

UNITED STATES PATENT AND TRADEMARK OFFICE

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**BEFORE THE PATENT TRIAL AND APPEAL BOARD**

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AQUESTIVE THERAPEUTICS, INC.

Petitioner

v.

IONO PHARMA, LLC

Patent Owner

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IPR2025-00874

U.S. Patent No. 11,021,437 B2

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**PETITIONER'S BRIEF OPPOSING DISCRETIONARY DENIAL**

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**EXHIBITS REFERENCED IN THIS BRIEF**

| <b>Exhibit</b> | <b>Description</b>                                                                                                                                                                                                                                                                             |
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| EX1001         | <b>The '437 Patent</b> - U.S. Patent No. 11,021,437 B2, entitled " <i>Pharmaceutical Formulation For Sublingual Or Buccal Delivery Of Epinephrine Or A Pro - Drug Thereof</i> ", filed as application serial number 16/347,625 on November 9, 2017, Almoazen inventor, issued on June 1, 2021. |
| EX1002         | <b>Truelove 1</b> - U.S. Patent No. 3,809,714, entitled "Novel Ester Of [(Methylamino)Methyl] Benzyl Alcohol", Hussain and Truelove inventors, issued on May 7, 1974.                                                                                                                          |
| EX1003         | <b>Ashraf</b> - Ashraf M and Sayeed VA, "Considerations in Developing Sublingual Tablets – An Overview," <i>Pharmaceutical Technology</i> <b>38</b> (11) 2014.                                                                                                                                 |
| EX1004         | <b>Fuchs</b> - U.S. Patent No. 4,136,145, entitled "Medicament Carriers In The Form Of Film Having Active Substance Incorporated Therein", Fuchs and Hilmann inventors, issued January 23, 1979.                                                                                               |
| EX1005         | <b>'437 File History</b> - Patent application prosecution history file for the '437 Patent, serial no. 16/347,625.                                                                                                                                                                             |
| EX1008         | <b>Truelove 3</b> - U.S. Patent No. 3,868,461, entitled "Ester Of 3,4-Dihydroxy-Alpha (Isopropylamino) Methyl Benzyl Alcohol Composition And Anti-Asthma Use Thereof", Hussain and Truelove inventors, issued on February 25, 1975.                                                            |
| EX1013         | <b>'437 Provisional</b> , '437 Patent Provisional Application serial no. 62,421,316, entitled " <i>Pharmaceutical Formulation For Rapid Delivery Of Epinephrine</i> ", filed on November 13, 2016.                                                                                             |
| EX1014         | <b>'437 PCT Application</b> , WO2018/089570 A1 (PCT/US2017/060761), entitled "Pharmaceutical Formulation For Sublingual Or Buccal Delivery Of Epinephrine", <b>Almoazen and Haynes</b> , co-inventors.                                                                                         |
| EX1015         | <b>Florence</b> - Florence AT and Attwood D, "Physicochemical Principles of Pharmacy", Fifth edition, Eds. Pharmaceutical Press (2011).                                                                                                                                                        |
| EX1021         | <b>Schobel</b> - U.S. Patent No. 11,191,737 B2, entitled "Enhanced Delivery Epinephrine Compositions", Schobel, <i>et al.</i> inventors,                                                                                                                                                       |

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|        | claiming benefit of provisional application No. 62/331,996, filed on May 5, 2016.                                                                                                                                                                                                                                                                                                |
| EX1022 | <b>Almoazen Paper</b> - Alaadin Alayoubi, <b>Lindsay Haynes</b> , Hemlata Patil, Baher Daihom, Richard Helms & <b>Hassan Almoazen</b> (2016): “ <i>Development of a fast dissolving film of epinephrine hydrochloride as a potential anaphylactic treatment for pediatrics</i> ”, Pharmaceutical Development and Technology, Early Online: 1-5, Published online 6 January 2016. |
| EX1033 | A copy of the ‘437 Patent (EX1001) showing in highlighting where material from the Almoazen Paper (EX1022) appears.                                                                                                                                                                                                                                                              |
| EX1035 | A copy of the Almoazen Paper (EX1022) highlighted to show where material from the Paper appears in the ‘437 Patent (EX1001).                                                                                                                                                                                                                                                     |
| EX1050 | <b>Rautio</b> - Declaration of Jarkko Rautio, Ph.D.                                                                                                                                                                                                                                                                                                                              |
| EX1051 | <b>Meanwell</b> - Declaration of Nicholas A. Meanwell, Ph.D.                                                                                                                                                                                                                                                                                                                     |
| EX1052 | <b>‘437 PCT File History</b> – PCT/US2017/060761, filed November 9, 2017.                                                                                                                                                                                                                                                                                                        |
| EX1053 | A copy of the ‘437 Provisional (EX1013) highlighted to show where material from the Almoazen Paper (EX1022) appears.                                                                                                                                                                                                                                                             |
| EX1054 | <b>Schobel Provisional</b> , Provisional Application, serial no. 62/331,996, filed May 5, 2016, to Schobel U.S. 11,191,737.                                                                                                                                                                                                                                                      |
| EX1060 | Motosue, <i>et al.</i> , “Risk factors for severe anaphylaxis in the United States”, Ann Allergy Asthma Immunol 119 (2017) 356-361.                                                                                                                                                                                                                                              |
| EX1061 | Dribin, et al., “Anaphylaxis definition, overview, and clinical support tool: 2024 consensus report—a GA <sup>2</sup> LEN project”, <a href="https://doi.org/10.1016/j.jaci.2025.01.021">https://doi.org/10.1016/j.jaci.2025.01.021</a> .                                                                                                                                        |
| EX1062 | U.S. Patent No. 12,023,309.                                                                                                                                                                                                                                                                                                                                                      |
| EX1063 | U.S. Patent No. 11,273,131.                                                                                                                                                                                                                                                                                                                                                      |
| EX1064 | Excerpts of quarterly report for the period ending 6-30-2025 filed with the SEC by Aquestive Therapeutics.                                                                                                                                                                                                                                                                       |
| EX1065 | Aquestive 6-16-2025 Press Release.                                                                                                                                                                                                                                                                                                                                               |
| EX1066 | Excerpts of 2023 annual report filed with the SEC by Aquestive Therapeutics.                                                                                                                                                                                                                                                                                                     |
| EX1067 | Excerpts of 2024 annual report filed with the SEC by Aquestive Therapeutics.                                                                                                                                                                                                                                                                                                     |

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| EX1068 | Excerpts of quarterly report for the period ending 3-31-2025 filed with the SEC by Aquestive Therapeutics.                                                                                                                                  |
| EX1069 | Excerpts of quarterly report for the period ending 6-30-2025 filed with the SEC by Aquestive Therapeutics.                                                                                                                                  |
| EX1070 | Prescription Drug User Fee Amendments,<br><a href="https://www.fda.gov/industry/fda-user-fee-programs/prescription-drug-user-fee-amendments">https://www.fda.gov/industry/fda-user-fee-programs/prescription-drug-user-fee-amendments</a> . |
| EX1071 | 5-27-2016 email from Steve Wargacki to Ramona McCudden re: Possible candidate source.                                                                                                                                                       |
| EX1072 | 6-3-2016 email from Ramona McCudden to Steve Wargacki re: MonoSol Rx (2).                                                                                                                                                                   |
| EX1073 | 6-16-2016 email from Ramona McCudden to Steve Wargacki re: MonoSol Rx (1).                                                                                                                                                                  |
| EX1074 | 10-23-2016 email from Steve Wargacki to Ramona McCudden re: email from Almoazen.                                                                                                                                                            |
| EX1075 | Declaration of Ramona McCudden – Aquestive Recruiting Specialist                                                                                                                                                                            |
| EX2001 | 2016-06-03 Email from Ramona McCudden to Hassan Almoazen re MonoSol Rx                                                                                                                                                                      |
| EX2002 | 2016-10-15 Email from Hassan Almoazen to Ramona McCudden re Epinephrine                                                                                                                                                                     |
| EX2003 | 2016-10-22 Email from Hassan Almoazen to Steve Wargacki re Email                                                                                                                                                                            |
| EX2005 | Excerpt of File History of Application No. 15/724,234                                                                                                                                                                                       |
| EX2006 | Excerpt of File History of Application No. 17/835,442                                                                                                                                                                                       |
| EX2008 | 2022-08-25 Email from Daniel Scola to Hassan Almoazen re Follow-up on our Discussions                                                                                                                                                       |
| EX2009 | 2023-12-06 Letter from Hemant Gupta to Daniel Scola re Collaboration Discussions with Iono Pharma, LLC<br>2024-03-29 Letter from Hemant Gupta to Daniel Scola<br>2024-04-09 Letter from Daniel Scola to Hemant Gupta                        |
| EX2014 | 2018-11-05 Email from Abby Trotter to Hassan Almoazen re 2018 Life Science Tennessee Venture Forum Class                                                                                                                                    |
| EX2015 | Email from Gareth Sheridan to Hassan Almoazen re update                                                                                                                                                                                     |
| EX2016 | Email from Amy Hopper to Hassan Almoazen re Delta I-Fund Semifinals Round 1                                                                                                                                                                 |

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| EX2017 | 2020-10-20 Email from Lili Jiang to China Focus re You have scheduled meetings at China Focus Virtual Partnering Conference |
| EX2019 | Declaration of Hassan Almoazen, Ph.D. under 37 C.F.R. § 1.130                                                               |
| EX2020 | Declaration of Hassan Almoazen, Ph.D.                                                                                       |

Petitioner, Aquestive Therapeutics, Inc., submits its Brief Opposing Discretionary Denial filed by Patent Owner, Iono Pharma, LLC. (Paper 7, “DD Req.”), in accordance with the March 26, 2025 Memorandum on Interim Processes for PTAB Workload Management (“Process Memorandum”)<sup>1</sup> as updated on the Interim Director Discretionary Process Webpage.<sup>2</sup>

## **I. INTRODUCTION**

The challenged claims of U.S. Patent No. 11,021,437 (“the ‘437 Patent”) are directed to sublingual or buccal administration of epinephrine prodrug compounds exhibiting half-life  $t_{1/2}$  values of 1-6 minutes using a rapidly dissolving film. *See generally* EX1001. Patent Owner, making several meritless arguments and misrepresenting the Grounds presented in the Petition (Paper 2), tries to shield the ‘437 Patent from an adjudication on the merits by requesting discretionary denial. At bottom, Patent Owner’s request for discretionary denial should be rejected for several reasons.

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<sup>1</sup> <https://www.uspto.gov/sites/default/files/documents/InterimProcesses-PTABWorkloadMgmt-20250326.pdf>.

<sup>2</sup> <https://www.uspto.gov/patents/ptab/interim-director-discretionary-process>.

**First**, the challenged patent is not involved in any parallel proceedings so that *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 11 (PTAB Mar. 20, 2020) (“*Fintiv*”) is not applicable, and Patent Owner cannot legitimately claim to have settled expectations that the validity of the ‘437 Patent would not be challenged. Petitioner had repeatedly informed Patent Owner that the ‘437 Patent suffered from many infirmities in its content and prosecution. *See infra*, pp.32-34. Importantly, the Petition was filed less than four (4) years after the June 1, 2021 issuance of the ‘437 Patent. Tellingly, Patent Owner has offered no evidence that the ‘437 Patent’s claimed subject matter has been commercialized, asserted, marked, licensed, or otherwise applied in Petitioner’s particular technology during the patent’s short lifetime.

Patent Owner claims to have spent “five figures” to “protect and commercialize” his claimed subject matter recited in the challenged patent. However, Patent Owner knew from publicly available information that Petitioner was investing large sums of money to get approval to market and sell its Anaphylm<sup>™</sup> product.<sup>3</sup> Patent Owner would have understood that prior to

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<sup>3</sup> *See, e.g.*, EX2009 (letters from Patent Owner’s attorney), p.1 (“It is exciting to see that Aquestive . . . is continuing to push forward with Anaphylm epinephrine

submitting its New Drug Application (“NDA”), Petitioner would have no need to consider incurring the significant costs on challenging its patent. However, when Petitioner announced promising clinical trial results and the subsequent filing of its NDA, any reasonable patent owner would have expected that Petitioner would then turn its attention to the ‘437 Patent to ensure it would not pose an obstacle to the potential approval and launch of its first-of-its-kind Anaphylm™ product.

Petitioner submitted an NDA seeking U.S. Food and Drug Administration (“FDA”) approval to market and sell the first orally-deliverable epinephrine prodrug product for the treatment of severe allergic reactions, including anaphylaxis. Petitioner’s product, Anaphylm™, a polymer matrix-based epinephrine prodrug administered sublingually (*i.e.*, under the tongue), is designed to provide quick delivery of epinephrine directly into the patient’s bloodstream. To support its NDA submission, Petitioner spent more than \$19 million conducting the requisite clinical trials needed to demonstrate the efficacy of Petitioner’s proposed new product and an additional \$4.3 million in FDA administrative filing fees.

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prodrug sublingual film delivery system”), p.2 (“Aquestive work toward getting . . . FDA approval”).

Upon submission of its NDA, Petitioner worked diligently and prepared and filed its Petition in approximately two months. In June, one month after its Petition was filed, Petitioner received notice that its NDA was formally accepted, and that the FDA would issue a decision by January 2026 whether Petitioner would be approved to market its Anaphylm™ product in the United States. Consequently, the prompt filing of the Petition in May was an important step to prevent Patent Owner from attempting to use the '437 Patent as an obstacle to jeopardize the launch of this life-saving product, assuming NDA approval is ultimately granted.

