

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 RESPONSE

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?, available at https://zonalta.in/
EX2021	Atossa Therapeutics Granted Additional Patent Protection for Endoxifen (August 28, 2024)
EX2022	Declaration of Megan Raymond
EX2023	U.S. Patent No. 12,245,997
EX2024	December 6, 2025 Collection of Email Communications with Intas's Counsel
EX2025	Declaration of Sayem Osman
EX2026	INTENTIONALLY OMITTED
EX2027	Declaration of Jacob Berman
EX2028	Declaration of Han Xu
EX2029	Declaration of Hayley LeBlanc
EX2030	Declaration of Stephen G. Davies, DPhil
EX2031	Transcript of January 9, 2026 Deposition of William Mayo, Ph.D.
EX2032	Transcript of January 16, 2026 Deposition of Jason McConville, Ph.D.
EX2033	Transcript of January 20, 2026 Deposition of Ron Bihovsky, Ph.D.
EX2034	S.R. Logan, <i>The Origin and Status of the Arrhenius Equation</i> 4 J. CHEM. ED. 279 (1982)
EX2035	Edina Vranić, <i>Recent Advances in the Identification and Prediction of Polymorphs</i> 3 BOSNIAN J. OF BASIC MED. SCIENCES 32 (2003)
EX2036	Trevor Laird, <i>Polymorphism and Impurities</i> 8 ORGANIC PROCESS RESEARCH & DEVELOPMENT 301 (2004)
EX2037	Masaki Okamoto, et al., <i>The Effects of Impurities on Crystallization of Polymorphs of a Drug Substance AE1-923</i> , 37 J. OF CHEM. ENGINEERING OF JAPAN 1224 (2004)
EX2038	Eun Hee Lee, <i>A Practical Guide to Pharmaceutical Polymorph Screening & Selection</i> , 9 ASIAN JOURNAL OF PHARMACEUTICAL SCIENCES 164 (2014)
EX2039	H. Sharma et al., <i>Preferential Nucleation during Polymorphic Transformations</i> , NATURE SCIENTIFIC REPORTS (2016)

Exhibit	Description
EX2040	Priyanka Maurya et al., <i>Pharmaceutical Polymorphism: The Phenomenon Affecting the Performance of Drug and an Approach to Enhance Drug Solubility, Stability and Bioavailability</i> , WORLD JOURNAL OF PHARMACEUTICAL SCIENCES (2016)
EX2041	John Spencer Evans, <i>Polymorphs, Proteins, and Nucleation Theory: A Critical Analysis</i> , 7 MINERALS 62 (2017)
EX2042	International Patent Application No. WO 2023/137044A2
EX2043	Declaration of Sayem Osman
EX2044	INTENTIONALLY OMITTED
EX2045	INTENTIONALLY OMITTED
EX2046	INTENTIONALLY OMITTED
EX2047	INTENTIONALLY OMITTED
EX2048	INTENTIONALLY OMITTED
EX2049	INTENTIONALLY OMITTED
EX2050	William E. Brown & Margareth R. Marques, <i>USP and Dissolution—20 Years of Progress</i> , DISSOLUTION TECHNOLOGIES (2014)

TABLE OF CONTENTS

I.	Introduction.....	1
II.	The Claims are Directed to a Novel, Non-Obvious Invention.....	3
	A. The '151 Patent.....	3
	B. The Prosecution History	5
III.	Liu Does Not Inherently Anticipate Claims 1-6, 16, 18, 21 (Ground 1)	6
	A. Dr. Bihovsky's Modification of Liu Could Have Affected the Crystal Form and Purity of His Final Products	9
	1. Changes to the Ratio of Starting Ingredients in Every Example of Liu.....	12
	2. Changes to Liu's Reaction Temperatures and Dissolving Instead of Suspending Liu's Reactants	22
	3. Additional Stirring, Scratching, and Filtering While Performing Liu's Example 7 Crystallization Step	28
	4. Other Additional Purification and Filtration Steps.....	34
	5. Additional Drying Step	40
	B. Petitioner's Modified Reproduction of Liu Is Legally Insufficient to Establish Inherency	41
	C. Petitioner's Modified Reproduction of Liu Failed, as a Matter of Fact, to Produce the Claimed Form I at the Claimed Purity	44
	D. Dependent Claims 2-6, 18, and 21 Are Not Anticipated.....	47
IV.	Liu and Ahmad in View of POSITA's Knowledge of the Art Fail to Render Obvious Claims 1-21 (Ground 2)	48
	A. Claims 1 and 16: The Liu and Ahmad Combination Does Not Remedy Petitioner's Failure to Show Liu Discloses the Claimed Form I.....	48
	B. Claims 2-15 and 17-21: Petitioner Fails to Establish that the Prior Art Discloses Additional Dependent Claim Elements.....	51
	1. Claims 2-6	52
	2. Claims 8-9	52
	3. Claims 10-12 and 15	53
	4. Claims 17 and 19-20	54
	5. Claim 21	55

V.	Dr. Mayo’s Testimony Should Be Given No Weight	57
A.	PO Has Been Deprived of the Ability to Question Any Knowledgeable Witness.....	59
B.	Dr. Mayo’s Opinions Fail to Provide Underlying Facts and Data	60
VI.	No Collateral Estoppel.....	64
VII.	Conclusion	67

TABLE OF AUTHORITIES

	Page(s)
Cases	
<i>Adobe Inc. v. Rah Color Techs. LLC</i> , No. IPR2019-00627, Pap.59 (Dec. 12, 2019).....	62
<i>Apple Inc. v. Smart Mobile Tech. LLC</i> , IPR2022-00981, Pap.34 (Nov. 7, 2023)	47
<i>Arbutus Biopharma Corp. v. Modernatx, Inc.</i> , 65 F.4th 656 (Fed. Cir. 2023)	7
<i>Azurity Pharms., Inc. v. Exelixis Inc.</i> , IPR2025-00210, Pap.11 (June 4, 2025).....	6, 31, 46
<i>CaptionCall, LLC v. Ultratec, Inc.</i> , IPR2020-01215, Pap.6 (Jan. 27, 2021).....	25, 30, 38
<i>Comair Rotron, Inc. v. Nippon Densan Corp.</i> , 49 F.3d 1535 (Fed. Cir. 1995)	65
<i>Enplas Display Device Corp. v. Seoul Semiconductor Co.</i> , 909 F.3d 398 (Fed. Cir. 2018)	6, 40
<i>Google LLC v. Hammond Develop. Int’l, Inc.</i> , 54 F.4th 1377 (Fed. Cir. 2022)	65
<i>Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.</i> , 821 F.3d 1359 (Fed. Cir. 2016)	47
<i>iRobot Corp. v. SharkNinja Operating LLC</i> , No. 2023-1398, 2024 WL 3687981 (Fed. Cir. Aug. 7, 2024).....	59
<i>In re Lee</i> , 277 F.3d 1338 (Fed. Cir. 2002)	53
<i>Mexichem Amanco Holdings S.A. de C.V. v. Honeywell Int’l, Inc.</i> , IPR2013-00576, Pap.36 (Sept. 5, 2014).....	59, 63

<i>In re Montgomery</i> , 677 F.3d 1375 (Fed. Cir. 2012)	6
<i>Net MoneyIN, Inc. v. Verisign, Inc.</i> , 545 F.3d 1359 (Fed. Cir. 2008)	25, 30, 38
<i>In re NuVasive, Inc.</i> , 841 F.3d 966 (Fed. Cir. 2016)	47
<i>PersonalWeb Techs., LLC v. Apple, Inc.</i> , 917 F.3d 1376 (Fed. Cir. 2019)	6, 31, 46
<i>Pfizer, Inc. v. Chugai Pharm. Co.</i> , IPR2017-01357, Pap.56 (Nov. 28, 2018)	7
<i>Praxair Distrib., Inc. v. Ino Therapeutics LLC</i> , IPR2015-00529, Pap.33 (Dec. 22, 2015).....	59, 63
<i>Rosellini Sci., LLC v. Grünenthal GmbH</i> , IPR2016-00471, Pap.11 (July 18, 2016)	40, 41, 42
<i>Sacramento Mun. Util. Dist. v. United States</i> , 566 F. App'x 985 (Fed. Cir. 2014)	66
<i>The Scotts Co. v. Encap, LLC</i> , IPR2013-00110, Pap.79 (June 24, 2014).....	60
<i>U.S. Water Servs., Inc. v. Novozymes A/S</i> , 843 F.3d 1345 (Fed. Cir. 2016)	6, 31, 46
<i>Valeant Int'l (Barb.) SRL v. Watson Pharms., Inc.</i> , No. 10-20526, 2011 WL 6792653 (S.D. Fla. Nov. 8, 2011)	40, 42, 43
<i>Valeant Int'l Berm. v. Actavis, Inc.</i> , 534 F. App'x 999 (Fed. Cir. 2013)	40, 42
<i>VirnetX Inc. v. Apple, Inc.</i> , 909 F.3d 1375 (Fed. Cir. 2018)	65
<i>Xerox Corp. v. Bytemark, Inc.</i> , IPR2022-00624, Pap.9 (Aug. 24, 2022)	52, 54

Other Authorities

37 C.F.R. § 42.51(b)(1)(iii).....	62
37 C.F.R. § 42.65(a).....	59
37 C.F.R. § 42.65(b)	60
37 C.F.R. § 42.104(b)(4).....	49

I. Introduction

Atossa Therapeutics Inc. (“PO”) submits this §42.220 Response to the above-captioned Petition (“Petition”/“Pet.”) challenging U.S. Patent 11,261,151 (“’151 Patent,” EX1001).

Each claim of the ’151 patent requires crystalline Form I of (Z)-endoxifen, defined by a specific X-ray powder diffraction (“XRPD”) fingerprint, and methods of its use. Petitioner’s arguments all depend on asserting this is inherent from Liu.¹ Petitioner’s expert Dr. Ron Bihovsky purported to recreate Liu’s experiments and asserts his results show the claimed “at least 90%” pure Form I (Z)-endoxifen would have inherently resulted from Liu’s disclosed experimental procedures. But Dr. Bihovsky altered Liu in so many significant ways—including changing the ratios of Liu’s starting ingredients and disclosed temperatures, adding stirring, scratching, purification, and drying steps, and making other clear deviations from Liu’s procedures—that no person of ordinary skill in the art (“POSITA”) could consider Dr. Bihovsky’s experiments to be a recreation of Liu. Instead, POSITA would have recognized the hindsight-driven outcomes of these wholly-different experiments

¹ “Form I” refers to this independent claim limitation: “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.”

could not be deemed indicative of the results POSITA would obtain from actually following Liu *as written*. While Dr. Bihovsky, in attempting to downplay his alterations of Liu, offers only conclusory, unsupported assertions, Petitioner's expert Dr. Davies, in sharp contrast, cites multiple references showing the very types of changes Dr. Bihovsky made are known to affect the polymorphic form a compound adopts and thus Dr. Bihovsky did not show Liu inherently results in the claimed Form I. Moreover, while Petitioner relies *exclusively* on another expert's X-ray powder diffraction testing to show Dr. Bihovsky produced the claimed Form I, Petitioner *failed to provide any information* about the experimental conditions used to test that material. This deprives the Board and PO of any ability to explore, let alone verify, the reliability of that testing—and without it Petitioner admits it cannot show Liu's (Z)-endoxifen is Form I.²

² The Petition does not cite to numerous paragraphs of Petitioner's expert's declarations. *E.g.*, EX1032, ¶¶17-23, 28-36, 39-40, 42-43, 45-49, 51-66; EX1033, ¶¶12-19, 27-33, 36-41, 75, 80, 82, 87; EX1034, ¶¶11-15, 20-21, 26 (EX1038, ¶¶11-15, 20-21, 26). Petitioner cannot rely on these uncited paragraphs.

