar cleavage of carbon-hydrogen bonds (see Section VIII.C above) since the more stable deuterium bond would require greater energy of activation (see Section VIII.C above). Haskins further provides that, based on the primary isotope effect, reactions requiring cleavage of a carbon-hydrogen bond will take place much slower when the hydrogen is replaced with a larger and heavier deuterium atom (see Section VIII.C above).

367. Further, Itou, citing Roth, suggests that there is a high kinetic isotope effect associated with a 1,5-sigmatropic shift (see Section VIII.C above) in pentadiene systems. EX1016 (Itou), 261. Specifically, Itou discloses that Roth conducted an experiment which found that the 1,5-sigmatropic shift of a deuterated 1,3-pentadiene (with a CD_3) would proceed 12.2 times slower than the protiated 1,3-pentadiene. EX1016 (Itou), 261. Therefore, in view of the '432 patent, a person having ordinary skill in the art would expect that substitution of the C_{20} methyl (CH_3) with deuterium (CD_3) would similarly expect to observe a large kinetic isotope effect associated with the 1,5-sigmatropic shift at the C_{20} position as described in Figure 2 of the '432 patent.

368. In addition, Mata and Fishkin both provide mechanisms that comprise the same [1,5] hydrogen shift present in Figure 2 of the '432 patent (see Section VIII.B above). Despite the visual and/or nomenclature differences between the mechanisms provided in Fishkin, Mata, and the '432 patent, it is my opinion that all three mechanisms provide a [1,5]-sigmatropic shift, which, as I explained above, was known to likely be the rate-limiting step of the mechanism.

369. Lastly, Mata expressly disclosed that inhibition of one or more steps in the A2E synthetic pathway may be an effective treatment strategy for macular degenerations associated with lipofuscin accumulation (see Section VIII.B above).

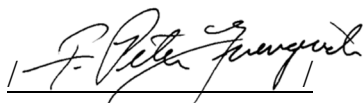
370. Accordingly, in my opinion, the administration of C₂₀-retinoids to slow the formation of A2E is not unexpected.

XV. CONCLUDING STATEMENTS

371. In signing this declaration, I understand that the declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I acknowledge that I may be subject to cross-examination in this case and that cross-examination will take place within the United States. If cross-examination is required of me, I will appear for cross-examination within the United States during the time allotted for cross-examination.

372. I declare that all statements made herein of my knowledge are true, and that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: 13 December, 2023

By: 
F. Peter Guengerich, Ph.D.

XVI. APPENDIX – LIST OF EXHIBITS

Exhibit No.	Description
1001	U.S. Patent No. 9,486,432 to Washington et al.
1003	<i>Curriculum Vitae</i> of Dr. F. Peter Guengerich.
1006	Robert Bergen, H., Furr, H. C., & Olson, J. A., Synthesis of Tri-, Tetra-, and Penta-deuterated Forms of Vitamin A, <i>Journal of Labelled Compounds and Radiopharmaceuticals</i> , 25(1), 11-21 (1988) (“Olsen 1988”).
1007	Furr, H. C., Amedee-Manesme, O., Clifford, A. J., Bergen 3rd, H. R., Jones, A. D., Anderson, D. P., & Olson, J. A., Vitamin A concentrations in liver determined by isotope dilution assay with tetradeuterated vitamin A and by biopsy in generally healthy adult humans, <i>The American Journal of Clinical Nutrition</i> , 49(4), 713-716 (1989) (“Olson 1989”)
1008	DE202006014588U1 (English Translation) (“Ortho Pharma”)
1009	WO 2006/007314 to Widder et al. (“Widder”)
1010	Mata, N. L. et al., Biosynthesis of a major lipofuscin fluorophore in mice and humans with ABCR-mediated retinal and macular degeneration, <i>Proceedings of the National Academy of Sciences of the United States of America</i> , 97(13), 7154-7159 (2000) (“Mata”)
1011	Fishkin et al., Isolation and Characterization of a Retinal Pigment Epithelial Cell Fluorophore: An All-trans-retinal Dimer Conjugate, <i>Proceedings of the National Academy of Sciences of the United States of America</i> , 102(20), 7091-7096 (2005) (“Fishkin”)
1012	Haskins, N. J., The Application of Stable Isotopes in Biomedical Research, <i>Biomedical Mass Spectrometry</i> , 9(7), 269-277 (1982) (“Haskins”)

