

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AQUESTIVE THERAPEUTICS, INC.
Petitioner

v.

IONO PHARMA, LLC
Patent Owner

Case No. IPR2025-00874
U.S. Patent No. 11,021,437

PATENT OWNER'S PRELIMINARY RESPONSE

TABLE OF CONTENTS

	<u>Page</u>
I. INTRODUCTION	1
II. LEVEL OF PERSON OF ORDINARY SKILL IN THE ART (POSITA).....	3
III. CLAIM CONSTRUCTION	3
IV. OBJECTIVE INDICIA OF NONOBVIOUSNESS WARRANT DENIAL OF INSTITUTION	4
A. Petitioner Fails To Address The Unexpected Results That The Examiner Expressly Found Overcome Its Obviousness Rejection During Prosecution	8
1. The Examiner Allowed The Claims Because They Demonstrated Unexpected Results	8
2. Despite “Unexpected Results” Being The Primary Reason For Allowance Of The Claims, Petitioner Does Not Explain How The Proposed Grounds Overcome That Objective Indicium Of Nonobviousness.....	11
B. Numerous Additional Objective Indicia Of Nonobviousness Outweigh Any Purported Obviousness Grounds Raised By Petitioner	15
1. Petitioner Deliberately Copied The ’437 Patent After Receiving The Published PCT Application	15
2. The ’437 Patent Solved The Long-Felt, Unmet Need of Providing A Method of Treating Anaphylaxis Without Injecting Epinephrine That Others Failed To Solve	22
3. Anaphylm™ Has Received Industry Praise As The First Sublingual Epinephrine Film With Results Comparable To An Epinephrine Autoinjector	27
V. PETITIONER’S RELIANCE ON REFERENCES THAT ARE NOT PRIOR ART IS FATAL TO ALL THREE GROUNDS	28

A.	The ’437 Patent Should Be Afforded A Priority Date Of November 13, 2016, Because The Provisional Application Incorporated By Reference Truelove 1	29
1.	The Almoazen Paper Is Not Prior Art	31
2.	Schobel Is Not Prior Art	32
B.	The Petition Relies Solely On References That Are Not Prior Art For The Limitation “Wherein The Compound Is Formulated In A Unit Dosage Form As A Rapidly Dissolving Film” In Every One Of The Challenged Claims In Every One Of The Proposed Grounds.....	34
VI.	EVEN IF PRIOR ART, NEITHER THE ALMOAZEN PAPER NOR SCHOBEL TEACH OR SUGGEST THAT THE CLAIMED EPINEPHRINE PRODRUG CAN BE “FORMULATED IN A UNIT DOSAGE FORM AS A RAPIDLY DISSOLVING FILM”	35
1.	The Almoazen Paper Does Not Teach Or Suggest The Claimed Epinephrine Prodrug Can Be Formulated As A Rapidly Dissolving Film	35
2.	The Petition Fails To Articulate Objective Rationale Why The Claimed Epinephrine <i>Prodrugs</i> Are Able To Form The Claimed “Fast Dissolving Film”	36
VII.	TRUELOVE 1 DOES NOT READ ON ANY OF THE CLAIMED COMPOUNDS OF CLAIM 1 WHEN PROPERLY READ	38
VIII.	GROUND 2 AND 3 ASK THE BOARD TO “PLAY ARCHAEOLOGIST” TO UNDERSTAND PETITIONER’S PROPOSED GROUNDS	44
A.	Ground 2 Is Unclear As To Which References Petitioner Is Relying On And The Board Should Not Be Asked To “Play Archaeologist” With Petitioner’s Deficient Petition.....	44
1.	If Petitioner Is Not Relying On Truelove 1 In Ground 2, None Of The References Relied Upon In Ground 2 (Truelove 3, Ashraf, And The Almoazen Paper) Read On Any Of The Claimed Compounds	45

2. Even If Petitioner Relies on Truelove 1 In Ground 2,
None Of The References Relied Upon In Ground 2 Read
On Any Of The Claimed Compounds Of Claim 1. 50

B. Ground 3’s “Kitchen Sink” Combination Fails: Petitioner’s
Seven-Reference Theory Has No Merits 51

1. Petitioner Identifies No Reference Disclosing Any
Compounds of Claim 1 51

IX. CONCLUSION.....52

TABLE OF AUTHORITIES

	<u>Page(s)</u>
<u>Cases</u>	
<i>Aardevo North America LLC v. Agventure B.V.</i> , IPR2025-00136, Paper 9 (PTAB May 1, 2025)	12
<i>Allergan, Inc. v. Sandoz Inc.</i> , 726 F.3d 1286 (Fed. Cir. 2013)	6
<i>Coalition for Affordable Drugs V LLC v. Hoffman–LaRoche, Inc.</i> , IPR2015-01792, Paper 14 (PTAB Mar. 11, 2016).....	7, 12
<i>DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.</i> , 567 F.3d 1314 (Fed. Cir. 2009)	16
<i>Droplets, Inc. v. E*TRADE Bank</i> , 887 F.3d 1309 (Fed. Cir. 2018)	30
<i>EmeraChem Holdings, LLC v. Volkswagen Group of Am.</i> , 859 F.3d 1341 (Fed. Cir. 2017)	31
<i>Immunex Corp. v. Sandoz Inc.</i> , 395 F. Supp. 3d 366 (D.N.J. 2019).....	22
<i>In re Katz</i> , 687 F.2d 450 (C.C.P.A. 1982)	31
<i>In re Magnum Oil Tools Int’l, Ltd.</i> , 829 F.3d, 1364 (Fed. Cir. 2016)	47, 52
<i>In re Yale</i> , 434 F.2d 666 (C.C.P.A. 1970)	50
<i>KSR Int’l Co. v. Teleflex Inc.</i> , 550 U.S. 398 (2007).....	6
<i>LG Elecs. Inc. v. Immervision, Inc.</i> , 39 F.4th 1364 (Fed. Cir. 2022)	50

<i>Liqwd, Inc. v. L’Oreal USA, Inc.</i> , 941 F.3d 1133 (Fed. Cir. 2019)	15
<i>Merial Ltd. v. Virbac</i> , IPR2014–01279, Paper 13 (PTAB Jan. 22, 2015)	7, 12
<i>Nearmap US, Inc. v. Eagle View Techs.</i> , IPR2024-00716, Paper 9 (PTAB October 8, 2024).....	45
<i>Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.</i> , 868 F.3d 1013 (Fed. Cir. 2017)	4
<i>Omron Oilfield & Marine Inc. v. MD/TOTCO</i> , IPR2013–00265, Paper 11 (PTAB Oct. 31, 2013)	12
<i>Parus Holdings, Inc. v. Google LLC</i> , 70 F.4th 1365 (Fed. Cir. 2023)	45
<i>Penumbra, Inc. v. RapidPulse, Inc.</i> , IPR2021-01466, Paper 34 (PTAB March 10, 2023)	32
<i>Realtime Data, LLC v. Iancu</i> , 912 F.3d 1368 (Fed. Cir. 2019)	4
<i>Sirona Dental Sys. GmbH v. Institut Straumann AG</i> , 892 F.3d 1349 (Fed. Cir. 2018)	47
<i>Stratoflex Inc. v. Aeroquip Corp.</i> , 713 F.2d 1530 (Fed. Cir. 1983)	6
<i>Stryker v. KFx Med., LLC</i> , IPR2019-00817, Paper 10 (PTAB September 16, 2019)	1, 6, 7, 12
<i>Tex. Instruments, Inc. v. U.S. Int’l Trade Comm’n</i> , 988 F.2d 1165 (Fed. Cir. 1993)	23
<i>Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.</i> , 699 F.3d 1340 (Fed. Cir. 2012)	6
<i>Univ. of Strathclyde v. Clear-Vu Lighting LLC</i> , 17 F.4th 155 (Fed. Cir. 2021)	44, 47, 50

<i>Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.</i> , 200 F.3d 795 (Fed. Cir. 1999)	4
<i>WBIP, LLC v. Kohler Co.</i> , 829 F.3d 1317 (Fed. Cir. 2016)	22, 27
<i>Wilson Elecs., LLC v. Cellphone-Mate, Inc.</i> , IPR2018-01778, Paper 10 (PTAB April 23, 2019)	8, 15

Statutes

35 U.S.C. § 102(b)(1)(A)	2, 32
35 U.S.C. §103	9, 34

Rules

37 C.F.R. § 1.132	9
37 C.F.R. § 1.57(c).....	30
37 C.F.R. § 42.107(a).....	15
37 C.F.R. § 42.22(a)(2)	51
Consolidated Trial Practice Guide (Nov 2019)	15

PATENT OWNER'S EXHIBIT LIST

Exhibit No.	DESCRIPTION
2001	2016-06-03 Email from Ramona McCudden to Hassan Almoazen re MonoSol Rx
2002	2016-10-15 Email from Hassan Almoazen to Ramona McCudden re Epinephrine
2003	2016-10-22 Email from Hassan Almoazen to Steve Wargacki re Email
2004	Excerpt of File History of Application No. 17/086,409
2005	Excerpt of File History of Application No. 15/724,234
2006	Excerpt of File History of Application No. 17/835,442
2007	Excerpt of File History of Application No. 18/413,556
2008	2022-08-25 Email from Daniel Scola to Hassan Almoazen re Follow-up on our Discussions
2009	2023-12-06 Letter from Hemant Gupta to Daniela Scola re Collaboration Discussions with Iono Pharma, LLC
2010	MonoSol Rx Changes Name to Aquestive Therapeutics and Expands CNS Product Portfolio
2011	2016-10-18 Email from Hassan Almoazen to Steve Wargacki re Epinephrine in fast dissolving film
2012	File History of U.S. 11,021,437
2013	File History of U.S. Provisional No. 62/331,996
2014	2018-11-05 Email from Abby Trotter to Hassan Almoazen re 2018 Life Science Tennessee Venture Forum Class
2015	Email from Gareth Sheridan to Hassan Almoazen re update
2016	Email from Amy Hopper to Hassan Almoazen re Delta I-Fund Semifinals Round 1
2017	2020-10-20 Email from Lili Jiang to China Focus re You have scheduled meetings at China Focus Virtual Partnering Conference
2018	A copy of the Almoazen Paper (Exhibit 1022) highlighted to show portions cited in Petitioner's claim mapping.
2019	Declaration of Hassan Almoazen, Ph.D. under 37 C.F.R. § 1.130
2020	Declaration of Hassan Almoazen, Ph.D.
2021	U.S. Provisional No. 62/331,993
2022	U.S. Provisional No. 62/929,737
2023	Reserved
2024	Aquestive Therapeutics June 16, 2025, Press Release

Exhibit No.	DESCRIPTION
2025	FDA GSRS UNII Substance Record — Dibutepinephrine (UNII: 3ZU4LVA3G9)
2026	F. Estelle R. Simmons, <i>First-aid treatment of anaphylaxis to food: Focus on epinephrine</i> , 113 Journal of Allergy and Clinical Immunology 837 (2004)
2027	Keith J. Simons and F. Estelle R. Simons, <i>Epinephrine and its use in anaphylaxis: current issues</i> , Current Opinion in Allergy and Clinical Immunology 354 (2010)
2028	Jacqueline A. Pongracic and Jennifer S. Kim, <i>Update on epinephrine for the treatment of anaphylaxis</i> , Current Opinion in Pediatrics 94 (2007)
2029	Phil Lieberman, <i>Use of epinephrine in the treatment of anaphylaxis</i> , Current Opinion in Allergy and Clinical Immunology 313 (2003)
2030	Xiaochen Gu et al., <i>Is Epinephrine Administration by Sublingual Tablet Feasible for the First-Aid Treatment of Anaphylaxis? A Proof-of-Concept Study</i> , Biopharmaceutics & Drug Disposition (2002)
2031	F. Estelle R. Simons et al., <i>Can Epinephrine Inhalations Be Substituted for Epinephrine Injection in Children at Risk for Systemic Anaphylaxis?</i> 106 Pediatrics 1040 (2000)
2032	U.S. Patent Publication No. 2018/0104195
2033	Dipivefrin: “Uses, Interactions, Mechanism of Action.” DrugBank Online. Retrieved September 4, 2025.
2034	FDA News Release, <i>FDA Approves First Nasal Spray for Treatment of Anaphylaxis</i> , available at https://www.fda.gov/news-events/press-announcements/fda-approves-first-nasal-spray-treatment-anaphylaxis
2035	HCP Live, <i>Positive Phase 3 Results Announced for Sublingual Epinephrine Treatment</i> , available at https://www.hcplive.com/view/positive-phase-3-results-announced-sublingual-epinephrine-treatment
2036	Fortune Business Insights, <i>Epinephrine Market Size, Share & Industry Analysis</i> , available at https://www.fortunebusinessinsights.com/epinephrine-market-104291
2037	Stock Titan, <i>Aquestive Therapeutics Announces that FDA Will Not Require an Advisory Committee Meeting to Discuss New</i>

