

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 AUTHORIZED RESPONSE
TO DIRECTOR REVIEW REQUEST

Patent Owner's Authorized Response to Director Review Request

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35 U.S.C. § 135 1

35 U.S.C. § 314(a) 1

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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

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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 <i>Journal of Allergy and Clinical Immunology</i> 837 (2004)
2027	Keith J. Simons and F. Estelle R. Simons, <i>Epinephrine and its use in anaphylaxis: current issues</i> , <i>Current Opinion in Allergy and Clinical Immunology</i> 354 (2010)
2028	Jacqueline A. Pongracic and Jennifer S. Kim, <i>Update on epinephrine for the treatment of anaphylaxis</i> , <i>Current Opinion in Pediatrics</i> 94 (2007)
2029	Phil Lieberman, <i>Use of epinephrine in the treatment of anaphylaxis</i> , <i>Current Opinion in Allergy and Clinical Immunology</i> 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> , <i>Biopharmaceutics & Drug Disposition</i> (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 <i>Pediatrics</i> 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 Drug</i>

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Exhibit No.	DESCRIPTION
	<i>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

Petitioner requests Director Review of the decision discretionarily denying institution (“Decision”) based on 35 U.S.C. §314(a). However, Petitioner’s request is based on an alleged erroneous finding of fact—suggesting that Deputy Director was not able to properly determine the issue date of the ’437 Patent—that is not present in the record, and raises arguments that do not even qualify under Director Review. Even if considered, none of Petitioner’s arguments have any merit. Accordingly, the Director should deny Petitioner’s request for Director Review.

II. APPLICABLE STANDARD FOR DIRECTOR REVIEW

Director Review is not a vehicle for relitigating the record. The United States Patent and Trademark Office (USPTO) guidelines make clear that “[r]equests for Director Review of a Board’s decision on institution under 35 U.S.C. §§ 135, 314, or 324 ... shall be limited to decisions presenting (a) an abuse of discretion, (b) important issues of law or policy, (c) erroneous findings of material fact, or (d) erroneous conclusions of law.” USPTO, *Director Review Process*, § 2.B, available at <https://www.uspto.gov/patents/ptab/decisions/director-review-process>.

III. PETITIONER'S REQUEST FOR DIRECTOR REVIEW SHOULD BE REJECTED

A. Petitioner Intentionally Misreads The Decision Denying Institution In Order To Fabricate An Erroneous Finding of Fact Not Present In The Record

In Petitioner's Request for Director Review ("DR Request"), Petitioner contends that "[t]he Decision erroneously relies on 2018 as the issue date of challenged of U.S. Patent No. 11,021,437, a date seven (7) years prior to the filing of the Petition." DR Request, 1. That is an intentional misreading of the Director's Decision Denying Institution ("Decision") in an attempt to fabricate a factual error that does not exist in the record.

The Decision explicitly states: "Patent Owner informed Petitioner of [1] *the preparation of a provisional application in 2016*, as well as [2] *the publication of the non-provisional PCT patent application* that matured into the challenged patent *in 2018*." Decision, 2 (emphasis added). Petitioner relies on the additional characterization provided by the Director—namely that the published PCT patent application is the same application that "matured into the challenged patent"—to argue that the Director misunderstood the issue date of the challenged patent. Not so. There is simply no evidence in the record to indicate that the Director would have misunderstood the issue date of the challenged patent.

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Patent Owner's Discretionary Denial Request Brief ("DD Brief") clearly stated that "[i]n June 2018, Dr. Almoazen provided Petitioner with a copy of the published 'PCT [application] for Epinephrine prodrug' that matured into the '437 Patent." DD Brief, 5 (alteration in original). Eight pages later, Patent Owner stated—yet again—that “on June 9, 2018, after the PCT application that eventually matured into the '437 Patent had published, Dr. Almoazen informed Dr. Wargacki [then Petitioner's Chief Science Officer] that it published, provided a hyperlink to the published PCT application, and again asked if Petitioner was interested in partnering with him to develop the technology behind the claimed epinephrine prodrugs.” *Id.*, 13 (citing EX2003, 1).

