

Filed on behalf of Intas Pharmaceuticals Ltd.

By: Alejandro Menchaca
Ben J. Mahon
McAndrews, Held & Malloy, Ltd.
500 West Madison Street
Chicago, Illinois 60661
Tel.: (312) 775-8000
Fax: (312) 775-8100
Email: amenchaca@mcandrews-ip.com

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

INTAS PHARMACEUTICALS LTD.,
Petitioner

v.

ATOSSA THERAPEUTICS, INC.,
Patent Owner

Case IPR2025-00799
Patent No. 11,261,151

**PETITIONER'S RESPONSE TO PATENT OWNER'S REQUEST FOR
DISCRETIONARY DENIAL OF INSTITUTION**

TABLE OF CONTENTS

I.	Introduction.....	1
II.	Discretionary denial is unwarranted.....	4
A.	There are no compelling health interests supporting discretionary denial	6
B.	Patent Owner’s incredibly narrow covenant not to sue does not favor discretionary denial.....	9
C.	Patent Owner does not have settled expectations justifying discretionary denial	11
D.	Section 325(d) does not favor discretionary denial	14
E.	The merits are exceptionally strong	15
F.	The Petition’s use of expert testimony does not favor discretionary denial	23
G.	Discretionary denial would eliminate any estoppel effects from the 334 patent which would not apply in district court.....	25
III.	Conclusion	26

TABLE OF AUTHORITIES

Cases

<i>Advanced Micro Devices, Inc. et al. v. Concurrent Ventures, LLC et al.</i> , IPR2025-00479, Paper 10 (July 10, 2025)	12
<i>Atrium Med. Corp. v. Bard Peripheral Vascular, Inc.</i> , IPR2021-01197, Paper 11 (Jan. 10, 2022)	19
<i>Azurity Pharms., Inc. v. Exelixis Inc.</i> , IPR2025-00210, Paper 11 (June 4, 2025)	26
<i>Cambridge Indus. USA, Inc. v. Applied Optoelectronics, Inc.</i> , IPR2025-00434, Paper 11 (Jun. 26, 2025)	13
<i>Contrast iRhythm Techs., Inc. v. Welch Allyn, Inc.</i> , IPR2025-00363, Paper 10 (June 6, 2025)	13
<i>cxLoyalty, Inc. v. Maritz Holdings Inc.</i> , 986 F.3d 1367 (Fed. Cir. 2021)	19
<i>Dabico Airport Sols., Inc. v. AXA Power ApS</i> , IPR2025-00408, Paper 21 (June 18, 2025)	14
<i>Eunsung Global Corp. v. Hydrafacial LLC</i> , IPR2025-00453, Paper 14 (July 10, 2025)	13
<i>Glaxo Inc. v. Novopharm Ltd.</i> , 52 F.3d 1043 (Fed. Cir. 1995)	23
<i>GoFire, Inc. v. Canopy Growth Corp.</i> , PGR2020-00044, Paper 8 (Oct. 9, 2020)	16
<i>Intas Pharms. Ltd. v. Atossa Therapeutics, Inc.</i> , PGR2023-00043, Paper 37 (Jan. 29, 2025)	10, 28
<i>OpenSky Industries, LLC v. VLSI Technology LLC</i> , IPR2021-01064, Paper 102 (Oct. 4, 2022)	11
<i>ParkerVision, Inc. v. Qualcomm Inc.</i> , 116 F.4th 1345 (Fed. Cir. 2024)	29
<i>Patent Quality Assurance, LLC, et al. v. VLSI Tech. LLC</i> , IPR2021-01229, Paper 102 (Dec. 22, 2022)	12
<i>Pfizer, Inc. v. Chugai Pharm. Co.</i> , IPR2017-01357, Paper 56 (Nov. 28, 2018)	24, 25

Response to Patent Owner’s Request for Discretionary Denial

<i>SNF S.A. v. Chevron U.S.A., Inc.</i> , IPR2022-01534, Paper 46 (Apr. 18, 2024).....	24, 25
<i>Vibrant Media, Inc. v. Gen. Elec. Co.</i> , IPR2013-00170, Paper 56 (June 26, 2014).....	19
<i>Xerox Corp. v. Bytemark, Inc.</i> , IPR2022-00624, Paper 9 (Aug. 24, 2022)	26

Statutes

21 U.S.C. § 355(j)(5)(B)(iii)	6
35 U.S.C. § 311(a)	5

Other Authorities

Memorandum for Interim Processes for PTAB Workload Management.....	4
Zirpoli, C.T. and Hickey, K.J., <i>The Patent Trial and Appeal Board and Inter Partes Review</i> , CONGRESSIONAL RESEARCH SERVICE R48016 (May 28, 2024).....	5

PETITIONER'S EXHIBIT LIST

EX.	DESCRIPTION
1001	USPN 11,261,151
1002	File history of USPN 11,261,151
1003	WO 2017/070651 ("Liu")
1004	USPN 9,333,190 ("Ahmad")
1005	Fauq, A.H., et al., <i>A convenient synthesis of (Z)-4-hydroxy-N-desmethyltamoxifen (endoxifen)</i> , 20 BIOORGANIC MED. CHEM. LETT. 3036-3038 (2010) ("Fauq")
1006	Ahmad, A. et al., <i>Endoxifen, a New Cornerstone of Breast Cancer Therapy: Demonstration of Safety, Tolerability and Systemic Bioavailability in Healthy Human Subjects</i> , 88(6) CLIN. PHARMACOLOGY & THERAPEUTICS 814-817 (2010) ("Ahmad 2010")
1007	Ahmad, A. et al., <i>Endoxifen for breast cancer: Multiple-dose, dose-escalation study characterizing pharmacokinetics and safety in metastatic breast cancer patients</i> , ASCO MEETING LIBRARY, presented June 4, 2012 ("Ahmad 2012")
1008	Cole, E., et al., <i>Enteric coated HPMC capsules designed to achieve intestinal targeting</i> , 231 INTL J. PHARMACEUTICS 83-95 (2002) ("Cole")
1009	Fan, J. et al., <i>Pharmacokinetics</i> , 81 BIOCHEM. PHARMACOLOGY 93-120 (2014) ("Fan")
1010	Urso, R. et al., <i>A short introduction to pharmacokinetics</i> , 6 EUR. REV. FOR MED. & PHARMACOLOGICAL SCIS., 33-44 (2002) ("Urso")
1011	Bunaciu, A. et al., <i>X-ray Diffraction: Instrumentation and Applications</i> , 45 CRITICAL REVIEWS IN ANALYTICAL CHEM. 289-99 (May 21, 2015) ("Bunaciu")
1012	Excerpts of HANDBOOK OF PHARMACEUTICAL EXCIPIENTS FIFTH EDITION (Rowe, R., Sheskey, J. & Owen, S., eds., 2006) (The "HPE")
1013	Stegemann, S., <i>Hard gelatin capsules today – and tomorrow</i> , CAPSUGEL LIBRARY (2002) ("Stegemann")