Exhibit No.	DESCRIPTION
	<i>Drug Application for Anaphlym™</i> , available at https://www.stocktitan.net/news/AQST/aquestive-therapeutics-announces-that-fda-will-not-require-an-pn3qzl5xbhix.html
2038	Healio, <i>FDA accepts new drug application for sublingual epinephrine film</i> , available at https://www.healio.com/news/allergy-asthma/anaphylaxis
2039	Clinical Trial Arena, <i>Aquestive maps out FDA approval for sublingual anaphylaxis drug</i> , available at https://www.clinicaltrialsarena.com/news/aquestive-maps-out-fda-approval-for-sublingual-anaphylaxis-drug/

I. INTRODUCTION

Patent Owner Iono Pharma, LLC (“Iono”) respectfully requests that the Board deny institution of Aquestive Therapeutics, Inc.’s (“Aquestive”) IPR Petition challenging U.S. Patent No. 11,021,437 (“the ’437 Patent”). As explained in both Patent Owner’s Brief in support of Discretionary Denial (Paper 7) and this POPR below, Aquestive’s Petition fails to establish a reasonable likelihood of success on the merits.

First, Petitioner fails to address any objective evidence of nonobviousness, i.e., secondary considerations. During the prosecution of the ’437 Patent, one particular objective indicia of nonobviousness—namely “unexpected results”—featured prominently in the Examiner’s Reasons for Allowance. And although all three of Petitioner’s Grounds relies on obviousness challenges, Petitioner fails to heed the Board’s warning “that petitions may be denied if they do not address known evidence of secondary considerations.” *Stryker Corp. and Howmedica Osteonics Corp. v. KFx Med., LLC*, IPR2019-00817, Paper 10 at 28–29 (PTAB September 16, 2019). Indeed, Petitioner says **nothing** regarding secondary considerations of obviousness that the Examiner noted as the primary reason for allowing the claims, and it fails to address any other pertinent considerations such as copying, long-felt unmet needs that others failed to solve, and industry praise. Those deficiencies permeate all three Grounds.

Second, all three Grounds rely on the “Almoazen Paper” (EX1022) and “Schobel” (EX1021), but those references are ***not*** prior art. As explained in Patent Owner's Brief in support of Discretionary Denial and in Section V of this POPR, the disclosures that Petitioner relies on from the Almoazen Paper were conceived solely by Dr. Almoazen, the sole inventor of the '437 Patent and therefore do not qualify as prior art under 35 U.S.C. § 102(b)(1)(A). Additionally, Petitioner relies on the filing date of Schobel's provisional application to demonstrate the reference is prior art, but Petitioner cites to disclosures found only in Schobel's nonprovisional application, which postdates the priority date of the '437 Patent. Because Petitioner relies on only those two non-prior art references for one limitation across ***all*** challenged claims and across ***all*** Grounds, the Board should deny institution.

Third, the Board should deny institution because the Petition lacks merit. As explained in Section VI, even if the Almoazen Paper and Schobel qualify as prior art—to be clear, they do not—both references fail to teach or suggest the limitation “wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.” Additionally, as explained in Patent Owner's Brief in support of Discretionary Denial and in Section VII below, Petitioner attempts to incorrectly clarify a typographical error in Truelove 1 in order to read the reference on claim 1, but its correction is not supported by the record. When properly considered, the compounds disclosed in Truelove 1 fall outside of the scope of claim 1. As such,

none of the Petitioners Grounds include a reference that discloses any compound recited in claim 1. Finally, as explained in Section VIII, Petitioners' remaining arguments fare far worse.

Accordingly, Iono respectfully requests that the Board deny institution.

II. LEVEL OF PERSON OF ORDINARY SKILL IN THE ART (POSITA)

Petitioner lays out a lengthy description of the education and skills a POSITA would have possessed, relying solely on the testimony of its experts. But Petitioner's experts merely repeat verbatim the purported level of the POSITA articulated in the Petition without any further citation to any other objective evidence or even an explanation demonstrating why that particular level of POSITA proffered by Petitioner is accurate. *See* Pet. at 16; EX1050, ¶¶22–25; EX1051, ¶¶39–42.

For the purposes of the Board's institution decision, Patent Owner does not take a position on the accuracy of Petitioner's proposed definition of a POSITA. Patent Owner reserves all rights to propose the proper level of a POSITA if needed at a later time and/or in a different venue.

III. CLAIM CONSTRUCTION

Petitioner proposes that the term “half-life $t_{1/2}$ ” should be construed as “the time for one-half of the epinephrine to be formed from its prodrug in human plasma.” Pet. at 17–18.

Because the Petition can be denied without resolving the proper construction of the term for the numerous reasons discussed herein as well as in Patent Owner's Discretionary Denial Brief filed on August 18, 2025, for the purposes of the Board's institution decision only, Patent Owner does not take a position on Petitioner's proposed construction. *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (“[W]e need only construe terms ‘that are in controversy, and only to the extent necessary to resolve the controversy.’” (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999))); *Realtime Data, LLC v. Iancu*, 912 F.3d 1368, 1375 (Fed. Cir. 2019) (same). Patent Owner reserves all rights to propose the proper construction of the term if needed at a later time and/or in a different venue.

IV. OBJECTIVE INDICIA OF NONOBVIOUSNESS WARRANT DENIAL OF INSTITUTION

Petitioner proffers three different Grounds summarized below.

Ground	References	Basis	Claims Challenged
1	Truelove 1 (EX1002), Ashraf (EX1003), Almoazen Paper (EX1022)	35 U.S.C. § 103	1-3
2	Truelove 3 (EX1008), Ashraf (EX1003), Almoazen Paper (EX1022)	35 U.S.C. § 103	1-3
3	Truelove 1 (EX1002), Truelove 3 (EX1008), Ashraf (EX1003), Almoazen Paper (EX1022), Fuchs (EX1004), Schobel (EX1021), Florence (EX1015)	35 U.S.C. § 103	1-3

Pet. at 4.

Ground 1 is largely based on references that were already expressly considered during prosecution (*i.e.*, Truelove 1 and Ashraf) in combination with a third reference that is not even prior art (*i.e.*, the Almoazen Paper). *See* Paper 7 (Patent Owner's Brief in Support of Discretionary Denial) at 37–40, 51–52. **Ground 2** replaces the primary reference (*i.e.*, Truelove 1) from Ground 1 with another reference (*i.e.*, Truelove 3) that does not even read on any of the claimed compounds. **Ground 3** combines the four references from Grounds 1 and 2 (*i.e.*, Truelove 1, Truelove 3, Ashraf, and the Almoazen Paper) and adds three more references (*i.e.*, Fuchs, Schobel, and Florence) to end up with a 7-way obviousness combination—presented in just two pages of the Petition (coupled with a claim chart).

In other words, every one of Petitioner's Grounds relies on **obviousness**. But the "question of obviousness is resolved on the basis of underlying factual determinations, including (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) *objective evidence of nonobviousness, i.e., secondary considerations.*" *Stryker*, IPR2019-00817, Paper 10 at 9 (citing *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007)) (emphasis in original). "[E]vidence of secondary considerations may often be the most probative and cogent evidence in the record. It may often establish that an invention appearing to have been obvious in light of the prior art was not." *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1349 (Fed. Cir. 2012) (quoting *Stratoflex Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983)).

During prosecution of the '437 Patent, one particular objective indicia of nonobviousness—namely "unexpected results"—featured prominently in the Examiner's Reasons for Allowance. See EX2012 at 385 ("Applicant has amended [the] claims and persuasively argued the **unexpected result of the claimed epinephrine prodrug genus** having a rapid half-life ranging from 1 to 6 minutes.") (emphasis added); see also *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1291 (Fed. Cir. 2013) ("Relevant secondary considerations include commercial success, long-felt but unsolved needs, failure of others, and unexpected results.").

In such instances, the Board has repeatedly “cautioned petitioners in prior proceedings that petitions may be denied if they do not address known evidence of secondary considerations.” *Stryker*, IPR2019-00817, Paper 10 at 28–29; *see also Merial Ltd. v. Virbac*, IPR2014–01279, Paper 13 at 27 (PTAB Jan. 22, 2015) (denying institution for failure to address objective indicia considered by Examiner during original prosecution and noting that “*Merial was aware of the unexpected results showing which the Examiner found persuasive Merial should have addressed unexpected results in the first instance.*”) (emphasis added); *Coalition for Affordable Drugs V LLC v. Hoffman–LaRoche, Inc.*, IPR2015-01792, Paper 14 at 17–18 (PTAB Mar. 11, 2016) (denying institution for failure to address objective indicia considered by Examiner during original prosecution). Here, Petitioner’s failure to address the unexpected results that the Examiner found persuasive for overcoming the art warrants denial of institution.

Importantly, other additional objective indicia of nonobviousness are also present in the instant case. Although the Examiner considered and rejected an earlier argument during prosecution regarding long-felt need (due to lack of sufficient underlying evidence), other relevant publications show that the ’437 Patent fulfills a long-felt need of the industry to develop a fast-dissolving film for sublingual or buccal administration that can treat anaphylaxis. Moreover, other indicia—failure of others to solve the long-felt need, copying by Petitioner, and industry praise—

also demonstrate the inventiveness of the claimed invention and warrant denial of institution. *See Wilson Elecs., LLC v. Cellphone-Mate, Inc.*, IPR2018-01778, Paper 10 at 29 (Apr. 23, 2019) (crediting Patent Owner's submission of "long-felt but unsatisfied need in the art for the claimed invention, industry praise for the claimed invention, and failure of others to obtain the claimed invention, as well as showing a nexus between these factors and the claimed invention" in denying institution).

A. Petitioner Failed To Address The Unexpected Results That The Examiner Expressly Found Overcome Its Obviousness Rejection During Prosecution

1. The Examiner Allowed The Claims Because They Demonstrated Unexpected Results

After entering national stage, on November 4, 2020, the Examiner issued a restriction requirement directed to two purportedly different groups of invention¹ and an election of species requirement among the specific compounds listed. EX2012 at 245–250. On December 1, 2020, applicant elected Group 1 and "the molecule which has the side group R= -C(Cl)₂CH₃." EX2012 at 256.

¹ The Examiner found that "Group I [was] drawn to a compound formulated for sublingual or buccal administration of claimed formula (prodrug formulations of epinephrine)" and "Group II [was] drawn to a method of delivering a prodrug of epinephrine that is formulated for sublingual or buccal administration." EX2012, 246.

On December 24, 2020, the Examiner issued a non-final office action rejecting several claims under 35 U.S.C. § 103 over US 2007/0202163 (“Rawas-Qalaji”) in view of U.S. 4,145,441 (“Bodor”). EX2012, 258–266. On January 22, 2021, Applicant filed a response that included, *inter alia*, a Declaration under 37 CFR § 1.132 from Dr. Kafait U. Malik that stated, without any supporting documentation, the following:

DECLARATION UNDER 37 CFR 1.132

1. I, Kafait U. Malik am a professor at the University of Tennessee Health Science Center in Memphis, Tennessee
2. In the field of pharmacology, I have studied:
3. Prompt injection of epinephrine in the mid-outer thigh (vastus lateralis muscle) using an auto-injector is the recommended first-aid treatment of anaphylaxis in community settings. At present, sublingual or buccal administration of epinephrine is not available to treat patients.
4. To date, no pharmaceutical industry was able to develop and market a sublingual tablet of epinephrine simply because of the erratic absorption behavior of epinephrine observed in many of Rawas-Qalaji's published animal studies.
5. However, effective sublingual or buccal administration of a pharmaceutical composition to treat anaphylaxis would meet a long felt need in the medical field.

