

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 IPR2024-00313
Patent RE47,045

Before ZHENYU YANG, TINA E. HULSE, and TAWEN CHANG,
Administrative Patent Judges.

CHANG, *Administrative Patent Judge.*

DECISION
Granting Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

Petitioner Gene Company Pty Ltd (“Petitioner”) filed a Petition for *inter partes* review of claims 1–54 of U.S. Patent No. RE47,045 (Ex. 1001, “the ’045 patent”). Paper 2 (“Pet.”). Patent Owner, the Trustees of Columbia University in the City of New York (“Patent Owner”), timely filed a Preliminary Response. Paper 9 (“Prelim. Resp.”). The parties further submitted an authorized Reply and Sur-Reply to the Preliminary Response. Paper 11 (“Reply”); Paper 12 (“Sur-Reply”); Ex. 3001.

For the reasons provided below, we determine Petitioner has satisfied the threshold requirement set forth in 35 U.S.C. § 314(a). Because Petitioner has demonstrated a reasonable likelihood that at least one claim of the ’045 patent is unpatentable, we institute an *inter partes* review of all challenged claims on each of the Grounds raised in the Petition. *See SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, 1359–60 (2018); *PGS Geophysical AS v. Iancu*, 891 F.3d 1354, 1360 (Fed. Cir. 2018) (interpreting the statute to require “a simple yes-or-no institution choice respecting a petition, embracing all challenges included in the petition”); *see also* Guidance on the Impact of SAS on AIA Trial Proceedings (April 26, 2018).¹

A. Real Parties-in-Interest

Petitioner identifies Gene Company Pty Ltd. as the real party-in-interest. Pet. 19. Patent Owner identifies “[t]he real parties-in-interest [as] The Trustees of Columbia University in the City of New York, the owner of

¹ Available at <https://www.uspto.gov/patents-application-process/patent-trial-and-appeal-board/trials/guidance-impact-sas-aia-trial> (“Guidance”).

[the '045 patent], and Alkeus Pharmaceuticals, Inc., the exclusive licensee of the '045 patent.” Paper 4, 2.

Patent Owner asserts in its Preliminary Response that the Petition should be denied because “it appears to have concealed the involvement of Lin BioScience and Belite Bio” and, thus, “does not meet the requirements of 35 U.S.C. § 312(a).” Prelim. Resp. 73; *see also* Sur-Reply 1. In its Reply, Petitioner Gene Company asserts that it named itself as the real party-in-interest in good faith and “requests Board authorization to identify Belite Bio and Lin Biosciences as potential real parties-in-interest to eliminate an unnecessary controversy.” Reply 5.

Under our precedent, where there is no time bar or estoppel implication with respect to alleged unnamed real parties-in-interest, the Board need not address, for the purposes of institution, whether such parties should be so named. *SharkNinja Operating LLC v. iRobot Corp.*, IPR2020-00734, Paper 11, 18–20 (PTAB Oct. 6, 2020) (precedential) (“*SharkNinja*”). In this case, Patent Owner has not alleged that either Lin BioScience or Belite Bio is barred or estopped from this proceeding.

Patent Owner suggests that “Belite Bio’s status as a publicly traded company with a vested interest in the outcome of this Petition, and the Petition’s failure to disclose Belite Bio as a [real party-in-interest,] raise concerns about its motivations.” Prelim. Resp. 75. However, Patent Owner has not pointed to any evidence tending to show beyond speculation that Petitioner purposefully omitted these parties to gain an unfair advantage. *SharkNinja* at 19. Accordingly, on this record, we will not consider whether Lin BioScience and Belite Bio must be named as real parties-in-interest and

do not grant Petitioner's request for authorization to identify Lin BioScience and Belite Bio as "potential" real parties-in-interest.

We emphasize, however, that the requirement that a petition identify all real parties-in-interest serves important notice functions both to "patent owners, to identify whether the petitioner is barred from bringing an IPR due to [a real party-in-interest] that is time-barred or otherwise estopped, and to the Board, to identify conflicts of interests that are not readily apparent from the identity of the petitioner." *SharkNinja* at 17. If and when Petitioner determines in good faith that Lin BioScience and Belite Bio, or any other parties, should be identified as real parties-in-interest under Section 312(a)(2), Petitioner may renew its request for authorization to add them at that time.

B. Related Proceedings

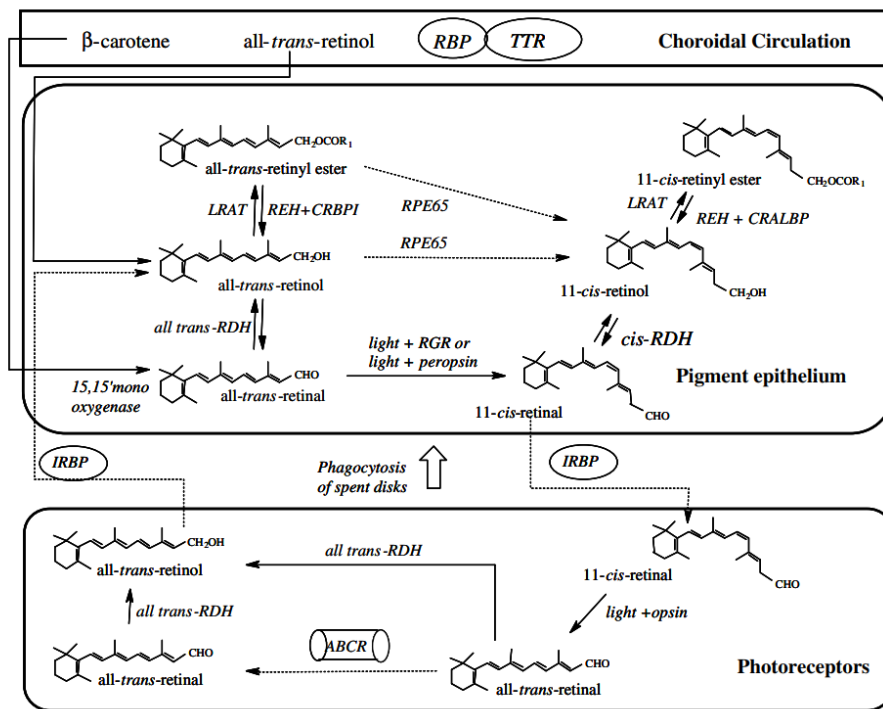
Petitioner states that "[a] petition was filed in IPR2024-00312 against U.S. Patent No. 9,486,432, which is a continuation" of U.S. Patent No. 8,877,809 B2 (the '809 patent), of which RE47,045 is a reissue. Pet. 19. Patent Owner similarly identifies IPR2023-00312 as a related matter and states that it is "unaware of any other judicial or administrative proceeding involving the '045 patent." Paper 4, 2.

The parties do not identify any other patent or application claiming, or that may claim, the benefit of the priority of the filing date of the '045 patent or Application Serial No. 15/343,016 ("the '016 application). Pet. 19–20; Paper 4, 2–3; Paper 6; 0–2; Paper 8, 1–3.

C. The '045 Patent and Relevant Background

1. Visual Cycle

“The phototransduction process in the eye relies on the light-induced isomerization of the chromophore, 11-*cis*-retinal (or derivative), to all-*trans*-isomer,” and “[t]he regeneration of pre-illumination conditions requires reformation of 11-*cis*-retinoids.” Ex. 1050, 2959, left col. In vertebrates, the “enzymatic, light-independent mechanism of chromophore regeneration” is “an endothermic process termed the ‘visual cycle’ or the retinoid cycle.” *Id.* The figure below, reproduced from Kuksa,² illustrates the steps in the visual cycle.



² Kuksa et al., Retinoid Cycle in the Vertebrate Retina: Experimental Approaches and Mechanisms of Isomerization, 43 VISION RES. 2959 (2003) (Ex. 1050, “Kuksa”).

The above figure is a “[s]chematic representation of the visual cycle in rod-dominant animals, based on genetic and biochemical evidence.” *Id.* at 2960, Fig. 1.³

2. Macular Dystrophies

“The macula is located at the back of the eye in the center of the retina. When the millions of cells in this light-sensitive, multilayer tissue deteriorate, central vision is lost.” Ex. 1001, 1:43–45. “This ‘macular degeneration’ principally affects the elderly,” but also may be found in younger populations in individuals with certain genetic disorders, such as Stargardt disease. *Id.* at 1:47–55.

Macular dystrophies are marked by the accumulation, in the retinal pigment epithelium (RPE), of lipofuscin, which are fluorescent deposits that contain the compounds N-retinylidene-N-retinylethanolamine (A2E) and all-trans-retinal dimer (ATR dimer), among others. Ex. 1001, 1:65–2:3. The ’045 patent states that A2E and ATR dimer are derived from reactions of all-trans-retinal — discussed above as part of the visual cycle — and “increasing the amount of all-trans-retinal in outer segments, such as occurs with the mutations in *abcr*—/— (responsible for recessive Stargardt disease),

³ The abbreviations used in the figure include: “ABCR, a photoreceptor-specific, ATP-binding cassette transporter; CRALBP, cellular retinaldehyde-binding protein; CRBP1, cellular retinol-binding protein 1; IRBP, interphotoreceptor retinoid-binding protein; LRAT, lecithin:retinol acyltransferase; RGR, RPE G protein-coupled receptor; RPE65, retinal pigment epithelial (cells) 65 kDa protein; RBP, retinol-binding protein; RDH, retinol dehydrogenase; REH, retinyl ester hydrolase, TTR, transthyretin.” Ex. 1050, 2960, Fig. 1 caption.

leads to the rapid accumulation of lipofuscin pigments.”⁴ *Id.* at 2:1–5, 2:13–17.

The '045 patent states that “A2E and the ATR-dimer are believed to be formed in vivo by a multi-step reaction sequence involving two molecules of all-trans-retinal,” as shown in its Figure 2 reproduced below. Ex. 1001, 7:60–63.

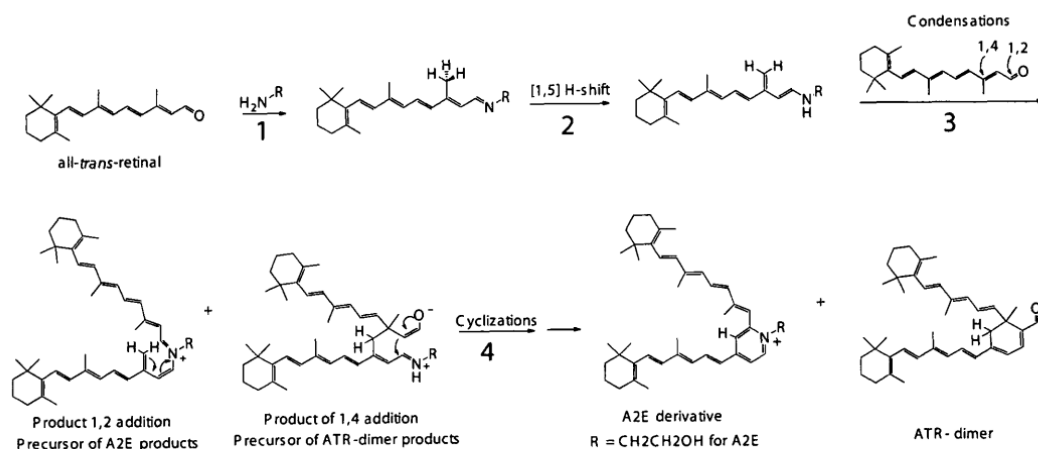


FIG 2.

The figure above sets forth “a reaction scheme showing the biosynthesis of A2E and ATR-dimer from all-trans-retinal and a biological amine.” *Id.* at 6:21–23. The '045 patent states, with respect to A2E and ATR-dimer, that

⁴ The ABCR (or the ABCA4) gene encodes “a photoreceptor-specific adenosine triphosphate (ATP)-binding cassette transporter,” which is needed in the visual cycle to “properly shuttle vitamin A (in the form of retinal) in the eye.” Ex. 1001, 2:26–30; Ex. 1050, 2960, Fig. 1. “ABCR^{-/-} mice accumulate large lipofuscin deposits in RPE cells of their eyes . . . and eventually experience delayed dark adaption.” Ex. 1001, 2:32–35. Such mice have been “used to test approaches to limit RPE lipofuscin formation.” *Id.* at 2:25–26.