Response to Patent Owner’s Request for Discretionary Denial

EX.	DESCRIPTION
1014	Benameur, H., Capsule Technology, Enteric Capsule Drug Delivery Technology – Achieving Protection Without Coating, 15(5) DRUG DEV. & DELIVERY 34-37 (2015) (“Benameur”)
1015	Prescribing Information for Zonalta
1016	Beasley, D. et al, <i>The Evolution of Stomach Acidity and Its Relevance to the Human Microbiome</i> , 10(7) PLoS ONE 1-12 (2015) (“Beasley”)
1017	Evans, D. et al, <i>Measurement of gastrointestinal pH profiles in normal ambulant human subjects</i> , 29 GUT 1035-41 (1988) (“Evans”)
1018	Goel, R. et al, <i>Clinical Significance of Half Life of Drugs</i> , 4(1) INT’L J. OF PHARMACOTHERAPY 6-7 (2014) (“Goel”)
1019	<i>Endoxifen</i> , PUB CHEM: COMPOUND SUMMARY (2024)
1020	Krahn, F. et al, <i>Effect of type and extent of crystalline order on chemical and physical stability of carbamazepine</i> , 53(1) INT’L J. OF PHARMACEUTICS 25-34 (1989) (“Krahn”)
1021	A FOCUS ON CRYSTALLOGRAPHY (FIZ KARLSRUHE 2005)
1022	Milroy, L. et al., <i>A multi-gram-scale stereoselective synthesis of Z-endoxifen</i> , 28 BIOORGANIC MED. CHEM. LETT. 1352-1356 (2018) (“Milroy”)
1023	Supporting information to Milroy, L. et al., <i>A multi-gram-scale stereoselective synthesis of Z-endoxifen</i> , 28 BIOORGANIC MED. CHEM. LETT. 1352-1356 (2018)
1024	Ali et al., <i>Endoxifen is a new potent inhibitor of PKC: A potential therapeutic agent for bipolar disorder</i> , 20 BIOORGANIC & MEDICINAL CHEM. LETT. 2665-2667 (2010) (“Ali”)
1025	Supporting information to Fauq, A.H., et al., <i>A convenient synthesis of (Z)-4-hydroxy-N-desmethyltamoxifen (endoxifen)</i> , 20 BIOORGANIC MED. CHEM. LETT. 3036-3038 (2010)
1026	Elkins et al., <i>Characterization of the isomeric configuration and impurities of (Z)-endoxifen by 2D NMR, high resolution LCMS, and quantitative HPLC analysis</i> , 88 J. PHARMACEUTICAL AND BIOMEDICAL ANALYSIS 174-179 (2014) (“Elkins”)

Response to Patent Owner’s Request for Discretionary Denial

EX.	DESCRIPTION
1027	SHARGEL, LEON & YU, ANDREW, APPLIED BIOPHARMACEUTICS & PHARMACOKINETICS (7th ed. 2016) (“Shargel”)
1028	Wieckhusen, D., <i>The Development of API Manufacturing Processes – Targets and Strategies</i> , 60(9) CHIMIA INT’L J. FOR CHEM. 598-604 (2006) (“Wieckhusen”)
1029	COULSON & RICHARDSON, COULSON & RICHARDSON’S CHEMICAL ENGINEERING (5th ed. 2002) (“Richardson”)
1030	ALLEN & ANSEL, ANSEL’S PHARMACEUTICAL DOSAGE FORMS & DRUG DELIVERY SYSTEMS (10th ed. 2013) (“Ansel”)
1031	USP 941
1032	Expert Declaration of Jason McConville, Ph.D. (“McConville”)
1033	Expert Declaration of Ron Bihovsky, Ph.D. (“Bihovsky”)
1034	Expert Declaration of Steven Miller, Ph.D. (“Miller”)
1035	Chen P. et al, <i>Orally administered endoxifen inhibits tumor growth in melanoma-bearing mice</i> , 23:3 CELLULAR & MOLECULAR BIOLOGY LETTERS (2018)
1036	Goetz MP et al, <i>First-in-Human Phase I Study of the Tamoxifen Metabolite Z-Endoxifen in Women With Endocrine-Refractory Metastatic Breast Cancer</i> , 35(30) J CLIN ONCOLOGY 3391 (2017)
1037	Takebe N et al, <i>Phase I study of Z-endoxifen in patients with advanced gynecologic, desmoid, and hormone receptor-positive solid tumors</i> , 12(4) ONCOTARGET 267-277 (2021)

I. INTRODUCTION

Patent Owner cannot credibly dispute the Petition establishes far more than a reasonable likelihood that Petitioner would prevail with respect to at least one of the challenged claims. Patent Owner cannot dispute that endoxifen was a well-known compound, and multiple references taught synthesizing it, including obtaining highly pure forms of the (Z)-enantiomer. Nor can it dispute that the art taught the use of endoxifen (including the (Z)-isomer) for the treatment of breast cancer—including references reflecting the work of Petitioner Intas Pharmaceuticals and a development partner Jina Pharmaceuticals. In fact, the *only* claimed feature Patent Owner argues is novel over the prior art was the Form I XRPD pattern. But Petitioner's testing demonstrates Liu's highly pure (Z)-endoxifen *is in fact* Form I. In other words, Patent Owner's claims would read on the product made by Liu—a classic case of anticipation.

Petitioner brings this Petition for the exact reasons Congress envisioned—an early challenge to an improvidently issued patent to resolve patentability long before any actual district court litigation. That there is no current litigation favors *institution*, not denial, as Petitioner cannot bring this challenge in district court, and absent this IPR the 151 patent will continue to threaten other parties from bringing endoxifen breast cancer treatments to market.

