

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

EYENOVIA, INC.,
Petitioner,

v.

SYDNEXIS, INC.,
Patent Owner.

Case No. IPR2022-00964
Patent 9,770,447

PATENT OWNER'S PRELIMINARY RESPONSE

35 U.S.C. §313; 37 C.F.R. §42.107

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I. INTRODUCTION

The petition falls far short of the threshold for institution and should be denied. Specifically, the petition's hindsight-driven obviousness case lacks the requisite motivation to combine with a reasonable expectation of success. The petition alleges that it would have been obvious to reformulate Chia's aqueous atropine children's eye drops with Siegel's D₂O formulation in order to address alleged stability concerns from storing atropine in aqueous solution at a pH of 5-6 (pD 5.4-6.4). Pet. 36-37 ("POSA would have recognized that pD 5.4-6.4 was optimal" to "balance long term stability with clinical considerations" including patient comfort).¹ But the petition's case suffers from at least two critical flaws. First, the alleged stability concerns on which the petition's case is based are unsubstantiated in the record—Petitioner never documents any relevant atropine stability concern in the prior art. In fact, Petitioner's own evidence undermines its unsubstantiated premise. Petitioner's cited references and its own expert testimony indicate that aqueous atropine already was viewed as highly-stable for years or even decades (e.g., 40 years), beyond the proposed shelf-life. Second, Petitioner

¹ This same Petitioner simultaneously argues in IPR Nos. 2022-00384, -00414, and -00415 that a POSA would have continued the conventional practice of using water, rather than deuterium oxide, for atropine eyedrops.

fails to demonstrate that a POSA would have expected Siegel's D₂O formulation to meaningfully address alleged atropine stability. Petitioner points to Siegel's gain of three days in half-life for procaine (*not* atropine). Even if the same stability gain could be assumed for the different drug atropine (it cannot), the petition fails to address why such a marginal increase in half-life (e.g., three days) would be desirable and why it would outweigh potential disadvantages of D₂O reported in Petitioner's own submitted references. Petitioner's failure to reckon with the clear teachings of the very references it relies upon to build its case provides ample reason to deny institution.

In all grounds of challenge, Petitioner relies on Chia to establish that 0.01% atropine ophthalmic eye drops achieved "comparable efficacy" to higher atropine concentrations (0.5 and 1%) when administered nightly for 2 years to children to treat myopia (nearsightedness). EX1003, Title & Abstract; Pet. 25. Petitioner asserts that Chia's atropine was formulated in "conventional" aqueous solution. Pet. 23, 35 ("H₂O formulation used successfully in *Chia*"). Petitioner then inexplicably assumes a stability problem where Chia reports none.

Not only does the petition fail to identify any prior art reference recognizing a stability problem for atropine using the "conventional" aqueous formulation, but Petitioner fails to account for the teaching of its Kondritzer grounds reference that aqueous atropine solutions already were shelf-life stable at Petitioner's proposed

solution pH. Indeed, Kondritzer itself explains that atropine sulfate solution was considered stable in storage “if the pH is kept at the range 2.8-6.0,” and that atropine stored at 20°C at pH 5 had a *half-life of 266 years*. EX1004, 532, 534 (Table III). In contrast, Petitioner’s expert—Dr. Stephen Byrn—notes that the largest atropine eyedrop bottles hold 300 administrations (IPR2022-00963 EX1002, ¶179), which is a 150-day supply for once-daily administration to each eye. Dr. Byrn testified in support of Petitioner’s earlier IPRs about aqueous atropine—relying on Kondritzer’s half-life data—that it would take *more than 40 years* for atropine to degrade even 10% in water at pH 5 at 20°C. EX2006, ¶¶107-08; *see also* Pet. 13, 33-35 (alleging “long-term stability” of 2-3 years). In light of its own evidence, Petitioner identifies no reason for a POSA to think existing aqueous atropine eyedrops lacked shelf-life stability at pH 5-6.

The predicate for Petitioner’s alleged motivation appears to be nothing but improper hindsight improperly gleaned from the challenged patent’s discovery of unexpected instability of low-concentration atropine in aqueous solution. Despite the teachings of Chia, Kondritzer, and other atropine literature submitted with the petition, Sydnexis determined that low-concentration atropine aqueous solution behaves differently than higher-concentration atropine aqueous solutions and lacked the storage stability that was characteristic in the prior art of atropine solutions. As part of a paradigm shift away from the prior art that was later

acknowledged by others, Sydnexis invented solutions to the stability problem it discovered and obtained patents for those solutions over a period of years. But neither the problem, nor the claimed solution, was predictable for atropine *at the critical date* given the teachings of Petitioner's grounds references.

Indeed, the second step in Petitioner's obviousness case fares no better than the first. Petitioner argues that it would have been obvious to solve atropine's (unknown) aqueous instability by replacing the conventional water solvent with deuterium oxide. Deuterium oxide, also called D₂O, deuterated water, or heavy water, was much more expensive² and rare than water, and the public historically associated it with nuclear reactors. EX1022, 368; EX1030, 6-7. Petitioner purports to justify this substitution because Siegel, a reference that was expressly considered during prosecution, used deuterium oxide as a solvent and observed a 3-day increase in the half-life of procaine, a different compound that was known to be labile in water, unlike atropine. But Siegel provides no suggestion that deuterium oxide would materially improve the stability of atropine, a very different compound.

² The cost estimate for pharmaceutical-grade D₂O in the literature submitted with the petition is \$11,400/kg. EX1029, 11

Indeed, the Examiner applied another reference (EP0332826, “Teva”), which teaches a stability improvement for a discrete class of labile esters (including benactyzine) when dissolved in deuterium oxide instead of water. But Teva teaches that deuterium oxide is not indicated for atropine, which was more stable. EX1052, 7:16-23. Teva’s solution pH, like the solution pH of 5-6 proposed in the petition, was within the pH range (2.8-6.0) at which Petitioner’s own Kondritzer reference teaches atropine aqueous solution was stable. EX1004, 532. Teva also 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.*, 2:10-20. Petitioner completely fails to substantiate its theory that Siegel’s report showing deuterium oxide increased procaine’s *half-life by 3 days* would have motivated a POSA to use deuterium oxide in place of water in Chia’s eyedrops for children, even if there were no downsides to the substitution. But Petitioner also fails to weigh any potential disadvantages of its proposed substitution (including disadvantages reported in Petitioner’s own references) against any potential benefits, further indicating that the case is motivated by nothing but improper hindsight.

In light of the petition’s many deficiencies, it is not surprising that the Examiner allowed the claims after considering Siegel and Teva, discussed above,

as well as references against which Chia and Kondritzer are merely cumulative. For both asserted grounds, Petitioner proposes to combine Chia and Kondritzer with Siegel.³ But Chia (EX1003) adds nothing not already considered in view of Chua & Tan (EX1018), which is the patent publication version of Chia by two of the same authors, and it even cites Chia. Kondritzer (EX1004) adds nothing not already considered in view of Lund (EX2002), which is a follow-up study to Kondritzer that cites and expressly discusses Kondritzer. Petitioner grudgingly admits that Siegel (EX1006) was expressly considered by the Examiner (Pet. 62). The Examiner also applied Teva in an office action, and Teva teaches that deuterium oxide was not indicated for atropine and that Siegel “provided no suggestion that it could be practical to use deuterium oxide for long term stabilization of pharmaceutical compositions of any kind.” EX1052, 2:10-20.

During prosecution, the Examiner asserted an obviousness rejection based on the use of deuterium oxide to stabilize an ophthalmic composition. But the Examiner ultimately withdrew that rejection based on applicant’s persuasive

³ Ground 2 merely invokes Remington (EX1005) for “conventional components of ophthalmic solutions, including a standard solution appropriate for atropine.” Pet. 12. Notably, Remington’s discussion regarding atropine does not mention deuterium oxide. EX1005, 1569.

showing that deuterium oxide was not expected to improve stability of atropine eye drops. There is no meaningful difference between the art and arguments presented by Petitioner and what was already considered and applied by the Examiner. Petitioner fails to show the Examiner erred in a manner material to patentability; the Examiner was aware of the pertinent art, and Petitioner's proposed modification appears to be motivated by nothing but hindsight, as discussed above. In light of the petition's many deficiencies, and the cumulative nature of the challenge, institution should be denied. *See* 35 U.S.C. §§314(a), 325(d); *Advanced Bionics, LLC v. MED-EL Eleckromedizinische Geräte GmbH*, IPR2019-01469, Paper 6, at 7-9 (Feb. 13, 2020) (precedential) ("*Advanced Bionics*").