**Second**, Patent Owner's arguments that discretionary denial is warranted under 35 U.S.C. § 325(d) is baseless and only serve to highlight Patent Owner's numerous omission and misrepresentations which led to the Examiner to materially err during prosecution and allowing the '437 Patent to issue. For example, one of the references Truelove 1 (EX1002), while listed in an IDS, was never discussed by the Examiner and was not the basis of any rejection during the '437 Patent's prosecution. Instead, Truelove 1 was introduced into the prosecution by the Patent Owner, not the Examiner, to misleadingly argue that claims amended to include the "half-life  $t_{1/2}$  range from 1-6 minutes" limitation were patentable over the prior art, alleging Truelove 1 only disclosed epinephrine prodrug compounds with half-life  $t_{1/2}$  values of 30 minutes. However, Patent Owner misleadingly neglected to inform

the Examiner that Table 3 of Truelove 1 (EX1002) disclosed epinephrine prodrug compounds with half-life values  $t_{1/2}$  from 1-6 minutes as recited in the challenged claims. That the Examiner never addressed or commented on Truelove 1's teachings during the prosecution of the '437 patent highlights the bankruptcy of Patent Owner's Section 325(d) arguments.

**Third**, Petitioner has presented strong unpatentability arguments. The first is based on Truelove 1, additional arguments are presented *infra*, pp.8-10, 36-74. To begin, as admitted by Patent Owner, a POSA would have understood Truelove 1, Table 3 as disclosing the epinephrine prodrug compounds claimed in the challenged claims. *See* DD Req. at 28-34.

More importantly, Truelove 1, Table 3 also discloses the half-lives  $t_{1/2}$  of these diester epinephrine prodrug compounds, that is, the time for half the epinephrine prodrug compound to be changed into epinephrine in human blood plasma. Rautio, EX1050, ¶¶106-114; Meanwell, EX1051, ¶¶100-108.

Importantly, several of the disclosed half-lives  $t_{1/2}$  fall within the 1-6 minutes limitation recited in the challenged claims. However, the Patent Examiner never considered Truelove 1, incorrectly accepting Patent Owner's argument that Truelove 1 stood for the proposition that the prior art epinephrine prodrugs were

limited to half-lives  $t_{1/2}$  of 30 minutes or greater forming the basis the Patent Examiner gave for overcoming a rejection and allowing the '437 Patent to issue.

Additionally, the Examiner made a second error in allowing the claims to issue. Namely, the Examiner mistakenly relied on Figure 9 in the Statement of Reasons for Allowance. Figure 9 only discloses the percent of epinephrine (not epinephrine prodrug) which separates from the disintegrating film over time in saliva.<sup>4</sup> Figure 9 as relied on by the Examiner, does not disclose: (i) an epinephrine prodrug; (ii) the hydrolytic transformation of an epinephrine prodrug to the epinephrine drug while in human blood plasma; nor (iii) the half-life of an epinephrine prodrug. Instead, in issuing the '437 Patent, the Examiner erred in relying on Figure 9 as an embodiment of the invention. Thus, the Examiner erred in using Figure 9 to support the claimed limitation of a half-life  $t_{1/2}$  value ranging from 1-6 minutes for an epinephrine prodrug. '437 File History, EX1005, pdf p.14; Rautio, EX1050, ¶90. The half-life  $t_{1/2}$  of a prodrug in human plasma and the disintegration of a film in saliva to release its constituents are two very different processes. Importantly, the '437 Patent provides no data supporting the "half-life

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<sup>4</sup> "FIG. 9 shows a release profile of the epinephrine from the optimized fast dissolving film in 500 ml Simulated Saliva at 37° C." EX1001, 4:13-15.

$t_{1/2}$  range from 1-6 minutes” claim limitation. Rautio, EX1050, ¶66. Thus, institution will at least provide the Board with a correct appreciation of Truelove 1 as supporting unpatentability, as well as the ability to correct the mistake of not considering Truelove 1’s full disclosure and mistake concerning the failure of Figure 9 to support patentability. As such, the Board upon institution will be able to fully consider Truelove 1’s disclosure in finding the ‘437 Patent unpatentable.

As detailed below, a holistic review of all the factors governing discretionary denial counsels in favor of the immediate merits review of challenged claims 1-3 the ‘437 Patent and denial of Patent Owner’s request for discretionary denial.

## II. DIRECTOR'S PROCESS MEMORANDUM CONSIDERATIONS DO NOT SUPPORT DISCRETIONARY DENIAL

The Process Memorandum lists several relevant considerations the parties may address to inform the Director in deciding whether to deny or grant Patent Owner's request for discretionary denial. The considerations and Petitioner's view of same are summarized below.

1. Whether the PTAB or another forum has already adjudicated the validity or patentability of the challenged patent claims.

*Neither the PTAB nor another forum has already adjudicated or has pending the validity or patentability of the challenged patent claims.*

2. Whether there have been changes in the law or new judicial precedent issued since issuance of the claims that may affect patentability.

*No changes.*

3. The strength of the unpatentability challenge.

*Petitioner's unpatentability grounds are very strong. See supra, pp.5-6; infra, pp. 36-74. For example, focusing just on Ground 1 and challenged claims 1-3: (i) Truelove 1 (EX1002) discloses claimed epinephrine diester prodrug compounds and their associated half-lives  $t_{1/2}$ ; (ii) the Almoazen Paper (EX1022) discloses everything from the '437 Patent related to unit dosage film formulation, as the '437*

*Patent disclosure was copied from it, but not disclosed to the Patent Office (Almoazen Paper); and (iii) and for claim 1, Asraf discloses the inherent and calculable Log P values for the prodrug compounds. Truelove 1, Table 3 expressly discloses to a POSA the diester epinephrine prodrug compounds in the challenged claims. Patent Owner agrees with the disclosure. DD Req. 28-34. Table 3 and the chart below provide the relationship between the Table 3 disclosure and the named claimed compounds of claim 3, which have the structures claimed in claim 2. See Rautio, EX1050, ¶¶178-179; Meanwell, EX1051, ¶¶80-81; DD Req. 28-34.*

Truelove 1, EX1002, Table 3

| TABLE 3                                                                                    |                                     |        |       |
|--------------------------------------------------------------------------------------------|-------------------------------------|--------|-------|
| Compound                                                                                   | Rate of hydrolysis in<br>t½ seconds |        |       |
|                                                                                            | Horse                               | Rabbit | Human |
| L-3,4-diacetyl- $\alpha$ -[(methylamino)-methyl]<br>benzyl alcohol hydroperchlorate.....   | 20                                  | 45     | 180   |
| L-3,4-dipropionyl- $\alpha$ -[(methylamino)methyl]<br>benzyl alcohol hydroperchlorate..... | 50                                  | 90     | 240   |
| L-3,4-di[butyryl- $\alpha$ -[(methylamino)-methyl]<br>benzyl alcohol hydroperchlorate..... | 100                                 | 160    | 360   |
| L-3,4-dipivalyl- $\alpha$ -[(methylamino)-methyl]<br>benzyl alcohol hydroperchlorate.....  | 600                                 | 720    | 1,800 |

| <b>Different Names Same Compounds</b>                                                                                                        |                                                                                                         |
|----------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|
| <b>Truelove 1, Table 3<br/>Disclosed Compounds</b>                                                                                           | <b>'437 Patent<br/>Claimed Compounds</b>                                                                |
| 3,4- <del>diacetyl</del> <b>acetoxy</b> - $\alpha$ -<br>[(methylamino)methyl]<br>benzyl alcohol<br>$t_{1/2}$ = 180 seconds = 3 minutes       | 4-[1-hydroxy-2-(methylamino)ethyl]-<br>1,2-phenylene diacetate<br><b>'437 Patent, Claims 2 &amp; 3</b>  |
| 3,4- <del>dipropionyl</del> <b>propionoxy</b> - $\alpha$ -<br>[(methylamino)methyl]<br>benzyl alcohol<br>$t_{1/2}$ = 240 seconds = 4 minutes | 4-[1-hydroxy-2-(methylamino)ethyl]-<br>1,2-phenylene dipropionate<br><b>'437 Patent, Claims 2 and 3</b> |
| 3,4- <del>dibutyryl</del> <b>butyroxy</b> - $\alpha$ -<br>[(methylamino)methyl]<br>benzyl alcohol<br>$t_{1/2}$ = 360 seconds = 6 minutes     | 4-(1-hydroxy-2-(methylamino)ethyl)-<br>1,2-phenylene dibutyrate<br><b>'437 Patent, Claim 1</b>          |

*As the Almoazen Paper is as complete a disclosure as the “enabling” disclosure found in '437 Patent for the remaining limitations, of at least claims 2 and 3 (claim 1 also has a Log P limitation), Petitioner's unpatentability challenge is exceptionally strong. See supra, pp.5-6; infra, pp. 36-74.*

4. The extent of the petition's reliance on expert testimony.

*The Petition relies on two expert declarations from experts in the field - Rautio (EX1050) and Meanwell (EX1051). Based on these declarations, Patent Owner could take no other position other than to*

*agree with our experts that a POSA would understand Truelove I, Table 3 as disclosing diester epinephrine prodrug compounds. See DD Req. 28-34.*

5. Settled expectations of the parties, such as the length of time the claims have been in force.

*The claims of the '437 Patent were in force less than four (4) years before Aquestive filed the Petition. See also supra, pp.2-4; infra, pp.12-34.*

6. Compelling economic, public health, or national security interests.

*Petitioner's epinephrine prodrug in a fast dissolving film (Anaphylm™) for sublingual administration should be approved for commercial use by late January 2026. Institution is necessary to ensure that the public has a sublingually administered epinephrine product to address anaphylaxis. See infra, pp.34-35.*

7. Any other considerations bearing on the Director's discretion.

*Institution is necessary to address: (i) Examiner error that Truelove I did not disclose claimed compounds with half-lives  $t_{1/2}$  falling within the scope of the claims, and (ii) Examiner error that '437 Patent, Figure 9 of the '437 Patent disclosed the disintegration of an*

*epinephrine prodrug film and not an assessment of half-life  $t_{1/2}$  of the prodrug in human plasma. See Pet., at 23-24; Rautio, EX1050, ¶90; see also supra, p.5-7; infra, pp.33-34, 38-40, 45-49.*

### III. PATENT OWNER'S ARGUMENTS REGARDING ALLEGED SETTLED EXPECTATIONS LACKS MERIT

#### A. Background

It is estimated that anaphylaxis affects up to 5% of the population in the United States (EX1060, p.1), and has been defined as:

a serious allergic (hypersensitivity) reaction that **can progress rapidly and may cause death**. It may involve the skin/mucosa (includes lip/tongue), respiratory (lungs, breathing), cardiovascular (heart, blood pressure), and/or gastrointestinal (stomach/gut) systems. **Life-threatening anaphylaxis is characterized by respiratory and/or cardiovascular involvement** and may occur without skin/mucosa involvement.

EX1061, p. 406 (emphasis added).

Epinephrine (*i.e.*, 3-4-dihydroxy- $\alpha$ -[(methylamino)methyl]benzyl alcohol), also called adrenaline, is the standard of care for the treatment of anaphylaxis. Due to its low lipophilicity, epinephrine is poorly absorbed through biological

membranes, such as the eye and oral mucosa,<sup>5</sup> Rautio, EX1050, ¶¶40-45, and is typically administered via intramuscular injection. *See* Meanwell, EX1051, ¶¶48-50; Rautio, EX1050, ¶45.

The term “prodrug” describes compounds that undergo chemical transformation within the body to release a parent drug. Rautio, EX1050, ¶¶31, 36, 38-40, 289-290. For example, a compound may be chemically modified by attaching a “promoiety” to create a new compound (*i.e.*, “prodrug”) to address pharmaceutical, pharmacokinetic, or pharmacodynamic barriers including, *inter alia*, poor lipophilicity, or inadequate permeability through biological membranes. *Id.*, ¶¶35-47. Typically, a parent drug (*e.g.*, epinephrine) and promoiety (*e.g.*, ester) are covalently attached to form a prodrug. *Id.*, ¶¶30, 45, 292-293.

Since 2004, Petitioner Aquestive, and its predecessor MonoSol Rx, LLC, has been a worldwide leader in film-based drug delivery applications using, *inter alia*, sublingual films such as its PharmFilm<sup>®</sup> drug delivery technology that uses thin

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<sup>5</sup> The oral mucosa includes the sublingual and buccal areas of the mouth.

Sublingual and buccal administration refers to placement under the tongue and inside the cheeks. Rautio, EX1050, ¶¶43, 41; Florence, EX1015, Figure 9.15, p.364.

dissolvable films for the oral or transmucosal administration of medications. In fact, since at least as early as the beginning of 2016, Petitioner has been developing polymeric sublingual film formulations that could be used to orally deliver various drugs, including epinephrine. Examples of this research are disclosed in a number of patents including, U.S. Patent Nos. 12,023,309, entitled “Enhanced Delivery Epinephrine Compositions” (EX1062), and 11,273,131, entitled “Pharmaceutical Compositions With Enhanced Permeation” (EX1063). Both patents claim priority to an application filed on May 5, 2016 and disclose, *inter alia*, polymeric films used to orally administer epinephrine.<sup>6</sup>

As part of Petitioner's efforts to develop and commercialize an orally administrable epinephrine product, clinical studies were commenced to evaluate the efficacy of Anaphylm™, the proprietary name given to Petitioner's proposed sublingual film epinephrine product. In March 2025, upon conclusion of the requisite clinical studies and analysis of those results, Petitioner submitted an NDA seeking approval to market and sell its Anaphylm™ product. EX1064, p. 36. If approved by the FDA, Anaphylm™ would become the first orally deliverable

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<sup>6</sup> U.S. Patent Nos. 12,023,309 (EX1062) and 11,273,131 (EX1063) are based on U.S.S.N. 17/835,442 (EX2006) and U.S.S.N. 15,724,234 (EX2005), respectively.

epinephrine product for the treatment of anaphylaxis in the United States. On June 16, 2025, Petitioner's NDA submission was formally accepted, and the FDA indicated it expects to issue its decision on whether Petitioner can market Anaphylm™ by January 31, 2026. EX1065.

