Filed on behalf of Intas Pharmaceuticals Ltd.

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

INTAS PHARMACEUTICALS LTD.,
Petitioner
v.
ATOSSA THERAPEUTICS, INC.,
Patent Owner

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

PETITION FOR *INTER PARTES* REVIEW

TABLE OF CONTENTS

I. Introduction 1

II. Mandatory Notices 2

III. Grounds for Standing 3

IV. Identification of Grounds 3

V. The 151 Patent 4

A. Subject Matter of the 151 Patent 4

B. Claims of the 151 Patent 5

C. Prosecution History 8

D. Person of Ordinary Skill in the Art 9

E. Claim Construction 10

VI. Summary of the Prior Art 10

A. WO 2017/070651 ("Liu") 10

B. US 9,333,190 ("Ahmad") 15

C. Additional Background References 16

1. Ahmad 2010 16

2. Ahmad 2012 18

3. Cole 19

VII. Discretionary Denial 21

A. 325(d) Based on Prosecution Activity 21

B. Other Bases for Discretionary Denial 23

VIII. RELATED PROCEEDINGS 24

IX. Ground 1: Claims 1-6, 16, 18, and 21 Are Anticipated by Liu 25

A. Claim 1 25

B. Claims 2-5 30

C. Claim 6 34

D. Claim 16 35

E. Claim 18 36

X. Ground 2: Claims 1-21 Are Obvious Over Liu and Ahmad in View of the Knowledge of a POSA.....37

A. Claims 1-6 37

B. Claims 7-9 39

C. Claims 13 and 14.....42

D. Claims 10-12 and 15 46

E. Claim 21 56

F. Claim 16 61

G. Claims 17 and 18.....63

H. Claims 19 and 20.....65

XI. Conclusion 67

TABLE OF AUTHORITIES

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Advanced Bionics, LLC v. Med-El Elektromedizinische Gerate GmbH
IPR2019-01469, Paper 6 (P.T.A.B. Feb. 13, 2020).....21

Amazon.com, Inc. v. Vb Assets, LLC
No. IPR2020-01346, 2021 WL 406294 (P.T.A.B. Feb. 4, 2021).....23

Apple Inc. v. Corephotonics, Ltd.
861 F. App'x 443 (Fed. Cir. 2021) 38

Apple Inc. v. Immervision, Inc.
No. IPR2023-00471, 2023 WL 5166410 (P.T.A.B. July 11, 2023).....23

Becton, Dickinson & Co. v. B. Braun Melsungen AG
IPR2017-01586, Paper 8 (P.T.A.B. Dec. 15, 2017) 21, 23

Constant v. Advanced Micro-Devices, Inc.
848 F.2d 1560 (Fed. Cir. 1988) 34

Google LLC v. Hammond Develop. Int'l, Inc.
54 F.4th 1377 (Fed. Cir. 2022) 24, 49

In re Donohue
766 F.2d 531 (Fed. Cir. 1985) 38

In re Huai-Hung Kao
639 F.3d 1057 (Fed. Cir. 2011) 47

Intas Pharms. Ltd. v. Atossa Therapeutics, Inc.
PGR2023-00043, Paper 37 at (P.T.A.B. January 29, 2025)..... passim

King Pharm., Inc. v. Eon Labs, Inc.
616 F.3d 1267 (Fed. Cir. 2010) 47

Koninklijke Philips v. Google
948 F.3d 1330 (Fed. Cir. 2020) 37

KSR Int'l Co. v. Teleflex Inc.
550 U.S. 398 (2007)..... 38, 60, 62

MaxLinear, Inc. v. CF CRESPE LLC
880 F.3d 1373 (Fed. Cir. 2018) 24

Papst Licensing GMBH & Co. KG v. Samsung Elecs. Am., Inc.
924 F.3d 1243 (Fed. Cir. 2019) 24

Realtime Data, LLC v. Iancu
912 F.3d 1368 (Fed. Cir. 2019) 37

Santarus, Inc. v. Par Pharm., Inc.
694 F.3d 1344 (Fed. Cir. 2012) 46

Spence v. Dep. of Veterans Affairs
831 F. App'x 949 (Fed. Cir. 2020) 24

Statutes

35 U.S.C. § 102(a) ..... passim

35 U.S.C. § 112 34

PETITIONER'S EXHIBIT LIST

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

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

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1027	SHARGEL, LEON & YU, ANDREW, APPLIED BIOPHARMACEUTICS & PHARMACOKINETICS (7th ed. 2016) ("Shargel")
1028	Wieckhusen, D., *The Development of API Manufacturing Processes – Targets aand Strategies*, 60(9) CHIMIA INT'L J. FOR CHEM. 598-604 (2006) ("Wieckhusen")
1029	COULSON & RICHARDSON, COULSON & RICHARDSON'S CHEMICAL ENGINEERING (5th ed. 2002) ("Richardson")
1030	ALLEN & ANSEL, ANSEL'S PHARMACEUTICAL DOSAGE FORMS & DRUG DELIVERY SYSTEMS (10th ed. 2013) ("Ansel")
1031	USP 941
1032	Expert Declaration of Jason McConville, Ph.D. ("McConville")
1033	Expert Declaration of Ron Bihovsky, Ph.D. ("Bihovsky")
1034	Expert Declaration of Steven Miller, Ph.D. ("Miller")

I. INTRODUCTION

Intas Pharmaceuticals Ltd. petitions for inter partes review of claims 1-21 of U.S. Patent No. 11,261,151 ("the 151 patent"; Ex. 1001). The claims of the 151 patent are directed to a composition comprising a crystalline form of endoxifen, wherein at least 90% by weight is the (Z)-isomer, and the crystalline form is Form I, characterized by a particular x-ray powder diffraction (XRPD) profile, and methods of treating hormone-dependent breast disorders with such compositions.