II. BACKGROUND

A. Overview of the '447 Patent

The '447 patent addresses an atropine stability issue discovered by its inventors at Sydnexis that was unknown at the time, according to Petitioner's own references. *See* Section V.A.i below. For example, the '447 patent states that the "present disclosure recognizes that there is a need for a stabilized ophthalmic composition with extended shelf-life upon storage" and that "there is a need for stabilizing an ophthalmic composition through arresting or reducing hydrolysis of at least some of its active ingredients." EX1001, 6:36-41. The '447 patent explains 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.*, 7:6-10. Increased concentration of atropine “contributes to the stability” of an aqueous ophthalmic solution by, for example, acting as a buffering agent to affect the pH of the composition. *Id.*, 7:10-17. The specification also states that atropine concentration “in some embodiments affects the interaction” between the atropine and other ingredients of the ophthalmic composition in a way that “affects the stability” of the composition. *Id.*, 7:17-22.

Following experimental examination, the specification recognizes that deuterium oxide stabilizes the low-concentration ophthalmic atropine composition. *Id.*, 7:23-32, 13:38-43, 21:51-22:6. In Examples 9 and 11, for example, the specification discloses that low-concentration atropine sulfate was more stable in deuterium oxide than in water. *Id.*, 70:59-72:28, 76:31-78:59 & Tables 15, 24A-B (compare formulations 3 and 7; 5 and 8; 10-11 and 9; 13 and 12). The ’447 patent also discloses that deuterium oxide formulations had lower main degradant (*id.*, 78:60-79:41) and had longer predicted shelf lives. (*id.*, 81:52-82:28 (Example 12, Table 30)). Notably the stability profile shown in the specification of low-concentration atropine aqueous solution was dramatically different than the stability profile presented in the prior art (e.g., Kondritzer/Lund). In some instances, “deuterated water further lowers the buffering capacity of an ophthalmic

composition, leading to less tear reflex in the eye.” *Id.*, 7:32-34; *see also id.*, 9:35-43; *id.*, 13:28-37, 22:11-21. The specification states that an excessive tear response can reduce the absorption of the drug in the eye. *Id.*, 7:3-5.

The ’447 patent has 19 claims, of which claims 1, 14, and 17 are independent. Claim 1 recites:

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 %.

Claim 14 is directed to an ophthalmic solution while claim 17 is directed to a method of arresting myopia progression.

B. Prosecution History

The same Examiner who evaluated the application that matured into the ’447 patent also examined the parent application that issued as U.S. 9,421,199 (the “’199 patent”) and the continuation applications that issued as U.S. Patent Nos. 10,076,515; 10,201,534; and 10,864,208.

The original IDS for the parent '199 patent—which was omitted from Petitioner's incomplete file history exhibits⁴—listed the same Siegel reference (EX1006) asserted here, a reference (EX1018) by two authors (Wei Han Chua and Donald Tan) of Chia (EX1003) discussing the same clinical trial results for 0.01% atropine as Chia, and a reference (Lund, EX2002) citing Kondritzer and discussing atropine hydrolysis. EX2001, 0090, 0093-94 (entries 008, 016, and 022); EX2002, 3085, 3096 (reference 8). The Examiner considered each of these references. EX2001, 0083, 0086-87, (entries 008, 016, and 022). The Examiner again considered these references during prosecution of the application that matured into the '447 patent. The original IDS for the '447 patent—which again was omitted from Petitioner's incomplete file history exhibits⁵—also listed Siegel, Chua & Tan, and Lund. EX2003, 0329, 0332-33 (entries 008, 016, and 022). The Examiner again considered each of these references. EX2003, 0316, 0319-20 (entries 008, 016, and 022). The Examiner also considered and applied EP0332826 ("Teva") which published decades after Siegel, interpreted Siegel, and points out that

⁴ EX1034-EX1035 and EX1039-EX1041. Sydnexis submits the missing prosecution history in EX2001.

⁵ EX1090-EX1095 and EX1097-EX1098. Sydnexis submits the missing prosecution history in EX2003.

Siegel's greatest half-life achieved with deuterium oxide (115 hours, fewer than five days) "provided no suggestion that it could be practical to use deuterium oxide for long term stabilization of pharmaceutical compositions of any kind." EX2001, 0090 (entry 003), 0083 (considered during prosecution of the '199 patent); EX1052, 2:10-20.

Having considered Siegel, Teva, Lund, and Chua & Tan during prosecution of the '199 patent, the Examiner rejected the pending claims under 35 U.S.C. §112 for not being limited to a specific muscarinic antagonist and as obvious over WoldeMussie (EX1036), Wildsoet (EX1037), and Herekar (EX1038). EX2001, 0071-0075. Applicant narrowed the claims to atropine and argued 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. *Id.*, 0043-50.

Applicant also discussed the unexpected technical effects of deuterium oxide on low-concentration atropine formulations, including increased stability, decreased main degradant, and increased shelf-life. *Id.*, 0050-54. The Examiner concluded that "the data presented to 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." *Id.*, 0023-24.

During prosecution of the application that issued as the '447 patent, the Examiner issued and ultimately withdrew a rejection based on Teva. Before

allowing the claims of the '447 patent, the Examiner adopted applicant's arguments that Teva does not teach using deuterium oxide to stabilize pharmaceutical formulations regardless of active agent, limits its teachings to using deuterium oxide as a stabilizing solvent for α -amino or α -hydroxy carboxylic acid derivatives (like benactyzine) that are different than the β -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 D₂O for the purpose of stabilizing atropine." EX2003, 0066-69; *id.*, 0048 (adopting applicant's arguments). Applicant noted that Teva's (EX1052) examples demonstrate that atropine's increased stability compared to benactyzine means that it had adequate shelf-life in ordinary water. EX2003, 100. Teva failed to recognize a stability problem for atropine formulations or to contemplate solutions for such problems, but instead teaches that atropine is stable in ordinary water at acidic solution pH. *Id.*, 0067-68 (citing *In re Omeprazole Patent Litig.*, 536 F.3d 1361 (Fed. Cir. 2008)). Applicant also argued unexpected results. *Id.*, 0069-73. Although the Examiner had asserted based on Teva that increased stability was the expected result of solubilizing atropine in deuterium oxide because this had been the case with a different ester, benactyzine, the Examiner ultimately allowed the claims because Teva teaches that atropine was stable in water. EX1052, 7:5-23; EX2003, 0048.

C. Asserted References

(i) Chia

Chia (EX1003) lists Wei-Han Chua and Donald Tan as authors. EX1003, 347, 354. These are the named inventors of International Patent Application No. PCT-SG20 12/000174 (EX1018, cover), the WIPO publication of which identifies the Chia reference and was considered during prosecution of the '447 patent. EX2003, 0329 (entry 008), 0316 (considered); EX1018, 31.

Just like Chua & Tan, Chia discusses the results of Dr. Chua and Dr. Tan's ATOM1 (EX1010) and ATOM2 trials regarding 0.01% atropine. EX1018, Abstract, Background of the Invention, Description of the Figures; EX1003, Abstract. Both references disclose that the 0.01% atropine trial involved nightly ocular administration to children for a period of two years. EX1003, Abstract (Intervention); EX1018, 5:20-25. Neither reference proposes administering atropine in deuterium oxide. Neither reference identifies any stability problem with the 0.01% atropine solution, much less a shelf-life stability problem.

(ii) Kondritzer

Kondritzer and Zvirblis's 1957 publication ("Kondritzer") carried out a kinetic study of the proton-catalyzed hydrolysis of atropine. EX1004, abstract. Kondritzer states that "[t]he pH of minimum hydrolysis [of atropine] has been calculated and found to vary with temperature from pH 4.11 at 0° to pH 3.24 at

100°.” *Id.* Kondritzer also gives calculated half-lives of atropine in aqueous solution over the range of pH 2 to 7 at temperatures from 20° to 100°C. *Id.* Kondritzer states that “[s]tability is claimed for 0.1% sterilized atropine sulfate solution in storage if the pH is kept in the range 2.8-6.0, distinct deterioration on storage occurring if the pH is kept at 7 or higher.” EX1004, 532 (left column). Kondritzer states that the half-life of atropine between pH 3 and 5 “is so great that its experimental determination is not practical.” *Id.*, 534 (right column). Table III discloses the half-life values that Kondritzer predicted for atropine between pH 3 (548 years) and pH 5 (266 years) at 20°C. *Id.*, 534 (Table III).

During prosecution of the ’447 patent, applicant identified Lund 1968 (EX2002), a more recent study of the kinetics of atropine in aqueous solution. EX2003, 0332 (entry 016), 0319 (considered). Sydnexis submits Lund as EX2002 because Petitioner elected not to submit Lund to the Board with its petition. Lund, which is essentially an update to Kondritzer, discusses Kondritzer as well as earlier and later kinetic studies of aqueous atropine solutions. EX2002, 3085, 3096 (reference 8). Lund discusses the “Kinetics of Atropine and Apotropine in Aqueous Solutions,” including the pH dependent nature of atropine hydrolysis. EX2002, 3085-3096. Lund specifically studied hydrogen and hydroxyl ion catalyzed atropine degradation reactions in water “in the pH range 1-6,” including

the range of pH 2-4 “where atropine has its maximum stability.” EX2002, 3087, 3096 & Table 6.