The Petition fails to prove any challenged claim unpatentable by a preponderance of the evidence.³

II. The 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 yields a specific crystalline form of (Z)-endoxifen (at least 90% by weight) with superior stability and commercial-scale feasibility. *See* EX1001, 27:23-40; EX2030, ¶31. The '151 patent teaches a synthetic pathway and purification process to create this highly pure (Z)-endoxifen. *See* EX1001, Examples 1, 4-9; EX2030, ¶31. The starting isomeric mixture of (E)/(Z)-endoxifen is first subjected to crystallization. EX1001, Examples 1, 4-9; EX2030, ¶32. Because the inventors observed that (E)-endoxifen is less soluble than (Z)-endoxifen, this initial crystallization step results in an enriched (Z)-endoxifen component (*e.g.*, a mother liquor or filtrate). EX1001 at 68:3-10; EX2030, ¶32. That enriched (Z)-endoxifen component is subjected to further crystallization to obtain pure (Z)-endoxifen solid in a free-base composition. EX1001 at 67:67-68:3;

³ 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.

EX2030, ¶33. The (Z)-endoxifen free-base solid composition obtained is stable in ambient conditions, with reduced isomeric conversion to the (E)-isomer. EX1001 at 84:20-29; EX2030, ¶33.

The challenged claims are directed to a crystalline Form I of (Z)-endoxifen, defined by a specific XRPD fingerprint, and methods of its use. EX1001, cl. 1, 16; *see id.* at cl. 2-15, 17-21; EX2030, ¶34. XRPD is an analytical technique used to characterize crystalline materials, including what polymorphic form those materials have adopted, by shooting a beam of X-rays at crystalline material. EX2030, ¶¶38-39.

The '151 patent identifies three separate polymorphs of (Z)-endoxifen based on XRPD peaks. EX2030, ¶40. Figures 9 and 10 show Form I, while Figures 11 and 12 show Form II, and Figure 13 shows Form III. EX1001, Figs. 9-14. And Petitioner's expert Dr. Bihovsky agrees (Z)-endoxifen can adopt more than one polymorphic form. EX2033, 239:10-240:19. Moreover, as was known at the time of Dr. Bihovsky's experiments, there are at least 14 additional polymorphic forms of (Z)-endoxifen and which form is adopted can be affected by changes to both temperatures and impurities in the relevant reactions. EX2042, [0030], [0034], [0036]-[0048], [0059]-[0083], [0278], [0280]-[0281], [0284]-[0312], [0315]-[0335], [0568]-[0677], [0708], Figs. 8-10, 20-92; EX2030, ¶41.

The claimed stable, highly-pure crystalline form of (Z)-endoxifen (“Form I”) addresses 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 1:61-2:57, 9:5-11:2, 27:23-40, 84:20-29, 96:42-98:11; EX2030, ¶¶31-34. Moreover, unlike existing synthetic/purification methods, the ’151 patent’s process for producing the claimed Form I with the claimed XPRD pattern achieves high yields, high purity, and long-term 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; EX2030, ¶¶31-34. 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... 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 challenged claims are distinct from the claims of previously-adjudicated related 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; *see also* §VI.

B. The Prosecution History

The application leading to the ’151 patent was subject to two rejections before the challenged claims were allowed, including affirmative consideration of

Petitioner's primary reference Liu (EX1002, 431 (rejection based on WO 2017/070651)), which, as Petitioner's expert concedes, does not identify the resulting (Z)-endoxifen as Form I or "report any X-ray powder diffraction ('XRPD') data of the compounds Liu synthesized." EX1033, ¶33; EX2030, ¶¶35-37.

In the first office action, the Examiner found: "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... *The reference does not teach, show, suggest or make obvious the instant Form I polymorph.*" EX1002, 433; EX2030, ¶36. The Examiner noted this same distinction in the Notice of Allowance. EX1002, 537; EX2030, ¶37.

III. Liu Does Not Inherently Anticipate Claims 1-6, 16, 18, 21 (Ground 1)

Inherency is an exacting standard that requires the missing element to be *necessarily, unavoidably*, and *inevitably* present based on the reference's explicit disclosure. *See U.S. Water Servs., Inc. v. Novozymes A/S*, 843 F.3d 1345, 1350 (Fed. Cir. 2016) ("the inherent result must inevitably result from the disclosed steps") (quoting *In re Montgomery*, 677 F.3d 1375, 1380 (Fed. Cir. 2012)); *Azurity Pharms., Inc. v. Exelixis Inc.*, IPR2025-00210, Pap.11, 28 (June 4, 2025) ("inherency... *must be the necessary result, not a possible expected result.*"). "Prior 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 exacting: “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.*; see also *Arbutus Biopharma Corp. v. Modernatx, Inc.*, 65 F.4th 656, 662 (Fed. Cir. 2023) (limitation inherent “if it is the ‘*natural result flowing from*’ the prior art’s explicit disclosure.”).

As discussed below, from the very outset of his multiple trial-and-error experiments purporting to follow Liu’s procedures, Dr. Bihovsky changed Liu’s starting material ratios to attempt to scale down Liu. EX2030, ¶¶46-48. As Dr. Davies explains, however, a reaction such as the one contemplated in Liu is like baking a cake such that slight changes to the ratios of ingredients can have profound effects on the outcome. EX2030, ¶49. Indeed, Dr. Bihovsky’s changes to Liu’s ratios starting with Example 2 (and continuing through Example 7) infected every subsequent experimental step. *E.g.*, EX1033, ¶71 (Dr. Bihovsky’s purification scheme showing use of materials from prior experiments in later experiments); EX2033, 137:2-139:8, 142:5-143:7; EX2030, ¶¶49-50. Coupled with Dr. Bihovsky’s other significant changes to Liu (detailed below)—including additional changes to the ingredient ratios in Liu’s later steps—the result is that Dr. Bihovsky’s final products were not the “‘natural result flowing from’ the prior art’s explicit

disclosure.” *Arbutus*, 65 F.4th at 662; *see Pfizer, Inc. v. Chugai Pharm. Co.*, IPR2017-01357, Pap.56, 23-30 (Nov. 28, 2018) (rejecting inherency where POSITA would “have had... a number of buffer formulations from which to choose—and selecting among them would not necessarily have resulted in a method that meets the claims.”). Instead, they are the result of Dr. Bihovsky’s contrived trial-and-error hindsight efforts to alter Liu to yield his preferred outcome. *E.g.*, EX2033, 186:15-18 (“Q. So on page 83 onto 84, this is another series of trial and error attempts at Liu’s Example 3 now; is that fair? A. Yes.”), 303:16-304:2.

Dr. Bihovsky dismisses his changes as “minor” or “routine” adjustments (EX1033, ¶47) but offers only conclusory, unsupported statements that his changes did not impact the final polymorphic form of his product. But Dr. Davies cites multiple references showing how the very types of changes Dr. Bihovsky made are known to impact the polymorphism. *E.g.*, EX2030, ¶¶51, 55, 59, 71, 76, 82-84, 92, 98, 108. Given the potential impact of *each* of Dr. Bihovsky’s changes, the only way to know what form Liu would have actually produced is to perform *Liu’s* experiments, not Dr. Bihovsky’s. *E.g.*, EX2030, ¶51; EX2037, 1 (reporting on experiments to investigate “[t]he effects of seven kinds of impurities on the solvent-mediated transformation of crystal polymorphs” of a compound); EX2036, 1 (“**For reproducible production of polymorphs**, a critical issue may be the presence or absence of key impurities....”).

Petitioner's inherent anticipation arguments, based on the results of Dr. Bihovsky's trial-and-error attempts to scale down Liu, thus fail as a matter of law.

A. Dr. Bihovsky's Modification of Liu Could Have Affected the Crystal Form and Purity of His Final Products

Petitioner and Dr. Bihovsky identify and purport to explain numerous ways in which Dr. Bihovsky deviated from Liu's express procedures, including raising certain reactions' temperatures, performing additional stirring, adding additional purification steps, and providing longer reaction times. *E.g.*, Pet.12 n.3; EX1033, ¶¶47-48, ¶51, ¶52 n.3 & n.4, ¶54 n.5, ¶59 n.6, ¶60 n.7, ¶61; EX2033, 61:21-62:8 (admitting he altered Liu's experiments for "optimization"). But they omit Dr. Bihovsky's *other* changes to Liu's procedures, beginning with changing the ratios of Liu's starting materials in Example 2 and subsequent examples, changing the temperature of at least one reaction mixture to which Dr. Bihovsky's altered ingredients were added, and performing extra purification steps Liu did not. EX2030, ¶54.

But it was well known in the art that changes to temperature, reaction time, additional agitation (*e.g.*, stirring), additional purification, and other changes can affect the final polymorphic form adopted by a crystalline structure. EX2030, ¶55; EX2041, 2; EX2040, 6; EX2038, 5; EX2035, 1-2; EX2036, 1; EX2037, 1; EX2033, 19:15-21:3 (admitting "initial temperature and the final temperature could conceivably cause different polymorphs"), 21:16-22:7 (impurities can "[p]ossibly"

affect what polymorph a material adopts), 23:14-24:6 (“occasionally there were trace impurities by NMR and TLC... before the first recrystallization”), 28:11-22 (“there could have been, let’s say 1 percent of some impurity or impurities”), 45:21-46:15 (“[i]n principle” the amount of stirring of a mixture “might” dictate polymorphic form).

As Dr. Davies explains, Dr. Bihovsky’s experimental changes to Liu are significant and potentially result altering. EX2030, ¶¶55-56; EX2033, 65:1-66:3 (Dr. Bihovsky admitting his changes to Liu Example 2 would have affected the purity of the final material obtained following Liu Example 7 and it would require “speculation” to determine what would have happened had he followed Liu Example 2 as written), 156:12-157:10 (“Q. Fair to say that you had to make changes to Liu in order to get results that were similar to Liu. A. Well, yeah. In order to improve the yield and the progress of the reaction.... I did obtain Liu’s product the very first time, but the yield was low.” (objection omitted)).

Examples confirming the ripple effects of Dr. Bihovsky’s changes include the difference between the isomers Bihovsky and Liu obtained, and the fact that Dr. Bihovsky obtained multiple “incomplete reactions” when attempting to follow Example 2. EX1033, ¶51 (“Initially ... I observed that the reaction was incomplete by TLC.”); EX2033, 153:16-154:13; EX2030, ¶52. For example, Dr. Bihovsky admits that after purportedly performing Liu’s Example 4, he obtained a mixture

with a different E:Z endoxifen ratio. EX1033, 59 n.7 (“Liu: 51/47 ratio of E/Z; my synthesis: 67:33 ratio”); EX2030, ¶57. And while allegedly performing Example 5, Dr. Bihovsky obtained a precipitate with a “95:5 ratio of (E)- to (Z)- endoxifen,” not Liu’s “68/30 ratio of E/Z.” EX1033, ¶60 (citing EX1003, ¶0072). Similarly, Dr. Bihovsky’s version of Example 5 yielded a product with a “33:67 ratio of (E)- to (Z)-endoxifen” whereas Liu disclosed “E/Z-ratio:19/77.” EX1033, ¶60 (citing EX1003, ¶0072).⁴ Differences in isomer ratios and impurities (such as those in Dr. Bihovsky’s results) can impact the final crystalline form of a molecule by, *e.g.*, changing the times at which each isomer crystalizes, leading to different polymorphic forms and purity. EX2030, ¶57.

These differences confirm Dr. Bihovsky’s below-discussed alterations to Liu were not simply “minor” or “routine adjustments” (EX1033, ¶47) with no effect on Liu’s outcome (which Dr. Bihovsky did not actually test), but potentially ***result-altering*** changes compelling a finding that he failed to follow Liu and performed

⁴ Dr. Bihovsky also testified that the yield of at least some of his experiments were better than Liu’s and that he could “only speculate” as to why. EX2033, 198:15-201:15.

what POSITA⁵ would have considered a completely different experiment (EX2030, ¶58; EX2033, 100:6-17).

