

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 11,261,151

PATENT OWNER'S REQUEST FOR DIRECTOR REVIEW

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Patent Owner Atossa Therapeutics, Inc. (“PO”) requests §42.75¹ Director Review of the Board’s decision granting institution (Pap.13, “Inst.”) based on Petitioner’s inherent anticipation theory. Inherent anticipation requires that the missing element be *necessarily, unavoidably*, and *inevitably* present based on the reference’s explicit disclosure. Here, Petitioner’s own testing showed that following the steps of its prior-art reference Liu did *not* necessarily result in the claimed compound at the claimed purity, and that any ability to achieve experimental results that purportedly satisfied the claims required multiple *modifications* to Petitioner’s prior-art reference. Indeed, even Petitioner’s testing, which it relied on in an attempt to prove inherency, resulted in at least one experiment in which the claimed compound was produced at only 88% purity rather than the claimed 90%. The Board ignored this evidence, and in so doing improperly applied inherency law. The Board also misapplied the law of inherency when it granted institution despite Petitioner’s admission that its expert had modified the process disclosed in Liu, which black letter anticipation law forbids.

In granting institution based on Petitioner’s deficient inherency theory, the Board made erroneous conclusions of law and material fact. Because of the Board’s

¹ Unless stated, statutory and regulatory citations are to 35 U.S.C. or 37 C.F.R., as context indicates, internal citations are omitted, and emphasis is added.

error, PO has been subjected to an “unnecessary trial[]” based on an anticipation ground that is insufficient as a matter of law. <https://www.uspto.gov/patents/ptab/decisions/director-review-process>, §2.B (“Director Review Process”).

Director Review of the Board’s decision granting institution is thus warranted.

I. FACTUAL BACKGROUND

U.S. Patent No. 11,261,151 (“the ’151 Patent”; EX1001) is a foundational patent owned by PO covering a crystalline polymorph of (Z)-endoxifen. (Z)-endoxifen is the active metabolite of tamoxifen. EX1001, 2:36-38. The ’151 Patent and its family relate to novel (Z)-endoxifen compositions, and include claims directed to the treatment of hormone-dependent and tamoxifen-resistant breast cancer. This patent family is an important asset of PO and reflects years of focused research and clinical investment by a small American biopharmaceutical company to develop a stable, purified form of (Z)-endoxifen and address a critical unmet need in hormone-sensitive breast cancer therapy. The Challenged Claims are directed to a crystalline Form I of (Z)-endoxifen, defined by a specific x-ray powder diffraction (XRPD) fingerprint, as well as methods of using this highly pure polymorphic form.²

² Reference to “Form I” refers to the following limitation of the independent claims:

“the crystalline form of the (Z)-isomer is Form I, characterized by an x-ray powder

Petitioner asserts anticipation based on the Liu reference—which was affirmatively considered by the Examiner during the '151 Patent's prosecution—yet concedes that Liu does not expressly disclose the Form I of (Z)-endoxifen required in all Challenged Claims or provide an XRPD characterization of the crystalline solids produced using Liu's disclosed methods. Pet.29; EX1033, ¶33; EX1034, ¶29; EX1032, ¶65; Pap.9, 7. Instead, Petitioner relies only on inherency based on attempts by its expert, Dr. Bihovsky, to synthesize Form I of (Z)-endoxifen at the claimed 90% purity through a purported recreation of Liu's methods. Pet.29; Pap.11, 1-2. In so doing, Petitioner omitted—and neither the decision referring the Petition to the Board nor the institution decision itself addressed—the fact that Dr. Bihovsky, admittedly using Liu's final acetone recrystallization step, conducted an experiment in which he obtained Form I of (Z)-endoxifen at only 88% purity rather than the claimed 90%. Pap.12, 3; Inst.14-15 (addressing only PO's arguments regarding other failed experiments); Pap.10, 18; Pap.11, 1-2.

Additionally, Dr. Bihovsky modified Liu's process in at least nine ways. *E.g.*, Pet.12 n.3, 14 n.4; EX1033, ¶¶47-48, ¶51, ¶52 n.3 & n.4, ¶54 n.5, ¶59 n.6, ¶60 n.7, ¶61; Pap.9, 11-19. For example, after multiple failed experiments producing

diffraction pattern comprising major peaks at $16.8\pm0.3^\circ$, $17.1\pm0.3^\circ$ and $21.8\pm0.3^\circ$ two theta."

