

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
DIRECTOR REVIEW**

TABLE OF CONTENTS

I.	Introduction.....	1
II.	The Board Correctly Instituted This IPR.....	2
	A. Patent Owner’s new argument regarding a different sample does not show the Board erred in instituting this IPR.....	3
	1. Patent Owner’s argument was not presented to the Board.....	4
	2. Patent Owner’s new argument does not show legal or factual error	7
	B. Patent Owner’s argument regarding inherency is legally erroneous and was correctly rejected	9
III.	Conclusion	14

TABLE OF AUTHORITIES

Cases

<i>Bae Sys. Info. & Elec. Sys. Integration, Inc. v. Cheetah Omni, LLC</i> , IPR2013-00175, 2013 WL 5653116 (P.T.A.B. July 23, 2013).....	6
<i>Cisco Sys., Inc. v. Focal IP, LLC</i> , IPR2016–01257, 2017 WL 506423 (P.T.A.B. Jan. 31, 2017).....	6
<i>Coherus Biosciences, Inc. v. Abbvie Biotechnology Ltd.</i> , IPR2016-00189, 2016 WL 8969302 (P.T.A.B. July 14, 2016).....	10
<i>Eisai Inc. v. Crystal Pharm. (Suzhou) Co., Ltd.</i> , PGR2021-00047, Paper 17 (P.T.A.B. Aug. 5, 2021)	12
<i>Eisai Inc. v. Crystal Pharm. (Suzhou) Co., Ltd.</i> , PGR2021-00047, Paper 58 (P.T.A.B. Aug. 8, 2022)	12
<i>Nxn Partners, LLC v. Nissan Chem. Industries, Ltd.</i> , IPR2016-00694, Paper 7 (P.T.A.B. Aug. 31, 2016).....	12, 13
<i>Rosellini Sci., LLC v. Grünenthal GmbH</i> , IPR2016-00471, Paper 11 (P.T.A.B. July 18, 2016)	11
<i>Salix Pharms., Ltd. v. Norwich Pharms. Inc.</i> , 98 F.4th 1056 (Fed. Cir. 2024)	13
<i>SmithKline Beecham Corp. v. Apotex Corp.</i> , 403 F.3d 1331 (Fed. Cir. 2005)	9, 10
<i>Valeant Int’l (Barbados) SRL v. Watson Pharms., Inc.</i> , No. 10-20526-CIV, 2011 WL 6792653 (S.D. Fla. Nov. 8, 2011).....	12

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> , 87 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")

EX.	DESCRIPTION
1014	Benameur, H., <i>Capsule Technology, Enteric Capsule Drug Delivery Technology – Achieving Protection Without Coating</i> , 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 Director Review

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 M. 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 3391-3400 (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 268-277 (2021)

I. INTRODUCTION

The only alleged difference between the claimed “invention” in the subject patent, U.S. Patent No. 11,261,151, and Liu is the crystal form of the resulting highly pure (Z)-endoxifen. There is no dispute Liu expressly teaches synthesis of highly pure (>90%) (Z)-endoxifen.

Petitioner's experts synthesized (Z)-endoxifen following Liu and showed unequivocally that the resulting (Z)-endoxifen is the claimed form I. Petitioner's expert explained that any minor modifications made to run the reaction at smaller scale would have no effect on the resulting crystal form, which would be driven by the final recrystallization process. On the current record, that testimony is unrebutted and established ***at least*** a “reasonable likelihood that the petitioner [will] prevail with respect to at least 1 of the claims challenged in the petition.”

First, Patent Owner asserts that there was “at least one experiment in which the claimed compound was produced at only 88% purity rather than the claimed 90%” while creating form I (Z)-endoxifen. This is a new argument never presented to the Board in Patent Owner's Preliminary Response and should not be considered. Regardless, that single sample was a different experiment *not* replicating Liu, which still generated Form I, and does not somehow show that as a matter of law, Liu cannot inherently teach Form I.