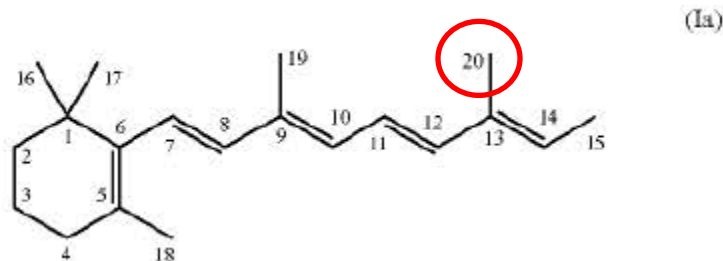
“[t]hese toxic retinal dimers have been shown to cause RPE cell death, which is thought to lead to photoreceptor cell degeneration and vision loss.” *Id.* at 2:5–8.

3. Claimed Invention

The '045 patent states that slowing the visual cycle, for instance by limiting dietary intake of vitamin A (retinol) and thereby retarding its delivery to RPE, “have been shown to impede or abolish RPE lipofuscin formation in animal models.” Ex. 1001, 2:8–17. The '045 patent states, however, that “[t]here are . . . disadvantages to slowing the visual cycle as a means to impede lipofuscin in order to prevent, e.g., macular degeneration.” *Id.* at 3:34–36. These disadvantages include “delayed dark adaptation and poor vision in dim light or at night”; “photoreceptor cell death and loss of vision” in the case of “long-term slowing of the visual cycle”; toxicities and potentially “significant adverse side effects” where vitamin A analogs are used to slow the visual cycle; and the likely need for “relatively large doses” of candidate drugs and concomitant increase in side effects. *Id.* at 3:38–5:18.

The '045 patent discloses using C₂₀-D₁₋₃-retinoid to retard formation of a lipofuscin pigment in the retina and to treat or ameliorate ophthalmologic disorders such as macular degeneration. *See, e.g.*, Ex. 1001, 8:29–32, 8:41–52, 9:3–13. In a C₂₀-D₁₋₃-retinoid, one, two, or three of the hydrogens attached to C₂₀ are replaced with deuterium, an isotope of hydrogen. *Id.* at 8:29–34. Formula Ia, reproduced below from the '045 patent, sets forth the scheme for numbering carbons in a retinoid for purposes of the invention. For clarity, we have circled C₂₀ in red in the

formula.



The above figure depicts a chemical formula setting forth the number scheme for carbons in retinoids, with C₂₀ circled in red. *Id.* at 10:17–34 (annotation in red added).

The '045 patent states that,

[w]hen 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). This kinetic isotope effect will slow A2E and ATR-dimer formation in vivo. Deuterated vitamin A is widely used in humans and shows no toxicity (45, 46). Thus, a treatment using a C₂₀-D₁₋₃-retinoid should be an effective and non-toxic therapy to treat or ameliorate macular degeneration without adverse visual effects.

Ex. 1001, 8:31–40.

D. Relevant Prosecution History

The '045 patent issued from the '016 application. Ex. 1001, code (21). The '045 patent is a reissue of the '809 patent, which issued from Application Serial No. 12/733,631 (“the '631 application”), which was originally filed on September 12, 2008 as PCT application US2008/010676 and which claims priority to provisional application No. 60/993,379, filed on September 12, 2007. *Id.* at codes (60), (64).

1. Application 12/733,631

a) *Restriction Requirement, Response, and Claim Amendments*

In the prosecution leading to the issuance of the '809 patent, the Examiner issued a Restriction Requirement requiring election between claims drawn to seven different groups, including, among others, “a method of treating or ameliorating the effects of a disease characterized by an accumulation of a lipofuscin pigment in a retina comprising administering to a patient C20-retinoid” (Group II) and “a composition of Formula I” (Group VI). Ex. 1031, 302.

In response, Applicant cancelled all originally filed claims in favor of new claims 50–114, electing for prosecution of claims 61–107, which it asserted were directed to the method of Group II. Ex. 1031, 286–290. Applicant noted that “[a]ll new claims now require a pharmaceutical composition comprising a substituted C₂₀-D₁₋₃-retinoid and a pharmaceutically acceptable carrier” and traversed the restriction as follows:

Applicant asserts that there is a special technical feature present in all of the claims, as amended, that distinguishes over the prior art. Specifically, all of the claims require a pharmaceutical composition comprising a substituted C₂₀-D₁₋₃-retinoid and a pharmaceutically acceptable carrier; and this feature distinguishes the claimed subject matter over the prior art and is therefore a special technical feature. No prior art of record has been identified to the contrary. Unless the Examiner can identify prior art which disclose or render obvious this pharmaceutical composition, unity of invention exists and

the restriction requirement is improper. Withdrawal is requested of the restrictions between groups I through VII.

Id. at 286, 291.

b) June 14, 2013 Non-Final Office Action

In an Office Action dated June 14, 2013, the Examiner rejected the claims as obvious over Radu,⁵ Boehm,⁶ Lang,⁷ and Widder 2007.⁸ Ex. 1031, 240. The Examiner found that “Radu teaches the use of isotretinoin, a C20-retinoid[,] for inhibition of lipofuscin pigment in a retina,” identifies the lipofuscin pigment as A2E, and “suggests that the treatment with isotretinoin may inhibit lipofuscin accumulation and thus delay the onset of visual loss in Stargardt’s patient.” *Id.*

The Examiner acknowledged that “Radu differs from the claimed invention in using substituted C20-D1-3 and the use of the secondary components” recited in various dependent claims. Ex. 1031, 240. However, the Examiner found that Boehm discloses a substituted C₂₀ retinoid and further teaches the use of deuterium labels. *Id.* The Examiner also found that Lang teaches “a composition for retarding the formation of a lipofuscin pigment in the retina comprising retinoid and a pharmaceutically acceptable carrier,” which can further include secondary components such as vitamins,

⁵ Radu et al., *Treatment with Isotretinoin Inhibits Lipofuscin Accumulation in a Mouse Model of Recessive Stargardt’s Macular Degeneration*, 100 PROC. NAT’L ACAD. SCIS. 4742 (2003) (Ex. 1035, “Radu”).

⁶ Boehm, WO 95/04018, published Feb. 9, 1995 (Ex. 1052, “Boehm”).

⁷ Lang, WO 2005/065669, published July 21, 2005 (Ex. 2004, “Lang”).

⁸ Widder et al, US 2007/0015827 A1, published Jan. 18, 2007 (Ex. 2005, “Widder 2007”).

minerals, antioxidants, and carotenoids. *Id.* at 241. Finally, the Examiner cited Widder 2007 for teaching “the use of phospholipids in combination with retinoid for the treatment of ophthalmic conditions, such as Stargardt’s disease.” *Id.*

The Examiner determined that

[i]t would have been obvious to a person skilled in the art to use the labeled retinoid instead of retinoid for the inhibition of lipofuscin and treat a disease, such as [S]targardt’s characterized by lipofuscin accumulation and to improve efficacy of treatment, motivated by Boehm, which teaches the advantage of radio labeled retinoid in bind[ing] to the retinoid receptors.

Ex. 1031, 240–41. The Examiner similarly determined that “[i]t would have been obvious to a person skilled in the art to add the secondary components to the composition of Radu and Boehm, motivated by the teachings of Lang and Widder [2007], which teach the addition of such agents to retinoid as old and well known.” *Id.* The Examiner noted that “Applicant has presented no evidence to establish the unexpected or unobvious nature of the claimed invention.” *Id.*

c) September 16, 2013 Response to Office Action

In response, Applicant amended the claims “to specifically exclude isotretinoin, the pharmacological active agent tested by Radu.” Ex. 1031, 167. Applicant further emphasized that isotretinoin inhibits formation of A2E dimers and lipofuscin by inhibiting an enzyme so as to slow the visual cycle, whereas the claimed C₂₀-deuterated retinoids “replace vitamin A with a C₂₀-deuterated vitamin A, which in itself would dimerize in the eye more slowly than non-deuterated vitamin A, because deuterium atoms are lost

more slowly from the C₂₀ position than protium during vitamin A dimerization.” *Id.* at 167–168. Applicant contended that, accordingly, the claimed C₂₀-deuterated retinoids have “unexpected advantages” over isotretinoin, because they “should have no effect on the retinoid pathway and are therefore not expected to reduce night vision nor to have the other side effects associated with isotretinoin.” *Id.* at 171.

Turning to Boehm, Applicant contended that, while “Boehm discloses a labeled retinoid, the labeling is not at the C₂₀ position but at the C₁₁ position, and such labeled retinoids do not fall into the claimed genus.” Ex. 1031, 168. Applicant contended that “tritium or deuterium in any position other than C₂₀ would not be expected to have any effect on A2E or lipofuscin formation,” because “carbon-hydrogen breakage would occur only at the C₂₀ position for the chemical synthesis of A2E.” *Id.* at 169. Applicant further contended that Boehm is “directed to using [labeled] retinoids as tools to better understand cellular retinoid receptors and for metabolic studies,” and “provides no motivation to modify Radu’s isotretinoin by substituting deuterium at position 20.” *Id.* at 170.

Finally, Applicant contended “Radu and Boehm are directed to very different problems — Radu to treating visual system diseases by slowing the visual cycle, Boehm to understanding cellular retinoid receptors and to metabolic studies — and thus would not be combined.” Ex. 1031, 171.

Applicant contended that Lang and Widder 2007 do not

overcome the combined deficiencies of Radu because neither reference teaches how to reduce formation of A2E lipofuscin dimers with deuterium incorporation into the C₂₀ position of retinoids, how to reduce formation of A2E

dimers without inhibiting the retinoid pathway in the eye and the retinal pigment epithelial nor how to treat ophthalmic condition associated with increased A2E dimer or lipofuscin formation without causing the side effects that are associated with isotretinoin.

Id. at 172.

Finally, Applicant once again requested withdrawal of the restriction requirement and examination of both method and pharmaceutical composition claims, stating that, for the reasons discussed in response to the obviousness rejection,

although WO95/04018 (Boehm) discloses deuterated retinoids, Boehm does not disclose retinoids ***substituted with deuterium at the C20 position***. Moreover, . . . a pharmaceutical composition comprising a C20 deuterium enriched retinoid and a pharmaceutically acceptable carrier or diluent is novel and non-obvious, not only in view of WO95/04018, but also in view of the combination of WO95/04018, Radu, Lang and Widder [2007].

Ex. 1031, 172–173.

d) Final Office Action, Amendment after Final, and Allowance

The Examiner withdrew the obviousness rejection in the Final Action without substantive comment. However, the Examiner maintained the rejections under 35 U.S.C. § 112.

The Examiner first asserted that Applicant failed to provide enabling disclosure for the claims because, although Applicant excluded the retinoids relied on for the prior art rejection from the claims and alleged such retinoids had adverse effects on the retina, Applicant failed to show lack of such

adverse effects for “the broadly claimed substituted C₂₀-D₁₋₃-retinoids.”
Ex. 1031, 142.

The Examiner further determined that the claims lacked adequate written description, because they are “directed to ‘[a] method of retarding the accumulation of a lipofuscin pigment in a retina’ using a ‘substituted C₂₀-D₁₋₃ retinoid’ and a pharmaceutically acceptable carrier,” but “[s]tructural identifying characteristics of group of substituted C₂₀-D₁₋₃ retinoid are not disclosed.” Ex. 1031, 143. The Examiner asserted that Applicant had “failed to establish the correlation between being a substituted C₂₀-D₁₋₃ retinoid and retarding accumulation of lipofuscin pigment in the retina.” *Id.*

In response, Applicant limited the claims to four retinoids, i.e., C₂₀-D₁₋₃-retinol, C₂₀-D₁₋₃-retinol ester, C₂₀-D₁₋₃-retinal, and C₂₀-D₁₋₃-pro-vitamin A carotenoids, which all “belong to the class of ‘vitamin A compounds’ and are known to transform into ‘C₂₀-D₁₋₃-retinal’ in the eye and body.”