Response to Patent Owner's Request for Discretionary Denial

Patent Owner first relies on alleged health interests to justify maintenance of its unpatentable claims—arguing the 151 patent is necessary for Patent Owner to bring endoxifen to patients. But Patent Owner does not need the 151 patent to develop endoxifen and attempt to bring it to market—the 151 patent does not vest in Patent Owner the right to make and sell, but only the right to *exclude* others from using or selling endoxifen as claimed in the 151 patent, including those such as Petitioner who had already begun investigating endoxifen well before Patent Owner filed its patent applications. Patent Owner has disclosed nothing novel to the public to justify a patent monopoly on endoxifen or its use in treating breast cancer. Indeed, permitting Patent Owner's 151 patent to avoid challenge would undermine public health concerns by preventing others from bringing to market therapies based on the long-known endoxifen molecule including by entitling Patent Owner to an automatic 30-month stay.

Patent Owner then seeks to avoid a patent challenge by offering an extremely narrow covenant not to sue. In fact, the covenant not to sue is so narrow it covenants only not to sue Petitioner for the *unclaimed* salt, for the *unclaimed* treatment of bipolar disorder. But Patent Owner should not be able to dictate what form of endoxifen Petitioner (and the public at large) pursue and for what treatments when the prior art already taught such forms for such uses.

Response to Patent Owner's Request for Discretionary Denial

Patent Owner then speciously argues it has “settled expectations” because its patent has been in force for 3 years and Petitioner first challenged the child 334 patent. But there were clear reasons for challenging the 334 patent first, including that the Petition to challenge that patent did not require Petitioner to carry out the synthesis of Liu and perform XRPD analysis because that patent contained no XRPD limitations. Petitioner gave Patent Owner no indication that it would challenge “only” the 334 patent and did not reasonably create any settled expectations.

Patent Owner then turns to Section 325(d), which Petitioner already addressed in the Petition. Patent Owner does not and cannot refute that the Examiner had no way to assess the XRPD crystal form of the highly pure (Z)-endoxifen taught in Liu, and thus the introduction of that evidence provides a strong basis for review of the 151 patent under the *Advanced Bionics* framework.

Patent Owner then addresses the merits, but Patent Owner cannot dispute that the **only** limitation Patent Owner raises is the crystal form limitation, which testing shows is the inherent, natural result of the synthesis taught by Liu. And on that, Patent Owner's only argument is that Petitioner's expert ran the reaction at small scale, necessitating minor adjustments to the synthesis. As Petitioner's expert explained in his declaration, none of these changes affect the final crystal form of the product, which is determined by the final recrystallization condition (taught in full detail by Liu and followed closely by Dr. Bihovsky). Patent Owner introduces

no contrary evidence and asks the Director to credit attorney argument over expert testimony, when the standard for institution is reasonable likelihood. Patent Owner may challenge that evidence with its own evidence during trial, but that is no basis for discretionary denial.

Finally, there is an additional factor here that weighs *against* discretionary denial. The Board has already addressed the child 334 patent and found all challenged claims unpatentable in an unappealed Final Written Decision. Those earlier findings limit what Patent Owner may argue in this proceeding but would not apply in district court where Patent Owner could proceed on claims and arguments the Board has rejected. The Board should institute review of Patent Owner's 151 patent because like the 334 patent claims, the claims here are similarly unpatentable.

II. DISCRETIONARY DENIAL IS UNWARRANTED

The Director's interim order provides that "consistent with the discretionary considerations enumerated in existing Board precedent (including *Fintiv*, *General Plastic*, and *Advanced Bionics*) and the Consolidated Trial Practice Guide (Nov. 2019), the parties are permitted to address all relevant considerations...."¹ While

¹ Memorandum for Interim Processes for PTAB Workload Management at 2–3, available at <https://www.uspto.gov/sites/default/files/documents/InterimProcesses-PTABWorkloadMgmt-20250326.pdf>.

Response to Patent Owner's Request for Discretionary Denial

Patent Owner argues “every relevant factor...demonstrates that discretionary denial is the proper outcome here,” Patent Owner does not even address the *Fintiv* or *General Plastic* factors, conceding that they do not apply.

Indeed, without citing it, Patent Owner turns *Fintiv* on its head, repeatedly emphasizing that because there is no current litigation, Intas has “no legitimate commercial interest” in the IPR. But Congress created IPRs specifically because “[w]hile entities accused of patent infringement have long been able to challenge the validity of the patents asserted against them in court, IPR and PGR allow a party to petition PTAB to hear a challenge to the validity of an already-issued patent in an administrative forum, regardless of whether the petitioner has been sued or threatened with suit for patent infringement.” Zirpoli, C.T. and Hickey, K.J., *The Patent Trial and Appeal Board and Inter Partes Review*, CONGRESSIONAL RESEARCH SERVICE R48016, at *1 (May 28, 2024), available at <https://www.congress.gov/crs-product/R48016>; see also 35 U.S.C. § 311(a) (any “person who is not the owner of a patent may file with the Office a petition to institute an inter partes review of the patent.”). Indeed, Patent Owner’s argument is essentially that its patents should be immune from challenge *until* it asserts them in litigation, undermining the purpose of IPR and *Fintiv*.

That is especially untenable in the context of pharmaceutical patents, where there are significant development and regulatory costs to bring a product to market

Response to Patent Owner's Request for Discretionary Denial

and the filing of a lawsuit alone entitles the patent owner to an *automatic* 30-month stay against generic competition. *See* 21 U.S.C. § 355(j)(5)(B)(iii); *Eli Lilly & Co. v. Teva Pharms. USA, Inc.*, 557 F.3d 1346, 1348 (Fed. Cir. 2009) (“If the patentee does file suit, the FDA may not approve the ANDA until expiration of the patent, resolution of the suit, or thirty months after the patentee’s receipt of notice, whichever is earlier”). Intas (and the public at large) have an especially weighty interest in the removal of unpatentable pharmaceutical claims *prior* to the filing of any lawsuit, allowing other parties to assess whether to invest in bringing a drug to market and to bring competing drugs to market quicker.

Because Intas has provided strong reasons demonstrating the 151 patent is (like the 334 patent) unpatentable, and there is no basis for discretionary denial, the Board should institute.

A. There are no compelling health interests supporting discretionary denial

Patent Owner suggests that the 151 patent is critical to allowing patients to receive endoxifen for the treatment of breast cancer. But what the 151 patent (like all patents) grants is the right to *exclude* others—not the right to practice the alleged

invention.² And here, Patent Owner seeks the right to *exclude* others from bringing endoxifen breast cancer treatments to patients, despite the prior art's extensive teachings of how to make highly pure (Z)-endoxifen, and its use for treating breast cancer. *See generally* Pet.; Exs. 1003-1007; Ex. 1022.