Indeed, as Petitioner admits in its DR Request, the issue date of the '437 Patent is prominently displayed on the first page of EX1001, reproduced below. Petitioner is essentially arguing that Deputy Director Stewart would not have been able to look at the first page of the '437 Patent (EX1001) to determine its correct issue date.

It is abundantly clear that Deputy Director Stewart did **not** consider 2018 to be the issue date of the '437 Patent because she accurately stated that “Patent Owner informed Petitioner of the ... the publication of the non-provisional PCT patent application ... in 2018.” Decision, 2 (citing EX2003, 1). In other words, “in 2018” modifies the date that Patent Owner informed the Petitioner of the publication of the

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PCT application—**not** the '437 Patent's issue date—just as Patent Owner explained in its DD Brief.

Petitioner further argues that “[t]he 2021 issue date of the '437 Patent was less than four (4) years from the filing date of the Petition (May 16, 2025), two (2) years before the six (6) year touchstone for favoring a Patent Owner's settled expectation.” DR Request, 3. Petitioner, however, provides no supporting case law demonstrating how or why there is or even should be a bright line rule that filing an IPR petition within six years of issuance overcomes Patent Owner's settled expectations. Indeed, Deputy Director has denied and explained other exemplary factors that can lead to denial of institution even when the Petition was filed **within** six years of issuance of the challenged patent, undercutting Petitioner's argument. *See Nvidia Corp. v. Neural AI, LLC*, IPR2025-00606, Paper 16, 2-3 (PTAB Jul. 31, 2025) (denying institution based on commercial relationship between the parties despite the fact that the IPR petition was filed 2 years from the reissue date of the challenged patent); *Amgen Inc. v. Bristol-Myers Squibb Co.*, No. IPR2025-00601, Paper 9, 2-3 (PTAB Jul. 24, 2025) (explaining exemplary factors that can create settled expectations for patents in force for even less than six years); *AscentCare Dental Prods., Inc. v. Solmetex, LLC*, IPR2025-01065, Paper 11 (PTAB Oct. 17, 2025) (explaining 35 U.S.C. §325(d) can lead to denial of institution even for patents that were in force less than two years); *MSN Pharm., Inc. v. Breckenridge Pharm., Inc.*, IPR2025-

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01107, Paper 11 (PTAB Oct. 17, 2025) (explaining that even though Petitioner is not a party to the suit, the existence of a parallel litigation can lead to discretionary denial); *Fujirebio Diag., Inc. v. Quanterix Corp.*, IPR2025-01060, Paper 13 (PTAB Oct. 13, 2025) (explaining 35 U.S.C. §325(d) can lead to denial of institution even for patents that were in force only three years); *Samsung Elecs. Co., Ltd. v. Telcom Ventures LLC*, IPR2025-00978, Paper 11 (PTAB Oct. 10, 2025) (explaining early district court trial can lead to denial of institution even for patents that were in force only one year).

The Decision denying institution was “based on a holistic assessment of all of the evidence and arguments presented,” (Decision, 2-3), and the 2016–2018 chronology highlighted by the Deputy Director in her Decision was merely part of that holistic assessment.

B. Petitioner's Next Three Arguments Do Not Meet The Director-Review Standard

After intentionally misreading the Decision in an effort to manufacture an “erroneous finding of material fact” that does not exist, Petitioner's next three issues do not even articulate how or why they meet the standard for Director Review. To be clear, they do not. *See* Request, 3-6. Director Review is limited to (a) an abuse of discretion, (b) important issues of law or policy, (c) erroneous findings of material fact, or (d) erroneous conclusions of law.” USPTO, *Director Review Process*, § 2.B,

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available at <https://www.uspto.gov/patents/ptab/decisions/director-review-process>.

None of Petitioner's next three issues fits into any one of those categories. Hence, these issues are moot for this reason alone. But even if considered, none of the arguments warrant overturning the Decision.