(iii) Siegel

The Applicant for the '447 patent identified the 1964 Siegel reference entitled “Stability of procaine in deuterium oxide” in the original IDS, and the Examiner considered Siegel before even issuing the first obviousness rejection. EX2003, 0333, 0320 (entry 022).

Siegel undertook a study of procaine stability in deuterium oxide because the compound was known to be “labile in an aqueous medium.” EX1006, 978 (left column). Siegel reports a maximum half-life of procaine in deuterium oxide of 115 hours, less than five days. *Id.*, 979 (Table I). This amounted to an increase in half-life of approximately 3 days as compared to using water. Siegel makes no claim that deuterium oxide improves the stability of procaine sufficiently to provide shelf-life stability, much less for 150 days or 2-3 years. Nor does Siegel make any claim that deuterium oxide improves the stability of any compound other than procaine, certainly not atropine.

(iv) Remington

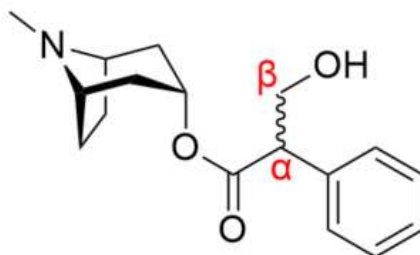
EX1005 provides certain excerpts of Volume II of the Nineteenth Edition of Remington, The Science and Practice of Pharmacy. EX1005, cover, TOC. These excerpts include a discussion of diluting agents, pharmaceutical solvents, and

ophthalmic preparations. EX1005, 21-24, 33-34, 46. Notably, these discussions never suggest or even contemplate using deuterium oxide for any of these purposes. Instead, Remington suggests dissolving water-soluble pharmaceutical formulations in water. *Id.*, 21-22. Remington recommends preparing a suitable vehicle for atropine salts using sterile purified water, but never mentions aqueous atropine solutions having any stability problem and does not indicate deuterium oxide should (or could) be used instead. EX1005, 52.

D. Technical Background

(i) Atropine

Atropine is a β -hydroxy carboxylic ester having the following structure:



It has a large, bulky eight-membered, bicyclic, tropane on one side of the ester. On the other side of the ester, atropine has a hydroxyl group bonded to the carbon that is in β -position to the carbonyl and an unsubstituted phenyl ring that is bonded to the α -carbon (not bonded directly to the carbonyl). Atropine thus has no electron withdrawing group alpha to the ester linkage.

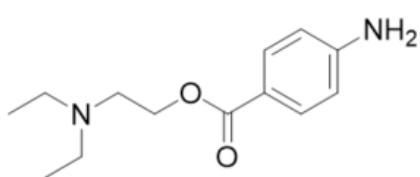
(ii) Hydrolysis

As discussed in detail below, the petition relies on an unproven premise that

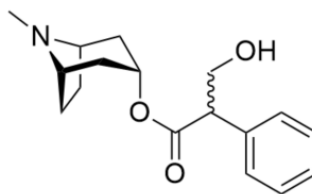
it would have been obvious to combine the deuterium oxide formulation used for procaine in Siegel with the atropine of Chia because both procaine and atropine are esters and are thus capable of undergoing degradation by hydrolysis. Petitioner's submitted references teach that stability of any compound in solution turns not only on whether hydrolysis *can* occur, but the *speed* at which it actually occurs. *See, e.g.*, EX1083, 6045 (“[A]t neutral pH, the rate of hydrolysis of most esters is very slow; the half-life for the uncatalyzed hydrolysis of ethyl acetate in water at 25°C is approximately 89 years.”). Petitioner submitted the Waterman reference (EX1080), which explains that “the presence of potentially hydrolytically reactive sites” such as an ester “should be viewed in terms of interpreting the experimental findings” for a particular compound “rather than as a prediction of hydrolytic instability” because “there are many factors related to the chemical structure of a drug and its environment in the dosage form” that impact its stability. EX1080, 119. Waterman elaborates that “[s]ome reactions are extremely slow and unlikely to be an issue,” especially ester hydrolysis which is “generally slow due to the poor leaving-group ability of alkoxide and requires chemical or enzymatic catalysis.” *Id.*, 119. In other words, the fact that two compounds each have an ester linkage does not demonstrate that both compounds will have comparable instability in water or that formulations designed to address water instability of one of them will improve the stability of the other.

(iii) Procaine

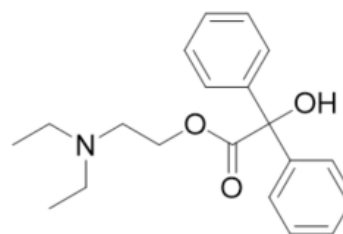
In stark contrast to atropine, which was understood to be relatively stable in its conventional aqueous formulations (as in Remington), Petitioner's submitted references indicate that procaine was known to be unstable in solution due to hydrolysis. *See, e.g.*, EX1033, 276 ("instability of procaine in solution is due mainly to the hydrolysis of the ester linkage"). Unsurprisingly, it is immediately apparent that the structure of procaine (and the resulting lability of its ester linker) is very different from atropine. Notably, procaine (below, left) has a para-aminated benzene ring directly bonded to the carbonyl carbon. This directly connects the electronics of the primary amine to the carbonyl via electron resonance. Such electron resonance is impossible in atropine (below, middle) because atropine's phenyl ring is not bonded to the carbonyl. Furthermore, when the primary amine of procaine is protonated (*i.e.*, at acidic pH), the para-aminated benzene ring has a significant electron withdrawing effect on the ester linkage, which makes procaine's ester linkage labile. Atropine also lacks the α -hydroxyl group to which the Teva reference attributed the instability of benactyzine (below, right).



Procaine



Atropine



Benactyzine

Both procaine and benactyzine also share the same diethylaminoethanol leaving group, the three dimensional shape and electronic characteristics of which are very different from atropine's large, bulky, tropane substituent. The petition never addresses any of these structural differences or explains why a POSA would expect the stability profile of procaine and impact thereon of deuterium oxide to be predictive for the structurally different atropine compound. *See* Section V.A.iii below.

(iv) Deuterium Oxide

Petitioner's own references describe deuterium oxide, commonly called "heavy water," as having a primary use as an "industrial chemical" in nuclear reactors. EX1022, 368; EX1030, 6. They explain that, over time, "heavy water gained notoriety as a feed material for nuclear weapons." *Id.*, 7. By 1975, almost *four decades before the critical date*, Blake (submitted with the petition) stated that heavy water was readily available to the scientific community "as a result of advances in nuclear technology." EX1022, 368. Petitioner's exhibit asserts that two accepted uses of deuterium beyond nuclear technology resulted from the "burgeoning interest" in it during the mid-twentieth century. *Id.* These two uses were (1) labeling drugs at specific molecular positions for drug distribution and metabolism studies; and (2) as a routine diagnostic agent for measuring total body water or in place of neutron radiography. *Id.*, 388; *see also* EX1021, Abstract.

Neither of these short-term exposures involve the use of deuterium oxide instead of water as a solvent to provide shelf-life stability to pharmaceutical compounds generally, or atropine in particular.

III. PERSON OF ORDINARY SKILL IN THE ART

For the purposes of this preliminary response, Sydnexis does not present a different level of ordinary skill than proposed in the petition. Pet. 22. However, Sydnexis notes that a POSA would have understood the state of the art as explained in Sections II.C-D above, would have understood the differences in the structure and chemistry of atropine and procaine, and would not have conflated them, as does the petition.

IV. CLAIM CONSTRUCTION

Sydnexis submits that no claim construction is necessary to find the petition fails to demonstrate a reasonable likelihood of success but reserves all rights to challenge Petitioner's claim construction.

V. THE PETITION FAILS TO ESTABLISH A REASONABLE LIKELIHOOD THAT ANY CHALLENGED CLAIM IS OBVIOUS

The petition is substantively defective because it proposes an illogical combination lacking any substantiated motivation to combine and fails to weigh what its own submitted literature reports as downsides of using deuterium oxide. "In determining whether there would have been a motivation to combine prior art references to arrive at the claimed invention, it is insufficient to simply conclude

the combination would have been obvious without identifying any reason why a person of skill in the art would have made the combination.” *Metalcraft of Mayville, Inc. v. Toro Co.*, 848 F.3d 1358, 1362 (Fed. Cir. 2017). The petition critically relies on two, foundational and essential premises but substantiates neither one of them. The first premise is that a POSA would have been motivated to abandon conventional *aqueous* formulations of atropine eyedrops to address an allegedly known stability problem. No such instability problem was recognized in petitioner’s submitted references. The second premise is that Siegel’s use of deuterium oxide to increase the half-life of procaine, a completely different compound from atropine, would have motivated a POSA with a reasonable expectation of success to employ Siegel’s D₂O formulation instead of the water used in Chia and Kondritzer. An increased half-life of three days would hardly solve a shelf life stability issue and a POSA would not have been motivated to use such an approach. But Petitioner fails to substantiate either premise, and each failure is independently fatal to its case.

