

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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EYENOVIA, INC.,  
Petitioner,

v.

SYDNEXIS.,  
Patent Owner.

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IPR2022-00964  
Patent 9,770,447 B2

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Before SUSAN L.C. MITCHELL, MICHAEL A. VALEK, and  
JAMIE T. WISZ, *Administrative Patent Judges*.

VALEK, *Administrative Patent Judge*.

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

## I. INTRODUCTION

Eyenovia, Inc. (“Petitioner”) filed a Petition (Paper 1, “Pet.”), seeking *inter partes* review of claims 1–19 of U.S. Patent No. 9,770,447 B2 (Ex. 1001, “the ’447 patent”). Sydnexis, Inc. (“Patent Owner”) filed a Preliminary Response. Paper 6 (“Prelim. Resp.”).

In its Preliminary Response, Patent Owner challenges the merits of the grounds in the Petition. Prelim. Resp. 20–45. In addition, Patent Owner asks the Board to apply discretion to deny institution under 35 U.S.C. § 325(d). *Id.* at 45–54.

Section 325(d) provides discretion to not institute a proceeding if the challenge to the patent is based on matters previously presented to the Office. For the reasons explained below, we exercise discretion under 35 U.S.C. § 325(d) to deny institution of *inter partes* review.

## II. BACKGROUND

### A. *Real Parties in Interest*

The parties identify themselves as the only real parties in interest. Pet. 64; Paper 4, 2.

### B. *Related Matters*

Along with the present Petition challenging the ’447 patent, Petitioner filed Petitions in IPR2022-00963, IPR2022-00965, and IPR2022-00966 challenging U.S. Pat. Nos. 9,421,199 (the “’199 patent”), 10,076,515 (the “’515 patent”), and 10,21,534 (the “’534 patent”), respectively. *See* Pet. 65–66, Paper 4, 2. The ’199 patent is the parent of the ’447 patent. Ex. 1001 code (63). The ’515 patent issued from a continuation of the ’447 patent application and the ’534 patent issued from a continuation of the ’515 patent application. Pet. 64

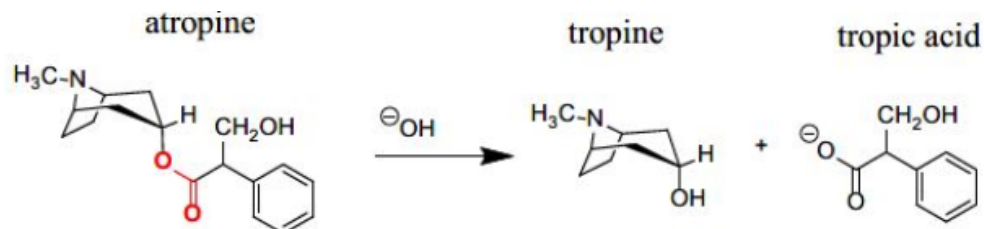
The same patents were previously challenged by a different Petitioner, Nevakar, Inc., in IPR2021-00439, IPR2021-00440, IPR2021-00441, and IPR2021-00442. Pet. 65. Each of those proceedings was terminated by joint motion of the parties prior to a decision on institution. Pet. 65; *see also* Ex. 2003, 1–3 (order terminating proceedings).

In addition, Petitioner previously filed petitions in IPR2022-00384, IPR2022-00414, and IPR2022-00415 challenging three other patents arising from applications that are continuations-in-part of the '199 patent application. Pet. 65. Review was instituted in those proceedings, which are currently pending. *Id.*; *see also* IPR2022-00384, Paper 9; IPR2022-00414, Paper 9; IPR2022-00415, Paper 9 (decisions instituting review). Unlike the claims at issue in IPR2022-00384, IPR2022-00414, and IPR2022-00415, the claims challenged in this proceeding recite the use of deuterated water, and the Petition relies on a different set of art and arguments to challenge them.

### *C. The '447 patent and Related Background*

The '447 patent describes ophthalmic compositions “including a low concentration of an ophthalmic agent and deuterated water.” Ex. 1001, Abstr. The Specification explains that, at least in some embodiments, the ophthalmic agent in these compositions is the muscarinic antagonist atropine. *Id.* at 1:27–32. According to the Specification, the “muscarinic antagonist (e.g. atropine or its pharmaceutically acceptable salts) prevents or arrests the development of myopia in humans, for example as evidenced by reduction of the rate of increase of myopia in young people.” *Id.* at 6:45–49.

The Petition explains that atropine was known to be subject to degradation via ester hydrolysis. Pet. 3–4. This reaction is depicted in Figure 1 of the Petition, which is reproduced below.



**Figure 1. Atropine hydrolysis reaction. Red denotes ester.**

*Id.* Petitioner's figure above shows that the carboxylic ester moiety in atropine (shown in red) reacts with  $\text{OH}^-$  ions to form the degradation products tropine and tropic acid. This process is referred to as "base-catalyzed hydrolysis." *Id.* at 4. According to Petitioner, "[a]t low  $\text{OH}^-$  concentrations (*i.e.*,  $\text{pH} < \sim 3\text{--}5$ ) the overall rate of reaction is slow, and atropine is relatively stable," but "[a]s  $\text{OH}^-$  concentration increases . . . the overall rate of the reaction increases, and atropine becomes more unstable ( $\text{pH} > \sim 5$ )." *Id.* (citing Ex. 1004, 8–9).