1. Patent Owner's Pre-Issuance Notices Were Properly Considered And Support Discretionary Denial

Petitioner argues that Patent Owner's 2016 and 2018 notices "do not counsel in favor of discretionary denial" because "[t]he trigger date for Patent Owner's settled expectations can only reasonably be the date the final claims issue because this is when their validity and patentability are available to be challenged." Request,

3. In support, Petitioner cites to the March 26, 2025 Memorandum on Interim Processes for PTAB Workload Management ("Process Memorandum"), which, according to Petitioner, "clearly indicates that settled expectation is decided based on 'the length of time the claims have been in force.'" *Id.* Petitioner, however, omits the fact that settled expectations are just one of "all relevant considerations" which "may [be] included," and "the length of time the claims have been in force" is merely just one example of the "[s]ettled expectations of the parties." Process Memorandum, 2. As explained above in Section III.A, there is no bright line rule that settled expectations can *only* begin after issuance of the patent. Indeed, the

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Process Memorandum clearly indicates that the Director will weigh “*all* relevant considerations.” *Id.* (emphasis added.)

And consistent with that holistic analysis, the Decision properly weighed the fact that “Petitioner had notice of Patent Owner’s *patent applications* and the resulting patent for several years before filing its Petition.” Decision, 2 (emphasis added.) The Patent’s age alone does not preclude consideration of other equitable circumstances, especially where, as here, Petitioner had repeated notices well before issuance and still declined to seek early review once the claims issued. Decision, 2. Such knowledge-and-diligence factors have repeatedly been found to be pertinent to § 314(a) analysis. *See, e.g., Nvidia*, IPR2025-00606, Paper 16, 2-3 (holding that “[a]lthough the patent originally issued in 2015, the patent reissued in 2023 with different claims from the original patent... Petitioner and the original patent owner ... had a commercial relationship and, in 2017, [patent owner] sent Petitioner a presentation that included ... the original patent,” “Petitioner had actual notice of the challenged patents and Petitioner’s failure to seek early review of the patents favors denial.”); *iRhythm Tech., Inc. v. Welch Allyn, Inc.*, IPR2025-00363, Paper 10, 2–3 (PTAB Jun. 6, 2025) (explaining that “Petitioner’s awareness of Patent Owner’s applications and failure to seek early review of the patents favors denial.”).

Finally, Petitioner asserts that “consideration of the PCT application and its relevance, if any, would have been premature until such amendments were made and

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a patent issued with those amended claims” because “the scope of the PCT application claims was so broad.” Request, 4. But that logic flips everything on its head because *Petitioner* admitted that Petitioner viewed the '437 Patent as “an obstacle” that could “jeopardize the launch of [the AnaphylmTM product]” that it spent tens of millions of dollars actively trying to develop and market. DD Opposition Brief, 3-4. If the claims in the PCT application were “so broad,” it would have caused even *greater* concerns for Petitioner and Petitioner should have been even *more* motivated to monitor the issuance of the claims. Petitioner provides no explanation for why its inaction for four (4) years after the issuance of the '437 Patent “does not favor discretionary denial.” Request, 4. Indeed, it is more logical for the Patent Owner to expect that Petitioner would have attempted to remove all “obstacles” before spending “over \$19 million to conduct the clinical trials needed to demonstrate AnaphylmTM's efficacy ... and approximately \$4.3 million in FDA administrative filing fees associated with the submission of its NDA,” (DD Opposition Brief, 15), when the IPR/PGR filing fees would have been less than \$60,000.

2. The Decision Correctly Considered IDS Citations As Evidence Of Petitioner's Actual Knowledge Of The '437 Patent

Petitioner's suggestion—that IDS citations “should not be a factor” because they merely reflect compliance with Rule 56—ignores how Director used this

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evidence. Request, 5. Those citations merely demonstrated contemporaneous evidence of Petitioner's actual notice of the '437 Patent and its claims during the period when earlier, more appropriate avenues of review were available. *See iRhythm*, IPR2025-00363, Paper 10, 2–3 (explaining that “having cited the then-pending application that issued as the challenged patent in an Information Disclosure Statement Petitioner filed in its own application—settled expectations favor denial of institution.”).

