

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 PRELIMINARY RESPONSE UNDER 37
C.F.R. §42.107**

LIST OF EXHIBITS

Exhibit	Description
EX2001	ATOSSA THERAPEUTICS, INC. QUARTERLY REPORT FORM 10-Q for the Quarterly Period Ended March 31, 2025
EX2002	Atossa Therapeutics Proposes Potentially Groundbreaking Study Aimed at Reducing Interval Breast Cancer in High-Risk Women at AACR 2025 (April 29, 2025)
EX2003	Atossa Therapeutics Announces Plans to Pursue Metastatic Breast Cancer Indication for (Z)-Endoxifen and Continued Engagement with FDA on Additional Indications (March 11, 2025)
EX2004	Financials – Intas Pharmaceuticals Ltd., http://www.intaspharma.com/financials/
EX2005	Atossa Therapeutics Announces Issuance of Key U.S. Patent Covering Endoxifen (March 8, 2022)
EX2006	Efficacy and Safety of Endoxifen in Bipolar I Disorder Patients, NCT06608641 (Last Updated March 17, 2025), https://clinicaltrials.gov/study/NCT06608641
EX2007	Declaration of Sayem Osman
EX2008	Atossa Covenant Not to Sue
EX2009	Atossa Therapeutics Announces Full Results from Phase 2 KARISMA-Endoxifen Study Demonstrating Statistically Significant Reductions in Mammographic Breast Density (Dec. 11, 2024)
EX2010	Atossa Therapeutics Announces First Quarter 2025 Financial Results and Provides a Corporate Update (May 13, 2025)
EX2011	<i>Intas Pharmaceuticals, Limited v. Atossa Therapeutics, Inc.</i> , PGR2023-00043, EX1030
EX2012	Breast Center Year in Review, An Unmet Need in HR-Positive Endocrine-Resistant Breast Cancer, <i>available at</i> https://jons-online.com/special-issues-and-supplements/2021/2021-year-in-review-breast-cancer/an-unmet-need-in-hr-positive-endocrine-resistant-breast-cancer
EX2013	ATOSSA THERAPEUTICS, INC. ANNUAL REPORT FORM 10-K for the Fiscal Year Ended December 31, 2024
EX2014	U.S. Patent No. 11,572,334
EX2015	Intas Requirements for Resolving Disputes with Atossa (FILED UNDER SEAL)
EX2016	Default Protective Order

Exhibit	Description
EX2017	<i>Intas Pharmaceuticals, Limited v. Atossa Therapeutics, Inc.</i> , PGR2025-00043, Pap.2 (Apr. 3, 2025)
EX2018	<i>Intas Pharmaceuticals, Limited v. Atossa Therapeutics, Inc.</i> , PGR2023-00043, Pap.1 (Aug. 18, 2023)
EX2019	Rishab Gupta & Swarndeeep Singh, <i>Endoxifen Approval for Bipolar in India, A Premature or a Pragmatic Decision?</i> , 43(1) J. CLINICAL PSYCHOPHARMACOLOGY 3 (2023)
EX2020	Zonalta, Why Zonalta?, <i>available at</i> https://zonalta.in/
EX2021	Atossa Therapeutics Granted Additional Patent Protection for Endoxifen (August 28, 2024)
EX2022	Declaration of Megan Raymond

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I. Introduction

As with Patent Owner Atossa Therapeutics Inc.’s (“PO” or “Atossa”) July 7 brief concerning Discretionary Denial (Pap.7), this §42.107 Preliminary Response confirms the Board should deny the above-captioned Petition (“Petition”/“Pet.”). The Petition fails to show claims 1-21 (“Challenged Claims”) of U.S. Patent No. 11,261,151 (“’151 Patent”; EX1001) are unpatentable.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 16.² Instead, Petitioner relies only on *inherency* based on Liu for this limitation. But Petitioner’s expert makes no fewer than *nine distinct deviations from Liu’s protocols* in attempting to arrive at the claimed Form I, and even then did not reliably obtain it. Thus, Petitioner’s own evidence confirms that Liu does *not* inevitably result in the claimed Form I of (Z)-endoxifen, Petitioner has failed to

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

² Reference to “Form I” herein 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 diffraction pattern comprising major peaks at $16.8 \pm 0.3^\circ$, $17.1 \pm 0.3^\circ$ and $21.8 \pm 0.3^\circ$ two theta.”

demonstrate the inherency on which its arguments rest, and Petitioner's Ground 1 fails.

Petitioner's Ground 2 fails for this same reason and more. To begin with, Petitioner's Ground 2 again relies on Liu as the base reference, and on its assertion that Liu inherently discloses Form I in connection with this limitation. Petitioner does not argue obviousness with respect to this limitation, and provides no additional or alternative argument regarding Form I to remedy its failure to show inherency, as discussed above for Ground 1. Therefore, Petitioner has not met its burden for Ground 2, either. In addition, Petitioner's Ground 2 fails to clearly identify which art the Petition relies on for many limitations, and in many instances fails to explain how it relies on Ahmad (its secondary reference for Ground 2) at all. And Petitioner's motivation to combine and reasonable expectation of success arguments are conclusory or missing for numerous claims, as well.

Because the Petition fails to show a reasonable likelihood of prevailing as to any claim of any Ground, institution should be denied.

II. Claims are Directed to A Novel, Non-Obvious Invention

A. The '151 Patent

Obtaining relatively pure and stable forms of (Z)-endoxifen proved a challenge until the '151 Patent, when the inventors developed a novel synthesis and purification 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. *See* EX1001, 27:23-40. The '151 Patent teaches a synthetic pathway and purification process to create this highly pure (Z)-endoxifen. *See id.* at Examples 1, 4-9. The starting isomeric mixture of (E)/(Z)-endoxifen is first subjected to crystallization. *Id.* Because the inventors observed that (E)-endoxifen is much less soluble than (Z)-endoxifen in a variety of solvents, this initial crystallization step results in an enriched (Z)-endoxifen component (*e.g.*, a mother liquor or filtrate). *See id.* at 68:3-10 (“(Z)-endoxifen was seen to be more soluble than (E)-endoxifen in EtOAc....Serial enrichment of Z-endoxifen by adding filtrates back to the first filtrate (first mother liquor) can also be performed.”). The enriched (Z)-endoxifen component is then subjected to further crystallization to obtain pure (Z)-endoxifen solid in a free-base composition. *See id.* at 68:6-8 (“Both solids and filtrates are useful for the preparation of (Z)-endoxifen free base.”). The (Z)-endoxifen free-base solid composition obtained is shown to have increased stability in ambient conditions, with reduced isomeric conversion to the (E)-isomer. *See id.* at 84:20-29 (“Results show that solid Z-endoxifen free base is stable for at least 9 months at 5° C. and 25° C./60% RH... (Z)-to-(E)”).