Consistent with Petitioner's explanation, the Specification of the '447 patent states that some atropine compositions "are formulated at a relatively lower pH range (e.g. less than 4.5) for stability of the muscarinic antagonist." Ex. 1001, 6:61–65. However, the Specification explains that this "lower pH range in some instances causes discomfort or other side effects such as pain or burning sensation in the eye" and "elicits a tear response which reduces absorption of the drug in the eye." *Id.* at 6:65–7:5. "Still further, the present disclosure recognizes that some muscarinic antagonist (e.g. atropine) liquid compositions formulated at lower concentrations (e.g. 0.001% to 0.05%) present stability challenges that are less so in higher concentrations (e.g. 0.1–1%)." *Id.* at 7:6–10. According to the Specification, "there is a need for stabilizing an ophthalmic composition through arresting or reducing hydrolysis of at least some of its active agents" while also providing "convenient and effective delivery of . . . atropine in

the eye of the patient” though the use of a “composition with extended shelf life upon storage.” *Id.* at 6:36–44.

To this end, the Specification discloses that “deuterated water stabilizes ophthalmic compositions.” Ex. 1001, 7:23–25. More particularly, the Specification explains that

deuterated water is a weak acid as compared to H<sub>2</sub>O, as such deuterated water comprises a lower concentration of the reactive species (e.g., —OD) which in some instances leads to base catalyzed hydrolysis of an active agent in the ophthalmic composition. As such, in some instances compositions comprising deuterated water lead[] to reduced base catalyzed hydrolysis when compared to compositions comprising H<sub>2</sub>O. In some instances, deuterated water further lowers the buffering capacity of an ophthalmic composition, leading to less tear reflex in the eye.

*Id.* at 7:24–34; *see also id.* at 21:51–22:6 (similar).

#### *D. Illustrative Claim*

The Petition challenges claims 1–19. Claims 1 and 14 are the only independent claims and are substantially the same. Claim 1 is illustrative for purposes of this decision. It reads as follows:

1. An ophthalmic composition, comprising one and no more than one ophthalmic agent, and deuterated water, at a pD of from about 4.2 to about 7.9, wherein the ophthalmic agent consists of atropine, atropine sulfate, or a combination thereof, at a concentration of from about 0.001 wt % to about 0.03 wt %.

Ex. 1001, 86:62–67.

#### *E. Asserted Grounds of Unpatentability*

Petitioner asserts the following grounds of unpatentability:

Claim(s) Challenged	35 U.S.C. § <sup>1</sup>	Reference(s)/Basis
1–3, 6, 7, 12–19	103	Chia, <sup>2</sup> Siegel, <sup>3</sup> Kondritzer <sup>4</sup>
1–19	103	Chia, Siegel, Kondritzer, Remington <sup>5</sup>

In support of these grounds, Petitioner relies on the declaration of Stephen Byrn, Ph.D. (Ex. 1002).

For ground 1, the Petition asserts that the challenged claims recite three main elements: (1) a “low-concentration atropine formulation;” (2) “D<sub>2</sub>O substituted for H<sub>2</sub>O to increase the formulation’s stability;” and (3) “pD levels that were well known to be desirable for treating myopia with atropine.” Pet. 23. The Petition relies on Chia for the first element. *See id.* at 6–7.

Regarding elements (2) and (3), the Petition relies on Kondritzer’s teaching “that degradation of atropine is primarily due to acid- and base-catalyzed hydrolysis” and that “above pH 4.5, the predominant catalytic reaction involves hydroxyl ion,” i.e., base-catalyzed hydrolysis. *Id.* at 8–9

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<sup>1</sup> The Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011) (“AIA”), included revisions to 35 U.S.C. § 103 that became effective before the filing of the applications to which the ’447 patent claims priority. Therefore, we apply the AIA version of the statute.

<sup>2</sup> Chia et al., *Atropine for the Treatment of Childhood Myopia: Safety and Efficacy of 0.5% , 0.1%, and 0.01% Doses (Atropine for the Treatment of Myopia 2)*, 112 OPTHALMOLOGY 347–54 (2012) (Ex. 1003) (“Chia”).

<sup>3</sup> Siegel et al., *Stability of Procaine in Deuterium Oxide*, 53 J. PHARM. SCI. 978-79 (1964) (Ex. 1006) (“Siegel”).

<sup>4</sup> Kondritzer et al., *Stability of Atropine in Aqueous Solution*, 156 J. AMERICAN PHARM. ASSOC. 531–35 (1957) (Ex. 1004) (“Kondritzer”).

<sup>5</sup> William J. Reilly, Jr. & Gerald Hecht., *Pharmaceutical Necessities and Ophthalmic Preparations*, in REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY VOL. II 1380–1416, 1563–1576 (Alfonso R. Gennaro ed., 1995) (Ex. 1005) (“Remington”).