Indeed, even Petitioner’s own references undermine both essential premises of Petitioner’s case. For example, Petitioner’s references recognize no known stability problem for conventional aqueous atropine formulations. In fact, the petition grounds begin with two references (Chia and Kondritzer) that teach that conventional aqueous atropine solutions were stable. Petitioner relies on Chia to

establish that highly-dilute 0.01% atropine ophthalmic solution achieved “comparable efficacy” to higher atropine concentrations when administered nightly for 2 years to children to treat myopia (nearsightedness). EX1003, Title & Abstract; Pet. 25. Petitioner asserts that Chia’s atropine was formulated in a “conventional” aqueous solution. Pet. 23, 35. Petitioner then inexplicably assumes a stability problem where Chia reports none. The petition fails to identify any prior art reference identifying a shelf-life stability problem in “conventional” aqueous formulations of atropine.

Petitioner fails to account for its second grounds reference, Kondritzer, which teaches that atropine was viewed as storage stable in a solution pH as high as 6.0. The petition relies on Kondritzer to show that atropine stability was “optimum at pH 3-5,” as if this indicated that atropine lacked shelf-life stability at pH 5-6 (pD 5.4-6.4), the range specifically proposed in the petition. Pet. 36-37. But Kondritzer itself explains that atropine sulfate solution was considered stable in storage “if the pH is kept at the range 2.8-6.0,” and that atropine stored at 20°C and pH 5 had a half-life of 266 years. EX1004, 532 534 (Table III).⁶ In fact, Petitioner’s own expert previously testified for Petitioner based on Kondritzer’s half-life data that it would take *more than 40 years* for even 10% of atropine to

⁶ Even at a solution pH as high as 6, Kondritzer reports a half-life of 27 years.

degrade in water at pH 5. EX2006, ¶¶107-08. The petition itself asserts that existing aqueous atropine ophthalmic solutions were routinely formulated at pH of 5-6. Pet. 37-38. Petitioner fails to substantiate its premise that a POSA would have been motivated to reformulate atropine to enhance its stability at pH 5-6 (pD 5.4-6.4).

Petitioner also fails to substantiate its second, critical premise, that a POSA would have been motivated to adopt Siegel's D₂O formulation for an ophthalmic atropine composition because of a marginal increase in half-life of a different compound, procaine. Pet. 9. Notably, Siegel achieved a maximum half-life of only 115 hours (~4.8 days) using deuterium oxide, a three-day increase over using water (38 hours, ~1.6 days). EX1006, 978-79 & Table I. Petitioner fails to substantiate its assumption that these results would have motivated the proposed modification with a reasonable expectation of success. Petitioner's failure is particularly deficient considering that the prosecution history of this patent and its family already includes Teva's prior art teachings that the 115-hour half-life would not have motivated a POSA to use deuterium oxide for any pharmaceutical formulation, much less for an ophthalmic formulation of atropine.

Moreover, even if Siegel's decades-old results would have been of interest to a POSA for stabilizing procaine for short-term use as an anesthetic, the petition fails to demonstrate a POSA would have been motivated to apply Siegel's

deuterium oxide formulation to Chia's aqueous atropine ophthalmic solution with a reasonable expectation of success. Siegel does not purport to teach that deuterium oxide would provide a stability improvement to any compound other than procaine, much less to the more stable atropine. Procaine is not atropine; it is immediately apparent that procaine has a different structure and a different chemical and stability profile than procaine. Petitioner fails to justify its premise that procaine, an anesthetic that is structurally and chemically different (and much less stable) than atropine, would be predictive of formulation outcomes for atropine. The petition's reliance on Siegel's deuterium oxide formulation to address an alleged hydrolytic instability problem of atropine, contrary to the express teachings of the prior art (e.g., Teva), is completely unjustified in view of even the references that Petitioner submitted.

In addition to failing to substantiate its own premises, Petitioner ignored countervailing evidence that it submitted, and which undermines its proposed motivation. Federal Circuit precedent requires the prior art to be considered "for all its teachings, not selectively." *Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1332 (Fed. Cir. 2019). For example, Teva addressed Siegel and explained that Siegel "provided no suggestion that it could be practical to use deuterium oxide for long term stabilization of pharmaceutical compositions of any kind." EX1052, 2:10-20. The petition also fails to grapple with numerous documented

complexities and cost issues associated with deuterium oxide and why even a marginal increase in half-life (e.g., three days) would outweigh those factors. *See Henny Penny Corp.*, 938 F.3d at 1332 (“The benefits, both lost and gained, should be weighed against one another” (quoting *Winner Int’l Royalty Corp. v. Wang*, 202 F.3d 1340, 1349 n.8 (Fed. Cir. 2002))).

For example, Petitioner’s own submitted exhibits report that the proposed substitution involved significant perceived disadvantages, including significantly increased cost and regulatory burdens and perceptions of potential toxicity. The petition’s failure to address the perceived disadvantages of its proposed substitution, like its failure to account for the teachings of its own grounds references that undermine the proposed combination rationale, suggests that the proposed substitution is based on nothing more than improper hindsight. *See Adapt Pharma Operations Ltd. v. Teva Pharms. USA, Inc.*, 25 F.4th 1354, 1382 (Fed. Cir. 2022) (“[W]orking backwards from [the invention] with the benefit of hindsight, once one is aware of it does not render it obvious.” (quoting *Amerigen Pharms. Ltd. v. UCB Pharma GmbH*, 913 F.3d 1076, 1089 (Fed. Cir. 2019))). Petitioner’s hindsight-driven approach to modifying the claims provides sufficient reason to deny institution.

A. The Petition Lacks a Substantiated Motivation to Combine

(i) The Petition Assumes Atropine Instability Without Corroborating Evidence

As discussed above, the petition depends on an unproven premise that a POSA would have thought aqueous atropine lacked storage stability at a solution pH of 5-6. Pet. 26-27, 36-37. The petition cites no prior art reference proposing or confirming its hypothesis of atropine instability. Instead, the petition itself asserts that atropine ophthalmic solutions already were routinely formulated at the petition's own proposed pH range of 5-6. Pet. 37-38. *See, e.g.*, EX1065 at 1-2 (0.04% atropine for chronic administration pH 4-6); EX1067 at 2-3 (0.05% atropine pH 4-6), EX1066 at 3 (1% atropine pH 3.5-6); *see also* Section II.C.iv above (discussing EX1005, 52, 54).

Petitioner's unstable-atropine premise also is undermined by the asserted grounds references. The grounds begin by arguing that a POSA would rely on Chia's 2012 disclosure that 0.01% atropine sulfate ophthalmic solution achieved "comparable efficacy" to 0.5% and 0.1% atropine sulfate when administered nightly for 2 years to children to treat myopia (nearsightedness). EX1003, Title & Abstract, Pet. 7, 25. The petition asserts that Chia used water for its atropine formulation and describes Chia's 0.01% atropine formulation as "conventional." Pet. 23, 35; *accord* EX1013, 45 (0.05% atropine solution prepared by diluting with distilled water); EX1012, Abstract, [0013], [0036] (similar); EX1045, 3 (similar);

EX1014, Abstract, 342 (similar for 0.025% atropine); EX1016, Abstract, 462-63 (similar for 0.05%-0.1% atropine over 3-7 years). Notably, Chia makes no mention of any shelf-life stability problem when using the “conventional” water solvent for atropine.

Kondritzer likewise undermines Petitioner’s unstable-atropine premise. For example, Kondritzer describes 0.1% atropine sulfate solution as stable in storage “if the pH is kept at the range 2.8-6.0” and provides a half-life at 20°C and pH 5 of 266 years. EX1004, 532, 534 (Table III). In contrast, Petitioner’s expert says that even the largest bottles of atropine ophthalmic eyedrops only needed to be stable enough to be administered “daily” for as many as “300 administrations.” IPR2022-00963 EX1002, ¶¶94, 179. Since each human has two eyes, this amounts to a 150-day supply in the largest bottles.

Even for injectable aqueous atropine solution used as an antidote for nerve poisoning, a shelf-life (retaining 90% potency) of 2-3 years was viewed as quite adequate. EX1020, 332. According to Petitioner’s expert Dr. Byrn, atropine’s half-life of 266 years at 20°C and pH 5 corresponds with more than 90% of the drug remaining intact after more than 40 years of storage. EX2006, ¶¶107-08.

Kondritzer thus undermines Petitioner’s argument that a POSA would have thought there was a hydrolysis instability problem in conventional aqueous formulations of atropine.