EX2012 at 317.

On March 3, 2021, the Examiner issued a final rejection, rejecting applicant's long-felt need argument because it lacked evidentiary support. *See* EX2012 at 334 (“Applicant further allege [sic] that there is a long felt medical need that the instant

claims have met. Applicant argues, and submits a declaration, by way of affidavit filed 01/22/2021, prompt injection of epinephrine is the recommended first-aid treatment of anaphylaxis and that at present sublingual or buccal administration of epinephrine is not available to treat patients. Applicant's argument is found unpersuasive due to not providing objective evidence of establishing a long-felt need.”).

On March 23, 2021, Applicant amended the claims to recite, among others, “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.” EX2012 at 352. The March 26, 2021 Examiner Interview Summary clarifies that Applicant explicitly argued that the amended claims demonstrate unexpected results:

Date of Interview: 23 March 2021

Issues Discussed:

Proposed Amendment(s)

Applicant proposes amendment including the requirements of being a rapidly dissolving film and the substituents having a half life ranging from 1-6 minutes. Applicant argued that prior art epinephrine prodrug has a half life of 30 minutes. It was suggested that this appears to be an unexpected result. It was suggested to further explain how the claimed substituents have the unexpected result of quicker hydrolysis. It was also indicated that this on its face overcomes the prior art of record, however, that further search and consideration would be required to indicate allowance.

EX2012 at 366.

On April 20, 2021, despite earlier rejecting the “long-felt need” argument as lacking objective evidence, the Examiner allowed the claims, explaining that “unexpected results” were her reason for withdrawing the pending rejection:

Applicant has amended claims and persuasively argued the unexpected result of the claimed epinephrine prodrug genus having a rapid half-life ranging from 1 to 6 minutes. Applicant points out that prior art prodrugs have 30 minute half-life. The instantly claimed genus is thus suitable for sublingual or buccal administration having a much shorter half-life. Subsequent to persuasive arguments the rejection is withdrawn.

EX2012 at 385.

2. Despite “Unexpected Results” Being The Primary Reason For Allowance Of The Claims, Petitioner Failed To Explain How The Proposed Grounds Overcome That Objective Indicium Of Nonobviousness

Clearly, the unexpected results of the challenged claims played a critical role in the Examiner's reasons for allowance. *See* EX2012 at 366, 385. But the Petition is silent on that issue. Rather, the *only* mention of any objective indicia of nonobviousness in the Petition is the “long-felt need” argument that was rejected by the Examiner. *See* Pet. at 22. But the actual objective indicia of nonobviousness that led to the allowance of the challenged claims (*i.e.*, “unexpected results”) is not mentioned even once in the Petition.

“[T]he PTAB has cautioned petitioners in prior proceedings that **known** evidence of secondary considerations should be addressed **in the Petition**.” *Aardevo North America LLC v. Agventure B.V.*, IPR2025-00136, Paper 9 at 32 (PTAB May 1, 2025) (emphases added). Here, Petitioner’s failure to address the known unexpected results of the challenged claims from the original prosecution is reason alone to deny institution. *See Merial*, IPR2014–01279, Paper 13 at 27 (denying institution for failure to address objective indicia considered by Examiner during original prosecution and noting that “Merial was aware of the unexpected results showing which the Examiner found persuasive Merial should have addressed unexpected results in the first instance.”); *see also Coalition for Affordable Drugs*, IPR2015-01792, Paper 14 at 17–18 (denying institution for failure to address objective indicia considered by Examiner during original prosecution); *see also Stryker*, IPR2019-00817, Paper 10 at 28–29 (“We have cautioned petitioners in prior proceedings that petitions may be denied if they do not address known evidence of secondary considerations.”); *see also Omron Oilfield & Marine Inc. v. MD/TOTCO*, IPR2013–00265, Paper 11 at 16 (PTAB Oct. 31, 2013) (denying institution for failure to address objective indicia successfully argued in a reexamination).

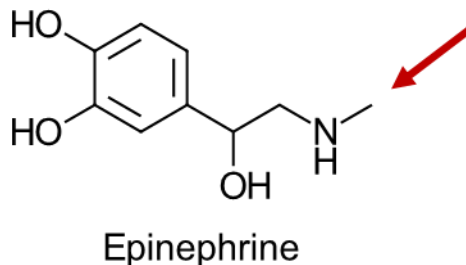
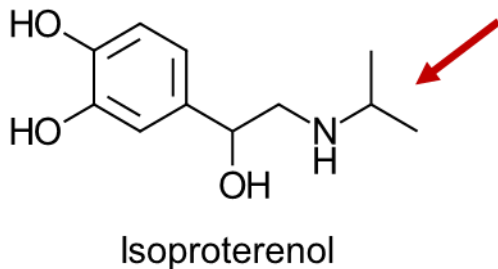
Petitioner’s failure to explain why its proposed Grounds have overcome those unexpected results is reason alone for denying institution. Indeed, it is not surprising

that Petitioner chose to remain silent on this issue because Petitioner cannot make such a showing.

Petitioner's **Ground 1** relies heavily on Truelove 1, which was extensively discussed not only during prosecution but throughout the '437 Patent's specification. EX2012, 268, 357–360; EX1001, 2:5–38; 4:9–10; 6:42–52. Similarly, Ashraf is relied upon for only the generic disclosure of typical log P ranges for marketed sublingual products, but that too was disclosed in the '437 Patent's specification for exactly the same purpose. EX1001, 5:6–12 (“The prodrugs of epinephrine preferably have a Log P value in the range of about 0.5-6.0, and more preferably between 1.0-5.0. This range was listed as a table of marketed sublingual tablets and films in Ashraf et. al ‘Considerations in developing sublingual tables—An overview’, Pharmaceutical Technology, 2014, 38(11).” And as more fully explained below in Section V.A.1 and in Patent Owner's Brief in Support of Discretionary Denial (Paper 7), Petitioner's third reference (*i.e.*, the Almoazen Paper) is not even prior art. Petitioner cannot make a showing that overcomes the unexpected results found by the Examiner when two of its three references were already considered by the Examiner and its third reference is not prior art.

Ground 2 replaces the primary reference (*i.e.*, Truelove 1) from Ground 1 with another reference (*i.e.*, Truelove 3) that does not read on any of the claimed compounds. Although Truelove 1 (already considered by the Examiner) describes

the claimed epinephrine prodrugs, Truelove 3 describes a different compound—diester isoproterenol derivatives.



Petitioner offers no meaningful analysis or rationale to explain why the teachings regarding isoproterenol in Truelove 3 reasonably apply to the claimed epinephrine prodrugs. Hence, Petitioner cannot make a showing that overcomes the unexpected results found by the Examiner when its new reference Truelove 3 does not even read on the claims.

Ground 3 combines the four references from Grounds 1 and 2 (*i.e.*, Truelove 1, Truelove 3, Ashraf, and the Almoazen Paper) and adds three more references (*i.e.*, Fuchs, Schobel, and Florence) to end up with a 7-way obviousness combination. But Petitioner provides no meaningful analysis on how and why those seven different references should be combined with any reasonable expectation of success. Indeed, other than a conclusory claim chart, Petitioner spends merely two pages discussing Ground 3. Not only can Petitioner not make a showing that overcomes the unexpected results, but Petitioner has failed to meet the bare minimum requirements for demonstrating obviousness in its Ground 3.

B. Numerous Additional Objective Indicia Of Nonobviousness Outweigh Any Purported Obviousness Grounds Raised By Petitioner

But unexpected results are not the only objective indicia of nonobviousness—more exist, including copying, long-felt but unsolved need and failure of others, and industry praise. “In determining whether the subject matter of a claim would have been obvious over the prior art, the Board will review any objective evidence of nonobviousness proffered by the patent owner where appropriate.” CTPG 41.8; *see also* 37 C.F.R. § 42.107(a) (“[A] preliminary response . . . can include supporting evidence”). And when “Patent Owner presents significant evidence of [objective indicia of nonobviousness] as well-as showing a nexus between these factors and the claimed invention[,] [t]hese factors weigh against a reasonable likelihood that [the challenged claims] would have been obvious.” *Wilson Elecs.*, IPR2018-01778, Paper 10 at 29.

1. Petitioner Deliberately Copied The '437 Patent After Receiving The Published PCT Application

Petitioner copied the invention disclosed in the '437 Patent—indeed, it replicated Patent Owner's claimed epinephrine-prodrug film and is now taking that product to market. As the Federal Circuit has explained, “copying by a competitor is a relevant consideration in the objective indicia analysis.” *Liqwd, Inc. v. L'Oreal USA, Inc.*, 941 F.3d 1133, 1137 (Fed. Cir. 2019). “Copying requires duplication of

features of the patentee's work based on access to that work.” *Liqwd, Inc. v. L'Oreal USA, Inc.*, 941 F.3d 1133, 1137 (Fed. Cir. 2019).

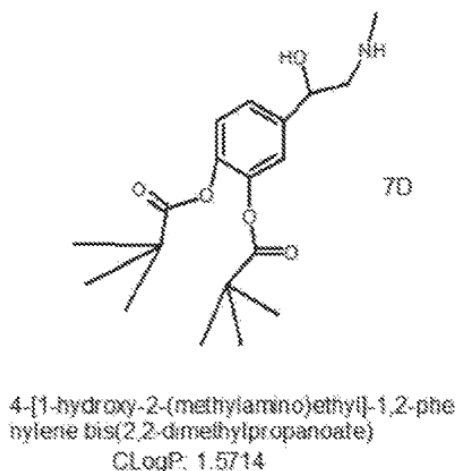
As discussed in the Discretionary Denial Brief, Petitioner first contacted Dr. Almoazen on June 3, 2016, to discuss employment opportunities. EX2001 at 8. At the time, Petitioner (then MonoSol Rx)² had filed two provisional patent applications directed to epinephrine-containing compositions: U.S. Provisional Application No. 62/331,996 (EX2013) and U.S. Provisional Application No. 62/331,993 (EX2021). Neither of those applications (nor any other Petitioner's applications from that period) disclosed epinephrine prodrugs, such as the epinephrine esters claimed in claims 1–3. Rather, those two provisional applications only disclosed epinephrine and epinephrine bitartrate—neither of which are the claimed epinephrine *prodrugs*. *See generally* EX2013; EX2021.

Then on May 4, 2017, Petitioner filed a non-provisional application that became Schobel (EX1021). Schobel contains only a single generic, boilerplate line about “epinephrine esters” with no identification of any ester species, no synthesis disclosures, and no guidance for selecting any specific epinephrine prodrug that would be useful for buccal/sublingual treatment of anaphylaxis. EX1021 at 15:62–

² MonoSol Rx changed its name to Aquestive Therapeutics on November 30, 2017. *See* EX2010.

65 (“In one example, a composition including epinephrine or its salts or esters can have a biodelivery profile similar to that of epinephrine administered by injection, for example, using an EpiPen.”).

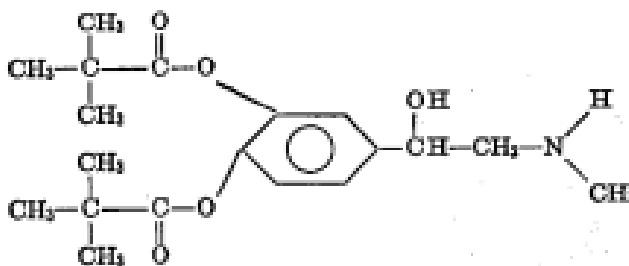
On October 23, 2017, Petitioner filed continuation-in-part application in the same family as Schobel and, for the first time, used the term “prodrug” in connection with epinephrine, specifically listing dipivefrin, reproduced in the '437 Patent below. EX2032, [0104].



EX1001 at Fig. 7D (dipivefrin).