Second, Patent Owner argues that as a matter of law the Board cannot find inherency because Dr. Bihovsky ran Liu's synthesis at a feasible laboratory scale necessitating some minor, routine adjustments. Patent Owner argues that such adjustments require discounting the evidence entirely. But Patent Owner provides no support for such rigid evidentiary rules. The question for anticipation is whether the evidence shows Liu's synthetic process would necessarily lead to the claimed form I. Whether Petitioner's evidence does so is a question of fact that the Board can determine after trial. Patent Owner's request that the Board (and now Director) simply credit its own attorney argument over Petitioner's expert testimony is unfounded. Moreover, Petitioner explained in Ground II how such modifications would have been obvious modifications (as the Board already found in a Final Written Decision an earlier PGR) that resulted in the claimed (Z)-endoxifen, rendering the claims obvious. That alternate ground further supports institution. The Board was correct to institute and Director review is unwarranted.

II. THE BOARD CORRECTLY INSTITUTED THIS IPR

Contrary to the evidence of record in this proceeding, Patent Owner states that "It Is Undisputed that the Prior-Art Process Does Not Necessarily Produce Form I (Z)-Endoxifen at the Claimed 90% Purity." Req. at 6. Patent Owner's statement is simply untrue. Petitioner demonstrated, supported by evidence, that Liu *does* necessarily produce form I (Z)-endoxifen at the claimed 90% purity. *E.g.*, Pet. at 15,

27-28. Indeed, as Dr. Bihovsky explained ***both*** of the synthetic pathways taught by Liu resulted in greater than 90% Form I (Z)-endoxifen. Pet. at 28 (citing Ex. 1033 (Bivhovsky) ¶71); Pet. at 29 (citing Ex. 1033 ¶ 43; Ex. 1034 ¶¶23-25, 29, 30-31).

Patent Owner may disagree with this argument and evidence or what conclusions to draw from it—but that is the purpose of trial. The Board correctly applied the law and made no material fact finding error in concluding that this evidence showed *at least* a reasonable likelihood that one or more claims would be unpatentable.

A. Patent Owner's new argument regarding a different sample does not show the Board erred in instituting this IPR

Patent Owner alleges error because the Board did not consider an argument never presented to it: that because one experiment in Dr. Bihovsky's lab notebook reports an 88% pure (Z)-isomer, that Liu somehow cannot anticipate. First, this argument was not previously presented. Director Review is not a chance to present new arguments, which alone should end the inquiry. Second, Patent Owner's argument is incorrect, unsupported, and irrelevant. That single experiment, which does not purport to follow Liu and in fact achieved Form I (Z)-endoxifen (albeit at 88% purity) does not somehow prove as a matter of law that Liu does not inherently meet the Form I limitation. If anything, this experiment is further evidence that Liu *does* necessarily lead to Form I because it also yielded Form I (Z)-endoxifen using the same crystallization solvent.

1. Patent Owner's argument was not presented to the Board

Patent Owner begins with a false premise, that “Petitioner does not dispute that Dr. Bihovsky—following Liu’s final acetone recrystallization step—produced at least one sample of Form I (Z)-endoxifen which was only 88% by weight of Form I of (Z)-endoxifen, which does not meet the Challenged Claims’ requirement of ‘at least 90% by weight of the (Z)-isomer....’” Req. at 6. Petitioner has had no opportunity to dispute this argument, because it was never made by Patent Owner.

Patent Owner argued only that the *Form I* limitation was not inherently met by Liu—it never disputed the 90% (Z)-limitation. Indeed, while Patent Owner argues it “raised this issue” at “Pap. 11, 1-2” a simple review of the record shows that it did not. *See* POPR at 1 (“Petitioner concedes that its prior art does not expressly disclose the ***Form I of (Z)-endoxifen*** required in all the Challenged Claims, including both independent claims 1 and 16. Instead, Petitioner relies only on inherency based on Liu for ***this limitation.***”) (emphasis added). Patent Owner never raised an argument that Liu does not meet the 90% (Z) limitation, let alone that it did not do so because of one of Dr. Bihovsky’s experiments.

While Patent Owner did raise an argument regarding Dr. Bihovsky’s testing of other samples, it did so **only** for the Form I limitation because certain samples were “Not Form I.” *See* POPR at 11 (“even Petitioner’s inadequate inherency arguments resting on multiple improper changes to Liu still failed to produce ***the***

claimed Form I for multiple samples, confirming Liu's non-disclosure of *this element*.”) (emphasis added); *see also* Paper 8 at 31 (same argument in request for discretionary denial).