It was already known in the art that endoxifen was a promising drug for treating hormone-dependent breast disorders, as it is the active metabolite of tamoxifen. It was further known that the (Z)-isomer was more active, and thus preferred. Multiple methods of making 90% (or higher) (Z)-endoxifen were known in the art. In fact, related claims were rejected over such references including Liu (discussed in more detail below). However, not having the ability to perform an XRPD analysis of the prior art compositions, the Examiner allowed the present claims reciting Form I and its accompanying XRPD patterns. But performing an XRPD analysis on compositions taught by Liu confirms that Liu also created Form I with the same XRPD patterns. Thus, the claims are inherently anticipated by Liu.

The dependent claims merely recite inherent characteristics of (Z)-endoxifen and routine and well-known applications of (Z)-endoxifen, such as including it in formulations and dosage forms including tablets, or inherent results of dosing

patients with such obvious formulations. It would have been readily apparent to a POSA to dose a patient with oral formulations of (Z)-endoxifen, as taught for example in Ahmad, achieving the claimed results with a reasonable expectation of success. Thus, any claim not anticipated, would have been obvious to a POSA.

II. MANDATORY NOTICES

Real parties-in-interest: Intas Pharmaceuticals Ltd. ("Intas") is the real-party-in-interest. Accord Healthcare, Inc. is a U.S. subsidiary of Intas who also has an interest in this proceeding. Other parties who may be interested in the outcome of this PGR include the National Cancer Institute/National Institutes of Health Clinical Center, Eli Lilly and Company, Pfizer Inc., Jina Pharmaceuticals Inc., Cheiljedang Corp., Alchem Laboratories Corporation, and Lambda Therapeutic Research Limited.

Related matters: PGR2023-00043, filed by Petitioner, addresses claims 1-22 of U.S. Patent No. 11,572,334 ("the 334 patent"), a continuation of the 151 patent. The PTAB found claims 1-22 of the 334 patent unpatentable. *See Intas Pharms. Ltd. v. Atossa Therapeutics, Inc.*, PGR2023-00043, Paper 37 at *1 (P.T.A.B. January 29, 2025). Petitioners are also at the same time filing a petition for Post Grant Review challenging related U.S. Patent No. 12,071,391 also assigned to Patent Owner and directed to (Z)-endoxifen formulations.

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Service information: Petitioner consents to service by email at: 151IPR@mcandrews-ip.com.

III. GROUNDS FOR STANDING

The 151 patent is available for *inter partes* review and Petitioner is not barred or estopped from requesting an *inter partes* review challenging claims 1-21 of the 151 patent on the grounds identified in this Petition.

IV. IDENTIFICATION OF GROUNDS

Petitioner identifies the following grounds of unpatentability:

Ground	Challenged Claims	Basis
1	1-6, 16, 18, 21	Anticipated by Liu
2	1-21	Obvious over Liu and Ahmad in view of the knowledge of a POSA

V. THE 151 PATENT

A. Subject Matter of the 151 Patent

The 151 patent is titled "Methods for making and using Endoxifen." Ex. 1001 at Cover. It was filed on February 15, 2020, but claims priority to a PCT filed September 10, 2018 and provisional applications dating back to September 11, 2017. *Id.* The 151 patent generally relates to a composition comprising crystalline forms of endoxifen characterized by XRPD (X-Ray Powder Diffraction) peaks,[1] wherein at least 90% by weight of endoxifen in the composition is the (Z)-isomer and methods of treating hormone-dependent breast disorder by using the (Z)-isomer of endoxifen.

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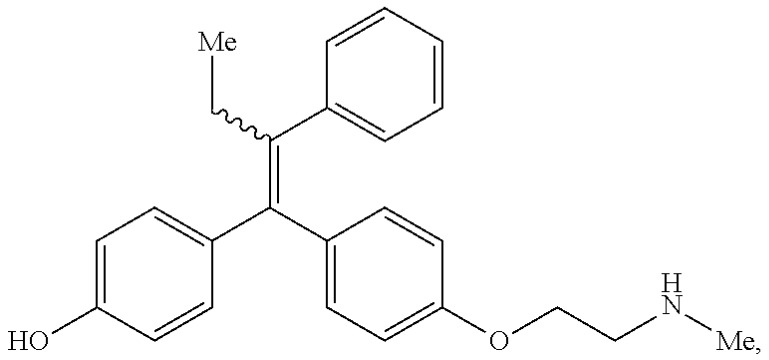
[1] XRPD is a method of exposing a crystalline form of a compound to X-rays, generating a pattern as a function of the scattering angle. Miller, ¶22.