Without considering research and development costs, Petitioner has spent over \$19 million to conduct the clinical trials needed to demonstrate Anaphylm™'s efficacy (*see, e.g.*, EX1066, p.73; EX1067, p.71; EX1068, p.42; EX1069, p.44), and approximately \$4.3 million in FDA administrative filing fees associated with the submission of its NDA. *See* EX1070, p.1.

**B. The Challenged Patent Issued In 2021 And Patent Owner Has No Settled Expectations That Support Discretionary Denial Notwithstanding Patent Owner's Arguments**

Petitioner filed its Petition less than four (4) years after the challenged '437 Patent issued. Importantly, the Director has acknowledged that "[e]arly challenges to patents favor robust, predictable patent rights are weighed against discretionary denial." *Telsa, Inc. v. Charge Fusion Technologies, LLC.*, IPR2025-00152, -00153, Paper 11, at 3 (Dir. June 12, 2025). Accordingly, Petitioner's "early challenge" strongly militates in favor of rejecting Patent Owner's discretionary denial request. *See, e.g., Microsoft Corporation v. Edge Networking Systems, LLC*, IPR2025-00617, -00618, -00619, Paper 12, at 2 (Dir July 31. 2025) (referring to the Board

because challenged patent that issued in 2021 has “not been in force for a significant period of time” and “Patent Owner has not developed strong settled expectations”); *Advanced Micro Devices, Inc. et al. v. Concurrent Ventures, LLC et al.*, IPR2025-00479, Paper 10, at 2 (Dir. July 10, 2025) (referring Petition to the Board because “the challenged patent issued in 2021, and Patent Owner has not developed strong settled expectations that favor discretionary denial”); *Berkshire Hathaway Energy v. Birchtech*, IPR2025-00274, -00278, -00280, -00281, Paper 23, at 3 (Dir. July 2, 2025) (referring Petitions to the Board because, *inter alia*, “the challenged patents issued in 2019 and 2020, such that Patent Owner has not developed strong settled expectations that favor discretionary denial”); *Cambridge Industries USA, Inc. v. Applied Optoelectronics, Inc.*, IPR2025-00434 -00436, -00437, Paper 11, at 2-3 (Dir. June 26, 2025) (declining to discretionarily deny petitions because the challenged patents issued about 5-6 years ago and “Patent Owner has not developed strong settled expectations”).

Patent Owner's misplaced assertion that discretionary denial is warranted, even though this Petition was filed only four (4) years after the issuance of the '437 Patent, DD Req. 9-19, is totally refuted and can be brought into sharper focus by considering the timing of Petitioner's filing. Prior to conducting the requisite clinical testing to obtain sufficient data to support the submission of an NDA for

the sublingual administration of an epinephrine prodrug for the treatment of anaphylaxis, Petitioner had no reason to challenge the '437 Patent. However, in March 2025, after the clinical testing was concluded and it was determined that the resulting pharmacokinetic, pharmacodynamic and safety data demonstrated the efficacy of the Anaphylm<sup>TM</sup> product, Petitioner prepared and submitted an NDA to the FDA. Upon submission of its NDA, Petitioner then diligently prepared and filed its Petition only two (2) months later in May 2025.

It is compelling that in trying to advance its claim of settled expectations, Patent Owner points to no evidence that the subject matter of the challenged patent has ever been commercialized, asserted, marked, licensed or otherwise used in Petitioner's technology space. This evidentiary deficiency weighs heavily against finding that Patent Owner had settled expectations that the validity of its young patent would not be challenged. *See, e.g., Shenzhen Tuozhu Technology Co., Ltd. v. Stratasys, Inc.*, IPR2025-00438 -00531, -00532, -00585, -00611, Paper 10, at p.2 (Dir. July 17, 2025). As the Director explained in *Intel Corp. v. Proxense LLC*, IPR2025-00327, -00328, -00329, Paper 12 (Dir. June 26, 2025), even a patent in force for over nine (9) years fails to create settled expectations if it has not been used or enforced:

**a patent may have been in force for years but may not have been commercialized, asserted, marked, licensed or otherwise applied in petitioner's particular technology space,** if at all. These non-exclusive examples provide considerations that **weigh against a patent owner's claim of settled expectations** and bears on the Director's discretion.

*Intel*, Paper 12, at 2-3 (emphasis added).

The Director's reasoning applies with greater force here, considering the challenged '437 Patent is 5 years younger than the patents challenged in *Intel*.

Patent Owner tries to prop-up its suspect settled expectations argument by averring that the named inventor, Dr. Almoazen, spent "five figures" in an effort to "protect and commercialize" the subject matter recited in the challenged patent.

DD Req. 9. Yet, Patent Owner provides no contemporaneous evidence of these so-called efforts. At most, Patent Owner points to a few e-mails discussing forums and fund raising efforts, each dated 1-3 years before the '437 Patent issued. *See, e.g.*, EX2014-EX2017. Additionally, with the exception of a lone e-mail, none mention epinephrine or Dr. Almoazen's patent application. At most that single e-mail from April 2018 simply refers to "[t]he epinephrine project is in a PCT that will be published next month." EX2015, p.1.

The paucity of evidence proffered by Patent Owner clearly does not support denying merits review of the '437 patent as is highlighted by the Director's denial of the request for discretionary denial in *Amgen Inc. v. Bristol-Myers Squibb Co.*, IPR2025-00601, -00602, -00603, Paper 9 (Dir. July 24, 2025). In *Amgen*, the Director stated:

that there may be good reason why a Patent Owner has strong settled expectations . . . , for example an explanation of how **an extraordinary amount of investment, time and resources dedicated to research, development, trials, and regulatory approval correlates to settled expectations, [but] Patent Owner has not sufficiently articulated such reasons in these proceeding. In the absence of such information, Patent Owner has not demonstrated that it has developed strong settled expectations that favor denial . . .**

*Amgen*, Paper 9, at 2-3 (emphasis added).

Patent Owner's purported "efforts" which include an unsupported, post-hoc assertion that "five figures" were spent to "protect and commercialize" his claimed subject matter, and a few e-mails that do not refer to the challenged '437 Patent, much less epinephrine, fall far short of the evidence that the Director stated in

*Amgen* was needed to demonstrate strong settled expectations on behalf of Patent Owner.

In stark contrast, it was Petitioner, not Patent Owner, that incurred significant expense and devoted substantial time and resources in the form of the underlying research and development efforts and necessary clinical trials that culminated with the submission of Petitioner's NDA for an orally deliverable epinephrine prodrug product. As detailed previously, Petitioner has spent over \$19 million to conduct the requisite clinical trials needed to demonstrate the efficacy of its proposed Anaphylm™ product and file its NDA. *Supra*, p.3. This figure does not even include the countless man-hours and research and development costs incurred by Petitioner since at least as early as the beginning of 2016 to develop and bring the first orally deliverable epinephrine prodrug product for the treatment of severe allergic reactions and anaphylaxis one step closer to being marketed in the United States, if its NDA is approved by the FDA in January 2026.

In a last-ditch attempt to salvage its claim of settled expectations, Patent Owner's points to actions taken by Petitioner and makes three unavailing arguments urging discretionary denial: (1) employment discussions between Petitioner and Dr. Almoazen that occurred five (5) years before the challenged patent issued; (2) the '437 Patent should have been challenged during the patent's

prosecution via a third party submission or immediately upon issuance via a PGR proceeding; and (3) Petitioner's offer and subsequent withdrawal of its offer to acquire rights to the '437 patent. DD Req. 16-19. These arguments, based on activities, most of which predate the 2021 issue date of the '437 Patent, fail to support Patent Owner's claim of settled expectations or its request for discretionary denial.

**C. Petitioner's Employment Discussions With Dr. Almoazen Fail To Support Patent Owner's Claim Of Settled Expectations**

Petitioner, seeking to fill open Entry Level Formulation Scientist positions, contacted Dr. Almoazen, in June 2016. The reason Dr. Almoazen was contacted had nothing to do with his Almoazen Paper as Patent Owner suggests. *See* DD Req. 10, 16. Rather, Dr. Almoazen was initially contacted because he was the Director of Pharmaceutical Sciences Graduate Program at the University of Tennessee, and Petitioner was looking to that Program for "any graduating or post doc that may fit the organization." EX1071; EX1072, p. 1 ("I reached out to Dr. Almoazen as you requested for some entry level Formulation Scientist[s] and . . . he will be happy to send me some candidates. . . ."); EX2001, p. 8 ("would you have a few minutes to speak about openings we have for entry level Formulation Scientists"). Additionally, contrary to Patent Owner's suggestion, Petitioner

reached out to other individuals, beside Dr. Almoazen, for the Formulation Scientist position. *See, e.g.*, EX1073, p.1.

Although Dr. Almoazen initially expressed interested in pursuing employment with Petitioner, in less than 2 weeks and the exchange of a few e-mails, Dr. Almoazen withdrew his name from consideration. EX2001, pp.4-8. Upon Dr. Almoazen's decision not to pursue employment with Petitioner, he was again asked whether he knew of any "former students" because Petitioner is "always looking for good talent." EX2001, p.4.

After a hiatus of approximately four months, it was Dr. Almoazen who approached Petitioner to request an interview. EX2001, pp.3-4. This time, however, the tenor of his discussions changed. Dr. Almoazen was now insisting to disclose confidential information during any discussions with Petitioner. EX2002, p.3 ("I would like to share confidential information that will be in my provisional patent"), p.4 ("I would like to have the opportunity to discuss [the subject of my provisional application to see] if [Petitioner] has an interest in this project"). Dr. Almoazen, not Petitioner, repeatedly pushed to disclose "confidential information" that would be included in a provisional patent application that he intended to file in the future. EX2002, pp.3-4. Because Petitioner had been working to develop an epinephrine product that could be administered sublingually since at least as early

as 2016, and already had filed at least one patent application directed to that research, Petitioner informed Dr. Almoazen in no uncertain terms that:

**we do NOT want you to disclose ANY confidential information to us . . . [because] we do not want our internal program compromised in any way through unsolicited disclosures.**

EX2002, p.2 (emphasis in original).

Responding to Petitioner's refusal to consider the work that would be included in his upcoming provisional application, the real reason why Dr. Almoazen initiated contact with Petitioner became readily apparent -- Dr Almoazen was seeking to form a partnership with Petitioner and have Petitioner take over his research:

I hoped to share my research with your company and  
**negotiate partnerships and employment agreements. . . .**

EX2002, p.2 (emphasis added).

Petitioner again rejected Dr. Almoazen's overtures to discuss his work or provisional application:

[due] to the **position of this particular [epinephrine] molecule in our pipeline, we do not want to compromise our position and IP by discussing potential art with you.**

I hope you can understand this from business perspective. I  
need to be clear on that.

EX2002, p.1 (emphasis added).

Refusing to take no for an answer, Dr. Almoazen reiterated the real purpose  
for reaching out to Petitioner:

I am open to reconsider **if the management** at MonoSol Rx  
[Petitioner] **is willing to talk about my provisional IP and**  
**discuss it as part of the hiring process.**

\* \* \*

**I am looking for a pharma company like MonoSol Rx to**  
**partner with me to advance my company.** I am open to  
talk about anything your company is willing to discuss **as**  
**long as my projects become your projects.**

EX2002, p.1 (emphasis added).

Less than 2 weeks after Dr. Almoazen approached Petitioner and  
approximately one month before the filing of his provisional application, Dr  
Almoazen was succinctly told by Petitioner: **“No further discussion needed.**  
Good luck with your company.” EX2003, p.1 (emphasis added). The next  
morning, in an internal email, Petitioner's Dr. Wargacki doubted the value of any  
relationship or contribution by Dr. Almoazen (“the guy was being deceptive . .  
[his] website looks like fluff”). EX1074, p.1. That the Almoazen Paper was not

even mentioned confirms Petitioner's belief was that Dr. Almoazen's work, and the co-authored Almoazen Paper, would not contribute anything meaningful to Petitioner's existing project to develop an orally administered epinephrine product.

The foregoing demonstrates that Dr. Almoazen's discussions had nothing to do with the Almoazen Paper or his '437 Provisional. To the contrary, it is clear that it was Dr. Almoazen, not Petitioner, who had an ulterior motive in attempting to disclose information regarding the Almoazen Paper and his proposed provisional application.

Patent Owner uses Dr. Almoazen's spurned efforts to disclose his provisional application to argue that Petitioner had knowledge of that application. DD Req. 1-2, 4-5, 16-17. In short, Patent Owner contends that strong settled expectations exist because Patent Owner repeatedly tried to disclose the '437 Provisional (EX1013) to Petitioner and that Petitioner was put on notice of the application as well as the '437 PCT Application (EX1014) that was published in 2018. Patent Owner's strained argument, unsupported by any case law, is unavailing.

Importantly, the relevant metric for evaluating a patentee's settled expectations is the date of issuance, not the date a provisional application was filed or the publication date of a corresponding PCT application. In fact, the Director's Process Memorandum suggests settled expectations are decided based on **“the**

**length of time the claims have been in force.”** A patent owner cannot reasonably hang its claim of settled expectations on an unendorsed, unexamined application that is still subject to rejection by the Patent Office. The issue date of the challenged patent, not the filing date of a provisional application nor the publication date of a corresponding PCT application, is the touchstone for assessing settled expectations.

Relying on *NVIDIA Corp. v. Neural AI, Inc.*, IPR2025-00606, -00608, Paper 18 (Dir. July 31, 2025), Patent Owner asserts that the communications between Dr. Almoazen and Petitioner, and Dr. Almoazen's rebuffed attempts to disclose the substance of his provisional application constitutes “long-standing knowledge and awareness of Dr. Almoazen's patent filings [which] alone demonstrate settled expectation that warrant discretionary denial.” DD Req. 16-17. Patent Owner's reliance on *NVIDIA* is misplaced. In *NVIDIA*, the parties had a “commercial relationship” during which Patent Owner sent Petitioner a “presentation that included a discussion of [Patent Owner's] patent portfolio” seven (7) years before the IPR was filed. *NVIDIA*, Paper 18 at pp. 2-3. Clearly, the few e-mails exchanged between Dr. Almoazen and Petitioner can hardly constitute the “commercial relationship” at issue in *NVIDIA*.

