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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.

Case No. IPR2024-00312
Patent No. 9,486,432

**PETITION FOR INTER PARTES REVIEW OF
U.S. PATENT NO. 9,486,432**

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LISTING OF CHALLENGED CLAIMS

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.
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 C₂₀-D₁₋₃-retinoid is C₂₀-D₃-retinol acetate.
4. The pharmaceutical composition according to claim 1, wherein the pharmaceutical composition is in unit dosage form.
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 C₂₀-D₁₋₃-retinoid inhibits the formation of A2E and/or ATR-dimer compared with the corresponding non-deuterium enriched retinoid.
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.
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.
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.
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.
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.
19. The pharmaceutical composition according to claim 1, wherein the substituted 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.
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.

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.

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

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

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

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.

Under 35 U.S.C. § 311 et seq., and 37 C.F.R. Part 42, Gene Company Pty Ltd, (“Petitioner”) requests inter partes review of United States Patent No. 9,486,432 (“the ’432 patent,” EX1001), which is currently assigned to the Trustees of Columbia University (“Patent Owner” or “PO”). This petition demonstrates there is a reasonable likelihood that at least one of claims 1-28 of the ’432 patent is unpatentable for failure to satisfy 35 U.S.C. §103.

I. INTRODUCTION

The challenged claims encompass vitamin A retinol or retinol acetate that is deuterated at Carbon 20, in a pharmaceutically-acceptable carrier. Olson 1988 (EX1006) discloses C₂₀-deuterated vitamin A retinol and retinol acetate, just as the claims require. During prosecution, the applicant never informed the Examiner that the claimed C₂₀-deuterated vitamin A was disclosed in the prior art.

Formulating C₂₀-deuterated vitamin A in a pharmaceutically-acceptable carrier would have been obvious and readily apparent to a POSA in view of Olson's teachings and knowledge in the art. For example, Olson 1988 specifically created its deuterated compounds for biological studies. A POSA would have understood that making use of these compounds conventionally involved formulation in a pharmaceutically-acceptable carrier. This is underscored by the fact that the subject patent permissively encompasses a very broad scope of conventional pharmaceutically-acceptable carriers and concedes that formulation

of these compounds was conventional. Accordingly, any difference between what is claimed and what is disclosed and suggested in Olson 1988 was obvious before the critical date in 2007.

Obviousness is further corroborated in view of prior art teaching successful formulation of vitamin A in pharmaceutically-acceptable carriers. In Ground 1, Olson 1989 demonstrates that the same research group as in Olson 1988 formulated deuterated vitamin A in a conventional, pharmaceutically-acceptable carrier (e.g., corn oil) for biological studies. Olson 1989 thus corroborates that using deuterated vitamin A entails formulation in a pharmaceutically-acceptable carrier and that doing so with a reasonable expectation of success was routine and conventional. In Ground 2, Ortho Pharma (EX1008), demonstrates that it was well-known by 2007 to formulate vitamin A in a pharmaceutically-acceptable carrier (e.g., water) for administration to a subject. In each case, the formulation of vitamin A in a pharmaceutically-acceptable carrier is confirmed to be conventional and well within the ordinary skill in the art.

The challenged claims are thus unpatentable under 35 U.S.C. §103 because they encompass subject matter that was obvious to a person of ordinary skill in the art before the earliest claimed priority date. Accordingly, *Inter Partes* Review should be instituted and the challenged claims canceled.

A. The '432 Patent

The '432 patent discusses "a substituted C₂₀-retinoid" in a pharmaceutically acceptable carrier. EX1001, Abstract. Among other substituted C₂₀-retinoids, the '432 patent discusses substituting 1-3 of the hydrogens at C₂₀ with fluorine or deuterium. *See, e.g.*, EX1001, 5:42-62. The '432 patent assumes that C₂₀-deuterated retinoids should be non-toxic because deuterated vitamin A (at other positions, e.g., 10 and 19 for tracing studies) was widely used in humans in the prior art without toxicity. EX1001, 8:17-21; EX1002, ¶¶23-25; EX1004, ¶¶21-23.

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

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.

Each of claims 2-28 depends directly or indirectly from claim 1. EX1002, ¶¶31-33; EX1004, ¶¶29-31. As discussed in detail in this petition, the prior art Olson 1988 reference discloses making the claimed compounds, C₂₀-D₃-retinol and

C₂₀-D₃-retinol acetate, for biological studies (which entails formulation in a pharmaceutically-acceptable carrier).

The '432 patent admits that “the compounds of the present invention are formulated into pharmaceutically-acceptable dosage forms by conventional methods known to those of skill in the art” and that suitable and acceptable carriers “can be determined using ordinary skill in the art.” EX1001, 15:3-8, 15:32-36 (citing Remington’s). The '432 patent further admits that “[p]harmaceutically acceptable carriers are well known in the art” and include, *inter alia*, water, saline solution, corn oil, and starch. EX1001, 15:9-27 (citing Remington’s); EX1002, ¶¶26-30; EX1004, ¶¶24-28.

B. Prosecution History

The '432 patent issued from U.S. Application No. 14/510,975, which was a divisional of U.S. Application No. 12/733,631 (filed as PCT/US2008/010676 on Sep. 12, 2008), which issued as U.S. Patent No. 8,877,809 and reissued as RE47,045. It claims priority to U.S. Provisional Patent Application No. 60/993,379, filed on Sep. 12, 2007.

Prosecution of the '432 patent involved: (1) Section 112 rejections; and (2) non-statutory obviousness-type double patenting rejections over the parent '631 application. Prosecution of the challenged patent did not involve even a single

prior art-based rejection. EX1032, 208 (PA), 57-60 (112 and double patenting rejections), 35-41 (response), 27-28 (allowance).

While there was no prior art rejection during prosecution of the '432 patent, arguments regarding the prior art were advanced during prosecution of the parent '631 application. During prosecution of the parent application, the only prior art combination applied against the independent claims in the parent application was Radu and Boehm. Applicant distinguished the prior art on the basis that they did not “disclose or suggest deuterium substitutions at C₂₀” and provided “no reason to think that substituting deuterium at position 20 would reduce lipofuscin accumulation or lead to any other desirable result.” EX1031, 171, 169; *see also id.*, 156 (“Applicant discloses retinoids selectively substituted at the retinoid’s carbon number 20, the C₂₀ position...whereby the protium (¹H or H) at the carbon 20 position have been replaced with deuterium (²H or D).”). Applicant argued that the Examiner was mistaken in believing that the prior art disclosed “a C₂₀ deuterated retinoid.” EX1031, 172-173. Applicant also argued that “[t]he claimed ***methods of treatment*** are based on the discovery that retinoids deuterated at the C₂₀ position inhibit the formation of A2E dimers in ABCR^{-/-} mice.”¹ *See, e.g.*, EX1031, 162; *see also id.*, 166 (“the claimed invention involves substitution at the C₂₀ position of

¹ All bold-italic emphases added unless other indicated.

retinoids, in order to slow the condensation reaction that produces A2E (and thus lipofuscin)").

Applicant never informed the Examiner that the prior art (e.g., Olson 1988) expressly disclosed claimed C₂₀-deuterated retinoids. Nor did Applicant inform 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. In view of this previously-unasserted prior art, and well-known teachings about using the deuterium kinetic isotope effect to slow reactions involving removal of a hydrogen when those reactions result in undesirable byproducts, the challenged claims would have been obvious before September 2007. *See* EX1002, ¶¶34-46; EX1004, ¶¶32-37.

C. Level of Skill in the Art

This petition is supported by the Declaration of Dr. Peter Guengerich, who is a Professor of Biochemistry at Vanderbilt University School of Medicine. EX1002; EX1003 (cv). Dr. Guengerich is an expert in biochemistry and the deuterium kinetic isotope effect. EX1002, ¶¶1-15. The petition also is supported by the Declaration of Dr. Andy Calman, who is a board-certified ophthalmologist with nearly 25 years of experience treating and preventing ocular disorders. EX1004, ¶¶1-13; EX1005 (cv). Drs. Guengerich and Calman are well-qualified by virtue of their education, experience, and training to opine regarding the perspective of a

person of ordinary skill in the art (POSA) at the relevant time. *See* EX1002, ¶¶1-10; EX1003 (cv); EX1004, ¶¶1-10; EX1005 (cv). Furthermore, the prior art reflects the appropriate level of skill at the time of the claimed invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001).

i. Qualifications of a POSA

The '432 patent describes the present invention as relating 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, 10:15-22. A POSA of the '432 patent in September 2007 would have had an advanced degree (e.g., Ph.D., M.D., M.S., or equivalent), in chemistry, biochemistry, pharmaceutical science, medicine, or a related field. This individual may have worked in consultation with a team including, e.g., a practicing physician who diagnoses and treats macular degeneration. Moreover, skilled artisans would have had practical knowledge about biological studies, pharmaceutical formulation, and the deuterium isotope effect, including the patents and publications discussed herein. EX1002, ¶¶47-50; EX1004, ¶¶38-40.

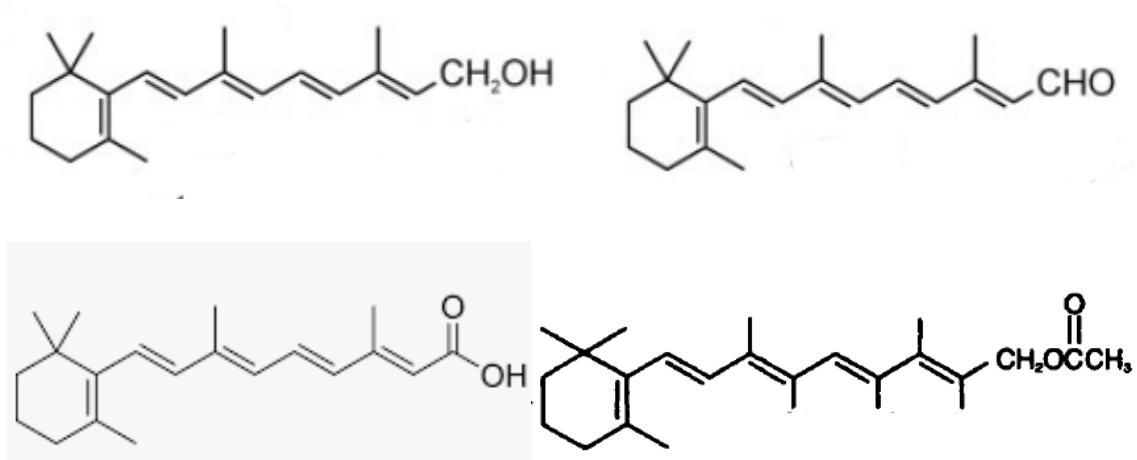
ii. Technological Background

The Applicant for the '432 patent did not invent the claimed C₂₀-deuterated vitamin A compounds or formulation of deuterated vitamin A in a

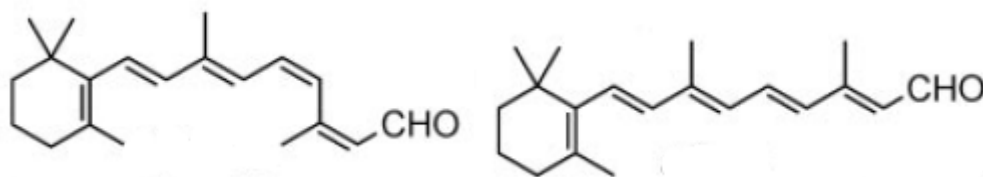
pharmaceutically-acceptable carrier. Moreover, they were not the first to teach treatment or prevention of ocular disorders such as macular degeneration by administering vitamin A and by inhibiting lipofuscin formation, to use deuterium to slow undesirable reactions, or to identify C₂₀ of vitamin A as the site of reaction through which lipofuscin was formed. Each of these things was disclosed in the prior art before the earliest claimed priority date, September 2007. EX1002, ¶¶53-118; EX1004, ¶¶44-95. Prior art references of particular relevance to the unpatentability of claims 1-28 of the '432 patent are discussed below.

1. The Role of Vitamin A in Ocular Health Was Well-Known.

Vitamin A refers to a group of retinoid compounds that include Vitamin A alcohol (retinol, top left), Vitamin A aldehyde (retinal, top right), Vitamin A acid (retinoic acid, below left), Vitamin A ester (retinyl acetate, below right), and provitamin A carotenoids such as beta-carotene.