B. Claims of the 151 Patent

<u>Independent claim 1 and claims 2-15, 21</u>

1. 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±0.3°, 17.1±0.3° and 21.8±0.3° two theta.

Claims 2-15 and 21 depend from Claim 1.

2. The composition of claim 1, wherein the x-ray powder diffraction pattern further comprises at least one peak selected from 16.0±0.3°, 18.8±0.3° and 26.5±0.3 two theta.

3. The composition of claim 1, wherein the x-ray powder diffraction pattern further comprises at least one peak selected from 12.3±0.3°, 28.0±0.3° and 29.0±0.3° two theta.

4. The composition of claim 1, wherein the x-ray powder diffraction pattern further comprises peaks at 12.3±0.3°, 16.0±0.3°, 18.8±0.3°, 26.5±0.3°, 28.0±0.3° and 29.0±0.3° two theta.

5. The composition of claim 1, wherein the crystalline form of the (Z)-isomer is characterized by an x-ray powder diffraction pattern substantially as set forth in FIG. 9 or FIG. 10.

6. The composition of claim 1, wherein greater than 90% by weight of the (Z)-isomer in the composition is crystalline Form I.

7. The composition of claim 1, further comprising a pharmaceutically acceptable carrier or diluent.

8. The composition of claim 7, wherein the composition is formulated for oral, parenteral, topical, or intraductal delivery.

9. The composition of claim 7, wherein the composition is formulated for oral delivery as a tablet, a caplet, a capsule, or a pill.

10. The composition of claim 7, wherein a mean half-life of the compound of Formula (III) in a subject treated with the composition is between 30 hours to 60 hours.

11. The composition of claim 1, formulated as an oral dosage form comprising 1 mg to 200 mg per unit dose of the composition, and wherein daily administration of the oral dosage form achieves in a subject treated with the composition one or more of:

a steady state plasma level of the compound of Formula (III) within 7 to 21 days;

a steady state plasma level of the compound of Formula (III) ranging from 25 nM to 300 nM;

a steady state plasma level of the compound of Formula (III) greater than 30 nM; or

maximal plasma levels of the compound of Formula (III) within 2 to 10 hours after administering.

12. The composition of claim 11, wherein a mean half-life of the compound of Formula (III) in the subject is between 40 hours to 55 hours.

13. The composition of claim 11, wherein the oral dosage form is formulated as an enteric tablet, an enteric caplet, an enteric capsule, a delayed-release tablet, a delayed-release caplet or a delayed-release capsule.

14. The composition of claim 11, wherein at least 80% of the compound of Formula (III) in the oral dosage form is released in the intestines of the subject.

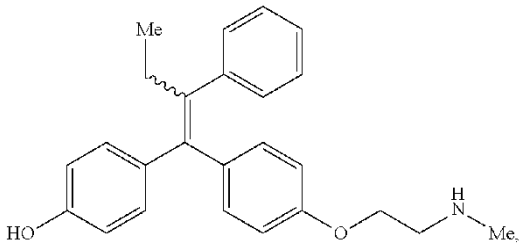
15. The composition of claim 11, having a mean area under the curve extrapolated to time infinity ($AUC_{0\text{-}inf}$) of the compound of Formula (III) of 200 hr*ng/mL to 10000 hr*ng/mL.

21. The composition of claim 1, wherein the composition is stable for at least 9 months at 5° C. and 60% relative humidity or at 25° C. and 60% relative humidity.

<u>Independent claim 16 and claims 17-20</u>

16. A method of treating a hormone-dependent breast disorder or a hormone-dependent reproductive tract disorder in a subject, the method comprising administering to the subject a composition comprising a crystalline form of a compound of Formula (III):

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±0.3°, 17.1±0.3° and 21.8±0.3° two theta, thereby treating the hormone-dependent breast disorder or the hormone-dependent reproductive tract disorder.

Claims 17-20 depend from claim 16.

17. The method of claim 16, wherein the subject has prostate cancer and wherein the subject further has or is at risk of having gynecomastia.

18. The method of claim 16, wherein the subject has tamoxifen-refractory or tamoxifen resistant hormone-dependent breast disorder or hormone-dependent reproductive tract disorder.

> 19. The method of claim 16, wherein the composition comprises 0.01 mg to 200 mg of the (Z)-isomer.
>
> 20. The method of claim 16, wherein a steady state plasma level of the compound of Formula (III) is achieved within 7 to 21 days of the first administration of the composition to the subject, and wherein the steady state plasma level of the compound of Formula (III) in the subject is greater than 30 nM.

C. Prosecution History

The 151 patent faced minimal prosecution. In addition to the current claims, Patent Owner originally sought a claim to a process for manufacturing (Z)-endoxifen through fractional crystallization (Claim 62). Claim 62 was rejected as obvious over the Liu reference discussed below because "the actual procedures of the prior art [Liu] method and the instant invention are [the] same." Ex. 1002 at 432. Patent Owner then cancelled claim 62. *Id.* at 465.