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. EX1001, cl. 1 (“A composition

comprising a crystalline form of a compound of Formula (III)... wherein the crystalline form of the (Z)-isomer is Form I”), 16 (“A method of treating a hormone-dependent breast disorder or a hormone-dependent reproductive tract disorder in a subject, the method comprising administering to the subject a composition comprising a crystalline form of a compound of Formula (III)... wherein the crystalline form of the (Z)-isomer is Form I”); *see id.* at cl. 2-15, 17-21.

The stable, highly-pure crystalline form of (Z)-endoxifen (“Form I”) claimed in the ’151 Patent aims to address the urgent need for a safer and more effective treatment and has improved bioavailability, bypassing metabolic limitations and providing consistent therapeutic benefit across diverse patient populations. *Id.* at 1:61-2:53, 2:57-11:2, 98:28-100:45. Moreover, unlike existing synthetic/purification methods, the process disclosed in the ’151 Patent to produce the claimed Form I with the claimed XPRD pattern achieves high yields, high purity, and improved stability, and is more economical and scalable for commercial production. *Id.* at 23:64-24:1, 27:23-40, 30:8-35, 82:5-19. The claimed Form I with improved stability addresses, *e.g.*, “a need for (Z)-endoxifen free base preparations that are sufficiently stable for preparation of pharmaceutical compositions that are suitable for administering to subjects, for example, at ambient temperatures as well as at higher temperature and humidity.” *See id.* at 82:5-19.

The invention described and claimed in the '151 Patent is not merely an incremental improvement; it is a breakthrough innovation for breast cancer therapy. The Challenged Claims are distinct from the claims of the previously-adjudicated related patent, U.S. Patent No. 11,572,334 (“the '334 Patent”), including because the previously-considered '334 claims do not have any Form I or XRPD requirement. EX2014, cl.1.

B. The Prosecution History

The application that led to the '151 Patent was subject to two rejections before PO overcame those rejections and the Challenged Claims were ultimately allowed by the Office. In the first office action, the Examiner rejected a subset of the claims under §112 and one claim under §103. EX1002, 426-433. With respect to §112, the Examiner found the reference to “Formula (III)” in independent claims 1 and 43 (and a number of dependent claims) to be unclear, and recommended adding the limitations of then-pending claim 4, which required “[t]he composition of claim 1, wherein the crystalline form is characterized by an x-ray powder diffraction pattern comprising major peaks at $16.8 \pm 0.3^\circ$, $17.1 \pm 0.3^\circ$ and $21.8 \pm 0.3^\circ$ two theta.” *Id.* at 385, 427; *see id.* at 467 (Patent Owner expressly “thank[ed] the Examiner for suggesting incorporating the limitations of claim 3, which Applicant has understood to mean claim 4 since claim 3 was previously canceled.”). In that same office action, the Examiner rejected then-pending claim 62 as obvious over Liu. *See id.* at 431-32

(referencing rejection based on WO 2017/070651). But the Examiner explained that many of the claims would be allowable once the §112 rejections were overcome: “The key to instant claims 1, 4-9, 32-35, 38-44, 46, 47, 49 and 52 is the polymorph of Form I. The closest prior art appears to be WO 2014/141292 A2, cited in the IDS, which teaches an endoxifen citrate polymorph (abstract; page 4, 5th full paragraph). (Instant diagramed Formula (III) is (E)/(Z)-endoxifen.) ***The reference does not teach, show, suggest or make obvious the instant Form I polymorph.***” *Id.* at 433.

In response to the rejection, PO withdrew claim 62 and amended claims 1 and 43 to include this limitation from what was then claim 4: “wherein the crystalline form of the (Z)-isomer compound of Formula (III) is Form I, characterized by an x-ray powder diffraction pattern comprising major peaks at $16.8 \pm 0.3^\circ$, $17.1 \pm 0.3^\circ$ and $21.8 \pm 0.3^\circ$ two theta.” *Id.* at 461, 464. The Examiner withdrew the original §112 and §103 rejections, but issued a new §112 rejection directed to a limited number of dependent claims. *Id.* at 498-503.

In response, PO amended those dependent claims to overcome the §112 rejection, *Id.* at 522-23, 525, and the Examiner withdrew the §112 rejection and allowed all pending claims. *Id.* at 537.

In the Notice of Allowance, the Examiner noted, “[a]s was stated in the 9/7/2021 Office Action, [that] the key to instant claims is the polymorph of Form I. The closest prior art appears to be WO 2014/141292 A2, cited in the IDS, which

teaches an endoxifen citrate polymorph (abstract; page 4, 5th full paragraph). (Instant diagramed Formula (III) is (E)/(Z)-endoxifen.) *The reference does not teach, show, suggest or make obvious the instant Form I polymorph.*” *Id.* at 537.

III. Asserted Art

A. Liu (EX1003)

Liu—affirmatively considered by the Examiner during the ’151 Patent’s prosecution—is an international patent application publication titled “Process for Preparing (Z)-Endoxifen of High Purity.” EX1003, 1. Liu provides various experimental protocols that it alleges result in (Z)-endoxifen. EX1003, ¶¶19-55, 56-59, 61-77. But as Petitioner’s expert concedes, “Liu does not report any X-ray powder diffraction (“XRPD”) data of the compounds Liu synthesized. Thus, Liu does not report whether its compounds exhibited the XRPD pattern recited in the claims of the 151 patent (i.e., Form I).” EX1033, ¶33.

B. Ahmad (EX1004)

U.S. Patent No. 9,333,190 (“Ahmad”)—cited on the face of the ’151 Patent—is titled “Endoxifen compositions and methods.” EX1004, Cover. Ahmad purports to disclose methods of treatment using compositions containing endoxifen and methods for making those compositions. EX1004, Abstract. Petitioner purports to rely on Ahmad as a secondary reference in Ground 2. Pet.3. But, for many claims in Ground 2 (at least claims 1-6, 16, and 21), Petitioner cites no particular aspect of Ahmad for its arguments. Pet.37-39, 56-62; *see also infra* Section V.A-B. Petitioner

does refer to Ahmad in its Ground 2 analysis of certain dependent claim limitations including, *e.g.*, limitations directed towards dosing, formulation, and treatments using the claimed Form I. *See* Pet.39-43, 45-46, 50, 52-56, 63-66 (addressing claims 7-15, 17-20).

Ahmad does not disclose the generation of specific polymorphs of endoxifen, methods of identifying different polymorphs via XRPD, or Form I—and Petitioner does not assert that it does. *See generally* EX1004.