Nor does the petition identify any prior art reference disclosing a shelf-life stability problem in “conventional” aqueous atropine formulations. To the contrary, Remington describes a suitable vehicle for atropine salts using sterile purified water with no mention of any stability problem. EX1005, 52. Petitioner also submitted excerpts from Remington (22nd Ed.) that identify certain compounds as requiring special formulation or handling to address stability issues but atropine is conspicuously absent from them. EX1046, 16.

Kondritzer, Chia, and Remington’s consensus that aqueous formulations of atropine were perceived to be storage stable is amply corroborated by other evidence Petitioner submitted. For example, Schier disclosed that aqueous atropine formulations were still stable with “no substantial amount” of primary degradant years and even decades *after the expiration dates*. EX1020, 329 & Abstract. Teva disclosed that atropine and benactyzine were two carboxylic esters that were co-administered to treat nerve and pesticide poisoning, that the susceptibility of benactyzine to hydrolysis “detracts from its usefulness,” but that atropine is “more stable” and could be formulated in ordinary water even when attempting to formulate less stable α -amino- or α -hydroxy-carboxylic esters in deuterium oxide to address their known stability problem. EX1052, 6:18-30, 7:17-23 & Example II (7:25-38). Despite being well aware of these references, and Teva being asserted during prosecution of the ’447 patent, the petition fails to persuasively rebut this

evidence. For example, Petitioner fails to explain why it views Siegel as informative of potential atropine stability in a solution pH of 5-6 at which its own Kondritzer reference teaches “[s]tability is claimed” (EX1004, 532), but attempts to distinguish Teva’s teachings about atropine’s relative stability because Teva also employed a solution pH in the range for which Kondritzer taught atropine stability. Pet. 18.

Moreover, the petition’s attempt to justify the proposed modification simply based on the general mechanism of action for hydrolysis of esters is unsubstantiated. Petitioner’s own submitted references teach that stability of a compound in solution turns not only on whether hydrolysis *can* occur, but the *speed* at which it actually occurs, and reports that hydrolysis of most esters is “very slow.” *See, e.g.*, EX1083, 6045; EX1080, 119. Petitioner’s literature teaches that observing that a compound has an ester bond is insufficient to make “a prediction of hydrolytic instability,” which is impacted by many additional factors. EX1080, 119. In particular, the “nature of the leaving group” and “the electrophilicity of the carbonyl group (or other center) play a fundamental role in modulating the reactivity.” *Id.*, 116. As discussed above in Section II.D.i-iii, it is readily apparent atropine’s hydrolytic stability benefited from (1) the lack of an electron withdrawing group that could activate the carbonyl; and (2) from the steric hindrance and poor leaving properties of the bulky bicyclic tropane substituent.

The petition's failure to establish a POSA would have known about, and been motivated by, an atropine stability problem is sufficient reason to deny institution. *See, e.g., In re Omeprazole Patent Litig.*, 536 F.3d 1361, 1380-81 (Fed. Cir. 2008). The petition's unsupported premise that aqueous atropine formulations were viewed as unstable appears to be supported by nothing more than improper hindsight obtained by reviewing the claims of the '447 patent. Accordingly, institution should be denied.

(ii) The Petition Fails to Show Siegel Provides a Solution to the Assumed Atropine Stability Issue

Instead of following the teachings of its grounds references to formulate atropine in water, Petitioner presumes that a POSA would have been motivated to formulate it in deuterium oxide because deuterium oxide marginally improved the stability of a different compound, procaine. Although the petition characterizes Siegel as disclosing "that D₂O increased the long-term stability" of procaine (Pet. 33), the petition fails to substantiate this premise of its proposed modification.

Siegel reports a maximum half-life of procaine in deuterium oxide of 115 hours, which is less than five days and only a 3-day increase over using water. EX1006, 979 & Table I. The petition fails to argue that a half-life of less than five days satisfies the "long-term stability," a shelf life "measured in years," proposed by the petition as the reason for the modification. Pet. 13, 26, 33-35 (seeking "2- to 3-year stability"). As noted above, Teva noted that Siegel's use of deuterium oxide

to stabilize procaine achieved a maximum half-life of only 115 hours and therefore provides “no suggestion that it could be practicable to use deuterium oxide for long term stabilization of pharmaceutical compositions of any kind.” EX1052, 2:10-26. The petition’s failure to address the teachings of its own grounds reference is fatal to its proposed motivation to modify. Accordingly, institution should be denied.

(iii) The Petition Fails to Show Siegel’s Procaine Experiments Are Relevant to Atropine

The petition also fails to justify its premise that a POSA would view Siegel’s experiments on procaine in deuterium oxide as predictive for formulating atropine. Siegel does not purport to teach that deuterium oxide would provide any stability improvement to atropine. Petitioner ignores the readily apparent structural and chemical differences between atropine and procaine, and fails to support its conclusory assertion that Siegel would predict an improved formulation for atropine.

The petition attempts to analogize atropine to procaine merely because both compounds contain carboxylic esters. But if Petitioner’s obviousness theory is correct, one might ask whether all pharmaceutical carboxylic esters are solubilized in deuterium oxide to improve stability. Clearly, they are not. Indeed, the petition identifies no pre-critical date FDA approval for any carboxylic ester solubilized in deuterium oxide. The petition does not even demonstrate that *any deuterated compound* had received FDA approval before the critical date despite decades of

practice. The exhibits submitted with the petition indicate there had been none. EX1022, 388 (deuterated drugs “have not found application in drug therapy”); EX021, 85 (“Some 15 years after Foster’s review, this still seems to be the case.”); EX1023, 3602 (still none); EX1030, 14 (same); EX1055, 319 (“deuterium-containing compounds have rarely been clinically explored as new therapeutic agents, and no deuterated compound has advanced beyond Phase II clinical evaluation”); EX1021, 85 (the action of deuterated drugs has been more easily understood than the physiological and pharmacological effects of D₂O on humans and other animals, “although with few practical therapeutic consequences”).

Moreover, Petitioner ignores significant and readily apparent differences between atropine and procaine. Unlike atropine, procaine was known to be “labile in an aqueous medium.” EX1006, 978 (left column). Among other structural differences, procaine has different moieties that contribute to lability of its ester bond, and a different chemical profile, all of which undermine Petitioner’s premise that procaine stability studies can be accepted as predictive for atropine. *See* Section II.D.i-iii, above. Among other differences, procaine has a primary amine in the para-position of the benzene ring that is bonded directly to its carbonyl carbon, which can have an electron-withdrawing effect that activates the carbonyl and facilitate breakage of the ester linker. Moreover, procaine has the same diethylaminoethanol leaving group as the unstable benactyzine compound.

Atropine has neither feature. *See* Section II.D.iii, above. Petitioner submitted the Anschel reference, which confirms that these features significantly increase the rate of hydrolysis of procaine. EX1033, 277-80 & Tables I, III. The petition fails to explain why it ignored the different electronic and steric profile of procaine as compared to atropine when deciding to analogize atropine to procaine. Petitioner's unsubstantiated premise of analogous behavior of atropine to procaine is another fatal flaw in its motivation to combine analysis. Petitioner's complete failure to address the teachings of its own evidence is another indication that its proposed motivation to combination is nothing more than wishful thinking based on hindsight.

The petition's use of improper hindsight in misreading Siegel is further demonstrated by other evidence of record. For example, the petition fails to address teachings of the very references it submitted, which teach that POSAs generally employed numerous tools to address hydrolysis problems, and that these tools did not include the use of deuterium oxide. *See, e.g.*, EX1080, 113, 133-38. Contrary to Petitioner's argument, its own submitted references teach that "the specific solution (if any) that apply" to a given drug "must be determined experimentally for the specific drug and formulation" because "each drug is a special case." EX1080, 133 (right column).

The petition also vastly overstates the predictability of successfully using deuterium to improve stability of chemical bonds. Petitioner's hindsight leads it to assert, incorrectly, that the improved stability of atropine in deuterium oxide disclosed in the '447 patent was "the expected stabilization of the atropine solution due to D₂O, followed by basic arithmetic." Pet. 54. As a threshold matter, the petition fails to justify its assumption that increased kinetic isotope effects of deuteration of compounds (i.e., replacing a hydrogen atom with deuterium atom by a covalent bond)—which is not the modification proposed here—is somehow informative of using deuterium oxide as a solvent for atropine. Perhaps more troubling, references that Petitioner submitted with the petition indicate that deuterium effects are very unpredictable. *See, e.g.*, EX1023, 3597 ("so many expected DKIEs [deuterium kinetic isotope effects] never materialize in a biological setting"), 3605 ("no hard and fast rules for predicting what examples will work"); EX1031, 3 (testing is "the only way to know whether deuteration of those compounds will make a clinically relevant difference"); EX1023, 3596 ("for the majority of studied cases in biological media, this observed change in rate, the kinetic isotope effect, is very small, often so small as to be difficult to detect"), 3597 (no available "method for predicting which cases will work *a priori*"); EX1088, 5 ("nothing to predict the influence of heavy water on stabilization [of] molecules solubilized by water, because phenomena other than the nature of the

bond between the solvent and the molecule occur”). Though the petition attempts to paint the use of deuterium to increase stability as a routine tool with predictable results, the literature Petitioner submitted indicates that the opposite is true.