(quotations omitted). The Petition further relies on Siegel’s teaching that “deuterium oxide ‘may prove of value . . . in the extemporaneous preparation of ophthalmic solutions, where stability and sterility are important considerations’” based on a study showing that substituting D<sub>2</sub>O for H<sub>2</sub>O reduced the rate of hydrolysis for a different active agent, procaine. *Id.* at 10–11 (quoting Ex. 1006, 6)<sup>6</sup>. According to the Petition, these teachings

would have motivated a POSA [i.e., a person of ordinary skill in the art] to substitute H<sub>2</sub>O with D<sub>2</sub>O to increase atropine’s stability at higher pHs, and a POSA would have expected success in doing so given the solvent isotope effect and increased stability that *Siegel* reported for procaine. As a POSA would readily understand, atropine shares many similarities with procaine and would have reasonably expected the benefits in stability and clinical efficacy obtained with D<sub>2</sub>O – procaine would translate to D<sub>2</sub>O – atropine formulations.

*Id.* at 24 (citations omitted). The Petition further contends that a POSA would have been motivated to optimize the pH of the formulation and a pD 5.4–6.4, which is equivalent to a pH of 5–6, “was optimal.” *Id.* at 36–37; *see also id.* at 5 n. 2; Ex. 1002 ¶ 42 n. 5 (explaining that pD is calculated by adding 0.4 to the pH value).

Ground 2 adds Remington, which Petitioner contends “discloses conventional components of ophthalmic solutions, including a standard solution appropriate for atropine,” to the references in ground 1. *See* Pet. 12. For the independent claims and the other claims already challenged in ground 1, the Petition relies on Remington as additional evidence that the recited pD range would have been obvious. *Id.* at 48–49. For dependent

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<sup>6</sup> As does the Petition, we cite the page numbers added to Exhibit 1006.

claims 4, 5, and 8–11, the Petition relies on Remington as evidence that certain additional elements recited in these claims, e.g., an osmolarity adjusting agent, buffer, or pD adjusting agent, would have been obvious. *Id.* at 49–54.

### III. DISCRETION UNDER 35 U.S.C. § 325(d)

Patent Owner argues that we should exercise discretion to deny the Petition under 35 U.S.C. § 325(d). Prelim. Resp. 45–54. According to Patent Owner, the Petition “relies on substantially the same art and arguments previously presented to the Office, and . . . does not demonstrate material error in the Office’s previous assessment.” *Id.* at 45. Patent Owner asserts that “[t]he Office has repeatedly considered whether a POSA would have been motivated to stabilize atropine with deuterium oxide for an ophthalmic formulation,” and “Petitioner has failed to show that no ‘reasonable minds can disagree regarding the purported treatment of the art or arguments’ that Petitioner now advances.” *Id.* at 46, 54 (quoting *Advanced Bionics, LLC v. MED-EL Electromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 at 9 (Feb. 13, 2020) (precedential) (“*Advanced Bionics*”)).

#### *A. Legal Standard*

Section 325(d) provides that the Director may elect not to institute a proceeding if the challenge to the patent is based on matters previously presented to the Office. The statute states, in pertinent part, “[i]n determining whether to institute . . . the Director may take into account whether, and reject the petition . . . because, the same or substantially the same prior art or arguments previously were presented to the Office.” 35 U.S.C. § 325(d).



The question of whether a petition presents art or arguments that are “the same or substantially the same” as art or arguments previously presented to the Office is a factual inquiry, which may be resolved by reference to the factors set forth in *Becton, Dickinson*.<sup>7</sup> The precedential section of that decision sets forth the following non-exclusive factors for consideration:

- (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 the prior art or arguments.

*Becton, Dickinson*, 17–18.

*Advanced Bionics* sets out a two-part framework for analyzing these factors. In the first part, we consider factors (a), (b), and (d) to determine whether the art or arguments presented in the petition are the same or substantially the same as those previously presented to the Office. *Advanced Bionics*, 8–10. “If, after review of factors (a), (b), and (d), it is determined that the same or substantially the same art or arguments previously were

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<sup>7</sup> *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 (PTAB Dec. 15, 2017) (precedential as to § III.C.5, first paragraph) (“*Becton, Dickinson*”).

presented to the Office,” then we advance to the second part of the analysis to determine “whether the petitioner has demonstrated a material error by the Office” in view of factors (c), (e), and (f). *Id.* *Advanced Bionics* instructs that “[i]f 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.” *Id.* at 9.

*B. Advanced Bionics Part One*

Regarding *Becton, Dickinson* factors (a) and (b), Petitioner contends that “the asserted combinations [of prior art in the Petition] are materially different than and not cumulative of the prior art involved during examination of the challenged claims.” Pet. 61. Patent Owner disagrees, urging that Siegel was considered by the Examiner and that two other references considered by the Examiner, i.e., Lund<sup>8</sup> and Chua & Tan,<sup>9</sup> are cumulative of Kondritzer and Chia respectively. *See* Prelim. Resp. 46–48.