By 2007, vitamin A retinoids were known to be important to eye health because of what is called the “visual cycle” or the “retinoid cycle.” EX1002, ¶¶41-42; EX1004, ¶¶44-45. The retinoid cycle is a series of light-driven and enzyme-catalyzed reactions. EX1009 (Widder), 1:12-16. Retinol is converted into 11-*cis*-retinal (below left) in the retinal pigment epithelium (RPE). 11-*cis*-retinal binds to opsin to form rhodopsin in rod cells and iodopsin in cone cells. The 11-*cis*-retinal is converted into all-trans-retinal (ATR, below right) when light enters the eye, generating a nervous signal to the brain that is interpreted as sight. ATR is then recycled to repeat the cycle. EX1009 (Widder), 6:1-9; EX1002, ¶¶56-59; EX1004, ¶47.



By 2007, POSAs were well aware that vitamin A deficiency was a major global public health problem. EX1019 (Furr), 596. For example, inadequate vitamin A was understood to lead to night blindness and corneal damage. EX1019 (Furr), 596. But it was also known that vitamin A could be obtained from the diet, as pro-vitamin A carotenoids (e.g., β -carotene) from fruits and vegetables or as pre-formed retinyl esters from liver, eggs, dairy products, and fortified foods. EX1019 (Furr), 596, 601; EX1002, ¶¶65-70; EX1004, ¶¶46-51. As Dr. Calman

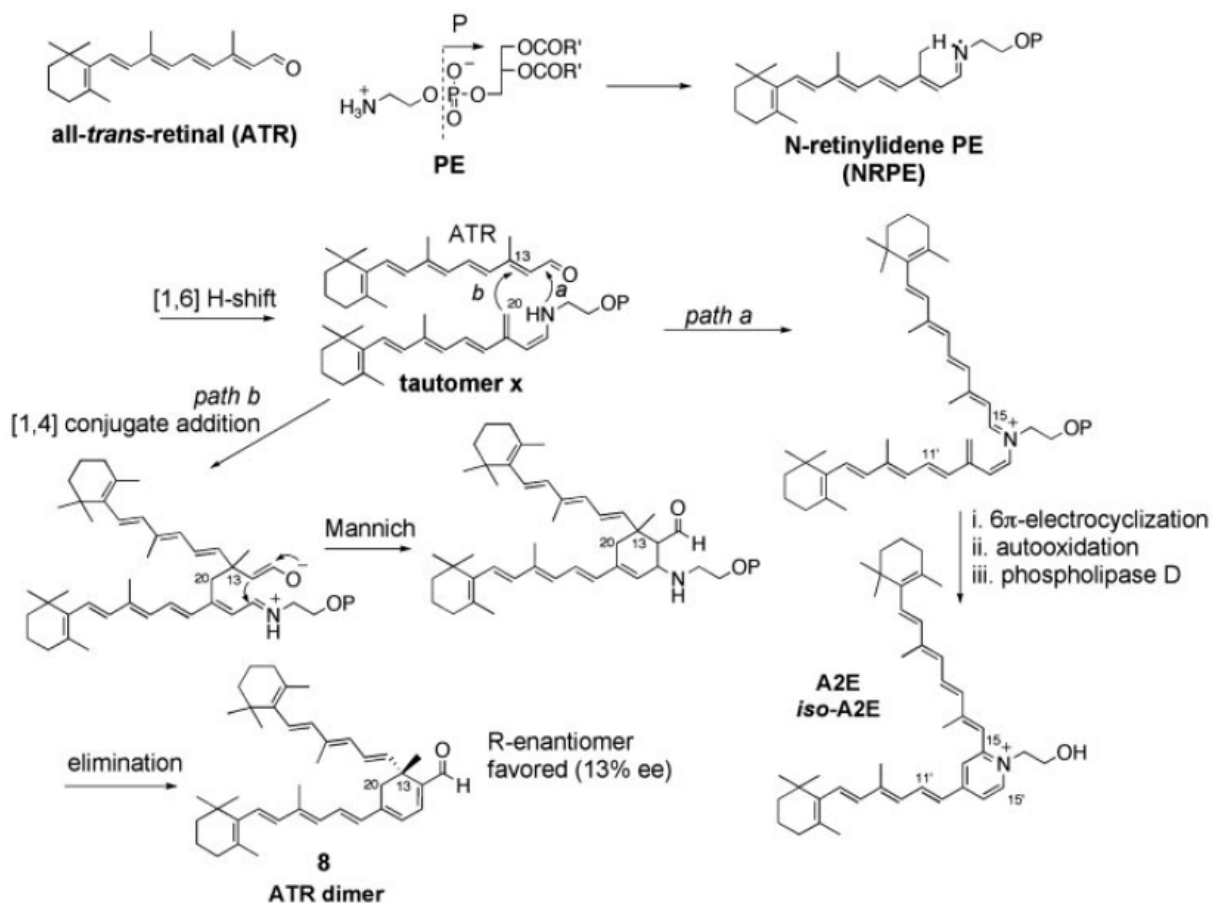
explains, nutritional administration of vitamin A in a pharmaceutically-acceptable carrier to individuals was also recognized as important. EX1004, ¶¶73-76. Indeed, administering vitamin A was the standard of care for treating patients with macular degeneration and other ocular diseases. *Id.*

Various techniques have been employed to assess the body's stores and deployment of vitamin A. EX1019 (Furr), 596-97; EX1002, ¶¶71-72.

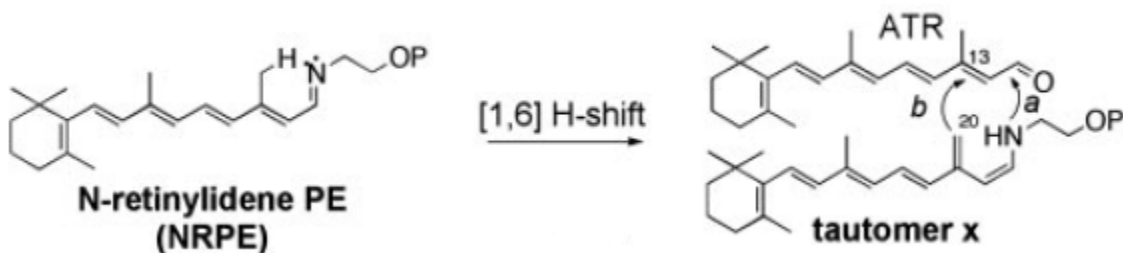
2. Toxic A2E Lipofuscin Associated with Macular Degeneration Was a Known Byproduct of the Visual Cycle.

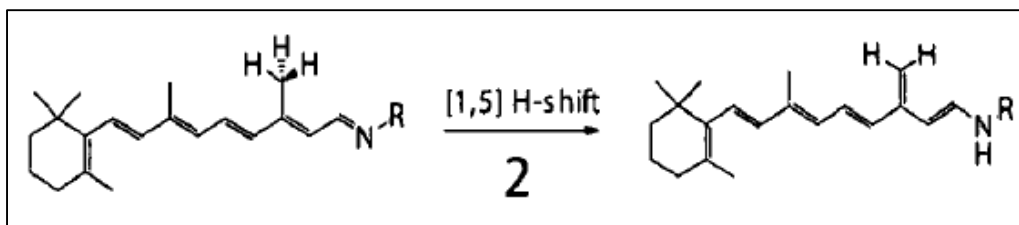
The production of lipofuscin pigment A2E as a byproduct of the visual cycle, and the association of lipofuscin toxicity with development of macular degeneration, was disclosed in the prior art by 2007. EX1004, ¶¶52-56. Fishkin, for example, discloses that lipofuscin fluorophores in the RPE originate in large part (>90%) from the retinoids of the visual cycle. EX1011, 7091. Fishkin discloses that they accumulate with age and also are particularly abundant in Stargardt's disease, a macular degeneration of juvenile onset. EX1011, 7091. Fishkin discloses that lipofuscin fluorophore accumulation in RPE cells contributes to the etiology of some forms of macular degeneration. EX1011, Abstract, 7091; EX1002, ¶¶73-75.

Fishkin identifies two lipofuscin fluorophores, N-retinylidene-N-retinylethanolamine (A2E) and ATR dimer. EX1011, 1091 & Abstract, 7094-95.



The proposed biosynthetic pathway of ATR dimer and A2E formation in Fishkin (Fig. 10, below top) is the same pathway that the '432 patent identifies ('432 Patent Fig. 2, below bottom). This biosynthetic pathway features what Fishkin calls a (1,6) H-shift, but which the patent calls a [1,5] H-shift:





Fishkin discloses that this C₂₀-mediated rearrangement can result in ATR dimer formation as well as A2E formation. EX1011, 7095; EX1002, ¶¶76-81; *see also id.*, ¶¶82-86 (citing EX1018, 14609, 14611, 14613) (known methods for quantifying A2E), 87-93 (citing EX1010, 7158-59) (prior art anticipated A2E's biosynthetic pathway); EX1004, ¶¶57-58.

3. Deuterium's Kinetic Isotope Effect Was Known to Slow Reactions Requiring Cleavage of Carbon-Hydrogen Bonds 5-10 Times.

Before 2007, POSAs appreciated that deuteration of a compound was useful for (1) tracking compounds *in vivo*; (2) identifying metabolites and sites of metabolic action; and (3) inhibiting (slowing) reactions that involve cleavage of a carbon-hydrogen bond. EX1002, ¶54; EX1002, ¶¶94-95.

Haskins, for example, teaches that deuterium is a “stable isotope” of hydrogen that is routinely used for biological studies. EX1012 (Haskins), 269. A stable isotope (sometimes called “heavy isotope”) is a non-radioactive isotope of an element. *Id.* Deuterium is commonly used to diagnose the amount of a given compound in an organism (e.g., stable isotope dilution assays), to identify and/or track metabolites, and in pharmacokinetic studies. *Id.* In isotope dilution assays,

the stable isotope is used to make a labelled internal standard that is chemically equivalent to the native compound. EX1012 (Haskins), 270-71. In this type of assay, deuterium labels are preferred because of their high isotopic purity and lower cost. *Id.* Applying three or more heavy atoms as a label on a given compound is preferred to distinguish the label from naturally-occurring heavy isotopes. *Id.*; EX1002, ¶¶96-98.

In addition to being used to diagnose compound concentrations in vivo, labeling a compound with “deuterium clusters” was a method that was well-known to a POSA for “metabolite identification.” EX1012 (Haskins), 272. In using deuterium for metabolite identification, a POSA was well-aware that deuterium has a “large isotope effect.” EX1012 (Haskins), 271-72. The primary isotope effect of deuterium is 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. EX1012 (Haskins), 273. Haskins explains that the more stable deuterium bond requires greater energy of activation and can therefore have “a profound effect on the rate of chemical reactions involving bond cleavage.” *Id.*, 273. The rate of bond cleavage for a deuterium is generally at least 2-5 times slower than for the hydrogen, and can be as high as 7-10 slower. *Id.*, 273; EX1002, ¶¶100-04.

By 2007, POSAs also appreciated that the first step in using deuterium

substitution is to evaluate whether the deuterated compound is chemically equivalent for the purposes being evaluated. EX1002, ¶¶99. When the objective is to label recovered drug and metabolites to prove them to be drug derived, it may be suitable to label the compound with deuterium in a position where primary isotope effects could occur. EX1012 (Haskins), 271. When the goal is to avoid impacting the rate of metabolism (e.g., in a stable isotope dilution assay), however, POSAs knew to avoid the strong primary isotope effect of deuterium by identifying sites of desired carbon-hydrogen bond cleavage and avoiding deuteration at those sites. 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. Accordingly, POSAs 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 reaction. EX1002, ¶¶105-11, 226-27; EX1002, ¶¶60; *see also* EX1013 (Baillie), 106 (“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.”); EX1014 (Langenhove), 383 (“[W]hen stable isotope-labeled compounds are used for mechanistic studies, isotope effects can be used to their advantage.”); EX1002, ¶¶111-17 (citing

EX1016, 261-62, Fig. 2; EX1015, 27-32; EX1024 (certifying EX1015 as translation of German publication)) (strong $12\times$ kinetic isotope effect (“KIE”) associated with a 1,5 sigmatropic shift confirmed in prior art).