“incomplete” reactions following Liu’s disclosed 45 to 50 °C temperature, Dr. Bihovsky raised the temperature to 70 °C and extended the reaction time by five hours. EX1033, ¶51; Pap.9, 12-13. Only after doing so did he observe a reaction that was “mostly complete.” EX1033, ¶51; Pap.9, 12-13. He also changed another step of Liu to use a nitrogen atmosphere instead of Liu’s argon. EX1033, ¶54, Pap.9, 14. And the Board acknowledged that Dr. Bihovsky made these changes. Inst.15 (“As noted by Patent Owner, Dr. Bihovsky acknowledged that he made ‘minor adjustments’ compared to the procedure disclosed in Liu.”). Despite this, the Board credited Dr. Bihovsky’s experiments and granted institution based solely on Petitioner’s inherency theory, incorrectly concluding that these deviations from Liu’s disclosed procedures did not defeat anticipation. Inst.14-15.

II. LEGAL STANDARDS AND STANDARD FOR REVIEW

The law is clear that “[p]rior art that must be modified to meet the disputed claim limitation does not anticipate the claim.” *Enplas Display Device Corp. v. Seoul Semiconductor Co.*, 909 F.3d 398, 405 (Fed. Cir. 2018). Moreover, inherency is an exacting standard that requires that the missing element be ***necessarily, unavoidably, and inevitably*** present based on the reference’s explicit disclosure. *See In re Montgomery*, 677 F.3d 1375, 1380 (Fed. Cir. 2012) (“The inherent result ***must inevitably result*** from the disclosed steps....”); *Azurity Pharms., Inc. v. Exelixis Inc.*, IPR2025-00210, Pap.11, 28 (June 4, 2025) (“That is not, however, the standard for

inherency. It *must be the necessary result, not a possible expected result.*”). “The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient.” *PersonalWeb Techs., LLC v. Apple, Inc.*, 917 F.3d 1376, 1382 (Fed. Cir. 2019). “Rather, a party must ‘show that *the natural result flowing from the operation as taught* would result in the performance of the questioned function.’” *Id.*

The Director may grant Director Review to address “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.” Director Review Process, §2.B. “The Director Review process provides a mechanism to correct errors at the institution stage, for example, to avoid unnecessary trials for patent owners.” *Id.* Director Review has been granted when, for example, the Board misapplies the law or makes erroneous findings of material fact. *Duration Media LLC v. Rich Media Club LLC*, IPR2023-00953, Pap.78, 8 (Dec. 12, 2024) (granting director review where “the Board conflated enablement and obviousness”); *Mastercard Inc. v. OV Loop, Inc.*, IPR2023-01289, Pap.41, 3 (June 10, 2025) (granting director review based on erroneous findings of material fact). “Decisions of the Board under Director Review are reviewed *de novo*.” Director Review Process, §5.A.ii.c.

III. ARGUMENT

The Board granted institution even though Petitioner’s expert Dr. Bihovsky (1) conducted at least one experiment using Liu’s final acetone recrystallization step

in which Form I was produced at a purity lower than what is claimed and (2) admitted that he made multiple modifications to Liu's disclosed process. Each defeats inherency and provides an independent reason compelling denial.

A. It Is Undisputed that the Prior-Art Process Does Not Necessarily Produce Form I (Z)-Endoxifen at the Claimed 90% Purity

Petitioner argues, based on Dr. Bihovsky's experiments, that "Liu inherently teaches the claimed Form I of (Z)-endoxifen" (Pet.29). *See generally* Pet.1, 29; Pap.10, 16, 22-23. But 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...." EX1033, 91; EX1001, cl.1; Pap.11, 1-2. This is shown in the below excerpt from Petitioner's brief opposing discretionary denial (Pap.10), which in turn excerpts a portion of Dr. Bihovsky's lab notebook. There, Petitioner argued that Dr. Bihovsky's sample "15-32-2P," obtained using Liu's final acetone recrystallization step, is the claimed Form I (shown by Petitioner's orange highlighting over "XRPD = Form I"). As shown by PO's red annotations, however, that sample yielded only "88% Z," which is less than the claimed 90% purity:

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)
	mix dx. Cool slowly (w/h) to 20° then 15°
Ref '651	for 2 days, vac filter, rinse ppt w/0.1 ml cold
0054	iPrOAc. Dry → 109 mg xlt. 97% Z- ^{NOT FORM I} 15-32-(P
	Rotavap filtrate → 98 mg from 36% Z- -15
10/27/23	Decidure 15-30-3P (98 mg) in dx acetone (1.00 ml)
	cool to 20° → 4° (stirring) for 1 day - cryst.
	vac filter + dry → 54 mg off white "solid" ^{cryst.} 15-32-2P
	88% Z- ^{XRPD = Form I}
	Rotavap filtrate → 31 mg v. lt. pink foam -25
	63% Z-