Regarding the present claims, the Examiner never considered whether the method taught by Liu would lead to the claimed XRPD patterns for Form I recited in the issued claims. To the contrary, the Examiner rejected the current claims only for 112 formalities and stated the "subject matter of claims 1, 4-9, 32-35, 38-44, 46, 47, 49, and 52 would be allowable once the 112 rejections outlined above have been overcome" because the "key" to the claims "is the polymorph of Form I," without considering whether Liu would lead to the claimed polymorph of Form I. *Id.* at 433. Patent Owner amended the claims per the Examiner's suggestions, and after a second 112 rejection for reciting that the claims prevented, rather than treated, breast

cancer, certain dependent claims were amended and the present claims were allowed. *Id.* at 461-65, 499-503, 520-24, 531-39.

D. Person of Ordinary Skill in the Art

A POSA for purposes of the 151 patent is someone with a graduate degree in organic chemistry, material science, medicinal chemistry, pharmaceutical chemistry, or a related field, and four to six years of experience in the synthesis, purification, analysis, design, and/or formulation of pharmaceutical compounds and derivatives. Bihovsky, ¶21; McConville, ¶25, Miller, ¶17; *see also Intas v. Atossa*, PGR2023-00043, Paper 37 at *9 (adopting same definition of a POSA). A POSA would have worked with a team of professionals with training in related disciplines, such as pharmacology, pharmacokinetics, formulation, drug discovery and/or drug development as of the date of the claimed inventions. Bihovsky, ¶21; McConville, ¶25; Miller, ¶17. Drs. McConville, Bihovsky, and Miller meet or exceed the level of skill of a POSA. Bihovsky, ¶¶22, 3-10, Appx. A; McConville, ¶¶26, 3-15, Appx. A;

Miller, ¶¶18, 3-7, Appx. A; *Intas v. Atossa*, PGR2023-00043, Paper 37 at *9-10 (stating Drs. McConville and Bihovsky are POSAs for related patent[2]).

E. Claim Construction

For purposes of this IPR, all terms should be given their plain and ordinary meaning, and Petitioner does not contend any claims require construction.

VI. SUMMARY OF THE PRIOR ART

A. WO 2017/070651 ("Liu")

International Application WO 2017/070651 ("Liu") was filed on October 24, 2016, and published on April 27, 2017. Ex. 1003, Cover. Thus, Liu is prior art under 35 U.S.C. § 102(a)(1).

Liu teaches that "Endoxifen exists as two forms, E and Z, with the Z form more active at the estrogen receptor" and that "there is a need in the art for a practical, scalable synthesis that gives access to highly pure (Z)-endoxifen." *Id.*, [0004]. Liu teaches: (i) synthesis followed by sequential recrystallizations, *id.*, [0021]-[0045], and (ii) synthesis followed by isomerization and sequential recrystallizations. *Id.*, [0046]-[0055]. As discussed below, Dr. Bihovsky reproduced the methods taught by

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[2] Dr. Miller was not an expert in *Intas v. Atossa*, PGR2023-00043, so the Board did not opine on his level of skill. As discussed, Dr. Miller meets or exceeds the above definition of a POSA.

Liu, as a POSA would have done, and obtained (Z)-endoxifen with isomeric purities of 100% and 93%. Bihovsky, ¶73.

Dr. Bihovsky first synthesized a mixture of (E)- and (Z)-endoxifen as taught by Liu. *Id.*, ¶¶49-59. The Z:E ratio of the mixture obtained by Dr. Bihovsky was 33:67. *Id.*, ¶59.

Liu teaches a first recrystallization step, which "can be carried out in a first solvent in which the E isomer (2) crystallizes well and is significantly less soluble than the Z isomer (1)." Ex. 1003, [0021]. Liu teaches that it "has been unexpectedly discovered that toluene, isopropyl acetate, methyl ethyl ketone, and methyl isobutyl ketone are particularly useful first solvents for carrying out this step, with isopropyl acetate particularly preferred." *Id.* Dr. Bihovsky dissolved the precipitate obtained via Liu's synthesis method in refluxing isopropyl alcohol for 1 hour, then cooled the solution slowly and stored it at 23°C for 6 hours. Bihovsky, ¶60. The precipitate was vacuum filtered, rinsed, and dried to give a solid with a 5:95 Z:E ratio. *Id.* The filtrate was evaporated to yield a solid of 67:33 Z:E endoxifen. *Id.*

"The second step (ii) in the disclosed process is recrystallizing a solid produced by concentrating the first mother liquor, or by removal of the first solvent from the first mother liquor, from a second solvent to give a second crystalline solid and a second mother liquor." Ex. 1003, [0025]. "Generally, this recrystallizing can be carried out in a second solvent in which the Z isomer (1) crystallizes well and in

which enrichment of the Z isomer can be increased upon crystallization." *Id.*, [0026]. "It has been unexpectedly discovered that acetone is a particularly useful second solvent for carrying out this step." *Id.* Dr. Bihovsky recrystallized the dried filtrate as taught by Liu by dissolving the dried filtrate in refluxing acetone, then cooling and stirring it for 40 hours at 4°C. Bihovsky, ¶61. Dr. Bihovsky scratched the flask to increase crystallization and stirred the solution at 4°C for 24 more hours.[3] *Id.* The precipitate was collected, rinsed, and dried, yielding endoxifen with a 94:6 Z:E ratio. *Id.* That precipitate was dissolved in refluxing acetone, filtered, and cooled/stirred for 50 hours at 4°C. *Id.*, ¶62. The resulting precipitate was collected, rinsed, and dried, which gave a solid that was 100% (Z)-endoxifen. *Id.*

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[3] Though Liu's Example 7 does not cool and stir the solution for additional time beyond the initial 40 hours, Liu expressly contemplates doing so. For example, Liu explains that the solution can be "held at the second temperature for 0.5 hours to 10 days or 2 to 72 hours." Ex. 1003, [0026]. In fact, Liu further contemplates that "[i]n some cases longer holding times at the second temperature may be required." *Id.* A POSA would have chosen to follow the description provided by Liu and held the mixture at the second temperature longer than provided in Liu's specific Examples to increase the yield of the reaction.