That was logical—as Petitioner *did not* rely on inherency for the 90% (Z)-endoxifen limitation as Liu expressly teaches such isomeric purity. *See, e.g.*, Pet. at 27 (citing Ex. 1003 [0073]-[0076] (“(Z)-endoxifen, with an isomeric purity of 99% (HPLC analysis)”)).

In its Opposition to Patent Owner's Request for Discretionary Denial, Petitioner first pointed out that “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.” Paper 10 at 17 (emphasis in original). That is, these experiments did not purport to reflect Liu's examples or demonstrate what polymorphic form Liu's synthetic process would yield.

Secondly, Petitioner pointed out that the single experimental result Patent Owner relied on as showing “Not Form I” (Z)-endoxifen (15-32-1P) was irrelevant – because it related to a *different* crystallization solvent than the final solvent used in Liu and thus did not demonstrate what crystal form Liu's synthesis would yield. *See* Paper 10 at 17-18. In fact, as Petitioner pointed out, the very page Patent Owner cited showed a further crystallization using the *same* solvent used as the final solvent

in Liu's example which *did* result in Form I (Sample 15-32-2P). Paper 10 at 18 (citing Ex. 1033 at p. 91).

And contrary to Patent Owner's current assertions, the Board *did* consider the arguments presented to it. See Paper 13 at 15 ("we acknowledge Patent Owner's argument that Dr. Bihovsky's experimental lab notebook identifies certain samples as 'XRPD – Not Form I,' however, the current record lacks sufficient information for us to discern what those samples represent."). The Board did not address Patent Owner's new argument regarding sample 15-32-2P and its isomeric purity because Patent Owner never presented it. See *Cisco Sys., Inc. v. Focal IP, LLC*, IPR2016–01257, 2017 WL 506423, at *1 (P.T.A.B. Jan. 31, 2017) ("we cannot have misapprehended or overlooked newly made arguments.").

According to the Board's guidelines, the "Director will not consider new evidence or new arguments not part of the official record."¹ The Director should not do so here. *C.f., Bae Sys. Info. & Elec. Sys. Integration, Inc. v. Cheetah Omni, LLC*, IPR2013-00175, 2013 WL 5653116, at *1 (P.T.A.B. July 23, 2013) ("A request for

¹ U.S. Patent & Trademark Office, *Director Review Process*, USPTO <https://www.uspto.gov/patents/ptab/decisions/director-review-process#RIDRP> (last visited Nov. 21, 2025) (Patent Owner did not seek authorization to present new arguments, nor would it have a basis to do so).

rehearing is not an opportunity to supplement an initial filing and make arguments a party did not make before.”).

2. Patent Owner's new argument does not show legal or factual error

Even considering Patent Owner's new argument, it does not show that the Board erred in instituting this IPR. At best, Petitioner shows that *one* sample using *only* the same recrystallization solvent as Liu's examples achieved 88% isomeric purity. This does not somehow demonstrate “as a matter of law” that Liu (which expressly teaches 90% pure (Z)-endoxifen) does not anticipate.

First, Patent Owner's new argument is entirely irrelevant. Petitioner does not rely on inherency or testing results to show that Liu meets the 90% (Z) limitation—which is explicitly taught in Liu (though Dr. Bihovsky experimentally confirmed Liu's method yields 90% pure (Z) isomer). The dispute is whether the >90% pure (Z)-endoxifen taught in Liu is form I. That a different sample was not 90% isomerically pure is simply irrelevant to whether Liu yields Form I.

Second, sample 15-32-2P ***is not*** a recreation of Liu's examples. Patent Owner appears to acknowledge this, repeatedly referring to it instead as Liu's “final acetone recrystallization step.” However, even this is incorrect—sample 15-32-2P was recrystallized from the same solvent (acetone) but was not generated from the “final acetone recrystallization step” of Liu. Paper 10 at 18. Indeed, as clearly shown in Dr. Bihivosky's notebook sample 15-32-2P was the result of a single acetone

recrystallization for 1 day, not the three-step acetone recrystallization process used in Liu's examples, which lasted 40, 50 and 22 hours respectively. *Compare* Ex. 1033 at p. 91 *with* Ex. 1003 at [0076].