1. Changes to the Ratio of Starting Ingredients in Every Example of Liu

POSITA knew that relative amounts of starting materials could impact the course and results of the reaction in Liu, including by changing the resultant polymorphic form. EX 2040, 6 (“Other factors which [] also affect the polymorphism and the factors are agitation, *supersaturation*....”); EX2030, ¶59; *see also* EX2033, 98:7-99:6. Indeed, as Dr. Bihovsky admitted, if ingredients are not scaled down proportionally, “[i]t’s possible or likely that the reaction would not proceed as it did—as it would have if everything was kept proportional.” EX2033, 98:7-99:6. Accordingly, POSITA, when scaling down an experiment, would have understood that ingredient amounts in the larger-scale experiment must be scaled down *proportionally* for the smaller-scale experiment, so the ratios among ingredients remain the same in both.⁶ EX2030, ¶59; EX2033, 96:4-8 (“Q. When

⁵ Petitioner does not dispute the POSITA definition the Board applied at Inst.8-9.

⁶ In smaller-scale experiments (such as Bihovsky’s) it is easier to keep a mixture homogenous, add material at a constant rate, and maintain a consistent temperature across the entire mixture. EX2030, ¶60. This reduces the likelihood (compared to

scaling up or down an experiment, is it important to scale up or down each ingredient proportionally? A. I would say yes, but you don't scale up or down the time or temperature.”), 98:7-99:6 (agreeing end results could be different). As a simple example, if Dr. Bihovsky performed Liu's Example 2 at one-half scale, then each ingredient should be present at 50% of the amount used in Liu (*e.g.*, Liu's 3.011kg of zinc bromide would be 1.5055kg, and Liu's 16.5kg of polyphosphoric acid would be 8.25kg). EX2030, ¶61; EX2033, 96:9-97:13. As this simplified example reflects, the zinc-bromide-to-polyphosphoric-acid ratio in each experiment would be the same, because each ingredient was scaled down proportionally: 5.4799kg of polyphosphoric acid for every 1kg of zinc bromide.⁷ EX2030, ¶62.

larger scale experiments like Liu's) that concentrations and temperatures will vary within the mixture, and thus reduces the chances that different crystals will seed in different parts of the mixture which can lead to different crystalline forms and purity levels. EX2030, ¶60.

⁷ The ratio of polyphosphoric acid to zinc bromide is obtained by dividing the amount of polyphosphoric acid by the amount of zinc bromide used in each version of the experiment. In this simplified example, 16.5kg/3.011kg and 8.25kg/1.5055kg both equal 5.4799.

But this is not what Dr. Bihovsky did. EX2030, ¶63. Instead, starting with Example 2 and continuing through Liu's final recrystallization step of Example 7, Dr. Bihovsky scaled down each ingredient in *different* proportions, thus altering their ratios. EX2030, ¶63. Importantly, even Dr. Bihovsky admits an experiment in which starting materials and reagents have not been scaled proportionally to one another would be *a different experiment* than the original. EX2033, 100:7-17 ("if you're taking the proportions, that is a different experiment"); EX2030, ¶64. And he admits that a difference in his ingredient ratios could have "[p]ossibly" changed his results. EX2033, 101:7-102:8; EX2033, ¶64.

Dr. Bihovsky's alteration of Liu's ratios is shown in the tables below. For each Liu example, Dr. Davies calculated the percentage at which Dr. Bihovsky scaled down each ingredient, and provided exemplary ratios between certain starting ingredients to show how Bihovsky's disproportional scaling *altered* those ratios.⁸

As these tables reveal, Dr. Bihovsky's alteration of Liu's ratios pervades Dr. Bihovsky's entire experimental process, including because in each subsequent step Dr. Bihovsky used the material from prior steps, each time with a different ratio than Liu did. EX2030, ¶¶65-67. For example, Dr. Bihovsky began with Liu's Example

⁸ Dr. Davies converted kilograms to grams and liters to milliliters where necessary to ensure proper comparison.

2, but used different ratios than Liu. He used the resulting material to perform Example 3 (again altering the starting ratios). EX2030, ¶66. This continued through Liu's Example 7, which Dr. Bihovsky again altered. EX2030, ¶66; EX1033, ¶71 (showing materials used at each step of Dr. Bihovsky's purification scheme). As Dr. Davies testifies, *each time Dr. Bihovsky altered Liu's steps, he compounded and magnified his deviations from Liu*, potentially resulting in a different final product than he would have obtained had he faithfully followed Liu. EX2030, ¶67.

Liu Example 2 (EX1003, ¶¶0062-0064)					
Ingredient	Liu Amount	Dr. Bihovsky Amount	Ratio of Listed Ingredients to Zinc Bromide (Liu)⁹	Ratio of Listed Ingredients to Zinc Bromide (Dr. Bihovsky)	Dr. Bihovsky Scale Down %¹⁰
Zinc bromide	3,011g	27.1g	n/a	n/a	0.9000
Polyphosphoric acid	16,500g	149g	5.4799	5.4982	0.9030
Hydroxybenzoic acid	974g	8.77g	.3235	.3236	0.9004
2-phenoxyethyl bromide	1302g	14.1g	.4324	.5203	1.0829
Phosphorous tribromide	2720g	24.51g	.9034	.9044	0.9011

⁹ This ratio is the amount of each ingredient divided by the amount of zinc bromide used by Liu or Dr. Bihovsky, as applicable. The ratio in Dr. Bihovsky's experiment of each listed ingredient to zinc bromide is different than in Liu. EX2030, ¶¶63-67. The corresponding columns in subsequent tables calculate the ratios of the identified ingredients in the same way and also show different ratios in Liu's and Dr. Bihovsky's experiments. EX2030, ¶¶67 & n.3, 5, 7, 9, 11, 13.

¹⁰ This equals the total amount of each ingredient used by Dr. Bihovsky divided by the amount used by Liu and then multiplied by 100 to obtain a percentage.

Liu Example 3 (EX1003, ¶¶0065-0067)					
Ingredient	Liu Amount	Dr. Bihovsky Amount	Ratio of Listed Ingredients to Zinc Dust (Liu)	Ratio of Listed Ingredients to Zinc Dust (Dr. Bihovsky)	Dr. Bihovsky Scale Down %
Zinc dust	4300g	32.23g	n/a	n/a	.7495
Anhydrous dimethoxyethane	26000mL	190mL	6.0465	5.8951	.7308
Titanium tetrachloride	6000g	26.4g	1.3953	.8191	.44
Propiophenone	542g	4.09g	.1260	.1269	.7546
Compound 5 ¹¹	1324g	9.99g	.3079	.31	.7545
Anhydrous dimethoxyethane	10000mL	75mL	2.3256	2.3270	.75
Methyl t-butyl ether	30000mL	220mL	6.9767	6.8259	.7333
HCl solution	13000mL	98mL	3.0233	3.0406	.7538

¹¹ Compound 5 is (4-(2-bromoethoxy)phenyl)(4-hydroxyphenyl)methanone, which was synthesized by Dr. Bihovsky purporting to follow Liu's Example 2. EX1033, ¶¶50-54.

Liu Example 4 (EX1003, ¶¶0068-0071)					
Ingredient	Liu Amount	Dr. Bihovsky Amount	Ratio of Compound 3 to Methylamine (Liu)	Ratio of Compound 3 to Methylamine (Dr. Bihovsky)	Dr. Bihovsky Scale Down %
Methylamine	55000mL	232mL	n/a	n/a	.4218
Compound 3 ¹²	1875g	7.72g	.0341	.0333	.4117

Liu Example 5 (EX1003, ¶0072)					
Ingredient	Liu Amount	Dr. Bihovsky Amount	Ratio of Isopropyl Acetate to Endoxifen (Liu)	Ratio of Isopropyl Acetate to Endoxifen (Dr. Bihovsky)	Dr. Bihovsky Scale Down %
Mixture of (E)- and (Z)-Endoxifen ¹³	5512g	.761g	n/a	n/a	.0138
Isopropyl acetate	55000mL	7.61mL	9.9782	10	.0138

¹² Compound 3 is the 4-(1-(4-(2-bromoethoxy)phenyl)-2-phenylbut-1-enyl)phenol synthesized by Dr. Bihovsky purporting to follow Liu's Example 3. EX1033, ¶¶55-56.

¹³ This mixture of (E)- and (Z)-endoxifen was synthesized by Dr. Bihovsky purporting to follow Liu Example 4. EX1033, ¶¶56-60.

Liu Example 6 (EX1003, ¶¶0073-0075)					
Ingredient	Liu Amount	Dr. Bihovsky Amount	Ratio of Isopropyl Acetate to Endoxifen (Liu)	Ratio of Isopropyl Acetate to Endoxifen (Dr. Bihovsky)	Dr. Bihovsky Scale Down %
Mixture of (E)- and (Z)-Endoxifen ¹⁴	2721g	.236g	n/a	n/a	.0087
Isopropyl acetate	27000mL	2.36mL	9.9228	10	.0087

¹⁴ This mixture of (E)- and (Z)-endoxifen was synthesized by Dr. Bihovsky purporting to follow Liu Example 5. EX1033, ¶¶60, 65-66.

Liu Example 7 (EX1003, ¶¶0076-0077)					
Ingredient	Liu Amount	Dr. Bihovsky Amount	Ratio of Acetone to Endoxifen (Liu)	Ratio of Acetone to Endoxifen (Dr. Bihovsky)	Dr. Bihovsky Scale Down %
Mixture of (E)- and (Z)-Endoxifen (from Example 5) ¹⁵	5013g	.416g	n/a	n/a	.0083
Acetone	52000mL	4.1mL	10.3730	9.8558	.0079
Mixture of (E)- and (Z)-Endoxifen (from Example 6) ¹⁶	5013g	.108g	n/a	n/a	.0022
Acetone	52000mL	1.1mL	10.3730	10.1852	.0021

Had Dr. Bihovsky properly scaled down Liu's experiments, his ratios of these ingredients would match Liu's. EX2030, ¶¶68. But as Dr. Davies's calculations confirm, for *each and every Liu example*, Liu's ratios of starting materials were *altered* by Dr. Bihovsky. EX2030, ¶¶67-68.

¹⁵ This mixture of (E)- and (Z)-endoxifen was synthesized by Dr. Bihovsky purporting to follow Liu Example 5. EX1033, ¶¶60-61.

¹⁶ This mixture of (E)- and (Z)-endoxifen was synthesized by Dr. Bihovsky purporting to follow Liu Example 6. EX1033, ¶¶69-70.

Dr. Bihovsky makes no mention of these deviations, and thus provided no explanation as to whether or how they affected not only the intermediate products he used in performing his version of each subsequent Liu step, but also the final purity and polymorphic form of the (Z)-endoxifen Bihovsky obtained from his altered version of Liu's Example 7. EX2030, ¶¶69. As Dr. Davies testifies, changing these ingredient ratios makes Dr. Bihovsky's experiment a completely different experiment than Liu's—one that encompassed different reactions potentially producing intermediate and final products with different impurity types and amounts, as well as potentially creating different polymorphic forms of the final crystalline material, including by changing the degree of supersaturation of the mixture. EX2030, ¶¶70-73; EX2033, 100:7-17; EX 2040, 6 (“Other factors which [] also affect the polymorphism and the factors are agitation, *supersaturation*....”); EX2038, 5; EX2035, 2.¹⁷

¹⁷ Dr. Bihovsky testified that a key difference between large-scale (*e.g.*, Liu's) and smaller reactions (*e.g.*, Dr. Bihovsky's) is that it takes a larger-scale reaction longer to heat up and cool down, and this difference affected his experiments' outcome. EX2033, 79:13-82:12; EX2030, ¶¶72-74; *see also* EX2033, 125:6-126:7 (discussing other differences between Liu's large-scale reaction and Dr. Bihovsky's experiments), 184:8-185:14.

2. Changes to Liu's Reaction Temperatures and Dissolving Instead of Suspending Liu's Reactants

Dr. Bihovsky also made significant and repeated changes to reaction temperatures (and associated changes) in multiple examples of Liu, thus speeding up and potentially creating new reactions rather than recreating Liu's. EX2030, ¶75.