Ex. 1031, 116. Applicant stated:

Because it is well accepted in the art that replacement of hydrogen with its isotope deuterium will not generally affect the ability of the substituted compounds to interact with proteins, persons of ordinary skill in the art 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. Further, based on the theory of kinetic isotope effect, one of ordinary skill in the art would also understand that it is not necessary to substitute with 3 deuterium atoms and that substituting just one or two hydrogens with deuterium would suffice to slow down dimerization, albeit potentially to a lower extent. As such, the subject application is enabling for the use of C₂₀-D₁₋₃-

vitamin A to inhibit A2E lipofuscin formation in the eye. Because the specifically defined deuterium-substituted retinoids, C₂₀-D₁₋₃-retinal, C₂₀-D₁₋₃-retinol ester, and C₂₀-D₁₋₃-pro-vitamin A carotenoids are all converted into C₂₀-D₁₋₃-retinal in the body, the full scope of amended Claim 61 is enabled.

Ex. 1031, 117. Applicant similarly asserted that “there is a structure/function relationship between these four [claimed] retinoids,” and the claims therefore satisfy the written description requirement. *Id.* at 117–118.

The Examiner subsequently allowed the claims to issue, with a minor Examiner’s amendment and without substantive comment. Ex. 1031, 36, 42, 46, 48.

2. Application 15/343,016

In the broadening reissue application, Applicant added claims 28–54. Ex. 1057, 211.

The Examiner rejected claims 9 and 44 as being of improper dependent form, and claim 48 as indefinite. Ex. 1057, 152–153. The Examiner provisionally rejected claims 1–54 on the ground of non-statutory double patenting as being unpatentable over a claim of co-pending U.S. Application No. 15/344,102 (“the ’102 application”), or a claim of the ’102 application in view of WO 2007/037188 and/or US 2008/0254140 A1. *Id.* at 153–164.

The Examiner stated, however, that “[t]he claims are free of the prior art. The prior art does not teach or suggest using the substituted C₂₀-D_{1,3}-retinoids as claimed for treating macular degeneration or for retarding the

accumulation of a lipofuscin pigment in a retina.” Ex. 1057, 164. The Examiner pointed to Kaufman⁹ as showing “the possible effectiveness of [the claimed] compounds in slowing lipofuscin deposition and the progression of common degenerative eye diseases.” *Id.*

Applicant amended the claims as detailed in Applicant’s Amendment in Response to Non-Final Office Action under 37 C.F.R. § 1.111 (Nov. 15, 2017). Ex. 1057, 131–140. Applicant stated that the ’102 application had been expressly abandoned and further noted that the claims of U.S. Application No. 15/785,423 (’423 application),¹⁰ a divisional of the ’102 application, “fall fully within the scope of the claims in Group VI of [the] restriction requirement” issued in the ’631 application, and “are therefore protected from obviousness-type double patenting rejections” in view of the claims of the ’016 application. *Id.* at 140.

The Examiner subsequently allowed the claims to issue without further substantive comment. Ex. 1057, 11, 32, 36.

⁹ Kaufman, *Deuterium Enrichment of Vitamin A at the C20 Position Slows the Formation of Detrimental Vitamin A Dimers in Wild-type Rodents*, 286 J. BIOLOGICAL CHEMISTRY 7958 (Ex. 2006, “Kaufman”).

¹⁰ The ’423 application issued as U.S. Patent No. 9,486,432 (’432 patent), which is the patent at issue in related IPR2024-00312. During the prosecution of the ’423 application, the claims were subject to a non-statutory obviousness type double patenting rejection over the claims of the ’809 patent, which was withdrawn after Applicant filed a terminal disclaimer. Ex. 1032, 40–42, 60. The Examiner made various other rejections with respect to the claims before allowing the claims, but no prior art rejections were made.

E. Overview of Challenged Claims

Claims 1, 28, and 29 are challenged independent claims. Independent claim 1 recites:

1. A method of retarding the accumulation of a lipofuscin pigment in a retina, comprising administering an effective amount of a pharmaceutical composition to a patient in need thereof, wherein the pharmaceutical composition comprises 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 C₂₀-D₁₋₃-pro-vitamin A carotenoids, and a pharmaceutically acceptable carrier.

Claim 28 recites a method of treating a macular degeneration, comprising administering an effective amount of the substituted C₂₀-D₁₋₃-retinoid recited in claim 1 to a patient in need thereof. Claim 29 recites a method of treating a macular degeneration, comprising administering an effective amount of the pharmaceutical composition recited in claim 1 to a patient in need thereof.

Among the challenged dependent claims, claims 2–27 and 30–54 depend directly or indirectly from claim 1 and 29, respectively.

Claims 4, 5, 10, 11, 16, 18, 32, 37, 38, 43, and 45, and their dependent claims, further limit the patient to those in need of treatment for particular condition or conditions: “a macular degeneration” (claim 4), “age-related macular degeneration” (claims 5, 32), “dry (non-neovascular) age-related macular degeneration” (claims 10, 37), “Stargardt disease” (claims 11, 38), “a macular degeneration selected from the group consisting of Vitelliform or Best disease, Sorsby’s fundus dystrophy, retinitis pigmentosa, and Malattia Leventinese” (claims 16, 17, 43, 44), or “macular degeneration characterized by one or more mutation(s) in the ABCA4 gene” (claims 18, 45).

Claims 2, 6–8, 12–14, 17, 30, 33–35, 39–41, and 44, and their dependent claims, are further limited to particular recited C₂₀-D₁₋₃-retinoid(s): C₂₀-D₃-retinoid (claims 2, 30); C₂₀-D₁₋₃-retinol or C₂₀-D₁₋₃-retinol ester (claims 6, 12, 33, 39); C₂₀-D₃-retinol, C₂₀-D₃-retinol ester, C₂₀-D₃-retinal, or a C₂₀-D₃-pro-vitamin A carotenoid (claims 7, 13, 34, 40); or C₂₀-D₃-retinol acetate (claims 8, 14, 17, 35, 41, 44).

Finally, claims 20–25 and 47–52 further comprise administering additional recited active(s); claims 3 and 31 further recite that “the pharmaceutical composition is suitable for use as a nutraceutical composition”; claims 9, 15, 26, 36, 42, and 53 further recite that “the C₂₀-D₁₋₃-retinoid forms A2E about 7 times slower than non-deuterium enriched retinoid”; and claims 19, 27, 46, and 54 further recite limitations regarding dosage amounts and route of administration.

F. Asserted Grounds of Unpatentability

Petitioner asserts the following grounds of unpatentability (Pet. 20–21):

Ground	Claim(s) Challenged	35 U.S.C § ¹¹	Reference(s)/Basis
1	1–9, 19–23, 25, 26, 28–36, 46–50, 52, 53	103	Ortho Pharma, ¹² Bergen ¹³
2	10–15, 18, 37–42, 45	103	Ortho Pharma, Bergen, Mata ¹⁴
3	16, 17, 24, 27, 43, 44, 51, 54	103	Ortho Pharma, Bergen, Mata, Widder ¹⁵

Petitioner further relies, *inter alia*, on the declarations of F. Peter Guengerich, Ph.D. (Ex. 1002) and Dr. Andrew Calman, M.D., Ph.D. (Ex.

¹¹ The Leahy-Smith America Invents Act (“AIA”), Pub. L. No. 112-29, 125 Stat. 284, 287–88 (2011), amended 35 U.S.C. § 103, effective March 16, 2013. Because the ’045 patent has an effective filing date before March 16, 2013, the pre-AIA version of § 103 applies. Our decision, however, would be the same under either version.

¹² DE 20 2006 014 588 U1, filed September 20, 2006 and published January 18, 2007 (English translation) (Ex. 1008, “Ortho Pharma”).

¹³ Bergen et al., *Synthesis of Tri-, Tetra-, and Penta-deuterated Forms of Vitamin A*, 25 J. LABELLED COMPOUNDS AND RADIOPHARMS. 11 (1988) (Ex. 1006, “Bergen”). We note that Petitioner, and on occasion Patent Owner, refers to Ex. 1006 as “Olson 1988.” We refer to Ex. 1006 as “Bergen,” according to the Board’s convention of using the first author’s last name to denote a reference. The parties should follow the Board’s convention in their future papers.

¹⁴ Mata et al., *Biosynthesis of a major lipofuscin fluorophore in mice and humans with ABCR-mediated retinal and macular degeneration*, 97 PNAS 7154 (2000) (Ex. 1010, “Mata”).

¹⁵ Widder et al., WO 2006/007314 A1, published Jan. 19, 2006 (Ex. 1009, “Widder”).

1004). Patent Owner similarly relies on the declaration of Johnathan L. Sessler, Ph.D. (Ex. 2036).

G. Overview of Asserted References

1. Overview of Ortho Pharma (Exhibit 1008)

Ortho Pharma is a certified translation of a German Patent Publication for a “[c]arotenoid-containing product.” Ex. 1008, code (54); Ex. 1023. Ortho Pharma teaches that age-related eye disease, such as age-related macular degeneration, “can be aggravated . . . by an incorrect diet or an inadequate supply of the necessary vitamins and nutrients.” Ex. 1008 ¶¶ 2–3.

Ortho Pharma teaches “a carotenoid-containing product that is particularly suitable for balanced nutritive supplementation of the diet in age-related eye diseases such as age-related macular degeneration or senile cataract.” Ex. 1008 ¶ 1; *see also id.* ¶¶ 11, 25 (teaching that “[p]roviding the eye with carotenoids may particularly help to provide nutritive support for the eye in age-related macular degeneration or senile cataracts”), 52 (stating “[t]he carotenoid-containing product can be used for dietary treatment of age-related eye diseases” such as age-related macular degeneration or senile cataract), 54.

Ortho Pharma teaches embodiments comprising particular amounts of vitamins A, B₁, B₂, B₆, B₁₂, C, D₃, and E; nicotinamide; folic acid; biotin; pantothenic acid; trace elements including zinc, selenium, and chromium; sulfur-containing amino acids including L-cystine, N-acetylcysteine, and taurine; omega-3 fatty acids; and secondary plant compounds including carotenoids and flavonoids. Ex. 1008 ¶ 19; *see also id.* ¶¶ 8, 9, 24, 36, 41–

44, 46, 47, 49.