"The third step (iii) is optionally recrystallizing the second crystalline solid from the second solvent one or more additional times to give a third crystalline solid, wherein the third crystalline solid has a ratio of (Z)-endoxifen (1) to (E)-endoxifen (2) greater than 20:1." Ex. 1003, [0028]. Dr. Bihovsky did not perform this third, optional crystallization, as he had already obtained 100% pure (Z)-endoxifen. Bihovsky, ¶62 n.8. A POSA would not have performed a third recrystallization, described as optional by Liu, when he had already obtained 100% pure (Z)-endoxifen. *Id.*

Liu teaches that its method achieved "1698 g (34%) of (Z)-endoxifen, with an isomeric purity of 99% (HPLC analysis)." Ex. 1003, [0076]. As discussed, Dr. Bihovsky obtained (Z)-endoxifen with an isomeric purity of 100% by following Liu's recrystallization method. Bihovsky, ¶62.

Liu further teaches a process whereby (Z)-endoxifen can be prepared via isomerization of (E)-endoxifen (or a mixture of (E)- and (Z)-endoxifen) followed by recrystallizations. Ex. 1003, [0046]-[0055]. Dr. Bihovsky also followed this procedure of Liu using the solid enriched in (E)-endoxifen (5:95 Z:E ratio) obtained during Liu's sequential recrystallization procedure. Bihovsky, ¶¶65-66. Dr. Bihovsky dissolved the precipitate enriched in (E)-endoxifen in refluxing iPrOAC and stirred at reflux for 4 hours. *Id.*, ¶66. The solution was then cooled slowly and kept at 15°C for 2 days. *Id.* The precipitate was collected, rinsed, and dried, and the

filtrate was evaporated. *Id.*, ¶¶66-67. As taught by Liu, Dr. Bihovsky repeated this isomerization procedure twice. *Id.*, ¶68. Dr. Bihovsky combined the solid material obtained after evaporation of the filtrates from the isomerization procedures and recrystallized the mixture from acetone as taught by Liu (and as described in detail above). *Id.*, ¶¶69-70. The recrystallization after isomerization yielded a solid that was 93% (Z)-endoxifen. *Id.*

Liu does not provide XRPD data for its disclosed (Z)-endoxifen crystalline form. While the Examiner rejected pending method claims as obvious over Liu because "the actual procedures of the prior art [Liu] method and the instant invention are [the] same," Ex. 1002 at 1549, the Examiner never considered whether this method would lead to the claimed XRPD patterns for the claimed Form I.[4] As

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[4] XRPD can be used to identify a specific polymorph structure. *See, e.g.*, Ex. 1011, 289 ("In the drug design, discovery, development, and formulation process, X-ray powder diffraction can help to establish a formulation by discovering the morphology and the degree of crystallinity, providing unique polymorph identification, and determining the quantity of each in mixture.") In other words, the same (or substantially similar) XRPD patterns for different samples of a substance

discussed above, Dr. Bihovsky performed the procedures taught by Liu and obtained (Z)-endoxifen with isomeric purities of 100% (recrystallization) and 93% (isomerization followed by recrystallization). Bihovsky, ¶¶71-73. Dr. Bihovsky subsequently sent those samples of (Z)-endoxifen for XRPD analysis. *Id.*, ¶74; *see also* Miller, ¶¶23, 29. The XRPD data confirmed that Liu's methods result in (Z)-endoxifen in the claimed Form I (*e.g.*, "characterized by an XRPD pattern comprising major peaks at 16.8±0.3°, 17.1±0.3° and 21.8±0.3° two theta"). Miller, ¶30.

B. US 9,333,190 ("Ahmad")

U.S. Patent No. 9,333,190 ("Ahmad") issued on May 10, 2016, from a PCT application filed November 21, 2007, and claims priority to provisional application No. 60/860,420, filed November 21, 2006. Ex. 1004, Cover. Thus, Ahmad is prior art under 35 U.S.C. § 102(a)(1) and (2).