Petitioner did not identify any other epinephrine prodrug as being useful for buccal/sublingual treatment of anaphylaxis in that application. And it is not surprising that dipivefrin was identified as the particular compound of choice because dipivefrin was long known as an epinephrine prodrug that was available on the market for ophthalmic applications. EX2033 at 1, 4–5. Indeed, it is the very

same compound 7D reported by Truelove 1 in 1974. *See* EX1001 at 2:5–38; EX2033 at 7 (listing Truelove 1 as a “synthesis reference” for dipivefrin).

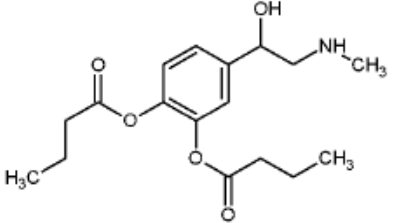
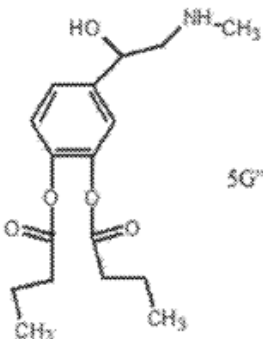
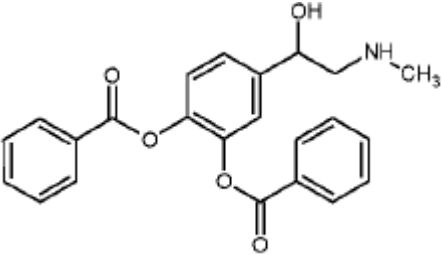
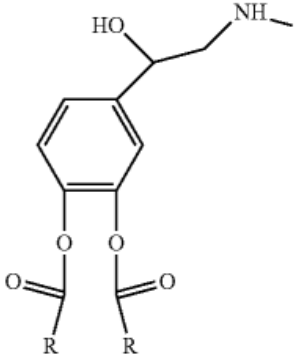


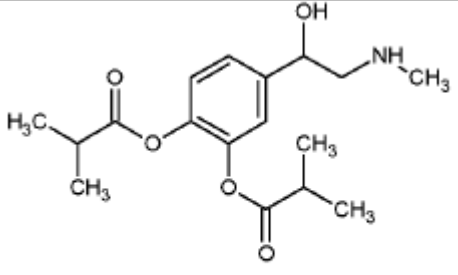
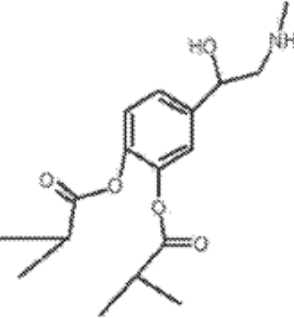
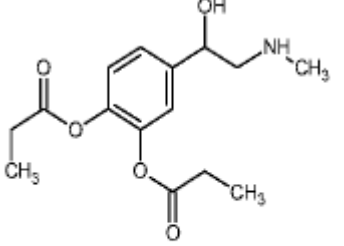
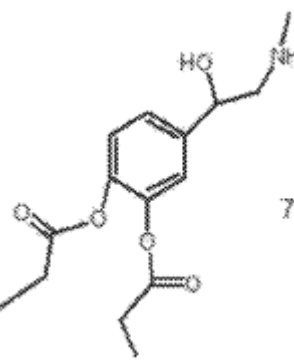
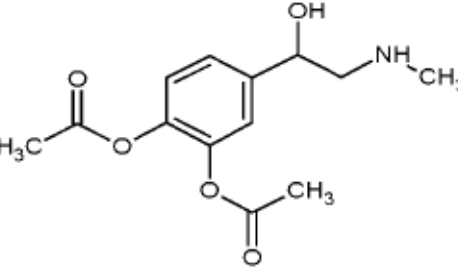
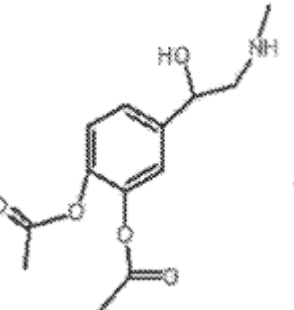
Formula 1

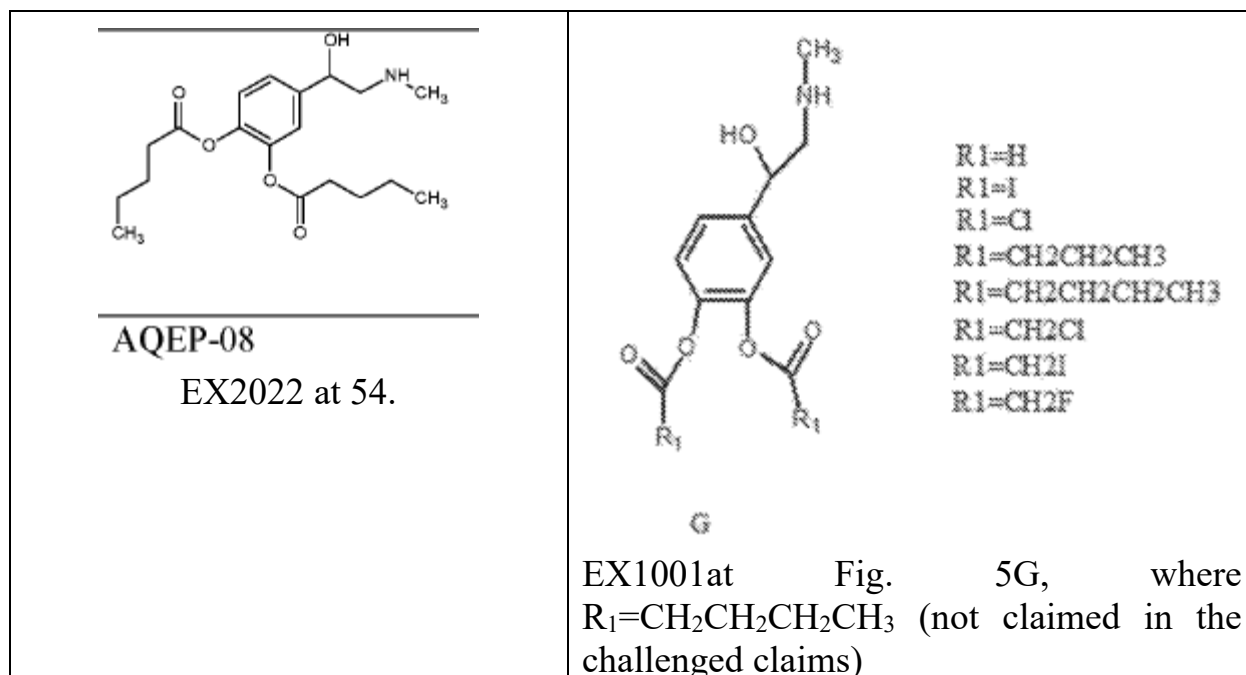
EX1002 at Formula 1 (dipivefrin). To be clear, Dr. Almoazen—the named inventor of the '437 Patent—recognized dipivefrin would not have the desired characteristics for sublingual or buccal administration. Hence, dipivefrin was specifically carved out from the claims and is *not* claimed by the '437 Patent.

On June 9, 2018, after the PCT application *that matured into the '437 Patent had published*, Dr. Almoazen emailed Petitioner's then-Chief Science Officer, Dr. Wargacki a hyperlink to the published PCT application. EX2003 at 1. This PCT application disclosed all the epinephrine prodrugs claimed in the '437 Patent. EX1014 at 17–20. In his e-mail, Dr. Almoazen expressed his desire to form a partnership with Petitioner to develop the claimed epinephrine prodrugs and bring them to market. EX2003 at 1. Petitioner did not respond. EX2020, ¶ 26.

Instead, on November 1, 2019, Petitioner filed a U.S. Provisional Application No. 62/929,737 (“Petitioner’s 2019 Provisional”), titled “***Prodrug*** Compositions And Methods Of Treatment.” EX2022 at 3, 5. In Petitioner’s 2019 Provisional, Petitioner lists the very same prodrug structures disclosed in the ’437 specification and targets epinephrine ***prodrugs*** “administered in sublingual or buccal dosage forms.” Compare EX2022 at 49 with EX1001 at 5:43–47. Some compounds that are listed in Petitioner’s 2019 Provisional and those that are found in the ’437 Patent are identified below:

Petitioner’s 2019 Provisional	Patent Owner’s ’437 Patent
 AQEP-05 EX2022 at 54.	 5G' EX1001 at Fig. 5G' claimed in Claim 1
 EX2022 at 54.	 EX1001 at claim 1, where R=C₆H₅

 AQEP-09 EX2022 at 54.	 7B EX1001 at Fig. 7B claimed in claims 2 and 3
 AQEP-10 EX2022 at 54.	 7C EX1001 at Fig. 7C claimed in claims 2 and 3
 AQEP-13 EX2022 at 55.	 7A EX1001, Fig. 7A claimed in claims 2 and 3



Among these compounds, Petitioner pursued a commercial product based on the same epinephrine prodrug found in Figure 7B of the '437 Patent (*i.e.*, AQEP-09). On June 16, 2025, U.S. Food and Drug Administration (FDA) accepted Petitioner's New Drug Application (NDA) for Anaphylm™ (AQST-109)—a sublingual epinephrine film. *See* EX2024. As shown below, the active ingredient AQST-109 corresponds to AQEP-09 that is disclosed as Figure 7B in the '437 Patent:

Synonyms and Mappings

- 2735735-23-4
- 4-((1R)-1-HYDROXY-2-(METHYLAMINO)ETHYL)-1,2-PHENYLENE BIS(2-METHYLPROPANOATE)
- AQEP-09
- AQST-109
- DIBUTEPINEPHRINE [INN]
- DIBUTEPINEPHRINE [USAN]
- DIISOBUTYRYL EPINEPHRINE
- DIISOBUTYRYL L-EPINEPHRINE
- PROPANOIC ACID, 2-METHYL-, 1,1'-(4-((1R)-1-HYDROXY-2-(METHYLAMINO)ETHYL)-1,2-PHENYLENE) ESTER

EX2025 (FDA precisionFDA UNII Search (GSRS) record for DIBUTEPINEPHRINE (UNII 3ZU4LVA3G9)).

Accordingly, Petitioner's copying of compound 7B claimed by the '437 Patent outweighs Petitioner's obviousness grounds.

2. The '437 Patent Solved The Long-Felt, Unmet Need of Providing A Method of Treating Anaphylaxis Without Injecting Epinephrine That Others Failed To Solve

“Evidence of a long felt but unresolved need tends to show non-obviousness because it is reasonable to infer that the need would have not persisted had the solution been obvious.” *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1332 (Fed. Cir. 2016). Satisfaction of a long-felt need can be shown by establishing that: “(1) a POSA recognized a problem that existed for a long period of time without a solution, (2) the long felt need had not been satisfied by another before the claimed invention, and (3) the invention in fact satisfied the long-felt need.” *Immunex Corp. v. Sandoz Inc.*, 395 F. Supp. 3d 366, 405 (D.N.J. 2019). Whether there is a “long-felt need is

analyzed as of the date of an articulated identified problem and evidence of efforts to solve that problem.” *Tex. Instruments, Inc. v. U.S. Int’l Trade Comm’n*, 988 F.2d 1165, 1178 (Fed. Cir. 1993).

Before November 13, 2016, the priority date of the ’437 Patent, a POSITA recognized that there was a need to treat anaphylactic shock that did not require epinephrine autoinjectors. Before then, a dose of epinephrine administered by an autoinjector (i.e., via an EpiPen[®]) was widely considered essential in treating sudden onset anaphylactic shock. *See, e.g.*, EX2026 at 1 (“The cornerstone of first-aid treatment of anaphylaxis is epinephrine injected intramuscularly in the vastus lateralis muscle (lateral aspect of the thigh).”); *see also* EX2027 at 1 (“Currently, the World Health Organization (www.who.int) and the World Allergy Organization consider epinephrine to be an essential medication for anaphylaxis treatment.”); EX2028 at 1 (“Epinephrine is the treatment of choice for anaphylaxis.”); EX2029 at 1 (“By consensus, epinephrine is the treatment of choice and the first drug to be administered in the therapy of anaphylaxis.”); EX2030 at 1 (“Prompt administration of epinephrine, preferably by intramuscular injection, is the cornerstone of systemic anaphylaxis treatment.”); EX2031 at 1 (“Injection of epinephrine, preferably by intramuscular route, is the treatment of first choice.”).