IV. Liu Fails to Anticipate Claims 1-6, 16, 18, 21 (Ground 1)

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...”); *Millennium Pharms., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1367 (Fed. Cir. 2017) (“fact that a certain thing **may** result” is insufficient (quoting *In re Oelrich*, 666 F.2d 578, 581 (C.C.P.A. 1981))); *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.**”); *Celltrion, Inc. v. Chugai Seiyaku Kabushiki Kaisha*, IPR2022-00579, Pap.72, 27 (Aug. 29, 2023) (“A reference may anticipate inherently if a claim limitation that is not expressly disclosed ‘is **necessarily present**, or inherent, in the single anticipating reference.’”) (quoting

Verizon Servs. Corp. v. Cox Fibernet Va., Inc., 602 F.3d 1325, 1337 (Fed. Cir. 2010)); *see also Arbutus Biopharma Corp. v. Modernatx, Inc.*, 65 F.4th 656, 662 (Fed. Cir. 2023) (“A limitation is inherent if it is the ‘**natural result flowing from the prior art’s explicit disclosure.**’”) (citations omitted); *Agilent Techs., Inc. v. Affymetrix, Inc.*, 567 F.3d 1366, 1383 (Fed. Cir. 2009) (holding that the “very essence of inherency is that one of ordinary skill in the art would recognize that a reference **unavoidably teaches** the property in question”). “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) (quoting *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1195 (Fed. Cir. 2014). “Rather, a party must ‘show that **the natural result flowing from the operation as taught** would result in the performance of the questioned function.’” *PersonalWeb*, 917 F.3d at 1382 (quoting *PAR*, 773 F.3d at 1195). As this binding precedent confirms, Petitioner’s inherency arguments fail as a matter of law.

A. Petitioner’s Inherency Arguments Are Legally Insufficient

Both independent claims 1 and 16 of the ’151 Patent require a composition wherein “**the crystalline form of the (Z)-isomer is Form I.**” *See* ’151 Patent, cl. 1, 16. As the Examiner found, Form I is a “key” novel and non-obvious advance over the prior art, including Petitioner’s Liu reference. EX1002, 433, 537. And just as in the original prosecution, this critical disclosure remains absent from the Petition

here: Petitioner and all three of its experts concede that Liu *fails* to disclose the claimed Form I with the x-ray powder diffraction pattern. Pet.29 (“*Liu does not disclose* that the (Z)-endoxifen he creates is the claimed ‘Form I’ or provide an XRPD characterization of the resulting crystalline solids.”); EX1034, ¶29 (“*Liu does not disclose* that the (Z)-endoxifen created is the claimed ‘Form I’ or provide an XRPD characterization of the resulting crystalline solids.”); EX1033, ¶33 (“*Liu does not report* whether its compounds exhibited the XRPD pattern recited in the claims of the 151 patent (*i.e.*, Form I).”); EX1032, ¶65 (“*[N]either Liu nor Ahmad specifically disclose* that their Z-endoxifen is the claimed ‘Form 1’”).

Instead, Petitioner rests its entire invalidity theory for Ground 1 (and 2) (Pet.3, 29, 38) on legally inadequate assertions of *inherent* disclosure by Liu in attempt to establish disclosure of the Form I (Z)-endoxifen. See Pet.29, 34, 35 (cl.1, cl.16 (“(Z)-isomer is Form I, characterized by an x-ray powder diffraction pattern comprising major peaks at $16.8\pm0.3^\circ$, $17.1\pm0.3^\circ$ and $21.8\pm0.3^\circ$ two theta”); cl.6 (“wherein greater than 90% by weight of the (Z)-isomer in the composition is crystalline Form I”).³ But Petitioner has clearly failed to demonstrate that the claimed Form I was

³ Indeed, Petitioner does not allege (nor could it) that any teaching from any other reference or that knowledge of POSITA discloses the XRPD pattern missing from Liu. See Pet.29, 38. Ground 2 rests on the same inherency theory advanced in

“necessarily present” within or that it will “inevitably result” from Liu’s disclosures. *See, e.g., PersonalWeb*, 917 F.3d at 1382; *Endo Pharms. Sols., Inc. v. Custopharm Inc.*, 894 F.3d 1374, 1381, 1383 (Fed. Cir. 2018); *In re Montgomery*, 677 F.3d at 1380; *Tummers v. Kleimack*, 455 F.2d 566, 569 (C.C.P.A. 1972) (“[W]here support must be based on an inherent disclosure, it is not sufficient that a person following the disclosure might obtain the result set forth in the counts; it must inevitably happen.”). Indeed, ***Petitioner’s evidence shows the opposite***: 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. EX1033, 89 (“***XRPD – Not Form I***”), 91 (“***Not Form I***”). Petitioner’s arguments thus fail as a matter of law.

1. Petitioner’s Modified Reproduction of Liu Is Legally Insufficient to Establish Inherency

Petitioner’s reliance on inherency is fundamentally undercut by its own expert’s admissions, which show Petitioner’s expert ***modified*** Liu, ***filled in gaps***, ***and made choices among various available implementation options*** in Liu’s disclosure to allegedly achieve supposedly “inherent” results that Petitioner argues satisfy the claims. *See e.g.,* EX1033, ¶¶51 (“I synthesized compound (5) by a

Ground 1 and provides no independent evidence or motivation concerning the Form I limitation.

modification of the procedure described by Liu”), 52n.3 (“*Liu does not explicitly state to use Celite* at this step.”), 52n.4 (“While *Liu does not specifically describe using chromatography...*”), 54n.5 (“*Liu states...argon atmosphere.... Instead of an argon atmosphere, I placed the reaction under a nitrogen atmosphere.*”); *see also* Pet.10-15, 29. The declaration of Petitioner’s expert, Dr. Bihovsky, reveals that *Liu’s process would not give him the result* he desired and relies upon *until he rewrote it in at least nine separate ways* (as numbered below)—and even then, *multiple results failed to yield the claimed Form I*, a fact that Petitioner conspicuously omits despite its direct *refutation* of “inherency.” *See id.*

Indeed, Petitioner’s deliberate alterations and resulting failures are the *opposite* of inherency, which requires that the missing element be *necessarily, unavoidably, and inevitably* present based on the reference’s explicit disclosure, as discussed above. *See In re Montgomery*, 677 F.3d at 1380. By Petitioner’s and Dr. Bihovsky’s own admissions, Dr. Bihovsky did not follow Liu as written. This is fatal to Petitioner’s inherency arguments. Instead, Dr. Bihovsky **(1)** ran the synthesis at a markedly smaller laboratory scale than Liu’s commercial-scale disclosures, making various changes to Liu as a result. EX1033, ¶¶48, 52n.4, 59n.6 (“centrifugation is a minor deviation from Liu’s procedure... was simply a more practical approach given the scale of the recrystallization I conducted...”). And contrary to Liu’s explicit disclosures, he then **(2)** increased the temperature in the

first reaction step to 70 °C (after various preliminary experiments failed), even though Liu expressly instructs 45-50 °C; he admitted that the reaction would not proceed as written and was “mostly complete” only after the temperature was elevated and reaction time was extended by five hours. *Id.* at ¶51. *See Endo*, 894 F.3d at 1383 (“Under the circumstances of this case, the incomplete description of the TU injection composition elements denied skilled artisans from having access to that composition, thereby precluding use of the inherency doctrine to fill in disclosure about the product missing from the Articles.”); *Pfizer, Inc. v. Chugai Pharm. Co.*, IPR2017-01357, Pap.56, 19-20 (Nov. 28, 2018) (“Petitioner does not argue either that there is only a single method for making Shadle’s elution buffer, which always yields a buffer having 100 mM or less total solute, or that every method for producing Shadle’s buffer results in a buffer with 100 mM or less total solute... The probability or possibility that an ordinarily skilled artisan would have used one of the four methods described by Dr. Przybycien to prepare Shadle’s elution buffer is insufficient to establish inherency.”).