Ahmad "provides compositions containing endoxifen, formulations and liposomes of endoxifen, methods of preparation of such agents and formulations, and use of such agents and formulations for the treatment of breast cancer and other

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indicate that the samples have the same polymorph structure. *Id.*; *see also* Miller, ¶¶22, 30.

breast diseases and diseases susceptible to endoxifen." Ex. 1004, Abstract. Ahmad teaches the use of the Z-isomer of endoxifen, including at over 90% purity. *Id.*, 12:14-17 ("One object of the present invention is to provide E-endoxifen or (Z)-endoxifen with at least 80% purity, such as at least 90% pure...."); *see also id.*, 2:24-40, 3:55-61. Ahmad teaches that "[i]n some embodiments, the composition comprises a tablet or a filled capsule, wherein said tablet or filled capsule optionally comprises an enteric coating material." *Id.*, 4:41-44. Ahmad further teaches that "[w]hen desired, [the] composition containing endoxifen or endoxifen-lipid complex can be encapsulated in enteric-coated capsules to protect it from acids in the stomach" and that the "term 'enteric' refers to the small intestine, and enteric coatings prevent release of medication before it reaches the small intestine." *Id.*, 18:19-26. Ahmad further teaches that "[m]ost enteric coatings work by presenting a surface that is stable at acidic pH but breaks down rapidly at higher pH." *Id.*

Thus, Ahmad teaches enteric coated formulations of highly pure (Z)-endoxifen, for the treatment of breast cancer and other breast diseases. McConville, ¶¶37-38.

C. Additional Background References

1. Ahmad 2010

Ahmad, A. et al., Endoxifen, a New Cornerstone of Breast Cancer Therapy: Demonstration of Safety, Tolerability and Systemic Bioavailability in Healthy

Human Subjects, 88(6) CLIN. PHARMACOLOGY & THERAPEUTICS 814-817 (2010) ("Ahmad 2010") was published and publicly available in 2010 and thus is prior art under 35 U.S.C. § 102(a)(1). Ex. 1006, 814.

Ahmad 2010 discloses pre-clinical trials of endoxifen citrate tablets showing that endoxifen is likely to be a safe and effective treatment for breast cancers.[5] Ahmad 2010 was published by the first named inventor on the Ahmad patent. *Compare* Ex. 1006 *with* Ex. 1004. Ahmad 2010 teaches that "Endoxifen is an active metabolite of tamoxifen, a drug used in the treatment of breast cancer." Ex. 1006, Abstract. "In order to be clinically effective, tamoxifen must be converted to endoxifen by cytochrome P450 2D6 (CYP2D6)." *Id.* Ahmad 2010 reports on a study "demonstrating that single oral doses of endoxifen are safe and well tolerated and have sufficient bioavailability to reach systemically effective levels in human subjects" for treatment of breast cancer. *Id.* "Furthermore, it was found that endoxifen is rapidly absorbed and systemically available and that it displays dose proportionality in peak drug concentrations in plasma (C_{max}) and area under the concentration–time curve extrapolated from 0 to ∞ ($AUC_{0-\infty}$) over the dose range 0.5-4.0 mg." *Id.*

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[5] Ahmad 2010 does not report the (E)/(Z) ratio.

Ahmad 2010 concluded that "we expect that multiple daily endoxifen doses of 2.0-4.0 mg will result in endoxifen exposures that would be similar to those found in patients with normal CYP2D6 function who are administered tamoxifen at 20 mg/day," or, in other words, "a dose of 4 mg of endoxifen should be appropriate for breast cancer prevention and therapy." *Id.*, 816. In summary, the authors "propose that substitution of endoxifen for tamoxifen will provide an improved approach toward treating patients with breast cancer because it bypasses the CYP2D6 enzyme that is required for metabolic activation of tamoxifen" and "[c]onsequently, its activity is not likely to be affected by either CYP2D6 genetic polymorphisms or drug-drug interactions that inhibit CYP2D6 activity." *Id.*

In sum, Ahmad 2010 teaches that endoxifen is likely to be safe and effective for the treatment of breast cancer because endoxifen is the active metabolite of the known drug tamoxifen. McConville, ¶41.

2. Ahmad 2012

Ahmad, A. et al., Endoxifen for breast cancer: Multiple-dose, dose-escalation study characterizing pharmacokinetics and safety in metastatic breast cancer patients, ASCO MEETING LIBRARY ("Ahmad 2012") is an abstract of a poster published online May 20, 2012, and presented on June 4, 2012, and thus is prior art under 35 U.S.C. § 102(a)(1). Ex. 1007 at 1.

Ahmad 2012 discloses pre-clinical trials of endoxifen further showing that it is likely to be a safe and effective treatment for breast cancers. Ahmad 2012 was presented by the first named inventor on the Ahmad patent. *Compare* Ex. 1007 *with* Ex. 1004. Ahmad 2012 teaches that "[d]irect administration of endoxifen would not be subject to pharmacogenetic variations or drug-drug interactions." Ex. 1007 at 1. It disclosed that the group's "preclinical studies (Breast Cancer Treat 122, 579-584, 2010) have validated the concept of using endoxifen for the treatment of breast cancer." *Id.* Ahmad 2012 disclosed test results showing that "the single oral doses tested up to 4 mg of endoxifen were safe, well tolerated and bioavailable." *Id.* Ahmad 2012 concludes that "[m]ultiple daily endoxifen doses of 4.0-8.0 mg resulted in endoxifen exposures that would be sufficient for effective therapy." *Id.* at 2.

In sum, Ahmad 2012 also teaches that endoxifen is likely to be safe and effective for the treatment of breast cancer. McConville, ¶44.

3. Cole

Cole, E., et al., *Enteric coated HPMC capsules designed to achieve intestinal targeting*, 231 INTL J. PHARMACEUTICS 83-95 (2002) ("Cole") was published and publicly available in 2002 and thus is prior art under 35 U.S.C. § 102(a)(1). Ex. 1008.