We agree with Patent Owner that Siegel, Chua & Tan, and Lund were considered during prosecution and are cumulative of the references asserted in the Petition. All three of these references appear in the references cited section of the ’447 patent and were identified in Information Disclosure Statements (“IDSs”) during prosecution of the ’447 patent and the ’199 patent. *See* Ex. 1001, code (56); Ex. 2001, 90 (listing Chua & Tan), 93–94 (listing Lund and Siegel); Ex. 2003, 329 (listing Chua & Tan), 332–33 (listing Lund and Siegel). Thus, these references were “previously

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<sup>8</sup> Lund et al., *The Kinetics of Atropine and Apotatropine in Aqueous Solutions*, 22 *Acta Chemica Scandinavica* 3085–3097 (1968) (Ex. 2002) (“Lund”).

<sup>9</sup> WO 2012/161655 A1, published November 29, 2012 (Ex. 1018) (“Chua & Tan”).

presented” for purposes of assessing the application of discretion under 35 U.S.C. § 325(d). *Advanced Bionics*, 7–8 (stating that previously presented art includes art cited in an IDS).

The disclosure in Chua & Tan is substantially the same as that which the Petition relies upon in Chia. Chua & Tan teaches that an “ultra-low atropine composition” comprising “about 0.01% atropine . . . reduces and/or prevents myopia progression with negligible side effects.” Ex. 1018, Abstr.; *see also id.* at 5:23–25 (explaining that the study results reported therein “showed that 0.01% atropine was found to induce negligible side-effects . . . compared to atropine at 0.1% and 0.05% and retains comparable efficacy in controlling myopia progression”). These are the same teachings the Petition cites in Chia. *See* Pet. 6–7, 25–26, 31–32, 47.<sup>10</sup> Thus, Chia is cumulative of the teachings previously presented in Chua & Tan.

Lund contains substantially the same disclosure as that which the Petition cites to in Kondritzer. Like Kondritzer, Lund reports studies of the kinetics of atropine in aqueous solution. Ex. 2002, 3085. Indeed, Lund cites Kondritzer and purports to improve upon Kondritzer’s earlier studies. *Id.* Lund teaches that atropine is subject to alkaline and acid hydrolysis and that the reaction is predominately catalyzed by OH<sup>−</sup> ions at pH values above 4. *Id.* at 3085, 3093. Lund further teaches that atropine has maximum stability between pH 1–6 (pD 1.4–6.4). *Id.* at 3087 (citing Kondritzer); *see also id.* at 3096 (disclosing computed half-life values at pH 4 (pD 4.4), which is within “the pH range where atropine has its maximum stability”). These are

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<sup>10</sup> For ground 2, the Petition additionally cites Chia’s disclosure of a low-concentration atropine solution “with 0.01% BAK preservative.” Pet. 47. Chua & Tan includes the same disclosure. Ex. 1018, 9:5–7.

substantially the same teachings as those the Petition relies upon from Kondritzer. *See* Pet. 8–10, 24, 26, 36 (arguing that Kondritzer discloses “atropine’s stability is optimum at pH 3–5 (pD 3.4–5.4)” and references other studies ranging from “pH 2.8–6 (pD 3.2–6.4) and that “these ranges overlap with and/or are encompassed by the pD 4.2–7.9 range of claim 1”).<sup>11</sup> Thus, Kondritzer is cumulative of the teachings previously presented in Lund.

The Petition’s limited reliance on Remington in ground 2 does not demonstrate any material difference between the prior art in the Petition and that previously presented to the Examiner. To the extent the Petition relies on Remington’s disclosure of overlapping pH values, those teachings are cumulative of the disclosure in Lund, which likewise teaches that atropine is stable at pH values and ranges that overlap with the pD ranges in the challenged claims. The Petition’s additional reliance on Remington’s disclosure of “conventional components of ophthalmic solutions” relates to only a few of the challenged dependent claims. *See* Pet. 12, 49–54. Nothing in the record suggests the Examiner considered the recitation of these components to distinguish those claims from the prior art presented during prosecution.

Regarding *Becton, Dickinson* factor (d), Petitioner argues that “there is little to no overlap because the Examiner did not use any of the ground references to reject any claim and did not make any arguments regarding

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<sup>11</sup> Lund’s pH ranges are not exactly the same as those in Kondritzer, but they are similar enough that when converted to pD they likewise overlap with the ranges recited in the challenged claims. *See* Pet. 5 n. 2; Ex. 1002 ¶ 42 n. 5 (explaining that pD can be calculated by adding 0.4 to the pH value).

them.” Pet. 62. Patent Owner disagrees, urging that “the Examiner considered the same argument presented in the petition: that other references using deuterium oxide to stabilize other compounds would have motivated a POSA to use deuterium oxide to stabilize atropine.” Prelim. Resp. 48.

Patent Owner points to the prosecution of the ’199 patent and the Examiner’s rejection of the claims there as obvious over Herekar<sup>12</sup> in combination with WoldeMussie<sup>13</sup> and Wildsoet<sup>14</sup> (“the Herekar rejection”). *Id.* at 11. According to Patent Owner, that rejection was overcome by its arguments that “a POSA would not read Herekar’s deuterium oxide ophthalmic formulation to predict that using deuterium oxide would extend the shelf-life of atropine” as well its data showing unexpected results for the combination of atropine and deuterium oxide. *Id.*

Patent Owner also points to the prosecution of the ’447 patent where the Examiner rejected the then-pending claims as obvious over Teva<sup>15</sup> in combination with WoldeMussie and Wildsoet (“the Teva rejection”). Prelim. Resp. 11. Patent Owner asserts that “[t]he Examiner relied on Teva’s use of deuterium oxide to improve the stability of benactyzine, an  $\alpha$ -hydroxy ester, to find motivation to use deuterium oxide to improve the stability of atropine,” but later withdrew that rejection in view of Patent Owner’s arguments that

Teva does not teach using deuterium oxide to stabilize pharmaceutical formulations regardless of active agent, limits its teachings to use deuterium oxide as a stabilizing solvent to  $\alpha$ -amino or  $\alpha$ -hydroxy carboxylic acid derivatives (like

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<sup>12</sup> US 2012/0203161 A1, published Aug. 9, 2012 (Ex. 1038) (“Herekar”).