Since the early 2000s, however, POSITA’s recognized significant shortcomings with injectable epinephrine delivery. Namely, using injection as the

delivery method resulted in significant underutilization of epinephrine. *See, e.g.*, EX2026 at 3–6; EX2027 at 2–5; EX2028 at 2–5; EX2029 at 2–3; EX2030 at 1–2; EX2031 at 1. For example, a November 2000 article in the Official Journal of The American Academy of Pediatrics reported that “many children with a history of anaphylaxis do not carry injectable epinephrine and many children, caregivers, and even physicians do not know how to use injectable epinephrine appropriately. In addition, concerns are often expressed about ... the inability to administer more than one epinephrine dose, if the need should arise because of progressive or biphasic anaphylaxis symptoms.” EX2031 at 1; *see also* EX2030 at 1 (2002 article noting that “reluctance to self-inject epinephrine promptly may be due to anxiety about a ‘needle.’”).

Similarly, a 2004 article in the Journal of Allergy and Clinical Immunology reported that “in studies of individuals dying from anaphylaxis, [epinephrine] has been consistently reported to be underused, and failure to inject it at all, delayed use, inappropriate dose, or inappropriate route of administration have been identified as contributing factors to death.” EX2026 at 6; *see also* EX2029 at 2 (2003 paper commenting that “it is well documented that [epinephrine] is underutilized” for treating anaphylaxis).

By 2010, this problem persisted, and it was well known that epinephrine auto-injectors are underused for a variety of reasons:

Table 4 Epinephrine auto-injectors in anaphylaxis: reasons for lack of use and apparent lack of response

Lack of use of epinephrine auto-injectors (common)

Not available for purchase in many countries

Not prescribed by physician

Not affordable

Prescription not filled or picked up

Not accessible when anaphylaxis occurred

Not used because:

Patient used another medication, e.g. H₁-antihistamine or asthma puffer^a

Reaction seemed to be mild

Reaction seemed to improve quickly

Patient was unsure when to inject

Patient was afraid to inject

Epinephrine was past expiry date

Previous systemic allergic reaction improved quickly^b

Apparent lack of response to epinephrine (uncommon)

Rapid progression of anaphylaxis

Empty ventricle syndrome

Patient taking another medication^c that interfered with epinephrine effect

Epinephrine injected too late

Epinephrine dose too low

On a mg/kg basis for body weight of patient

Due to auto-injector being past the expiry date

Delayed absorption

Route of injection not optimal

Site of injection not optimal

Epinephrine injected using incorrect technique, e.g. not enough force

Adverse reaction to sodium metabisulfite preservative in the epinephrine solution (rare)

EX2027 at Table 4; *see also* EX2028 at 2 (2007 paper discussing “alternative delivery systems” for epinephrine because “fear/dislike of needles appears to be a common reason for autoinjector underuse”).

By November 13, 2016, the priority date of the '437 Patent, the long-felt need of a needleless delivery system for epinephrine remained unsolved. Although

several alternative methods of epinephrine delivery were explored, none of them were able to solve this problem. *See* EX2026 at 6 (noting that “[a]dministration of epinephrine through ... metered-dose inhalers ... is impractical for the treatment of other systemic effect” and that “oral epinephrine administration is ineffective because of metabolism”); EX2030 at 2 (hypothesizing “that epinephrine would be well absorbed and rapidly absorbed after sublingual administration in a tablet formation”); EX2031 (concluding that epinephrine inhalers are not a safe alternative to injections because “[d]espite expert coaching, because of the number of epinephrine inhalations required and the bad taste of the inhalations, most children were unable to inhale sufficient epinephrine to increase their plasma epinephrine concentrations promptly and significantly”). Indeed, as of the November 2016 priority date of the '437 Patent, the only FDA-approved treatments for anaphylactic shock required a needle injection.³

The '437 Patent solved this long-felt need by being the first to disclose fast dissolving films that contained epinephrine *prodrug*. The patent claims novel ester

³ The first FDA approved epinephrine product for the treatment of anaphylaxis is “neffy (epinephrine nasal spray)” which was approved on August 9, 2024, eight years after the priority date of the '437 Patent. *See* EX2034.

epinephrine prodrugs that demonstrate heightened “permeability through the biological membranes (sublingual and buccal tissues in the oral cavity).” EX1001 at Abstract. And, as explained above, Petitioner copied those epinephrine prodrugs in its patent application and is now taking the first fast dissolving film product called Anaphylm™ to market that contains the same epinephrine *prodrugs* disclosed in the ’437 Patent. *See supra* Section IV.B.1. Accordingly, the long-felt, unsolved need for needleless epinephrine delivery that existed since at least 2000 outweighs Petitioner’s obviousness grounds.

3. Anaphylm™ Has Received Industry Praise As The First Sublingual Epinephrine Film With Results Comparable To An Epinephrine Autoinjector

“Evidence that the industry praised a claimed invention or a product which embodies the patent claims weighs against an assertion that the same claim would have been obvious.” *WBIP*, 829 F.3d at 1334.

As noted above, Petitioner is bringing to market Anaphylm™, which is a fast-dissolving film product that contains the same epinephrine *prodrug* disclosed in the ’437 Patent as compound 7B. *See supra* Section IV.B.1. And Anaphylm™ has received industry praise for being the first sublingual epinephrine film. *See, e.g.*, EX2035 at 2 (“Anaphylm is a promising needle-free alternative to the current standard of care, allowing patients to easily carry and administer this life-saving medication.”); EX2036 at 5 (commenting that Anaphylm™ is “[a] pioneering

advancement in the management of anaphylaxis” whose “PK and PD data were comparable to epinephrine delivered through an autoinjector or a manual intramuscular injection (IM).”); EX2037 at 2 (noting Anaphlym™ is a “[n]ovel needle-free alternative addressing patient fear of injections” and its “[p]otential to be [the] first FDA-approved non-invasive oral epinephrine treatment for anaphylaxis”); EX2038 at 1 (praising Anaphlym™ because its “time to maximum epinephrine concentration is faster than other delivery vehicles”); EX2039 at 2 (praising Anaphlym™ for “maintain[ing] plasma concentrations equal to or greater than existing injection products” and being “well tolerated with no reported severe adverse events”). Accordingly, Anaphlym™’s industry praise—which is directed towards a compound claimed by the ’437 Patent—outweighs Petitioner’s obviousness Grounds.

V. PETITIONER’S RELIANCE ON REFERENCES THAT ARE NOT PRIOR ART IS FATAL TO ALL THREE GROUNDS

As explained in Patent Owner’s Discretionary Denial Brief, and summarized in the Table below, Petitioner relies exclusively on the Almoazen Paper and Schobel as allegedly meeting the limitation “wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.”

	“wherein the compound is formulated in a unit dosage form as a rapidly dissolving film”		
	Claim 1	Claim 2	Claim 3
Ground 1	Almoazen Paper (Pet. at 50)	Almoazen Paper (Pet. at 54)	Almoazen Paper (Pet. at 57)
Ground 2	Almoazen Paper (Pet. at 59)	Almoazen Paper (Pet. at 62)	Almoazen Paper (Pet. at 65)
Ground 3	Almoazen Paper Schobel (Pet. at 68)	Almoazen Paper Schobel (Pet. at 71)	Almoazen Paper (Pet. at 74)

Specifically, Petitioner asserts that the lack of disclosure of a “half-life $t_{1/2}$ range from 1-6 minutes” in the '437 Patent's provisional application renders the earliest effective filing date to be the filing date of PCT application. *See* Pet. at 14-15. But that is incorrect. Petitioner ignores the fact that the '437 Patent's provisional application *incorporated by reference* Truelove 1, which Petitioner admits discloses a “half-life $t_{1/2}$ range from 1-6 minutes.” Hence, the priority date of the '437 Patent is the filing date of the provisional application (*i.e.*, November 13, 2016) and disqualifies both the Almoazen Paper and Schobel as being prior art.

A. The '437 Patent Should Be Afforded A Priority Date Of November 13, 2016, Because The Provisional Application Incorporated By Reference Truelove 1

As Petitioner admits, Truelove 1 discloses a “half-life $t_{1/2}$ range from 1-6 minutes.” *See* Pet. at 25 (“Importantly, Table 3 [of Truelove 1] reports that three diester epinephrine compounds have a half-life range from 1-6 minutes as recited in

the challenged claims.”); *see also id.* at 23 (discussing “the diester epinephrine compounds disclosed in Truelove 1 with half-life $t_{1/2}$ values of 1-6 minutes”).

Moreover, although Petition admits that the '437 Patent incorporated by reference Truelove 1, *see* Pet. at 9–10, Petitioner omits the fact that the '437 Patent's *provisional application also incorporated by reference Truelove 1*. *See* EX1013 at 22 (“Now referring to FIG. 7, the compounds of the invention as shown in US patent 3,809,714 [“Truelove 1”] and US patent 3,825,583 *hereby incorporated by reference.*”) (emphasis added).

Under the USPTO's rule, “essential material”—*i.e.*, material necessary to satisfy § 112—may be incorporated by reference from “a U.S. patent or U.S. patent application publication which ‘does not itself incorporate such essential material by reference.’” *Droplets, Inc. v. E*TRADE Bank*, 887 F.3d 1309, 1318 (Fed. Cir. 2018) (citing 37 C.F.R. § 1.57(c)). Thus, because the provisional application incorporated by reference Truelove 1, which Petitioner admits discloses “diester epinephrine compounds have a half-life range from 1-6 minutes as recited in the challenged claims,” Pet. at 25, the provisional application provides written description support for the limitation “half-life $t_{1/2}$ range from 1-6 minutes.” Hence, the priority date of the '437 Patent is November 13, 2016, the filing date of the provisional application.

Having established that the proper priority date of the '437 Patent is November 13, 2016 (*i.e.*, the filing date of the provisional application), neither the Almoazen Paper nor Schoebel qualify as prior art.

1. The Almoazen Paper Is Not Prior Art

The portions of the Almoazen Paper's disclosures that the Petitioner relies on for the limitation "wherein the compound is formulated in a unit dosage form as a rapidly dissolving film" are highlighted in EX2018. *See* Petition at 50, 54, 57, 59, 62, 65, 68, 71, 74, 89, 91, 94, 98, 102, and 103. As Dr. Almoazen declares, these portions of the Almoazen Paper were conceived solely by Dr. Almoazen himself and not by any of the other listed authors of the Almoazen Paper. EX2019, ¶¶ 1-7; *see also In re Katz*, 687 F.2d 450, 455-56 (C.C.P.A. 1982) (holding that "joint inventorship cannot be inferred in the face of sworn testimony" that the co-authors "were students working under the direction and supervision of the inventor"); *EmeraChem Holdings, LLC v. Volkswagen Group of Am.*, 859 F.3d 1341, 1347 (Fed. Cir. 2017) (agreeing with the rationale in *Katz* that "Mr. Katz's explanation 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.")