Cole teaches the use of enteric coated capsules. Cole teaches that "Enteric coated products are designed to remain intact in the stomach and then to release the active substance in the upper intestine" and that "the reasons for using enteric coated

preparations are well documented." *Id.* at 83. "The polymers commonly used to achieve enteric properties are anionic polymethacrylates (copolymerisate of methacrylic acid and either methylmethacrylate or ethyl acrylate (Eudragit®), cellulose based polymers, e.g. cellulose acetate phthalate (Aquateric®) or polyvinyl derivatives, e.g. polyvinyl acetate phthalate (Coateric®)." *Id.* Cole notes that "site specific delivery into the upper intestine has been achieved for many years by the use of pH-sensitive coatings…" *Id.* at 84. While capsules were traditionally made from gelatin, Cole notes that "HPMC capsules have been available commercially…for approximately 10 years." *Id.*

Cole "describe[d] the manufacture of two different Eudragit® coated HPMC capsules and their in vitro/in vivo performance." *Id.* at 84. Cole found that no drug "was released over 2 h at pH 1.2 from the capsules coated with 6 and 8 mg cm^{-2} Eudragit® L 30 D-55" while at "pH 6.8 release of paracetamol was rapid…." *Id*. at 89. The 151 patent acknowledges Cole, and uses Cole's method. Ex. 1001 at 85:61-65.

In sum, Cole teaches the effective use of an enteric coating to form capsules that will bypass the stomach and release drug in the intestine. McConville, ¶50.

VII. DISCRETIONARY DENIAL

A. 325(d) Based on Prosecution Activity

The Board engages a two-step inquiry in determining whether it should deny institution based on prosecution activity: (1) whether the same or substantially the same art or arguments previously were presented to the Office (*Becton, Dickinson* factors (a), (b), and (d)), and if so, (2) whether Petitioner demonstrates material error by the Office (*Becton, Dickinson* factors (c), (e), and (f)). *Advanced Bionics, LLC v. Med-El Elektromedizinische Gerate GmbH*, IPR2019-01469, Paper 6 at *10 (P.T.A.B. Feb. 13, 2020) (precedential), citing *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 (P.T.A.B. Dec. 15, 2017).

Advanced Bionics Part 1: Whether the same or substantially the same art or arguments were previously presented to the Office

BD Factor (a) "the similarities and material differences between the asserted art and the prior art involved during examination"

BD Factor (b) "the cumulative nature of the asserted art and the prior art evaluated during examination"

BD Factor (d) "the extent of the overlap between the arguments made during examination and the manner in which petitioner relies on the prior art"

Liu, Ahmad, Ahmad 2010, Ahmad 2012 and Cole were cited by the Examiner. Ex. 1001; *see also* Ex. 1002 at 431-32. However, the Examiner did not have the

benefit of XRPD testing Liu to determine what form of (Z)-endoxifen was created via Liu's disclosed method, and issued no rejection of the present claims over any of the references. Thus, the arguments presented here were not considered by the Examiner.

Advanced Bionics Part 2: Whether the Office erred

BD Factor (c) "the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection"

BD Factor (e) "whether petitioner has pointed out sufficiently how the examiner erred in its evaluation of the asserted prior art"

BD Factor (f) "the extent to which additional evidence and facts presented in the petition warrant reconsideration of the prior art or arguments"

The Examiner correctly rejected pending claim 62 to a method of forming 90% (Z)-endoxifen as being unpatentable over Liu. Ex. 1002 at 431-32. Rather than attempting to distinguish Liu, Patent Owner cancelled claim 62. *Id.* at 465.

However, not being capable of performing XRPD on Liu to determine if the (Z)-endoxifen taught by Liu was the claimed Form I, the Examiner found the pending claims allowable. *Id*. at 520-24, 531-39. In particular, the Examiner found that "the key" to the claims was "the polymorph of Form I"—without the ability to determine the polymorph synthesized by Liu—and therefore found that "the closest prior art" was WO 2014/141292, "which teaches an endoxifen citrate polymorph...."

Id. at 537. Without the benefit of XRPD analysis, the Examiner erred in not rejecting the claims over Liu.

Indeed, as the evidence herein conclusively demonstrates, the (Z)-endoxifen taught by Liu is Form I and exhibits the claimed XRPD pattern. This evidence strongly warrants reconsideration. *See, e.g.*, *Apple Inc. v. Immervision, Inc.*, No. IPR2023-00471, 2023 WL 5166410, at *13 (P.T.A.B. July 11, 2023) ("*Becton, Dickinson* factor (f) weighs against exercising discretion to deny institution because the additional evidence (i.e., Dr. Kessler's detailed testimony) and facts presented in the Petition warrant reconsideration of Shiota...."); *Amazon.com, Inc. v. Vb Assets, LLC*, No. IPR2020-01346, 2021 WL 406294, at *4 (P.T.A.B. Feb. 4, 2021) ("Factor (f) weighs against a discretionary denial because Petitioner has presented new evidence...and arguments...that warrant reconsideration of Kennewick. Because the Examiner does not appear to have appreciated or considered the teachings of Kennewick discussed above, we find that Petitioner has demonstrated material error by the Office.").