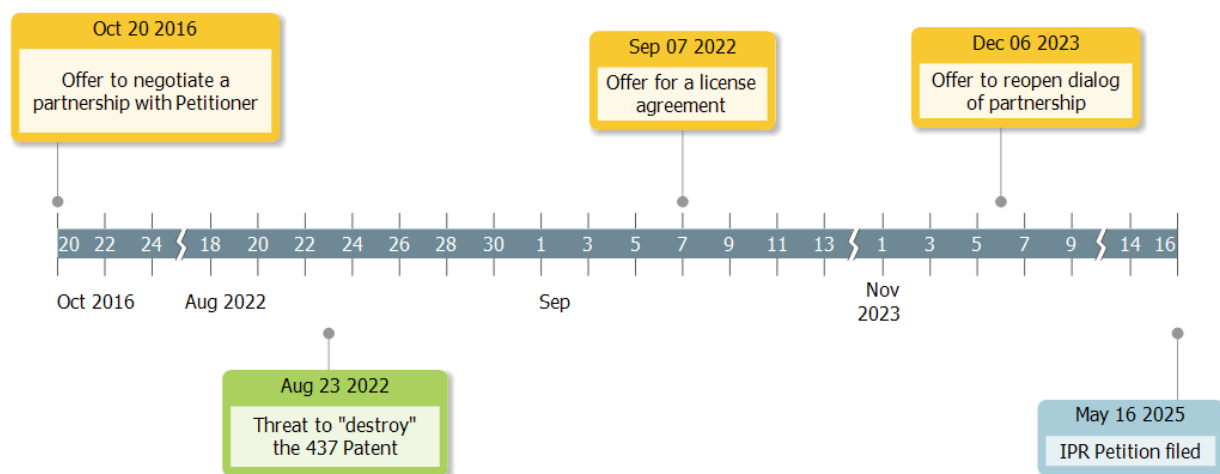
As previously explained in Patent Owner's DD Brief, Petitioner not only knew of the applications that matured into the '437 Patent but also knew of the '437 Patent when it issued in 2021, even citing it in its own applications. DD Brief, 7-15. Despite that knowledge, the Petitioner chose not to file a post-grant review (PGR) within the nine-month window—a proceeding that is “favored” because it occurs “close in time to examination” and “before expectations in the patent rights are strongly settled.” *LifeVac, LLC v. DCSTAR Inc.*, IPR2025-00454, Paper 11, 2 (PTAB Jul. 11, 2025) (“[P]etitions for post-grant review are favored because they must be filed no later than nine months from the grant of the patent (35 U.S.C. § 321(c)), are close in time to examination, and occur before expectations in the patent rights are strongly settled.”); *Therabody Inc. v. Datafeel Inc.*, PGR2025-00026, Paper 10, 2 (PTAB Jul. 17, 2025) (same).

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Other than its mere say so, Petitioner cannot point to any authority why submission of an IDS “should not be a consideration” when weighing the evidence for discretionary denial. Request, 5. Rule 56 does not erase what the IDS citations show. They are evidence that Petitioner had actual knowledge of the '437 Patent since at least 2021, 2023, and 2024, yet chose not to seek early review.

3. Petitioner's Attempts To Purchase The '437 Patent Favor Discretionary Denial

Petitioner argues that its attempt to purchase the '437 Patent should not favor denial because buying the patent could have conserved Board resources. Request, 5. Even if that were true, Petitioner ignores the fact that Board resources would also have been conserved had Petitioner agreed to either form a “partnership” or take a license to the '437 Patent. As summarized below, such offers from the Patent Owner began as early as 2016 and continued to 2023—only to be repeatedly rejected by the Petitioner. *See, e.g.*, DD Brief, 11-15.



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For example, between October 20-22, 2016, Petitioner rejected Dr. Almoazen attempts to “negotiate [a] partnership and employment agreements’ rather than “abandon [his] research ideas.” DD Brief, 12-13 (*citing* EX2020, ¶ 23). On September 7, 2022, Dr. Almoazen indicated “he would ‘be interested in a licensing agreement,’” but Petitioner “failed to respond.” DD Brief, 15. On December 6, 2023, Patent Owner “reached out to Petitioner to ‘reopen the dialog’ of a partnership ... [but] [a]gain, Petitioner failed to respond.” *Id.*

In between those repeated offers for a partnership and/or license was Petitioner's initial threat on August 23, 2022, to “destroy” the '437 Patent if Dr. Almoazen did not sell it to the Petitioner. DD Brief, 14. Yet Petitioner waited close to *three years* after that threat before filing its IPR Petition on May 16, 2025. At a minimum, those three years of inaction created a strong, settled expectation for the Patent Owner that the '437 Patent would not be challenged. Indeed, Deputy Director Stewart fully considered all those relevant facts when making her “holistic” determination to grant discretionary denial. Decision, 2 (“Although certain arguments are highlighted above, the determination to exercise discretion to deny institution is based on a holistic assessment of all of the evidence and arguments presented.”).