It was well known that raising reaction temperature speeds up all reactions (not just the reactions of interest) and thus affects polymorphism. EX2030, ¶76; EX2041, 2 (“polymorph selection is thus determined by the correct combination of polymorph-specific thermodynamic [factors] (e.g., *temperature*, pressure, volume)....”); EX2040, 6 (“One of the predominant and generally considered as operational factors *is [t]emperature* that affect nucleation, growth and transformation of polymorphs.”) EX2038, 5 (“In addition, *heating and cooling rates, crystallization temperature*... are variables which can affect crystallization process and thus, polymorphs formed.”); EX2035. Indeed, as Dr. Davies explains, the Arrhenius equation teaches that rate of reaction increases as temperature increases. EX2034, 1-2; EX2030, ¶¶76, 83-84. POSITA would also have been aware that, as a rule of thumb, every 10°C temperature increase doubles reaction rate, potentially introducing impurities not present in Liu. EX2030, ¶76. Here, Dr. Bihovsky admits he raised Liu's Example 2 reaction temperature by **20°C** in one experiment (EX1033, ¶51) and by **25°C** in another (EX1033, p.81, “75°” internal

temperature; EX2033, 144:1-146:15), and he drew his material for Example 3 from these experiments (EX2033, 186:6-188:3; EX2030, ¶77).

It was also well known that raising a reaction's temperature risks starting *new reactions* that would not have started at lower temperatures, thus also affecting polymorphism. EX2030, ¶76. This can also introduce new impurities not present in Liu's original, lower-temperature reaction, which in turn can yield different crystalline forms with different purity. EX2030, ¶76; EX2038, 3; EX2036, 1 ("For reproducible production of polymorphs, a critical issue may be the presence or absence of *key impurities in the material used to make the polymorphs....*"); EX2037, 1 ("it is important to understand *the effects of the impurities on appearance of crystal polymorphs.*"). Despite these well-known issues, Dr. Bihovsky made multiple temperature changes. **First**, Dr. Bihovsky tried and failed four times to reproduce Example 2. EX1033, ¶51; EX2030, ¶79. On his first attempt he "observed that the reaction was incomplete by [thin layer chromatography]," because he had obtained "mostly starting material."¹⁸ EX1033, ¶51; *id.* at p.79 ("Ex

¹⁸ Dr. Bihovsky's use of thin layer chromatography (TLC) to "monitor reaction progress throughout the synthesis"—not disclosed in Liu—is indicative of the results-oriented nature of his work. Dr. Bihovsky also added a chromatography step

2 x 1/1000”); EX2033, 153:16-155:10; EX2030, ¶79. Dr. Bihovsky then tried three more times recreate Liu’s Example 2 (EX2033, 167:11-168:3, 168:6-8, 174:5-12, 175:12-15, 176:19-177:7, 179:18-180:5), making additional changes to Liu’s procedures each time (*e.g.*, EX2033, 174:5-12), and even concluded the material produced by one of those attempts was so poor it was not even worth determining its yield. EX2033, 178:4-179:17; EX1033, ¶51; *id.* at pp.80-81; EX2030, ¶¶52, 80. Finally, on his fifth attempt, Dr. Bihovsky scaled up his prior 1/1000th versions of Liu by a factor of nine (but, as discussed above in Section III.A.1, did not do so properly). EX1033, p.82 (“scale up 15-22-2 x9”); EX2033, 182:14-183:3 (“Now that I thought I had a reasonable procedure, I could carry those out on -- on a larger scale”). In this new experiment, rather than perform the reaction at Liu’s “40-50°C... without heating,” Dr. Bihovsky “heated [the mixture] to 68 to 70 °C over 1 hour, then stirred at 70 °C (internal temperature) for 5 more hours” until chromatography showed the reaction “was mostly complete.” EX1033, ¶51; *id.* at p.82; EX2030, ¶81. He relied on the material produced from this experiment, as well as a prior preliminary experiment conducted at 75°C, to provide material for

to Liu Example 2, which he admitted “was the only way that I would know that I was getting the same product from Example 2 as Liu got.” EX2033, 163:13-18.

Liu's next step, Example 3. EX2033, 61:21-62:8, 184:8-185:14; EX2030, ¶¶81; *see also* EX1033, p.81.

The deviation from Liu's disclosed 40-50°C to Dr. Bihovsky's 68-70°C and 75°C is a significant change POSITA would have understood would (1) at least double the rate of all reactions (not just reactions of interest) and (2) potentially start reactions that would not otherwise have started at lower temperatures. EX2030, ¶¶76, 82-84. This has significant potential to introduce new impurities that were not in Liu. EX2030, ¶¶82. These impurities, in turn, could have affected the polymorphic form and purity of Dr. Bihovsky's products. EX2030, ¶¶82-86; EX2033, 107:15-108:18, 109:6-19; EX2041, 2; EX2040, 6; EX2038, 5; EX2035, 2. This change could have also allowed the reaction to proceed in the first place, by overcoming the activation barrier. EX2030, ¶¶85.

Second, in attempting to perform Liu Example 6, Dr. Bihovsky disregarded Liu's express teaching that endoxifen was "suspended" in isopropyl acetate and that the "*suspension* was heated at **85°C** for two hours." EX1003, ¶0073; EX2030, ¶¶87. Instead, Dr. Bihovsky used "*refluxing*" (*i.e.*, boiling liquid in which vapor is collected and returned to the liquid, EX2030, ¶¶88; EX2033, 84:1-85:2, 85:19-86:5) isopropyl acetate¹⁹ and *dissolved* (instead of suspended) the endoxifen in the

¹⁹ The reflux temperature of isopropyl acetate is 89°C. EX2030, ¶¶88.

isopropyl acetate.²⁰ EX1033, ¶66 (“I *dissolved* the endoxifen precipitate... in *refluxing [isopropyl acetate] for 4 hours.*” EX1033, ¶66; EX2033, 270:3-271:6, 271:14-21; EX2030, ¶¶87-88. Dr. Bihovsky’s temperature change and dissolving the endoxifen at this step (rather than suspending it) is yet another departure from Liu, and could have further impacted the polymorphic form and purity of Dr. Bihovsky’s final material by increasing reaction speed and creating differing concentrations of reactants across the suspension (unlike a solution), both of which

²⁰ Dr. Bihovsky also doubled Liu’s Example 6 reaction time to four hours, which could have affected the outcome. EX2030, ¶90. Dr. Bihovsky attempts to justify this increased time and temperature by citing Liu paragraph 46. EX1033, ¶66. But Liu paragraph 46 is a different, exemplary embodiment (“In some embodiments...”) that Dr. Bihovsky *does not follow*. EX1003, ¶0046; EX1033, ¶¶65-66; EX2033, 246:5-15, 252:15-253:9; EX2030, ¶90. And, in any event, mixing and matching from different embodiments is not permitted for anticipation. *Net MoneyIN, Inc. v. Verisign, Inc.*, 545 F.3d 1359, 1369-71 (Fed. Cir. 2008); *CaptionCall, LLC v. Ultratec, Inc.*, IPR2020-01215, Pap.6, 16-17 (Jan. 27, 2021). Moreover, the additional time spent in a “refluxing” mixture—which involves boiling, and thus further physically mixing Dr. Bihovsky’s ingredients—could have further altered Liu’s results. EX2030, ¶90.

risk changing whether and what impurities form. EX2030, ¶¶88, 91-92; EX2033, 86:17-87:21 (agreeing that a hot mixture is different than a refluxing mixture and using a hot mixture as opposed to a refluxing mixture would affect the experiment or results by changing rate of reaction), 90:18-91:16 (“higher temperatures could lead to other side products, which would be categorized as impurities”), 107:15-108:18, 109:6-19; EX2039, 1 (“Two important conditions for preferential solid-state nucleation are: i) *the presence of heterogeneous sites in the material...*”); EX2038, 3, 5; EX2041, 2; EX2040, 6; EX2035, 2.

Dr. Bihovsky’s declaration never acknowledged these deviations. EX1033, ¶66; EX2030, ¶89. At deposition, Dr. Bihovsky admitted (1) suspensions and solutions are different; (2) it was likely there was undissolved (E)-isomer in Liu’s suspension; and (3) this could have seeded Liu’s crystallization steps, such that Liu produced more (E)-endoxifen (and thus less (Z)-endoxifen) than if Liu’s (E)-endoxifen had been fully dissolved like Dr. Bihovsky’s. EX2033, 130:5-20, 131:22-133:1, 272:22-273:9, 276:19-277:9, 277:11-278:1; EX2030, ¶92. Dr. Bihovsky avoided this potential problem by dissolving all of his (E)-endoxifen. EX2030, ¶93.

Dr. Bihovsky’s changes to Liu’s temperature, and dissolving rather than suspending Liu’s Example 6 materials, are two additional independent reasons Dr. Bihovsky failed to recreate Liu, and that their results cannot be equated. EX2030, ¶93.

3. Additional Stirring, Scratching, and Filtering While Performing Liu's Example 7 Crystallization Step

While he acknowledges certain other changes, Dr. Bihovsky asserts he followed Liu's Example 7 "extremely closely," and that his other changes don't matter because "the polymorphic form that a crystal adopts is driven by the final crystallization of the material." EX1033, ¶47. As discussed throughout Section III.A, Dr. Davies's testimony shows the contrary, detailing why and how Dr. Bihovsky's modifications to Liu's other examples could have altered the outcome. EX2030, ¶94. But even if Dr. Bihovsky were correct (he is not) that his other modifications had no effect on the final polymorphic form of his synthesized material, *Dr. Bihovsky did change Liu's Example 7*—in both his sequential recrystallization experiment and his isomerization followed by sequential recrystallizations—by performing additional stirring, scratching, and purification. EX1033, ¶¶61, 70; EX2030, ¶95. He did this even though agitation (*e.g.*, stirring) and the presence of trace impurities were known to affect polymorphism, and despite his admission that, without his scratching, his mixture may not have crystallized. EX 2040, 6; EX2037, 1; EX2030, ¶95; EX2033, 110:15-111:10.

a. Additional Stirring and Scratching

Liu Example 7 discloses *40 hours of stirring* in its first recrystallization step without any scratching of the flask. EX1003, ¶0076 ("resulting solution was cooled and stirred for 40 hours at 1 to 5 °C."). Despite this, Dr. Bihovsky *stirred for 64*

hours—one full day of additional stirring—in his sequential recrystallization experiment at this step of Liu and scratched the flask “to increase crystallization” after he noticed “a small amount of precipitate.” EX1033, ¶61; *id.* at p.94 (“scratch, total 64h”); EX2030, ¶96. And in his isomerization followed by sequential recrystallizations experiments, Dr. Bihovsky *stirred for 88 hours* at this step of Liu. EX1033, ¶70; *id.* at p.95 (“88h”); EX2030, ¶96.

Notably, Dr. Bihovsky could not rule out that his additional stirring altered Liu’s results, admitting that “[y]ou’d have to do the experiment” to determine whether additional stirring would increase crystallization of Liu’s materials. EX2033, 111:11-112:9. And if it had turned out that the “small amount of precipitate” observed by Dr. Bihovsky in his sequential recrystallization experiment had been the crystallized material Dr. Bihovsky had been trying to produce, Dr. Bihovsky “could only speculate” as to what the purity of that material would have been. EX2033, 118:2-11. Thus, Petitioner cannot show that without Dr. Bihovsky’s additional stirring and scratching steps his experiments would have produced the claimed Form I (Z)-endoxifen at the requisite purity. EX2030, ¶97; EX2038, 5; EX2040, 6.

Moreover, these additional scratching and stirring steps—which Dr. Bihovsky added to address the problem that he observed only a “small amount of precipitate” (EX1033, ¶61) while purporting to follow Liu (EX2033, 112:17-115:9)—could have

changed both the purity and polymorphic form of the final crystalline product (in addition to being the only reason that Dr. Bihovsky was even able to continue his reactions and obtain final products (EX2033, 116:6-117:5)). EX2030, ¶97; EX2040, 6 (“Other factors which are also affect the polymorphism and the factors are **agitation**, supersaturation and growth rate dispersion”); *see also* EX2033, 111:11-112:9. Indeed, as Dr. Davies explains, any additional stirring or other manipulation could significantly affect the final outcome of the procedure. EX2030, ¶98. For example, one purpose of stirring is to keep a reaction homogenous across the entire reaction vessel. EX2030, ¶99. Without stirring, different portions of a reaction vessel can contain different concentrations, which in turn can change the status of reactions across the vessel, including the rate of crystallization and types and amounts of impurities. EX2030, ¶¶99-101. As with Dr. Bihovsky’s other changes, this could have affected the purity and polymorphic form of the final product. EX2030, ¶¶99-102.²¹

²¹ In yet another stirring-related difference, Dr. Bihovsky admitted that in his attempted Example 3 recreation Dr. Bihovsky was only able to stir for **five minutes**, while Liu disclosed stirring for **six hours**. EX1033, ¶54; EX2033, 198:9-200:21; EX2030, ¶99.