Similar uncertainty existed when contemplating employing heavy water as a solvent. *See, e.g.*, EX1088, 5 (“although it is known that heavy water brings an increase in the energy of hydrogen bonds by a factor of 0.24 kilocalories per mole, there was ***nothing to predict the influence of heavy water on stabilization [of] molecules solubilized by water***, because phenomena other than the nature of the bond between the solvent and the molecule occur” (emphasis added)). The petition’s decision to ignore the unpredictable task of attempting to address a hydrolytic instability problem for one compound based on a different compound is another indication that the petition is premised on improper hindsight gleaned from reviewing the ’447 patent.

Even Dr. Byrn admits that comparisons of deuterium oxide-stabilizing solvent isotope effects were only applicable to ***analogous compounds*** and reaction types. EX1002, ¶259. As discussed above in Section V.A.i, Petitioner’s own submitted literature explains that the fact that atropine has a carboxylic acid ester does not predict the ***speed*** of hydrolysis. *See, e.g.*, EX1083, 6045; EX1080, 116, 119. As discussed above, carboxylic ester hydrolysis varies based on numerous factors, including the different steric and electronic properties of the moieties

surrounding the carboxylic ester. The petition fails to address why deuterium oxide experiments involving different compounds with very different leaving groups (*e.g.*, procaine, ethyl halogen acetates, trifluoroacetates, O-dichloroacetylsalicylate, phenyl and alkyl formates) would lead a POSA to expect deuterium oxide to improve hydrolytic stability of atropine.

Petitioner's hindsight-driven assertion that improved stability of atropine in deuterium oxide was expected also is contradicted by other companies in the industry. Nevakar—a company unaffiliated with Sydnexis and who challenged Sydnexis's patents in prior IPR petitions—told the USPTO when prosecuting its own patent that Sydnexis had unexpectedly and beneficially improved atropine stability by formulating it in deuterium oxide. In response to a rejection of its patent application over WO2016/172712, which issued as U.S. Patent No. 9,421,199 (EX2005, 0042), Nevakar cited the '447 patent's parent (*i.e.*, the '199 patent) as evidence that POSAs knew by 2018 that atropine degradation in aqueous solution “is notably accelerated with reduced concentrations of atropine,” and praised the inventors of the '199 patent, who it said “*unexpectedly discovered* that D₂O in place of H₂O as a solvent for such low dose formulations provided *superior stability*.” EX2005, 0027-28 (emphases added). Nevakar explained that the difference between using deuterium oxide as the solvent in place of water “is not trivial.” *Id.* Nevakar recognized that the '199 patent's “Tables 16 and 25A and 25B

provide *clear and convincing factual evidence that the use of D₂O* in the solvent system of the '712 publication [which issued as the '199 patent] *is the critical factor* in stability improvement.” *Id.*, 0031 (emphases added).

Nevakar also explained that the disclosure in the '199 patent amply demonstrates the claimed effect. For example, Nevakar stated that the '712 publication “is replete with teachings and examples that establish that D₂O is *the* determinant factor in increasing atropine stability.” *Id.*, 0028; *see also id.*, 0024 ¶14 (Dr. Stella testifying that “[t]he data in the WO 2016/172712 publication clearly establish that D₂O is the critical factor in atropine stability”). Nevakar also stated that the disclosure “provides ample examples” to the effect that “the atropine stability problem” disclosed in the '199 patent was addressed “by replacement of H₂O with D₂O.” *Id.*, 0028 (citing '712 publication Tables 16 and 25A/B). Of course, each of these statements are equally applicable to the '447 patent. This unsolicited industry commentary serves to emphasize the falseness of Petitioner’s litigation-driven petition argument that the stability results disclosed in the patent are the expected results of using deuterium oxide for atropine.

The petition’s selective, incomplete, and in many cases misleading analysis of the prior art fails to substantiate its proposed motivation to combine. Accordingly, institution should be denied.

B. The Petition Fails To Weigh Potential Disadvantages of Deuterium Oxide Perceived at the Time of Invention

The petition's analysis also is deficient because it ignores disadvantages of deuterium oxide perceived at the time of invention, as reported in the very references Petitioner submitted. For example, the petition ignores perceived disadvantages of employing deuterium oxide in pharmaceutical products, including the expected financial and regulatory costs, as well as side effects reported in the references Petitioner submitted. The Federal Circuit has explained that failing to take into account perceived disadvantages is an incomplete and erroneous obviousness analysis. *See Henny Penny Corp.*, 938 F.3d at 1332; *Winner Int'l Royalty Corp.*, 202 F.3d at 1349 n.8. But that is exactly what Petitioner did here.

Petitioner's own petition materials report that using deuterium oxide in a pharmaceutical product imposed significant costs and regulatory burdens that would not be undertaken unless the perceived benefits outweigh the costs. The cost estimate in the literature submitted with the petition reports \$11,400/kg for pharmaceutical-grade deuterium oxide. EX1029, 11. Because of the significant cost, documents submitted by Petitioner state that deuterium oxide "would only be useful for compounds that are expensive[,], unstable[, and administered in] small volume parenteral" or i.v. EX1029, 12. Petitioner fails to show that atropine was believed to satisfy these criteria. Moreover, as discussed above, deuterium oxide was historically associated with nuclear reactors. EX1022, 368; EX1030, 6-7. It

was thus often subject to government restrictions and commitments in many countries. EX1027, 3. The petition ignores the substantial and perceived disadvantages of replacing water with deuterium oxide.

In addition to real cost and regulatory downsides, Petitioner's literature reports that there were risks perceived to using deuterium oxide for chronic daily administration to children, as proposed in the petition, that also had to be weighed. For example, Petitioner's own submitted literature asserts that deuterium from deuterium oxide was readily incorporated into biological molecules (*e.g.*, proteins and carbohydrates) with ill effects for living organisms. EX1022, 375; *id.*, 372; EX1021, 80. Petitioner's own literature also asserts that deuterium had serious negative health impacts, including on "liver activity, kidney function, blood constituents, enzyme systems, reproductive capacity and cell division, the heart, the nervous system, metabolism, and even the wound-healing process." EX1022, 388; *see also* EX1025, 19 ("deuterium substitution affects virtually all aspects of metabolism and physiological function....[Mammals show] severe difficulty with protein synthesis, decreased enzyme levels, decreased erythrocyte production, impaired carbohydrate metabolism, hormone imbalance, central nervous system disturbance, difficulty with mitosis, and increasingly impaired reproductive capability"); EX1021, 81 (antimitotic activity, causes sterility and impaired hematopoiesis), 82 (inhibits "bioelectrogenesis and contractility in nerve and

muscle preparations,” inhibits sodium-potassium ion ATPase in animal membranes, and interferes with chloride ion exchange in liver); EX1022, 372 (“pronounced effect on cell division in most organisms” because of its “antimitotic activity”). Petitioner’s submitted literature further asserts that deuterium oxide stabilizes “(in relative terms) highly reactive and toxic forms of oxygen.” EX1021, 83. Petitioner nevertheless proposes having parents instill deuterium oxide in their children’s eyes every night before bedtime *for years* without any analysis of any perceived risks of doing so. The petition, however, never addresses how a POSA would have approached these issues identified in its own submitted references before the critical date.

Relying on the safety of infrequent administration of small quantities of deuterium oxide (e.g., for diagnostic purposes) due to the speed at which the body water is excreted (*see* EX1021, 81), the petition does not consider how a POSA would determine whether chronic daily administration of deuterium oxide to children over a period of years was safe. For example, Petitioner submitted the Blake reference, which asserts that “deuterium probably elicits harmful effects in subtle ways even in low concentration.” EX1022, 370. Petitioner also submitted the Krumbiegel reference, which asserts that deuterium was placed “into a category of toxic compounds.” EX1030, 3. Despite relying on these references, Petitioner provides absolutely no evaluation of their teachings or consideration of

the effects of chronic administration of deuterium oxide to ocular tissue. Notably, none of the accepted diagnostic uses of deuterium that Petitioner relies upon involved chronic daily pharmaceutical administration to humans, as is proposed in the petition.

Petitioner's obviousness analysis appears to be fundamentally and improperly infected by post-critical date knowledge about the safety and efficacy of Sydnexis's use of deuterium oxide in its atropine product under clinical development. But Petitioner may not work backwards in this manner to reach the claims. *See Adapt Pharma Operations Ltd.*, 25 F.4th at 1382.