Additionally, Patent Owner attempts to make much of the fact that the '437 Patent was submitted to the Patent Office during prosecution of a number of Petitioner's patents. DD Req. 16. That Petitioner satisfied its duty of candor and included the '437 Patent on various IDS's submitted during the prosecutions fails to support Patent Owner's discretionary denial argument. *See infra*, pp.47-49.

**D. Patent Owner's Contention That Petitioner Should Have  
Challenged The '437 Patent Sooner Is Meritless**

Patent Owner's contention that settled expectations exist because Petitioner failed to file a third party submission during the prosecution of the '437 Patent or file a PGR upon the '437 Patent's issuance is meritless and legally unavailing. *See* DD Req. 17-18. As detailed previously, Petitioner had no reason to challenge the '437 Patent until the successful completion of the clinical trials demonstrating the efficacy of its proposed Anaphylm™ product and the submission of its NDA to the FDA. *Supra*, pp.15-16.

There is no rule or case law mandating that a Petitioner must submit relevant art to the Patent Office via a third party submission or file a PGR to challenge a patent within nine (9) months of the patent's issuance.

First, Patent Owner's criticism of Petitioner for failing "to challenge the patentability [of the '437 Patent] early" by filing a third-party submission during

the prosecution is meritless. *See* DD Req. 17. Third party submissions pursuant to 37 C.F.R. § 1.290 do not permit a third party to make unpatentability “arguments.” Rather, the third party is limited to only a “concise description of relevance” which may or may not be considered by the Examiner.

Second, although the AIA expressly provides that PGR proceedings must be filed within nine (9) months of the patent's issuance, Congress did not include a corresponding temporal limitation with respect the filing of an IPR. In fact, the Director has repeatedly found that filing an IPR Petition less than 6 years after a patent issued, as is the case here, is an “early challenge” that weighs against discretionary denial. *See, e.g., Telsa*, IPR2025-00152, Paper 10, at 2. Patent Owner's argument is also contrary to Congressional intent when it enacted the AIA and provided no temporal limits based on a patent's issue date for when a IPR could be filed.

Patent Owner's citation to *iRhythm Techs, Inc. v. Welch Allyn, Inc.*, IPR2025-00363, -00374, -00376, -00377, -00378, Paper 10 (Dir. June 6, 2025), *NVIDIA*, IPR2025-00606, Paper 18 (Dir. July 31, 2025); *LifeVac, LLC v. DC STAR, Inc.*, IPR2025-00454, Paper 11 (Dir. July 11, 2025); *Therabody Inc. v. Datafeel Inc.*, PGR2025-00026, Paper 10 (Dir. July 17, 2025) is unavailing. DD Req. 17-18. Each case is readily distinguishable.

First, none of these decisions refer to third party submissions. Additionally, in *iRhythm*, the five (5) challenged patents were in force 7-13 years before the Petition was filed. *iRhythm*, Paper 10, at 3. Patent Owner's reliance on *NVIDIA* fails no better. In *NVIDIA*, the Director found settled expectations because Petitioner had actual notice of the challenged patents and that there was a "commenced relationship" that included a discussion of patent owner's patent portfolio 7 years before the IPR was filed. *NVIDIA*, Paper 18, at 2-3. Finally, Patent Owner's reliance on *LifeVac* and *Therabody* is curious since the Director rejected Patent Owner's requests for discretionary denial and referred both challenges to the Board for merits review. *LifeVac*, Paper 11, at 3; *Therabody*, Paper 10, at 3.

**E. Patent Owner's Offer To License And Subsequent Withdrawal Of That Offer Demonstrates Patent Owner Did Not Have Settled Expectations That The '437 Patent Would Not Be Challenged**

Patent Owner asserts the existence of settled expectations based on the fleeting discussions regarding Petitioner possibly licensing or acquiring rights to '437 Patent. *See* DD Req. 5-6, 18-19. Importantly during those discussions, Petitioner expressly told Dr. Almoazen his '437 Patent had numerous infirmities and would be challenged if the parties could not arrive at a reasonable business resolution.

That Petitioner inquired whether it could license or acquire rights to the '437 Patent simply shows the exercise of good business practices. After years of research and in the midst of clinical trials, Petitioner desired to protect its labors and avoid the expense and distraction associated with an IPR, as well as insulate itself from a possible district court proceeding that could potentially impact the launch of its Anaphylm™ product. Importantly, encouraging parties to engage in license negotiations to possibly eliminate future proceedings and avoid costly patent challenges that would burden either the PTAB or the courts should be rewarded not punished. *See Rates Tech., Inc. v. Speakeasy, Inc.*, 685 F.3d 163, 172 (2d Cir. 2012) (“courts have recognized a strong judicial policy favoring the settlement of litigation, including patent litigation”). To hold against Petitioner, for purposes of discretionary denial, its attempt to obtain rights to the '437 Patent would undermine sound public policy of encouraging parties to resolve disputes privately. Petitioner's laudable conduct should weigh in favor of institution, not be used by Patent Owner as a trap to be sprung after its unconscionable license terms have been rejected. *See infra*, pp.30-32.

Second, the argument that Patent Owner had settled expectations that the patentability of the '437 Patent would not be challenged because of Petitioner's refusal to accept Patent Owner's unreasonable license proposal strains credulity.

DD Req. 18-19. It is not disputed that after clinical trial began in connection with its proposed Anaphylm™ product, Petitioner approached Patent Owner to inquire about the availability of the '437 Patent. As part of that inquiry, Petitioner candidly informed Patent Owner that its '437 patent could be challenged and invalidated but that would be costly to both parties. Instead, Petitioner's

**strong preference would be to a suitable arrangement for Aquestive to obtain rights to [the '437] patent, rather than challenging it** and ultimately destroy it.

\* \* \*

I hope we can come to a solution **without placing the ['437] patent at risk, because doing so would necessitate a costly defense on your end, and a likely loss of the patent** . . . [A] preferred situation would be for Aquestive to buy the ['437] patent for a price less than the cost of invalidating it, which would be a win-win situation for both parties.

EX2008, p.4 (emphasis added).

Rather than engage in good faith negotiations, Patent Owner responded by making an absurd license demand that would require Petitioner to pay, even though the Anaphylm™ product was not even approved for sale, **an annual payment equal to the base salary of an executive**, such as Petitioner's chief scientific

officer, retroactive to the June 2021 issue date of the '437 Patent, **PLUS** a royalty of **4-7% of gross total sales once the product** was approved by the FDA.

EX2008, p.2. Clearly, Patent Owner was not negotiating in good faith, and negotiations quickly came to an end.

Undeterred, Dr. Almoazen approached Petitioner approximately 14 months later seeking "to reopen the dialog to explore how the parties can work together" EX2009, p. 1. However, after further review of the patent's validity during the intervening 14 months, Petitioner responded that the '437 patent:

suffers from numerous infirmities . . . [and that] **the infirmities in its content and prosecution are troublesome.**

As you are aware, Aquestive's research and patent filings in connection with oral film delivery of epinephrine prodrugs pre-date Dr. Almoazen's patent filing. This fact, along with **other material prior art and prosecution infirmities, represent additional obstacles and further call into questions the value of [the '437] patent.**

Please don't hesitate to reach out to [Petitioner's counsel] . . . if you believe you can properly address the deficiencies noted above.

EX2009, p.4 (emphasis added).

In sum, Dr. Almoazen was told that the '437 Patent was of questionable value and that its patentability could be challenged. Consequently, Patent Owner's assertion that it possessed settled expectations that the '437 Patent would not be challenged is belied by the communications between Petitioner and Dr. Almoazen.

Importantly, even if Patent Owner had an arguable claim of settled expectations, they are offset and overcome by Patent Owner's misrepresentations and omissions that occurred during prosecution that related to material errors by the Patent Examiner that resulted in the issuance of the '437 Patent. *See infra*, pp.38-46.

In *Anthony Inc. v. ControlTec LLC*, IPR2025-00559, -00636, Paper 12, at 2 (Dir. July 16, 2025) although "challenged patents have been in force for approximately eighteen and seventeen years", discretionary denial was not appropriate because "Petitioner appears to show a material error by the Office." Like *Anthony*, the material errors in examination of the '437 Patent resulted from the Examiner's lack of appreciation for relevant prior art. *Anthony*, at 2 (noting that "the patent examiner erred by overlooking the teachings of Carter"); *infra*, pp.40-46. Here, the challenged '437 Patent is more than ten years younger than the patents-at-issue in *Anthony*, and thus, any material error in the examination of the

'437 Patent is a much more "appropriate use of Office resources to review the potential error." *Id.*

#### **IV. OTHER PROCESS MEMORANDUM FACTORS FAVORS MERITS REVIEW**

##### **A. The Inapplicability Of *Fintiv* Weighs Against Discretionary Denial**

There are no parallel proceedings, and this would be the first time the '437 Patent's claims are subject to post-issuance scrutiny. This fact weighs in favor of institution. *Amgen*, at 2 (counseling against discretionary denial because "the parties are not currently engaged in a parallel proceeding involving the challenged patent[]") thus avoiding "concern of inconsistent outcomes and duplication of efforts resulting from two proceedings operating in parallel").

##### **B. Public Health Interests Associated With Petitioner's Anaphylm<sup>TM</sup> Product Weigh Heavily In Favor Of Merit Review**

Public health interests strongly favor immediate merits review of the patentability of challenged claims 1-3. As discussed previously, Petitioner has invested substantial resources in developing its Anaphylm<sup>TM</sup> prodrug product for the treatment of anaphylaxis and submitting its NDA to the FDA. *Supra*, pp.3, 19. The FDA's final decision on the approval status of Petitioner's Anaphylm<sup>TM</sup>

epinephrine prodrug product is expected in January 2026. If approved, Anaphylm™ would become the first and only orally administered epinephrine option for the treatment of severe allergic reactions, including anaphylaxis in the United States.

Should the Director deny institution and not refer this Petition to the Board for careful evaluation of the patentability of the challenged claims of the '437 patent, Patent Owner could use these improvidently granted claims as an obstacle to hinder Petitioner's efforts to market its new Anaphylm™ product in the United States, assuming FDA approval is granted. Thus, discretionary denial has the potential of depriving the public the benefit of this new life-saving drug, especially small children, who experience severe allergic reactions, including anaphylaxis.

**V. 35 U.S.C. § 325(d) DOES NOT SUPPORT DISCRETIONARY DENIAL  
-- CORRECTING THE EXAMINER'S MATERIAL ERROR THAT  
ALLOWED THE CLAIMS OF THE '437 PATENT TO ISSUE  
WOULD BE AN EFFECTIVE USE OF THE BOARD'S RESOURCES**

As noted by the Director:

In determining whether to discretionarily deny a petition under § 325(d), Office policy requires a determination of "(1) whether the same or substantially the same art previously was presented to the Office or whether the same or substantially

the same arguments previously were presented to the Office; and (2) if either condition of first part of the framework is satisfied, whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims.”

*Tesla*, IPR2025-00152, -00153, Paper 11, at 2 (citing *Advanced Bionics*, IPR2019-01469, Paper 6 at 8 (precedential)). Applying the two-part framework discussed in *Advanced Bionics*, it is evident that Section 325(d) does not support discretionary denial.

#### **A. The ‘437 Patent Claims**

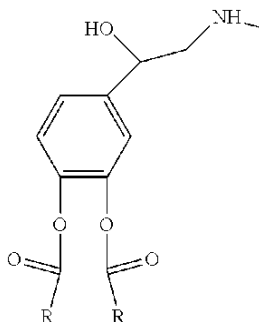
The ‘437 Patent recites diester epinephrine compounds with half-life  $t_{1/2}$  values of 1-6 minutes administered sublingually or buccally via a rapidly dissolving films. Only claims 1-3 of the ‘437 patent are being challenged:<sup>7</sup>

##### **1. Claim 1**

A compound formulated as a pharmaceutical composition in a unit dosage form configured for sublingual or buccal administration of a Formula:

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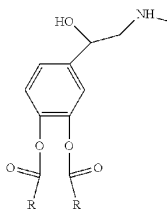
<sup>7</sup> The remaining claims of the ‘437 Patent, claims 4-5, are not being challenged because they recite chlorinated substituents which, upon release from the epinephrine compounds, generate a potentially toxic by-product. *See Rautio*, ¶68.



wherein R is selected from the group consisting of: . . .—**CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>**,—. . . or a pharmaceutically acceptable salt thereof, wherein said compound has a Log P value in the range of about 0.5-6.0 and wherein the compound is formulated in a unit dosage form as a rapidly dissolving film and has a half-life  $t_{1/2}$  range from 1-6 minutes.

## 2. Claim 2

A compound of a Formula



wherein R is selected from the group consisting of: **CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub> and CH(CH<sub>3</sub>)<sub>2</sub>** wherein the compound is formulated in a unit dosage form as a sublingual or buccal administration and wherein the compound is formulated in a unit dosage form as a rapidly dissolving film and has a half-life  $t_{1/2}$  range from 1-6 minutes.

## 3. Claim 3

The compound of claim 2, wherein the compound is selected from the group consisting of: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene di-

acetate 4-(1-hydroxy-2(methylamino)ethyl)-1,2-phenylene bis(2-methylpropanoate) 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene dipropionate; and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.

Claim 3 simply recites the names of the compounds whose structures are claimed in Claim 2. *See, e.g.,* Rautio, EX1050, ¶¶178-179.

**B. Truelove 1 Discloses Epinephrine Prodrug Compounds With Half-Life  $t_{1/2}$  Values Of 1-6 Minutes**

The Examiner overlooked and misapprehended Truelove 1 by failing to recognize, discuss and apply Table 3's disclosure of epinephrine prodrug compounds with half-life  $t_{1/2}$  values of 1-6 minutes. The prosecution history establishes that the Examiner materially erred in allowing the claims of the '437 Patent to issue and demonstrates that discretionary denial is not appropriate.