In view of the forgoing, it was known before 2007 to treat or prevent ocular disorders such as macular degeneration by administering vitamin A and by inhibiting lipofuscin formation, to use deuterium to slow undesirable reactions, and that deprotonation at C₂₀ was how lipofuscin was formed. EX1002, ¶118; EX1004, ¶¶71-79.

D. Summary of Asserted References

i. Olson 1988 (EX1006)

“Synthesis of Tri-, Tetra-, and Penta-Deuterated Forms of Vitamin A” by Bergen, Furr, and Olson (“Olson 1988,” EX1006) was published in the *Journal of Labelled Compounds and Radiopharmaceuticals* in 1988. Olson 1988 is prior art under pre-AIA 35 U.S.C. §102(b).

Olson 1988 discloses the same C₂₀-D₃-retinoids that are claimed in the ’432 patent, that were used in the experiments in the ’432 patent, and that Applicant asserted during prosecution were not disclosed in the prior art. Specifically, Olson 1988 discloses C₂₀-D₃-retinol and C₂₀-D₃-retinyl acetate. EX1006, Abstract; *id.*, 12-13, 14, 15-19. C₂₀-D₃-retinyl acetate is also known as C₂₀-D₃-retinol acetate. Using Olson 1988’s procedure, nearly 94% of the retinyl acetate was deuterated

and the majority was trideuterated ($C_{20}-D_3$). EX1006, 18. Olson 1988 teaches preparative-scale purification of products may be performed by HPLC. EX1006, 15. Olson 1988 created and purified C_{20} -deuterated vitamin A for biological studies in humans. EX1006, 11; EX1002, ¶¶119-36; EX1004, ¶¶ 97-99.

Olson 1988 was not applied by the Examiner of the '432 patent.

ii. Olson 1989 (EX1007)

“Vitamin A concentrations in liver determined by isotope dilution assay with tetradeuterated vitamin A and by biopsy in generally healthy adult humans” by Furr, Amedee-Manesme, Clifford, Bergen, Jones, Anderson, and Olson. (“Olson 1989,” EX1007) was published in the *American Journal of Clinical Nutrition* in 1989. Olson 1989 is prior art under pre-AIA 35 U.S.C. §102(b).

Olson 1989 discloses that it was conventional to formulate deuterated vitamin A in a pharmaceutically-acceptable carrier for biological studies of vitamin A metabolism. Olson 1989 took deuterated 10,19,19,19-tetradeuterated retinyl acetate (99% pure) that was synthesized and purified as described in Olson 1988, formulated it in corn oil (a pharmaceutically-acceptable carrier), and then administered it to 11 humans for biological studies. EX1007, 713-14 & Abstract. Olson 1989 successfully used the same pharmaceutically-acceptable carrier (corn oil) to formulate both the deuterated and the non-deuterated forms of vitamin A employed in the biological studies. EX1002, ¶¶137-43; EX1004, ¶¶100-02.

Olson 1989 was not before the Examiner of the '432 patent.

iii. Ortho Pharma (EX1008)

German Patent Application Number 20 2006 014 588, entitled “Carotenoid-containing product,” published on January 18, 2007 (“Ortho Pharma,” EX1008).

See EX1023 (certifying EX1008 as translation of published German application).

Ortho Pharma is prior art at least under pre-AIA 35 U.S.C. §102(a).

Ortho Pharma discloses compositions comprising vitamin A together with other vitamins, antioxidants, and minerals for promoting eye health in patients with age-related eye diseases, such as macular degeneration. EX1008 (Ortho Pharma), ¶[0008]. Ortho Pharma teaches administering the vitamins and minerals “in a liquid dosage form” is “particularly well-tolerated” and identifies water, a pharmaceutically-acceptable carrier, as a preferred solvent for the vitamins and minerals in solution. EX1008, ¶¶[0012]-[0015], [0038]-[0042], [0044], [0046]; EX1002, ¶¶144-61; EX1004, ¶¶103-08.

Ortho Pharma was not before the Examiner of the '432 patent.

iv. Widder (EX1009)

International Patent Publication No. WO 2006/007314 by Widder et al. (“Widder,” EX1009) published on January 19, 2006. Widder is prior art under pre-AIA 35 U.S.C. §102(b).

Widder discloses administering vitamin A in combination with fenretinide to reduce lipofuscin formation and thereby treat ocular diseases, including macular degeneration. EX1009 (Widder), 46:25-47:6, 47:21-27. Widder also teaches administering negatively-charged phospholipids to treat macular degeneration and administering macular degeneration treatment directly to the eye. EX1009 (Widder), 33:1-7, 25:16-35; EX1002, ¶¶162-69; EX1004, ¶¶109-18.

Widder was not applied by the Examiner of the '432 patent.

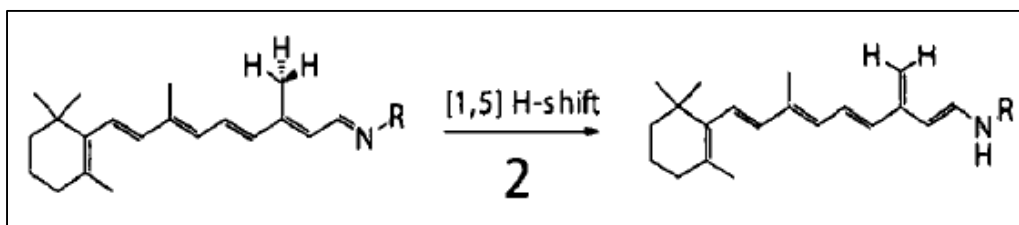
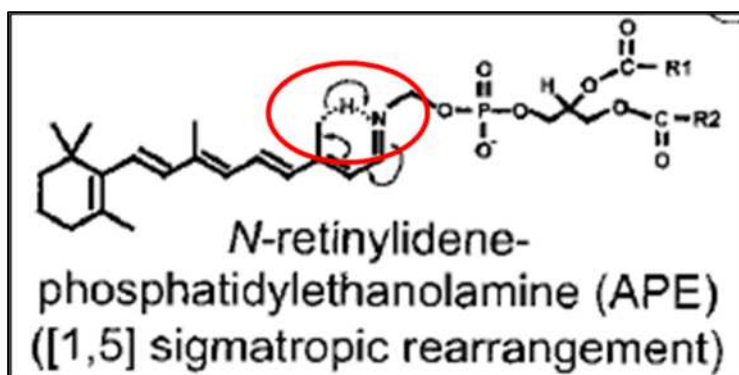
v. Mata (EX1010)

“Biosynthesis of a major lipofuscin fluorophore in mice and humans with ABCR-mediated retinal and macular degeneration” by Mata et al., (“Mata,” EX1010) was published in *Proceedings of the National Academy of Science* on June 20, 2000. Mata is prior art under Pre-AIA 35 U.S.C. §102(b).

Mata discloses that age-related macular degeneration (AMD) is a common cause of blindness in the elderly and is characterized by the accumulation of fluorescent extracellular deposits called drusen and fluorescent lipofuscin granules in cells of the retinal pigment epithelium (RPE). EX1010, 7154 & Abstract. Mata discloses that lipofuscin accumulation in the RPE is also associated with Stargardt’s disease and recessive forms of macular degeneration that affect children. EX1010, 7154; EX1002, ¶¶170-73.

Mata identifies A2E as a major fluorophore of lipofuscin that is toxic to RPE cells. EX1010, 7154 & Abstract. A hypothetical A2E biosynthetic pathway had been identified. *Id.* Mata corroborated this biosynthesis pathways by identifying three critical intermediates in ocular tissues. EX1010, 7154 & Abstract, 7157-7158, Fig. 5 & Caption. Mata teaches that humans with macular degeneration associated with lipofuscin formation may slow progression of their disease by limiting exposure to light or, alternatively, by targeting the A2E precursors that Mata identified. EX1010, 7154 & Abstract, 7159. Additionally, 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, 7159; EX1002, ¶¶88-92, 174-80; *see also id.*, ¶¶181-83 (avenues for slowing disease progression).

The biosynthetic pathway that Mata corroborated (Mata Fig. 5, below top) is the same pathway that the ’432 patent identifies (’432 Patent Fig. 2, below bottom). This biosynthetic pathway features a (1,5) sigmatropic rearrangement, which the ’432 patent calls a [1,5] H-shift:



As explicitly disclosed in Mata, the (1,5) sigmatropic rearrangement (red circle added) requires breaking the C₂₀-bond with its hydrogen. EX1002, ¶¶184-86; EX1004, ¶¶119-25.

Mata was not before the Examiner of the '432 patent.

II. STANDING CERTIFICATIONS (37 C.F.R. §42.104(a))

The '432 patent is available for IPR. Petitioner is not barred or estopped from requesting IPR on the grounds identified.

III. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8

Real Party-in-Interest (37 C.F.R. § 42.8(b)(1)): Gene Company Pty Ltd.

Related Matters (37 C.F.R. § 42.8(b)(2)): None

Lead and Back-Up Counsel (37 C.F.R. § 42.8(b)(3)):

Lead Counsel: Jad A. Mills (Reg. No. 63,344)

Back-Up Counsel: Michael T. Rosato (Reg. No. 52,182); Matthew
Bresnahan (Reg. No. 62,452)

Service Information (37 C.F.R. § 42.8(b)(4)): Petitioner hereby consents to
electronic service.

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Tel.: 206-883-2554

Fax: 206-883-2699

**IV. STATEMENT OF THE PRECISE RELIEF REQUESTED FOR EACH CLAIM
CHALLENGED 37 C.F.R. §42.104(b)**

Petitioner requests review of claims 1-28 of the '432 patent under 35 U.S.C.

§311. The grounds for relief are as follows:

Ground	Claims	Description
1	1-6 & 28	Obvious under 35 U.S.C. §103 over Olson 1988 as evidenced by Olson 1989.
2	1-6, 8-23, 25 & 27-28	Obvious under 35 U.S.C. §103 over Ortho Pharma 2006 and Olson 1988.
3	7, 24, 26	Obvious under 35 U.S.C. §103 over Ground 2 in further view of Widder.

V. CLAIM CONSTRUCTION

Claims should be understood according to their ordinary and customary meaning as understood by POSA at the time of the invention in light of the language of the claims, the specification, and the prosecution history of record. 37 C.F.R. §42.100; *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-14 (Fed. Cir. 2005) (en banc). The Board need construe claims only to the extent necessary to resolve a controversy. *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co. Matal*, 868 F.3d 1013, 1017 (Fed. Cir. 2017). Petitioner submits that no construction should be necessary to institute this petition. EX1002, ¶187; EX1004, ¶96.

The specification of the '432 patent confirms that the claim term “pharmaceutically acceptable carrier” encompasses a wide variety of conventional carriers, including water, saline solution, corn oil, and starch. EX1001, 15:9-27 (citing Remington’s); EX1002, ¶¶26-30; EX1004, ¶27.

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

A. Brief Summary

Ground 1 demonstrates that an embodiment squarely encompassed by claims 1-6 and 28 of the '432 patent would have been obvious to a POSA before the critical date. Olson 1988 discloses making and purifying claimed C₂₀-D₁₋₃-retinoids, including C₂₀-D₁₋₃-retinol and a C₂₀-D₁₋₃-retinol ester (e.g., C₂₀-D₃-retinol acetate). EX1006, Abstract; *id.*, 12-13, 15-19.

Formulating C₂₀-deuterated vitamin A in a pharmaceutically acceptable carrier would have been obvious and readily apparent to a POSA in view of Olson's teachings and knowledge in the art. For example, Olson 1988 specifically created its deuterated compounds for biological studies. EX1006, 11. A POSA would have understood that making use of these compounds, as directed by Olson, conventionally involved formulation in a pharmaceutically acceptable carrier. This is underscored by the fact that the subject patent permissively encompasses a very broad scope of conventional, pharmaceutically-acceptable carriers, and concedes that formulation of these compounds was conventional. EX1001, 15:3-27, 15:32-36 (citing Remington's); EX1002, ¶¶26-30. Accordingly, any difference between what is claimed and what is disclosed and suggested in Olson 1988 was obvious before the critical date in 2007.

Obviousness is further corroborated in view of prior art teaching successful formulation of vitamin A in pharmaceutically-acceptable carriers. In Ground 1, Olson 1989 demonstrates that the same research group as in Olson 1988 formulated deuterated vitamin A in a conventional, pharmaceutically-acceptable carrier (e.g., corn oil) for biological studies. EX1007, 713-14 & Abstract. Olson 1989 thus corroborates that using deuterated vitamin A entails formulation in a pharmaceutically-acceptable carrier and that doing so with a reasonable expectation of success was routine and conventional.