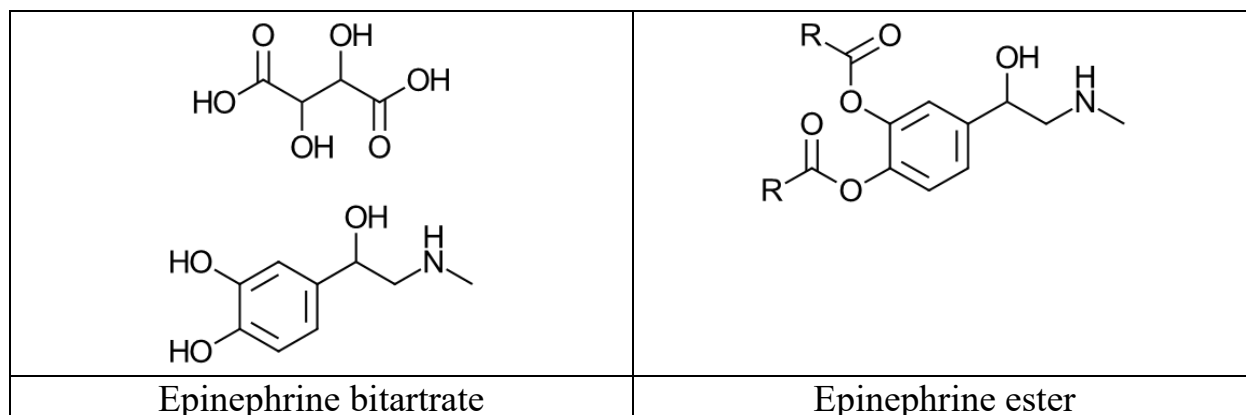
Thus, because the Almoazen Paper published on January 6, 2016, within a year of the filing date of the earliest provisional application filed on November 13,

2016, and the portions Petitioner relies upon were conceived of solely by Dr. Almoazen, the Almoazen Paper does not qualify as prior art. *See* 35 U.S.C. § 102(b)(1)(A) (“A disclosure made 1 year or less before the effective filing date of a claimed invention shall not be prior art to the claimed invention under subsection (a)(1) if the disclosure was made by the inventor or joint inventor or by another who obtained the subject matter disclosed directly or indirectly from the inventor or a joint inventor.”). Hence, all of Petitioner's Grounds fail because all three Grounds rely on the Almoazen Paper for the limitation “wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.”

2. Schobel Is Not Prior Art

Claims 1 and 2 of Ground 3 additionally rely on Schobel for the limitation “wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.” Like the Almoazen Paper, however, Schobel also does not qualify as prior art. The Petition relies on Schobel's May 5, 2016, *provisional* filing date without having carried out the proper analysis to determine whether Schobel's “provisional ... to which the reference patent document claims a right of priority ... ‘describe[s] the subject matter’ relied upon in the reference patent as prior art.” *Penumbra, Inc. v. RapidPulse, Inc.*, IPR2021-01466, Paper 34 at 32 (PTAB March 10, 2023) (precedential).

Specifically, the Petitioner relies on Schobel for the disclosure of “films designed for administration of *epinephrine and salts and esters thereof*, i.e. epinephrine *prodrugs*, to human mucosa” found in Schobel’s *nonprovisional* application. Pet. at 66 (emphasis added) (citing EX1021 at 15:62–65). But Schobel’s *provisional* application discloses only *epinephrine and epinephrine bitartrate*—not the *epinephrine prodrug* compounds recited in claims 1–3. See generally EX2014. First, epinephrine bitartrate is different from an epinephrine ester.



Nor is epinephrine bitartrate a prodrug. Epinephrine bitartrate is merely a salt of epinephrine—dissociating to free epinephrine in solution—rather than a chemically modified precursor requiring enzymatic conversion to release epinephrine. Hence, Schobel’s provisional application does not provide written description support for “epinephrine and salts and esters thereof, i.e., epinephrine prodrugs.” Petitioner cannot establish that Schobel serves as prior art because the disclosure found in Schobel’s *non-provisional* application is not found in Schobel’s

provisional application, rendering Schobel's *non-provisional* filing date of May 4, 2017, as the earliest possible prior art date. That date post-dates the '437 Patent's November 13, 2016, effective filing date. Because Schobel is not prior art to the relied-upon subject matter, it cannot be considered in the § 103 analysis.

B. The Petition Relies Solely On References That Are Not Prior Art For The Limitation “Wherein The Compound Is Formulated In A Unit Dosage Form As A Rapidly Dissolving Film” In Every One Of The Challenged Claims In Every One Of The Proposed Grounds

In summary, because Petitioner relies exclusively on the Almoazen Paper and Schobel for the limitation “wherein the compound is formulated in a unit dosage form as a rapidly dissolving film,” and neither of these references are prior art, Petitioner has failed to raise a prior art challenge for each of its proposed Grounds. Hence, denial of institution is warranted.

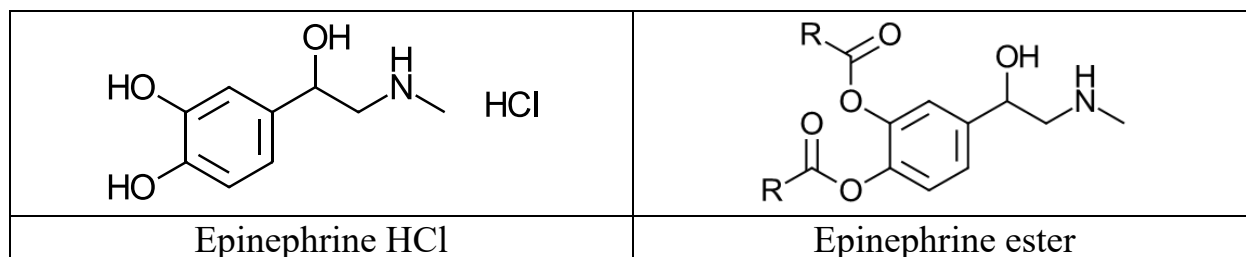
	“wherein the compound is formulated in a unit dosage form as a rapidly dissolving film”		
	Claim 1	Claim 2	Claim 3
Ground 1	Almoazen Paper (Pet. at 50)	Almoazen Paper (Pet. at 54)	Almoazen Paper (Pet. at 57)
Ground 2	Almoazen Paper (Pet. at 59)	Almoazen Paper (Pet. at 62)	Almoazen Paper (Pet. at 65)
Ground 3	Almoazen Paper Schobel (Pet. at 68)	Almoazen Paper Schobel (Pet. at 71)	Almoazen Paper (Pet. at 74)

VI. EVEN IF PRIOR ART, NEITHER THE ALMOAZEN PAPER NOR SCHOBEL TEACH OR SUGGEST THAT THE CLAIMED EPINEPHRINE PRODRUG CAN BE “FORMULATED IN A UNIT DOSAGE FORM AS A RAPIDLY DISSOLVING FILM”

1. The Almoazen Paper Does Not Teach Or Suggest The Claimed Epinephrine Prodrug Can Be Formulated As A Rapidly Dissolving Film

Even if the Almoazen Paper were prior art—which it is not—it does not actually disclose any of the *claimed* epinephrine *prodrug compounds*. The mere fact that some form of epinephrine may be formulated as a “rapidly dissolving film” does not necessarily mean a POSITA would have found it obvious that the *claimed epinephrine prodrugs* of claims 1-3 can also be formulated as a “rapidly dissolving film” prior to the '437 Patent. And the Petition doesn't even attempt to provide such an explanation.

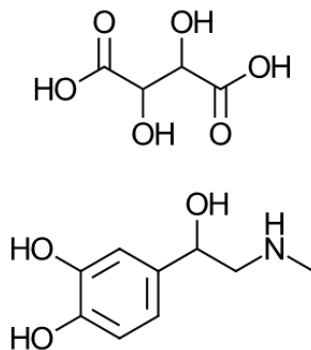
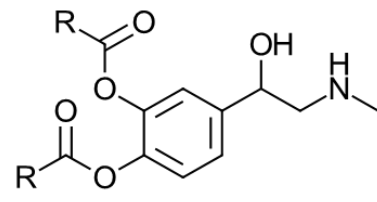
Specifically, the Almoazen Paper only discusses the formulation of a fast dissolving film that utilizes epinephrine hydrochloride (HCl)—not any one of the compounds claimed in claims 1-3. Epinephrine HCl's chemical structure is distinct from those claimed in claim 1-3.



And such structural differences matter. For example, epinephrine HCl is not claimed because it does not possess the optimized set of properties, such as sufficient permeability rate (which in turn is influenced by log P value) or half-life (*i.e.*, $t_{1/2}$ values) that is required for the invention to properly function. *See* EX1001 at 1:46–47 (stating that epinephrine has log P value of -0.68); EX1001, 5:43–47 (explaining that the claimed half-life refers to the “form[ation of] epinephrine when delivered” “by plasma enzymes”). Moreover, Petitioner has not established any evidence demonstrating or even attempting to explain why a POSITA would have considered the claimed epinephrine prodrugs of claims 1-3 to be formulated as a fast dissolving film merely because epinephrine HCl can be formulated as fast dissolving film.

2. The Petition Fails To Articulate Objective Rationale Why The Claimed Epinephrine Prodrugs Are Able To Form The Claimed “Fast Dissolving Film”

As explained above, Schobel's *provisional* application discloses only epinephrine and epinephrine bitartrate—not the epinephrine prodrug compounds recited in claims 1–3. Epinephrine bitartrate's chemical structure is distinct from those claimed in claim 1-3.

	
Epinephrine bitartrate	Epinephrine ester

The two compounds' structural differences matter. For example, epinephrine bitartrate is not claimed in claims 1-3 because it does not possess the optimized set of properties, such as sufficient permeability rate (which in turn is influenced by log P value) or half-life (*i.e.*, $t_{1/2}$ values) that is required for the invention to properly function. See EX1001, 1:46-47 (stating that epinephrine has log P value of -0.68); EX1001, 5:43-47 (explaining that the claimed half-life refers to the “form[ation of] epinephrine when delivered” “by plasma enzymes”). Moreover, Petitioner has not provided any evidence demonstrating or even attempting to explain why a POSITA would have considered the ***claimed epinephrine prodrugs*** of claims 1-3 to be able to be formulated as a fast dissolving film, merely because **epinephrine bitartrate** was able to be formulated as fast dissolving film.

VII. TRUELOVE 1 DOES NOT READ ON ANY OF THE CLAIMED COMPOUNDS OF CLAIM 1 WHEN PROPERLY READ

In Ground 1, the only reference Petitioner relies on to teach the claimed compound in claim 1 is Truelove 1. Pet. at 48–57. However, when Truelove 1 is properly read, it never teaches any compound of claim 1.

Both parties agree that Table 3 of Truelove 1 mis-labels epinephrine “esters” as “ketones” (*i.e.*, “yl-”) and that a POSITA would have recognized where the missing ester –O– (*i.e.*, “oxy–”) groups should be inserted. Pet. at 26–34.

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

EX1002 at Table 3.

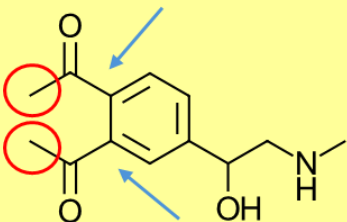
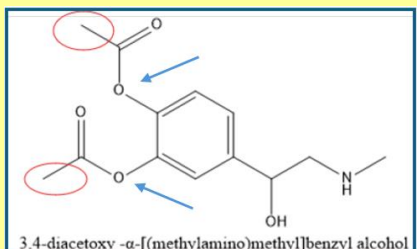
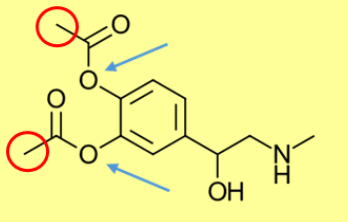
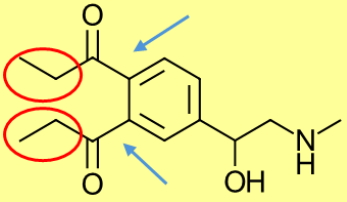
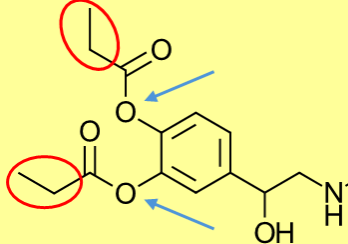
The table below illustrates the original Truelove 1, Table 3 compound nomenclature and corresponding chemical structure on the left, Petitioner's Proposed Correction to the Table 3 compound nomenclature and the corresponding chemical structure in the middle, and Patent Owner's/Proper Correction to the Table