1013	Baillie, T. A., The Use of Stable Isotopes in Pharmacological Research, <i>Pharmacological Reviews</i> , 33(2), 81-132 (1981) (“Baillie”)
1014	Van Langenhove, A., Isotope Effects: Definitions and Consequences for Pharmacologic Studies, <i>The Journal of Clinical Pharmacology</i> , 26(6), 383-389 (1986) (“Langenhove”)
1015	Roth and König, Kinetic Isotope Effect of the 1.5-Hydrogen Displacement in <i>cis</i> -Pentadiene-(1.3), <i>Justus Liebigs Annalen Der Chemie</i> (1966) (“Roth”).
1016	Itou et al., Quantum Treatment of Hydrogen Nuclei in Primary Kinetic Isotope Effects in a Thermal [1, 5]-Sigmatropic Hydrogen (or Deuterium) Shift from (Z)-1, 3-Pentadiene. <i>The Journal of Physical Chemistry A</i> , 111(2), 261-267 (2007) (“Itou”)
1017	Remington: The Science and Practice of Pharmacy, 19th ed. (1995) (chs. 80 & 89) (“Remington”)
1018	Parish et al., Isolation and One-step Preparation of A2E and Iso-A2E, Fluorophores from Human Retinal Pigment Epithelium, <i>Proceedings of the National Academy of Sciences</i> , 95(25), 14609-14613 (1998) (“Parish”)
1019	Furr et al. Stable Isotope Dilution Techniques for Assessing Vitamin A Status and Bioefficacy of Provitamin A Carotenoids in Humans, <i>Public Health Nutrition</i> , 8(6), 596-607 (2005) (“Furr”)
1020	Shaban & Richter, A2E and Blue Light in the Retina: The Paradigm of Age-related Macular Degeneration, <i>Biol. Chem.</i> , 383(3-4), 537-45 (2002) (“Shaban & Richter”)
1021	Shaban et al., Phosphatidylglycerol Potently Protects Human Retinal Pigment Epithelial Cells Against Apoptosis Induced by A2E, a Compound Suspected to Cause Age-related Macula Degeneration, <i>Experimental eye research</i> , 75(1), 99-108 (2002) (“Shaban”)

1022	Age-Related Eye Disease Study Research Group, A Randomized, Placebo-controlled, Clinical Trial of High-dose Supplementation with Vitamins C and E, Beta Carotene, and Zinc for Age-related Macular Degeneration and Vision Loss: AREDS report no. 8. <i>Archives of Ophthalmology</i> , 119(10), 1417-1436 (2001) (“AREDS”)
1031	File History of U.S. Patent Application No. 12/733,631
1032	File History of U.S. Patent Application No. 14/510,975
1035	Radu, Roxana A. et al. “Treatment with Isotretinoin Inhibits Lipofuscin Accumulation in a Mouse Model of Recessive Stargardt’s Macular Degeneration.” <i>Proceedings of the National Academy of Sciences of the United States of America</i> 100:4742-4747 (2003) (“Radu”)
1050	Kuksa V, Imanishi Y, Batten M, Palczewski K, Moise AR. Retinoid Cycle in the Vertebrate Retina: Experimental Approaches and Mechanisms of Isomerization, <i>Vision Res.</i> 43(28):2959-81 (2003) (“Kuska”)
1051	Miwa, GT & Lu, AY, Kinetic Isotope Effects and ‘Metabolic Switching’ in Cytochrome P450-catalyzed Reactions, <i>BioEssays</i> , 7(5), 215-219 (1987) (“Miwa”)
1052	WO 95/04018 to Marcus F. Boehm (“Boehm”)