Truelove 1 describes "a novel and useful therapeutic ester of benzyl alcohol" and discloses comparative diester epinephrine compounds in Table 3. EX1002, 1:28-30, 9:26-38. Specifically, Table 3 discloses four diester epinephrine compounds with different promoieties, including a "dipivalyl" compound, as well as three other epinephrine compounds with half-life  $t_{1/2}$  values of 1-6 minutes as recited in the challenged claims.

| TABLE 3                                                                                    |                                            |        |       |
|--------------------------------------------------------------------------------------------|--------------------------------------------|--------|-------|
| Compound                                                                                   | Rate of hydrolysis in<br>$t_{1/2}$ seconds |        |       |
|                                                                                            | Horse                                      | Rabbit | Human |
| L-3,4-diacetyl- $\alpha$ -[(methylamino)-methyl]<br>benzyl alcohol hydroperchlorate.....   | 20                                         | 45     | 180   |
| L-3,4-dipropionyl- $\alpha$ -[(methylamino)methyl]<br>benzyl alcohol hydroperchlorate..... | 50                                         | 90     | 240   |
| L-3,4-dibutyryl- $\alpha$ -[(methylamino)-methyl]<br>benzyl alcohol hydroperchlorate.....  | 100                                        | 160    | 360   |
| L-3,4-dipivalyl- $\alpha$ -[(methylamino)-methyl]<br>benzyl alcohol hydroperchlorate.....  | 600                                        | 720    | 1,800 |

Truelove 1, EX1002, 9:28-37.

Importantly, Patent Owner concedes that the compounds in Table 3 of Truelove 1 are misidentified as ketone derivatives instead of diester derivatives. DD Req. 28, 44-45. Nevertheless, the epinephrine prodrug compounds of Truelove 1, Table 3 correspond to three (3) of the epinephrine prodrug species recited in challenged claims 1-3. *See Chart supra* p.9. Specifically, (1) L-3,4-diacetyl- $\alpha$ -[(methylamino)-methyl] benzyl alcohol hydroperchlorate is the salt form of the compound recited in claim 2 where the R substituent is CH<sub>3</sub>; (2) L-3,4-dipropionyl- $\alpha$ -[(methylamino)-methyl] benzyl alcohol hydroperchlorate is the salt form of the compound recited in claim 2 where the R substituent is CH<sub>2</sub>CH<sub>3</sub>; and (3) L-3,4-dibutyryl- $\alpha$ -[(methylamino)-methyl] benzyl alcohol hydroperchlorate is the salt form of the compound recited in claim 1 where the R substituent is

CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>. Rautio, EX1050, ¶¶138-151; Meanwell, EX1051, ¶¶80-91. As Petitioner's experts explained, a POSA would have readily understood and expected that the salt-form of the epinephrine prodrug compounds disclosed in Table 3 of Truelove 1 would have the same half-life  $t_{1/2}$  values as the compounds of the corresponding non salt-forms of the epinephrine prodrug compounds recited in challenged claims 1-3. Rautio, EX1050, ¶¶135-137; Meanwell, EX1051, ¶¶86, 88, 90.

### **C. Patent Owner's Section 325(d) Arguments Are Unavailing And Fail To Support Discretionary Denial**

In arguing discretionary denial is appropriate pursuant to Section 325(d), Patent Owner states Trulove 1 was "extensively discussed and considered by the Examiner," and argues that Patent Owner "clearly disclosed and discussed all relevant compounds from Truelove 1, including their half-lives . . . and that the Examiner fully considered this information." DD Req. 40-41. Patent Owner is wrong. Additionally, while the prosecution history confirms otherwise, Patent Owner also erroneously asserts "[a]pplicant also explicitly informed the Examiner . . . during prosecution . . . that Truelove 1 discusses half-life values." DD Req. 49. Not surprisingly, Patent Owner does not provide any citation to the prosecution history supporting this false assertion.

As an initial matter, in proposing that Section 325(d) supports discretionary denial, Patent Owner cannot legitimately argue that Truelove 1 was applied, considered or discussed by the Examiner, because it was not. The prosecution history provides no insight on the key aspect of Truelove 1 that Petitioner applies against the challenged claims Table 3's disclosure of epinephrine prodrug compounds with half-life  $t_{1/2}$  values of 1-6 minutes. In fact, nothing took place during of the prosecution of the '437 Patent indicating the Examiner fully appreciated that Table 3 of Truelove 1 expressly discloses epinephrine prodrug compounds with half-life  $t_{1/2}$  values of 1-6 minutes as recited in the challenged claims 1-3.

Importantly, during prosecution, **Patent Owner, not the Examiner**, introduced Truelove 1 into the prosecution when arguing claims amended to include a new "half-life  $t_{1/2}$  range of 1-6 minutes" limitation were patentable because Truelove 1 purportedly failed to disclose epinephrine compounds with half-life  $t_{1/2}$  values of less than 6 minutes. Specifically, in response to the Examiner's Final Rejection, Patent Owner amended pending claims 1 and 19 (which issued as challenged claims 1 and 2) to include the limitation "a half-life  $t_{1/2}$  range from 1-6 minutes." In support of this amendment, and in an attempt to overcome the Examiner's rejection, Patent Owner *sua sponte* presented the

Examiner with a cropped and misleading characterization of Truelove 1, focusing exclusively on the “dipivalyl” epinephrine compound (L-3,4-dipivalyl]- $\alpha$ -[(metlylamino)-methyl-] benzyl alcohol hydroperchlorate) disclosed in Table 3 of Truelove 1. Pet., at 22-23; *see* Rautio, EX1050, ¶¶79-81. Notably, up until this point in the prosecution, neither the Examiner nor Patent Owner had mentioned Truelove 1. Then, Patent Owner misleadingly argued that the Truelove 1<sup>8</sup> “dipivalyl” compound and its 30 minute half-life was the basis for amending the claims to include the “a half-life  $t_{1/2}$  range from 1-6 minutes,” and which purportedly demonstrated that the amended claims were patentable. ‘437 File History, EX1005, pdf pp.47-48.

Patent Owner compounds the misdirection committed during prosecution by doubling down and now asserting that “Applicant also explicitly informed the Examiner . . . during prosecution . . . that Truelove 1 discussion half-life ( $t_{1/2}$ ) values.” DD Req. 49. Patent Owner’s assertion is belied by the disingenuous arguments made during prosecution. For example, Patent Owner argued:

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<sup>8</sup> Patent Owner never directs the Examiner explicitly to Table 3, only referring in general to Truelove 1.

**The claims have been amended to add the limitation of [a 1-6 minute] hydrolysis rate . . . because [Truelove 1] showed hydrolysis data for the trimethyl derivative of 30 minutes.**

\* \* \*

**For a successful epinephrine prodrug to be used for anaphylaxis, the half-life should be 1-6 minutes. . . .**

Furthermore, and **to our knowledge no prodrug had similar structure** or similar chloro substitution making the discovery of these compounds more novel and unexpected.

\* \* \*

**[Truelove 1] wanted a prodrug design that hydrolyze in plasma at 30 minutes or more.** Opposite to [Truelove 1's] idea, and in order to treat anaphylaxis, we need to develop a prodrug that . . . hydrolyzed quickly.

‘437 File History, EX1005, pdf. pp.47-48 (emphasis added).

Patent Owner's statements are misleading at best and at worst false. For example, Patent Owner's assertion that Truelove 1 "showed hydrolysis data for the trimethyl [dipivalyl] derivative of 30 minutes" neglects to mention Table 3 at all or that Truelove 1 also expressly disclosed three (3) other epinephrine prodrug compounds with half-life  $t_{1/2}$  values of 6 minutes or less as recited in the challenged claims. *See* Truelove 1, EX1002, 9:26-37.

Additionally, Patent Owner's representation that it had **“knowledge [of] no prodrug [having] similar structure”** to the “dipivalyl” compound disclosed in Table 3 strains credulity. Patent Owner could not truthfully disclaim knowledge of epinephrine prodrug compounds having structures similar to Truelove 1's “dipivalyl” compound when diacetyl, dipropionyl, and dibutryl epinephrine prodrug compounds are also disclosed in Table 3 and have only slightly different R substituents.

| <b>Table 3<br/>Compound</b> | <b>R Substituent</b> | <b>Half-life (<math>t_{1/2}</math>)<br/>(seconds)</b> |
|-----------------------------|----------------------|-------------------------------------------------------|
| dipivalyl                   | $C(CH_3)_3$          | 1800                                                  |
| diacetyl                    | $CH_3$               | 180                                                   |
| dipropionyl                 | $CH_2CH_3$           | 240                                                   |
| dibutryl                    | $CH_2CH_2CH_3$       | 360                                                   |

See Rautio, EX1050, ¶¶178-179.

Further, in the March 26, 2021 Applicant-Initiated Interview Summary, Patent Owner again highlighted that the amended claims recite a half-life  $t_{1/2}$  of 1-6 minutes by focusing on only the “dipivalyl” compound disclosed in Truelove 1 and disingenuously arguing that the **“prior art epinephrine prodrug has a half-life of 30 minutes”** while remaining silent with respect to the three (3) other epinephrine compounds disclosed in Table 3 with half-life  $t_{1/2}$  values of 1-6 minutes. EX1005, pdf. p.25 (emphasis added).

Finally, in the Reasons for Allowance, the Examiner, incorrectly accepting Patent Owner's cropped and misleading arguments regarding Truelove 1, simply stated that Patent Owner:

has amended claims and persuasively argued the unexpected result of the **claimed epinephrine genus having a rapid half-life ranging from 1 to 6 minutes. [Patent Owner] points out that prior art prodrug have 30 minutes half-life.**

EX1005, pdf p.14 (emphasis added).

Patent Owner's argues that this statement demonstrates that Truelove 1 was "not overlooked" by the Examiner. DD Req. 50. Patent Owner's argument is pure conjecture, belied by the fact that Truelove 1 and its Table 3 compounds with half-life  $t_{1/2}$  values of 1-6 minutes for epinephrine prodrug compounds was not mentioned, discussed or applied by the Examiner during the prosecution of the '437 Patent.

In sum, the Examiner, without considering the epinephrine "diester" prodrug compounds disclosed in Table 3 with half-life  $t_{1/2}$  values of 1-6 minutes, accepted Patent Owner's mischaracterizations of Truelove 1 at face value and allowed the claims to issue. This is confirmed by the fact that the Examiner:

- did not comment or acknowledge Patent Owner's mischaracterizations of Truelove 1,
- failed to discuss or apply Truelove 1 during prosecution
- never used Truelove 1 as a basis of any rejection, and
- did not mention Truelove 1 in the Reasons for Allowance.

The Examiner's **silence** regarding the diester epinephrine compounds disclosed in Truelove 1 with half-life  $t_{1/2}$  values of 1-6 minutes speaks volumes and demonstrates that the Examiner erred in a manner material to the patentability of the challenged claims by overlooking and misapprehending the significance of Table 3's disclosure. *See, e.g., Klein Tools, Inc. v. Milwaukee Electric Tool Corp.*, IPR2024-01400, Paper 17, at 25-26 (PTAB Apr. 8, 2025) (granting institution because of material error where, despite patent owner's argument that the Examiner clearly understood the art, "[g]iven the prosecution history's **silence** on [relied on prior art], however, we do not view the alleged understanding as in any way 'clear[]'" (emphasis added); *Amazon.com Inc. v. Nokia Technologies OY*, IPR2024-01140, Paper 9, at 16 (PTAB Feb. 12, 2025) (finding material error and granting institution where the prosecution was **silent** as to the key prior art reference and "there is no discussion or analysis of [the reference] apart from its inclusion on the IDS") (emphasis added).

Patent Owner's misrepresentations and incomplete portrayal of Truelove 1's disclosure were at best misleading and at worst false and militate strongly in favor of referring this Petition to the Board. Even though the Board does not adjudicate equitable defenses, "the Office may consider unfair dealings as a factor when determining whether to exercise discretion to deny institution." *Tessell, Inc. v. Nutanix, Inc.*, IPR2025-00322, Paper 14, at 2 (Dir., June 12, 2025). Patent Owner's selective, incomplete and misleading characterizations and misrepresentations of Trulove 1's disclosure during prosecution violated his duty of candor. *See Calcar, Inc. v. American Honda Motor Co.*, 768 F.3d 1185, 1190 (Fed. Cir. 2014) ("[p]artial disclosure of material information about the prior art to the PTO cannot absolve a patentee . . . if the disclosure is intentionally selective"); *see Luv N' Care, Ltd. v. Laurain*, 98 F.4th 1081, 1099 (Fed. Cir. 2024) ("purposeful omission or misrepresentation of key teachings of prior art references may . . . be indicative of a specific intent to deceive the PTO").

When a Patent Owner ***misleads*** an Examiner into committing a material error, as is the case here, the Board has refused to exercise its discretion and deny institution. *See, e.g., Dr. Falk Pharma v. Ellodi Pharmaceuticals, L.P.*, IPR2025-00056, Paper 10, at 15-17 (PTAB June 3, 2025) (declining to discretionarily deny institution, the Board agreed that [patent owner] "**misled the Examiner**" into

incorrectly analyzing the key prior art reference during prosecution) (emphasis added); *Samsung Bioepis Co. Ltd. v. Alexion Pharma. Inc.*, IPR2023-01070, Paper 9, at 66 (PTAB Dec. 19, 2023) (declining to discretionarily deny institution, the Board “agree[d] with Petitioner that the Examiner was **misled** by [Patent Owner] and misapprehended [the prior art] as evidenced by the Reason for Allowance”) (emphases added); *Medtronic CoreValve LLC v. Speyside Medical, LLC*, IPR2021-00239, Paper 9, at 22-23 (PTAB Aug. 16, 2021) (declining discretionary denial, the Board agreed with petitioner that “**the Examiner was misled** by the applicant’s assertion that ‘Leonhardt does not disclose replacing the leaflet actuation of the native aortic heart valve’”) (emphasis added).