2. Overview of Bergen (Exhibit 1006)

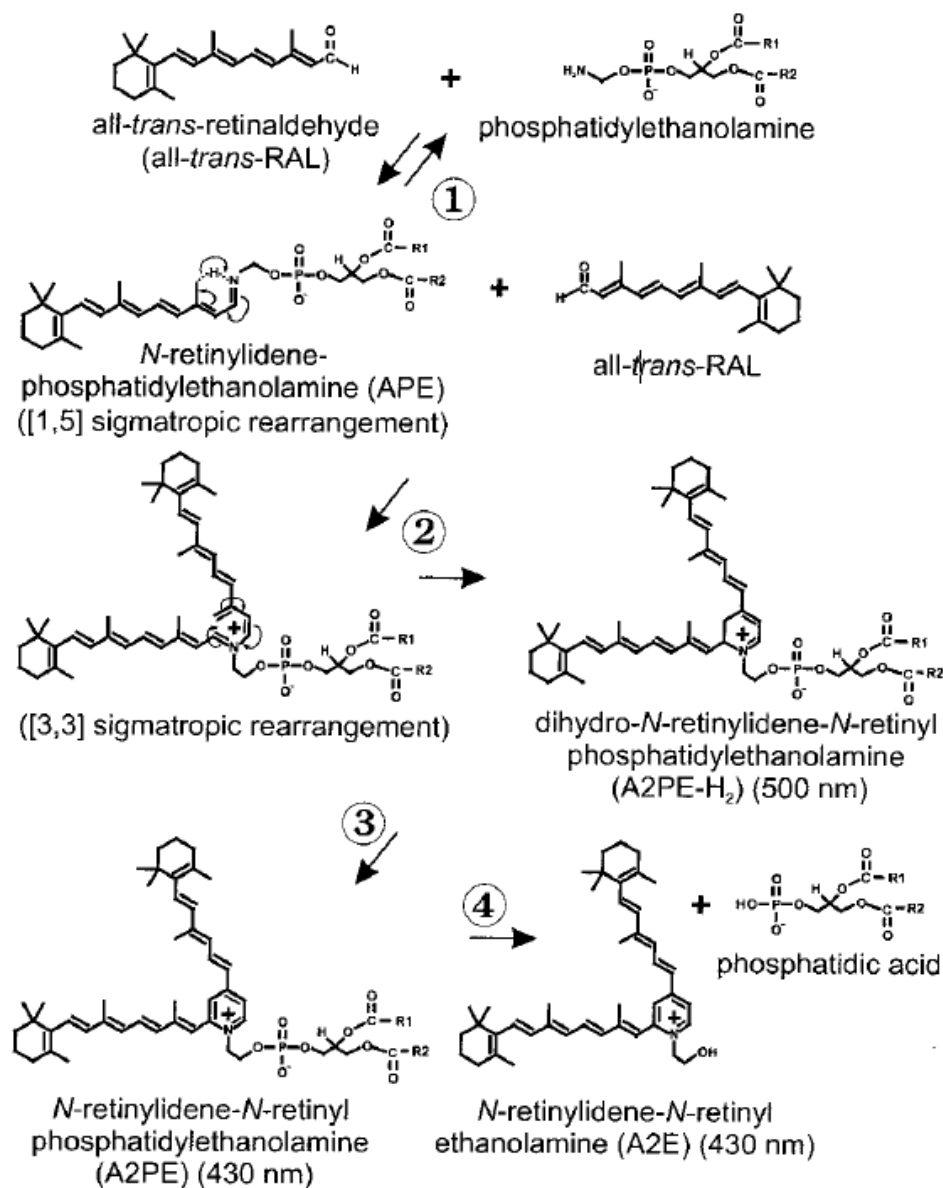
Bergen teaches methods of synthesis for “20, 20, 20-trideutero, 14, 20, 20, 20-tetradeutero, 12, 14, 20, 20, 20-pentadeutero . . . analogs of retinoic acid ethyl ester and retinyl acetate.” Ex. 1006, 11, Abstract. Bergen teaches that such “nonradioactive deuterated or ¹³C labeled compounds of high purity are desired” for studying the metabolism of vitamin A in humans. *Id.* at 11.

3. Overview of Mata (Exhibit 1010)

Mata studies the biosynthesis of A2E in mice and humans with ABCR-mediated retinal and macular degeneration. Ex. 1010. Mata teaches that increased lipofuscin accumulation in RPE cells is seen in “several forms of macular degeneration” and that the toxic A2E is a major fluorophore of lipofuscin. *Id.* at 7154, Abstract. Mata teaches that the mouse *abcr* gene “encodes rim protein (RmP), an ATP-binding cassette transporter in rod outer segments,” and that “[m]ice lacking RmP accumulate A2E in RPE cells at a greatly increased rate over controls.” *Id.*

Mata identifies “three precursors of A2E in ocular tissues from *abcr*–/– mice and humans with ABCR-mediated recessive macular degenerations” — *N*-retinylidene-phosphatidylethanolamine (APE), dihydro-*N*-retinylidene-*N*-retinylphosphatidylethanolamine (A2PE-H₂), and *N*-retinylidene-phosphatidylethanolamine (A2PE) — and suggests a biosynthetic pathway for A2E. Ex. 1010, 7154, Abstract, 7157, right col.

Mata's Figure 5, reproduced below, illustrates its "[h]ypothetical biosynthetic pathway for A2E in mice and humans lacking the RmP transporter." Ex. 1010, 7158, Fig. 5 caption.



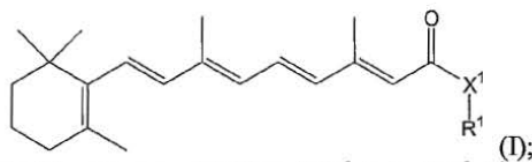
The above figure sets forth a hypothetical pathway for the biosynthesis of A2E in mice and humans lacking the RmP transporter. *Id.* Mata suggests

that “[t]he precursors of A2E identified in [its] study may represent pharmacological targets for the treatment of *ABCR*-mediated macular degeneration” and that “[p]harmacologic inhibition of one or more steps in the A2E synthetic pathway may . . . be an effective treatment strategy for other macular degenerations associated with lipofuscin accumulation.” *Id.* at Abstract, 7159, right col.

4. Overview of Widder (Exhibit 1009)

Widder is a PCT patent publication entitled “Methods and Compositions for Treating Ophthalmic Conditions with Retinyl Derivatives.” Ex. 1009, 1:1–2. Widder provides an overview of the visual cycle and teaches that toxic products, such as A2E, may “accumulate from excess production of visual cycle retinoids, such as all-*trans*-retinal (atRAL).” *Id.* at 1:12–22. Widder teaches that “the over-accumulation of toxic products is partially responsible for the symptoms associated with the macular degenerations and retinal dystrophies.” *Id.* at 1:26–28.

Widder teaches methods for reducing the formation of lipofuscin in the eye of a mammal by administering retinyl derivatives having the structure of Formula (I), reproduced below, wherein X¹ and R¹ are selected from specified groups:



Ex. 1009, 3:4–12, 3:18–20. The figure depicted above is the chemical structure of Widder’s Formula (I). Widder further teaches methods for treating ophthalmic conditions and controlling symptoms associated with

such conditions, wherein the ophthalmic conditions are “macular degenerations, macular dystrophies and retinal dystrophies” including, e.g., Stargardt Disease, recessive retinitis pigmentosa, and dry-form age-related macular degeneration. *Id.* at 2:25–28, 5:4–10.

Widder teaches that “[t]he compounds of Formula (I) can be administered in a variety of ways, including all forms of local delivery to the eye.” Ex. 1009, 25:16–17. Widder further teaches that compounds having the structure of Formula (I) may be used in combination with other treatments that have been “shown to benefit patients with macular degenerations and dystrophies,” including, for instance, certain negatively-charged phospholipids such as cardiolipin and phosphatidylglycerol. *Id.* at 33:1–5. Widder teaches that its compounds may also be used together with certain carotenoids. *Id.* at 33:8–17.

II. ANALYSIS

A. Principles of Law

“In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable.” *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (citing 35 U.S.C. § 312(a)(3) (2012) (requiring *inter partes* review petitions to identify “with particularity . . . the evidence that supports the grounds for the challenge to each claim”)). This burden of persuasion never shifts to Patent Owner. *See Dynamic Drinkware, LLC v. Nat’l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015) (discussing the burden of proof in *inter partes* review).

A claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time invention was made to a person having ordinary skill in the art to which the subject matter pertains. *See KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness, if any. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

In analyzing the obviousness of a combination of prior art elements, it can be important to identify a reason that would have prompted one of skill in the art “to combine . . . known elements in the fashion claimed by the patent at issue.” *KSR*, 550 U.S. at 418. A precise teaching directed to the specific subject matter of a challenged claim is not necessary to establish obviousness. *Id.* Rather, “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.” *Id.* at 420. Accordingly, a party that petitions the Board for a determination of unpatentability based on obviousness must show that “a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.” *In re*

Magnum Oil Tools Int'l, Ltd., 829 F.3d 1364, 1381 (Fed. Cir. 2016) (internal quotations omitted).

We address Petitioner's challenges with these standards in mind, and in view of the definition of the skilled artisan and the claim constructions discussed below.

B. Person of Ordinary Skill in the Art

Factual indicators of the level of ordinary skill in the art include “the various prior art approaches employed, the types of problems encountered in the art, the rapidity with which innovations are made, the sophistication of the technology involved, and the educational background of those actively working in the field.” *Jacobson Bros., Inc. v. U.S.*, 512 F.2d 1065, 1071 (Ct. Cl. 1975); *see also Orthopedic Equip. Co. v. U.S.*, 702 F.2d 1005, 1011 (Fed. Cir. 1983) (quoting with approval *Jacobson Bros.*).

Petitioner asserts that a person of ordinary skill for purposes of the '045 patent

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.

Pet. 7 (citing Ex. 1002 ¶¶ 52–55; Ex. 1004 ¶¶ 47–49).

Patent Owner did not address the above definition in its Preliminary Response, or propose a separate definition. Patent Owner's declarant, Dr.

Sessler, also did not provide a separate definition of a person of ordinary skill in the art for purpose of the '045 patent. However, Dr. Sessler stated that, for the limited purpose of his declaration submitted with Patent Owner's Preliminary Response, he has provided his opinion "based on the Petitioner's definition of a person of ordinary skill in the art." Ex. 2036 ¶ 17.

On the current record, we accept Petitioner's proposed definition, as it appears consistent with the level of skill in the art reflected in the prior art of record and the disclosure of the '045 Patent. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) ("the prior art itself [may] reflect[] an appropriate level" as evidence of the ordinary level of skill in the art) (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985)). The parties are welcome to further address this definition at trial, if necessary.

C. Claim Construction

We construe claims "using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. [§] 282(b)." 37 C.F.R. § 42.100 (2021). Therefore, we construe the challenged claims under the framework set forth in *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–19 (Fed. Cir. 2005) (en banc). Under this framework, claim terms are given their ordinary and customary meaning, as would be understood by a person of ordinary skill in the art, at the time of the invention, in light of the language of the claims, the specification, and the prosecution history of record. *Id.*

Petitioner bears the burden of stating “[h]ow the challenged claim is to be construed.” 37 C.F.R. § 42.104(b)(3). But only those terms that are in controversy need be construed, and only to the extent necessary to resolve the controversy. *Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999); *see also Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (applying *Vivid Techs.* in the context of an AIA trial proceeding).

Petitioner “submits that no construction should be necessary to institute this petition.” Pet. 21 (citing Ex. 1002 ¶ 185; Ex. 1004 ¶ 105). Both of Petitioner’s declarants, Dr. Guengerich and Dr. Calman, also stated that they “have applied the plain and ordinary meaning of the claims” in their analyses. Ex. 1002 ¶ 185; Ex. 1004 ¶ 105. Neither Petitioner nor Patent Owner proposes any specific definitions for any claim limitation.¹⁶

However, Petitioner states in its analysis of claim 28 that “[t]he preamble is not limiting and is entitled to no patentable weight.” Pet. 23. Petitioner then states that, “[n]evertheless, Ortho Pharma teaches a method of treating a macular degeneration,” i.e., the limitation of the preamble. *Id.* at 24 (citing Ex. 1008; Ex. 1004 ¶¶ 134–137). Similarly, both of Petitioner’s

¹⁶ In the Petition’s section on claim construction, Petitioner does note that “[t]he specification of the ’045 patent confirms that the claim term ‘pharmaceutically acceptable carrier’ encompasses a wide variety of conventional carriers, including water, saline solution, corn oil, and starch.” Pet. 21. Patent Owner did not controvert this statement; neither does the resolution of any of the parties’ disputes rest on this claim term. Accordingly, we need not, and do not, construe “pharmaceutically acceptable carrier” at this time.

declarants state in their declarations that they understand the preamble of claim 28 is not limiting and is not given patentable weight. Ex. 1002 ¶ 190; Ex. 1004 ¶ 136. That said, both declarants opine that, even if the preamble were limiting, the asserted prior art disclosed the limitation of the preamble. Ex. 1002 ¶ 190; Ex. 1004 ¶ 136.

Patent Owner has not explicitly challenged Petitioner’s construction of the preamble of claim 28 in its Preliminary Response. Regardless, because we disagree with Petitioner’s construction, we expressly construe the preamble of claim 28 as limiting for the reasons set forth below. *Cf. Qualcomm Inc. v. Intel Corp.*, 6 F.4th 1256, 1263 (Fed. Cir. 2021) (holding that “the Board needed to provide notice of and an adequate opportunity to respond” where its construction of a claim limitation “diverged from the [parties’] agreed-upon . . . requirement for the term”)); *accord Axonics, Inc. v. Medtronic, Inc.*, 75 F.4th 1374, 1381 (Fed. Cir. 2023) (“In a formal adjudication under the APA, such as an IPR proceeding, the Board must inform the parties of “the matters of fact and law asserted,” 5 U.S.C. § 554(b)(3), and “give all interested parties opportunity for . . . the submission and consideration of facts [and] arguments,” *id.* § 554(c)”).