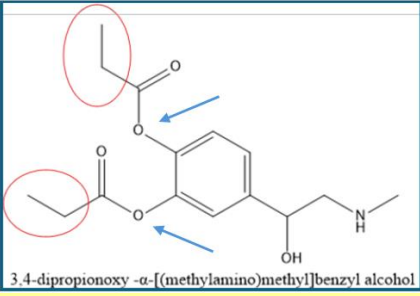
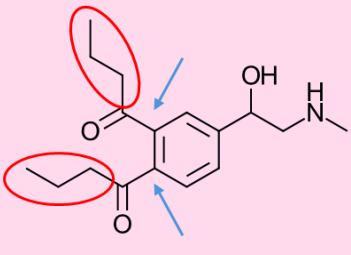
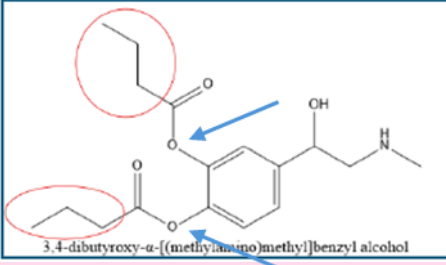
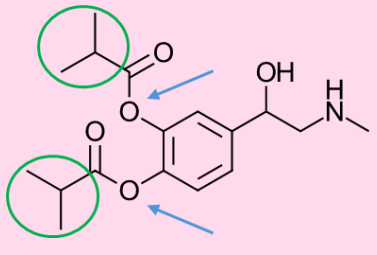
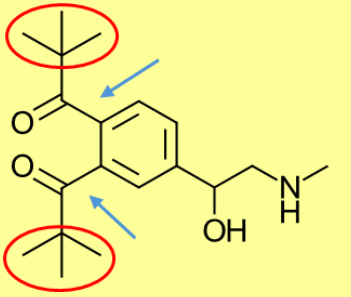
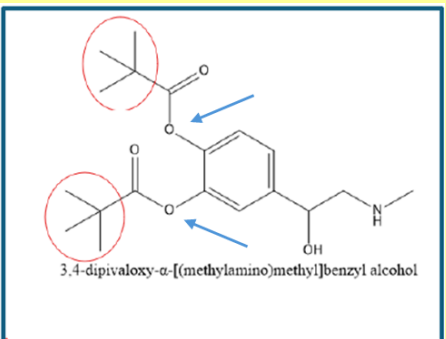
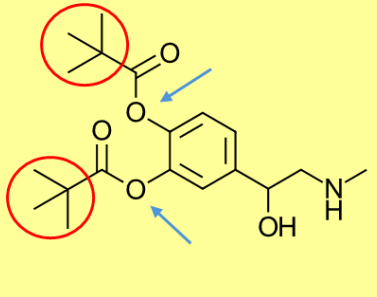
3 compound nomenclature and the corresponding chemical structure on the right.

Both parties agree that a POSITA would read the first, second, and fourth compounds in Table 3 above and in the table below (highlighted in yellow) as

diacetoxy-, **dipropion**oxy-, and **dipival**oxy-epinephrine, respectively. Pet. at 36-38.

Namely, the parties agree that only the portions in blue in the table below should be corrected to form esters. The only dispute concerns the third entry in Table 3 above and the table below (highlighted in pink).

Truelove 1 Table 3	Petitioner's Proposed Correction	Patent Owner's/Proper Correction
L-3,4-diacetyl-α- [(methylamino)- methyl]benzyl alcohol 	3,4-diacet<u>oxy</u>-α- [(methylamino)- methyl]benzyl alcohol  Pet. at 36	3,4-diacet<u>oxy</u>-α- [(methylamino)- methyl]benzyl alcohol 
L-3,4-dipropionyl-α- [(methylamino)- methyl]benzyl alcohol 	3,4-dipropion<u>oxy</u>-α- [(methylamino)- methyl]benzyl alcohol	3,4-dipropion<u>oxy</u>-α- [(methylamino)- methyl]benzyl alcohol 

Truelove 1 Table 3	Petitioner's Proposed Correction	Patent Owner's/Proper Correction
	 3,4-dipropionyloxy-α-[(methylamino)methyl]benzyl alcohol Pet. at 37	
L-3,4- dibutyryl -α- [(methylamino)- methyl]benzyl alcohol	3,4- dibutyroxy -α- [(methylamino)- methyl]benzyl alcohol	3,4- diisobutyroxy -α- [(methylamino)- methyl]benzyl alcohol
	 3,4-dibutyroxy-α-[(methylamino)methyl]benzyl alcohol Pet. at 38	
L-3,4- dipivalyl -α- [(methylamino)- methyl]benzyl alcohol	3,4- dipivaloxy -α- [(methylamino)- methyl]benzyl alcohol	3,4- dipivaloxy -α- [(methylamino)- methyl]benzyl alcohol
	 3,4-dipivaloxy-α-[(methylamino)methyl]benzyl alcohol Pet. at 38	

Examining the compound highlighted in pink, Petitioner rewrites L-3,4-**dibutyryl**-α-[(methylamino)-methyl]benzyl alcohol as 3,4-**dibutyroxy**-α-

[(methylamino)-methyl]benzyl alcohol, citing only the unsupported statements from its two experts. *See* Pet. at 33 (citing “Rautio (EX1050), ¶¶146–151, 170–178; Meanwell (EX1051), ¶¶59–60, 76, 80–81, 84, 90”).

But the intrinsic record shows that both the **red** and the **blue** portions require correction in Truelove 1 because it is clear that Truelove 1 meant the “**iso–**” “**oxy–**” form, *i.e.*, 3,4-**diisobutyroxy**- α -[(methylamino)-methyl]benzyl alcohol. This compound is first introduced at col. 8, lines 22–32 of Truelove 1, along with the names of the other three yellow highlighted compounds in the same order:

acylated and other acylated compounds as a control. The observed results indicated no mydriasis for L-3,4-dihydroxy - α - [(methylamino)methyl]benzyl alcohol bitartrate, no mydriasis for L-3,4-diacetyl- α -[(methylamino)methyl]benzyl alcohol hydroperchlorate, marginal mydriasis for L - 3,4-dipropionyl- α -[(methylamino)methyl]benzyl alcohol hydroperchlorate, marginal mydriasis for L-3,4-diisobutynyl- α -[(methylamino)methyl]benzyl alcohol hydroperchlorate, and extensive mydriasis for L-3,4-dipivalyl- α -[(methylamino)methyl]benzyl alcohol hydroperchlorate.

EX1002 at 8:22–32. Truelove 1 identifies the particular compound as L-3,4-**diisobutyryl**- α -[(methylamino)-methyl]benzyl alcohol. The identical “**iso–**” name appears in Table 1 (EX1002 at 8:50–63) and Table 2 (EX1002 at 9:3–14), again along with the names of the other three yellow highlighted compounds in the same order:

TABLE 1

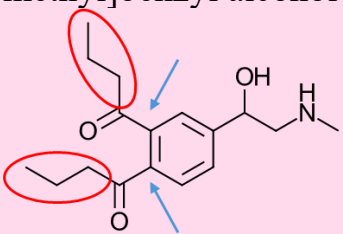
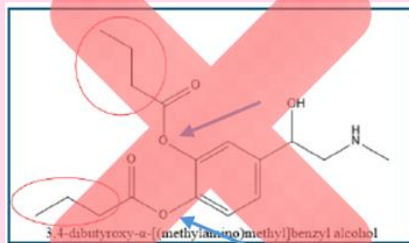
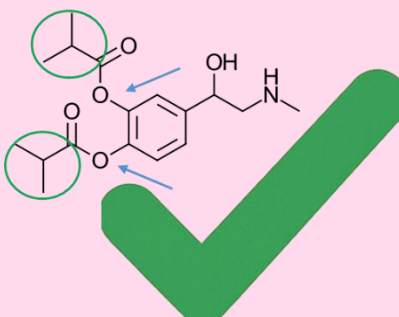
Compound:	Delay before onset of seizure in minutes
Control -----	1-2
L - 3,4 - dihydroxy- α -[(methylamino)methyl]benzyl alcohol bitartrate -----	5.5
L - 3,4 - diacetyl - α -[(methylamino)methyl]benzyl alcohol hydroperchlorate -----	4
L - 3,4 - dipropionyl- α -[(methylamino)methyl]benzyl alcohol hydroperchlorate -----	5
L - 3,4-diisobutyryl- α -[(methylamino)methyl]benzyl alcohol hydroperchlorate -----	5
L - 3,4 - dipivalyl- α -[(methylamino)methyl]benzyl alcohol hydroperchlorate -----	8-10

TABLE 2

Compound	Hydrolysis, $t_{1/2}$	Oxidation, days
L-3,4-dihydroxy- α -[(methylamino)methyl]benzyl alcohol bitartrate -----		15
L-3,4-diacetyl- α -[(methylamino)methyl]benzyl alcohol hydroperchlorate -----	30	20
L-3,4-dipropionyl- α -[(methylamino)methyl]benzyl alcohol hydroperchlorate -----	34	35
L-3,4-diisobutyryl- α -[(methylamino)methyl]benzyl alcohol hydroperchlorate -----	50	35
L-3,4-dipivalyl- α -[(methylamino)methyl]benzyl alcohol hydroperchlorate -----	700	300

Only in Table 3, which lists the “rate of hydrolysis in $t_{1/2}$ seconds” for the four compounds that Truelove 1 had been discussing in Example 1 of Truelove 1, does the “*iso*–” drop out. This is an obvious second typo that a POSITA would have been able to correct.

Thus, the pink highlighted compound 3 in Table 3 contains *two* typographical errors, not just one. Correcting both—consistent with how the compound was described in other parts of Truelove 1—yields an L-3,4-diisobutyroxy-α-[(methylamino)-methyl]benzyl alcohol— which does not match *any* structure recited in claim 1.

Truelove 1 Table 3	Petitioner's Proposed Correction	Patent Owner's/Proper Correction
L-3,4- dibutyryl -α-[(methylamino)-methyl]benzyl alcohol 	L-3,4- dibutyroxy -α-[(methylamino)-methyl]benzyl alcohol 	L-3,4- <u>diisobutyroxy</u> -α-[(methylamino)-methyl]benzyl alcohol 

The reason why Petitioner is proposing this “single” typographical error of L-3,4-**dibutyroxy**-α-[(methylamino)-methyl]benzyl alcohol instead of the proper “double” typographical error of L-3,4-diisobutyroxy-α-[(methylamino)-methyl]benzyl alcohol is self-evident. It is only with the “single” typographical error correction that Truelove 1 reads on claim 1, where the claimed “R” is “—CH₂CH₂CH₃.” If Truelove 1 is properly read to correct the “double” typographical error, Truelove 1 does not read on *any* of the claimed compounds of claim 1.

Because the Petition identifies no prior-art compound meeting every structural limitation of claim 1, Ground 1 fails on the merits. “An obviousness determination generally requires a finding that ‘all claimed limitations are disclosed in the prior art.’” *See Univ. of Strathclyde v. Clear-Vu Lighting LLC*, 17 F.4th 155, 160 (Fed. Cir. 2021) (quoting *PAR Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1194 (Fed. Cir. 2014)).

VIII. GROUNDS 2 AND 3 ASK THE BOARD TO “PLAY ARCHAEOLOGIST” TO UNDERSTAND PETITIONER’S PROPOSED GROUNDS

A. Ground 2 Is Unclear As To Which References Petitioner Is Relying On And The Board Should Not Be Asked To “Play Archaeologist” With Petitioner’s Deficient Petition

Ground 2 allegedly relies solely on the combination of Truelove 3 with Ashraf and the Almoazen Paper.

2. Specific Statutory Grounds on Which the Challenge is Based (37 C.F.R. § 42.104(b)(2))			
Ground	References	Basis	Claims Challenged
1	Truelove 1 (EX1002), Ashraf (EX1003), Almoazen Paper (EX1022)	35 U.S.C. § 103	1-3
2	Truelove 3 (EX1008), Ashraf (EX1003), Almoazen Paper (EX1022)	35 U.S.C. § 103	1-3

Pet. at 4. But Petitioner confusingly incorporates by reference the teachings of Truelove 1 into Ground 2.

B. Ground 2: Truelove 3, Ashraf, Almoazen Paper [Claims 1-3]

The arguments in support of Ground 1 and the disclosures of Truelove 1, Ashraf, and the Almoazen Paper are incorporated herein. *Supra* pp.48-57.