Patent Owner’s remaining Section 325(d) arguments can be easily disposed of. DD Req. 44-49, 51-52. Patent Owner argues that the typographical errors in Table 3 did not lead to Examiner error and complains that “[t]he Petition offers no evidence that the Examiner relied on the erroneous naming [of the diester epinephrine prodrug compounds] in Table 3 in any way that affected the patentability analysis” misinterprets Petitioner’s argument. *See* DD Req. 44-48. The Examiner’s material error stems not from a failure to recognize that the diester compounds in Table 3 are misnamed, but rather from the Examiner’s failure to appreciate or recognize Truelove 1’s teachings at all, as evidenced her failure to

discuss or apply Truelove 1 during the prosecution of the '437 Patent. *Supra*, pp.39-46.

Next Patent Owner criticizes Petitioner for failing to proffer evidence showing that the Examiner committed material error in connection with Truelove 1's disclosure of buccal administration. DD Req. 48-49. Again, as detailed previously, the Examiner's material error is based on the failure to appreciate and recognize that Table 3 of Truelove 1 discloses the diester epinephrine prodrug compounds recited in the challenged claims and their corresponding half-life values  $t_{1/2}$  of 1-6 minutes. *Supra*, pp.39-46.

Finally, Patent Owner's argument regarding the Examiner's consideration of Ashraf can be given short shrift. DD Req. 51-52. In spite of all its hand-waving, Patent Owner does not dispute that "Asraf was not discussed or applied by the Examiner." *See* Pet. at 43.

**VI. THE PETITION PRESENTS COMPELLING ARGUMENTS THAT THE CHALLENGED CLAIMS ARE UNPATENTABLE**

Notwithstanding Patent Owner's arguments to the contrary (DD Req. 19-24), Petitioner's unpatentability grounds are very strong.

**A. The Petition Grounds**

Petitioner provides three grounds in its Petition to have claims 1-3 of U.S. of the '437 Patent declared unpatentable as obvious under 35 U.S.C. § 103. Only challenged claim 1 has the Log P claim limitation, for which Ashraf is used in Grounds 1 and 2, and Ashraf and Florence are used in Ground 3.

1. Ground 1: Truelove 1, Ashraf, and Almoazen Paper.

*Truelove 1*

Truelove 1 (EX1002), which though listed as a reference on the face of the '437 Patent, was never addressed by the Examiner, discloses several of the '437 Patent's compounds recited in the challenged claims, *i.e.*, ester prodrugs of epinephrine and their respective half-lives  $t_{1/2}$  of 1-6 minutes. EX1002, 9:28-37; Pet., at 24-39; Rautio, EX1050, ¶¶179-180; *supra*, pp.4-10, 35-40. The '437 Patent admits that Truelove 1 "synthesized four different prodrugs . . . (see structures [of Figures] 7A, 7B, 7C, 7D)," which are "compounds of the invention." EX1001, 2:11-12; 6:42-7:9; *see id.*, 4:8-10 ("FIG. 7 shows Anwar A. Hussain and

James E. Truelove [Truelove 1] compounds.”). Rautio, EX1050, ¶¶54, 56-60; Meanwell, EX1051, ¶¶34-37. Of these admitted Truelove 1 epinephrine prodrugs, the ‘437 Patent figures depict compounds claimed by the ‘437 Patent. For example, ‘437 Patent admitted Truelove 1 synthesized compounds shown in Figures 7A-7C as claimed in Claims 2 and 3 of the ‘437 Patent. *See, e.g.,* Pet., at 8-13; Rautio, EX1050, ¶¶178-179; *see also, supra*, pp.5, 8-9.

*Ashraf*

Ashraf (EX1003) teaches that satisfactory absorption of drugs through oral mucosa has been observed over a range of log P values of 1 to 5. Asraf also lists log P values of clinically used sublingually administered drugs which have log P values ranging between 0.94 and 4.9. *See* Pet., at 42-43; Rautio, EX1050, ¶¶194-197. Asraf was mentioned in the ‘437 Patent in connection with preferred Log P values (EX1001, 5:6-12), but was never discussed or applied by the Examiner. The ‘437 Patent claims compounds having log P values in the range of about 0.5-6.0. Moreover, the Examiner observed that the Log P limitation of the claims was an inherent property of the compounds: “Furthermore, the claimed limitation of Log P value is deemed inherent to the claimed structures, unless evidence to the contrary.” ‘437 File History, EX1005, pdf p. 91. Patent Owner in its Response, did

not contest the Examiner's finding that Log P value limitation was inherent to the claimed structures. EX1005, pdf pp.73-87.

*The Almoazen Paper*

The Almoazen Paper (EX1022) is not listed on the face of the '437 Patent. It discloses epinephrine in a unit dosage form configured for sublingual or buccal administration in rapidly or fast dissolving films, a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient. *See* Pet., at 41-42; Rautio, EX1050, ¶¶181-193.

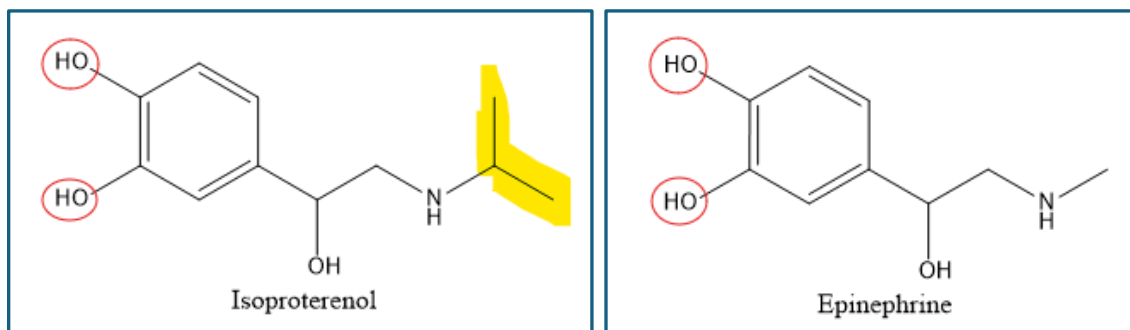
*Motivation to Combine*

A POSA would have possessed reasons and motivation to combine the teachings of Truelove 1, Ashraf, and the Almoazen Paper because each relate to the same field of endeavor (*i.e.*, the buccal administration of drug formulations), and would have had a reasonable expectation of obtaining the diester epinephrine compounds having half-life  $t_{1/2}$  values of 1-6 minutes as recited in claims 1-3 of the '437 patent. Pet., at 74-78; *see also* Rautio (EX1050), ¶¶288-300, 305-306, 308-310, 315-316, 318-358.

2. Ground 2: Truelove 3, Ashraf, and Almoazen Paper.

*Truelove 3*

Truelove 3 (EX1008) is not listed on the face of the '437 Patent nor does it appear in an IDS. Truelove 3 discloses several of the '437 Patent's claimed ester promoieties used in forming its isoproterenol prodrugs and discloses their respective half-lives  $t_{1/2}$  ranging from 1-6 minutes with the same ester promoieties as recited in challenged claims 1-3 of the '437 Patent. There is significant structural similarity between the isoproterenol and epinephrine active drug compounds (molecules) and the position of the ester promoieties linked thereto, shown in circled -OH groups below. The difference in structures is highlighted in yellow.



See Pet., at 44-46; Rautio, EX1050, ¶¶209-210. Accordingly, a POSA would have readily expected that the half-lives  $t_{1/2}$  of epinephrine prodrugs recited in challenged claim 1-3 and the isoproterenol prodrugs of Truelove 3 would have been substantially the same, if not identical, because of the structural similarity

between the isoproterenol and epinephrine molecules, the use of identical ester promoieties, and the positions of the promoieties on the active drug molecules. Thus, a POSA would have understood that Truelove 3 teaches the use of these ester moieties to form prodrugs and would have been motivated to use the teachings of Truelove 3 with the active drug epinephrine to synthesize diester epinephrine prodrugs. Moreover, in view of the teachings of Truelove 3, a POSA would therefore have had a reasonable likelihood of success, without undue experimentation, of being able to achieve the compounds recited in the challenged claims and the claimed half-lives, *i.e.*, diester prodrugs of epinephrine and their respective half-lives  $t_{1/2}$  of 1-6 minutes. *See* Pet., at 44-46; Rautio, EX1050, ¶¶215-217.

*Ashraf*

*Supra*, pp.51-52.

*The Almoazen Paper*

*Supra*, p.52.

*Motivation to Combine*

A POSA would have also been motivated to combine Truelove 3, Ashraf, and the Almoazen Paper because each relates to the same field of endeavor (*i.e.*, the buccal administration of drug formulations) and would have had a reasonable

expectation of arriving at the diester epinephrine compounds with half-life  $t_{1/2}$  values as recited in claims 1-3 of the '437 patent. Pet., at 79-83; *see also* Rautio, EX1050, ¶¶288-300, 305-306, 308-310, 359-402.

3. Ground 3: Truelove 1, Truelove 3, Ashraf, Almoazen Paper, Fuchs, Schobel, and Florence.

Ground 3 combines the references of Grounds 1 and 2 with additional references, in case one or more of the Ground 1 and/or 2 references and/or their disclosures are challenged.

*Truelove 1, Truelove 3, Ashraf and The Almoazen Paper*

*Supra*, p.50-55.

*Fuchs*

Fuchs (EX1004) discloses films which incorporate pharmaceutically active ingredients that can be administered mucosally. *See* Pet., at 43; Rautio, EX1050, ¶¶198-201. In fact, the '437 Patent states: "Films that incorporate a pharmaceutically active ingredient are disclosed in U.S. Pat. No. 4,136,145 to Fuchs, et al. ("Fuchs"). EX1001, 2:39-47.

*Schobel*

Schobel (EX1021), which is not listed on the face of the '437 Patent, teaches the use and methods of making oral rapidly dissolving films for delivery of

epinephrine compositions including epinephrine prodrugs to the oral mucosa. *See* Pet., at 46-47; Rautio, EX1050, ¶¶ 234-240.

### *Florence*

Florence (EX1015) provides guidance on optimal log P values for various absorbing membranes and provides an ideal range. *See* Pet., at 46; Rautio, EX1050, ¶¶ 223-226.

### *Motivation to Combine*

A POSA seeking to develop epinephrine prodrugs with rapid half-life  $t_{1/2}$  values that could be administered sublingually or buccally would have considered disclosures relating to the ester moieties used to synthesize prodrugs, their associated half-life values and the salt form of those prodrugs, as disclosed in Truelove 1 and Truelove 3, and would have had a reasonable expectation of obtaining diester epinephrine compounds that could penetrate the oral mucosa and have the same half-life  $t_{1/2}$  values of 1-6 minutes. Pet., at 83-84, *see, also*, Rautio, EX1050, ¶¶ 318-402.

A POSA would have been aware that Florence discloses the ideal Log P values for buccal absorption is typically 3.52-5.52. EX1015, p.334. A POSA would have also known references such as Fuchs and Schobel teach films designed for mucosal drug administration. Rautio, EX1050, ¶¶ 198-200, 234-239. For

example, Fuchs describes “unit dosage forms” adapted for administration to body cavities. EX1004, 2:33-38; *see* EX1001, 2:39-47 (Fuchs discloses “[f]ilms that incorporate a pharmaceutically active ingredient” that can be administered to “mucosal membrane areas of the body”). Schobel describes rapidly dissolving film used for oral administration of epinephrine compounds, including epinephrine prodrugs. EX1021, 1:36-45, 13:37-67, 14:13-18, 15:62-65, 45:19-20; *see id.*, 16:57-27.2; *see also* Pet., at 84-85; *see generally*, Rautio, EX1050 ¶¶288-316.

## **VII. PATENT OWNER’S MERITLESS ARGUMENTS ARE EASILY REBUTTED**

Notwithstanding Patent Owner’s arguments to the contrary (DD Req. 19-24), Petitioner’s unpatentability grounds are very strong. Grounds 1-3 demonstrate that the prior art disclosed not only the challenged claimed compounds with half-life values of 1-6 minutes, but also that those prodrug compounds can be “formulated in a unit dosage form as a rapidly dissolving film.”

To begin, Patent Owner misstates Petitioner’s support for Ground 3’s prior art disclosure of the methods and formulations for rapidly dissolving films. *See* DD Req. at 20 (Table). In order to address the possibility that Patent Owner would attack one or more references, Ground 3, in an abundance of caution, relies on

three overlapping references for the fast dissolving dosage film limitation of the challenged claims, namely the Almoazen Paper, Fuchs and Schobel.

Disingenuously, Patent Owner omits from its chart one or more of these references.

Namely, Patent Owner omits the items in red.

|          |                                                                                         |                                                                                    |                                                                                |
|----------|-----------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
|          | “wherein the compound is formulated in a unit dosage form as a rapidly dissolving film” |                                                                                    |                                                                                |
|          | Claim 1                                                                                 | Claim 2                                                                            | Claim 3                                                                        |
| Ground 3 | Almoazen Paper<br>Fuchs<br>Schobel<br>(Pet., at 50, 66, 68-69 and Claim Chart at 104)   | Almoazen Paper<br>Fuchs<br>Schobel<br>(Pet., at 50, 71 and Claim Chart at 107-108) | Almoazen Paper<br>Fuchs<br>Schobel<br>(Pet., at 50, 74 and Claim Chart at 109) |

#### **A. The Almoazen Paper Is Prior Art.**

Notwithstanding Patent Owner's arguments to the contrary (DD Req. 19-23), the Almoazen Paper qualifies as prior art to the '437 Patent because: (i) the '437 Provisional (EX1013) does not disclose a material claim limitation of the '437 Patent and thus does not support the '437 Patent's priority claim; and (ii) contrary to Dr. Almoazen's *post-hoc*, self-serving declaration (EX2019), contemporaneous documentary evidence demonstrates he was neither the sole inventor of the '437 Provisional nor the sole inventor of the '437 PCT Application.