First, the Federal Circuit “has not hesitated to hold preambles limiting when they state an intended purpose for methods of using a compound.” *Eli Lilly & Co. v. Teva Pharms. Int’l GmbH*, 8 F.4th 1331, 1342 (Fed. Cir. 2021). And where, as here, the claims are directed to methods of using a compound for a specific purpose (i.e., treating a macular degeneration), and the method comprises a single step of administering that compound in an

effective amount, the Federal Circuit “[has] generally construed statements of intended purpose in such method claims as limiting.” *Id.* at 1340.

Moreover, “[w]hen limitations in the body of the claim rely upon and derive antecedent basis from the preamble, then the preamble may act as a necessary component of the claimed invention.” *Eaton Corp. v. Rockwell Int’l Corp.*, 323 F.3d 1332, 1339 (Fed. Cir. 2003); *see also Eli Lilly & Co.*, 8 F.4th at 1341. In this case, claim 28 recites “[a] method of treating a macular degeneration, comprising administering an effective amount of a substituted C₂₀-D₁₋₃-retinoid to *a patient in need thereof*.” The preamble of “treating a macular degeneration” is necessary to understand the patients to whom the substituted C₂₀-D₁₋₃-retinoid should be administered; thus, it limits the claim. *See Eli Lilly & Co.*, 8 F.4th at 1341–42 (citing *Jansen v. Rexall Sundown, Inc.*, 342 F.3d 1329, 1332–33 (Fed. Cir. 2003)); *Rapoport v. Dement*, 254 F.3d 1053, 1059 (Fed. Cir. 2001) (holding the preamble to be limiting in a claim directed to “[a] method for treatment of sleep apneas comprising administration of a therapeutically effective amount of a [recited] compound . . . to a patient in need of such treatment,” because otherwise “the phrase ‘to a patient in need of such treatment’ would not have a proper antecedent basis”).

Thus, we construe the preamble of claim 28 as limiting and give patentable weight to the phrase “method of treating a macular degeneration.” To the extent either party disagrees with our construction, the parties are welcome to further address this issue at trial.

D. Merits Analysis

As noted above, Petitioner asserts three grounds involving four references. Pet. 20–21. Ground 1 is based on Ortho Pharma and Bergen. *Id.* at 20. Ground 2 is based on the analysis of Ground 1 in further view of Mata. *Id.* Ground 3 is based on the analysis of Ground 2 in further view of Widder. *Id.* at 21. Patent Owner does not presently challenge the prior art status of any asserted reference. *See* Prelim. Resp. We focus below on Petitioner’s obviousness ground based on Ortho Pharma and Bergen (Ground 1).

As Ground 1, Petitioner challenges independent claim 1 and its dependent claims 2–9, 19–23, 25, and 26, independent claim 28, and independent claim 29 and its dependent claims 30–36, 46–50, 52, and 53. Petitioner’s challenge includes an element-by-element comparison of the claims to the cited art. Pet. 23–46. Patent Owner has not disputed these comparisons. At this stage of the proceeding, we find Petitioner has shown sufficiently that the cited art teaches or suggests each limitation of the challenged claims of Ground 1.

Although Patent owner does not dispute Petitioner’s element-by-element comparison, Patent Owner does dispute Petitioner’s asserted motivation to combine the cited references to arrive at the claimed invention, with a reasonable expectation of success. Prelim. Resp. 11–37. Patent Owner further asserts that the Petition fails to address unexpected results. *Id.* at 37–40. We focus our analysis on these disputed issues, i.e., motivation to combine, reasonable expectation of success, and unexpected results.

1. Motivation to Combine and Reasonable Expectation of Success

a) *Petitioner's Position*

Petitioner asserts Ortho Pharma discloses “administering vitamin A in combination with additional vitamins and minerals” to “treat or prevent eye diseases such as macular degeneration,” and Bergen “discloses making and purifying claimed C₂₀-D₁₋₃-retinoids,” including C₂₀-D₁₋₃-vitamin A (retinol and retinol acetate). Pet. 21–22 (citing, e.g., Ex. 1008 ¶¶ 1–3, 8; Ex. 1002, ¶ 188), 40 (citing, e.g., Ex. 1006, Abstract).

Petitioner asserts that “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,” such as those disclosed in Bergen. Pet. 41.

In particular, Petitioner notes Mata teaches that progression of lipofuscin-associated macular degeneration may be slowed by limiting a patient's exposure to light, by targeting A2E precursors, or by “[p]harmacologic inhibition of one or more steps in the A2E synthetic pathway.” Pet. 40 (citing, e.g., Ex. 1010, 7154, 7159) (alteration in original). Petitioner notes Mata teaches deprotonation at C₂₀ of retinal as a prerequisite for undesirable A2E formation, and, relying on Dr. Guengerich's testimony, argues a skilled artisan “would have recognized that this deprotonation likely was a rate-limiting step in A2E formation and that substituting deuterium in place of the hydrogen at C-20 would slow A2E formation due to the powerful, primary kinetic isotope effect expected from these substitutions.” *Id.* at 41 (citing Ex. 1002 ¶¶ 259–260; Ex. 1010,

7154, Abstract, 7157–58, Fig. 5); *see also id.* at 22–23.

As an additional reason for administering C-20 deuterated vitamin A to reduce lipofuscin formation and treat macular degeneration, Petitioner points to Dr. Calman’s testimony that C20-deuterated vitamin A would reduce undesirable lipofuscin formation without interfering with the normal function of the visual cycle, which “does not involve conversion of retinoids at C-20.” Pet. 42–43 (citing Ex. 1004 ¶ 146).

Petitioner argues that a skilled artisan would have had a reasonable expectation of success practicing the methods of the claims, because (1) the claimed C₂₀-deuterated vitamin A was disclosed in the prior art; (2) compositions formulating deuterated vitamin A in a pharmaceutically acceptable carrier were known in the art; (3) “Ortho Pharma teaches administering its formulations to individuals to treat or prevent eye diseases such as macular degeneration”; (4) Mata teaches that “[p]harmacologic inhibition of one or more steps in the A2E synthetic pathway” may be “an effective treatment strategy for other macular degenerations associated with lipofuscin accumulation” and that “deprotonation at C-20 of retinal was a pre-requisite for undesirable A2E formation”; (5) Dr. Guengerich testifies to “the reasonable expectation that C₂₀-deuteration of vitamin A would slow A2E/lipofuscin formation by 5-10 times”; (6) Dr. Calman testifies that a skilled artisan “would have recognized, at least based on the disclosures of Ortho Pharma and Mata, the desirability of this expected slowing of A2E/lipofuscin formation for patients in need of treatment for ocular diseases associated with A2E/lipofuscin accumulation, including macular degeneration”; and (7) “the ’045 patent admits that formulation of the

claimed compounds was conventional and within the skill of the art.” Pet. 43–45.¹⁷

b) Patent Owner’s Position

In general, Patent Owner argues the Petition fails to establish obviousness because (1) the Petition fails to establish motivation or reasonable expectation of success for the *therapeutic* use of C₂₀-deuterated vitamin A; (2) the Petition fails to show that a skilled artisan “would have anticipated that breaking the C₂₀-CH bond of vitamin A was the rate-limiting step in the multistep reaction sequence by which lipofuscin pigments form,” such that use of C₂₀-deuterated vitamin A would have been expected to retard lipofuscin pigment formation; and (3) a skilled artisan would not have combined Ortho Pharma and Mata, which are inconsistent. Prelim. Resp. 11–37. We discuss Patent Owner’s arguments in greater detail below as part of our analysis.

¹⁷ Petitioner further argues that “[t]he ’045 patent . . . admits that C₂₀-deuterated retinoids, when administered to a patient, can ‘retard[] formation of a lipofuscin pigment in the retina’ and ‘treat[] . . . the effects of a disease characterized by an accumulation of a lipofuscin pigment in a retina’ (e.g., macular degeneration).” Pet. 46. Petitioner argues that Patent Owner “may not now take a contradictory position that a POSA before 2007 would not have had a reasonable expectation of success for making and administering to a patient in need thereof what is claimed.” *Id.* At first glance, this argument appears to be an attempt “[t]o imbue one of ordinary skill in the art with knowledge of the invention in suit,” which is improper if “no prior art reference or references of record convey or suggest that knowledge.” *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983).

c) Analysis

(1) Therapeutic use

Patent Owner asserts that, “[a]t the time of the invention, KIE [kinetic isotopes effects] was primarily used as a research tool, e.g., to study reaction mechanisms and drug metabolism.” Prelim. Resp. 12. Patent Owner asserts that “use of KIE to alter enzyme-mediated metabolism are distinct from its use in the Patent,” which relates to “non-enzymatic non-metabolic process.” *Id.* at 16. Patent Owner asserts that the Petition cites no examples suggesting “replacing a molecule like vitamin A with a deuterated version for therapeutic use,” or “using deuterium to affect processes like lipofuscin pigment formation, which are unrelated to enzyme-mediated metabolism.” *Id.* at 13.

However, “the test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them.” *In re Rosselet*, 347 F.2d 847, 851 (CCPA 1965).

In this case, the Petition, relying on the testimonies of Drs. Guengerich and Calman, asserts that, as of the time of the invention, a skilled artisan would have appreciated that deuteration of a compound was useful for, among other things, “inhibiting (slowing) reactions that involve cleavage of a carbon-hydrogen bond.” Pet. 12 (citing Ex. 1002 ¶¶ 99–100). Such inhibition may be used, for example, to “lower the production of toxic metabolites while also retaining [a compound’s] pharmacological

properties.” Ex. 1004 ¶ 99 (citing Kushner¹⁸).

The Petition points to Mata’s express suggestion of “[p]harmacologic inhibition of one or more steps in the A2E synthetic pathway’ as ‘an effective treatment strategy for other macular degenerations associated with lipofuscin accumulation.” Pet. 31 (quoting Ex. 1010, 7159) (alteration in original). The Petition, again relying on Dr. Guengerich’s testimony, further explains Mata taught that deprotonation at C-20 of retinal — involving cleavage of a carbon-hydrogen bond — was “a pre-requisite for undesirable A2E formation,” and that a skilled artisan “would have recognized that this deprotonation likely was a rate-limiting step in A2E formation” such that slowing the deprotonation “would slow A2E formation,” i.e., lower the production of a toxic reaction product. *Id.* at 41 (citing Ex. 1002 ¶¶ 259–260).

Moreover, although the evidence of record may suggest that, at least as of 1999, “there are no drugs on the market that contain deuterium in the molecule,” Ex. 1046, 85, left col., Petitioner has also provided evidence, for instance in the form of Dr. Calman’s testimony, that “there was significant interest in making deuterated versions of known therapeutics in order to slow rates of undesirable reactions.” Ex. 1004 ¶ 96; *see also* Pet. 15 (stating that “it was known before 2007 to . . . use deuterium to slow undesirable reaction”) (citing Ex. 1002 ¶ 123; Ex. 1004 ¶¶ 96–102).

¹⁸ Kushner et al., *Pharmacological Uses and Perspectives of Heavy Water and Deuterated Compounds*, 77 CANADIAN J. PHYSIOLOGY & PHARMACOLOGY 79 (1999) (Ex. 1046, “Kushner”).

Finally, we note that claim 1, at least, is not directed to a method of treating any particular disease, but only a method of retarding the accumulation of particular compounds (i.e., lipofuscin pigments). We are persuaded, at least at this stage of the proceeding and based on the present record, that Petitioner has shown sufficiently that a skilled artisan would have had a reason to use C₂₀-deuterated vitamin-A in the manner suggested in the Petition, with a reasonable expectation of success, based on alleged similarities between the use of deuterated compounds in the claimed method and use of such compounds to, e.g., lower production of toxic metabolites.

Citing Kushner, Baillie,¹⁹ and Foster²⁰ as support, Patent Owner asserts that “[t]he use of KIE in drug design had been tried, failed, and was regarded as an academic curiosity.” Prelim. Resp. 14–15. Although Kushner, Baillie, and Foster all appear to acknowledge that, at least as of the time of those references, “there are no drugs on the market that contain deuterium in the molecule,” bringing drugs to market involves considerations that may not be relevant to an obviousness analysis. *See, e.g.*, Ex. 2007, 35–36; Ex. 1046, 85, left col. (“A deuterated drug would, for regulatory purposes, still be considered a new one, and very great expenses are needed to bring any new drug intended for humans to the market.”). For example, while cost considerations may prevent a drug from being brought

¹⁹ Baillie, *The Use of Stable Isotopes in Pharmacological Research*, 33 PHARMACOLOGICAL REVS. 81 (1981) (Ex. 1013, “Baillie”).