In other words, that one experimental procedure performing a single recrystallization in acetone did not produce 90% (Z)-isomer (though quite close), does not somehow negate Liu's express teaching of 90% (Z)-isomer using a multistep process ending in three acetone recrystallizations.² Nor does it in any way show that Liu's process does not necessarily result in Form I (Z)-endoxifen.

Patent Owner provides no evidentiary support for its new argument, which is fundamentally flawed. Indeed, the 15-32-2P sample using acetone resulted in Form I. Thus, if anything, this example provides *further evidence* that Liu's final recrystallization would result in form I, because as Dr. Bihovsky explained, "the polymorphic form that a crystal adopts is driven by the final crystallization of the material." *See* Ex. 1033 ¶ 47. Rather than showing error, Patent Owner's new argument shows that the Board correctly instituted because the *only* alleged

² Charitably, Patent Owner's argument could be interpreted as arguing that Liu does not enable 90% (Z)-endoxifen. But Patent Owner does not even make this argument because it was already rejected in the earlier PGR. *See* 334 FWD at 29-30.

difference from Liu—the Form I XRPD pattern—is a necessary inherent result of Liu's synthesis.

B. Patent Owner's argument regarding inherency is legally erroneous and was correctly rejected

Patent Owner makes the same overly rigid and legally erroneous argument that the Board already rejected – that to prove inherency a party must recreate the prior art with no deviation whatsoever. Unsurprisingly, it cites no authority standing for this proposition. To be clear, “[p]rior art that must be modified to meet the disputed claim limitation does not anticipate the claim” and “a party must ‘show that the natural result flowing from the operation as taught would result in the performance of the questioned function’” as Patent Owner argues. Req. at 9-10.

But Petitioner did not argue that Liu “must be modified” in order to meet Form I limitation for Ground I. Rather, Petitioner's argument was and is that Dr. Bihovsky's testing shows that the synthesis “as taught” in Liu necessarily results in Form I because any adjustments Dr. Bihovsky made based on scale had no effect on the resulting polymorphic form. Ex. 1033 ¶ 47. In other words, Dr. Bihovsky provided currently unrebutted evidence that Liu necessarily results in Form I (Z)-endoxifen. *See, e.g., SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1344 (Fed. Cir. 2005) (“The '196 patent discloses a method of manufacturing PHC anhydrate that naturally results in the production of PHC hemihydrate. Consequently, applying the facts as found by the district court to the correct standard,

this court holds that claim 1 of the '723 patent is invalid for anticipation by the '196 patent.”). Indeed, Patent Owner in essence seeks to prohibit the public from practicing Liu—the very wrong inherent anticipation seeks to prevent. *SmithKline Beecham Corp.*, 403 F.3d at 1346 (“one of the principles underlying the doctrine of inherent anticipation is to ensure that ‘the public remains free to make, use or sell prior art compositions or processes, regardless of whether or not they understand their complete makeup or the underlying scientific principles which allow them to operate.’”) (citation omitted).

While Patent Owner may disagree with Dr. Bihovsky’s testimony, its own attorney argument cannot show material factual error, especially where it has offered no evidence to the contrary. Indeed, the Board noted that “Patent Owner’s arguments may have merit” but that its “arguments are largely unsupported on the current record” and thus it was “persuaded that Petitioner has established a reasonable likelihood of prevailing in showing that claims 1 and 16 of the ’151 patent are anticipated by Liu” quoting Dr. Bihovsky’s testimony. Paper 13 at 15. Patent Owner simply raises a factual dispute that should be resolved through trial. *See, e.g., Coherus Biosciences, Inc. v. Abbvie Biotechnology Ltd.*, IPR2016-00189, 2016 WL 8969302, at *1 (P.T.A.B. July 14, 2016) (“We understand Patent Owner’s desire not to undergo the expense of trial, but again find that these factual disputes would best

be resolved during trial when we are able to assess Petitioner's and Patent Owner's evidence and arguments upon review of the entire record.”).

And, despite Patent Owner's conclusory statements that it “was legal error for the Board” to find a reasonable likelihood of anticipation based on Dr. Bihovsky's testimony that any minor modifications did not affect the resulting polymorph, it cites no authority supporting its position.