Throughout the synthesis, Dr. Bihovsky also experimented with additional or substitute process *steps not found in Liu*. For example, he (3) pre-dried zinc bromide at 230 °C to remove moisture, a step Liu does not mention. *Id.* at ¶51n.1. Dr. Bihovsky does not show Liu removed the moisture at all, and, even if Liu had done so, Dr. Bihovsky did not establish that every way in which the moisture could

have been removed would have yielded the same result. He also (4) used a Celite pad to filter an emulsion, claiming it was a judgment a skilled chemist would make (but admitting it was not the only possible option (EX1033, ¶52n.3 (“Liu does not explicitly state to use Celite... Celite is a commonly employed filtration medium...”))), and he (5) added a column chromatography purification that Liu does not disclose, justifying it as a “common” small-scale adjustment (*id.* at ¶52n.4 (“I decided to employ chromatography”))). He also (6) substituted a nitrogen atmosphere in place of Liu’s argon (*id.* at ¶54n.5), and (7) replaced filtration with centrifugation during a key recrystallization step because it was more “practical” (*id.* at ¶59n.6). Despite these interventions, the (8) resulting product still differed in E/Z isomer ratio: 33% Z, rather than the 47% Z disclosed in Liu (*id.* at ¶60n.7). Finally, because only a “small amount of precipitate” had formed, Dr. Bihovsky (9) physically scratched the flask and continued stirring for 24 more hours to *force* crystallization (*id.* at ¶61).

A summary of ways in which Dr. Bihovsky’s analysis deviated from the disclosures in Liu is below:

Process Step	Liu’s Disclosure	Dr. Bihovsky’s Experiment Disclosure
(1)Experiment Scale	[¶0005] “The procedure provides a very attractive approach for obtaining the compound as it proceeds efficiently from commercially available	[¶48] “I performed Liu’s method on a smaller scale than disclosed in Liu’s Examples (which is on a large, commercial manufacturing scale).”

	starting materials... and enables facile scale-up operations in multi-kilogram quantities.	
(2)Reaction Temperature in First Synthesis Step	[¶0062] “Stirring at 40 - 50°C was continued for 1 hour and overnight (16 hours) without heating. ”	[¶51] “I performed the reaction at 70 °C.... The mixture was slowly heated to 68 to 70 °C over 1 hour, then stirred at 70 °C (internal temperature) for 5 more hours, at which time TLC2 showed that the reaction was mostly complete”
(3)Zinc Bromide Drying	[¶0060] “The reagents and solvents used were commercial anhydrous grade. They were used without further purification.”	[¶51, n.1] Prior to using, I dried the zinc bromide at 230 °C. While Liu does not specify how the zinc bromide was dried, Liu does state that “[t]he reagents and solvents used were commercial anhydrous grade.”
(4)Celite Filtration	[¶0063] “The formed solid was separated by filtration , washed with ethyl acetate and discarded. The aqueous phase was separated from the organic filtrate and discarded.”	[¶52] “I stirred and shook the aqueous mixture with ethyl acetate and vacuum filtered it through Celite to break up the emulsion.” [¶52, n.3] “While Liu states that the mixture is filtered, Liu does not explicitly state to use Celite at this step.... Liu reports using Celite in the following step to remove Zinc power.”

(5)Column Chromatography Step	[¶0062] “Completion of the reaction was confirmed by NMR.”	[¶52] “The product was purified by column chromatography ⁴ on silica gel (7 X 30 cm)....” [¶52, n.4] “While Liu does not specifically describe using chromatography in [0062], Liu teaches that chromatography should be employed after the following reaction in Example 3, described below.”
(6)Argon Atmosphere Reaction	[¶0065] “Zn dust (4.3 kg, 65.8 mol) was suspended in anhydrous dimethoxyethane (26 L) in a 100-L jacketed glass reactor under argon atmosphere , and the contents of the reactor were cooled to 2°C.”	[¶54] “I then placed the mixture under nitrogen ⁵ and cooled the mixture in an ice bath under a nitrogen atmosphere.” [¶54, n.5] “Instead of an argon atmosphere, I placed the reaction under a nitrogen atmosphere . A POSA would understand that nitrogen could be used in place of argon to achieve an inert atmosphere.”

(7)Centrifugation Step	[¶0070] “The resulting crystalline material was collected by filtration (initial weight 2336 g) and dried in vacuo to give 1395 g of a mixture of E- and Z-Endoxifen.”	[¶59] “The cold mixture was quickly centrifuged to isolate the solid precipitate. ⁶ ” [¶59, n.6] “I note that centrifugation is a minor deviation from Liu’s procedure, which isolated the solid via filtration. Centrifugation was simply a more practical approach given the scale of the recrystallization I conducted in my laboratory.”
(8) Differing isomer ratio	[¶0070] “The total yield of endoxifen (E/Z-isomer ratio:51/47) from two recrystallizations was 1468 g (87%).”	[¶60, n.7] “Liu, however, obtained a crude endoxifen mixture with a slightly different ratio of E:Z endoxifen (Liu: 51/47 ratio of E/Z; my synthesis: 67:33 ratio.... ”
(9)Crystallization Manipulation	[¶0073] “The mother liquor (containing 71 % Z-isomer) was removed from the reactor,	[¶61] “ The flask was scratched to increase crystallization and

	evaporated to provide a solid and dried at 35°C to constant weight: 1314 g (48%, Z-isomer content: 73%).”	stirred at 4 °C for 24 more hours.”
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The Board rejected a similarly inadequate inherency argument in *SNF S.A. v. Chevron U.S.A., Inc.*, where the supposedly inherent property (a specific filter ratio) was achieved only after petitioner’s expert added a “dewatering” step not described in the reference. IPR2022-01534, Pap.46, 25-27 (Apr. 18, 2024). The Board emphasized that inherency “may not be established by probabilities or possibilities,” and “[t]he mere fact that a certain thing *may* result from a given set of circumstances is not sufficient.” *Id.* at 23–24 (quoting *Cont’l Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991)); *see also Pharmacyclics LLC v. Alvogen, Inc.*, No. 2021-2270, 2022 WL 16943006, at *10 (Fed. Cir. Nov. 15, 2022) (“[T]he district court likewise found no evidence that only Form A could have been used to achieve the results... those findings dictate rejection of Alvogen’s inherent anticipation argument.”); *Crown Operations Int’l, Ltd. v. Solutia Inc.*, 289 F.3d 1367, 1377 (Fed. Cir. 2002) (“it must be necessarily present”); *Trintec Indus., Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1295 (Fed. Cir. 2002) (“Inherent anticipation requires that the missing descriptive material is ‘necessarily present,’ not merely probably or possibly present, in the prior art.” (quoting *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999))).