Olson 1988 in combination with Olson 1989 discloses each and every element of claims 1-6 and 28 and renders each of these claims obvious as a whole. EX1002, ¶¶188-90.

B. Detailed Analysis of the Obviousness of the Claims

As explained in detail below, each of claims 1-6 and 28 of the '432 patent was obvious as a whole over Olson 1988 and Olson 1989. EX1002, ¶188; EX1004, ¶¶41, 126.

i. Claim 1

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

Olson 1989 discloses a pharmaceutical composition comprising a purified, deuterated form of vitamin A in a pharmaceutically acceptable carrier (e.g., corn oil). EX1006, Abstract (“45-mg oral dose of tetradeuterated retinyl acetate (99% pure).”), 714 (“[E]ach subject was given 45 mg all-*trans* 10,19, 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 ([EX1006, Olson 1988]).”). Olson 1988 specifically created its deuterated compounds for biological studies. EX1006, 11. Olson 1989 administered the pharmaceutical composition to 11 humans to perform a vitamin A stable isotope dilution assay study to diagnose the adequacy of the body’s vitamin A reserves. EX1007, 713-14 & Abstract.

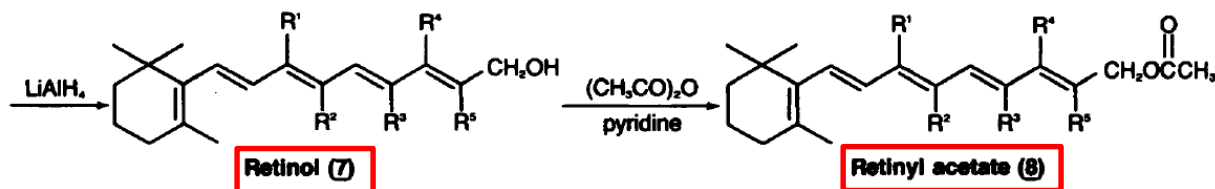
Accordingly, Olson discloses a pharmaceutical composition comprising a pharmaceutically-acceptable carrier. EX1002, ¶¶191-93; EX1004, ¶¶127-31.

There can be no dispute that Olson discloses a pharmaceutical composition comprising a pharmaceutically acceptable carrier as that term is used in the claims. First, the '432 patent admits that corn oil ("oils (e.g., corn...") is a pharmaceutically acceptable carrier that was known in the art. EX1001, 15:3-36 (& admitting (citing "Remington's Pharmaceutical Sciences") that formulation of the claimed compounds is done "by conventional methods known to those of skill in the art" and that carriers suitable for a selected dosage form "can be determined using ordinary skill in the art"). Second, Remington teaches corn oil among its short list of pharmaceutically acceptable "diluting agents (vehicles or carriers)," teaching that it is an appropriate vehicle for injections and for oral administration. EX1017, 21 ("Diluting Agents"), 23 ("Corn Oil"). Accordingly, Olson discloses a pharmaceutical composition comprising a pharmaceutically acceptable carrier. EX1002, ¶¶194-98.

...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.

Olson 1988 discloses making and purifying claimed C₂₀-D₁₋₃-retinoids, including C₂₀-D₁₋₃-retinol and a C₂₀-D₁₋₃-retinol ester (e.g., C₂₀-D₃-retinol acetate). EX1006, Abstract; *id.*, 12 (Scheme 2 discloses synthesis routes for preferential

formation of all-trans isomer of 20,20,20-trideuteroretinol (Scheme 2, R⁴-C²H₃) and 20,20,20-²H₃-retinyl acetate),¹³ (scheme 2), 15-19 (“Synthesis of 20,20,20-trideuteroretinyl acetate”); EX1002, ¶¶199-200, *see id.*, ¶¶201-207 (synthesis route).



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).

Olson 1988 specifically makes its deuterated compounds for biological studies.

EX1006, 11. Accordingly, Olson 1988 and 1989 together render obvious claim 1 as a whole. EX1002, ¶208; EX1004, ¶¶132-42.

ii. 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.

As discussed above, Olson 1988 and Olson 1989 render claim 1 obvious. As also discussed above for claim 1, Olson 1988 discloses making and purifying the

claimed C₂₀-D₃-retinol and a C₂₀-D₃-retinol ester (e.g., C₂₀-D₃-retinol acetate). EX1006, Abstract; *id.*, 12-13, 14, 15-19. For example, Olson 1988 specifically discloses C₂₀-D₃ retinol and C₂₀-D₃ retinol acetate (also known as retinyl acetate and retinoic acid ethyl ester) in Scheme 2. Accordingly, each of claims 2 and 3 was obvious over Olson 1988 and 1989. EX1002, ¶¶209-12; EX1004, ¶143.

iii. Claim 4: Dosage Forms

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

As discussed above, Olson 1988 and 1989 render claim 1 obvious. 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. EX1007, 714. Accordingly, Olson 1988 and 1989 together render claim 4 obvious as a whole. EX1002, ¶¶213-16; EX1004, ¶144.

iv. Claims 5-6, 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.

As discussed above, Olson 1988 and Olson 1989 render claim 1 obvious.

The additional limitations of claims 5, 6, and 28 all encompass the property of the aldehyde of C₂₀-D₃-all-trans-retinol acetate that it forms A2E about 7 times slower (claims 5 and 28) and inhibits the formation of A2E (claim 6) as compared to the non-deuterium-enriched retinoid. In other words, claims 5-6 and 28 merely recite properties that naturally result from deuteration at C-20. EX1002, ¶¶217-19; EX1004, ¶145.

Indeed, the '432 patent identifies the 7 times slower formation of A2E and the slower formation of ATR-dimer as compared to the non-deuterium-enriched retinoid as the result of deuterating carbon 20. *See, e.g.*, EX1001, 6:9-38 & Figs. 2-4 (“C₂₀-D₃-all-trans-retinal forms A2E about 7-times slower than all-trans-retinal.”), 8:13-17 (“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).”), 18:10-58 (“Replacing the C20 Hydrogens of all-Trans-Retinal with Deuteriums Slows the Formation of A2E [and ATR-Dimer] In Vitro”). The '432 patent repeatedly admits that replacing the C-20 hydrogens with deuteriums slows formation of A2E. EX1001, 6:39-67, 18:60-19:57 (“Replacing the C₂₀ Hydrogens of all-Trans-Retinal with Deuteriums Slows the formation of A2E”). During prosecution, Applicant obtained allowance of the claims by

convincing the Examiner that slowed A2E-formation flowed so naturally from C₂₀-deuteration that it was a class wide effect whether or not all of the hydrogens were replaced. EX1031, 157 (“the person skilled in the art would understand that substituting the retinoids’ C₂₀ hydrogen atoms (1 or more hydrogens)...would also result in substituted C₂₀-retinoids that slow down vitamin A dimerization”), 160 (similar), 117 (similar). Accordingly, PO cannot now argue that the increased resistance to lipofuscin formation of the C₂₀-D₃-retinoid corresponding to the aldehyde of the C₂₀-D₃-retinol acetate is anything but the natural result of the C₂₀-D₃-substitution.

As discussed above for claim 1, Olson 1988 discloses making and purifying claimed C₂₀-D₁₋₃-retinoids, including C₂₀-D₃-retinol and a C₂₀-D₃-retinol ester (e.g., C₂₀-D₃-retinol acetate). EX1006, Abstract; *id.*, 12-13, 14, 15-19. As explained above in Section I.C.ii.1, the body naturally converts retinol and retinol acetate into all-trans-retinal in the visual cycle. Because the claimed reductions in A2E and ATR-dimer formation is an inherent property of the C₂₀-D₃-retinoids disclosed in Olson 1988, each of claims 5-6 and 28 was obvious over Olson 1988 and 1989. EX1002, ¶219.

Further supporting the obviousness of these claims, a POSA would have reasonably expected that the aldehyde of the C₂₀-D₃-retinol acetate disclosed in Olson 1988 would reduce A2E formation as compared to the non-deuterated

retinoid. EX1002, ¶221. Mata identified deprotonation of Carbon 20 through a 1,5-sigmatropic shift as a prerequisite for A2E formation. EX1010, 7158-59 & Fig. 5. As Dr. Guengerich explains, a POSA would have been well aware of the deuterium isotope effect and that the C₂₀-D₃-retinoids, including C₂₀-D₃-retinol acetate and its aldehyde, would have been reasonably expected to have slower elimination of the C₂₀-deuterium bond as compared to the C₂₀-protium bond, thereby slowing the formation of A2E. EX1002, ¶¶221, 94-118. As explained above in Section I.C.ii.3, it was common for deuteration to slow a deprotonation reaction by 3-10 times. As explained by Dr. Guengerich, prior art teachings about the deuterium isotope effect specifically for a sigmatropic [1,5] shift indicated that A2E formation would be reduced by as much as 12 times. EX1002, ¶233. A POSA thus had good reason and a reasonable expectation that the aldehyde of C₂₀-D₃-all-trans-retinol acetate would form A2E 7 times slower (claims 5 and 28) and inhibit the formation of A2E (claim 6) as compared to the non-deuterium-enriched retinoid.

Accordingly, each of claims 5, 6, and 28 was obvious over Olson 1988 and 1989. EX1002, ¶222.

C. Rational Underpinnings for the Combination

All that is required to prove claims obvious is to show that the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious to a POSA before the critical date. *Galderma*

Labs., L.P. v. Tolmar, Inc., 737 F.3d 731, 737-38, 741 (Fed. Cir. 2013) (reversing judgment of non-obviousness where the prior art disclosed the claimed compound, and the inactive ingredients in the claimed formulation were routine, obvious, and non-inventive). A petitioner is not required to prove that a POSA would have been motivated to depart from prior art embodiments that were already in use. *Id.* Nor does disclosure of a preferred prior art embodiment render less-preferred prior art solutions non-obvious. *Par Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1197-98 (Fed. Cir. 2014) (“Our precedent, however, does not require that the motivation be the best option, only that it be a suitable option from which the prior art did not teach away.”).

By September 2007, formulating C₂₀-deuterated vitamin A in a pharmaceutically acceptable carrier would have been obvious and readily apparent to a POSA in view of Olson's teachings and knowledge in the art. EX1002, ¶¶223-24. For example, Olson 1988 specifically makes its deuterated compounds for biological studies. EX1006, 11. A POSA would have understood that making use of these compounds, including as directed by Olson, conventionally involved formulation in a pharmaceutically acceptable carrier. EX1002, ¶¶225-26. This is underscored by the fact that the subject patent permissively encompasses a broad scope of conventional, pharmaceutically-acceptable carriers, and concedes that formulation of these compounds was conventional. EX1001, 15:3-27, 15:32-36

(citing Remington's); EX1002, ¶¶237-38. Accordingly, any difference between what is claimed and what is disclosed and suggested in Olson 1988 was obvious before the critical date in 2007.

Obviousness is further corroborated in view of prior art teaching successful formulation of vitamin A in pharmaceutically-acceptable carriers. Olson 1989 demonstrates that the same research group as in Olson 1988 formulated deuterated vitamin A in a conventional pharmaceutically-acceptable carrier (e.g., corn oil) for biological studies. EX1007, 713-14 & Abstract. Olson 1989 thus corroborates that using deuterated vitamin A entails formulation in a pharmaceutically-acceptable carrier and that doing so with a reasonable expectation of success was routine and conventional. EX1002, ¶226.

Relying on Olson 1988, Olson 1989 employed retinol acetate that was deuterated at carbons 10 and 19 for isotope dilution assays because of its high isotopic integrity and because it contains three or more deuterium atoms in metabolically and chemically stable positions. EX1007, 713-714 (citing EX1006 as ref. 9). 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. EX1002, ¶¶227-30; EX1012 (Haskins), 270-73; EX1013

(Baillie), 106 (“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.”); EX1014 (Langenhove), 383 (“[W]hen stable isotope-labeled compounds are used for mechanistic studies, isotope effects can be used to their advantage.”). As explained in Section I.C.ii.3 above, POSAs appreciated before the critical date that deuteration of a compound, depending on the location of deuteration, was useful for (1) tracking compounds in vivo; (2) identifying metabolites and sites of metabolic action; and (3) inhibiting (slowing) reactions that involve cleavage of a carbon-hydrogen bond. EX1002, ¶¶231-32. Accordingly, measuring the impact of deuteration at a specific location was a threshold inquiry to determine for which biological assays a given deuterated analogue was best suited. EX1002, ¶¶231.