Indeed, as expressed below, Patent Owner seeks to preserve the right to *exclude* Petitioner Intas Pharmaceuticals (as well as Jina Pharmaceuticals)³ from pursuing breast cancer treatments *despite* Intas and Jina's *prior art* work on using endoxifen for such treatment. *See, e.g.*, Ex. 1006 (2010 Intas and Jina paper: "Endoxifen, a New Cornerstone of Breast Cancer Therapy: Demonstration of Safety,

² Moreover, Congress provides for regulatory exclusivity encouraging parties to be the first to bring a drug to market. *See, e.g.*, <https://www.fda.gov/files/drugs/published/Exclusivity-and-Generic-Drugs--What-Does-It-Mean-.pdf>. Thus, Patent Owner has every incentive to bring its drug to market even without patent protection.

³ As shown in Ahmad 2010 (Ex. 1006), Intas and Jina are separate companies each with an interest in developing endoxifen treatments. Intas is the Petitioner and real party in interest and the sole party funding this IPR, though Jina has its own interest in the outcomes. Regardless, adding Jina as a real party in interest has no effect on this IPR as neither Intas nor Jina are barred from pursuing this IPR.

Tolerability, and Systemic Bioavailability in Healthy Human Subjects”); Ex. 1007 (same authors: “Endoxifen for breast cancer: Multiple-dose, dose-escalation study characterizing pharmacokinetics and safety in metastatic breast cancer patients.”).⁴ Patent Owner seeks the ability to exclude others from practicing the prior art (including by an automatic 30-month stay as described above) and bringing treatments to patients. That harms the public health; it does not favor it.

The public health interest favors removing the 151 patent—which is unpatentable as explained in Intas’ petition—not granting Atossa the exclusive right

⁴ Atossa seeks to create the impression that it alone is working on cancer therapies employing endoxifen. Req. at 13 (“The threat posed by Petitioner’s IPR is not just to Patent Owner’s patent rights and clinical development, but to the patients who stand to benefit from a safer, more reliable breast cancer treatment.”). Such an understanding is wrong. Several others, including Intas and Jina Pharmaceuticals, have conducted substantial and independent research and development on endoxifen, including preclinical, clinical, and regulatory work. *See* Exs. 1006, 1007, 1035-1037; *see also e.g.*,

<https://clinicaltrials.gov/study/NCT01273168?term=endoxifen&rank=2>;

<https://clinicaltrials.gov/study/NCT03931928?term=endoxifen&rank=4>.

to market breast cancer treatment even over parties who began such research years before.

B. Patent Owner's incredibly narrow covenant not to sue does not favor discretionary denial

Patent Owner's covenant not to sue is illusory. Patent Owner covenants not to sue Intas or Jina for any "product that incorporates the salt form of (Z)-endoxifen...for the treatment of bipolar disorder" but the 151 patent does not cover the salt form of (Z)-endoxifen or bipolar disorders. Patent Owner's claims (at least under its own construction which the Board adopted in the 334 PGR) do not cover (Z)-endoxifen salts. *See Intas Pharms. Ltd. v. Atossa Therapeutics, Inc.*, PGR2023-00043, Paper 37 ("334 FWD") at *11-12 (Jan. 29, 2025) (construing Formula (III) as depicted as limited to the free base). The 151 patent does not mention or claim bipolar disorder. Thus, Patent Owner's "covenant not to sue" is little more than a covenant not to assert its claims over products and methods that its claims do not cover while reserving the right to sue Petitioner (and others) for any use of the free base and all other uses of the salt.

Patent Owner's arguments hinge on the unproven and unexplained assumption that "Intas's only commercial interest in (Z)-endoxifen appears to be in treating bipolar disorder using a salt form of (Z)-endoxifen." Req. at 14. But that is Petitioner's speculation about Intas's (and others) commercial interest. While Intas (and Jina) are not required to share their highly sensitive "commercial interests,"

Response to Patent Owner's Request for Discretionary Denial

Patent Owner should certainly not be able to dictate what those interests are and avoid IPR by “permitting” Intas and Jina to use *only* a (Z)-endoxifen *salt*, and *only* for bipolar disorder—compounds and uses that are not claimed by the 151 patent. As discussed above, Intas and Jina have already invested in pursuing breast cancer treatment, demonstrating their commercial interest in such treatments.

Further, Patent Owner misrepresents the prior history between the parties in an attempt to suggest that Intas is merely trying to extract payment from Patent Owner by the filing of these proceedings. Intas (and Jina) did not request any compensation from Patent Owner simply to drop these proceedings. Indeed, as Patent Owner acknowledges, Intas offered terms for settlement only “***when Atossa initially reached out about settlement***” to discuss a cross-license. (Req. at 15.) Intas has an entirely proper purpose in seeking to invalidate the 151 patent—the right to prevent Patent Owner from unfairly excluding Intas (and all others) from practicing what was already taught in the prior art—not to extract money from Patent Owner.⁵ *Contrast OpenSky Industries, LLC v. VLSI Technology LLC*, IPR2021-01064, Paper

⁵ Patent Owner also argues that Petitioner has not asserted any patents against Patent Owner yet still seeks a royalty. (Req. at 15.) Neither Intas nor Jina have asserted any patents because Patent Owner does not sell a product, and development for FDA approval is protected under 35 U.S.C. §271(e)(1).

Response to Patent Owner's Request for Discretionary Denial

102, at *1, *3 (Oct. 4, 2022) (recognizing “OpenSky’s behavior in this proceeding is entirely distinguishable from conventional settlement negotiations that take place in an adversarial proceeding” where “OpenSky’s only apparent business activity is the filing of two IPR petitions against VLSI” and its “conduct made clear that OpenSky was using the IPR process to extract payment from either Intel or VLSI without meaningfully pursuing unpatentability grounds” which “differs from typical settlement negotiations between adversaries during AIA proceedings, in which parties may offer payment or other consideration in return for settlement of the dispute”); *Patent Quality Assurance, LLC, et al. v. VLSI Tech. LLC*, IPR2021-01229, Paper 102 (Dec. 22, 2022) (same).