The same reasoning applies here. Petitioner's expert modified Liu's process not once, as in *SNF*, but in *at least nine ways*, and, as discussed in detail below, *still repeatedly failed to yield the claimed Form I*. The purported "inherency" here is merely the result of Petitioner selectively reporting the one success while omitting the multiple failures. As in *SNF*, Petitioner's numerous modifications, and (as discussed *infra*, §IV.A.2) its numerous failures even with these modifications, affirmatively *negate* its claim that Form I naturally flows from Liu's teachings. Instead, they prove the contrary: this result is *not necessary, unavoidable, or inevitable*, and thus *not inherent*.

Dr. Bihovsky tries to wave away his changes to Liu as "minor" with a blanket disclaimer at the beginning of his analysis (EX1033, ¶47), and later asserts that certain changes would have "no effect" on the final crystal form. EX1033, ¶¶47, 48, 51n.1, 52n.4, 54n.5, 59n.6, 60n.7. But even assuming "minor" changes were permissible in proving inherency (they are not), Dr. Bihovsky never cites evidence or provides any explanation for why many of his changes would be considered "minor" or be expected to have "no effect," including at least the following, where he, at most, argues that POSITA would "understand" these changes: his change in reaction temperature (¶51); his drying of zinc bromide prior to synthesis (¶51n.1) ("POSA would understand that zinc bromide, a hygroscopic reagent, should be dried prior to use in this synthesis"); his timing of the filtration with Celite (¶52, ¶52n.3)

(“POSA would have understood that Celite is a commonly employed filtration medium to break up an emulsion and/or remove fine particles from a solution.”); his use of column chromatography (§52n.5) (“POSA would understand that chromatography would have been a commonly used purification strategy that could be employed at this stage”); his substitution of nitrogen for argon (§54n.4) (“POSA would understand that nitrogen could be used in place of argon to achieve an inert atmosphere”); and his scratching of the flask to increase crystallization (§61). Dr. Bihovsky further fails to explain *why* he made at least the following changes *at all*: his change in reaction temperature (§51) and his substitution of nitrogen for argon (§54n.4).

Moreover, although there are instances where Dr. Bihovsky’s provides some explanation regarding certain alleged “minor” changes, these self-serving assertions (although critical to his inherency argument) are conclusory and lack citation to and support by evidence. EX1033, §§47 (“I made some minor adjustments compared to Liu’s Examples. Each of these adjustments were routine adjustments a POSA following Liu would have likely made. In my opinion, none of the modifications had any impact on the resulting crystalline solids....”), 48 (“there is no indication that performing Liu’s method on a smaller scale would result in a different compound than the claimed Form I of Formula (III), i.e., (Z)-endoxifen... Other minor adjustments that I made compared to Liu’s Examples are described below”),

59n.6 (“I note that centrifugation is a minor deviation from Liu’s procedure, which isolated the solid via filtration.”), 60n.7 (“This is a distinction without a difference.”). That is insufficient to meet Petitioner’s burden. For example, in *Atrium Med. Corp. v. Bard Peripheral Vascular, Inc.* the Board rejected an expert’s argument that the prior art made certain inherent disclosures, because “the witness ***merely concludes this without citation to supporting evidence,***” and those conclusory statements were “meager evidence of an alleged inherent disclosure intended to be a foundation of Petitioner’s challenges.” IPR2021-01197, Pap.11, 16n.5 (Jan. 10, 2022). Similarly, as the Federal Circuit has confirmed, “conclusory expert testimony is inadequate to support an obviousness determination on substantial evidence review.” *TQ Delta, LLC v. CISCO Sys., Inc.*, 942 F.3d 1352, 1358–59 (Fed. Cir. 2019); *see cxLoyalty, Inc. v. Maritz Holdings Inc.*, 986 F.3d 1367, 1378 (Fed. Cir. 2021) (“We do not accord weight to conclusory expert testimony.”); 37 C.F.R. §42.65(a) (“Expert testimony that does not disclose the underlying facts or data on which the opinion is based is entitled to little or no weight.”); *Xerox Corp. v. Bytemark, Inc.*, IPR2022-00624, Pap.9, 15 (Aug. 24, 2022) (precedential) (denying institution and according petitioner’s expert “little weight” where the expert’s declaration was conclusory and failed to “cite to any additional supporting evidence or provide any technical reasoning to support his statement”); *Motorola Mobility LLC v. Maxell, Ltd.*, IPR2023-00110, Pap.7, 34-35 (June 15,

2023) (finding cited declaration testimony was “conclusory, unsupported, and entitled to little or no weight” where it did not provide “any additional supporting evidence or technical reasoning”).⁴

Further, when Dr. Bihovsky added or substituted steps not in Liu, he never showed that *any and all* ways to perform the added or substituted step would have still resulted in Form I. *See Pharmacyclics*, 2022 WL 16943006, at *10; *Pfizer*, Pap.56, 19-20. Instead, he failed to provide support showing each change, whether in temperature, atmosphere, purification, isolation method, physical handling, or the very act of triggering crystallization, did not affect the crystallization pathway and

⁴ Dr. Miller’s opinions are also conclusory and unsupported by sufficient explanation. For example, he states that “[t]he experimental test and analysis conditions used for the XRPD testing is attached to this declaration as Appendix B,” but his declaration ***does not contain an Appendix B***. EX1034, ¶23. Dr. Miller’s entire analysis for claims 1-5 and 16 relies on the experimental data in the ***absent*** Appendix B. His entire opinion is thus unsupported and should be accorded no weight because it relies on a conclusory analysis that is unsupported by sufficient explanation. And because Dr. Miller was responsible for testing all of Dr. Bihovsky’s samples, this appendix also would be expected to include tests for the samples later identified by Dr. Bihovsky as “Not Form I.” EX1033, ¶¶89, 91.

outcome. As in *Pfizer*, Petitioner offers only a hand-picked menu of concocted process **changes** from Liu, proving that Form I is, at best, only one possible outcome among many—**not** the inevitable result of following Liu. *See Pfizer*, Pap.56, 19-20 (“The probability or possibility that an ordinarily skilled artisan would have used one of the four methods described by Dr. Przybycien to prepare Shadle’s elution buffer is insufficient to establish inherency.”).

Dr. Bihovsky’s analysis, which departs from the disclosures of Liu in at least nine ways, fails to meet the standard for inherent anticipation.