Pap.10, 18 (red annotations added) (citing EX1033, 91); see also Pap.11, 1-2. Despite claiming that "Liu inherently teaches the claimed Form I of (Z)-endoxifen" (Pet. 29), Petitioner never asserts and cannot assert that sample 15-32-2P—which Petitioner says was produced by Liu's final acetone recrystallization step—meets the claimed 90% purity. Pap.10, 18.³ There can thus be no dispute that the disclosed

³ Petitioner asserts that "the final crystal form of the product... is determined by the final recrystallization condition (taught in full detail by Liu and followed closely by

steps in Liu did **not** inevitably result in the claimed “at least 90% by weight of... the (Z)-isomer.” EX1001, cl.1. Instead, at least one experiment yielded only 88% by weight of the Form I (Z)-isomer.

This should have doomed Petitioner’s inherency theory under controlling case law, which requires that “[t]he inherent result must inevitably result from the disclosed steps.” *Montgomery*, 677 F.3d at 1380; *Azurity*, Pap.11, 28; *see also* Pap.9, 8-12. The decision referring the Petition to the Board and the institution decision itself did not address this undisputed material fact (even though PO raised this issue, Pap.11, 1-2)—which is mentioned nowhere in either decision—and in so doing committed an error of law by finding that Petitioner’s inherency theory was not legally foreclosed. Inst.14-15. Director Review should be granted and institution denied on this independent basis.

Dr. Bihovsky)” (Pap.10, 3), and Dr. Bihovsky contends that he followed Liu’s acetone recrystallization step in both his relied-upon “sequential recrystallizations” and “isomerization reaction followed by selective recrystallization” experiments. EX1033, ¶31, ¶47 (“With respect to Liu’s crystallization of a mixture of (E)- and (Z)-endoxifen to produce greater than 90% (Z)-endoxifen, I followed Liu extremely closely.”), ¶61, ¶64 (both stating that Dr. Bihovsky followed Liu’s Example 7 for the final recrystallization step performed in each relied-upon experiment).

B. The Board Committed Legal Error By Granting Institution Despite Petitioner’s Modifications to Liu’s Disclosed Process

Dr. Bihovsky’s multiple modifications of Liu’s disclosed process also provide a separate and independent basis for denial of institution. Petitioner and Dr. Bihovsky admit that they modified Liu’s process and that only using Liu’s modified process did they ever arrive at the claimed Form I at the requisite 90% purity by weight. *E.g.*, Pet.12 n.3, 14 n.4; EX1033, ¶¶47-48, ¶51, ¶52 n.3 & n.4, ¶54 n.5, ¶59 n.6, ¶60 n.7, ¶61. PO previously summarized the nine ways in which Dr. Bihovsky deviated from Liu’s disclosed process. Pap.9, 11-18. As just one example, after Liu’s disclosed 45 to 50 °C temperature yielded multiple “incomplete” reactions, Dr. Bihovsky raised the temperature to 70 °C and increased the reaction time by five hours and only then achieved a reaction that was “mostly complete.” EX1033, ¶51; Pap.9, 12-13. The institution decision acknowledged those modifications, but pointed to Dr. Bihovsky’s testimony that they were just “minor adjustments” and “routine adjustments a POSA following Liu would have likely made.” Inst.15 (citing EX1033 ¶47).

But whether the modifications were “minor,” “routine,” or otherwise has no bearing on the *inherency* analysis. *E.g.*, Pap.9, 11-13, 18-19. Instead, it is black letter law that “[p]rior art that must be modified to meet the disputed claim limitation does not anticipate the claim.” *Enplas*, 909 F.3d at 405; *see also Apple Inc. v. Corephotonics, Ltd.*, 861 F. App’x 443, 450 (Fed. Cir. 2021) (non-precedential);

PersonalWeb, 917 F.3d at 1382 (“[A] party must ‘show that the natural result flowing from the operation *as taught* would result in the performance of the questioned function.”); *Rosellini Sci., LLC v. Grünenthal GmbH*, IPR2016-00471, Pap.11, 8-12 (July 18, 2016) (explaining that “[i]nherency is not ‘established by probabilities or possibilities’” and denying institution based on an inherent anticipation theory where Dr. Bihovsky, serving as the petitioner’s expert in that case, “did not follow each of the steps of Example 25 of [the prior-art reference] (including the preceding steps required to perform Example 25)” and as a result “Petitioner has not shown sufficiently that those steps would necessarily and inevitably yield” the claimed compound); Pap.9, 9-12. It was legal error for the Board to conclude otherwise, and the anticipation inquiry should have ended there.