C. Patent Owner does not have settled expectations justifying discretionary denial

Patent owner then argues that the Petition comes too late. But Patent Owner has no basis for asserting it had “settled expectations” that Intas would not challenge the 151 patent, which issued in 2022. *See Advanced Micro Devices, Inc. et al. v. Concurrent Ventures, LLC et al.*, IPR2025-00479, Paper 10, at *2 (July 10, 2025) (“the challenged patent issued in 2021, and Patent Owner has not developed strong settled expectations that favor discretionary denial.”); *Eunsung Global Corp. v. Hydrafacial LLC*, IPR2025-00453, Paper 14, at *2 (July 10, 2025) (for a patent issued in 2022, “Patent Owner has not developed strong settled expectations that favor discretionary denial”); *Cambridge Indus. USA, Inc. v. Applied*

Response to Patent Owner's Request for Discretionary Denial

Optoelectronics, Inc., IPR2025-00434, Paper 11, at *2-3 (Jun. 26, 2025) (“most of the challenged patents have not been in force for a significant period of time (issued in 2020, 2019, and 2019), and, accordingly, Patent Owner has not developed strong settled expectations that favor discretionary denial as to at least those patents.”).

First, Intas has hardly “delayed” in bringing the 151 petition, which was issued just over three years ago. *Contrast iRhythm Techs., Inc. v. Welch Allyn, Inc.*, IPR2025-00363, Paper 10, at *3 (June 6, 2025) (12 years after issuance); *Dabico Airport Sols., Inc. v. AXA Power ApS*, IPR2025-00408, Paper 21, at *2-3 (June 18, 2025) (8 years after issuance).

Second, Intas’ decision to first challenge the 334 child patent is easily explained. As Patent Owner notes, the 334 patent does not contain the Form I/XRPD limitations and thus did not require synthesis and XRPD testing to file the Petition. *See* PGR2023-00043, Paper 1.⁶ It made logical sense to file the 334 petition while Intas was performing laboratory work to confirm its suspicions that the “Form I” and XRPD pattern claimed was simply the XRPD pattern of (Z)-endoxifen created in the prior art. Nor did Intas ever signal or give any indication to Patent Owner that it

⁶ Petitioner did submit laboratory experiments related to Liu and carried out by Dr. Bihovsky *on reply* on July 16, 2024 (Ex 2011), 9 months after filing the 334 petition to respond to Petitioner’s argument that the prior art was not enabled.

Response to Patent Owner's Request for Discretionary Denial

would not challenge the 151 patent. Indeed, Intas even voluntarily produced its expert's lab notebooks referencing XRPD testing, giving Patent Owner every indication that Intas was in the process of preparing a challenge to the 151 patent. *See* PGR2023-00043, Ex. 2029 ¶ 26 (Patent Owner's expert stating "I further note that in several instances, Dr. Bihovsky's laboratory notebook referenced X-ray powder diffraction (XRPD) and identified the product as 'Form I' or 'not form I'").

Moreover, by the time Intas was ready to file its petition challenging the 151 patent, the child patent number 12,071,391 had issued on August 27, 2024. Thus, Intas prepared both petitions and filed them simultaneously within the 9-month window to file a PGR against the 391 patent.⁷

⁷ In PGR2025-00043 related to patent no. 12,071,391, Patent Owner does not raise the issue of settled expectations. *See* PGR2025-00043, Paper 8. The claims at issue in PGR2025-00043 are similarly directed to compositions of (Z)-endoxifen.

Petitioner submits that any consideration to Patent Owner's assertion of "settled expectations" here should be diminished because of the common subject matter at issue in PGR2025-00043 where Patent Owner concedes no "settled expectations." Petitioner expects that should both the instant proceeding and PGR2025-00043 be instituted, they will proceed together and result in a common hearing.

In short, Intas has timely and expeditiously filed challenges to Patent Owner's patents, and any alleged "settled expectations" are unfounded. Patent Owner has been aware since at least March 2023, when Intas filed the 334 petition, that Intas intended to challenge Patent Owner's (Z)-endoxifen patents and cannot credibly claim settled expectations in unpatentable subject matter.

D. Section 325(d) does not favor discretionary denial

As Intas explained in its Petition, section 325(d) does not favor discretionary denial here, where it is undisputed that the Examiner did not have the ability to determine whether the (Z)-endoxifen taught by Liu exhibited the claimed Form I XRPD pattern. *See* Pet. 21-23. Further, as explained the Petition provided testing demonstrating that when the synthesis of Liu is performed, the resulting (Z)-endoxifen is Form I—not merely unsupported attorney argument assuming a missing limitation. *See* Pet. at *e.g.*, 25-30. *Contrast GoFire, Inc. v. Canopy Growth Corp.*, PGR2020-00044, Paper 8, at *14 (Oct. 9, 2020) (party provided only attorney argument for missing claim limitation).

At bottom, Patent Owner only challenges whether Petitioner has shown that Liu's synthesis results in Form I (Z)-endoxifen—an issue that should be resolved during the trial phase because the evidence provided by Patent Owner was indisputably never considered by the examiner.

E. The merits are exceptionally strong

Patent Owner does not dispute that the *only* alleged novelty of the 151 claims over Liu is the XRPD pattern recited as Form I.⁸ And despite Patent Owner's rhetoric that Liu "fails" to show the claimed Form I, that is simply because Liu does not perform XRPD testing of its resulting (Z)-endoxifen. That is hardly surprising, there is nothing particularly important or novel about an XRPD pattern—it is simply a

⁸ As noted above, Patent Owner cannot credibly dispute the Petition establishes a classic case of anticipation and its current Request for Discretionary Denial admits as much when it argues that the inventive contribution is not the (Z)-Endoxifen or the purity, but instead the method of making the (Z)-Endoxifen. Req. at 5: "The inventors of the '151 Patent developed a novel synthesis process that avoids the inefficiencies and instabilities of prior methods, yielding a crystalized form of (Z)-endoxifen (at least 90% by weight) with superior stability and commercial-scale feasibility." The 151 patent does not claim the alleged novel synthesis process, but instead compositions including the known (Z)-endoxifen and methods of using those compositions. Notably, as Patent Owner admits, it *cancelled* the only synthesis claim because it was rejected over Liu. Req. at 20 ("Liu was explicitly considered during examination and was used as a basis in rejecting then-pending, later-cancelled claim 62 (a process claim for manufacturing (Z)-endoxifen) as obvious over Liu.").

Response to Patent Owner's Request for Discretionary Denial

fingerprint of a particular crystal form, and Patent Owner does not even argue there are benefits to that crystal form over any others that may exist for (Z)-endoxifen.