<sup>13</sup> US Patent 5,716,952, issued Feb. 10, 1998 (Ex. 1036) (“WoldeMussie”).

<sup>14</sup> US 2012/0015035 A1, published Jan. 19, 2012 (Ex. 1037) (“Wildsoet”).

<sup>15</sup> EP0332826 A1, published Sept. 20, 1989 (Ex. 1052) (“Teva”).

benactyzine) that are different than the  $\beta$ -hydroxy carboxylic ester in atropine, and teaches through Examples 1-2 that atropine is stable in ordinary water and does not require the more expensive D<sub>2</sub>O for the purpose of stabilizing atropine.

*Id.* at 49–50 (quotations omitted).

As explained below, Patent Owner has the better argument regarding *Becton, Dickinson* factor (d) because there is significant overlap between the arguments considered by the Examiner during prosecution and Petitioner's grounds in this proceeding. We begin by summarizing the pertinent arguments in the '199 and '447 patent prosecutions.

The Herekar rejection during prosecution of the '199 patent involved claims similar to those challenged here. *See* Ex. 2001, 550 (listing claims), 554 (electing atropine); 75–76 (Non-final Rejection mailed March 7, 2016). The Examiner relied on WoldeMussie and Wildsoet as teaching atropine in an aqueous ophthalmic formulation. *Id.* at 75. The Examiner found that Herekar taught the use of deuterated water instead of regular water in an ophthalmic formulation containing riboflavin “increases the shelf life and reduces the amount of active ingredient needed for pharmaceutical activity.” *Id.* at 75–76. Based on this teaching, Examiner concluded “it would have been obvious to a person skilled in the art to add deuterated water to a pharmaceutical formulation with the expectation of getting an increased shelf life and stability.” *Id.* at 76.

Patent Owner responded to the Herekar rejection by arguing that a POSA would “not read Herekar as teaching the use of deuterated water for the purpose of extending shelf life of its riboflavin formulation, much less other ophthalmic formulations such as atropine formulations.” Ex. 2001, 49 (Applicant Response dated April, 5, 2016). Patent Owner urged that any

beneficial effect of the deuterated water taught in Herekar was “specifically tied to the underlying biological mechanism disclosed in Herekar” and did not apply to atropine. *Id.* at 49–50. In addition, Patent Owner asserted that “surprising data” in the Specification showed “unexpected properties” including “better stability,” “lower main degradant,” and “longer shelf-life” for atropine formulations in deuterated water as compared to regular water. *Id.* at 50–54; *see also id.* at 39 (Interview Summary mailed April 13, 2006, noting that “Applicant discussed the advantages of the claimed composition and referred to the portions of specification to show such advantage.”). The Examiner subsequently withdrew the Herekar rejection stating that “the data presented to [show] the advantages of the combination of atropine and deuterated water in comparison to the combination of atropine and water has placed the application in condition for allowance.” Ex. 2001, 23–24 (Notice of Allowance mailed June 13, 2006).

The Teva rejection similarly relied on WoldeMussie and Wildsoet, but asserted Teva in place of Herekar for its teachings regarding deuterated water. *See* Ex. 2003, 100–01 (Final Action mailed Jan. 25, 2017). Teva teaches injectable pharmaceutical solutions with a pH between “about 1.5 to about 5.5” in which “at least a major part of the ordinary water” is replaced by deuterated water in order to improve the shelf life of a “water-hydrolyzable derivative” of an “ $\alpha$ -amino or  $\alpha$ -hydroxy-carboxylic acid” such as benactyzine. Ex. 1052, 5:15–44. Teva Example 1 describes a “multistage automatic injector” in which benactyzine is dissolved in deuterium oxide and other “relatively more stable active ingredients (such as atropine and trimedoxime)” are “dissolved in ordinary water in one or more . . . separate compartment(s).” *Id.* at 7:8–23. Teva Example 2 describes a solution

containing benactyzine, atropine, and trimedoxime dissolved in deuterium oxide at pH 2.7. *Id.* at 7:29–32. Teva teaches that the shelf life of the compositions in both examples “was considerably enhanced as compared to similar compositions prepared with ordinary water.” *Id.* at 7:39–42. In view of these teachings, the Examiner found that Teva “makes clear that the use of deuterated water instead of water as a solvent is advantage[ous] in dissolving atropine” and it would have been obvious “to use atropine in combination with deuterated water for ophthalmic use.” Ex. 2003, 100–101.