Dr. Bihovsky cites Liu paragraph 26 in attempt to justify additional stirring. EX1033, ¶¶61, 70. But Liu paragraph 26 lists different exemplary embodiments that Dr. Bihovsky does not purport to follow. EX1003, ¶0026 (listing multiple solvents and providing exemplary temperature other than the temperatures specified in Example 7); EX2030, ¶103. Dr. Bihovsky admitted that paragraph 26 gives exemplary conditions that are “broader” than those in Example 7 and that it would be possible to follow the broader parameters of paragraph 26 and not be within Example 7’s more specific parameters. EX2033, 289:1-13, 290:15-19. Mixing and matching from different embodiments—paragraph 26, on the one hand, and Example 7, on the other—as Dr. Bihovsky does, is not permitted for anticipation. *Net MoneyIN*, 545 F.3d at 1369-71; *CaptionCall*, 16-17. In any case, the statement from paragraph 26 that Dr. Bihovsky quotes (“[T]he resulting solution is... held at the second temperature for 0.5 hours to 10 days or 2 to 72 hours. In some cases longer holding times at the second temperature may be required”) does not say that any additional stirring should or can be performed. EX2030, ¶104. Instead, it merely states that “longer **holding** times may be required,” which means the solution is held at that second temperature, not that any additional stirring or other manipulation is performed. EX2030, ¶104; EX1003, ¶0026; EX2033, 290:20-291:22.

As to his added scratching step, Dr. Bihovsky admitted that the purpose of scratching a flask is “to induce the mixture to yield crystals if it is, one might say, reluctant to do so,” and that it is possible that in some situations the addition of flask scratching is necessary to cause a compound to crystallize. EX2033, 110:15-111:10; EX2030, ¶¶102, 105.

Notably, Dr. Bihovsky admitted that without his additional stirring and scratching, it would not have been possible, or, at minimum, “maybe... possible” to proceed to the next step of Example 7. EX2033, 116:12-117:5; EX2030, ¶106. Thus, by Dr. Bihovsky’s own admission, one possible outcome of Liu’s procedure, as written, is an experiment that could not have been completed. EX2030, ¶106. Based on this testimony alone, a finding of inherent anticipation is precluded as a matter of law. *U.S. Water*, 843 F.3d at 1351-52 (“District Court erred in deeming irrelevant the fact that ‘[Patentee] adduced evidence, including expert testimony[,] that practicing [asserted prior art] will not *always* result in [claimed invention].’”); *Azurity*, 28; *PersonalWeb Techs.*, 917 F.3d at 1382.

b. Additional Purification

It was known that “[p]olymorphism is often affected by a trace amount of impurities.” EX2037, 1; EX2030, ¶107. Nevertheless, Dr. Bihovsky also added a filtration step to Example 7 in his sequential recrystallization experiment: “This precipitate... was then dissolved in refluxing acetone (2.2 mL), *filtered while hot to*

remove a slight precipitate, then cooled and stirred for 50 hours at 4 °C.” EX1033, ¶62; EX2033, 293:20-294:21; EX2030, ¶107. Dr. Bihovsky makes no attempt to explain whether or how this additional removal of material affected his results, and admitted that he “did not characterize” the material he removed, agreed that what he removed was “something other than Z-endoxifen,” and agreed that it was “probably” impurities. EX2033, 294:22-295:22; EX2030, ¶107. He also admitted that had he followed Liu as written, those impurities would have been present in his final product following Liu Example 7 and that by doing so he likely prevented contamination of that product. EX2033, 296:10-297:2; EX2030, ¶107.

By removing this precipitate on the very last recrystallization step he performed, Dr. Bihovsky potentially altered the polymorphic form of the material he obtained. EX2030, ¶¶108-110; EX2038, 4-5; *see also* EX2041, 2; EX2040, 6; EX2036, 1; EX2037, 1. Indeed, it was well known that “for reproducible production of polymorphs, a critical issue may be the presence or absence of key impurities in the material used to make the polymorphs” (EX2036, 1), and POSITA would have understood that, by changing the impurity profile, Dr. Bihovsky may have changed the final polymorph that resulted. EX2030, ¶¶110-111; *see also* EX2037, 1.

Thus, far from following Liu’s Example 7 “extremely closely,” Dr. Bihovsky deviated from Liu’s procedures in at least three significant ways, and made no attempt to explain whether or how those deviations affected the very experimental

step that Dr. Bihovsky contends drives “the polymorphic form that a crystal adopts.” EX1033, ¶47; EX2030, ¶111. On this basis alone a finding of no anticipation is warranted.

4. Other Additional Purification and Filtration Steps

Throughout his purification scheme, Dr. Bihovsky added purification and filtration steps *Liu did not use*. EX2030, ¶112. As discussed, it was known that “[p]olymorphism is often affected by a trace amount of impurities.” EX2037, 1; EX2030, ¶112. Thus, each additional purification step—alone or cumulatively—could have impacted the purity and polymorphic form of Dr. Bihovsky’s final product. EX2030, ¶112; EX2036, 1; EX2037, 1.

First, Dr. Bihovsky added *column chromatography* to every attempted recreation of Example 2. EX1033, ¶52, n.4 (“Liu does not expressly describe using chromatography in [0062]....”); EX2030, ¶113; EX2033, 62:9-63:15 (“that was necessary that I do chromatography so that I could get the pure compound out that I thought was the product”), 173:8-174:1. But Dr. Bihovsky admitted adding this step “generally [] will give purer product” than Liu’s disclosed washing step. EX2033, 67:9-12, 67:16-68:9; *see also* EX2033, 92:9-93:4, 165:2-12. He also admitted that determining whether he “would have gotten some of the desired product” from Example 3 using unpurified product (that is, product not subjected to Dr. Bihovsky’s additional chromatography step) “would be kind of speculation” and “you wouldn’t

know until you try it.” EX2033, 69:1-71:5; EX2030, ¶114. And notably, he admitted that the purification step he added to Example 2 allowed him to avoid ending up “with an inseparable mess at the end of the synthesis process.” EX2033, 165:18-166:11; EX2030, ¶114.

Importantly, Dr. Bihovsky performed this same additional chromatography step in both versions of Example 2 from which he drew the material he used to perform Example 3,²² thus infecting every later step of his purification process with

²² Dr. Bihovsky’s narrative explanation omitted that his “Example 3” starting material included material from *two separate attempts* at Example 2, using different temperatures than each other (and Liu), and included this additional chromatography step. EX2033, 186:15-188:3, 189:18-190:12; EX2030, ¶115. Dr. Bihovsky also omitted that, for the acetone recrystallization portion of Example 4 (EX1033, ¶71), he used material from two different attempts to perform Example 4’s initial portions, *despite testifying in his declaration’s narrative that he had only used material from a single attempt*. EX1033, ¶71 (showing material 15-27-1 used for Example 4’s acetone recrystallization step); EX2033, 220:12-221:20 (admitting he used both 15-27-1 and 15-27-2 for this portion of Example 4); EX2030, ¶115. This combining of materials from multiple different experiments with different conditions is yet another

the material he altered by adding this additional chromatography step to Example 2. EX2033, 72:2-18, 73:6-75:16; EX1033, 84 (“sm [starting material] (15-22-2A + 15-23-1a),” denoting starting material from the Example 2 versions on pages 22 and 23 of Dr. Bihovsky’s lab notebook); EX2030, ¶¶114-115. And Dr. Bihovsky confirmed “[i]t’s possible” that the impurities in Liu’s Example 3 material and in his material were different due to adding chromatography. EX2033, 74:20-76:4; *see also* EX2033, 166:5-167:10 (Dr. Bihovsky’s chromatography step removed an “unknown” impurity), 200:22-201:15 (“one possibility is that my chromatography in the previous step removed other impurities”); EX2030, ¶116. Importantly, Dr. Bihovsky admitted that his additional chromatography step affected not only the intermediate material obtained from Example 2, but that it would also have affected the material he obtained from Liu Example 7 and that it would require “speculation” to determine what would have happened he followed Example 2 as written. EX2033, 65:1-66:3; EX2030, ¶116.

As Dr. Davies explains, this extra purification step—performed during the first step of Dr. Bihovsky’s purification scheme—significantly changes the entire process and could cause Liu’s final product, which depends on the products

reason Dr. Bihovsky cannot be said to have recreated Liu (which never did this). EX2030, ¶115.

produced in each of Liu's earlier steps, to differ in purity and polymorphic form because it was well known that "[p]olymorphism is often affected by a trace amount of impurities." EX2030, ¶117; EX2037, 1; *see also* EX2038, 4-5; EX2036, 1. For example, by purifying the intermediate material Dr. Bihovsky generated from his versions of Example 2, he removed excess starting material that remained in his final product. EX2030, ¶117. The presence of this starting material in future reactions could have affected those reactions, including Liu's Example 7 final recrystallization procedure, by potentially yielding other products that could not be removed by crystallization. EX2030, ¶117. This could change both the purity and polymorph of the final product. EX2030, ¶117.

Dr. Bihovsky attempts to excuse his addition of this step by pointing to chromatography used *in a different example of Liu* (EX1033, ¶52 n.4) and asserts that high performance liquid chromatography ("HPLC") "would have been a commonly used purification strategy that *could* be employed at this stage." EX1033, ¶52 n.4; EX2030, ¶118. Dr. Bihovsky acknowledges, however, that it is "often desirable to minimize the number of chromatography steps." EX1033, ¶52 n.4; EX2030, ¶118. And although Dr. Bihovsky points to another example of Liu which did use chromatography, he ignores Liu's statement that Liu's process "avoids the use of chromatography in the separation of the Z-and E-isomers." EX1003, ¶0005; EX2030, ¶118. Although this statement refers to a different step of Liu, it would

have dissuaded POSITA from unnecessarily adding column chromatography steps to Liu simply because it “could” be done. EX2030, ¶118; EX2032, 58:17-59:11 (“I would imagine it would be better not to use HPLC if you could.”).²³

Second, Dr. Bihovsky added a centrifugation step not present in Liu’s Example 4. EX1033, ¶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.”); EX2030, ¶120. This is yet another step that could have impacted the material produced by Example 4 (which was later used in Liu’s final recrystallization step (EX1033, ¶71)) by removing impurities that would not have been removed by Liu’s expressly disclosed *filtration* rather than centrifugation. EX1003, ¶0070 (“The resulting crystalline material was collected by filtration....”); EX2030, ¶120. As discussed immediately above in this section, this could have affected the purity and polymorphic form of Dr. Bihovsky’s final product. EX2030,

²³ PO does not agree that Dr. Bihovsky’s modifications to Liu are permitted for inherent anticipation, and thus whether POSITA would have been motivated to modify Liu does not excuse Dr. Bihovsky’s modifications (and Petitioner does not assert single-reference obviousness based on Liu) or cure the substantive defects with Dr. Bihovsky’s analysis. *See* §IV.A.

¶121. For justification, Dr. Bihovsky cites Liu paragraph 21, which lists exemplary embodiments that Dr. Bihovsky does not purport to follow, and which does not mention centrifugation. EX1003, ¶0021 (listing multiple solvents for carrying out Liu's recrystallization procedure and providing alternative separation methods (which Dr. Bihovsky says would include centrifugation)); EX2030, ¶122. But mixing and matching from different embodiments, as Dr. Bihovsky again attempts, is not permitted for anticipation. *Net MoneyIN*, 545 F.3d at 1369-71; *CaptionCall*, 16-17.