Moreover, Patent Owner brazenly misrepresents Dr. Bihovsky's work. While true Dr. Bihovsky ran Liu at a laboratory scale necessitating minor modifications to the *synthesis* portion of Liu, as the Board has already found Dr. Bihovsky "modified the methods of Liu in a way that was within the level of ordinary skill in the art." 334 FWD at 28. Patent Owner provides no authority stating that to prove anticipation a party must run the exact method taught by the prior art at commercial scale. But Patent Owner fails to put forward any plausible reason, let alone evidence, that the minor adjustments affected the outcome of Dr. Bihovsky's testing.

As Dr. Bihovsky explained, none of the minor modifications he made to accommodate a smaller scale *synthesis* reaction occurred during the *recrystallization* phase. As Dr. Bihovsky explained, "the polymorphic form that a crystal adopts is driven by the final crystallization of the material" which Dr. Bihovsky followed studiously (and thus any minor adjustments to make Liu at smaller scale had no impact on the XRPD results), demonstrating that Liu necessarily and inherently led to Form I (Z)-endoxifen. Ex. 1033 ¶ 37.

Dr. Bihovsky's statement is factual testimony based on his extensive experience—it is not simply an unsupported legal conclusion provided without explanation. *See, e.g., Vibrant Media, Inc. v. Gen. Elec. Co.*, IPR2013-00170, Paper

Response to Patent Owner's Request for Discretionary Denial

56, at *34 (June 26, 2014) (“we disagree with GE that an expert could not resort to common sense or common knowledge of one with ordinary skill in the art”); *contrast exLoyalty, Inc. v. Maritz Holdings Inc.*, 986 F.3d 1367, 1378 (Fed. Cir. 2021) (“Although Maritz points to expert testimony, that testimony merely labels, in conclusory fashion, the invention as a technological solution to a technological problem.”); *Atrium Med. Corp. v. Bard Peripheral Vascular, Inc.*, IPR2021-01197, Paper 11, at *16 n.5 (Jan. 10, 2022) (“Petitioner’s witness relies on Melsky’s disclosure that its port can withstand pressures of 200 psi or more as inherently disclosing a power injectable port; however, the witness merely concludes this without citation to supporting evidence.”).

Nor did Dr. Bihovsky “repeatedly fail[] to yield the claimed Form I” following Liu, as Patent Owner suggests. Req. at 29. Rather, as Dr. Bihovsky can explain during the merits portion of trial, Patent Owner refers to *unrelated* testing of *different samples* not following Liu’s examples buried in Dr. Bihovsky’s notebook. For example, Patent Owner refers to Dr. Bihovsky’s page 89 reference to sample 15-30-1P with the “clear conclusion: ‘**XRPD-Not Form I.**” Req. at 31. But that is hardly surprising, as this sample is *E*-endoxifen, as clearly noted:

D14 ppt → 1.13mg white solid
NMR (RMS) 100% E. XRPD - Not Form I 15-30-1P

Response to Patent Owner's Request for Discretionary Denial

Ex. 1033 at p.89. Further, Patent Owner refers to page 91 of Dr. Bihovsky's report, but page 91 references sample testing following recrystallization in isopropyl acetate ("iPrOAc"), which is *not* the final solvent used in Liu (Liu uses acetone). When Dr. Bihovsky performed the acetone recrystallization, he obtained Form I (Z)-endoxifen, as shown in the very laboratory notebook page on which Patent Owner relies.

Compare Ex. 1033 at p.91:

10/24/23	Decidure 15-30-45 (206 mg) iPrOAc (2.06 ml)	
	brdg Δx. Cool slowly (~1h) to 20° then 15°	
Ref '651	for 2 days. Vac filter, miss ppt ~0.1 ml cold	
0054	iPrOAc. Dry → 109 mg xlt. 97% Z- ^{NOT FORM I} 15-32-(P	
	Rotavap filtrate → 98 mg foam 36% Z- -15	
10/24/23	Decidure 15-30-3P (98 mg) in Δx acetone (1.00 ml)	
	cool to 20° → 4° (stirring) for 1 day -	
	miss w/ cold acetone	
	Vac filter + dry → 54 mg off white "solid" 15-32-2P	
	88% Z- ^{XRPD = Form I}	
	Rotavap filtrate → 31 mg v. lt. pink foam -25	
	63% Z-	

with Ex. 1003 (Liu) at [0073]-[0076] (Examples 6 and 7):

Response to Patent Owner's Request for Discretionary Denial

[0073] Endoxifen (2721 g, E/Z ratio ~70/30,) was suspended in isopropyl acetate (27 L) in a 100-L reactor. The suspension was heated at 85°C for 2 hours. The E/Z ratio of the solution was determined to be ~1/1 by HPLC analysis. The mixture was cooled slowly to 15°C, resulting in the preferential crystallization of the E-isomer. The mother liquor (containing 71% Z-isomer) was removed from the reactor, evaporated to provide a solid and dried at 35°C to constant weight: 1314 g (48%, Z-isomer content: 73%).

[0074] The above operations were repeated twice with the residual E-isomer crystals in the reactor to provide two additional crops of Z-enriched material: 817 g (Z-isomer content: 71%) and 220 g (Z-isomer content: 69%). The total amount of Z-enriched endoxifen isolated in this manner was 2348 gram (86%).

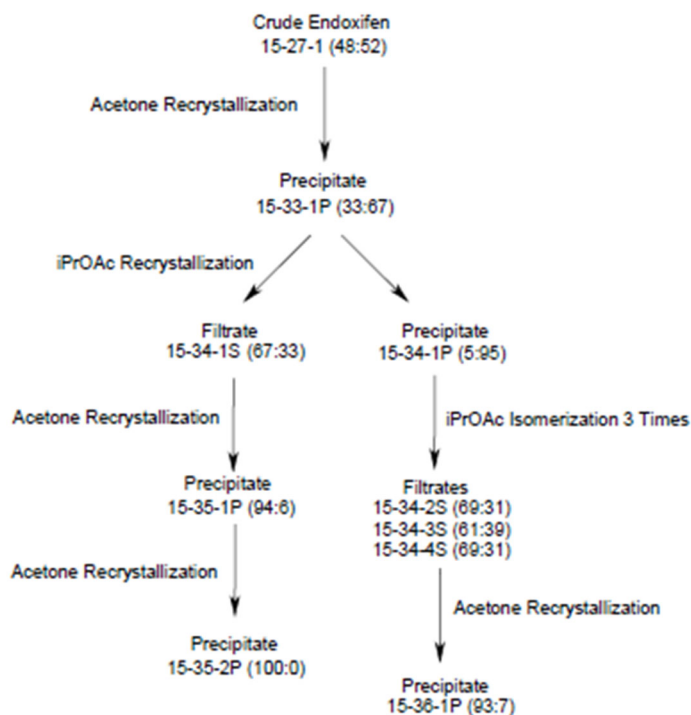
[0075] The residual crystalline material (342 g, 13%), collected from third recrystallization, was mainly (E)-Endoxifen with an isomeric purity of 96%. The material recovery of this step is 99%.