²⁰ Foster, *Deuterium Isotope Effects in the Metabolism of Drugs and Xenobiotics: Implications for Drug Design*, 14 ADVANCES IN DRUG DESIGN 1 (1985) (Ex. 2007, “Foster”).

to the marketplace, they do not render an invention non-obvious. *See, e.g., Orthopedic Equip.*, 702 F.2d at 1013 (The “fact that . . . two disclosed apparatus would not be combined by businessmen for economic reasons is not the same as saying that it could not be done because skilled persons in the art felt that there was some technological incompatibility that prevented this combination. Only the latter fact is telling on the issue of nonobviousness.”).

Similarly, although Patent Owner quotes Baillie as stating that “[t]he future use of stable-isotope-labelled drugs must be considered to be a more speculative area of application in pharmacological research,” Prelim. Resp. 14 (emphasis omitted, alteration in original), Baillie also appears to describe deuterium, the isotope at issue in this case, as “[t]he only stable isotope that can be expected to modify significantly the pharmacological or toxicological properties of a drug . . . , by virtue of the large primary (or in rare cases secondary) kinetic isotope effects on metabolism observed with this nuclide.” Ex. 1013, 121, right col.

Relying on Blake²¹ and the declaration of Dr. Sessler, Patent Owner asserts that “a significant reason for the lack of practical interest in deuterated therapeutics was that KIE observed *in vitro* repeatably failed to translate to therapeutic gains *in vivo*.” Prelim. Resp. 15. Patent Owner asserts that “[t]his ‘[e]vidence showing unpredictability in the art’ . . . suggests ‘that one of ordinary skill *would not have been motivated* to

²¹ Blake et al., *Studies with Deuterated Drugs*, 64 J. PHARM. SCIS. 367 (1975) (Ex. 1047, “Blake”).

combine the references with a reasonable expectation of success.” *Id.* at 16 (quoting *Honeywell Int’l Inc. v. Mexichem Amanco Holding S.A. DE C.V.*, 865 F.3d 1348, 1354 (Fed. Cir. 2017)) (second alteration in original).

Patent Owner also cites to Dr. Guengerich’s declaration from another *inter partes* review, *Incyte Corp. v. Concert Pharms., Inc.*, IPR2017-01256 (“*Incyte*”), as well as transcripts from his deposition in that case and in *Alzheon, Inc. v. Risen (Suzhou) Pharma Tech Co., Ltd.*, IPR2021-00347 (“*Alzheon*”), as “consistent” with the evidence of the unpredictability of kinetic isotope effects. Prelim. Resp. 15–16 (citing Exs. 2008, 2009, 2010).

We acknowledge the evidence Patent Owner has proffered to show that theoretical kinetic isotope effects may not always translate to therapeutic effect in vivo. However, for purposes of obviousness, “expectation of success need only be reasonable, not absolute.” *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). Furthermore, claim 1 requires neither treatment of a particular disease, nor a particular degree of retarding lipofuscin accumulation.

Regarding Dr. Guengerich’s testimony from prior cases in particular, Dr. Guengerich generally testified as to the factors that may affect whether an observation of kinetic isotope effect in vitro would translate to such an effect in vivo. *See, e.g.*, Ex. 2008 ¶ 108; Ex. 2009, 103:16–104:1, 109:10–18. On this record, however, it does not appear that he testified a skilled artisan would not have had a *reasonable* expectation of success when developing deuterated versions of known pharmaceuticals. In any event, these are issues that can be further probed during Dr. Guengerich’s cross-examination.

Accordingly, at least at this stage of the proceeding, and based on the present record, we are persuaded that Petitioner has provided sufficient evidence of a reasonable expectation of success.

Finally, Patent Owner argues “[t]hat ‘skilled artisans had long failed to appreciate the problem solved by that invention’ underscores the non-obviousness of the claimed invention.” Prelim. Resp. 18. Patent Owner argues that “[t]he *decades-old references* disclosing deuterated retinoids without any suggested therapeutic use exposes the Petition’s hindsight.” *Id.* at 17.

We note, however, that “mere age of the references is not persuasive of the unobviousness of the combination of their teachings, absent evidence that, notwithstanding knowledge of the references, the art tried and failed to solve the problem.” *In re Wright*, 569 F.2d 1124, 1127 (CCPA 1977). At this stage of the proceedings, and to the extent Patent Owner is asserting objective evidence of nonobviousness regarding failure of others or long-felt need, the record on these issues is insufficiently developed. For instance, although Patent Owner alleges that deuterated-vitamin A has been known since the 1970s, the arguments and record have not been sufficiently developed with respect to, for example, attempts by, and failure of, others in the art to solve the particular problem Patent Owner alleges to have been solved by the invention. Based on the record before us, therefore, Patent Owner’s evidence of long-felt need and failure of others does not outweigh the record evidence of obviousness at this stage of the proceeding. Additional evidence and arguments regarding secondary considerations, if presented, may be further developed at trial and will be fully evaluated when

the ultimate determination of obviousness is made.

(2) *Rate-limiting step*

As an initial matter, Patent Owner asserts that Petitioner's argument regarding whether a skilled artisan would have considered C₂₀-deprotonation a rate-limiting step merely incorporates by reference arguments in the Guengerich Declaration. Prelim. Resp. 22, 33. Patent Owner asserts that this incorporation by reference violates Rule 42.6(a)(3).

"It is improper to incorporate by reference arguments from one document into another document." *Cisco Sys., Inc. v. C-Cation Tech., LLC*, IPR2014-00454, Paper 12, 10 (PTAB Aug. 29, 2014) (informative) (citing 37 C.F.R. § 42.6(a)(3)). However, not every statement made by a declarant needs to be repeated in a brief to avoid incorporation by reference. *See, e.g., Sumitomo Elec. Indus., Ltd. v. United Techs. Corp.*, IPR2017-00966, Paper 7, 11 (PTAB Sept. 13, 2017). Here, Petitioner argues that a skilled artisan "would have recognized [the] deprotonation [at C₂₀ of retinal] 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 these substitutions," and cites Dr. Guengerich's testimony and the Petition's discussion of technological background as support. Pet. 41 (citing Ex. 1002 ¶¶ 259–260; Pet. Section I.C.ii); *see also id.* at 42, 67 (stating that a skilled artisan "would have understood from Mata's description of the synthetic pathway that [the] C₂₀-deprotonation was likely a rate-limiting step for which deuterium substitution would result in significant slowing [of] the formation of A2E").

Several paragraphs of Dr. Guengerich's testimony, which we cite below in our analysis, provide appropriate technical detail underlying these arguments. *See, e.g.*, Ex. 1002 ¶¶ 98, 178. They do not provide wholly new arguments not found in the Petition. Indeed, the Petition restates some of Dr. Guengerich's underlying rationale just before and after the sentence quoted by Patent Owner. *Compare* Pet. 42 *with* Ex. 1002 ¶¶ 261–262. Accordingly, we do not find the circumstances here to amount to improper incorporation by reference or an attempt to circumvent our word count limits.

Turning to the substance of the arguments, Patent Owner asserts that, “[t]o obtain a deuterium KIE, the deuterated carbon-hydrogen bond must break in the *rate-determining step*” of the “multistep reaction sequence by which lipofuscin pigments form,” but the Petition fails to show that a skilled artisan “would have anticipated that breaking the C₂₀-CH bond of vitamin A” was such a step. Prelim. Resp. 21 (emphasis added). Patent Owner asserts that, instead, the Petition relies only on the testimony of Dr. Guengerich, which is itself speculative, for the proposition that deprotonation at C₂₀ was “likely” rate-limiting. *Id.* at 22 (emphasis omitted).

Patent Owner first asserts that Dr. Guengerich's opinion “rests on assuming the validity of *Mata 2000*'s expressly ‘*hypothetical*’ pathway,” which had been called into question by others at the time, and “ignor[ed] other potentially rate-limiting steps in *Mata 2000* and alternative pathways.” Prelim. Resp. 22–23; *see also id.* at 24, 27–30, 31–33.

On this record at this stage of the proceeding, we are not persuaded. We acknowledge Mata describes its biosynthetic pathway as “hypothetical.”

However, we note Mata also states that the pathway is corroborated by data discussed in the reference. Ex. 1010, 7154, Abstract (“identify[ing] three precursors of A2E in ocular tissue from *abcr*–/– mice and humans with ABCR-mediated recessive macular generations” and stating that the “results corroborate [a] scheme proposed . . . for the biosynthesis of A2E,” upon which Mata’s pathway is based).

Furthermore, as Petitioner asserts, although other prior art references have proposed somewhat different biosynthetic pathways for A2E, the proposed pathways generally appear similar, particularly in the inclusion of the C₂₀ deprotonation step relied on by Petitioner to show motivation. Pet. 11–12. Specifically, Petitioner’s declarant Dr. Guengerich explains, with respect to Figure 10 of Fishkin 2005, that “the [1-6] hydrogen-shift in Fishkin [2005] in the reaction step between [N-retinylphosphatidyl-ethanolamine (NRPE)] and tautomer x” is, “[c]hemically, . . . the exact same reaction that the patent describes as a [1,5] hydrogen-shift. The difference in nomenclature does not reflect any difference in the chemical reaction. In each case, the H-shift requires breaking a C₂₀-bond with the hydrogen.” Ex. 1002 ¶ 86; Ex. 1011, 7095, left col. (defining NRPE). Dr. Guengerich further explains that the [1,5]-sigmatropic rearrangement described in Mata is also the same as the [1,5] hydrogen-shift described in the ’045 patent. *Id.* ¶ 94. The step labeled “tautomerization” in Figure 1 of Fishkin 2003 likewise appears to require the breaking (in NRPE) of a C₂₀-bond with the hydrogen. Ex. 1036, 1101, Fig. 1.

We are also not persuaded at this stage of the proceeding by Patent Owner’s argument that a skilled artisan would not have looked to Mata

because its proposed pathway has been called into question. Patent Owner points to Fishkin 2005 as “suggesting the 500-nm pigment isolated by [Mata] ‘was not A2-PE-H2’ and propos[ing] an alternative A2E scheme.” Prelim. Resp. 27. Patent Owner similarly points to Kim²² for stating that its data “do not support the identification of dihydro-A2PE as a 510/260 nm absorbing-species [as disclosed by [Mata]].” *Id.* at 28 (first alteration in original). As noted above, however, the A2E biosynthetic pathway proposed by Fishkin 2005 continues to require a cleavage of carbon-hydrogen bond at C₂₀ similar to the reaction step disclosed in Mata, and, despite noting that its data do not support Mata’s identification of dihydro-A2PE (a A2E precursor) as a 510/260 nm absorbing-species, Kim agreed that dihydro-A2PE is an intermediate in the A2E biosynthetic pathway, and Kim’s proposed A2E biosynthetic pathway also appears to include a C₂₀ deprotonation, described as a step wherein NRPE undergoes “a [1,6]-proton tautomerization.” *See* Ex. 2019, Abstract, 7, 10.

In short, given the apparent similarities between the A2E biosynthetic pathways proposed by various prior art references, and based on the current record, we are not persuaded that Petitioner fails to show a reasonable likelihood of prevailing for purposes of institution because it focused in particular on the pathway proposed by Mata.²³

²² Kim, *Characterization of dihydro-A2PE: An Intermediate in the A2E Biosynthetic Pathway*, 46 BIOCHEMISTRY 10122 (2007) (Ex. 2019, “Kim”).

²³ Patent Owner also argues that Petitioner’s focus on Mata is problematic because Petitioner failed to address whether a skilled artisan would have

Patent Owner asserts that the Guengerich Declaration does not identify any reference “teaching or suggesting that deprotonation at C₂₀ was the rate-limiting step in *Mata 2000*’s hypothesized A2E pathway” and ignores the art’s alternative characterization of the C₂₀ deprotonation step, which Mata describes as a “1,5-sigmatropic shift,” as a “tautomerization,” which Patent Owner characterizes as inherently fast. Prelim. Resp. 24–27.