Third, Dr. Bihovsky elected to use Celite in Example 2 even though Liu does not use Celite at this step. *See* EX1033, ¶52 n.3 ("Liu does not explicitly state to use Celite at this step."); EX2030, ¶119. Dr. Bivhosky's use of Celite is yet another liberty taken by Dr. Bihovsky that could have influenced not only the outcome of Example 2, but also Liu's later Example 7 recrystallization step. EX2030, ¶119. That is because Dr. Bihovsky's Celite step may have filtered out different impurities than other filtration methods that Liu could have used. EX2030, ¶119; EX2036, 1; EX2037, 1. Dr. Bihovsky does not explain whether the use of Celite at this step, as compared to another available filtration method, could have altered Liu's results. EX1033, ¶52 n.3; EX2030, ¶119.

Accordingly, Dr. Bihovsky's additional purification and filtration steps provide another basis for finding that Dr. Bihovsky failed to reproduce Liu's

experiments because those additional steps could have altered his results. EX2030, ¶¶122-123.

5. Additional Drying Step

Dr. Bihovsky also performed a drying step not disclosed by Liu Example 2: “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.’” EX1033, ¶51 n.1 (citing EX1003, ¶0060). Dr. Bihovsky does not attempt to explain whether or how his drying procedure, as compared to the procedures that could have been used to dry the anhydrous material Liu did use, would have altered Liu’s results. EX2030, ¶124. And Dr. Bihovsky agreed that the degree to which the zinc bromide starting material was dried (1) can affect whether water remains in the zinc bromide, (2) that water “would actually turn some of that into zinc hydroxide, which would interfere with the reaction,” and (3) that water could also turn into hydrobromic acid, which also could interfere with the reaction. EX2033, 157:11-158:18; EX2030, ¶125. This could have affected the outcome of Example 2, as well as subsequent steps using Example 2’s material. EX2030, ¶¶124-126; *see also* EX2033, 159:3-18 (“And it worked. The yield – was improved.”).

B. Petitioner's Modified Reproduction of Liu Is Legally Insufficient to Establish Inherency

Dr. Bihovsky's synthesis scheme, which departs from Liu in the numerous ways discussed above (§§III.A.1-5), cannot, as a matter of law, support inherent anticipation. *Enplas*, 909 F.3d at 405 ("Prior art that must be modified to meet the disputed claim limitation does not anticipate the claim."); *Valeant Int'l (Barb.) 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 Berm. v. Actavis, Inc.*, 534 F. App'x 999 (Fed. Cir. 2013) (non-precedential); *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).

Dr. Bihovsky admits that (1) without his additional chromatography steps in Example 2 he would have obtained "an inseparable mess" (EX2033, 165:2-166:11; EX2030, ¶114), (2) the results of at least one of his attempts at Example 2 were so poor that it was not even worth determining the yield of that experiment (EX2033, 178:4-179:17; EX2030, ¶¶52, 80), (3) determining whether he "would have gotten

some of the desired product” from Example 3 using unpurified product from his first attempt at Liu Example 2 “would be kind of speculation” and “you wouldn’t know until you try it” (EX2033, 69:1-71:5; EX2030, ¶114), and (4) without his additional stirring and scratching steps that it may not have been possible to proceed to the next step of Example 7 (EX2033, 116:12-117:5; EX2030, ¶106).

The institution decision acknowledged Dr. Bihovsky’s modifications, but pointed to his testimony that they were just “minor adjustments” and “routine adjustments a POSA following Liu would have likely made.” Inst.15 (citing EX1033, ¶47). But Dr. Bihovsky’s testimony in this regard is conclusory and cites no literature for support and his above-discussed deposition testimony belies those assertions. *E.g.*, EX2033, 100:1-17.

Dr. Davies’s testimony also confirms that Dr. Bihovsky’s modifications were far from “minor” or “routine.” EX2030, ¶¶47-126. Instead, they were so significant that POSITA would not have viewed Dr. Bihovsky’s experiments as a recreation of Liu, but rather a completely different set of experiments. EX2030, ¶¶47, 64, 91; *see also id.*, ¶¶47-126. Moreover, here, as in *Rosellini*, Dr. Bihovsky failed to explain numerous of his deviations from Liu’s experimental protocol, including his modification to the ratios of ingredients in Liu (§III.A.1) his use of higher temperature or refluxing isopropyl acetate where Liu expressly specified lower temperatures at which isopropyl acetate would not reflux (§III.A.2), and his

additional purification step in Example 7 (§§III.A.3-4). *Rosellini*, 8-12. It would be legal error to conclude, based on this record, that Petitioner has shown that Liu inherently anticipates claims 1-6, 16, 18, and 21.

Indeed, the Federal Circuit affirmed a finding of no inherent anticipation in similar circumstances. *Valeant*, 2011 WL 6792653, at *5, *aff'd sub nom.*, *Valeant Int'l Berm. 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 I bupropion hydrobromide.” *Id.* at *1, *2, *4-5. The patent challenger contended that “following Example 1 of the [asserted prior-art] patent invariably results in Form I 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 I 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 “[c]laim 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.* Here, as in *Valeant*, it is undisputed that but for Dr. Bihovsky’s changes he would not have been able to obtain the material that he says meets the claimed Form I and purity limitations. EX2033, 165:18-166:11, 69:1-71:5, 116:12-117:5; EX2030, ¶¶52, 80, 106, 114; *see also id.*, ¶¶47-126. That is not inherency.

C. Petitioner’s Modified Reproduction of Liu Failed, as a Matter of Fact, to Produce the Claimed Form I at the Claimed Purity

Claim 1 of the ’151 patent requires, *inter alia*, “at least 90% by weight of the compound of Formula (III) in the composition is (Z)-isomer, and wherein the crystalline form of the (Z)-isomer is Form I.” EX1001, cl.1; *see also* EX1001, cl.16.

And because it is undisputed that Liu does not disclose whether its (Z)-endoxifen is Form I (Pet.14) for Liu to inherently anticipate claim 1, it must disclose that the (Z)-endoxifen produced by following Liu's method is necessarily Form I at the claimed at least 90% purity. Petitioner thus cannot rely on Liu's isolated disclosure of an unknown form of (Z)-endoxifen with greater than 90% purity. Pet.27. That is particularly true where, as Dr. Bihovsky admits, (Z)-endoxifen has multiple polymorphic forms and thus, as Dr. Bihovsky's own results in which he got "97% Z – Not Form I" show (EX1033, p.91), it is not always the case that 90%+ pure (Z)-endoxifen will be Form I.²⁴ E.g., EX2033, 238:22-240:19 ("that was before XRPD, and that was also not Form 1, even though it was 97 percent pure Z... So again, recrystallizing from acetone gives you Form 1; recrystallizing from isopropyl acetate

²⁴ Despite relying on other experiments in which he changed Liu, Dr. Bihovsky attempts to dismiss this result as irrelevant "because it was recrystallized through isopropyl acetate rather than acetone" as taught by Liu. EX2033, 239:2-240:19. This lays bare the self-serving nature of Dr. Bihovsky's opinions: experiments generating results he does not prefer should be discounted because he did not follow Liu exactly, whereas other experiments with results he does prefer should be credited even though he modified Liu in those experiments.

gives you a different form.”); EX1001, Figs.11-12 (showing XRPD for Form II), Fig.13 (showing XRPD for Form III); EX2030, ¶¶127-128.

Dr. Bihovsky’s lab notebook shows, however, that he did not always obtain Form I (Z)-endoxifen at the claimed at least 90% purity. EX1033, p.91. As shown below, Dr. Bihovsky’s sample 15-32-2P yielded only “88% Z”:

10/24/23	bundle 15-30-3P (98 mg) in Dx acetone (1.00 ml)
	cool to 20° → 4° (stirring) for 1 day - <i>mix w/ 100% acetone</i>
	vac filter + dry → 54 mg off white <i>cryst</i> 15-32-2P
	88% Z XRPD = Form I
	Polysorp filtrate → 31 mg v. lt. pink foam -25
	63% Z

EX1033, p.91; EX2030, ¶129.

Dr. Bihovsky admitted that when he followed Liu Example 7’s final recrystallization procedure *he did not always get the claimed Form I (Z)-endoxifen at the claimed 90% or greater purity*:

Q. So the three times you [tried] Liu’s Example 7, all three times you got Form 1 of (Z)-endoxifen, one of the times it was 88 percent pure, one of the times it was 93 or 94 percent pure, and one of the times it was 100 percent pure; is that correct?

A. I think that’s correct.

EX2033, 262:16-263:1 (objection omitted); *see also* EX2033, 259:16-260:4 (“Q. Okay. So what you found in performing Liu’s example seven recrystallization

procedure, you got (Z)-endoxifen, which was 88 percent pure, right? A. Yes. 88 percent Z, 22 percent E, Form 1.”) (objection omitted); EX2030, ¶130.²⁵

This admission dooms Petitioner’s inherent anticipation theory. The law is clear that inherency requires that the missing element be *necessarily, unavoidably, and inevitably* present based in the reference. *U.S. Water*, 843 F.3d at 1350-52; *Azurity*, 28; *PersonalWeb Techs.*, 917 F.3d at 1382. Yet Dr. Bihovsky admitted that Liu’s Example 7, even as Dr. Bihovsky modified it, can, in some cases, yield (Z)-endoxifen that does not meet the claimed purity. EX2030, ¶¶131-132. That is not inherency.

D. Dependent Claims 2-6, 18, and 21 Are Not Anticipated

Because Petitioner has failed to prove anticipation of claim 1 (§§III.A-III.C, *supra*), claims 2-6, 18, and 21 also cannot be anticipated. EX2030, ¶¶133-135.

²⁵ Dr. Bihovsky testified that had he recrystallized this sample again that he “would still get Form 1 and a higher percentage of Z than 88 percent.” EX2033, 253:10-255:1. But Dr. Bihovsky did not do so, and thus has not shown that recrystallizing this sample would have resulted in higher purity or that it would have been Form I. EX2030, ¶131.

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

A. Claims 1 and 16: The Liu and Ahmad Combination Does Not Remedy Petitioner's Failure to Show Liu Discloses the Claimed Form I

Petitioner's Ground 2 obviousness arguments as to claim 1 add nothing to Ground 1. Ground 2 therefore fails, first and foremost, because Petitioner relies on the same erroneous arguments that Liu inherently discloses Form I as it does in Ground 1. Pet.38 ("the claimed XRPD patterns are inherently taught by Liu"), 61-62; *see also* EX1033, ¶¶43, 89; EX2030, ¶136. Moreover, having failed to do so in the Petition, Petitioner cannot now argue that Dr. Bihovsky's specific modifications to Liu would have been obvious to arrive at the claimed Form I.²⁶ Indeed, Petitioner nowhere explains in its two-page Ground 2 argument for claims 1-6 and approximately one-page claim 16 argument: (1) which disclosures in Liu would need

²⁶ Petitioner cannot change its theory in Reply or offer additional modifications to remedy its deficient arguments here. *In re NuVasive, Inc.*, 841 F.3d 966, 972-73 (Fed. Cir. 2016) (vacating final written decision when Board relied on factual assertion by petitioner made only after patent owner's response); *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1369-70 (Fed. Cir. 2016); *Apple Inc. v. Smart Mobile Tech. LLC*, IPR2022-00981, Pap.34, 35-36 (Nov. 7, 2023).

to be modified to achieve Form I at the requisite purity; (2) why POSITA would have been motivated to make those modifications; or (3) why POSITA would have reasonably expected those modifications to result in the claimed invention. EX2030, ¶137.

Instead, Petitioner simply asserts, with no further explanation, that POSITA would have arrived at the claimed inventions “utilizing known, conventional, and predictable processes.” *See, e.g.,* Pet.37-39, 62; EX2030¶¶138-140. That is insufficient to carry Petitioner’s burden to establish that POSITA would have been motivated with a reasonable expectation of success to make the numerous modifications that Dr. Bihovsky made to Liu to arrive at the claimed Form I.