2. Petitioner’s Modified Reproduction of Liu Failed, as a Matter of Fact, to Produce the Claimed Form I, Confirming Liu’s Non-disclosure

Even after all of the modifications discussed above, multiple samples produced by Dr. Bihovsky still ***failed to produce the claimed Form I***. This, too, is fatal to Petitioner’s inherency arguments. *See Knauf Insulation, Inc. v. Rockwool Int’l A/S*, 788 F. App’x 728, 734–35 (Fed. Cir. 2019) (“That a prior art reference satisfies these limitations in the reactants is not enough to allow the Board to find inherency in the products of the reaction, unless there is evidence that ***any reaction*** meeting these quantity of reactant limitations would result in the quantity of product limitation.”); *Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 1047-48 (Fed. Cir. 1995); *see also Azurity Pharms., Inc. v. Exelixis Inc.*, IPR2025-00210, Pap.11, 29 (June 4, 2025) (denying institution based on the merits, finding that “on the current record

Petitioner has not shown that the combination of [the asserted art] would inherently result in [the claimed limitation] and Petitioner has not shown that it has a reasonable likelihood that it would prevail on the obviousness ground.”).

Dr. Bihovsky’s lab notebook entries explicitly state this: sample “15-30-1P” is annotated with the clear conclusion “**XRPD – Not Form I**,” EX1033, 89 (annotation added):

	'651 P 73	
10/12/23	combine E- ppts 15-28- 2P, 3P, 4P, 5P + 15-29-1P, 2P, 5P, 5S (1.336g)	
2:40	Reflux (at bp 88°) with iPrOAc (13.4 ml) with stirring for 2h. Most dissolved over 2h → turbid soln. Cool slowly to 15°. (20° O.N. then 15° 2h). Vac filter rapidly Rotary filtrate → 160 mg pink solid NMR (DMSO) 44% z- + impurity 15-30-15 Dry ppt → 1.13 mg white solid NMR (DMSO) 100% E. XRPD – Not Form I 15-30-1P	

And sample “15-32-1P” is likewise marked “**Not Form I**,” EX1033, 91 (annotation added):

32	
10/24/23	Decidure 15-30-45 (206 mg) iPrOPAc (2.06 mg)
	brief ΔX. Cool slowly (with) to 20° then 15°
Ref '651	for 2 days. Vac filter, rinse with ~0.1 mg cell
0054	iPrOPAc. Dry → 109 mg xll. 97% Z. NOT FORM I 15-32-(P
	Rotavapo filtrate → 98 mg from 36% Z. -15

Yet neither Petitioner nor any of its three experts make any attempt to explain *or even acknowledge* these failed results, which are conspicuously omitted from the declarations' main text and buried only in an appendix. See EX1033, 89, 91. This underscores not only that Liu's methods did not yield the claimed Form I (and are therefore not inherent), but also that Petitioner's inherency theory depends entirely on selectively reporting only favorable outcomes while masking the very evidence from Petitioner's expert that affirmatively *disproves* inherency. See *Glaxo*, 52 F.3d at 1047-48 (finding no inherency when claimed compound was not produced every time by following the reference's teachings even though expert performed prior art example 13 times and obtained claimed material). The Board should not permit such deceptive and manufactured disclosures to serve as the basis for institution.

In sum, the many modifications and failed attempts undertaken by Petitioner demonstrate that its synthesis of the claimed Form I was far from a straightforward execution of Liu's teachings; instead, it was a trial-and-error, result-driven quest

affirmatively *departing* from Liu and marked by hindsight-driven adjustments and selective reporting of only the favorable outcomes. Indeed, if the outcome had truly been inherent, Petitioner would have had no need to resort to these extensive laboratory interventions and alterations, and would not have experienced multiple failed attempts to yield the claimed subject matter.

3. The Dependent Claims Challenged in Ground 1 Are Not Anticipated

The Board need go no further before rejecting Petitioner's challenges to *all* of the claims challenged in Ground 1. Because Liu fails to disclose a necessary element of independent claims 1 and 16, Liu also fails to anticipate the Challenged Claims that depend from them, all of which require the claimed Form I. Thus, Petitioner has failed to show by a preponderance of the evidence that Liu discloses each and every limitation of the Challenged Claims.⁵

⁵ Claims 2-5 have additional XRPD requirements beyond those in claim 1 and claim 6 has a purity requirement. Petitioner's inherency arguments fail with respect to the additional requirements of those dependent claims for substantially the same reasons as Petitioner's claim 1 inherency arguments fail. *See* Pet.30-33.

V. Liu and Ahmad in View of POSITA's Knowledge of the Art Fail to Render Obvious Claims 1-21 (Ground 2)

A. Petitioner's Obviousness Combination Does Not Overcome its Failure to Prove That Liu Inherently Discloses Form I

Petitioner's obviousness arguments are directed towards *combining* Liu's alleged (but failed) inherent disclosure of the claimed Form I with alleged disclosures of *other claim elements*. *See, e.g.*, Pet.37-39 ("arriving at the invention claimed in the 151 patent from Liu would have involved simply utilizing known, conventional, and predictable processes, and a POSA would have had a reasonable expectation of success in doing so,") 62 ("arriving at the invention claimed in the 151 patent from Liu would have involved simply utilizing known, conventional, and predictable processes, and a POSA would have had a reasonable expectation of success in doing so."). Petitioner's Ground 2 therefore fails, including because Petitioner relies on the same erroneous arguments that Liu inherently discloses Form I to support its asserted combination. Pet.38 ("As discussed above, the claimed XRPD patterns are inherently taught by Liu"), 61-62 ("the claimed XRPD patterns are inherently taught"); *see also* EX1033, ¶¶43, 89.

B. Petitioner Additionally Fails to Clearly Identify Its Claimed Combinations

Petitioner's arguments regarding Ground 2 (including claims 1 and 16) additionally fail for lack of clarity. §42.104(b)(4) states that an IPR petition "must specify where each element of the claim is found in the prior art patents or printed

publications relied upon,” and here, Petitioner’s arguments for several dependent claims, including for at least claims 1-6, 16, and 21, fail to meet Rule 104(b)(4)’s requirements. For example, Ground 2 purports to address obviousness “over Liu and Ahmad in view of the knowledge of a POSA,” but Petitioner ***does not identify any teachings of Ahmad*** that it relies on for various Challenged Claims, including claims 1-6, 16, or 21. Pet.37-39, 61. This lack of clarity regarding what Petitioner is purportedly relying on for which limitations is an additional reason that Ground 2 fails to make the showing required to justify a trial here. *See In re Magnum Oil Tools Int’l, Ltd.*, 829 F.3d 1364, 1380 (Fed. Cir. 2016) (“To satisfy its burden of proving obviousness, a petitioner cannot employ mere conclusory statements. The petitioner must instead articulate specific reasoning, based on evidence of record, to support the legal conclusion of obviousness.”); *In re Lee*, 277 F.3d 1338, 1345 (Fed. Cir. 2002) (“The board cannot rely on conclusory statements when dealing with particular combinations of prior art and specific claims, but must set forth the rationale on which it relies.”); *Mediatek, Inc. v. Mosaid Techs. Inc.*, IPR2024-00718, Pap.10, 24-25 (Oct. 9, 2024) (denying institution, finding that Petitioner’s analysis failed to “stat[e] which reference’s teaching is used in the combination and [did] not clearly identify[] the proposed combination”).