In response, Patent Owner argued that “Teva does not teach the use of deuterium oxide to stabilize pharmaceutical formulations in general regardless of the active agents it contains,” but rather only a “very specific active agent –  $\alpha$ -amino or  $\alpha$ -hydroxy carboxylic acid derivatives (esters or amides).” Ex. 2003, 66 (Applicant Response dated April 27, 2017). Patent Owner explained that benactyzine is an  $\alpha$ -hydroxy carboxylic ester whereas atropine is a  $\beta$ -hydroxy carboxylic ester, which Teva describes as “more stable” than benactyzine. *Id.* at 66–67. For this reason, Patent Owner urged that “Teva does not recognize the stability problem for ultra-diluted atropine formulation” and therefore a POSA “would not consider Teva’s Example II as teaching the us[e] of D2O to stabilize atropine formulations in which the  $\alpha$ -amino or  $\alpha$ -hydroxy carboxylic acid derivatives (*e.g.*, benactyzine) is not present,” *i.e.*, where “atropine is the **monotherapeutic agent**.” *Id.* at 68–69. Patent Owner also relied on the unexpected results arguments it had previously asserted during prosecution of the ’199 patent. *See id.* at 69–73. Ultimately, after the claims were amended to recite a single ophthalmic agent consisting of atropine or atropine sulfate or a combination thereof, the Examiner withdrew the Teva rejection and allowed the presently challenged



claims. *See* Ex. 2003, 47–49 (Notice of Allowance mailed May 30, 2017); *see also id.*, 61–65 (Amendment/Response dated April 27, 2017).

The arguments raised in this proceeding are substantially similar to the arguments the Examiner considered during prosecution. For both grounds, the Petition relies on Siegel, which teaches the use of deuterated water to improve the stability of procaine in an aqueous solution, and asserts that based on Siegel’s teachings regarding procaine it would have been obvious to use deuterated water to stabilize a different active agent, atropine. In this regard, the Herekar and Teva rejections are similar to Petitioner’s grounds because they likewise relied on combining the teachings in one reference (Herekar or Teva) regarding the use of deuterated water to stabilize a different active agent with other references (WoldeMussie and Wildsoet) that taught ophthalmic compositions containing atropine.

Of these two rejections, the Teva rejection is the most similar to the grounds in the Petition. The Teva rejection considered whether Patent Owner’s claims would have been obvious over a reference teaching deuterated water specifically for the purpose of improving shelf-life by reducing hydrolysis of the active ingredient, benactyzine. Like atropine and the procaine taught in Siegel, benactyzine contains a carboxylic ester that is “water-hydrolyzable.” Ex. 1052, 5:25–36; *see also* Prelim. Resp. 18 (showing chemical structures of procaine, atropine, and benactyzine). As such, Petitioner’s argument that a POSA would have been motivated to use deuterated water with atropine because “atropine shares many similarities with procaine” (*see* Pet. 24) substantially overlaps with the arguments the Examiner considered when determining whether it would have been obvious to apply Teva’s teachings regarding benactyzine to atropine. In addition,

Teva teaches the use deuterated water to stabilize an agent at a pH range (“about 1.5 to about 5.5”) that overlaps with the equivalent range<sup>16</sup> in the challenged claims. Ex. 1052, 5:15–17. In this regard, Teva is closer to the claims than Siegel, which studied the rate of hydrolysis of procaine “over the pH range 8.0 to 11.0.” Ex. 1006, 4.

Petitioner attempts to distinguish the arguments considered during prosecution by pointing to differences between the references in the Petition and those considered in the Herekar and Teva rejections. *See* Pet. 15, 61–62. In particular, Petitioner asserts that, unlike Siegel, the references cited in the Herekar and Teva rejections do not disclose the kinetic solvent isotope effect (“SIE”). Pet. 15, 61–62. The Petition explains that the SIE is “[t]he difference in the rate of reaction in D<sub>2</sub>O compared to that in H<sub>2</sub>O.” *Id.* 5.

We disagree with Petitioner’s argument that Teva does not disclose the SIE. Teva teaches that using deuterated water in place of regular water stabilizes benactyzine, and similar carboxylic esters, against hydrolysis. *See* Ex. 1052, 1:1–7 (explaining that “water has a destabilizing influence” on some active ingredients and “may cause such ingredients to hydrolyze”); 2:21–36 (teaching that using deuterated water enhances stability and prolongs long term shelf-life of such compositions in aqueous solution). Thus, Teva demonstrates the SIE by teaching that the rate of hydrolysis of benactyzine is slower in deuterated water as compared to regular water. *See id.* at 7:38–42 (explaining that the “shelf life at room temperature of the

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<sup>16</sup> Claim 1 recites a pD range of about 4.2 to about 7.9. According to Petitioner’s calculations, this range is equivalent to a pH range of about 3.8 to about 7.5. *See* Pet. 5 n.2; Ex. 1002 ¶ 42 n. 5 (explaining that pD is calculated by adding 0.4 to pH).

compositions” in both Examples was found to be “considerably enhanced as compared to similar compositions prepared in ordinary water”). In this regard, Teva is similar to Siegel in that both references demonstrate the SIE for a particular carboxylic ester containing compound, but not for atropine itself.