EXAMPLE 7. RECRYSTALLIZATION OF AN ENDOXIFEN MIXTURE ENRICHED IN Z ISOMER

[0076] Endoxifen (5013 g, E/Z ratio ~30/70) was dissolved in 50 L of acetone which was heated to reflux in a 100-L reactor. The resulting solution was cooled and stirred for 40 hours at 1 to 5 °C. The mother liquor was removed from the reactor by aspiration. The remaining crystalline material was re-dissolved in boiling acetone (52 L). The resultant solution was stirred for 50 hours at 1 to 5 °C. The mother liquor was removed. The remaining crystalline material was again dissolved in boiling acetone (48 L). The hot solution was filtered and kept for 22 hours at 1 to 5 °C. The crystalline material which precipitated was collected by filtration and washed with ice-cooled acetone. The solid was dried in vacuo at 35 °C to a constant weight to give 1698 g (34%) of (Z)-endoxifen, with an isomeric purity of 99% (HPLC analysis). ¹H NMR (300 MHz, DMSO-d₆) 0.85 (3H, t, CH₃), 2.28 (3H, s, CH₃-N), 2.43 (2H, q, C=C-CH₂), 2.73 (2H, t, CH₂-N), 3.86 (2H, t, CH₂-O), 6.58 (2H, d, Ar), 6.69-6.77 (4H, m, Ar), 6.98 (2H, d, Ar), 7.10-7.18 (5H, m, Ar), 9.45 (1H, s, Ar-O-H); ¹³C NMR (100 MHz, DMSO-d₆) 13.3, 28.5, 36.1, 50.3, 67.0, 113.3, 115.0, 125.9, 127.8, 129.3, 130.0, 131.3, 133.9, 135.5, 137.9, 139.9, 142.2, 156.1, 156.5; MS (ES-MS) 374.1 (MH⁺), 396.6 (M-Na⁺).

Dr. Bihovsky and Dr. Miller did not discuss these samples because they were not a part of following Liu's examples as clearly laid out in Dr. Bihovsky's report:

Response to Patent Owner's Request for Discretionary Denial



Ex. 1033 ¶ 72.

The testing of these precipitates showed Form I (Z)-endoxifen, as Dr. Miller explained. In other words, Dr. Bihovsky did not “repeatedly fail” to obtain Form I following Liu’s examples – rather *other* tests of *other* samples did not lead to Form I, while *every* test of Liu’s examples led to Form I (Z)-endoxifen. *Contrast Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 1047–48 (Fed. Cir. 1995) (holding claims to Form II not shown anticipated where “the district court found that the practice of Example 32 could yield crystals of either polymorph. It specifically found that Glaxo’s David Collin originally made Form 1 by practicing Example 32, and that Glaxo’s expert, Nicholas Crouch, did too. We are not persuaded that these findings

Response to Patent Owner's Request for Discretionary Denial

are clearly erroneous.”). Unlike *Glaxo*, here there is no evidence Liu’s examples could result in anything but Form I (Z)-endoxifen.

Further, in *Glaxo*, the Federal Circuit rejected an argument that the testing resulting in Form I should be disregarded because it “employed procedures that sometimes departed from the strict letter of Example 32” because the “district court found that one skilled in the art would understand that these procedures were consistent with the teaching of Example 32” and did “not see where the court erred in this finding.” *Id.* at 1047 n.4. Dr. Bihovsky’s tests were consistent with Liu’s examples in every way that matters and led to Form I, demonstrating conclusively that Liu’s synthesis results in Form I. If Patent Owner believes that is inaccurate, it is free to try to show that with evidence during the trial phase.

Indeed, Patent Owner also relies on *Pfizer, Inc. v. Chugai Pharm. Co.*, IPR2017-01357, Paper 56 (Nov. 28. 2018) and *SNF S.A. v. Chevron U.S.A., Inc.*, IPR2022-01534, Paper 46 (Apr. 18. 2024). But in both cases the Board ruled after a trial on the merits, considering all of the evidence—not as a basis for discretionary denial. The Board should similarly proceed to trial on the merits here.

The above cases cited by Patent Owner are also readily distinguishable. For example, in *Pfizer*, the panel held “[t]hat four common and conventional ways of preparing Shadle’s buffer each satisfy the elution buffer molarity requirement of the challenged claims is insufficient to establish that Shadle’s elution buffer necessarily

meets that requirement” where the patent owner showed there were other ways of preparing the buffer that *would not* meet the requirement and “Shadle is agnostic as to how its elution buffer is prepared.” *Pfizer*, Paper 56, . at *20-24. The issue was not that the expert ran a test at a smaller scale, but that the expert assumed certain methods were used that led to the claimed result, when it was clear other methods could have been used that would *not* have resulted in the claimed result.

Similarly, in *SNF S.A.*, the issue was not that the expert had made routine modifications to run the prior art at scale, but that the expert’s testing showed that “every test conducted *before* dewatering, that is following Li’s disclosed examples, failed to establish the specific filter ratio required by all the challenged claims” and the expert admitted dewatering was not taught in the anticipatory reference. IPR2022-01534, Paper 46 at *27. In other words, the claimed result was obtained *because* of the addition of a step not taught in the prior art. Here, as Dr. Bihovsky explained, the crystalline Form I formed because of Liu’s recrystallization process.

Petitioner has shown that it is at least “reasonably likely” that Liu inherently anticipates the claims. Indeed, Dr. Bihovsky and Dr. Miller showed that ***two different methods*** of Liu ***both*** resulted in Form I (Z)-endoxifen. Ex. 1034 ¶¶ 29-31; *contrast Azurity Pharms., Inc. v. Exelixis Inc.*, IPR2025-00210, Paper 11, at *28 (June 4, 2025) (expert testimony that a “POSA would have expected there to be a

decrease” in an impurity did not show the combination “would inherently result in less than 200 ppm impurity”).