The timeline regarding the relevant dates for the various publications and filings is given below.

|                               | Almoazen Paper (EX1022)                                                                                       | '437 Provisional (EX1013)                                                                                                             | '437 PCT Application (EX1014, EX1052)    | '437 Patent (EX1001) |
|-------------------------------|---------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------|----------------------|
| Filing Date/ Publication Date | January 6, 2016                                                                                               | November 13, 2016                                                                                                                     | November 9, 2017                         | November 9, 2017     |
| Author(s) or Inventor(s)      | Alaadin Alayoubi, <b>Lindsay Haynes</b> , Hemlata Patil, Baher Daihom, Richard Helms & <b>Hassan Almoazen</b> | <b>Almoazen, Assignment from Haynes saying she invented</b> "Epinephrine Film and Methods Thereof" described in provisional (pdf p.2) | <b>Almoazen and Haynes, co-inventors</b> | <b>Almoazen</b>      |

1. The Almoazen Paper is prior art as the '437 Provisional cannot be used to establish an earlier priority date.

Patent Owner does not address let alone refute the fact that the '437 Provisional (EX1013) fails to disclose or otherwise support the '437 Patent's material claim limitation of a half-life  $t_{1/2}$  in the range of 1-6 minutes, which was added to overcome a rejection. *See, e.g.*, DD Req. 20-21. Namely, that the '437 Provisional fails to disclose that "the compound . . . has a half-life  $t_{1/2}$  range from

1-6 minutes.” *See, e.g.,* Pet., at 14-15; *see also* Rautio, EX1050, ¶¶63-67; and EX1033. Because the ‘437 Provisional cannot be the basis for a claim of priority, the ‘437 Patent’s effective filing date is November 9, 2017. Thus, the Almoazen Paper, filed more than a year earlier on January 6, 2016, qualifies as prior art to the ‘437 Patent, irrespective of any disputed claims of authorship. *See* Pet., at 14-15; *see also* Rautio, EX1050, ¶¶ 63-67.

2. The Almoazen Paper is prior art because Almoazen is not the sole author/inventor.

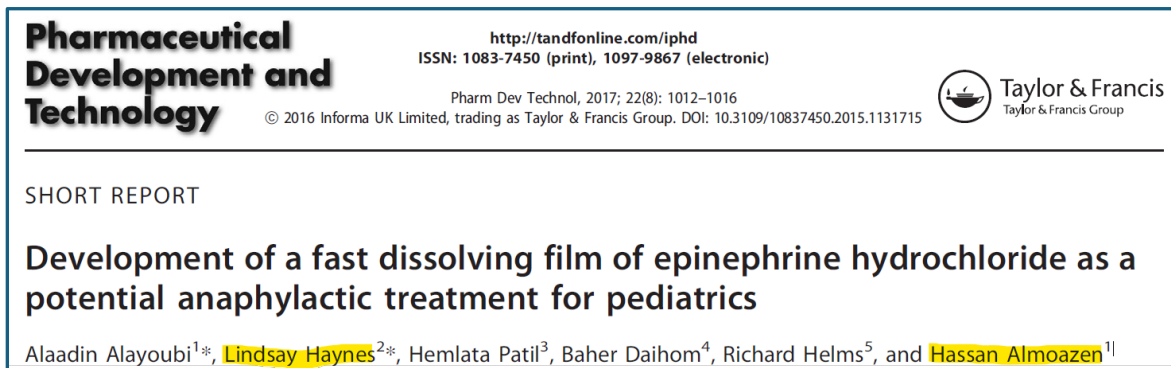
Patent Owner argues that it is entitled to use the grace period afforded by 35 U.S.C. § 102(b)(1)(A) because Dr. Almoazen allegedly solely conceived of the relevant disclosures in the Almoazen Paper. DD Req. 20-21. Patent Owner’s arguments fail, because Almoazen’s claim to sole inventorship is refuted by contemporary evidence.

Patent Owner proffers a self-serving Declaration (EX2018) allegedly purporting to show select portions of the Almoazen Paper that Petitioner is relying on to support its obviousness arguments. *See* DD Req. 20. Importantly, the portions of the Almoazen Paper copied into the ‘437 Patent, other than the applicant admitted prior art, such as Fuchs, constitutes the ‘437 Patent’s full disclosure relating to the claimed film formulations. This is demonstrated by the

markup of the '437 Patent, prepared by Petitioner's expert, Dr. Rautio (EX1033), detailing where the '437 Patent copied essentially all of its disclosure regarding same verbatim from the Almoazen Paper. *Id.*; see Pet., at 41-42; Rautio, EX1050, ¶¶180-192.

Just based on the face of the Almoazen Paper, as well as the filings at the PTO with respect to the '437 Provisional and the '437 PCT Application, Lindsay Haynes is a contributor and a *joint inventor*.

Dr. Haynes was a named author of the Almoazen Paper. See below from EX1022, p.1012.

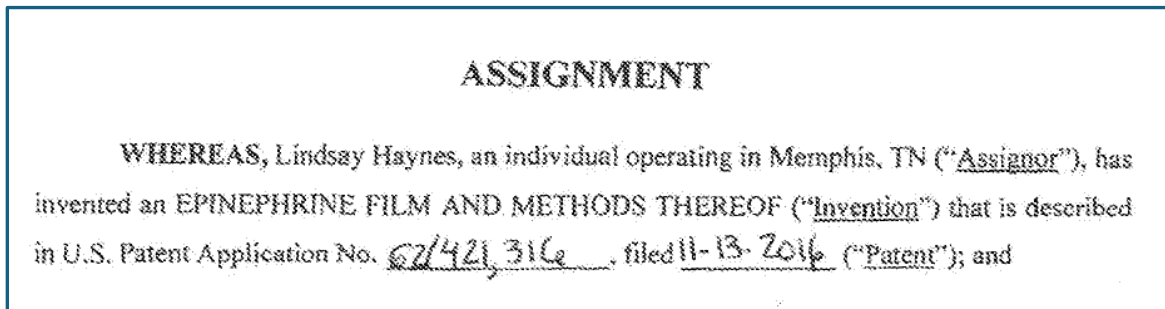


Dr. Haynes also executed an assignment of invention in connection with the '437 Provisional, Ser. No. 62/421,316. Notably, Dr. Haynes' referred to the

invention in her assignment as “*Epinephrine Films and Methods Thereof*”.

EX1013, pdf p.2.<sup>9</sup>

See below from EX1013, pdf p.2.



Dr. Haynes was also named as a joint inventor on the ‘437 PCT Application, WO2018/089570 A1 (PCT/US2017/060761), entitled “Pharmaceutical Formulation For Sublingual Or Buccal Delivery Of Epinephrine”. See below from EX1014, p.1.

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<sup>9</sup> See also EX1035 (a copy of the Almoazen Paper (EX1022) highlighted to show where material from the Almoazen Paper appears in the ‘437 Patent); see also EX1033 (a copy of the ‘437 Patent (EX1001) showing where material from the Almoazen Paper (EX1022) appears in highlighting). Both exhibits were prepared by Petitioner’s expert, Dr. Rautio, EX1050, ¶¶182-192.

|                                                                                    |                                                                                                                                                              |                                                                                                                                                         |
|------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|
| (12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT) |                                                                                                                                                              |                                                                                                                                                         |
| (19) World Intellectual Property Organization<br>International Bureau              |                                                                                                                                                              |                                                                        |
| (43) International Publication Date<br>17 May 2018 (17.05.2018)                    |                                                                                                                                                              | <br>(10) International Publication Number<br><b>WO 2018/089570 A1</b> |
| <hr/>                                                                              |                                                                                                                                                              |                                                                                                                                                         |
| (51) International Patent Classification:<br><i>A61K 31/137</i> (2006.01)          | (72) Inventors: <b>ALMOAZEN</b> , Hassan; 3133 Hill Lake Drive, Bartlett, TN 38135 (US). <b>HAYNES</b> , Lindsay; 2068 Horizons Dr, Ooltewah, TN 37363 (US). |                                                                                                                                                         |
| (21) International Application Number:<br><b>PCT/US2017/060761</b>                 | (74) Agent: FENTRESS, Susan, B.; Veritay Group, IP, 20 Dudley Suite 803, Memphis, TN 38103 (US).                                                             |                                                                                                                                                         |
| (22) International Filing Date:<br>09 November 2017 (09.11.2017)                   | (81) Designated States (unless otherwise indicated, for every                                                                                                |                                                                                                                                                         |

At the U.S. national stage of the '437 PCT Application for the '437 Patent, PCT/US2017/060761, in an application entitled "*Pharmaceutical Formulation For Sublingual Or Buccal Delivery Of Epinephrine*", Dr. Haynes was named a joint inventor, and together with Dr. Almoazen claimed priority to the Almoazen Provisional Application; and finally, Patent Owner, Iono Pharma, LLC was only entitled to apply for and be granted the '437 Patent by obtaining assignments from both Almoazen and Haynes. See copies from U.S. national stage below from EX1052, pdf pp.76, 77, 79.

Sheet No. 2

**Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)**  
*If none of the following sub-boxes is used, this sheet should not be included in the request.*

|                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                         |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)<br><b>Hassan Almoazen</b><br><b>3133 Hill Lake Drive</b><br><b>Bartlett, TN 38135</b><br><b>USA</b> | This person is:<br><input type="checkbox"/> applicant only<br><input type="checkbox"/> applicant and inventor<br><input checked="" type="checkbox"/> inventor only (If this check-box is marked, do not fill in below.)<br>Applicant's registration No. with the Office |
| State (that is, country) of nationality:                                                                                                                                                                                                                                                                                                                                                                                    | State (that is, country) of residence:                                                                                                                                                                                                                                  |
| This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input type="checkbox"/> the States indicated in the Supplemental Box                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                         |
| Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)<br><b>Lindsay Haynes</b><br><b>2068 Horizons Dr</b><br><b>Coltawah, TN 37363</b><br><b>USA</b>      | This person is:<br><input type="checkbox"/> applicant only<br><input type="checkbox"/> applicant and inventor<br><input checked="" type="checkbox"/> inventor only (If this check-box is marked, do not fill in below.)<br>Applicant's registration No. with the Office |
| State (that is, country) of nationality:                                                                                                                                                                                                                                                                                                                                                                                    | State (that is, country) of residence:                                                                                                                                                                                                                                  |

**Box No. VI PRIORITY CLAIM AND DOCUMENT**

The priority of the following earlier application(s) is hereby claimed:

| Filing date of earlier application (day/month/year) | Number of earlier application | Where earlier application is:                  |                                       |                                             |
|-----------------------------------------------------|-------------------------------|------------------------------------------------|---------------------------------------|---------------------------------------------|
|                                                     |                               | national application: country or Member of WTO | regional application: regional Office | international application: receiving Office |
| item (1)<br>13/11/2016<br>13 NOV 2016               | 62/421,316                    | US                                             |                                       |                                             |
| item (2)                                            |                               |                                                |                                       |                                             |

Sheet No. 5

**Box No. VIII (B) DECLARATION: ENTITLEMENT TO APPLY FOR AND BE GRANTED A PATENT**  
*The declaration must conform to the standardized wording provided for in Section 212; see Notes to Boxes Nos. VIII, VIII (C) to (V) (in general) and the specific Notes to Box No. VIII (B). If this Box is not used, this sheet should not be included in the request.*

Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51 bis, I (a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate:  
 In relation to this international application Iono Pharma, LLC is entitled to apply for and be granted a patent by virtue of the following assignments: an assignment of Hassan Almoazen dated 13 NOV 2016 and Lindsay Haynes dated 12 OCT 2016.

These contemporaneous documentary filings with the Patent Office establish Dr. Haynes as a co-author/contributor/inventor of the subject matter disclosed in the Almoazen Paper, and a joint inventor on the '437 Provisional and the '437 PCT Application. However, Dr. Haynes is not named as an inventor of the '437 Patent. Thus, contrary to Patent Owner's assertion, the 35 U.S.C. § 102(b)(1)(A) one year grace period is not applicable.

Dr. Almoazen's attempt in his 37 C.F.R. § 1.130 Declaration (EX2019) to establish his sole contributor/inventor of the Almoazen Paper disclosure, or for that matter of the '437 Provisional, fails. Dr. Almoazen's argument that he was the sole contributor to the Almoazen Paper, is belied by the simple facts: (i) Dr. Haynes needed to execute an assignment for the '437 Provisional (which film formulation in its entirety was copied from the Almoazen Paper); (ii) Dr. Haynes appears as a co-inventor on the '437 PCT Application (which film formulation in its entirety was copied from the Almoazen Paper); and (iii) Dr. Haynes is not listed as a co-inventor on the '437 Patent (which film formulation in its entirety was copied from the Almoazen Paper). See EX1033; see also EX1053, which is a copy of the '437 Patent Provisional Application (EX1013) highlighted to show where material from the Almoazen Paper (EX1022) appears.

Finally, Patent Owner's reliance on *EmeraChem Holdings, LLC v. Volkswagen Grp. of Am., Inc.*, 859 F.3d 1341 (Fed. Cir. 2017) and *In re Katz*, 687 F.2d 450 (C.C.P.A. 1982) is misplaced. Among other things, these decisions rely on the fact that the inventor's declaration and evidence was un rebutted.<sup>10</sup> Here, Almoazen, an inventor who founded Patent Owner (EX2020, ¶8), provided a self-serving Rule 130 Declaration (EX2019) which claims he was the sole inventor of the disclosure from the Almoazen Paper recited in the '437 Patent, and that the other authors on the Almoazen Paper contributed nothing to the disclosed "invention" therein. Patent Owner's arguments point to *Katz* and *EmeraChem* and *Katz's* reliance on an inventor's declaration which "explains that his co-authors were students under his direction and supervision ... provides a clear alternative conclusion to the board's inference that their names were on the article because they were coinventors". DD Req. 21. Here, however, Petitioner has rebuttal evidence, in the form of contemporaneous filings with the Patent Office, confirming Dr. Haynes was at least a joint inventor of the Almoazen '437 Provisional's film formations and methods (see Assignment of the invention for "*Epinephrine Films and Methods Thereof*" (EX1013, pdf p.2)), and also

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<sup>10</sup> They also concerned pre-AIA 35 U.S.C. § 102.

contributed to the disclosure in the Almoazen Paper and the film formation and related material that was copied directly into the '437 Provisional, the '437 PCT Application, and the '437 Patent.