Indeed, the Federal Circuit affirmed a finding of no inherent anticipation in similar circumstances. *Valeant Int’l (Barbados) SRL v. Watson Pharms., Inc.*, No. 10-20526-CIV, 2011 WL 6792653, at *5 (S.D. Fla. Nov. 8, 2011), *aff’d sub nom.*, *Valeant Int’l Bermuda v. Actavis, Inc.*, 534 F. App’x 999 (Fed. Cir. 2013) (non-precedential). In *Valeant*, following a bench trial, the district court found that the patent challenger failed to prove inherent anticipation of a patent claiming “a specific crystalline form of bupropion hydrobromide” known as “Form 1 bupropion hydrobromide.” *Id.* at *1, *4-5. The patent challenger contended that “following Example 1 of the [asserted prior-art] patent invariably results in Form 1 bupropion

hydrobromide” such that the challenged claim was inherently anticipated. *Id.* at *5. In support of this argument the patent challenger’s expert synthesized Form 1 bupropion hydrobromide using Example 1 in the asserted prior-art patent and concluded that “following Example 1 invariably results in Form I bupropion hydrobromide.” *Id.* The expert admitted, however, that he had “modif[ied] Example 1 to produce bupropion hydrobromide by using hydrobromic acid instead of [the disclosed] hydrochloric acid.” *Id.* The court found no anticipation, explaining that “because [patent challenger’s expert] did not follow the explicit disclosure of Example 1 of the [prior-art] patent, his experiment is simply not probative of the issue of inherent anticipation, as it clearly does not demonstrate that Form I bupropion hydrobromide is the ‘natural result flowing from the explicit disclosure of the prior art.’” *Id.* The Federal Circuit summarily affirmed. 534 F. App’x 999.

Notably, the patent challenger in *Valeant* argued—as Petitioner does here—that a person of skill in the art would have modified the prior-art process, arguing that “claim 1 is nevertheless inherently anticipated because a person of ordinary skill in the art would have known that the hydrochloric acid used in Example 1 of the [prior-art] patent could be replaced by hydrobromic acid to form bupropion hydrobromide.” *Valeant*, 2011 WL 6792653, at *5. The district court rejected this argument, “find[ing] this line of reasoning unpersuasive, as the law of anticipation is clear that the challenging party may not rely upon the knowledge of one skilled in

the art to supply missing elements from the claimed invention.” *Id.* The result should have been the same here, but for the Board’s error of law. Institution should be denied on this separate and independent basis.

IV. CONCLUSION AND REQUEST FOR RELIEF

For the foregoing reasons, the institution decision should be vacated and institution of the IPR should be denied.

Respectfully submitted: /Megan Raymond/

November 17, 2025

Megan Raymond (Reg. No. 72,997)
GROOMBRIDGE, WU, BAUGHMAN & STONE LLP
801 17th Street, NW, Suite 1050
Washington, DC, 20006
P: (202) 505-5878
megan.raymond@groombridgewu.com

Attorneys for Patent Owner Atossa Therapeutics, Inc.

CERTIFICATE OF PAGE COUNT

The undersigned certifies that the foregoing PATENT OWNER'S REQUEST FOR DIRECTOR REVIEW complies with the 15-page limit set forth in 37 C.F.R. §§ 42.24(a)(1)(v) and 42.75.

Dated: November 17, 2025

Respectfully Submitted,

By: /Megan Raymond/
Megan Raymond (Reg. No. 72,997)
Groombridge, Wu, Baughman & Stone
LLP
801 17th Street, NW, Suite 1050
Washington, DC, 20006
P: (202)-505-5878
megan.raymond@groombridgewu.com

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing has been served in its entirety on Petitioner on November 17, 2025, by causing the aforementioned document to be electronically mailed to the following attorneys of record for the Petitioner listed below:

Lead Counsel:	Alejandro Menchaca Registration No.: 34,389 Email: amenchaca@mcandrews-ip.com McAndrews, Held & Malloy, Ltd. 500 West Madison Street, 34th Floor Chicago, Illinois 60661 Tel: (312) 775-8000 Fax: (312) 775-8100 By Electronic Mail
Backup Counsel:	Ben J. Mahon Registration No.: 78,178 Email: bmahon@mcandrews-ip.com Amanda C. Jackson Registration No.: 77,549 Email: ajackson@mcandrews-ip.com McAndrews, Held & Malloy, Ltd. 500 West Madison Street, 34th Floor Chicago, Illinois 60661 Tel: (312) 775-8000 By Electronic Mail

Dated: November 17, 2025

Respectfully submitted,

By: /Sayem Osman/
Sayem Osman