Instead, it simply cites cases addressing different records where a court or agency addressing a different record ruled differently. For example, in *Rosellini Sci., LLC v. Grünenthal GmbH*, IPR2016-00471, Paper 11, at *8-12 (P.T.A.B. July 18, 2016) the Petitioner and expert started with commercially available product rather than following the steps of the prior art and “fail[ed] to explain why they deviated from the protocol disclosed in Example 25 or why that deviation would have had no impact on the synthesized compound as compared to the compound of Example 25.” It does not stand for a broad legal bar than any deviation, no matter the reason and the explanation provided, as a matter of law precludes proving inherency. And here Petitioner and Dr. Bihovsky did precisely what was missing in *Rosellini*—explaining that modifications were done to run the reaction at scale and why those modifications would not impact the final crystal form.

Indeed, other cases from the Board have found testimony like Dr. Bihovsky's (including his own testimony in prior proceedings) sufficient. *See, e.g., Eisai Inc. v.*

Crystal Pharm. (Suzhou) Co., Ltd., PGR2021-00047, Paper 17, at *18 (P.T.A.B. Aug. 5, 2021) (“Although we recognize that Dr. Bihovsky’s experiments were done at one-tenth scale of Moniz’s experiments, we are not persuaded at this stage that changing the scale of the experiments in such a manner would have affected the crystallization of lemborexant.”); *see also id.* Paper 58) (finding claims invalid for inherent anticipation crediting Dr. Bihovsky’s testimony), *aff’d without opinion* (Fed. Cir. Sep. 6, 2024); *Nxn Partners, LLC v. Nissan Chem. Industries, Ltd.*, IPR2016-00694, Paper 7, at *16-17 (P.T.A.B. Aug. 31, 2016) (“Although Petitioner’s expert, Dr. Bihovsky did not exactly follow Examples 20 and 21 of Mita, at this stage of the proceeding we credit Dr. Bihovsky’s testimony that ‘the crystalline form of fluralaner produced in Example 21—via the synthetic procedure set forth in Examples 5, 20, and 21—will only be determined by the final step of the procedure.’”).

Valeant Int'l (Barbados) SRL v. Watson Pharms., Inc., No. 10-20526-CIV, 2011 WL 6792653, at *5 (S.D. Fla. Nov. 8, 2011) is even more readily distinguishable. There, “the explicit disclosure of Example 1 of the Mehta patent produces only bupropion *hydrochloride*, not bupropion hydrobromide” and the expert “admitted at trial that Watson instructed him to modify Example 1 to produce bupropion hydrobromide by using hydrobromic acid instead of hydrochloric acid.” *Id.* Plainly a reference teaching bupropion hydrochloride cannot anticipate a claim

to bupropion hydrobromide. But that does not mean as a matter of law that running a laboratory scale version of Liu cannot show that Liu inherently results in Form I (Z)-endoxifen and anticipates.³ See *Nxn*, Paper 7, at *17 (“the fact pattern of *Valeant* is different than in the instant proceeding, in that the claim was drawn to a specific and stable form of bupropion *hydrobromide*, and it was undisputed that the prior art was drawn to the production of bupropion *hydrochloride*.”) (emphasis in original).

At bottom, Patent Owner asks the Board to accept its own attorney argument over Petitioner's expert testimony. But Patent Owner at best raises an argument

³ Further, Patent Owner ignores Ground II, where Petitioner raised obviousness. See Pet. at 37-39. Thus, even assuming modification to Liu were necessary to form claim I (they were not), the Board may hold the claims unpatentable as obviousness, because a POSA would have arrived at the claimed invention. See, e.g., *Salix Pharms., Ltd. v. Norwich Pharms. Inc.*, 98 F.4th 1056, 1066 (Fed. Cir. 2024) (finding claims to polymorph obvious because the “scope and content of the prior art here includes preparations of crystalline rifaximin, which expert testimony supports would have yielded the β form of rifaximin”). Notably, the Board already found previously that the minor modifications to run the reaction at lower scale made by Dr. Bihovsky were “within the level of ordinary skill in the art.” 334 FWD at 28. This additional reason warrants institution.

about the weight to give Dr. Bivhosky's testimony—a classic factual dispute—that should be resolved through trial, as the Board correctly found.

III. CONCLUSION

For the above reasons, Patent Owner's Request for Director Review should be denied.

Respectfully submitted,

McANDREWS, HELD & MALLOY, LTD.

Dated: November 24, 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 DIRECTOR REVIEW** 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: November 24, 2025

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