Instructive are the cautionary comments by the Court in *EmeraChem*:

We have treated uncorroborated testimony from an alleged inventor asserting priority with skepticism. . . . This concept stems from the concern that “inventors . . . would be tempted to remember facts favorable to their case by the lure of protecting their patent or defeating another's patent.” These concerns particularly arise when uncorroborated testimony comes from an interested person recalling long-past events.

*EmeraChem*, 859 F.3d at 1346 (citations omitted).

The Court in *EmeraChem* continued: “We have recognized that contemporaneous documentary evidence can serve as ‘the most reliable proof that the inventor's testimony has been corroborated.’ . . . But it is ‘[a]n evaluation of *all* pertinent evidence [that] must be made so that a sound determination of the credibility of the inventor's story may be reached’.” *EmeraChem* 859 F.3d at 1347 (citations omitted).

Contemporaneous evidence of record in publications and filings with the Patent Office contradicts Almoazen argument that he was a sole author/inventor of

the Almoazen Paper and thus Patent Owner cannot claim the one-year grace period under 35 U.S.C. § 102(b)(1)(A).

**B. The Almoazen Paper Completely Discloses The Rapidly Dissolving Film Formulation Limitation of the Challenged Claims.**

Patent Owner disingenuously argues the Almoazen Paper is not relevant to demonstrating the claimed epinephrine prodrug film formulation limitation because it only discloses film formulations for epinephrine HCl compounds and purportedly fails to disclose film formulations for epinephrine prodrug compounds. DD Req. 21-23. However, the '437 Patent's film formulation disclosure, copied from the Almoazen Paper, is presumed enabling, even if, like the Almoazen Patent, it only discloses film formulations for epinephrine HCl compounds. 35 U.S.C. § 112(a). Thus, Patent Owner's misplaced argument, that the Almoazen Paper is not relevant for obviousness purposes, must be premised on '437 Patent's failure to enable film formulations pursuant to Section 112(a). *See* '437 Patent, 8:31-11:55 and EX1033.

Finally, the '437 Patent admits that the following subject matter was disclosed in the prior art: (i) films that incorporate active ingredients that can be applied mucosally; (ii) films that can be fast or rapidly dissolving; and (iii) water soluble polymers specifically manufactured for aqueous film coatings in immediate

release oral dosage forms. EX1001, 2:39-47, 7:33-39.<sup>11</sup> The admitted prior art referenced in the '437 Patent may also be relied on to establish the background knowledge possessed by a POSA.

As a patentee's admissions about the scope and content of the prior art provide a factual foundation as to what a skilled artisan would have known at the time of invention, *Randal Manufacturing v. Rea*, 733 F.3d 1355, 1362-63 (Fed. Cir. 2013), it follows that AAPA may be used in similar ways in an *inter partes* review, *see McCoy v. Heal Sys., LLC*, 850 F. App'x 785, 789 (Fed. Cir. 2021) ("The Board did not err by accepting the specification's own assertions of what is well known in the art . . . . By characterizing certain parts as conventional in the specification, the patentee effectively admits that such things would be known to a POSA."). Such uses include, for example, furnishing a motivation to combine, *see Randal Manufacturing*, 733 F.3d at 1363, or supplying a missing claim limitation, *Koninklijke Philips*, 948 F.3d at 1337-38. Thus, even though evidence such as expert testimony and party admissions are not themselves prior art references, they are permissible evidence in an *inter partes* review

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<sup>11</sup> The '437 Patent also admits that the preferred Log P values for epinephrine prodrugs is between about 0.05 and 6.0 and that this value can be calculated (EX1001, 5:9-17). If it can be calculated it must be inherent.

for establishing the background knowledge possessed by a person of ordinary skill in the art.

*Qualcomm Inc. v. Apple Inc.*, 24 F.4th 1367, 1376 (Fed. Cir. 2022).

### **C. Schobel Is Prior Art.**

Contrary to Patent Owner's assertion (DD Req. 23-24), Ground 3 relies on Schobel (EX1021) and is asserted against all 3 challenged claims. Schobel discloses fast dissolving sublingual films containing epinephrine and epinephrine prodrugs. *See* Pet., at 46-47, 68, 71, 74, 104, 106-107, 109; Rautio, EX1050, ¶¶233-239, 313, 317, 319, 410.

First, as the effective filing date of the '437 Patent is November 9, 2017<sup>12</sup>, Schobel, with a filing date of May 4, 2017, makes it prior art under 35 U.S.C. § 102(a)(2).

Second, the Schobel Provisional (EX1054), entitled "*Enhanced Delivery Epinephrine Compositions*" does disclose the formulation of fast dissolving films as well as the use of the "prodrugs" of actives such as epinephrine to overcome the barrier properties of the buccal mucosa. EX1054, pdf pp.29, 30, 34 (penultimate paragraph), 37-48. Thus, the priority date of the Schobel Provisional of May 16,

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<sup>12</sup> See Pet., at 14-15; Rautio, EX1050, ¶¶63-67.

2016 applies, which is before the '437 Provisional was filed on November 13, 2016. Thus, even if Patent Owner could prove an earlier filing date, Schobel would still be prior art.

**D. Petition Ground 2 Clearly Does Not Rely On Truelove 1.**

Patent Owner relies on the Petition's incorporation by reference of Ground 1 arguments into Ground 2 appearing in the first sentence of Ground 2, which is entitled "Ground 2: Truelove 3, Ashraf, Almoazen Paper [Claims 1-3]" (Pet., at 57), to argue that Ground 2 is unclear. DD Req. 24-25. To the extent that Petitioner incorporated the arguments from Ground 1 for Ashraf and the Almoazen Paper, it is correct as they are references for Ground 2 as well as Ground 1. The reference to Truelove 1 in the first sentence was a typographical error that any reader would readily understand. First, as required by 37 C.F.R. § 42.104(b)(2), and as admitted by Patent Owner (DD Req. 24), Petitioner specified that Ground 2 relied solely on Truelove 3, Ashraf and the Almoazen Paper. Pet., at 4. Moreover, the remaining 8 pages of the Ground 2 section make no mention of Truelove 1. Pet., at 58-65. The concluding sentence of the analysis of each claim states that the claim would have been obvious under 35 U.S.C. § 103 in view of Truelove 3 (not Truelove 1), Asraf, and the Almoazen Paper. Pet., at 60, 63 and 65. Finally, the Ground 2 Claim Chart refers to Truelove 3, not Truelove 1. Pet., at 95-103.

1. Patent Owner's arguments that Truelove 3 did not literally recite epinephrine prodrug compounds confuses obviousness with anticipation.

As detailed in the Petition, Truelove 3 was not discussed or applied by the Examiner, and Patent Owner only offers unsupported attorney argument to challenge a POSA's understanding of the scope of Truelove 3's teachings. DD Req. 25-27. Importantly, the diester isoproterenol compounds disclosed in Table 3 of Truelove 3 have identical ester promoieties as the diester epinephrine compounds disclosed in the challenged claims. Rautio, EX1050, ¶¶202-216, 288, 316, 402. Given the close structural similarity of the isoproterenol and epinephrine compounds, a POSA would have expected that isoproterenol and epinephrine compounds with the same ester promoieties would have the same half-life  $t_{1/2}$  values. Rautio, EX1050, ¶¶211-214; *see Valeant Pharms. Int'l, Inc. v. Mylan Pharms. Inc.*, 955 F.3d 25, 32 (Fed. Cir. 2020) (“[o]ur case law reflects an understanding that skilled artisans can expect structurally similar compounds to have similar properties”); *Anacor Pharms., Inc. v. Iancu*, 889 F.3d 1372, 1384-85 (Fed. Cir. 2018) (“similarity in properties can be inferred from structural similarity”).

**E. Petitioner Provided A Detailed Explanation Of The Combination Of References Relied On In Ground 3.**

Patent Owner's assertion that Petitioner did not provide a detailed explanation of the basis for Ground 3 is baseless. DD Req. 27-28. To the extent that the Ground 3 references are also found in Grounds 1 and 2, it was not necessary for Petitioner when addressing Ground 3 to repeat verbatim the detailed analysis previously presented in connection with Grounds 1 and 2. Ground 3 merely relies on the references from Grounds 1 and 2 in combination with additional references to amplify the prior art and provide alternative references. *See* Pet., at 65-74 (incorporating 48-65), 83-85 (incorporating 74-83), 104-109 (Claim Chart, incorporating material from Grounds 1 and 2). Petitioner's expert declared "I have reviewed the '437 Patent Claim Chart attached hereto as Appendix C [which is the same Claim Chart found in the Petition] considering the prior art discussed previously and as further amplified below. In my opinion, a POSA would have been motivated to combine the various disclosures in the references found in each Ground and would have had a reasonable likelihood of success, without undue experimentation, separately for each Ground to arrive at the subject matter of claims 1-3 of the '437 Patent." Rautio, EX1050, ¶317.

Nothing more was required for Petitioner to meet its burden.

**F. Patent Owner's Argument About An Alleged Typographical Error About A Compound Appearing In Table 3 Should Be Referred To The Board.**

Initially, Patent Owner agrees with Petitioner and its experts that Truelove 1, Table 3 explicitly discloses epinephrine “ester” prodrug compounds, and not epinephrine “ketone” compounds and that those compounds are recited in challenged claims 1-3. DD Req. 28-35. However, Patent Owner argues that one of the epinephrine “diester” prodrug compounds relied on by Petitioner contains a typographical error and actually discloses a different epinephrine “diester” prodrug compound recited in Claim 2 (and necessarily claim 3). DD Req. 34. Once again, Patent Owner offers only attorney argument. The Petition relies on the testimony of its experts as to the compounds disclosed in Truelove 1, Table 3. Rautio, EX1050, ¶¶127, 128-137, 170; Meanwell, EX1051, ¶¶90-91.

Importantly, even assuming Patent Owner is correct and the diester prodrug compound recited in Truelove 1, Table 3 is a typographical error and instead a compound recited in Claims 2 and 3, Patent Owner's argument should be referred to the Board, and, if necessary decided on the merits after full consideration of proffered expert testimony.

**VIII. DISCRETIONARY DENIAL PURSUANT TO THE PROCESS MEMORANDUM VIOLATES THE ADMINISTRATIVE PROCEDURE ACT AND IS UNCONSTITUTIONAL**

Petitioner respectfully submits that the Process Memorandum violates the Administrative Procedure Act (“APA”) and is unconstitutional. *First*, as binding agency policy that affects private interest, the Process Memorandum is a substantive rule that had to be promulgated through notice-and-comment rulemaking. *Mendoza v. Perez*, 754 F.3d 1002, 1020 (D.C. Cir. 2014). *Second*, the Process Memorandum exceeds the Director’s authority and violates the AIA. Nothing in the AIA authorizes the Director to deny IPR petitions based on the amorphous factors referenced in the Process Memorandum. For example, it is unclear as to how the director will consider and weigh “settled expectations,” “reliance on expert testimony,” “workload,” and “[c]ompelling economic, public health, or national security interest.” For example the settled expectations doctrine cannot be found in any statute, rule, notice or policy. Indeed, the AIA statute sets up the opposite expectation. *See, e.g.*, 35 U.S.C. § 311(c) (precluding IPRs filed prior to 9 months after grant but allowing them thereafter); 35 U.S.C. § 315(b) (precluding IPRs filed more than 1 year after suit but otherwise allowing them at any time); 35 U.S.C. § 282 (no time-dependent change to the presumption of validity). *Third*, the factors and considerations identified in the Process

Memorandum are arbitrary and capricious. The Process Memorandum introduces several additional unpredictable and malleable factors. *Fourth*, discretionary denial for any basis other than as authorized in 35 U.S.C. § 314 is improper. The Director does not have absolute discretion regarding whether to institute IPR; that discretion is limited to the bases authorized in 35 U.S.C. § 314.

Petitioner requests that Patent Owner's request for discretionary denial be rejected for these additional reasons.

## **IX. CONCLUSION**

For all the foregoing reasons, Petitioner requests that Patent Owner's request for discretionary denial be denied and the Petition be referred to the Board.

Dated: September 18, 2025

Respectfully,

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**CERTIFICATE OF COMPLIANCE**

Pursuant to 37 C.F.R. § 42.24(d) and the Process Memorandum, the undersigned certifies that the foregoing Petitioner's Brief Opposing Discretionary Denial complies with the type-volume limitation of 37 C.F.R. § 42.24(a). As Patent Owner's Discretionary Denial Brief was due before September 1, 2025, the foregoing Petitioner's Brief Opposing Discretionary Denial is limited to 14,000 words as per the Process Memorandum as updated on the Interim Director Discretionary Process webpage. The word count application of the word processing program used to prepare the foregoing Petitioner's Brief Opposing Discretionary Denial indicates that the Petition contains 13,977 words out of 14,000, excluding the parts of the brief exempted by 37 C.F.R. § 42.24(a) (that is, the word count does not include the table of contents, table of authorities, the exhibit list, the certificate of service, or the certificate of compliance).

Dated: September 18, 2025

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**CERTIFICATE OF SERVICE**

Pursuant to 37 C.F.R. § 42.6(e), the undersigned certifies that on September 18, 2025, a complete copy of the foregoing Petitioner's Brief Opposing Discretionary Denial and all exhibits not already of record in this proceeding on P-TACTS were served on counsel of record for the Patent Owner by filing this document and the exhibits through P-TACTS and by sending this document and the exhibits via electronic mail and/or links to the following addresses:

|                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                               |
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