Petitioner’s attempt to distinguish Teva because it discloses “an injectable solution of benactyzine . . . for the treatment of poisoning” is also unavailing. *See* Pet. 62. First, it is unclear how, if at all, the indication or mode of administration bears on Teva’s teaching that deuterated water stabilizes benactyzine and similar carboxylic esters against hydrolysis. The Petition does not sufficiently explain how such differences distinguish its grounds from the arguments considered for the Teva rejection. Second, the Examiner relied on Wildsoet for its disclosure of atropine-containing, ophthalmic compositions used to treat myopia. *See* Ex. 2003, 100; *see also* Ex. 1037, Abstr., ¶ 30 (teaching compositions comprising muscarinic antagonists such as atropine for treatment of myopia). Thus, in the Examiner’s view, the combination of references in the Teva rejection taught atropine in an ophthalmic composition for a similar indication as the combinations of references asserted in the Petition. *See Soft Gel Techs., Inc. v. Jarrow Formulas, Inc.*, 864 F.3d 1334, 1341 (Fed. Cir. 2017) (explaining that a “focused attack” on one reference did not undermine the obviousness determination because it was “based on a combination of references”).

Petitioner’s attempt to distinguish the arguments considered by the Examiner by contrasting the disclosure in WoldeMussie and Wildsoet with that in Chia is likewise unavailing. *See* Pet. 61 (arguing that WoldeMussie does not disclose atropine and Wildsoet discloses a “laundry list of

muscarinic antagonists,” whereas Chia “specifically disclosed atropine eye drops” at the recited concentration). First, Chia is cumulative of Chua & Tan, which was before the Examiner during prosecution. Thus, the same disclosure Petitioner relies on in Chia was presented during prosecution. Second, atropine is clearly identified as a preferred agent for Wildsoet’s compositions. *See* Ex. 1037, ¶¶ 30, 31 (listing atropine first in its lists of “suitable” and “[r]epresentative muscarinic antagonists”); Fig. 2 (depicting atropine in preferred embodiment). Accordingly, we do not see a material difference between Wildsoet and Chia as it relates to selection of atropine as an active agent for an ophthalmic composition. Third, the arguments considered by the Examiner did not focus on the distinctions Petitioner attempts to draw now. Rather, the arguments previously presented for the Teva rejection focused on whether it would have been obvious to use deuterated water in an atropine formulation based on Teva’s teachings for benactyzine. *See* Ex. 2003, 65–73. Those arguments significantly overlap with the arguments Patent Owner offers in opposition to Petitioner’s grounds here. *See* Prelim. Resp. 26–44 (arguing that the references in the Petition do not recognize any problem with the storage stability of atropine and that Petitioner has not shown that a POSA would understand Siegel’s teachings for procaine to be applicable to atropine).

For these reasons, we determine that both the art and the arguments presented in the Petition are substantially the same as those previously presented to the Examiner.

### *C. Advanced Bionics Part Two*

Regarding *Becton, Dickinson* factor (e), Petitioner argues the Examiner erred in allowing the claims because “the Examiner was simply

not aware’ of the teachings of the most pertinent art and ‘[t]he Petition . . . presents different prior art than the Office was aware of.’” Pet. 63 (quotations omitted). In addition, Petitioner argues that “the Examiner allowed the claims because of an amendment that excluded *Teva*’s disclosure of benactyzine and atropine in D<sub>2</sub>O.” *Id.* According to Petitioner, “[t]hat analysis did not consider that it was nonetheless obvious to improve low-concentration atropine with D<sub>2</sub>O as a monotherapy for treating myopia.” *Id.*<sup>17</sup>

Patent Owner disagrees with Petitioner, urging that “Petitioner’s argument is premised on ignoring the references expressly considered by the Examiner” including Chua & Tan, Lund, Siegel, and Teva. Prelim. Resp. 52. Patent Owner further contends that the Petition “fails to establish that using deuterium oxide was expected to improve long-term stability of atropine.” *Id.* Patent Owner points to evidence suggesting that atropine was known to have “a half-life of decades or even hundreds of years,” which is “much longer than required to use up the 150-day supply Dr. Byrn testified about in the largest bottles of atropine eye drops.” *Id.* at 52–53. Thus, urges Patent Owner, a POSA would have “no reason . . . to think existing aqueous atropine eyedrops lacked shelf-life stability.” *Id.* at 53.

In addition, Patent Owner argues that Petitioner “fails to justify its reliance on S[ie]gel for modifying Chia’s atropine formulation.” Prelim. Resp. 53. According to Patent Owner, Siegel observed a modest “improvement in the half-life of procaine using deuterium oxide,” but

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<sup>17</sup> Petitioner asserts that *Becton, Dickinson* factor (f) “is inapplicable because none of the asserted combinations were substantively considered by the Examiner.” Pet. 63.

“provides no suggestion that deuterium oxide would improve the stability of atropine, a very different compound.” *Id.* Patent Owner argues that “Teva teaches that deuterium oxide is not indicated for atropine, which was *more stable*” than benactyzine. *Id.* Patent Owner also points out that Teva “addresses Siegel, and explains that Siegel’s disclosure of achieving a 115-hour half-life (fewer than five days) using deuterium oxide ‘provided no suggestion that it could be practical to use deuterium oxide for long term stabilization of pharmaceutical compositions of any kind.’” *Id.* at 53–54 (quoting Ex. 1052, 2:10–20). In sum, Patent Owner asserts that “Petitioner has failed to show that no ‘reasonable minds can disagree regarding the purported treatment of the art or arguments’,” and therefore material error has not been shown. *Id.* (quoting *Advanced Bionics*, 9).