F. The Petition’s use of expert testimony does not favor discretionary denial

The Petition relies on expert experimentation to prove one simple point: that the 90% (Z)-endoxifen made by Liu is in fact Form I. That is hardly the type of “gap-filling” that favors discretionary denial. *Contrast Xerox Corp. v. Bytemark, Inc.*, IPR2022-00624, Paper 9, at *16 (Aug. 24, 2022) (precedential) (“Petitioner’s only support for the assertion that ‘[a] POSITA would find it obvious that blocking the account of the purchaser from further use of the system would including storing a data value indicating the fraudulent activity in a data record associated with the user account’ is Dr. Jones’ Declaration. Pet. 28. Again, however, Dr. Jones offers only a *verbatim* restatement of the assertion being supported, without any supporting evidence or technical reasoning.”).

Patent Owner notably does not accuse Dr. Bihovsky or Dr. Miller of failing to provide expert analysis. Nor are Dr. McConville’s opinions “largely verbatim or near-verbatim assertions merely parroted from the Petition without any independent analysis or supporting evidence.” Req. at 35 (citing Ex. 1032 ¶¶ 67-103). To the contrary, they are replete with citations to the record supporting Dr. McConville’s testimony (which relates to formulation and pharmacokinetic issues unrelated to the Form I issue—the sole limitation Patent Owner addresses in its motion). *E.g.*, Ex.

Response to Patent Owner's Request for Discretionary Denial

1032 ¶ 67 (citing Dr. Bihovsky and Dr. Miller's testing), ¶ 68 (citing Liu and Ahmad); ¶ 69 (citing Ahmad); ¶ 70 (citing the Handbook of Pharmaceutical Excipients ("HPE")) (Ex. 1012), Stegemann (Ex. 1013)).

Patent Owner's criticism of Dr. McConville's testimony is especially faulty given that the 334 panel *repeatedly* credited Dr. McConville's testimony on similar formulation/pharmacokinetic issues as being well-supported by the same references. *E.g.*, 334 FWD at *35 ("We credit Dr. McConville's testimony that applying enteric coatings would have been routine (Ex. 1020 ¶ 71; Ex. 1031 ¶ 5), which is consistent with Ahmad's disclosure that the enteric coating 'can be done as methods known in the art.' Ex. 1003, 18:27-29...We credit the formulation expertise of Dr. McConville...we agree with Dr. McConville..."), 38 ("we credit the testimony of Dr. McConville, who explains that a POSA would understand Benamuer's teachings with a model drug would be application to (Z)-endoxifen..."), 42 ("we credit the testimony of Dr. McConville, who notes that the HPE generally lists known incompatibilities...We are persuaded by Dr. McConville's testimony..."), 46 ("we credit the well-supported testimony of Dr. McConville that it would have been routine for a POSA to run experiments like those described in Ahmad 2010 and 2012"). Dr. McConville's testimony here is supported by the record, and not a basis for discretionary denial.

G. Discretionary denial would eliminate any estoppel effects from the 334 patent which would not apply in district court

The Petition does not rely significantly on collateral estoppel (and certainly does not rely on it for the Form I limitation) but merely notes that many subsidiary issues that were decided limit what Patent Owner may argue. For example, while it is clear Liu teaches 90% (Z)-endoxifen and thus Petitioner need not rely on collateral estoppel, Patent Owner may not argue that Liu does not teach or enable 90% (Z)-endoxifen. *See e.g.*, 334 FWD at *22 (“others, like Liu and Fauq, had successfully purified at least 90% (Z)-endoxifen by the earliest possible effective filing date of the invention.”); *id.* at *25, *30-31 (similar). Nor can patent owner dispute that enteric capsules were well-known in the art. *See* 334 FWD at *35 (“We credit Dr. McConville’s testimony that applying enteric coatings would have been routine”).

The findings of the panel, while subject to collateral estoppel effect in future Board proceedings are (under current Federal Circuit precedent) *not* binding on Patent Owner in district court. *See, e.g., ParkerVision, Inc. v. Qualcomm Inc.*, 116 F.4th 1345, 1361–62 (Fed. Cir. 2024) (“Although we have not previously addressed the question of whether a finding underlying an unpatentability decision in an IPR proceeding collaterally estops a patentee from making validity arguments regarding separate, related claims in district court litigation, we now hold that it does not.”). This strongly weighs *against* discretionary denial and favors the Board continuing to reevaluate the patentability of Patent Owner’s patent claims in light of the

arguments presented and certainly does not weigh in favor of denying further review of related patents that contain many overlapping limitations.

III. CONCLUSION

Petitioner has established a reasonable likelihood of prevailing as to each of claims 1-21 of the 151 patent, and therefore respectfully requests that the Board institute *inter partes* review of those claims.

Respectfully submitted,

McANDREWS, HELD & MALLOY, LTD.

Dated: August 7, 2025

By: /Alejandro Menchaca/
Alejandro Menchaca
Reg. No. 34,389
Lead Counsel for Petitioner
Intas Pharmaceuticals, Ltd.

CERTIFICATE OF WORD COUNT

I certify under 37 CFR § 42.24 that this **RESPONSE TO PATENT OWNER'S REQUEST FOR DISCRETIONARY DENIAL** contains 6,616 words, as determined by Microsoft Word.

Dated: August 7, 2025

By: */Alejandro Menchaca/*
Alejandro Menchaca
Reg. No. 34,389
Lead Counsel for Petitioner
Intas Pharmaceuticals, Ltd.

CERTIFICATE OF SERVICE

Under 37 C.F.R. §§ 42.6(e)(4) and 42.105, the undersigned certifies on this date, a true and correct copy of **PETITIONER'S RESPONSE TO PATENT OWNER'S REQUEST FOR DISCRETIONARY DENIAL OF INSTITUTION** and **EXHIBITS 1035-1037** were served by electronic mail to:

Megan Raymond
GROOMBRIDGE, WU, BAUGHMAN & STONE LLP
801 17th Street, NW, Suite 1050
Washington, DC, 20006
megan.raymond@groombridgewu.com

J. Steven Baughman (Reg. No. 47,414)
GROOMBRIDGE, WU, BAUGHMAN & STONE LLP
801 17th Street, NW, Suite 1050
Washington, DC, 20006
steve.baughman@groombridgewu.com

Atossa-Intas@groombridgewu.com

Dated: August 7, 2025

By: /Alejandro Menchaca/
Alejandro Menchaca
Reg. No. 34,389
Lead Counsel for Petitioner
Intas Pharmaceuticals, Ltd.