Moreover, Petitioner argues “POSA would have been able to draw on teachings in the art available before the time of the invention, such as, for example,

Fauq (Ex. 1005) and Milroy (Ex. 1022).” Pet.38; *see also id.* at 62 (“arriving at the invention claimed in the 151 patent from Liu would have involved simply utilizing known, conventional, and predictable processes, and a POSA would have had a reasonable expectation of success in doing so.”). But Petitioner fails to identify *what*, if any, actual disclosures from these references on which it relies, or to explain *how* Fauq or Milroy in view of POSITA’s knowledge of the art would disclose or render obvious the various dependent claims. *See* Pet.37-39, 62. Petitioner merely waves this generalized, conclusory assertion of obviousness about like some magic wand of invalidity—arguing, without further explanation, that POSITA would have “draw[n] on teachings in the art available before the time of the invention, such as, for example, Fauq (Ex. 1005) and Milroy (Ex. 1022).” Pet.38. Again, Petitioner’s conclusory assertions are insufficient to satisfy Rule 104(b)(4) and to meet its burden to demonstrate unpatentability (*see In re Magnum Oil Tools*, 829 F.3d at 1380; *In re Lee*, 277 F.3d at 1345; *Mediatek*, Pap.10, 24-25), and, if trial were instituted, the failure of the Petition to articulate any actual theory would unfairly require PO and the Board to confront new unarticulated theories in clear violation of the AIA’s minimum requirements.

C. Petitioner’s Conclusory Assertions Regarding Motivation to Combine Also Fail

Petitioner also fails to articulate anything beyond conclusory assertions for why POSITA would have been motivated to combine the asserted art for many

Challenged Claims, including the independent claims from which all the other Challenged Claims depend.

First, Petitioner fails to identify the specific gaps in Liu it seeks to fix by asserting obviousness and makes *no arguments regarding any particular motivation to combine tied to the specifics of the claims in, e.g., its analysis of claims 1-6*. See Pet.37-39. The details of Petitioner’s claim 16 arguments are similarly vague. Pet.62. Thus, Ground 2 fails regarding these claims for this independent reason. *Google LLC v. Jawbone Innovations, LLC*, IPR2022-00889, Pap.12, 20, 22 (Nov. 14, 2022) (denying institution where petitioner failed to explain “motivat[ion] to solve a problem [the reference] already solves”); *Apple Inc. v. Identity Security LLC*, IPR2022-00170, Pap.9, 28 (July 5, 2022) (denying institution when Petitioner failed to “sufficiently articulate[]” why a person of ordinary skill in the art would have combined the asserted references); *Quest Diagnostics Inc. v. Ravgen, Inc.*, IPR2021-00790, Pap.21, 34 (Oct. 19, 2021) (denying institution, explaining that Petitioner failed to “provide a sufficient evidence-backed theory on how [the asserted art] would be combined... Doing so might be straightforward. Or there may have been known or unknown complexities still to be explored.”); *Axon Enter., Inc. v. Digital Ally, Inc.*, IPR2017-00515, Pap.10, 18-19, 38 (July 6, 2017) (denying institution, stating neither petitioner nor its expert “explains in sufficient

detail the nature of Petitioner’s proposed modification... Petitioner does not explain in sufficient detail how the proposed modification is supposed to work”).

Moreover, for claims 8-9, for example, Petitioner provides nothing more than the unsupported, conclusory assertions that POSITA would have been “motivated to use the teachings of Ahmad to develop formulations of highly pure (Z)-endoxifen for the treatment of breast cancer and other breast diseases” and “a POSA would have been motivated to use [the claim limitation].” Pet.39, 41. Similarly, for claims 10-12 and 15, Petitioner asserts only that “a POSA would have been aware of the target pharmacokinetics [never specified by Petitioner] expected to be efficacious and would have been motivated to optimize a formulation to achieve them,” without further explanation of why POSITA would be so motivated. Pet.49-56. Further, for claim 14, for example, Petitioner does not explain why POSITA would target ***at least 80%*** of the compound being released in the intestines. *See* Pet.44-45. And for claim 17, Petitioner says only that “a POSA would have been motivated to use the highly pure (Z)-endoxifen of Liu in patients with prostate cancer who have or at risk of having gynecomastia to simultaneously treat both conditions.” Pet.63. Petitioner’s conclusory obviousness statements, unsupported by evidence or explanation, are not enough to meet Petitioner’s burden and to provide sufficient detail as to what the combination is, which claim elements are missing from the base reference, or why

POSITA would have been motivated to modify the base reference. Pet.39-42, 46-56; *Google*, Pap.12, 20; *Apple*, Pap.9, 28; *Quest*, Pap.21, 34; *Axon*, Pap.10, 18-19.

D. Petitioner’s Conclusory Assertions Regarding Reasonable Expectation of Success Also Fail

Petitioner’s reasonable expectation of success arguments are also impermissibly conclusory, and cannot carry Petitioner’s burden. For claims 1-6 and 16, Petitioner simply asserts without explanation that “a POSA would have had a reasonable expectation of success in” achieving the claims. Pet.38, 62. And Petitioner relies on similarly conclusory assertions for its arguments regarding reasonable expectation of success for many other dependent claims: for claim 14, Petitioner states only a “POSA would have had a reasonable expectation of success, as this was known in the art,” Pet.46; and for claims 10-12 and 15, Petitioner states only that “a POSA would have been aware of the target pharmacokinetics [never specified by Petitioner] expected to be efficacious for (Z)-endoxifen compositions and would have been motivated to optimize a formulation to achieve them with a reasonable expectation of success (e.g., as taught by Ahmad 2010 and Ahmad 2012).” Pet.51, 54, 55. These conclusory statements are insufficient to meet Petitioner’s burden to establish unpatentability. *In re Lee*, 277 F.3d at 1345 (“The board cannot rely on conclusory statements when dealing with particular combinations of prior art and specific claims, but must set forth the rationale on which it relies.”); *Quest*, Pap.21, 34-35 (denying institution, concluding “we are not persuaded on this record that

Petitioner has shown how the art would have been combined with a reasonable expectation of success in arriving at the claimed subject matter.”); *Hewlett Packard Enter. Co. v. Intell. Ventures II LLC*, IPR2022-00115, Pap.9, 12-16 (Mar. 29, 2022) (denying institution, concluding “Petitioner does not explain sufficiently, let alone with particularity, how or why the skilled artisan would have combined such distinct embodiments [of the asserted reference] or had an expectation of success in doing so.”); *Luitpold Pharms., Inc. v. Apicore US LLC*, IPR2018-01640, Pap.19, 24 (Mar. 6, 2019) (denying institution where petitioner “fail[ed] to explain adequately for institution why the ordinarily skilled artisan would have reasonably expected success under the particular facts of this case, especially where, as the Federal Circuit noted” in a prior decision involving the challenged patent that “the path to arrive at [the claim limitation at issue] was not known before the relevant date of the [challenged patent]”).