Prior art information that became known to a POSA well after Olson 1989 provided additional reason to formulate Olson’s C₂₀-D₃-retinol acetate in a pharmaceutically-acceptable carrier. For example, Mata taught that deprotonation at C-20 of retinal was a pre-requisite for undesirable A2E formation. EX1010, 7154 & Abstract, 7157-7158, Fig. 5 & Caption. As Dr. Guengerich explains, a POSA 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. EX1002, ¶¶231-32; *see also* Section I.C.ii.3 above. A POSA thus had good reason to formulate Olson's C₂₀-D₃-retinol or retinol acetate in a pharmaceutically-acceptable carrier (e.g., corn oil) at least for biological studies (1) tracking compounds in vivo; (2) identifying metabolites and sites of metabolic action; or (3) inhibiting (slowing) reactions that involve cleavage of a hydrogen to C-20. EX1002, ¶¶231-32.

The challenged claims were obvious for reasons set forth above. While the '432 patent specification proposes C₂₀-deuterated retinol for treatment purposes, the challenged claims do not require use of C₂₀-deuterated retinol for treatment purposes. Moreover, it is well established that demonstrating claims obvious does not require proving a POSA would have been motivated by the same thing that motivated the named inventors. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 419-20 (2007) ("any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed"). To clarify, as discussed above, the ability to use C₂₀-deuterated retinol in at least some biological studies is a rational underpinning that is sufficient to render the claims challenged herein obvious. Nevertheless, the desire to reduce lipofuscin formation in patients provided an independent and additional reason to formulate the C₂₀-deuterated vitamin A in a pharmaceutically-acceptable carrier.

For example, Mata provides good reason to prepare and administer a pharmaceutical composition comprising a C₂₀-deuterated form of vitamin A in a pharmaceutically acceptable carrier to reduce lipofuscin formation and thereby treat or prevent macular degeneration. Mata discloses C₂₀ as a site of action for the metabolic pathway creating lipofuscin pigments associated with macular degeneration. EX1010, 7154 & Abstract, 7157-7158, Fig. 5 & Caption. Mata explicitly discloses that this synthetic pathway depends on removing a hydrogen atom from C₂₀ through a 1,5-sigmatropic shift. EX1010, 7158, FIG. 5. Mata expressly suggests inhibiting this synthetic pathway to reduce lipofuscin formation as a means for treating or preventing macular degeneration. EX1010, 7154 & Abstract, 7159. As Dr. Guengerich explains, a POSA 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 that step in the pathway would reduce A2E formation. EX1002, ¶¶232-33.

As Dr. Guengerich further explains, a POSA would have understood that deuterating C₂₀ would slow A2E formation because 1,5-sigmatropic shifts were known to be subject to strong primary deuterium KIEs. EX1002, ¶233; EX1015 (Roth) 24-32; EX1016 (Itou) 111, 261-67 (left column) (12.2 times slower 1,5-sigmatropic shift upon deuteration). As Dr. Calman explains, a POSA would have had good reason to deuterate vitamin A at C-20 to reduce lipofuscin formation

from vitamin A's essential role in the visual cycle, including when administering vitamin A to treat macular degeneration. EX1004, ¶¶44, 124, 138. Such treatment would provide C₂₀-deuterated vitamin A to reduce undesirable lipofuscin formation without interfering with the normal function of the visual cycle, which does not involve conversion of retinoids at C-20. *See* EX1002, ¶¶55, 60-64; EX1004, ¶¶86, 141, 170; *supra* Section I.C.ii (understanding of POSA); *see also* EX1031, 117 (admitting that "it is well accepted in the art" that deuteration "will not generally affect the ability of the substituted compounds to interact with proteins" and that POSAs "would immediately conclude that C₂₀-D₃-vitamin A will be used as natural substrates in the visual cycle and not cause any side effects in patients"). Accordingly, a POSA had good reason to formulate Olson's C₂₀-D₃-retinol acetate 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. EX1002, ¶234.

D. Reasonable Expectation of Success

A POSA before 2007 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, Olson 1988 teaches that POSAs already had created claimed C₂₀-deuterated retinoids. EX1006, Abstract; *id.*, 12-13, 15-19. Olson 1989 teaches that POSAs already had formulated

deuterated vitamin A retinoids in a pharmaceutical composition comprising a pharmaceutically-acceptable carrier. EX1007, 713-14 & Abstract. Accordingly, a POSA before 2007 would have had a reasonable expectation of success for making what is claimed. EX1002, ¶¶235.

The reasonable expectation of success is not subject to reasonable dispute because the '432 patent admits that formulation of the claimed compounds was conventional and within the skill of the art. For example, the '432 patent admits that effective dosage forms, modes of administration, and dosage amounts may be determined “empirically” and that making such determinations “is within the skill of the art.” EX1001, 14:31-34. The '432 patent states that the pharmaceutical composition may be administered by a variety of means, including orally by ingestion or locally to the eye. EX1001, 14:49-56. “Regardless of the route of administration selected,” the '432 patent admits that “the compounds of the present invention are formulated into pharmaceutically-acceptable dosage forms by conventional methods known to those of skill in the art” and that suitable and acceptable carriers “can be determined using ordinary skill in the art.” EX1001, 15:3-8, 15:32-36 (citing Remington’s). The '432 patent further admits that “[p]harmaceutically acceptable carriers are well known in the art” and include, *inter alia*, water, saline solution, or corn oil. EX1001, 15:9-27 (citing Remington’s). Accordingly, PO may not now take a contradictory position that a

POSA before 2007 would not have had a reasonable expectation of success for making what is claimed. EX1002, ¶¶236-38.

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

A. Summary

Ground 2 demonstrates that embodiments within the scope of claims 1-6, 8-23, 25 and 27-28 of the '432 patent would have been obvious to a POSA before the critical date. Ortho Pharma discloses formulating vitamin A in a pharmaceutically-acceptable carrier, including in combination with additional vitamins (e.g., C, D, and E) and minerals (e.g., zinc). EX1008, ¶¶[0008] (a daily dose of active ingredients including 50-500 mg vitamin C, 0.1-2 mg vitamin A, 10-400 mg vitamin E, and 0.1-10 µg vitamin D₃, 2-30 mg zinc in a liquid dosage form separate from carotenoid-containing solid dosage form), [0019] (larger doses of vitamins and minerals), [0036] (larger doses of vitamins and minerals), [0049] (active ingredients include vitamin A acetate, vitamin E, vitamin D, ascorbic acid, and zinc). Ortho Pharma teaches that administering the vitamins and minerals “in a liquid dosage form” is “particularly well-tolerated” and even more available to the organisms than when administered in solid dosage forms. EX1008, ¶¶[0012]-[0015]. Ortho Pharma identifies water as a preferred solvent for the vitamins and minerals in the solution. EX1008, ¶¶[0038]-[0042], [0044], [0046]. 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, ¶¶[0050]-[0051]. Ortho Pharma teaches administering this formulation to individuals to treat or prevent eye diseases such as macular degeneration, including as a nutritional supplement. EX1008, ¶¶[0001]-[0003], [0008], [0010]-[0011], [0052]-[0054]; EX1002, ¶¶239-49; EX1004, ¶¶148-53.

As discussed above in Ground 1 (Section VI above), Olson 1988 teaches making and purifying claimed C₂₀-D₁₋₃-retinoids that a POSA would have recognized would reduce undesirable lipofuscin byproduct formation as compared to the non-deuterated retinoid. Accordingly, Ortho Pharma and Olson 1988 together obviate each of claims 1-6, 8-23, 25, and 27-28, as illustrated below. EX1002, ¶250; EX1004, ¶147.

B. Detailed Analysis of the Obviousness of the Claims

As explained in detail below, each of claims 1-6, 8-23, 25 and 27-28 of the '432 patent was obvious as a whole over Ortho Pharma and Olson 1988. EX1002, ¶94. EX1004, ¶¶41, 146.

i. Claim 1

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

Ortho Pharma discloses making and using pharmaceutical compositions (e.g., solutions) comprising vitamin A in a pharmaceutically-acceptable carrier. EX1002, ¶¶99, 103-06. For example, Ortho Pharma discloses formulating vitamin

A together with other vitamins and minerals in a liquid dosage form for oral administration. EX1008, ¶[0008]. Ortho Pharma teaches that administering the vitamins and minerals “in a liquid dosage form” is “particularly well-tolerated” and even more available to the organisms than when administered in solid dosage forms. EX1008, ¶¶[0012]-[0015]. Ortho Pharma identifies water as a preferred solvent for the vitamins and minerals in the solution. EX1008, ¶¶[0038]-[0042], [0044], [0046]. 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, ¶¶[0050]-[0051]. Ortho Pharma teaches administering its formulations to individuals to treat or prevent eye diseases such as macular degeneration, including as a nutritional supplement. EX1008, ¶¶[0001]-[0003], [0008], [0010]-[0011], [0052]-[0054]. Accordingly, Ortho Pharma discloses a pharmaceutical composition comprising a pharmaceutically acceptable carrier. EX1002, ¶¶251-55; EX1004, ¶¶154-60.

There can be no dispute that Ortho Pharma 2006 discloses a pharmaceutical composition comprising a pharmaceutically acceptable carrier as that term is used in the claims. First, the '432 patent admits that “water” is a pharmaceutically acceptable carrier that was known in the art. EX1001, 15:9-26 (& citing “Remington’s Pharmaceutical Sciences” and admitting formulation done “by conventional methods” and “using ordinary skill in the art”). Second, Remington

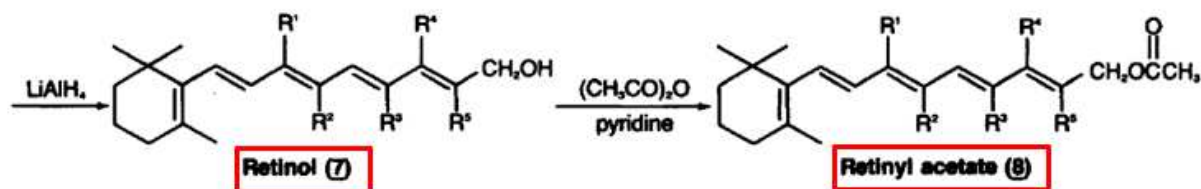
teaches water among its short list of pharmaceutically acceptable “diluting agents (vehicles or carriers),” teaching that it is an appropriate vehicle or solvent for oral administration or injection of compounds. EX1017, 21-23 (“Diluting Agents”). Accordingly, Ortho Pharma 2006 discloses a pharmaceutical composition comprising a pharmaceutically acceptable carrier. EX1002, ¶¶257-62; EX1004, ¶¶160-62, 165.

...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.

Ortho Pharma’s pharmaceutical composition formulated vitamin A together with other vitamins (e.g., C, D, and E) and minerals (e.g., zinc). EX1002, ¶¶252-53; EX1008, ¶¶[0008] (a daily dose of active ingredients including 50-500 mg vitamin C, 0.1-2 mg vitamin A, 10-400 mg vitamin E, and 0.1-10 µg vitamin D₃, 2-30 mg zinc in a liquid dosage form), [0019] (larger doses), [0036] (larger doses), [0049] (active ingredients include vitamin A acetate, vitamin E, vitamin D, ascorbic acid, and zinc). Ortho Pharma teaches administering this formulation to individuals to treat or prevent eye diseases such as macular degeneration, including as a nutritional supplement. EX1008, ¶¶[0001]-[0003], [0008], [0010]-[0011], [0052]-[0054]; EX1002, ¶256.

Olson 1988 discloses making and purifying deuterated forms of vitamin A within the scope of claim 1. EX1002, ¶¶99, 103-06. In particular, Olson 1988

discloses making and purifying the claimed C₂₀-D₁₋₃-retinoids, including C₂₀-D₃-retinol and a C₂₀-D₃-retinol ester (e.g., C₂₀-D₃-retinol acetate). EX1006, Abstract; *id.*, 12 (Scheme 2 discloses synthesis routes for preferential formation of all-trans isomer of 20,20,20-trideuteroretinol (Scheme 2, R⁴-C²H₃) and 20,20,20-²H₃-retinyl acetate), 13 (scheme 2), 15-19 (“Synthesis of 20,20,20-trideuteroretinyl 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).