We again determine that Patent Owner has the better position. As explained above, the Examiner considered substantially the same art during prosecution. Although there was no rejection issued over the particular references cited in the Petition, those references were either before the Examiner (Siegel) or are cumulative of references (Chua & Tan and Lund) before the Examiner. There is no evidence that suggests the Examiner overlooked the most pertinent teachings in the art presented during prosecution. Indeed, the Teva rejection presented substantially the same arguments as the grounds in the Petition, including Patent Owner’s argument that there was “insufficient rationale to combine Teva and other references to produce a D<sub>2</sub>O-based formulation in which atropine is the monotherapeutic agent because atropine and its derivatives are specifically recognized as stable in ordinary water.” Ex. 2003, 69, 87–88. The Examiner credited this argument by withdrawing the Teva rejection and allowing the

'447 patent. Thus, we do not agree with Petitioner's argument that the Examiner failed to consider whether it would have been "obvious to improve low-concentration atropine with D<sub>2</sub>O as a monotherapy for treating myopia." *See* Pet. 63.

Nor has Petitioner shown that Siegel is any more relevant to the challenged claims than Teva. Both references teach the use of deuterated water to stabilize an active ingredient that, like atropine, has a hydrolyzable carboxylic ester moiety. Moreover, Teva expressly addresses Siegel, stating:

Siegel et al . . . proposed to stabilize solutions of procaine, which may be suitable for ophthalmic use, by substituting the ordinary water in these solutions by deuterium oxide. Siegel's experiments relate to the stabilization of these solutions in the alkaline pH range at 40°C; in no case does such stabilization lead to a half-life greater than 115 hours. Thus, there is no suggestion that it could be practicable to use deuterium oxide for long term stabilization of pharmaceutical compositions of any kind.

Ex. 1052, 2:10–20. This teaching supports the Examiner's decision to withdraw the Teva rejection because it suggests that a POSA would not read Siegel (or Teva) to teach the use of deuterated water to stabilize pharmaceutical formulations generally. It also suggests that a POSA might not interpret Siegel's statement that deuterated water "may prove of value" in the "preparation of ophthalmic formulations" to have as much weight as the Petition suggests that it would. *See* Pet. 1, 10, 23, 27, 33, 62 (quoting Siegel and asserting that "the use of D<sub>2</sub>O to improve stability was well known and specifically expected to be 'of value'").

Teva also supports Patent Owner's argument during prosecution (and in its Preliminary Response) that "there is no reason to substitute ordinary water" in an atropine formulation. *See* Ex. 2003, 67. Teva describes atropine

as a “relatively more stable active ingredient[]” that can be “dissolved in ordinary water” as opposed to deuterated water. *Id.* at 7:19–22. Petitioner argues this does not mean that “atropine is stable,” but rather that it is more stable than benactyzine which “was the limiting reagent” in Teva’s formulations. Pet. 18 n. 6. Even so, Kondritzer teaches that the half-life of atropine in regular water at 20°C is 1800 years at pH 4,<sup>18</sup> 266 years at pH 5 and 27 years at pH 6. Ex. 1004, 4 (Table III). Petitioner’s declarant, Dr. Byrn has testified in a related proceeding that based on Kondritzer’s half-life data it would take over 40 years for just 10% of the atropine in a low concentration formulation at pH 5 to degrade. Ex. 2006 ¶¶ 107–08 (Declaration submitted by Petitioner in IPR2022-00963). Patent Owner contrasts this with Dr. Byrn’s testimony that the largest bottle of atropine eye drops is intended to last only 150 days. Prelim. Resp. 52–53 (citing IPR2022-00963, Ex. 1002 ¶ 179). Although Dr. Byrn’s testimony was not before the Examiner, this testimony is consistent with Teva’s teaching that atropine is “relatively more stable” and tends to show that a POSA would understand that atropine formulated at the pH Petitioner alleges is optimal (pH 5–6) is already sufficiently stable in regular water to provide adequate shelf-life. In view of such evidence, we cannot say that the Examiner materially erred in accepting Patent Owner’s argument that a POSA would not have had sufficient motivation to use deuterated water to stabilize atropine.

Accordingly, Petitioner has not demonstrated that the Examiner materially erred.

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<sup>18</sup> Lund calculates a half-life of  $6.38 \times 10^6$  hours, i.e., ~ 728 years, at pH 4.0 and 20°C. Ex. 2002, 3096 (Table 6).



*D. Conclusion*

Based on the foregoing, we determine that the circumstances of this case warrant the exercise of discretion under 35 U.S.C. § 325(d) and therefore deny institution.

ORDER

After due consideration of the record before us, and for the foregoing reasons, it is:

ORDERED that the Petition is denied, and no *inter partes* review is instituted.

IPR2022-00964  
Patent 9,770,447 B2

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