Petitioner also asserts that “to the extent a POSA required other teachings... a 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. But Petitioner does not ever state what specific claim limitations it contends Fauq and Milroy are relevant to, does not identify any disclosures of Fauq and Milroy, or explain why POSITA would have been motivated to use these unspecified aspects of Fauq or Milroy to arrive at the claimed inventions. EX2030, ¶140. In fact, the above-quoted sentence is the only mention of Milroy in the entire Petition, and Petitioner’s expert Dr. McConville admitted that he mentioned Milroy only once in passing (in paragraph 67 of his declaration) and provided no explanation or

discussion of which teachings of Milroy, if any, would be applicable here.²⁷

EX2032, 61:16-62:8. Petitioner has thus failed to show claim 1 is obvious based on any purported knowledge of POSITA drawn from Fauq, Milroy, or elsewhere. EX2030, ¶¶139-140.

Moreover, although Petitioner asserts that Liu in view of Ahmad renders obvious claim 1 and 16 (in addition to claims 2-6) and that POSITA would have looked to Fauq and Milroy (which are not named in the Ground), Petitioner never identifies what specific portions of Ahmad, Fauq, or Milroy it relies on or how any such portions should be combined with Liu. Under §42.104(b)(4) an IPR petition “must specify where each element of the claim is found in the prior art patents or printed publications relied upon,” and Petitioner’s citation to Ahmad, Fauq, and Milroy without further explanation is insufficient to meet its burden. Further, Petitioner offers only conclusory reasons POSITA would have been motivated to combine Ahmad’s disclosures with Liu with a reasonable expectation of success in achieving the inventions of claims 1 and 16, generally arguing that POSITA would have arrived at the claimed inventions “utilizing known, conventional, and predictable processes.” *See, e.g.*, Pet.38 (“arriving at the invention claimed in the

²⁷ To the extent Petitioner attempts to rely on its claim 21 argument regarding Fauq, that argument would fail for the same reasons as detailed below as to claim 21.

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. Petitioner’s failure to identify any disclosures in Ahmad, and its failure to provide more than conclusory motivation for why POSITA would combine those disclosures with Liu, is insufficient to carry its burden to demonstrate unpatentability.²⁸

B. Claims 2-15 and 17-21: Petitioner Fails to Establish that the Prior Art Discloses Additional Dependent Claim Elements

As with claim 1, Petitioner’s Ground 2 arguments regarding dependent claims 2-15 and 17-21 fail because Petitioner failed to show that Liu discloses or renders obvious Form I at the requisite purity for the reasons discussed above (§§III, IV.A) and because Dr. Miller’s XRPD testing and Dr. Mayo’s reliance thereon should be given no weight (§V). EX2030, ¶141. Further, Petitioner in many cases provides no more than conclusory arguments regarding why POSITA would have allegedly been motivated to modify the prior art to arrive at the claimed inventions and why POSITA would have had a reasonable expectation of success in doing so. *E.g.*, Pet.37-39; EX2030, ¶142. These arguments are so devoid of explanation that in

²⁸ Petitioner could have asserted a single-reference obviousness ground for claims 1-6 and 16 based on Liu alone but did not, choosing instead to assert ground purporting to combine Liu and Ahmad.

many cases it is difficult for PO to meaningfully respond to such arguments. *E.g.*, Pet.37-39 (claims 1-6), 41-42 (claims 8-9), 63-67 (claims 17-20).

1. Claims 2-6

Petitioner fails to identify the specific gaps in Liu it seeks to address by combining Liu with Ahmad and POSITA's knowledge, and further fails to explain why POSITA would have been motivated to do so to arrive at the specific inventions of these claims with a reasonable expectation of success. Petitioner instead provides a conclusory, high-level assertion that it would have been obvious to do so. *E.g.*, Pet.37-39; EX1032, ¶67; EX1033, ¶¶88-90; EX2030, ¶144. In addition, as discussed with respect to claims 1 and 21 (§§IV.A, IV.B.5), for claims 2-6 Petitioner fails to explain how or why POSITA would have looked to Fauq and Milroy. EX2030, ¶¶138-140.

2. Claims 8-9

Claims 8 and 9 require specific dosage forms of the (Z)-endoxifen of claim 1. EX1001, cl.8, cl.9. Petitioner does not identify any motivation for formulating (Z)-endoxifen as claimed by claims 8 and 9 or provide any detail as to why POSITA would have specifically chosen any of the claimed dosage forms. Pet.41-42. Instead, Petitioner simply argues that these dosage forms "were well-known in the art and a POSA would have been motivated to use them and would have had a reasonable expectation of success" in doing so. Pet.41-42. And Petitioner's expert

Dr. McConville offers this same conclusory opinion with no explanation as to motivation to combine or reasonable expectation of success. *E.g.*, EX1032, ¶¶72-73. Such conclusory testimony, which simply parrots the Petition, should be given no weight. *Xerox Corp. v. Bytemark, Inc.*, IPR2022-00624, Pap.9, 15 (Aug. 24, 2022) (precedential).

3. Claims 10-12 and 15

Claim 11, which depends from claim 1, requires, *inter alia*, “an oral dosage form” that achieves specific claimed pharmacokinetic properties. EX1001, cl.11; EX2030, ¶145. As an initial matter, for the reasons discussed with respect to claims 8 and 9 (§IV.B.2), Petitioner has failed to explained why POSITA would have been motivated to select an oral dosage form.

Petitioner argues that “[b]ecause the composition was known in the art at the time of the invention (*e.g.*, Liu) the pharmacokinetics of that composition were inherent in that composition.” Pet.46. But Petitioner’s expert Dr. McConville admitted that pharmacokinetic properties such as those claimed by claim 11 (*e.g.*, $T_{\max}$ and $C_{\max}$) can both be affected by how a drug is formulated and by impurities in the drug and thus are not inherent properties. *E.g.*, EX2032, 17:11-18:9, 20:15-21:15, 23:4-14, 24:11-25:12, 27:2-16, 42:17-43:7; *see also* EX1027, 47 (showing different pharmacokinetic parameters including $C_{\max}$, $T_{\max}$, elimination rate constant,

and AUC(0-infinity) for different tested formulations of 600mg aspirin); EX2030, ¶146.

Claims 10 and 12 specify the half-life of the composition claimed in claim 11 and claim 15 requires a specific area under the curve 0-infinity (“AUC_{0-inf}”) of the composition of claim 11. EX1001, cl.10, cl.12, cl.15. For the same reasons as discussed with respect to claim 11, Petitioner has failed to show these additional limitations are obvious. EX2030, ¶¶145-150. In addition, for these claims, Dr. McConville does not explain why POSITA would have been motivated to obtain the target pharmacokinetics and thus fails to show obviousness. EX2030, ¶151.

4. Claims 17 and 19-20

As to claims 17 and 19-20, Petitioner provides no assertions about reasonable expectation of success, instead only referencing motivation. Pet.63, 65-67. Petitioner’s statements are insufficient to carry its obviousness burden by identifying particular disclosures and establishing that POSITA would have been motivated to combine them with a reasonable expectation of success. *See In re Lee*, 277 F.3d 1338, 1345 (Fed. Cir. 2002). Petitioner’s conclusory obviousness statements do not 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.

Additionally, Petitioner's expert simply parrots Petitioner's conclusory assertions and thus should be given no weight. *E.g.*, EX1032, ¶¶98 (claim 17), 101 (claim 19), 102-103 (claim 20); *Xerox*, 15. Further, as to claim 20, Petitioner has failed to show obviousness for the same reasons as discussed above as to claims 10-12 and 15. Pet.66-67; EX1033, ¶102 ("claim 20 merely recites inherent properties...").

5. Claim 21

Claim 21 requires that the composition of claim 1 be stable for at least nine months at certain, specified conditions. EX1001, cl.21. Petitioner does not provide nine months of stability testing. Pet.56-61 (Dr. Bihovsky's 10-day stability test), EX2030, ¶¶152-153. Petitioner instead asserts that because Liu discloses the claimed Form I (Z)-endoxifen, it inherently discloses the claimed stability. Pet.57. Dr. Bihovsky admitted, however, that the purity of a compound affects its stability (EX1033, ¶¶92, 95; EX2033, 126:13-127:9; EX2030, ¶154) and that the (Z)-endoxifen he produced contains 1 weight % of residual acetone and that his attempt to remove it only reduces it to 0.6 weight % (EX1033, ¶97). And Dr. Davies explains that any excess solvent (such as acetone) could affect (Z)-endoxifen's stability. EX2030, ¶154.

Petitioner also points to Fauq's (EX1005) disclosure of HPLC of (Z)-endoxifen as one possible way to purify (Z)-endoxifen to increase stability. Pet.59-

60. But neither Petitioner nor its experts explain why POSITA would have been motivated to modify Liu using Fauq’s disclosures of separating (E)- and (Z)-endoxifen using HPLC given Liu’s disclosure that its process “avoids the use of chromatography in the separation of the Z- and E-isomers.” EX1003, ¶0005; EX2030, ¶155. Notably, despite offering the opinion that POSITA would have looked to Fauq (EX1032, ¶67), Dr. McConville testified that “[m]anufacturing is not completely my area of expertise[,] I would imagine it would be better not to use HPLC if you could” (EX2032, 58:8-59:11). *See also id.* at 59:12-61:15 (“I’ve said it is not really my area of expertise, a scaleup, and I assume that using chromatography is more expensive, but maybe there’s benefits to it that I’m – that go beyond the cost, I don’t know.”), 63:12-21 (“I think Liu is potentially cheaper on paper, but what do I know? I’ve never scaled anything up. So I can’t say yes or no to your question.”).

Petitioner also cites Elkins (EX1026) and argues that Elkins’s stability studies of a different sample of (Z)-endoxifen (i.e., not Dr. Bihovsky’s samples) show that the claimed stability “would not have been surprising to a POSA.” Pet.57-58. But Petitioner has not shown that Elkins’s (Z)-endoxifen has the same impurity profile as Dr. Bihovsky’s (Z)-endoxifen and thus cannot show that Elkins’s disclosures are applicable to Dr. Bihovsky’s (Z)-endoxifen. EX2030, ¶156.

* * *

Thus, Petitioner's arguments regarding Ground 2 fail both because Petitioner has not established that Liu inherently discloses Form I at the requisite purity and because Petitioner has failed to demonstrate that the prior art rendered obvious the additional claim limitations of the above-discussed dependent claims.

V. Dr. Mayo's Testimony Should Be Given No Weight

As originally filed, the Petition relied on XRPD testing performed by Dr. Steven Miller, which purported to show that the (Z)-endoxifen synthesized by Dr. Bihovsky, when tested, had the same polymorphic structure and XRPD pattern as claimed in the '151 patent. EX1034; Pet.1, 14-15. Without this testing, Petitioner cannot show Liu discloses the Form I (Z)-endoxifen required by every claim. *E.g.*, Pet.14-15, EX1033, ¶¶33, 79; EX1038, ¶¶21, 29.

Although Dr. Miller's declaration described an "Appendix B" that purportedly contained "[t]he experimental test and analysis conditions used for the XRPD testing" (EX1034, ¶23) Dr. Miller's declaration had no Appendix B, and no Appendix B was submitted with the Petition. Nor did Petitioner (despite objection from PO, Pap.16, 4) submit Appendix B as supplemental information in §42.123's one-month period.

Petitioner later substituted Dr. William Mayo for Dr. Miller. Dr. Mayo adopted Dr. Miller's opinions and filed a replacement declaration that restated Miller's opinions verbatim. Dr. Mayo performed no additional testing and included

no additional results, and had no personal knowledge of Dr. Miller's testing.²⁹
EX1038; EX2031, 9:1-12, 20:7-22:15, 58:7-59:5.

Dr. Mayo's declaration (like Dr. Miller's) is missing any "Appendix B." Dr. Mayo's written testimony (like Dr. Miller's) describes Appendix B as "[t]he experimental test and analysis conditions used for the XRPD testing" Dr. Miller performed. EX1038, ¶ 23. But Dr. Mayo has no independent knowledge of the "conditions" used by Dr. Miller (EX2031, 20:7-22:15, 58:7-59:5), and those conditions are not present anywhere else in testimony from either expert. The Board and PO thus have no ability to explore any details or assess the reliability of Petitioner's relied-upon XRPD testing, which Dr. Mayo admitted could be affected by the very testing parameters and conditions missing from his declaration.³⁰

²⁹ Consistent with Board practice for substitutions, the replacement declaration only updated the background section and changed first- to third-person when discussing Dr. Miller's testing.