Petitioner also argues that a rise in patent filings for deuterated copies of existing therapeutics somehow reflects widespread industry acceptance of using deuterium oxide for chronic administration of ophthalmic pharmaceuticals. *See, e.g.*, Pet. 6, 30; EX1032, 6, 15 (Fig. 2). This argument suffers from many problems. Among these, making a deuterated drug (*i.e.*, selective and permanent replacement of an H-C bonds with a D-C bond) ***is not the modification to the prior art that is proposed in the petition***. Petitioner's literature indicates that selective deuteration of organic compounds was used to identify the location of enzymatic degradation during *in vivo* drug metabolism. EX1021, Abstract, 83 (deuterium oxide and deuterated compounds used in "studies of ***metabolism*** and movement of drugs and toxic substances") (emphasis added). Petitioner's literature indicates that

replacing a hydrogen-carbon covalent bond with a deuterium-carbon covalent bond was hoped to slow *in vivo* drug metabolism when the breaking of the hydrogen-carbon covalent bond was the rate-limiting step for enzymatic degradation. EX1022, 369 (“An observable isotope effect will only be apparent, of course, where the breaking of a C-H or C-D bond is involved in the rate-determining step.”). But the petition does not propose intentionally modifying any C-H bond of atropine.

Nor does the petition propose using deuterium oxide to improve the biostability or heat stability of biological materials or macromolecules (e.g., vaccines, nucleic acids, carbohydrates), yet it cites to such uses for support. *See, e.g.*, Pet. 4-6, 30, 34; EX1088, Abstract (macromolecules); EX1027, 1591 (deuterium oxide “can have important practical effects when vaccines and other heat-sensitive therapeutic substances must be distributed in developing countries[.]”); EX1057, Abstract (live attenuated poliovirus vaccine). None of Petitioner’s references propose using deuterium oxide to achieve shelf-life stability for atropine.

Furthermore, the petition fails to address the skepticism against the use of deuterium in therapeutics reported in the literature submitted with the petition. At least as late as 2014, even proponents of deuterated drugs admitted that “until that final approval by the FDA, the actual incorporation of deuterium into a medicine

will continue to be a curiosity to most, something to poke with a stick[.]” EX1023, 3595. Deuterium advocates admitted that it was “daring to use a new nucleus,” was “never easy,” and they struggled to overcome “preconceptions.” *Id.*, 3595-96; *see also* EX1027, 9 (public perception of radioactivity is a problem). Petitioner’s Kushner reference asserted near the turn of the century that the action of deuterated drugs has been more easily understood than the physiological and pharmacological effects of deuterium oxide on humans and other animals, “although with few practical therapeutic consequences.” EX1021, 85.

Though attempts had been made to advance deuterated drugs as clinical candidates, Petitioner does not even assert that any of these candidates had been successful at the critical date. Petitioner’s Blake reference asserts, for example, that despite the “impressive number” of deuterated drugs synthesized for study, “they have not found application in drug therapy[.]” EX1022, 388. In 1975, Blake specifically asserted that drinking deuterated water was explored for controlling tumor growth in mice but that it was unsuccessful because “the mice on deuterium oxide died faster because of the toxic side effects of deuterium oxide.” *Id.*, 373 (left column). Even *decades later*, Petitioner’s documents indicate that no deuterated compound had received FDA approval. EX021, 85 (“In his review on metabolism of deuterated drugs, Foster (1984) remarked that Blake et al. (1975) in a review 10 years earlier had commented ‘At the present time there are no drugs on

the market that contain deuterium in the molecule’ and that the situation had not changed since. Some 15 years after Foster’s review, this still seems to be the case.”).

Petitioner’s Kushner reference later asserted again that no deuterated drugs had been approved in the intervening decades, and cautioned that 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.” EX1021, 85. The petition materials indicate that this status quo was maintained still nearly *two more decades* after Kushner. *See, e.g.*, EX1023, 3602 (right column: “only a few companies” have put deuterated drug into the clinic; “Merck struck out with fludalanine”; “BiRDS, Auspex, and Concert also have agents in the clinic at this writing,” though it is not clear any will have enough “clinically meaningful impact” to move forward); EX1030, 14 (Concert Pharmaceuticals decided not to further develop deuterated version of paroxetine after completing phase 1 clinical trials); EX1031, 4 (same); EX1055, 319 (“deuterium-containing compounds have rarely been clinically explored as new therapeutic agents, and no deuterated compound has advanced beyond Phase II clinical evaluation”). Indeed, it was still several years *after* the critical date before any deuterated drug would receive FDA approval. The petition’s reliance on speculation about future

success—especially about a different approach than that proposed in the petition—simply does not support the prior art combination proposed in the petition.

For the reasons discussed above, the petition should be rejected.

VI. THE PETITION SHOULD BE DENIED UNDER §325(D) AND *ADVANCED BIONICS*

Denial of institution is warranted in view of the petition’s reliance on “substantially the same prior art or arguments” previously considered by the Office. *See* 35 U.S.C. §325(d). The Board’s §325(d) analysis applies a two-part framework guided by several non-exclusive *Becton, Dickinson* factors. *Advanced Bionics*, 7-9; *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 at 17-18 (precedential, §III.C.5 ¶1) (“*Becton, Dickinson*”). First, the Board considers whether “the same or substantially the same” art or arguments were previously presented to the Office. *Advanced Bionics*, 8. If so, the Board considers whether the petition demonstrates that the Office “erred in a manner material to the patentability of challenged claims.” *Id.* A material error must be a clear, egregious error: “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.” *Id.*, 9.

As explained below, the petition relies on substantially the same art and arguments previously presented to the Office, and the petition does not demonstrate material error in the Office’s previous assessment. The prosecution

record is much more robust than Petitioner acknowledges. *See* Section II.B above. Given the full prosecution history, it is perfectly appropriate to deny institution under §325(d).

A. The Petition Presents Substantially the Same Art and Arguments Previously Considered by the Office

The Office has repeatedly considered whether a POSA would have been motivated to stabilize atropine with deuterium oxide for an ophthalmic formulation. The Office previously considered this question not only when allowing the '447 patent, but also during prosecution of one parent and three continuation patents. In every instance, the same question of patentability raised by Petitioner has been addressed and overcome. Petitioner nonetheless rehashes this same issue not only in this IPR, but in three other IPRs. *See* IPR2022-00963; IPR2022-00965; IPR2022-00966.

Considered and applied during prosecution of the '447 patent:

Regarding prosecution of the '447 patent, Petitioner incorrectly states that the “Examiner did not consider any reference analogous to Kondritzer.” Pet., 62. As shown by the portions of the prosecution history that Petitioner excluded from its submissions, the Examiner expressly considered Lund (EX2002). EX2003, 0319 (entry 16). Lund is essentially an update to Kondritzer. Lund cited Kondritzer as a foundation for Lund’s own study of the kinetics of atropine degradation at pH 1-6, disclosed that atropine’s pH range of maximum stability was 2-4, disclosed

equations for the kinetics of atropine degradation, and disclosed that base-catalyzed ester hydrolysis was understood to be the primary mechanism of atropine degradation above pH 5. EX2002, 3085, 3087, 3096, Table 6, Reference 8.

Petitioner's cursory §325(d) argument fails to identify, as was its burden, anything that Kondritzer adds that is materially different than what Lund discloses.

Petitioner also misleadingly asserts that "Chia was neither cited nor considered during prosecution." Pet. 7. Petitioner fails to account for Chua & Tan (EX1018), which Petitioner admits is a "patent application directed to the work of Chia" (Pet. 2), and which itself cites Chia. EX1018, 31. The Examiner expressly considered Chua & Tan during prosecution. EX2003, 0316 (entry 008).

Chua & Tan is the patent application version of Chia authored by two of the authors of Chia, and it discusses the same clinical trial results for 0.01% atropine as Chia. That Chia is cumulative to Chua & Tan is evidenced even by reading the abstract. EX1018, Abstract ("composition comprises about 0.01% atropine...reduces and/or prevents myopia progression with negligible side effects"). As with Lund, Petitioner curiously omits the Examiner's consideration of Chua & Tan from the prosecution file history. Petitioner's argument fails to identify, as was its burden, anything that Chia adds that is materially different than what Chua & Tan discloses.

Seigel also was expressly considered during prosecution. Though Petitioner concedes that Siegel was listed on an IDS, Petitioner erroneously argues that this fact should be given no weight. Pet. 62. But *Advanced Bionics* itself makes clear (at 7-8) that the petition's §325(d) analysis must account for "art provided to the Office by an applicant, such as on an Information Disclosure Statement (IDS)[.]" Though Petitioner certainly was aware of the IDS references considered during prosecution (they appear on the face of the patent), Petitioner failed to submit the IDS documents to the Board, never adequately accounts for these references, and cursorily dismisses even those references Petitioner recognizes were disclosed therein.