C. Petitioner's Arguments Under § 325(d) Also Fail

Petitioner devotes more than half of its Director Review Request to supposed “material factual errors made during prosecution [that] were [allegedly] fundamental to the improper issuance of the ’437 Patent. Request, 6-12. But that issue is governed by 35 U.S.C. §325(d). Indeed, both parties briefed that issue accordingly. *See* DD Brief, 35-65; DD Opposition Brief, 35-49. In contrast, the Deputy Director made clear that “the Petition is denied under *35 U.S.C. § 314(a)*”—not under 35 U.S.C. §325(d). Decision, 3. Hence, seeking Director Review based on any alleged “material factual errors made during prosecution” is improper, irrelevant, and moot.

But even if these arguments had any relevance to Director Review (they do not), they are meritless. Specifically, Petitioner argues that (1) that the Examiner treated Figure 9 and Table 5 (epinephrine-film in simulated saliva) as evidence of a prodrug's plasma half-life, and (2) that the Examiner “accepted without analysis” Patent Owner's discussion of Truelove 1 while “ignoring” purported 1–6-minute half-life data. Request 7, 11.

As to the half-life limitation, Petitioner itself concedes that Truelove 1 “reports that three diester epinephrine compounds have a half-life range from 1-6 minutes as recited in the challenged claims.” Pet., 25; Request, 12. That concession undercuts its attempt to elevate Figure 9 and Table 5. As explained in the Patent Owner's Preliminary Response (“POPR”), the ’437 Patent's provisional application

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incorporated Truelove 1 by reference. *See* POPR, 30 (citing EX1013, 22). And it is well established that “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)). Because the provisional application incorporated by reference Truelove 1, which Petitioner admits discloses the 1–6 minute half-life for diester epinephrine prodrugs, Pet., 25, the provisional application provides written description support for the limitation “half-life $t_{1/2}$ range from 1-6 minutes.” Any alleged misreading of Figure 9/Table 5 is therefore immaterial and cannot establish a prosecution error. *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019- 01469, Paper 6, 8 (PTAB Feb. 13, 2020) (precedential).

Nor is there merit to Petitioner's claim that the Examiner “ignored” Truelove 1's shorter half-life data by focusing on compound 7D's 30-minute value. Request, 11-12. Applicant highlighted compounds 7A–7C in not only the specification, but also during prosecution, and explained their relevance to sublingual/buccal delivery and plasma hydrolysis. *See* EX1001, 2:5-38 (“Anwar A. Hussain and James B. Truelove were granted patents related to the synthesis of novel esters of [(methylamino)methyl] benzyl alcohol which is epinephrine. (see structures 7A, 7B, 7C, 7D).”); EX2012, 357; EX1001, 6:42-57 (“Now referring to FIG. 7, the

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compounds of the invention as shown in U.S. Pat. Nos. 3,809,714 [Truelove 1] ... hereby incorporated by reference. Representative molecules include: 7A ... 7B ... 7C ... 7D"). Those molecules—7A, 7B, 7C, and 7D—were presented to the Office in Figure 7 of the '437 Patent, confirming that the shorter half-life species were front-and-center, not obscured.

If anything, Petitioner's primary reliance on Truelove 1 in the Petition—a reference that was already extensively considered during prosecution—further weighs in favor of discretionary denial. Truelove 1 was before the Office and was considered without material error; § 325(d) therefore independently warrants denial of institution. *See Advanced Bionics*, IPR2019-01469, Paper 6, 7 (precedential); *see also Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8, 17-18 (PTAB Dec. 15, 2017) (precedential); DD Brief, 37-50.

IV. CONCLUSION

For at least the reasons provided above, Patent Owner requests that the Director denies Petitioner's request for Director Review.

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Dated: November 4, 2025

Respectfully submitted,

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), the undersigned certifies that on November 4, 2025, a complete copy of the foregoing Patent Owner's Authorized Response to Director Review Request was 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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