Accordingly, Olson 1988 discloses the claimed deuterated form of vitamin A.

EX1002, ¶¶263-267; EX1004, ¶164.

The combination of Ortho Pharma and Olson 1988 thus teaches all of the elements of claim 1 and renders the claim obvious as a whole. EX1002, ¶268; EX1004, ¶163.

ii. 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.

As discussed above, Ortho Pharma and Olson 1988 render claim 1 obvious.

As discussed above for claim 1, Olson 1988 discloses making and purifying the claimed C₂₀-D₃-retinol and a C₂₀-D₃-retinol ester (e.g., C₂₀-D₃-retinol acetate).

EX1006, Abstract; *id.*, 12-13, 14, 15-19. 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. Accordingly, each of claims 2 and 3 was obvious over Ortho Pharma and Olson 1988. EX1002, ¶¶269-71; EX1004, ¶172.

iii. Claim 4: Dosage Forms

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

As discussed above, Ortho Pharma and Olson 1988 render claim 1 obvious.

Ortho Pharma discloses a composition in a unit dosage form. For example, Ortho Pharma discloses daily doses of the liquid dosage form. EX1008, ¶¶[0008], [0019] (larger doses of vitamins and minerals), [0036] (larger doses of vitamins and minerals), [0056]-[0058] (larger doses of vitamins and minerals in solution in a drinking vial). Accordingly, Ortho Pharma and Olson 1988 together render claim 4 obvious as a whole. EX1002, ¶¶272-75; EX1004, ¶¶173-74.

iv. Claims 5-6, 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.

As discussed above, Ortho Pharma and Olson 1988 render claim 1 obvious.

As discussed above in Section VI.B.iv, the additional limitations of claims 5, 6, and 28 all encompass the property of the aldehyde of C₂₀-D₃-all-trans-retinol acetate of forming A2E about 7 times slower (claims 5 and 28) and inhibiting the formation of A2E (claim 6) as compared to the non-deuterium-enriched retinoid. In other words, claims 5-6 and 28 merely recite properties that naturally result from deuteration at C-20. EX1002, ¶112. Accordingly, each of claims 5, 6, and 28 was obvious over Ortho Pharma and Olson 1988. EX1002, ¶¶276-78; EX1004, ¶¶175-77.

v. 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**.

As discussed above, Ortho Pharma and Olson 1988 render claim 1 obvious.

Ortho Pharma discloses the composition also comprises one or more additives as required by claim 8, including the specific additives recited in claim 9. EX1008 (Ortho Pharma) at Abstract (**vitamin A** (0.1-2 mg), **vitamin E** (10-400 mg), **vitamin D₃** (0.1-10 µg), **zinc** (2-30 mg)), ¶¶[0008] (similar), [0019] (larger doses), [0036] (larger doses), [0049] (active ingredients include vitamin A acetate, vitamin E, vitamin D, and zinc). Accordingly, claims 8 and 9 were obvious over Ortho Pharma and Olson 1988. EX1002, ¶¶279-81; EX1004, ¶¶178-80.

vi. 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.

As discussed above, Ortho Pharma and Olson 1988 render claim 9 obvious.

Ortho Pharma discloses that the composition comprises 2-30 mg of zinc. EX1008, Abstract (2-30 mg zinc), ¶[0008] (2-30 mg zinc), [0019] (5-25 mg zinc). This range overlaps with the ranges of “between about 3 to about 80 mg” as in claim 10,

“between about 3 to about 10 mg” as in claim 11, and “between about 10 to about 80 mg” as in claim 12. Accordingly, claims 10-12 were obvious over Ortho Pharma and Olson 1988. EX1002, ¶¶282-85; EX1004 ¶¶181-82. *See UCB, Inc. v. Actavis Laboratories UT, Inc.*, 65 F.4th 679, 689-90 (Fed. Cir. 2023) (presumption of obviousness for range overlapping with prior art range).

vii. 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.

As discussed above, Ortho Pharma and Olson 1988 render claim 9 obvious. Ortho Pharma discloses the composition comprises 10-400 mg vitamin E.” EX1008, Abstract, ¶[0008]. This range overlaps with “between about 3 to about 3,000 mg” as in claim 13, “between about 3 to about 15 mg” as in claim 14, and “between about 15 to about 3,000 mg” as in claim 14, and “between about 15 to about 3,000 mg” as in claim 15. Accordingly, claims 13-15 were obvious over Ortho Pharma and Olson 1988. EX1002, ¶¶286-89; EX1004, ¶¶183-84. *See UCB*, 65 F.4th at 689-90 (overlapping ranges).

viii. 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.

As discussed above, Ortho Pharma and Olson 1988 render claim 9 obvious.

Ortho Pharma discloses the composition comprises 0.1-10 µg (0.0001-0.01 mg) vitamin D₃. EX1008, Abstract, ¶[0008]. This range overlaps with “between about 0.005 to about 0.1 mg” as in claim 16, and “between about 0.005 to about 0.015 mg” as in claim 17. Ortho Pharma also discloses the composition comprises 0.4-45 µg (0.0004-0.045 mg) vitamin D₃ EX1008, ¶[0036]. This range overlaps with “between about 0.015 to about 0.1 mg” as in claim 18. Accordingly, claims 16-18 were obvious over Ortho Pharma and Olson 1988. EX1002, ¶¶290-93; EX1004, ¶¶185-87; *see UCB*, 65 F.4th at 689-90 (overlapping ranges).

ix. 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.

As discussed above, Ortho Pharma and Olson 1988 render claim 1 obvious. Ortho Pharma discloses the composition comprises 0.1-2 mg of vitamin A. EX1008, Abstract, ¶[0008] (0.1 mg to 2 mg of vitamin A). This range overlaps with “about 0.1 to about 90 mg/day” as in claim 19. Accordingly, claim 19 was obvious over Ortho Pharma and Olson 1988. EX1002, ¶¶294-97; EX1004, ¶¶188-89; *see UCB*, 65 F.4th at 689-90 (overlapping ranges).

x. 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.

As discussed above, Ortho Pharma and Olson 1988 render claim 1 obvious. As discussed above in Sections VII.B.iv-vii, Ortho Pharma discloses the composition also comprises additional actives as required by claim 20, including

the specific antioxidants and minerals recited in claims 21-23. EX1008 (Ortho Pharma) at Abstract (**vitamin C** (50-500 mg), vitamin A (0.1-2 mg), **vitamin E** (10-400 mg), vitamin D₃ (0.1-10 µg), **zinc** (2-30 mg)), ¶¶[0008] (similar), [0019] (larger doses), [0036] (larger doses). Ortho Pharma discloses inclusion of each of these vitamins and minerals as an additional active. *See, e.g.*, EX1008, ¶¶[0043], [0049]. Ortho Pharma also discloses administration of zinc (II) chloride, beta-carotene and selenium-containing compounds as additional actives. EX1008, ¶¶[0043], [0049]. Ortho Pharma thus discloses an additional active within the scope of each of claims 20-23 (bold emphases). Accordingly, each of claims 20-23 was obvious over Ortho Pharma and Olson 1988. EX1002, ¶¶298-301; EX1004, ¶¶190-92.

i. Claims 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.

As discussed above, Ortho Pharma and Olson 1988 render claim 1 obvious. Ortho Pharma discloses the product contains “**carotenoids, preferably 12 mg lutein, and/or 840 µg zeaxanthin**, and/or 1 mg lycopene, and/or 2 mg beta-carotene” administered in combination with vitamin A. EX1008, ¶[0041]-[0042] (“carotenoids selected from the group comprising lutein, zeaxanthin, and lycopene”), ¶[0043] (“16 mg carotenoids, thereof preferably 12 mg of lutein,

and/or 840 µg of zeaxanthin”). Ortho Pharma thus discloses the carotenoids within the scope of claim 25. Accordingly, claim 25 was obvious over Ortho Pharma and Olson 1988. EX1002, ¶¶302-04; EX1004, ¶¶193-95.

i. Claims 27: Nutraceuticals

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

As discussed above, Ortho Pharma and Olson 1988 render claim 1 obvious. Ortho Pharma and Olson 1988 also render claim 27 obvious. As used in the ’432 patent, a nutraceutical is a nutrient substance or dietary supplement that is not necessarily FDA-approved to treat illness or disease but is suggested to have therapeutic or health benefits. EX1004, ¶196; EX1001, claim 27 (nutraceutical composition within scope of pharmaceutical composition). Ortho Pharma teaches administering its vitamin A composition to individuals to treat or prevent eye diseases such as macular degeneration, including as a nutritional supplement. EX1008, ¶¶[0001]-[0003], [0008], [0010]-[0011], [0052]-[0054]. This disclosure falls within the scope of claim 27. Accordingly, claim 27 was obvious over Ortho Pharma and Olson 1988. EX1002, ¶¶305-08; EX1004, ¶¶196-98.

C. Rational Underpinning

As discussed above, Olson 1988 discloses making and purifying C₂₀-D₁₋₃-vitamin A (retinol and retinol acetate). EX1006, Abstract; *id.*, 12-13, 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]. A POSA would have had a good reason to employ C₂₀-D₁₋₃-vitamin A (retinol and retinol acetate) in a pharmaceutical composition, such as disclosed in Ortho Pharma, in place of the non-deuterated forms of vitamin A. EX1002, ¶¶309-10.

As Dr. Guengerich explains, there was good reason to replace non-deuterated forms of vitamin A being used to treat or prevent macular degeneration, as in Ortho Pharma, with C₂₀-deuterated vitamin A. For example, Mata taught that deprotonation at C-20 of retinal was a pre-requisite for undesirable A2E formation. EX1010, 7154 & Abstract, 7157-7158, Fig. 5 & Caption. As Dr. Guengerich explains, a POSA 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. EX1002, ¶311; *see also* Section I.C.ii.3 above. A POSA thus had good reason to replace non-deuterated vitamin A being used to treat or prevent macular degeneration, as in Ortho Pharma, with Olson's C₂₀-D₁₋₃-retinol or retinol acetate to inhibit (slow) reactions that involve cleavage of a hydrogen from C-20 (e.g., A2E formation). EX1002, ¶311.

Indeed, Mata provides good reason to employ Olson's C₂₀-deuterated vitamin A to reduce lipofuscin formation and thereby treat or prevent macular degeneration. Mata discloses C₂₀ as a site of action for the synthetic pathway creating lipofuscin pigments associated with macular degeneration. EX1010, 7154 & Abstract, 7157-7158, Fig. 5 & Caption. Mata discloses that this synthetic pathway depends on removing a hydrogen atom from C₂₀ through a 1,5-sigmatropic shift. EX1010, 7158, FIG. 5. Mata expressly suggests inhibiting this synthetic pathway to reduce lipofuscin formation as a means for treating or preventing macular degeneration. EX1010, 7154 & Abstract, 7159. As Dr. Guengerich explains, a POSA 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 that step in the pathway would reduce A2E formation. EX1002, ¶312; EX1004, ¶168.

As Dr. Guengerich further explains, a POSA would have understood that deuterating C₂₀ would slow A2E formation because 1,5-sigmatropic shifts were known to be subject to strong primary deuterium KIEs. EX1002, ¶¶313, 94-117; EX1015 (Roth), 24-32; EX1016, 261-67 (left column) (12.2 times slower 1,5-sigmatropic shift upon deuteration). As Dr. Calman explains, a POSA would have had good reason to deuterate vitamin A at C-20 to reduce lipofuscin formation from vitamin A's essential role in the visual cycle, including when administering

vitamin A to treat macular degeneration. EX1004, ¶168; *see also supra* Section VI.C (treatment would be expected to avoid interference in visual cycle).

Accordingly, POSA 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. EX1002, ¶¶313-14; EX1004, ¶¶169-71.