Patent Owner asserts that, “[b]esides a comparison of the 1,5- and 3,3-sigmatropic shift steps that is contradicted by the literature, the Guengerich Declaration simply dismisses, without bases, other potentially rate-limiting steps in *Mata 2000*” and in alternative A2E biosynthetic pathways proposed in other prior art references. Prelim. Resp. 28–33. Patent Owner points in particular to steps described in visual cycle and/or A2E biosynthetic pathways proposed in Fishkin 2005, Law,²⁴ and Kuksa. *Id.* at 31–33.

Patent Owner asserts that Roth²⁵ and Itou,²⁶ cited in the Petition (Pet. 42, 67–68) and discussed in the Guengerich Declaration (Ex. 1002 ¶¶ 116–

considered the C₂₀ deprotonation step to be rate-limiting in view of alternative characterization of the step as, e.g., tautomerization, and/or in view of the additional or different reaction steps in the A2E biosynthetic pathways proposed in other references. Prelim. Resp. 22–23, 31–33; *see also* Sur-Reply 3–4. We address this argument below.

²⁴ Law & Rando, *The Molecular Basis of Retinoic Acid Induced Night Blindness*, 161 BIOCHEMICAL & BIOPHYSICAL RSCH. COMMUN 825 (1989) (Ex. 1037, “Law”).

²⁵ Roth & König, *Hydrogen Displacements, IV: Kinetic Isotope Effect of the 1.5-Hydrogen Displacement in Cis-Pentadiene-(1.3)*, 699 ANNALS OF CHEMISTRY 24 (1966) (Ex. 1015, “Roth”).

²⁶ Itou et al., *Quantum Treatment of Hydrogen Nuclei in Primary Kinetic*

122) as showing “a large kinetic isotope effect value (e.g., 12.2) associated with the 1,5-sigmatropic shift in diene systems,” do not show motivation, because the declaration “fails to address *why* a POSA would expect the KIE for pentadiene to translate to *Mata 2000*’s 1,5-sigmatropic shift or account for basic differences in chemical structure and symmetry between the simple tiny pentadiene with *Mata 2000*’s complex intermediate.” Prelim. Resp. 33–37. Patent Owner notes that, in contrast, others have cited the ’045 patent as “discovering that cleavage of the C₂₀-CH bond was the rate-limiting step in lipofuscin pigment formation.” *Id.* at 23 (citing Exs. 2014–2017).

Once again, “expectation of success need only be reasonable, not absolute.” *Pfizer*, 480 F.3d at 1364. At this stage of the proceeding, we find Petitioner has provided sufficient evidence, in the form of declaration testimony and prior art references, to support its position that a skilled artisan would reasonably have expected that replacing hydrogen with deuterium at C₂₀ of a retinoid in the A2E biosynthetic pathway will retard the accumulation of A2E.²⁷ In particular, Dr. Guengerich testifies that “a person

Isotope Effects in a Thermal 1,5]-Sigmatropic Hydrogen (or Deuterium) Shift from (Z)-1,3-Pentadiene, 111 J. PHYSICAL CHEMISTRY A 261 (2007) (Ex. 1016, “Itou”).

²⁷ It is not clear that the C₂₀-deprotonation must be *the* rate-limiting step in order to exhibit a deuterium kinetic isotope effect. We note, for instance, that Dr. Guengerich testified in *Incyte* that, “in a series of steps, there can be one rate-limiting step or there may be two or more steps that contribute significantly to limiting the overall rate.” Ex. 2009, 44:13–18. Dr. Guengerich testified that the breaking of a carbon hydrogen bond can have a “response to deuterium substitution” so long as it is “at least partially rate limiting.” *Id.* at 44:8–12.

of ordinary skill in the art . . . would have recognized that the [1,5]-sigmatropic shift was likely a rate-limiting step” described in Mata’s A2E biosynthetic pathway, because the step requires breaking the bond between C₂₀ and a hydrogen, which a skilled artisan would have recognized as already relatively slow under physiological conditions, and because, based on the literature regarding kinetic isotope effects including Roth and Itou, a particularly large kinetic isotope effect would have been expected by replacing hydrogen with deuterium at C₂₀ of a retinoid in the A2E biosynthetic pathway. Ex. 1002 ¶¶ 98, 178.

We acknowledge Patent Owner has cited declaration testimony and other references opposing Petitioner’s position and in support of its own arguments, as described above. However, based on the current record, we find the question of whether, at the time of the invention, a skilled artisan can *reasonably* expect the C₂₀ deprotonation to be a rate determining step in the A2E biosynthetic pathway to be a fact intensive issue that would benefit from further development during trial.²⁸

²⁸ An example of an issue that may benefit from fuller development of the record is whether a skilled artisan would have understood Law and Kuksa to suggest “enzyme-mediated isomerization of all-trans-retinal to 11-cis-retinol in the visual cycle [to be] the rate-limiting step in the formation of A2E lipofuscin pigments,” as Patent Owner alleges. Prelim. Resp. 32–33. Kuksa, for instance, states that, in mouse retina, the reduction of all-*trans*-retinal by all-*trans*-retinol dehydrogenases is the rate-limiting step of the *retinoid cycle*, but it is unclear whether a skilled artisan would understand the “retinoid cycle” to include the formation of lipofuscin pigments. We have not located discussion by Patent Owner’s declarant on this issue. Ex.

Accordingly, at this stage of the proceeding, we determine that Petitioner has established a reasonable likelihood of prevailing on its assertion that at least one challenged claim is unpatentable as obvious over Ortho Pharma and Bergen.²⁹

(3) *Combination of Mata and Ortho Pharma*

Patent Owner contends that “the Petition fails to rationalize [the] contradictory teachings [of Mata and Ortho Pharma] which render the combination ‘inappropriate for an obviousness inquiry.’” Prelim. Resp. 18. Patent Owner asserts that “[t]he premise of [Mata] is to reduce A2E formation by reducing the vitamin A precursors that react to form A2E, such as, vitamin A itself and retinal (*all-trans-RAL*) in particular.” *Id.* at 19.

2036 ¶¶ 70–74 (discussing Fishkin 2005 but not Law or Kuksa). Similarly, with respect to Patent Owner’s argument that Fishkin 2005 teaches a possible alternative rate limiting step of a “‘slow’ rearrangement of ATR Dimer to [form] A2E,” Prelim. Resp. 32, we note that the possible “slow rearrangement” from ATR Dimer to A2E appears to be one of two *alternative* pathways to A2E formation discussed in Fisher 2005. Ex. 1011, Fig. 10. It is not clear why slowing A2E formation in *one* of the alternative pathways by using a C₂₀-deuterated retinoid would not retard lipofuscin formation at least to some degree.

²⁹ Patent Owner cites to *Neptune Generics LLC v. Auspex Pharms., Inc.*, IPR2015-01313, Paper 25 (PTAB Dec. 9, 2015) (“*Neptune*”) as an example in which institution was denied “where the effect of deuteration was not predictable ‘due to the presence of other possible rate-limiting steps.’” Prelim. Resp. 31; Sur-Reply 3 (citing *Neptune* as recognizing that “‘***the presence of other possible rate-limiting steps***’ precludes Petitioner from having establish[ed] an expected KIE as is necessary for its alleged motivation”). However, each case must be determined on its own facts, and the evidence in the instant case differs from that in *Neptune*.

Patent Owner asserts that, in contrast, Ortho Pharma “teaches *administering more* vitamin A to treat AMD. . . . *Ortho Pharma’s* supplemental vitamin A can feed the visual cycle to *increase* formation of the *all-trans-RAL* that in *Mata 2000* forms toxic A2E.” *Id.* at 20–21.

However, the test for obviousness does not require “the features of a secondary reference [to] be bodily incorporated into the structure of the primary reference”; neither does it require that “the claimed invention . . . be expressly suggested in any one or all of the references.” *In re Keller*, 642 F.2d 413, 425 (CCPA 1981). “Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art.” *Id.*

The combined teachings of Ortho Pharma and Mata may suggest that vitamin A can both promote eye health *and* lead to accumulation of lipofuscin, which is harmful to eye health. On this record at this stage of the proceeding, we find that Petitioner has sufficiently explained why the teachings of Mata would have provided a skilled artisan reason to modify Ortho Pharma using the C₂₀-D₁₋₃-retinoids of Bergen, *see, e.g.*, Pet. 40–43, and, accordingly, do not find the combination of Mata and Ortho Pharma to be inappropriate.

2. Unexpected Results

Patent Owner asserts that the Petition fails to address unexpected results at least as to (1) “slowing of ATR-dimer formation” (rather than only A2E formation); (2) “slowing of lipofuscin pigment formation without slowing the visual cycle or lowering amounts of vitamin A lipofuscin pigment precursors”; and (3) the large KIE effect in vivo of replacing

hydrogen with deuterium at Carbon 20 of the claimed retinoids. Prelim. Resp. 37–40.

On the current record, we find that Patent Owner’s unexpected results argument involves fact intensive issues best resolved on a full trial record. For instance, a fuller development of the record would be helpful in determining whether, given the biosynthetic pathways proposed for A2E and ATR-dimer in the prior art and the allegedly known kinetic isotope effect of replacing hydrogen with deuterium in a compound in certain situations, use of C₂₀-D₁₋₃ retinoid would in fact be expected to exhibit a large KIE effect in vivo and, consequently, to slow lipofuscin pigment formation, including ATR-dimer formation, without slowing the visual cycle or lowering the amounts of vitamin A lipofuscin pigment precursors. *See, e.g.*, Ex. 1002 ¶¶ 347, 355.

3. Other Claims and Grounds

Other than the issues regarding motivation to combine, reasonable expectation of success, and unexpected results, Patent Owner does not presently dispute Petitioner’s argument that the cited references alone or in combination teach or suggest each limitation of the claims. As discussed above, we find Petitioner has shown sufficiently, at this stage of the proceeding, that an ordinarily skilled artisan would have been motivated to combine the references to arrive at the challenged claims with a reasonable expectation of success. Having considered the arguments and evidence presented by the parties, we find Petitioner likewise has shown sufficiently, at this stage of the proceeding, that each limitation is taught or suggested by the cited references. Accordingly, on this record, we find Petitioner has

shown a reasonable likelihood that the challenged claims are unpatentable for the reasons set forth in Grounds 1–3.

We emphasize our determination in this Decision is not a final determination on the construction of any claim term or the patentability of any challenged claim and, thus, leaves undecided any factual issues necessary to determine whether sufficient evidence supports Petitioner’s contentions by a preponderance of the evidence in the final written decision. *See TriVascular, Inc. v. Samuels*, 812 F.3d 1056, 1068 (Fed. Cir. 2016) (noting that “there is a significant difference between a petitioner’s burden to establish a ‘reasonable likelihood of success’ at institution, and actually proving invalidity by a preponderance of the evidence at trial”) (quoting 35 U.S.C. § 314(a) and comparing § 316(e)).

E. Discretionary Denial under 35 U.S.C. § 325(d)

The parties dispute whether the Board should exercise its discretion to deny the Petition under 35 U.S.C. § 325(d). *See generally* Prelim. Resp. 41–73; Pet. 65–68; Reply 4–5; Sur-Reply 4–5.

1. Legal Standards

Institution of *inter partes* review is discretionary. *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1367 (Fed. Cir. 2016) (explaining that “the PTO is permitted, but never compelled, to institute an IPR proceeding”). The Patent Office may, for example, deny institution under 35 U.S.C. § 325(d), which provides, in pertinent part, that “[i]n determining whether to institute or order a proceeding under this chapter, . . . the Director may take into account whether, and reject the petition or request because, the same or

substantially the same prior art or arguments previously were presented to the Office.”

In evaluating whether the same or substantially the same prior art or arguments were previously presented to the Office, the Board has identified several non-exclusive factors that may be considered. *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 at 17–18 (PTAB Dec. 15, 2017) (precedential as to § III.C.5, first paragraph) (“*Becton, Dickinson*”). Those factors are as follows:

- (a) the similarities and material differences between the asserted art and the prior art involved during examination;
- (b) the cumulative nature of the asserted art and the prior art evaluated during examination;
- (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection;
- (d) the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or Patent Owner distinguishes the prior art;
- (e) whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and
- (f) the extent to which additional evidence and facts presented in the Petition warrant reconsideration of prior art or arguments.