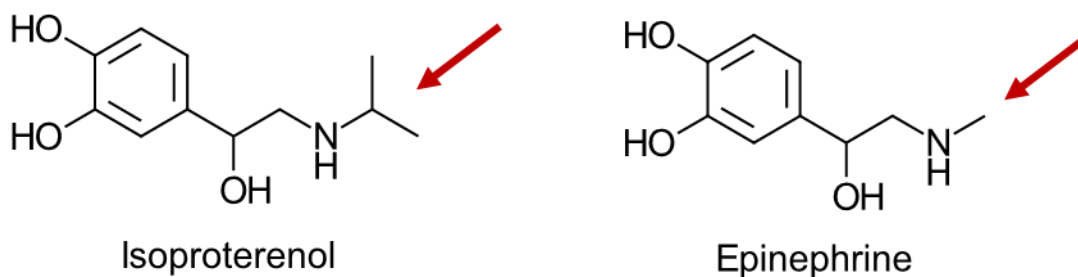
Pet. at 57. It is entirely unclear whether Ground 2 relies on Truelove 1 or not.

In an IPR petition, the “Petitioner has the responsibility to make plain its challenges to the disputed claims.” *Nearmap US, Inc. v. Eagle View Techs.*, IPR2024-00716, Paper 9 at 13 (PTAB October 8, 2024). “It is not the Board’s responsibility to weave together Petitioners evidence into a cohesive case.” *Id.* Petitioner cannot ask the Board “to play archaeologist with the record.” *Parus Holdings, Inc. v. Google LLC*, 70 F.4th 1365, 1372 (Fed. Cir. 2023). That alone warrants denial of institution.

1. If Petitioner Is Not Relying On Truelove 1 In Ground 2, None Of The References Relied Upon In Ground 2 (Truelove 3, Ashraf, And The Almoazen Paper) Read On Any Of The Claimed Compounds

Taking Petitioner’s proposed Ground 2 at face value (*i.e.*, relying only on the combination of Truelove 3, Ashraf, and the Almoazen Paper only (and not Truelove 1)), none of the references relied upon in Ground 2 read on the claimed compounds. And Petitioner’s assertion that Truelove 3 “teaches the structure recited in claim 1,”

Pet. 59, is wrong on its face: Truelove 3 discloses isoproterenol diesters⁴, whereas claims 1-3 recite epinephrine diesters. Petitioner concedes that Truelove 3 describes diester isoproterenol derivatives—not epinephrine prodrugs. See Pet. at 58 (“Truelove 3 also describes diester isoproterenol compounds...”). As shown below, isoproterenol and epinephrine are structurally distinct compounds:



Importantly, Petitioner never argues that Truelove 3 renders compounds of claims 1–3 “obvious.” Pet. at 59 (“Accordingly, Truelove 3 teaches the structure recited in challenged claim 1 where both R substituents are CH₂CH₂CH₃.”); Pet. at 62 (“Accordingly, Table 3 of Truelove 3 teaches the diester epinephrine compounds recited in claim 2 where the R substituents are CH₃ or CH₂CH₃.”); Pet. at 65 (“Accordingly, Truelove 3 discloses the compounds named in claim 3.”). The Board must assess what the Petition actually presents; it is not “free to adopt arguments on

⁴ The Petition does not rely on either Ashraf or the Almoazen Paper as disclosing the structures of the claimed compounds. See Pet. at 79-83, 95-103.

behalf of petitioners that could have been, but were not, raised by the petitioner.” (*In re Magnum Oil Tools Int’l, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016)). The Board cannot “deviate from the grounds in the petition and raise its own” theories of invalidity. *Sirona Dental Sys. GmbH v. Institut Straumann AG*, 892 F.3d 1349, 1356 (Fed. Cir. 2018).

Because Petitioner’s Ground 2 provides no prior-art compound that meets the structural limitations of independent claims 1 or 2, there is no credible unpatentability case. “An obviousness determination generally requires a finding that ‘all claimed limitations are disclosed in the prior art.’” *Univ. of Strathclyde*, 17 F.4th at 160 (quoting *PAR Pharm.*, 773 F.3d at 1194).

Petitioner also offers no meaningful analysis or rationale to explain why the teachings regarding isoproterenol esters in Truelove 3 reasonably apply to the claimed epinephrine prodrugs—beyond an assertion of structural similarity. *See* Pet. at 80. For example, other than its expert’s conclusory statement, Petitioner offers no objective evidence showing that Truelove 3’s isoproterenol compounds could be formulated in a unit dosage form for sublingual or buccal administration. *See, e.g.*, Pet. at 59. Similarly, Petitioner’s assertion that a POSITA would expect epinephrine diesters to “have the same 1-6 minute half-life $t_{1/2}$ ” rests entirely on attorney and expert speculation. Pet. at 60. There is no objective evidence proffered by Petitioner to demonstrate that Truelove 3’s isoproterenol derivatives would

exhibit similar properties as the claimed epinephrine prodrugs other than mere attorney arguments and its experts' say-so.

Finally, when properly read, Truelove 3 contains a typographical error like the one addressed above in connection with Truelove 1. *See supra* Section VII. In particular, Truelove 3 does not disclose isoproterenol compounds where "R substituents of both ester promoieties are CH₂CH₂CH₃ (i.e., 3,4-dibutyroxy- α -[(isopropylamino)]-methyl]benzyl alcohol)." Pet. at 59. Petitioner relies on Table 3 of Truelove 3 for alleged disclosure of this compound:

TABLE 3

Compound	Rate of Hydrolysis in t _{1/2} Seconds		
	Horse	Rabbit	Human
3,4-diacetoxy- α 1[(isopropylamino)-methyl]benzyl alcohol hydrochloride	20	45	180
3,4-dipropionyxy- α 1[(isopropylamino)-methyl]benzyl alcohol hydrochloride	50	90	240
3,4-dibutyroxy- α 1[(isopropylamino)-methyl]benzyl alcohol hydrochloride	100	160	360
3,4-dipivaloxy- α 1[(isopropylamino)-methyl]benzyl alcohol hydrochloride	600	720	1800

EX1008 at Table 3 (annotated); *see also* Pet. at 44.

The intrinsic record of Truelove 3, however, shows that this compound is actually 3,4-di*isob*utyroxy- α -[(isopropylamino)]-methyl]benzyl alcohol. Truelove 3 introduces this compound in Tables 1 and 2 using its correct name.

TABLE 1

Compound	Delay Before Onset Of Seizure in Min.
Control	1 - 2
3,4-dihydroxy- α -[(isopropylamino)-methyl]benzyl alcohol hydrochloride	5.5
3,4-diacetoxy- α -[(isopropylamino)-methyl]benzyl alcohol hydrochloride	4
3,4-dipropionyloxy- α -[(isopropylamino)-methyl]benzyl alcohol hydrochloride	5
3,4-diisobutyroxy- α -[(isopropylamino)-methyl]benzyl alcohol hydrochloride	5
3,4-dipivaloxy- α -[(isopropylamino)-methyl]benzyl alcohol hydrochloride	8 - 10

EX1008 at Table 1 (annotated).

TABLE 2

Compound	Hydrolysis $t_{1/2}$	Oxi- dation Days
3,4-dihydroxy- α -[(isopropylamino)-methyl]benzyl alcohol hydrochloride		15
3,4-diacetoxy- α -[(isopropylamino)-methyl]benzyl alcohol hydrochloride	30	20
3,4-dipropionyloxy- α -[(isopropylamino)-methyl]benzyl alcohol hydrochloride	34	35
3,4-diisobutyroxy- α -[(isopropylamino)-methyl]benzyl alcohol hydrochloride	50	35
3,4-dipivaloxy- α -[(isopropylamino)-methyl]benzyl alcohol hydrochloride	700	300

EX1008 at Table 2 (annotated).

Only in Table 3 is the “iso—” absent. That is an obvious typo that a POSITA would have been able to correct. As the Federal Circuit has explained, “where a prior art reference includes an obvious error of a typographical or similar nature that

would be apparent to one of ordinary skill in the art who would mentally disregard the errant information as a misprint or mentally substitute it for the correct information, the errant information cannot be said to disclose subject matter.” *LG Elecs. Inc. v. Immervision, Inc.*, 39 F.4th 1364, 1372 (Fed. Cir. 2022) (citing *In re Yale*, 434 F.2d 666, 669 (C.C.P.A. 1970)).

Accordingly, without Truelove 1, Ground 2 identifies no prior art compound that meets the structural limitations of the compounds claimed by independent claims 1 and 2. Instead, Petitioner relies on conclusory assertions to import properties from isoproterenol, a different molecule altogether. Therefore, Ground 2 fails on the merits.

2. Even If Petitioner Relies on Truelove 1 In Ground 2, None Of The References Relied Upon In Ground 2 Read On Any Of The Claimed Compounds Of Claim 1.

As discussed above in Section VII above, Truelove 1 fails to disclose any of the compounds of claim 1. And, as discussed above, none of Truelove 3, Ashraf, or the Almoazen Paper cure that deficiency. Because Petitioner identifies no prior-art compound meeting every structural limitation of claim 1, Ground 2, like Ground 1 fails on the merits. *See Univ. of Strathclyde*, 17 F.4th at 160 (quoting *PAR Pharm.*, 773 F.3d at 1194).

B. Ground 3's "Kitchen Sink" Combination Fails: Petitioner's Seven-Reference Theory Has No Merits

Ground 3 fails on the merits. Petitioner's Ground 3 stitches together seven separate references—Truelove 1, Truelove 3, Ashraf, Almoazen Paper, Fuchs, Schobel, and Florence—but offers barely 2 pages (and a claim chart) of analysis, failing to properly explain how and why a POSITA would have combined them with a reasonable expectation of success. *See* Pet. at 83-85, 104-109.

In an IPR petition, the petitioner "must include ... a detailed explanation of the significance of the evidence," 37 C.F.R. § 42.22(a)(2), and "cannot be met simply by throwing mountains of evidence at the Board without explanation or identification of the relevant portions," *Parus*, 70 F.4th at 1371. As the Federal Circuit has held, a "brief must make all arguments accessible to the judges, rather than ask them to play archaeologist with the record." *Id.* at 1372. Yet Petitioner improperly asks the Board to do that here. Its seven-way combination is a scattershot collage of cumulative disclosures, supported only by conclusory assertions. On this record, Petitioner has not shown a reasonable likelihood of prevailing on any claim for Ground 3.

1. Petitioner Identifies No Reference Disclosing Any Compounds of Claim 1

In Ground 3, Petitioner relies on Truelove 1 and Truelove 3 as allegedly disclosing "specific compounds" of claim 1. Pet. at 66–68. As already discussed in

Sections VII and VIII.A.1 above, neither of those references teach any of the compounds recited in claim 1. And importantly, as previously discussed, Petitioner never argues that Truelove 1 or Truelove 3 render obvious any of the compounds of claim 1. The Board cannot supply an obviousness theory Petitioner did not raise, and unpatentability fails where no prior art discloses all claim limitations. *Magnum Oil*, 829 F.3d at 1381 (Fed. Cir. 2016).

IX. CONCLUSION

For the reasons discussed above, Patent Owner respectfully requests that the Board denies institution of this *inter partes* review proceeding.

Dated: September 18, 2025

Respectfully submitted,

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*Lead Counsel for Patent Owner,
Iono Pharma, LLC*

CERTIFICATION UNDER 37 C.F.R. § 42.24(d)

I hereby certify that this Patent Owner's Preliminary Response for *Inter Partes* Review of U.S. Patent No. 11,021,437 has, excluding the portions exempted under 37 C.F.R. § 42.24(a), 8,711 words as counted by the word-processing system used to prepare this document, in compliance with 37 C.F.R. § 42.24(d).

Dated: September 18, 2025

Respectfully submitted,

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Lead Counsel for Patent Owner,

Iono Pharma, LLC

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 Patent Owner's Preliminary Response and corresponding exhibits were served on counsel of record for the Petitioner by filing this document through P-TACTS and by sending this document via electronic mail to the following addresses:

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