D. Reasonable Expectation of Success

A POSA 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. EX1002, ¶¶315-16. This conclusion is supported by the fact that compositions formulating vitamin A (including deuterated forms of vitamin A) in a pharmaceutically acceptable carrier were known in the art, and the claimed C₂₀-deuterated vitamin A was disclosed in the prior art. Indeed, as discussed above, Olson 1988 discloses the claimed deuterated forms of vitamin A, and Ortho Pharma discloses oral dosage formulations for vitamin A. EX1008 (Ortho Pharma), Abstract, ¶¶[0008]. Ortho Pharma identifies water as a preferred solvent for the vitamins and minerals in the solution. EX1008, ¶¶[0038]-[0042], [0044], [0046]. 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,

¶¶[0050]-[0051]. Olson 1989 further supports reasonable expectation of success by teaching 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. EX1007, 714.

Furthermore, and as explained above under Ground 1, the reasonable expectation of success is not subject to reasonable dispute because the '432 patent admits that formulation of the claimed compounds was conventional and within the skill of the art. For example, the '432 patent admits that effective dosage forms, modes of administration, and dosage amounts may be determined “empirically” and that making such determination “is within the skill of the art.” EX1001, 14:31-34. The '432 patent states that the pharmaceutical composition may be administered by a variety of means, including orally by ingestion or locally to the eye. EX1001, 14:49-56. “Regardless of the route of administration selected,” the '432 patent admits that “the compounds of the present invention are formulated into pharmaceutically-acceptable dosage forms by conventional methods known to those of skill in the art” and that suitable and acceptable carriers “can be determined using ordinary skill in the art.” EX1001, 15:3-8, 15:32-36 (citing Remington’s). The '432 patent further admits that “[p]harmaceutically acceptable carriers are well known in the art” and include, *inter alia*, water, saline solution, or corn oil. EX1001, 15:9-27 (citing Remington’s). Accordingly, PO may not now

take a contradictory position that a POSA before 2007 would not have had a reasonable expectation of success for making what is claimed. EX1002, ¶¶317-19; EX1004, ¶¶166-67.

VIII. [GROUND 3] CLAIMS 7, 24, AND 26 ARE OBVIOUS OVER GROUND 2 IN FURTHER VIEW OF WIDDER.

A. Summary

Ground 3 incorporates Ground 2 (Section VII above) as a whole but adds the teachings of Widder (EX1009). As discussed above in Ground 2, Ortho Pharma discloses treating eye disorders, such as age-related macular degeneration, by administering a composition comprising vitamin A in a pharmaceutically-acceptable carrier. In Ground 2, Olson 1988 discloses C₂₀-deuterated vitamin A, which a POSA would have recognized would be a useful substitution for non-deuterated vitamin A that would reduce lipofuscin formation in patients with, or at risk of, ocular disorders including macular degeneration. EX1004, ¶200. Ground 3 builds upon Ground 2 with the addition of Widder. EX1002, ¶¶320-23.

Widder teaches combining vitamin A with fenretinide for the purpose of reducing lipofuscin formation to treat or prevent macular degeneration. EX1009 (Widder), 47:21-27. Widder teaches that fenretinide decreases the amount of A2E in the RPE 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; *see also id.*, EX1009 (Widder), Abstract, 1:17-28, 3:18-20, 14:34-

15:10, 15:14-32. 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. Accordingly, each of dependent claims 7, 24, and 26 was obvious over Ground 2 in further view of Widder, as illustrated below. EX1002, ¶¶324-29; EX1004, ¶201.

B. Detailed Analysis of the Obviousness of the Claims

As explained in detail below, claims 7, 24, and 26 of the '432 patent were obvious as a whole over Ground 2 in further view of Widder. EX1004, ¶¶41, 199, 202.

i. Claim 7: Supplements

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.

As discussed above in Ground 2, claim 1 was obvious over Ortho Pharma and Olson 1988. Claim 7 additionally recites the pharmaceutical composition further comprises an effective amount of a supplement selected from a group that includes fenretinide. Widder discloses a pharmaceutical composition comprising an effective amount of fenretinide co-administered with vitamin A. For example, 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 (Example 15); *see also id.*, 14:34-15:10 (“or in combination with other agents”), 40:3-5 (fenretinide effective amount); *id.*, 42:15-19, 43:17-23, 43:31-39, 44:3-11, 45:1-10, 45:35-46:7 (dosing). Accordingly, Ground 2 in further view of Widder renders claim 7 as a whole obvious. EX1002, ¶¶330-34; EX1004, ¶¶215-17.

As Dr. Calman explains, a POSA 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. EX1004, ¶¶215-18. As discussed above in Ground 2, 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. 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. EX1009 (Widder), Abstract, 1:17-28, 3:18-20, 14:34-15:10. Widder discloses that fenretinide decreases the amount of A2E in the RPE by lowering the amount of retinol delivered to the eye and also by lowering the steady state levels of all-trans retinal. EX1009 (Widder), 46:25-47:6; *see also id.*, 15:14-32. A POSA would have understood that replacing the vitamin A in Widder’s combination therapy 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. EX1004, ¶¶215-20; *see also* EX1002, ¶¶335-37.

A POSA 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. EX1002, ¶¶338-40. First of all, Widder already discloses making a combination therapy comprising vitamin A and fenretinide. EX1009 (Widder), 47:21-27 (Example 15). Second, Widder discloses that a diversity of conventional means were 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 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). Fourth, as discussed above in Ground 2, Ortho Pharma discloses that vitamin A also can be formulated in various excipients, including aqueous solutions. Consistent with the prior art, the challenged patent readily admits that formulating C₂₀-deuterated vitamin A was conventional and within the ordinary skill of the art in view of Remington. EX1001, 14:31-34, 14:49-56, 15:3-36. *See* Sections I.A, VI.D, and VII.D above. Accordingly, PO may not now take a contradictory position that a POSA before 2007 would not have had a reasonable expectation of success for making what is claimed.

ii. 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.

As discussed above in Ground 2, Ortho Pharma and Olson 1988 render claims 1 and 21 obvious. Claim 24 additionally recites the negatively-charged phospholipid is selected from a group that includes cardiolipin and phosphatidylglycerol. Widder discloses the pharmaceutical composition comprises cardiolipin and phosphatidylglycerol as additional actives within the scope of claims 21 and 24.

For example, Widder teaches that “[t]he use of certain negatively-charged phospholipids has also been shown to benefit patients with macular degenerations and dystrophies.” EX1009 (Widder), 33:1-7 (citing EX1020-EX1021). Widder specifically identified “cardiolipin and phosphatidylglycerol” as “[e]xamples of suitable negatively charged phospholipids that could be used in combination with” fenretinide for the treatment of macular degeneration. *Id.*; *see also id.*, 6:7-8. Accordingly, Ground 2 in further view of Widder renders claim 24 as a whole obvious. EX1002, ¶¶341-43; EX1004, ¶¶203-04.

As Dr. Calman explains, a POSA would have had good reason to include each or both of cardiolipin and phosphatidylglycerol as additional actives in the formulation, thereby satisfying each of claims 21 and 24, because Widder teaches

that these negatively charged phospholipids have been shown to benefit patients with macular degeneration. EX1004, ¶¶204-05. The Shaban references teach 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,” and that “[p]hosphatidylglycerol... readily inhibits apoptosis.” EX1020, Abstract; EX1021, Abstract. Accordingly, a POSA had good reason to include one or both of cardiolipin and phosphatidylglycerol as an additional active in the formulation to inhibit apoptosis caused by existing A2E even while inhibiting the formation of additional A2E by the use of the C₂₀-deuterated vitamin A. EX1004, ¶¶204-05; *see also* EX1002, ¶¶344-46.

A POSA 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. EX1002, ¶¶347-53. First of all, 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 (Example 15), 33:1-7, 6:7-8. Second, Widder discloses that a diversity 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 discussed

above in Ground 1, Olson 1989 discloses that vitamin A and deuterated vitamin A can be formulated in the same pharmaceutically-acceptable carriers (e.g., corn oil). Fourth, as discussed above in Ground 2, Ortho Pharma discloses that vitamin A also can be formulated in various excipients, including aqueous solutions. Consistent with the prior art, the challenged patent readily admits that formulating C₂₀-deuterated vitamin A was conventional and within the ordinary skill of the art in view of Remington. EX1001, 14:31-34, 14:49-56, 15:3-36. *See* Sections I.A, VI.D, and VII.D above. Accordingly, PO may not now take a contradictory position that a POSA before 2007 would not have had a reasonable expectation of success for making what is claimed.

i. Claim 26: Ocular Administration

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

As discussed above in Ground 2, claim 1 was obvious over Ortho Pharma and Olson 1988. Claim 26 additionally recites the pharmaceutical composition is suitable for administration directly to the eye. As used in the '432 patent, "suitable for administration directly to the eye" includes administration as "eye drops, ointment, or injection." EX1001, 9:55-58; EX1002, ¶254.

Widder discloses the additional limitation of claim 26. For example, Widder discloses that ophthalmic conditions including macular degeneration and Stargardt

disease can be treated by administering an active agent through a variety of routes of administration, specifically by ophthalmic delivery (“local delivery to the eye”), 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).

Widder specifically discloses a pharmaceutical composition for treating ophthalmic conditions comprising 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.

Accordingly, Ground 2 in further view of Widder renders claim 26 as a whole obvious. EX1002, ¶¶355-58; EX1004, ¶¶206-09.

As Dr. Calman explains, a POSA had good reason to make the pharmaceutical composition of Ground 2 suitable for administration directly to the eye. EX1004, ¶¶210-14. For example, a POSA would have recognized, as evidenced 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. EX1004, ¶¶210-14. 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 POSA 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. EX1004, ¶¶210-14. Moreover, 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. EX1004, ¶¶210-14. 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. EX1004, ¶¶210-14.

A POSA 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. EX1004, ¶¶210-14; EX1002, ¶¶359-61. 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. Remington teaches formulations for administering active ingredients directly to the eye. EX1017, 46-56 (ophthalmic preparations). Similar to Widder, the challenged patent readily admits 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, 14:31-34, 14:49-56, 15:3-36. *See* Sections I.A, VI.D. and VII.D above. Accordingly, PO may not now take a contradictory position that a POSA before 2007 would not have had a reasonable expectation of success for making what is claimed.

IX. MATERIAL DIFFERENCES FROM PROSECUTION AND MATERIAL ERROR WARRANT INSTITUTION

There were no prior art rejections during prosecution of the challenged patent. *See* Section I.B above; EX1032. None of Olson 1988, Olson 1989, Ortho Pharma, Widder, or Mata was ever asserted as a basis of rejection during prosecution of the challenged claims nor during prosecution of the parent application. *See* Section I.B above; EX1031-EX1032. Olson 1989, Ortho Pharma, and Mata were not even of record during prosecution.

The prior art and arguments presented herein are materially different than those applied during prosecution. The Examiner asserted no prior art against the

challenged claims. When evaluating the claims of the parent application, the Examiner exclusively pointed to references disclosing compounds that are *not* within the scope of the present claims. For example, Applicant noted that the Radu reference discloses isotretinoin, which is a different compound than those claimed, and the Boehm reference does not disclose deuterium substitution at C₂₀. EX1031, 171.

Applicant acknowledged that compounds that could slow the formation of vitamin A into lipofuscin “have been sought as treatments for diseases characterized by the accumulation of lipofuscin, and/or vitamin A dimers such as A2E,” but argued that the present application “discloses retinoids selectively substituted at the retinoid’s carbon number 20” and that the Examiner was mistaken in believing that the prior art disclosed “a C₂₀ deuterated retinoid.” EX1031, 156, 172-173. Here, Olson 1988 expressly discloses this exact C₂₀ substitution (compounds that are specifically claimed), which substitution was accomplished to use the compounds in biological studies (which entails the use of a pharmaceutically acceptable carrier as evidenced by Olson 1989). Ortho Pharma similarly teaches formulating forms of vitamin A in a pharmaceutically-acceptable carrier for administration to individuals with eye diseases including macular degeneration. Accordingly, each ground presents prior art that was not of record

(Olson 1989 or Ortho Pharma) or that was not asserted during prosecution (Olson 1988 or Widder) and which demonstrate the obviousness of the challenged claims.