Furthermore, 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. Before issuing any rejections, the Examiner considered references teaching that deuterium oxide improved the stability of certain ester compounds subject to base-catalyzed hydrolysis that were very different from atropine. EX2003, 0316 (entry 003); EX1052 (Teva: α -hydroxy esters and amides like benactyzine); EX2003, 0320 (entry 0022: "Siegel et al. Stability of procaine in deuterium oxide"). As discussed above, Teva published decades after Siegel and pointed out that Siegel's greatest half-life (115 hours, fewer than five days) achieved with deuterium oxide

“provided no suggestion that it could be practical to use deuterium oxide for long term stabilization of pharmaceutical compositions of any kind.” EX1052, 2:10-20. Teva also observed that atropine was *more stable*. EX1052, 7:16-23. Teva’s solution pH, like the solution pH of 5-6 proposed in the petition, was within the pH range (2.8-6.0) at which Petitioner’s own Kondritzer reference teaches atropine aqueous solution was stable. EX1004, 532.

The Examiner relied on Teva’s use of deuterium oxide to improve the stability of benactyzine, an α -hydroxy ester, to find motivation to use deuterium oxide to improve the stability of atropine. Applicant pointed out 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 α -amino or α -hydroxy carboxylic acid derivatives (like benactyzine) that are different than the β -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 D₂O for the purpose of stabilizing atropine.” EX2003, 100, 0067-68; *In re Omeprazole Patent Litig.*, 536 F.3d 1361 (Fed. Cir. 2008)). Although the Examiner had asserted based on Teva that increased stability was the expected result of solubilizing atropine in deuterium oxide because this had been the case with a different ester, benactyzine, the Examiner ultimately allowed the claims

because Teva teaches that atropine was stable in water. EX1052, 7:5-23; EX2003, 0048.

The petition thus recycles the same arguments that already had been rejected in the literature and that have been considered and rejected by the Examiner during prosecution.

Applied in additional cases: The same Examiner already previously considered and ultimately rejected the argument that using deuterium oxide to improve one ester would have motivated a POSA to use deuterium oxide to improve the stability of atropine during prosecution of the '199 patent. *See SynQor, Inc. v. Vicor Corp.*, 988 F.3d 1341, 1351 (Fed. Cir. 2021) (“Factual determinations made by the expert agency entrusted by Congress to make those determinations—and to make them finally—need not be endlessly reexamined.”). The Examiner rejected the claims based on Herekar, arguing that using deuterium oxide to increase shelf-life of lower concentration riboflavin would have motivated a POSA to use deuterium oxide to increase shelf-life of atropine. EX2001, 0075-76. The Examiner ultimately withdrew this rejection based on applicant’s persuasive arguments that deuterium oxide was not expected to improve atropine stability. EX2001, 0043-54, 0023-24.

Considered in additional cases: The Office has also considered the same art and arguments in the prosecution of numerous other patent applications. In

total, the Examiner allowed claims related to using deuterium oxide for low-dose atropine ophthalmic solutions in *two additional continuation patents* after expressly considering the argument that using deuterium oxide to stabilize certain esters would have motivated a POSA to use the “more expensive D₂O for the purpose of stabilizing” atropine. EX2003, 0067. Accordingly, the Office has thoroughly considered and rejected the same or substantially similar argument as are currently presented in the petition.

Despite filing IPR petitions against at least three of these patents in IPR Nos. 2022-00963, -00965, -00966, and certainly being aware of the Examiner’s consideration of Teva and its teachings undermining Petitioner’s Siegel-based motivation, Petitioner fails to persuasively address this evidence in the petition. Petitioner’s failure to faithfully address the prior Patent Office proceedings provides ample reason to deny institution.

B. The Petition Fails to Demonstrate Material Error

Because Petitioner’s invalidity arguments merely seek to rehash substantially the same art and arguments considered and rejected during prosecution, Petitioner was obligated to demonstrate “that the Office erred in a manner material to the patentability of challenged claims” and that “reasonable minds” cannot “disagree regarding the purported treatment of the art or

arguments.” *Advanced Bionics* at 7-9. As explained below, it failed to do so.

Institution thus should be denied.

Petitioner wrongly alleges “the Examiner was simply not aware” of the most pertinent prior art references, and that the petition “presents different prior art than the Office was aware of.” Pet. 63. Petitioner’s argument is premised on ignoring the references expressly considered by the Examiner and omitted by Petitioner from the prosecution history (Chua & Tan, Lund, Siegel, and Teva as discussed above). As a legal matter, Petitioner’s attempt to ignore references considered as part of an IDS is wrong and contrary to precedent. *Advanced Bionics* at 7-8.

Petitioner’s assertions that the Office was unaware of the most pertinent art and that the petition presents different references that the Office was not aware of are demonstrably false.

Moreover, as discussed above and in further detail in Section V, the petition fails to establish that using deuterium oxide was expected to improve long-term stability of atropine. Atropine was understood to be much more stable in water than procaine, having a half-life of decades or even hundreds of years. EX1004, 534 & Table III. Chia identified no stability problem using a “conventional” aqueous formulation. Pet. 23, 35. Using Dr. Byrn’s own calculations based on Kondritzer’s data, aqueous atropine already was expected to experience less than 10% degradation after storage for more than 40 years (pH 5) or 4 years (pH 6),

much longer than required to use up the 150-day supply Dr. Byrn testified about in the largest bottles of atropine eye drops. EX2006, ¶¶107-08 (more than 40 years); IPR2022-00963 EX1002, ¶179 (300 administrations in largest bottle). In light of its own evidence, Petitioner identifies no reason for a POSA to think existing aqueous atropine eyedrops lacked shelf-life stability. *See also* Section V.A.i above.

Petitioner similarly fails to justify its reliance on Siegel for modifying Chia's atropine formulation. The petition asserts that Chia used water for its atropine formulation and describes Chia's 0.01% atropine formulation as "conventional." Pet. 23, 35. Petitioner purports to justify substituting deuterium oxide in place of water because Siegel observed a 3-day improvement in the half-life of procaine using deuterium oxide. But Siegel provides no suggestion that deuterium oxide would improve the stability of atropine, a very different compound. *See also* Section V.A.ii above. Indeed, Teva teaches that deuterium oxide is not indicated for atropine, which was *more stable*. EX1052, 7:16-23. Teva's solution pH, like the solution pH of 5-6 proposed in the petition, was within the pH range (2.8-6.0) at which Petitioner's own Kondritzer reference teaches atropine aqueous solution was stable. EX1004, 532.

Teva also 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.” EX1052, 2:10-20. Petitioner completely fails to substantiate its theory that Siegel’s 5-day half-life in deuterium oxide would have motivated a POSA to abandon aqueous atropine solution, which the asserted Kondritzer reference teaches already enjoyed a half-life of decades or hundreds of years. Petitioner also fails to demonstrate that Siegel’s experiments on procaine, which is a very different compound than atropine, provides any predictive value for atropine. *See also* Section V.A.iii above. Indeed, Nevakar—a company unaffiliated with Sydnexis and who challenged Sydnexis’s patents in prior IPR petitions—told the USPTO when prosecuting its own patent that Sydnexis had unexpectedly and beneficially improved atropine stability by formulating it in deuterium oxide. *Id.*; EX2005, 0027-28, 0031, 0024 ¶14. Moreover, Petitioner fails to weigh the costs of its proposed substitution against any expected benefits. *See* Section V.B above. The petition simply fails to satisfy its burden of showing material error.

At bottom, Petitioner has failed to show that no “reasonable minds can disagree regarding the purported treatment of the art or arguments” that Petitioner now advances. *Advanced Bionics*, 9. Accordingly, the Board should exercise its discretion under §325(d) to deny institution.

VII. CONCLUSION

Accordingly, for at least the reasons set forth above, institution of *inter partes* review should be denied.

Respectfully submitted,

Date: August 11, 2022

/ Michael T. Rosato /

Michael T. Rosato, Lead Counsel
Reg. No. 52,182

CERTIFICATE OF COMPLIANCE

Pursuant to §42.24(d), the undersigned certifies that this paper contains no more than 14,000 words, not including the portions of the paper exempted by §42.24(b). According to the word-processing system used to prepare this paper, the paper contains 11,746 words.

Respectfully submitted,

Date: August 11, 2022

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VIII. APPENDIX

EXHIBIT NO.	DESCRIPTION
2001	File History for U.S. Patent No. 9,421,199
2002	Lund et al., <i>The Kinetics of Atropine and Apotatropine in Aqueous Solutions</i> , ACTA CHEMICA SCANDINAVICA 22 (1968) 3085-97
2003	File History for U.S. Patent No. 9,770,447
2004	Intentionally Left Blank
2005	File History for U.S. Patent No. 10,251,875
2006	<i>Eyenovia, Inc. v. Sydnexis Inc.</i> , IPR2022-00384, Exhibit 1002 (Declaration of Dr. Stephen Byrn, Ph.D.) (Dec. 29, 2021).

CERTIFICATE OF SERVICE

The undersigned certifies that the foregoing Patent Owner's Preliminary Response and accompanying Exhibits 2001-2006 were served on August 11, 2022, on the Petitioner at the electronic correspondence address of the Petitioner as follows:

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