Moreover, for claims 17-20, Petitioner provides *no assertion whatsoever about reasonable expectation of success* (and frequently omits specifics about how Liu would be implemented in the obviousness combination such that reasonable expectation of success could be assessed). Instead, Petitioner mentions, at most, an alleged motivation to combine the cited references:

- For claim 17, Petitioner says only “a POSA would have been motivated to use the highly pure (Z)-endoxifen of Liu in patients with prostate

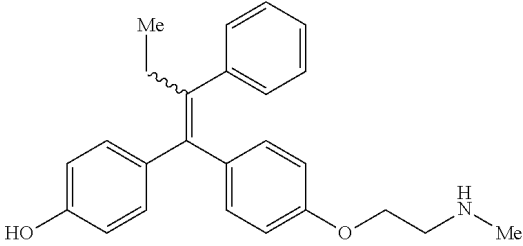
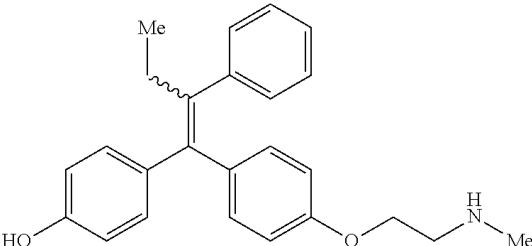
cancer who have or at risk of having gynecomastia to simultaneously treat both conditions.” Pet.63.

- For claim 18, Petitioner says only “A POSA would have therefore understood that endoxifen was expected to be efficacious in patients who were tamoxifen-resistant or tamoxifen-refractory due to metabolic deficiencies,” and “a POSA would have understood both Liu and Ahmad to teach a method of using (Z)-endoxifen for tamoxifen-refractory or resistant conditions.” Pet.64-65.
- For claim 19, Petitioner says only “a POSA would have understood that the formulations of Liu in view of Ahmad should include dosages from 0.01 mg to 200 mg of the more active, (Z)-endoxifen,” and, “at the very least, it would have been obvious for a POSA to try dosages in the range of 0.01 mg to 200 mg of (Z)-endoxifen.” Pet. 65-66. *See Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346,1357 (Fed. Cir. 2013) (indicating obvious to try is pertinent to motivation to combine not reasonable expectation of success).
- For claim 20, Petitioner says only “a POSA would have understood that one way to adjust the steady state plasma level of (Z)-endoxifen would be to adjust the concentration and/or purity of (Z)-endoxifen given to the patient—increasing the steady state plasma level by increasing the concentration and/or purity of (Z)-endoxifen administered to the patient, or decreasing the steady state plasma level by decreasing the concentration and/or purity of (Z)-endoxifen administered to the patient.” Pet.66-67.

Petitioner's failure to articulate *any* reasonable expectation of success for these claims is independently fatal. *In re Lee*, 277 F.3d at 1345; *Hewlett Packard*, Pap.9, 12-16; *Luitpold*, Pap.19, 24.

VI. Collateral Estoppel Does Not Apply and Does Not Fix the Gap Caused by the Petition's Failed Inherency Arguments

Petitioner's cursory attempt to invoke "collateral estoppel," without identifying a single specific issue that is "identical" to that decided in PGR2023-00043 (*see, e.g.*, EX2018, 24–25), is legally deficient and fundamentally inapplicable, and cannot remedy the failings of this substantively inadequate Petition. *See VirnetX Inc. v. Apple, Inc.*, 909 F.3d 1375, 1377 (Fed. Cir. 2018) (requiring "a prior action present[ing] an *identical* issue" and that "the prior action actually [was] litigated" for collateral estoppel to apply); *Sacramento Mun. Util. Dist. v. United States*, 566 F. App'x 985, 994 (Fed. Cir. 2014) (requiring "identity of the issues in a prior proceeding" and "actual litigation of those issues" for collateral estoppel to apply). The anticipation and obviousness grounds asserted in PGR2023-00043 were based on *a different base reference (Ahmad)*, and the claims of the challenged '334 Patent *did not recite any Form I or XRPD limitations at issue here*. *See, e.g.*, EX2014, cl.1. As illustrated by the table below, the '334 Patent did not contain the key Form I limitation of the '151 Patent:

Claim 1 of '334 Patent	Claim 1 of '151 Patent
An oral formulation comprising an endoxifen composition encapsulated in an enteric capsule, wherein the endoxifen composition comprises a compound of Formula (III):  Formula (III) wherein at least 90% by weight of the compound of Formula (III) is (Z)-endoxifen.	A composition comprising a crystalline form of a compound of Formula (III):  Formula (III) wherein at least 90% by weight of the compound of Formula (III) in the composition is the (Z)-isomer, and wherein the crystalline form of the (Z)-isomer is Form I, characterized by an x-ray powder diffraction pattern comprising major peaks at $16.8 \pm 0.3^\circ$, $17.1 \pm 0.3^\circ$ and $21.8 \pm 0.3^\circ$ two theta.

Thus, the issues of Form I, XRPD, and Liu's alleged inherency were neither raised nor adjudicated in the '334 PGR, let alone "essential" to the '334 PGR judgment. Indeed, Petitioner's attempt to invoke "collateral estoppel" fails under the very authority it cites. *See Google LLC v. Hammond Develop. Int'l, Inc.*, 54 F.4th 1377, 1381 (Fed. Cir. 2022) (holding that for collateral estoppel to apply, a

party must show, *inter alia*, “resolution of the issue was essential to a final judgment in the first action”).

VII. Conclusion

For the reasons stated above, Petitioner has failed to show a reasonable likelihood that it will prevail. The Petition’s entire case, including its anticipation ground (Ground 1) and obviousness ground (Grounds 2), relies on the failed argument that Liu inherently discloses the claimed composition of the independent claims, which requires the key Form I polymorph. The fundamental failure of Liu to disclose the claimed composition inherently—affirmatively demonstrated by Petitioner’s need to make multiple modifications to Liu to try to generate the argued result, and then its unacknowledged repeated failure to do so even with these modifications—extends to both of the Petition’s grounds. The Board should not expend its resources on a Petition whose central premise is so legally and factually flawed, or reward a Petitioner for burying the affirmative evidence from its own expert that disproves it. The Petition should be denied.

Respectfully submitted,

Dated: August 5, 2025

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CERTIFICATE OF WORD COUNT

The undersigned certifies that the foregoing Patent Owner’s Brief In Support Of Discretionary Denial Under 35 U.S.C. §314(a) complies with the type-volume limitation in 37 C.F.R. §42.24(c)(1) and the “Interim Processes for PTAB Workload Management” (Mar. 26, 2025). According to the word-processing system’s word count, the brief contains 8,145 words, excluding the parts of the brief exempted by 37 C.F.R. §42.24(a)(1).

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of Patent Owner's Brief In Support Of Discretionary Denial Under 35 U.S.C. §314(a) and the accompanying exhibits have been served in their entirety on August 5, 2025, by causing the aforementioned documents to be electronically mailed to the following attorneys of record for the Petitioner listed below.

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