Applicant also argued that Boehm provided no reason to make the C₂₀ substitution, asserting that Boehm “provides no reason to think that substituting deuterium at position 20 would reduce lipofuscin accumulation or lead to any other desirable result.” EX1004, ¶¶35-37; *see also id.*, 166 (“the claimed invention involves substitution at the C₂₀ position of retinoids”). But Mata explicitly discloses that A2E/lipofuscin is formed by removal of a hydrogen from the C₂₀ of vitamin A and expressly suggests pharmacologically inhibiting this synthesis pathway to provide an effective treatment for macular degeneration. *See* Section I.D.v above. As Dr. Guengerich explains, a POSA would have understood from Mata’s description of the synthetic pathway that this C₂₀-deprotonation was likely a rate-limiting step for which deuterium substitution would result in significantly slowing the formation of A2E. EX1002, ¶¶93, 180; EX1015 (Roth) 24-32; EX1016 (Itou) 111, 261-67 (left column) (12.2 times slower 1,5-sigmatropic shift upon deuteration). But Dr. Guengerich’s testimony, and the Mata, Roth, and Itou references that corroborate it, were not before the Examiner during prosecution. Accordingly, each ground of this petition presents materially different arguments for unpatentability than were evaluated during prosecution.

As a result of accepting Applicant's arguments during prosecution of the parent application, the Examiner erred by: (1) believing that the prior art failed to disclose the claimed C₂₀-deuterated vitamin A; and (2) believing that the prior art failed to provide reason to make the claimed C₂₀-deuterated vitamin A. Olson 1988 demonstrates that the prior art does, in fact, disclose the claimed compounds.

Olson 1988, Olson 1989, Ortho Pharma, Mata, Roth, and Itou and Dr.

Guengerich's testimony regarding the same demonstrate that the prior art provided good reason to formulate the claimed compounds in a pharmaceutically acceptable carrier (e.g., to perform biological studies and to slow lipofuscin formation to prevent or treat eye disorders, including macular degeneration). The Examiner's failure to identify and address the teachings of these references constitutes material error justifying institution. *See Advanced Bionics, LLC v. MED-EL*

Elektromedizinische Geräte GmbH, IPR2019-01469, Paper 6 at 8 (PTAB Feb. 13, 2020) (precedential) (recognized material error for failing to develop the record fully regarding salient prior art).

Because there are material differences between the art and arguments presented here and what was considered during prosecution, and because the challenged claims issued based on the material error of failing to consider the evidence discussed herein, including the Olson 1988, Olson 1989, Ortho Pharma, Mata, Roth, and Itou, institution should be granted.

X. NO UNEXPECTED RESULTS

The '432 patent discusses some *in vitro* and murine experiments, including several “massive dosing” experiments. The '432 patent asserts that administering C₂₀-fully deuterated all-trans-retinal 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, 18:9-59 (Examples 1-2). The '432 patent reports that administering C₂₀-fully deuterated all-trans-retinal 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, 18:60-19:57, 20:21-52 (Examples 3-4, and 6). 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, 19:58-20:20 (Example 5); EX1002, ¶¶362-65. But none of these experiments are legally probative of non-obviousness.

As explained above in Sections I.C.ii.2-3, VI.B.iv, VI.C, VII-B.iv, and VII.C, the deuterium kinetic isotope effect was well-known, such that C₂₀-deuterium substitution was reasonably expected to slow A2E and ATR-dimer formation as much as 5-10 times. EX1002, ¶¶366-70. The results are thus not unexpected, and certainly do not represent any difference in kind. *See Bristol-*

Myers Squibb Co. v. Teva Pharmaceuticals USA, Inc. (“BMS”), 752 F.3d 967, 977 (Fed. Cir. 2014).

Moreover, the asserted slowing of lipofuscin formation must be compared to the closest prior art. *BMS*, 752 F.3d at 978. Here, the prior art includes the claimed C₂₀-fully deuterated all-trans-retinol acetate (Olson 1988) and prior art teaching administration of vitamin A to animals including humans (Olson 1989, Ortho Pharma, Mata) in a pharmaceutically-acceptable carrier, such as oil or water. The patent attributes the results to the C₂₀-deuterium substitution, and even argues that reduced lipofuscin formation using the C₂₀-D₁- and C₂₀-D₂-retinoid is a predictable result based on the use of the C₂₀-D₃-retinoid. *See* Section VI.B.iv above; EX1001, 6:9-67 & Figs. 2-4, 8:13-17, 18:10-19:57; EX1031, 157 (“the person skilled in the art would understand that substituting the retinoids’ C₂₀ hydrogen atoms (1 or more hydrogens)...would also result in substituted C₂₀-retinoids that slow down vitamin A dimerization”), 160 (similar), 117 (similar). Because the closest prior art is the same deuterium substitution responsible for the asserted results, there can be no unexpected results probative of non-obviousness.

XI. CONCLUSION

For the reasons set forth above, claims 1-28 of the ’432 patent are unpatentable. Petitioners therefore request that inter partes review of these claims be instituted and that the claims be canceled.

Respectfully submitted,

Dated: December 19, 2023

/Jad. A. Mills/

Jad A. Mills, Lead Counsel

Reg. No. 63,344

XII. CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. §42.24(d), the undersigned certifies that this Petition complies with the type-volume limitation of 37 C.F.R. §42.24(a). The word count application of the word processing program used to prepare this Petition indicates that the Petition contains 13,862 words, excluding the parts of the brief exempted by 37 C.F.R. §42.24(a).

Respectfully submitted,

Dated: December 19, 2023

/Jad. A. Mills/
Jad A. Mills, Lead Counsel
Reg. No. 63,344

XIII. PAYMENT OF FEES UNDER 37 C.F.R. §§ 42.15(A) AND 42.103

The required fees are submitted herewith. If any additional fees are due at any time during this proceeding, the Office is authorized to charge such fees to Deposit Account No. 23-2415.

XIV. APPENDIX – LIST OF EXHIBITS

Exhibit No.	Description
1001	U.S. Patent No. 9,486,432 to Washington
1002	Declaration of Dr. F. Peter Guengerich, Ph.D.
1003	<i>Curriculum Vitae</i> of Dr. Guengerich.
1004	Declaration of Dr. Andrew Calman, M.D., Ph.D.
1005	<i>Curriculum Vitae</i> of Dr. Calman.
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”)
1023	First Declaration of Irinia Hinrichs
1024	Second Declaration of Irinia Hinrichs
1025	McCullough FS, Northrop-Clewes CA, Thurnham DI. The Effect of Vitamin A on Epithelial Integrity, <i>Proc Nutr Soc.</i> 58(2):289-93 (1999) (“McCullough”)
1026	J. A. Olson, The Biosynthesis and Metabolism of Carotenoids and Retinol (Vitamin A). <i>J. Lipid Res.</i> 5(3):281-99 (1964) (“Olson 1964”)
1027	Del Priore LV, Kuo YH, Tezel TH. Age-related Changes in Human RPE Cell Density and Apoptosis Proportion <i>in situ</i> , <i>Invest Ophthalmol Vis Sci.</i> 43(10):3312-8 (2002) (“Del Priore”)
1028	Wolf, G., A History of Vitamin A and Retinoids. <i>The FASEB Journal</i> , 10: 1102-1107 (1996) (“Wolf”)
1029	Sommer, A., Effects of Vitamin A Deficiency on the Ocular Surface, <i>Ophthalmology</i> 90(6):592-600 (1983) (“Sommer”)
1030	Radu, Roxana A. et al., Reductions in Serum Vitamin A Arrest Accumulation of Toxic Retinal Fluorophores: A Potential Therapy for Treatment of Lipofuscin-Based Retinal Diseases, <i>Invest. Ophthalmol. Vis. Sci.</i> 46(12):4393-4401 (2005) (“Radu 2005”)
1031	File History of U.S. Patent Application No. 12/733,631
1032	File History of U.s. Patent Application No. 14/510,975

1033	Sparrow JR, Fishkin N, Zhou J, Cai B, Jang YP, Krane S, Itagaki Y, Nakanishi K, A2E, a Byproduct of the Visual Cycle, <i>Vision Res.</i> 43(28):2983-90 (2003) (“Sparrow”)
1034	Wolf G., Lipofuscin and Macular Degeneration., <i>Nutr Rev.</i> 61(10):342-6 (2003) (“Wolf 2003”)
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”)
1036	Fishkin N, Jang YP, Itagaki Y, Sparrow JR, Nakanishi K. A2-Rhodopsin: A New Fluorophore Isolated from Photoreceptor Outer Segments. <i>Org Biomol Chem.</i> 1(7):1101-5. (2003) (“Fishkin 2003”)
1037	Law WC & Rando RR, The Molecular Basis of Retinoic Acid Induced Night Blindness, <i>Biochem Biophys Res Commun.</i> 161(2):825-9 (1989) (“Law”)
1038	Sieving PA, Chaudhry P, Kondo M, Provenzano M, Wu D, Carlson TJ, Bush RA, Thompson DA. Inhibition of the Visual Cycle in vivo by 13-cis Retinoic Acid Protects from Light Damage and Provides a Mechanism for Night Blindness in Isotretinoin Therapy, <i>Proc Natl Acad Sci USA.</i> (2001) (“Sieving”)
1039	Chopdar A, Chakravarthy U, Verma D, Age Related Macular Degeneration. <i>BMJ</i> (2003) (“Chopdar”)
1040	Berson EL, Rosner B, Sandberg MA, Hayes KC, Nicholson BW, Weigel-DiFranco C, Willett W. A Randomized Trial of Vitamin A and Vitamin E Supplementation for Retinitis Pigmentosa. <i>Arch Ophthalmol.</i> 111(6):761-72. (1993) (“Berson”)
1041	Jacobson SG, Cideciyan AV, Regunath G, Rodriguez FJ, Vandenberg K, Sheffield VC, Stone EM. Night Blindness in Sorsby’s Fundus Dystrophy Reversed by Vitamin A. <i>Nat Genet.</i> 11(1):27-32. (1995) (“Jacobson”)

1042	Alberts D et al., Safety and Efficacy of Dose-intensive Oral Vitamin A in Subjects with Sun-damaged Skin. <i>Clin Cancer Res.</i> (2004) (“Alberts”)
1043	Ross DA, Recommendations for Vitamin A Supplementation. <i>J Nutr.</i> 132(9 Suppl):2902S-2906S (2002) (“Ross”)
1044	Haskell MJ et al., Use of the Deuterated-retinol-dilution Technique to Assess Total-body Vitamin A Stores of Adult Volunteers Consuming Different Amounts of Vitamin A. <i>Am J Clin Nutr.</i> 70(5):874-80 (1999) (“Haskell”)
1045	Haskell MJ, et al., Assessment of Vitamin A Status by the Deuterated-retinol-dilution Technique and Comparison with Hepatic Vitamin A Concentration in Bangladeshi Surgical Patients, <i>Am J Clin Nutr.</i> 66(1):67-74 (1997) (“Haskell 1997”)
1046	Kushner DJ, Baker A, Dunstall TG, Pharmacological Uses and Perspectives of Heavy Water and Deuterated Compounds, <i>Can J Physiol Pharmacol.</i> 77(2):79-88 (1999) (“Kushner”)
1047	Blake MI, Crespi HL, Katz JJ, Studies with Deuterated Drugs, <i>J Pharm Sci.</i> 64(3):367-91 (1975) (“Blake”)
1048	McCarty LP, Malek RS, Larsen ER. The Effects of Deuteration on the Metabolism of Halogenated Anesthetics in the Rat, <i>Anesthesiology</i> 51(2):106-10 (1979) (“McCarty”)
1049	Bull E. What is Nutraceutical? <i>Pharm J.</i> 265:57-58 (2000) (“Bull”)
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”)

1053	Ribaya-Mercado et al., “Dietary vitamin A intakes of Filipino elders with adequate or low liver vitamin A concentrations as assessed by the deuterated-retinol-dilution method: implications for dietary requirements,” <i>The American Journal of Clinical Nutrition</i> , 79(4), 633-641 (“Ribaya-Mercado”)
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1055	Rosenfeld, P.J. et al. Ranibizumab for Neovascular Age-Related Macular Degeneration. 355 <i>New England Journal of Medicine</i> 1419-31 (October 5, 2006) (“Rosenfeld”)
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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a), this is to certify that I caused to be served a true and correct copy of the foregoing Petition for Inter Partes Review (and accompanying Exhibits 1001-1056 and 1058) by overnight courier (Federal Express or UPS) on this 19th day of December, 2023, on the Patent Owner at the correspondence address of the Patent Owner's Counsel as follows:

McCarter & English, LLP
265 Franklin St.
Boston, MA 02110

Respectfully submitted,

Dated: December 19, 2023

/Jad A. Mills/

Jad A. Mills, Lead Counsel
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