Id.; see also The Patent Trial and Appeal Board Consolidated Trial Practice Guide (“Trial Practice Guide”) (Nov. 2019) at 62–63 (citing the *Becton, Dickinson* factors).³⁰

³⁰ Available at <https://www.uspto.gov/TrialPracticeGuideConsolidated>.

As more recently explained in *Advanced Bionics, LLC v. MED-EL Electromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 at 8–10 (Feb. 13, 2020) (precedential) (“*Advanced Bionics*”), the Board addresses § 325(d) applying a “two-part framework.” In the first part of the framework, we ask whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office. *Advanced Bionics* at 8. Factors (a), (b), and (d) of *Becton, Dickinson* come into play under this first part of the framework. *Id.* at 8–10. If *either* condition of the framework’s first part is met, we move to part two of the framework, asking “whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of [the] challenged claims.” *Id.* at 8. Factors (c), (e), and (f) of *Becton, Dickinson* fall within part two of the framework. *Id.* at 10 (“[F]actors (c), (e), and (f) relate to whether the petitioner has demonstrated material error by the Office.”).

Only if the same or substantially the same art or arguments were previously presented to the Office do we then consider whether petitioner has demonstrated error. *Advanced Bionics* at 8–10. “If the petitioner fails to show that the Office erred, the Director may exercise his discretion not to institute *inter partes* review.” *Id.* at 8–9. “At bottom, this [§ 325(d)] framework reflects a commitment to defer to previous Office evaluations of the evidence of record unless material error is shown.” *Id.* at 9 (“If reasonable minds can disagree regarding the purported treatment of the art or arguments, it cannot be said that the Office erred in a manner material to patentability.”).

2. Analysis

a) § 325(d) Framework: Part One

Petitioner's unpatentability challenges rely on four different prior art references: Ortho Pharma, Bergen, Mata, and Widder. Pet. 20–21.

Bergen was before the Office during the prosecution leading to the '809 patent, of which the '045 patent is a reissue. Prelim. Resp. 42–44. In particular, Bergen was listed on an Information Disclosure Statement (“IDS”) filed during prosecution. *Id.* at 43 n.10 (citing Ex. 1031, 51). The Examiner certified that “all references” on the relevant IDS were “considered except where lined through.” Ex. 1031, 55 (emphasis omitted). There is no line through Bergen. *Id.* at 51; *see Advanced Bionics* at 7–8 (explaining that “[p]reviously presented art includes art made of record by the Examiner, and art provided to the Office by an applicant, such as on an Information Disclosure Statement (IDS), in the prosecution history of the challenged patent”).

With respect to the remaining asserted references, Patent Owner argues that, for purposes of the disclosures relied upon in the Petition, Ortho Pharma, Mata, and Widder are substantially the same, respectively, as Lang, Radu and Fishkin 2005, and Widder 2007. Prelim. Resp. 44–59. For purposes of this Decision, we assume that Patent Owner's showing as to the cumulative nature of Lang, Radu, Fishkin 2005, and Widder 2007 previously presented to the Patent Office justifies proceeding to the second part of the *Advanced Bionics* framework.

b) § 325(d) Framework: Part Two

In part two of the framework, we consider “whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of [the] challenged claims,” taking into consideration *Becton, Dickinson* factors (c), (e), and (f). *Advanced Bionics* at 8.

As to *Becton, Dickinson* factor (e), “whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art,” Petitioner asserts that the Examiner erred during the prosecution of the ’631 application by “(1) believing that the prior art failed to disclose the claimed C20-deuterated vitamin A; (2) assuming that the prior art failed to provide reason to make the claimed C20-deuterated vitamin A.” Pet. 67–68. In response, Patent Owner asserts that “[t]he Petition’s inferred beliefs and assumptions cannot establish error,” and, in any event, is belied by the evidence of record. Prelim. Resp. 66. We evaluate these opposing arguments in light of *Becton, Dickinson* factors (c) and (f).

Relevant to *Becton, Dickinson* factor (c), “the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection,” Petitioner argues that “the grounds presented are materially different than the *rejections applied* during prosecution because [the grounds] identify prior art disclosure of the claimed C₂₀-deuterated vitamin A *and* that C₂₀-deprotonation is a pre-requisite to A2E/lipofuscin formation.” Reply 4; *see also* Pet. 65–66 (contending that “[w]hen evaluating the challenged claims during prosecution, the Examiner exclusively pointed to references disclosing compounds that are *not* within the scope of the present claims,” noting that “Radu . . . discloses isotretinoin,

which is a different compound than those claimed, and the Boehm reference does not disclose deuterium substitution at C₂₀”).

We agree that neither Bergen, nor another prior art reference containing similar disclosure of C₂₀D₁₋₃ vitamin A, formed the basis of a rejection during the prosecution leading to the '045 patent. *See generally* Exs. 1031, 1057. In addition, during prosecution of the '631 application, Applicant distinguished the invention over the prior art by relying on the limitation of “a pharmaceutical composition comprising a substituted C₂₀-D₁₋₃-retinoid and a pharmaceutically acceptable carrier,” both in the context of responding to the restriction requirement and the obviousness rejection. Ex. 1031, 168, 172–173, 291. Although the Examiner did not withdraw the restriction requirement based on these arguments, neither did the Examiner explicitly point to Bergen in response to Applicant’s arguments regarding the lack of pharmaceutical composition comprising a substituted C₂₀-D₁₋₃-retinoid in the prior art. Finally, the same Examiner examined the '631 application as well as its divisional '975 application, which issued as the '423 patent and claims the pharmaceutical formulation recited in the methods of the '045 patent. Ex. 1032, 1, 12; *compare* Ex. 1032, 22 *with* Ex. 1031, 46 (electronic signature of primary examiner). However, as Petitioner points out, the Examiner did not reject the claims of the '975 application in light of Bergen, despite the fact that Bergen disclosed a substituted C₂₀-D₁₋₃-retinoid recited in the claims. Reply 4–5.

We further note, with respect to *Becton, Dickinson* factor (f), relating to “the extent to which additional evidence and facts presented in the Petition warrant reconsideration of the prior art or arguments,” that the

Guengerich testimony and associated evidence presented in the Petition warrant reconsideration of the prior art in front of the Patent Office.

In particular, although Radu, which discloses a biosynthetic pathway for A2E that appears similar to the pathway disclosed in Mata, was relied on by the Examiner in rejecting the claims, the Examiner cites to Radu for its “use of isotretinoin, a C20-retinoid[,] for inhibition of lipofuscin pigment in a retina.” Ex. 1031, 240. In contrast, the Petition relies on Mata, together with the Guengerich Declaration and the evidence regarding kinetic isotope effect discussed therein, to provide a reason for making the claimed C₂₀-deuterated vitamin A and using it in the claimed method, with a reasonable expectation of success. Pet. 40–45, 67.

Accordingly, in light of the lack of discussion of Bergen during prosecution of the ’631 application, and the additional evidence and facts presented in the Petition, including Dr. Guengerich’s testimony, we are not persuaded that we should exercise our discretion and decline institution under § 325(d) based on Patent Owner’s allegation that Bergen was specifically considered by the Examiner and that the Petition fails to show the asserted references in the Petition are materially different or more relevant than those applied during prosecution. Prelim. Resp. 66–67, 68–70, 71–72 (arguing that Bergen and other references mentioned in the Petition do not provide motivation to substitute deuterium at carbon-20, and “the 1,5-tautomerization in *Mata 2000* relied upon by the Petition is chemically identical[to the step] shown in *Radu 2003*”).

Patent Owner further asserts that error cannot “be established simply because the Examiner did not rely on some [references] for a ground of

rejection.” Prelim. Resp. 66; *see also id.* at 67 (“[F]ailure to identify and address,’ even if true . . . , does not constitute material error.” (first alteration in original)). Patent Owner asserts that material error is not established merely because “the Petition views the art differently.” *Id.* at 70; *see also id.* at 72 (arguing that the interpretations of Mata by the Petitioner and its declarants “provide no basis to infer material error or institute” where the relevant disclosures of Mata and Radu are identical). Patent Owner contends that “testimony from Petitioner’s declarations [do not] tip in favor of institution.” *Id.* at 67–68.

We are not persuaded for the reasons discussed above. In this regard, we note that “[a]n example of material error may include misapprehending or overlooking specific teachings of the relevant art where those teachings impact patentability of the challenged claims.” *Advanced Bionics* at 8–9 & n.9. In this case, we find the Examiner overlooked the disclosures in the prior art regarding (1) C₂₀-D₁₋₃ retinoids and (2) the relevance of A2E biosynthetic pathways to patentability, particularly with respect to a reason to use the recited C₂₀-D₁₋₃ retinoids to retard formation of lipofuscin pigments when the pathways are considered together with facts and evidence in the Petition that were not present before the Examiner (e.g., the Guengerich Declaration and the prior art understanding of kinetic isotope effects). For these reasons, we are similarly unpersuaded by Patent Owner’s argument that the Patent Office “[s]ubstantively [c]onsidered the [s]ame or [s]ubstantially the [same] [a]rguments” set out in the Petition. Prelim. Resp. 60–61 (emphasis omitted).

Finally, Patent Owner argues that “none of the art or arguments advanced by the Petition would have affected the outcome.” Prelim. Resp. 63. Patent Owner argues that “[t]he Examiner in parent ’631 application withdrew her rejection and granted allowance in response to Applicant’s arguments based on, among other things, unexpected results,” and that, likewise, a different Examiner “in the reissue application . . . did not enter a 103 rejection because the art did not suggest *using* C20-D3-vitamin A *to treat AMD* and given the unexpected advantages of the claimed methods.” *Id.* Patent Owner contends that “the Petition only contrasts [*Bergen*]’s disclosure of a C₂₀ deuterated retinoid within the scope of the claims with a distinction made during prosecution that *Boehm* does not disclose deuterium substitution at C₂₀,” but

does not argue that a non-therapeutic C20 deuterated retinoid according to [*Bergen*] would fill the gaps addressed during the prosecution of (1) “using the substituted C20D3-retinoids as claimed for treating macular degeneration or for retarding the accumulation of a lipofuscin pigment in a retina’ and (2) unexpected results over isotretinoin as disclosed in *Radu 2003*.”

Id. at 64.

We have discussed Patent Owner’s arguments regarding unexpected results in Section II.D.2. With respect to Patent Owner’s arguments that the art and arguments advanced in the Petition would not have affected the outcome of the prosecution, we note that the Examiner during the prosecution of the ’631 application withdrew the obviousness rejection without substantive comments. Ex. 1031, 140–145. The Examiner during reissue stated only that “[t]he prior art does not teach or suggest using the

substituted C20-D1,3-retinoids as claimed for treating macular degeneration for retarding the accumulation of a lipofuscin pigment in a retina” and cited Kaufman as showing “the possible effectiveness of these compounds in slowing lipofuscin deposition and the progression of common degenerative eye diseases.” Ex. 1057, 164. We do not find that the above, without more, suffices to show that the claims were allowed due to unexpected results.

Considering *Becton, Dickinson* factors (c), (e), and (f) together, we conclude that Petitioner sufficiently demonstrates Examiner error based on the grounds in its Petition, with support from declaration testimony not before the Examiner, which shows that the Examiner overlooked or did not appreciate the materiality of the disclosures of Bergen and Radu. We conclude that the circumstances presented here do not warrant us exercising our discretion to deny institution based on § 325(d).

III. CONCLUSION

For the reasons provided above, we decline to exercise our discretion under § 325(d) and institute *inter partes* review based on all the Grounds presented in the Petition.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that, pursuant to 35 U.S.C. § 314(a), an *inter partes* review of claims 1–54 of U.S. Patent No. RE47,045 is instituted with respect to all challenged claims and all grounds set forth in the Petition; and

FURTHER ORDERED that, pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial, which will commence on the entry date of this decision.

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Patent RE47,045

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