³⁰ Petitioner provided an Appendix B to Patent Owner via email on December 22, 2025 (over eight months after the petition was filed, and more than one month after institution), but has made no effort to properly introduce Appendix B into the record of the proceeding by, *e.g.*, filing a motion to submit supplemental information under §42.123 or otherwise seeking Board approval. Even if it had, PO would have had

**A. PO Has Been Deprived of the Ability to Question Any
Knowledgeable Witness**

Dr. Mayo was not present for Dr. Miller's testing, and thus had to speculate as to the *facts* surrounding Dr. Miller's actual testing, including what testing procedures were followed. *See also* n.30. For example, Dr. Mayo speculated that Dr. Miller "would be foolish not to follow the [standard operating procedure]" because by doing so his testing laboratory (H&M Analytical Services) "risk[s] losing the FDA certification." EX2031, 20:20-22:2. But Dr. Mayo readily admitted that neither H&M's standard operating procedure nor any information regarding H&M's purported FDA certification is mentioned in his declaration, and he had no independent knowledge of whether Dr. Miller followed these procedures. EX2031, 20:7-22:15, 59:6-60:7. Dr. Mayo also admitted to further guessing: he supposedly "gleaned" Dr. Miller's experimental conditions from Dr. Miller's reported results and "ha[s] a pretty good idea of what the testing conditions were" based on his prior work at H&M and his "muscle memory" from writing H&M's standard operating procedures, but that none of that information is in his declaration and he had no independent knowledge of whether Dr. Miller followed those procedures. EX2031, 20:7-22:15; 82:11-83:19, 113:18-114:9.

no opportunity to explore the provenance, handling, or content of Appendix B with the knowledgeable witness, given Dr. Miller's unavailability.

PO is thus forced to rely on Dr. Mayo’s speculation and “muscle memory” about these foundational facts, rather than on information actually provided by Dr. Miller—the only person who has personal knowledge of the facts surrounding his testing. This effectively deprives PO of the chance to depose *any* witness about the *facts* underlying these opinions, and thus of “a fair opportunity to challenge the testimony” and of due process. *E.g.*, *Praxair Distrib., Inc. v. Ino Therapeutics LLC*, IPR2015-00529, Pap.33, 2 (Dec. 22, 2015); *Mexichem Amanco Holdings S.A. de C.V. v. Honeywell Int’l, Inc.*, IPR2013-00576, Pap.36, 3 (Sept. 5, 2014). Accordingly, Dr. Miller’s testing and Dr. Mayo’s reliance thereon should receive no weight. *See Praxair*, 2; *Mexichem*, 3.

B. Dr. Mayo’s Opinions Fail to Provide Underlying Facts and Data

“Expert testimony that does not disclose the underlying facts or data on which the opinion is based is entitled to *little or no weight*.” §42.65(a); Patent Trial and Appeal Board, Consolidated Trial Practice Guide, 40 (Nov. 2019); *see iRobot Corp. v. SharkNinja Operating LLC*, No. 2023-1398, 2024 WL 3687981, at *5 (Fed. Cir. Aug. 7, 2024) (non-precedential) (appropriate for Board to accord “little or no weight” to testimony that “is only conclusory with inadequate supporting evidence”). In addition, “[i]f a party relies on a technical test or data from such a test, the party must provide an affidavit explaining,” *inter alia*, “[h]ow the test was performed and the data was generated,” and “[a]ny other information necessary for

the Board to evaluate the test and data.” §42.65(b); *see also The Scotts Co. v. Encap, LLC*, IPR2013-00110, Pap.79, 20-21 (June 24, 2014) (refusing to credit expert declaration that “does not provide sufficient details regarding the underlying testing upon which he appears to rely”).³¹

Here, Dr. Mayo (and Dr. Miller) failed to provide information about numerous parameters Dr. Mayo admitted could affect the outcome of Petitioner’s XRPD testing. For example, Dr. Mayo agreed that “the way that the sample is made into a powder and put into the sample holder can affect the quality of the data,” and whether that has occurred “depends upon the details of the material, and the particular sample holder and the instrument.” EX2031, 23:16-24:5. But such information regarding the sample holder is not part of his declaration (EX2031, 24:21-25:7), and Dr. Mayo has no personal knowledge of that information. Dr. Mayo also agreed that milling of a sample and “preparation of the powdered material and the mounting of the specimen in a suitable holder can greatly affect the quality of the data to be collected in the XRPD analysis” (EX2031, 40:2-41:8, 46:2-12, 51:9-54:16), but again admitted that information about the holder Dr. Miller used is not

³¹ At his deposition, Dr. Mayo attempted to discuss certain information in Appendix B, but that information was not previously filed as an exhibit or made part of Dr. Miller or Dr. Mayo’s declarations.

in his declaration (EX2031, 48:12-49:8) and milling information is also not in his declaration.³² *See also* EX1031 (“controlling document for XRPD testing of various materials” (EX2031, 43:21-44:6) detailing “critical steps” that “can greatly affect the quality of data to be collected” including “mounting of the specimen in a suitable holder” (EX1031, 7)). And although he testified that changes to sample temperature should be avoided “[b]ecause we do not want to introduce any changes to the sample” (EX2031, 30:15-31:19), Dr. Mayo also admitted he did not know how Dr. Bihovsky’s samples were isolated and prepared for shipment to Dr. Miller, and his declaration contained no information as to how the samples received from Dr. Bihovsky were stored after being received by Dr. Miller. EX2031, 73:11-74:12, 76:6-78:6.³³

Other testing conditions and parameters that Dr. Mayo admitted could also affect the quality or reliability of results but that are not addressed in his declaration

³² Liu discloses producing crystalline solids by crystallization (EX1003, ¶¶0075, 0077), and thus Dr. Mayo’s speculation that Dr. Bihovsky’s materials were sent as powers because they were “prepared by precipitation” (EX2031, 74:13-76:2) is inconsistent with Liu. EX2030, ¶159.

³³ Dr. Mayo was also unable to answer whether Dr. Miller tested any samples other than the two samples referenced in Dr. Mayo’s declaration. EX2031, 61:1-62:14.

include: (1) the degree of alignment or misalignment of the testing instrument (EX2031, 49:19-51:8; EX1031, 8); (2) H&M’s calibration procedures (EX2031, 34:2-4); (3) which instrument was used to test the samples (EX2031, 32:14-20, 34:7-35:19) (admitting that some instruments are “notoriously inaccurate”); and (4) the temperature at which Dr. Miller’s analysis was performed (EX2031, 30:15-31:19, 77:4-20, 78:12-79:1).

Dr. Bihovsky also testified that he had sent at least two additional samples to Dr. Miller—including two samples which Dr. Miller apparently reported to Dr. Bihovsky to be “Not Form I.” EX1033, pp.89, 91; EX2033, 231:17-233:16, 236:6-237:4, 237:9-238:18, 239:10-240:19, 240:21-241:12); *see also* EX2033, 259:21-262:6. But neither Petitioner, Dr. Bihovsky, nor Dr. Miller provided the data for those tests or even mentioned them in their declarations. EX2033, 261:3-262:6; EX2031, 62:9-14 (Dr. Mayo testifying “I noticed[] that Dr. Miller tested two samples. That’s all I know.”). PTAB requirements are clear, however, that all test results—including those that are potentially *unfavorable* to a party—must be disclosed. §42.51(b)(1)(iii); *Adobe Inc. v. Rah Color Techs. LLC*, No. IPR2019-00627, Pap.59, 3-7 (Dec. 12, 2019) (requiring disclosure of “facts or data” underlying testimony, including “any relevant information that is inconsistent with Petitioner’s positions.”).

* * *

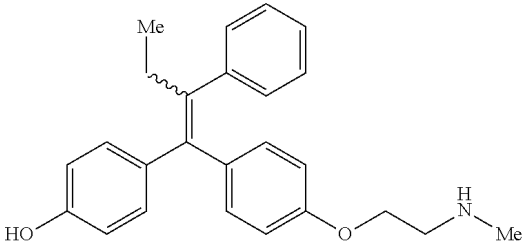
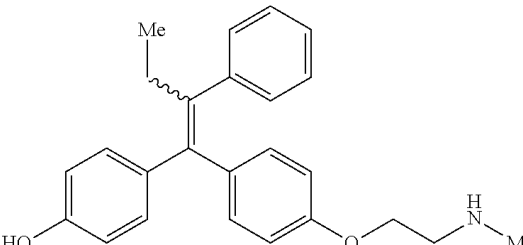
Petitioner's failure to provide this information has deprived the Board, PO, and PO's expert of the ability to verify the reliability of Dr. Miller's testing and the propriety of Dr. Mayo's reliance thereon, as well as the ability to verify this information through the testimony of someone with personal knowledge of Dr. Miller's testing. Petitioner's XRPD testing—which is necessary to show whether the material synthesized by Dr. Bihovsky was the claimed Form I—should thus be given no weight. *See Praxair*, 2; *Mexichem*, 3. Moreover, because Liu itself provides no information about the polymorphic form of its (Z)-endoxifen, a finding that Dr. Miller's XRPD testing receives no weight requires finding that Liu does not anticipate or render obvious the challenged claims.³⁴

VI. No Collateral Estoppel

The Institution Decision correctly finds that collateral estoppel does not apply here because “the issues present in this proceeding concern Liu's alleged inherency and the Form I or XRPD limitations recited in the challenged claims, which are issues that are not identical to issues presented in the anticipation and obviousness grounds asserted in PGR2023-00043.” Inst.3-4. There can be no other conclusion,

³⁴ For the same reasons that Dr. Mayo's declaration should be given no weight, Petitioner has failed to show that Dr. Miller's XRPD testing reliably and accurately disclosed the XRPD patterns set forth in those claims. EX2030, ¶¶158-165.

as 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. This is confirmed by the table below, which shows that 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. *See Comair Rotron, Inc. v. Nippon Densan Corp.*, 49 F.3d 1535, 1539 (Fed. Cir. 1995) (“[W]e point out that separate patents describe ‘separate and distinct [inventions],’” “and it can not be presumed that related patents rise and fall together.”). Here, Form I is required by every challenged claim and any determination regarding validity would require consideration of Form I, and therefore, raise an issue critical to the determination that was not present in the ’334 PGR. 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”). Petitioner’s arguments for each challenged claim involve issues regarding Form I and are therefore not identical to the issues presented in the ’334 PGR.

Moreover, 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.*, Pet.24–25), is legally deficient and fundamentally inapplicable. *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, 993-94 (Fed. Cir. 2014) (requiring “identity of the issues in a prior proceeding” and “actual litigation of those issues” for collateral estoppel to apply). Thus, Petitioner’s collateral estoppel arguments should be rejected.

VII. Conclusion

The Petition fails to show, by a preponderance of the evidence, that Dr. Bihovsky’s altered version of Liu’s experiments yielded the same results as Liu’s actual experiments would have, and thus failed to show, by a preponderance of the evidence, that Liu inherently disclosed the claimed Form I of (Z)-endoxifen at the claimed purity. Moreover, Dr. Mayo’s declaration should receive no weight, and accordingly Petitioner has failed to show by a preponderance of the evidence that Dr. Miller’s XRPD results match those required by the claims of the ’151 patent.

Respectfully submitted,

Dated: January 26, 2026

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CERTIFICATE OF WORD COUNT

The undersigned certifies that the foregoing Patent Owner's Response complies with the type-volume limitation in 37 C.F.R. §42.24(a)(1) and §42.24(b)(2). According to the word-processing system's word count, the brief contains 13,962 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 Response and the accompanying exhibits have been served in their entirety on January 26, 2026, by causing the aforementioned documents to be electronically mailed to the following attorneys of record for the Petitioner listed below.

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