B. Other Bases for Discretionary Denial

There is no pending litigation between Patent Owner and Petitioner or to the best of Petitioner's knowledge any potential party-in-interest. Petitioner is not aware of any other proceeding involving the 151 patent. Finally, Petitioner's grounds are not redundant or excessive.

VIII. RELATED PROCEEDINGS

As discussed above, PGR2023-00043 found all claims of the 334 patent, a continuation of the 151 patent, unpatentable, considering many of the same references as here. *Intas**Error! Bookmark not defined.** v. Atossa*, PGR2023-00043, Paper 37. As discussed in more detail below, collateral estoppel from the Board's final written decision in PGR2023-00043 applies to various issues relevant to this IPR. *See MaxLinear, Inc. v. CF CRESPE LLC*, 880 F.3d 1373, 1376 (Fed. Cir. 2018) ("It is well established that collateral estoppel, also known as issue preclusion, applies in the administrative context."); *Papst Licensing GMBH & Co. KG v. Samsung Elecs. Am., Inc.*, 924 F.3d 1243, 1251 (Fed. Cir. 2019) (stating issue preclusion can apply to final PTAB decisions). To invoke collateral estoppel, a party must show:

> (1) the issue is identical to one decided in the first action; (2) the issue was actually litigated in the first action; (3) resolution of the issue was essential to a final judgment in the first action; and (4) [the party against whom collateral estoppel is being asserted] had a full and fair opportunity to litigate the issue in the first action.

Google LLC v. Hammond Develop. Int'l, Inc., 54 F.4th 1377, 1381 (Fed. Cir. 2022). "Issue preclusion applies not only to ultimate determinations in a prior adjudication but to subsidiary determinations if sufficiently 'essential' to the ultimate determinations." *Spence v. Dep. of Veterans Affairs*, 831 F. App'x 949, 955 (Fed. Cir. 2020).

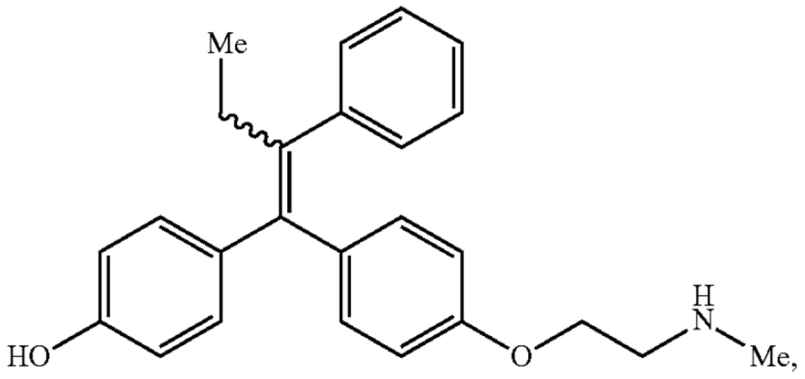
Here, as discussed in more detail below, many of the claims of the 151 patent present the same factual inquiries as those determined by the Board in PGR2023-00043. Moreover, the issues discussed below were actually litigated in PGR2023-00043 and necessary to the final judgment, and Atossa had a full and fair opportunity to litigate them. Therefore, collateral estoppel applies to the issues discussed below that were at issue in the 334 PGR. Thus, Atossa may not reargue factual findings resolved against it in the 334 PGR.

IX. GROUND 1: CLAIMS 1-6, 16, 18, AND 21 ARE ANTICIPATED BY LIU

A. Claim 1

1. A composition comprising a crystalline form of a compound of Formula (III):

Formula (III)

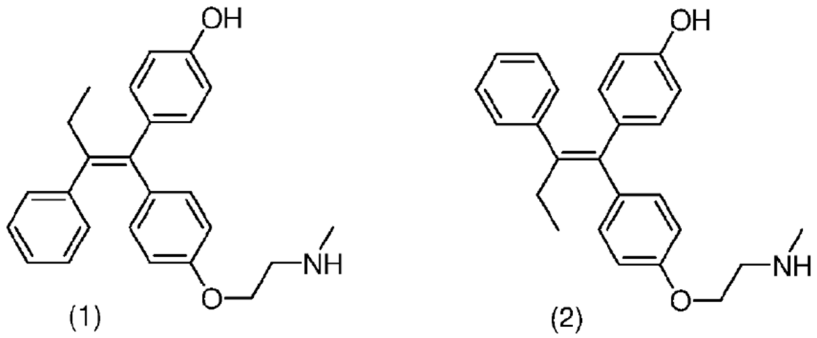


wherein at least 90% by weight of the compound of Formula (III) in the composition is the (Z)-isomer

Formula (III) recited in the claims is endoxifen (including E- and/or (Z)-endoxifen). *See* Ex. 1001 at 8:15-16. As described in the 151 patent, Formula (III)

can include the polymorphic salt, free base, co-crystal, and/or solvate forms of (Z)-endoxifen.[6] *See id.* at 12:48-52.

Liu teaches "a process for preparing (Z)-endoxifen" with "a ratio of (Z)-endoxifen (1) to (E)-endoxifen (2) greater than 20:1." Ex. 1003 at Abstract.



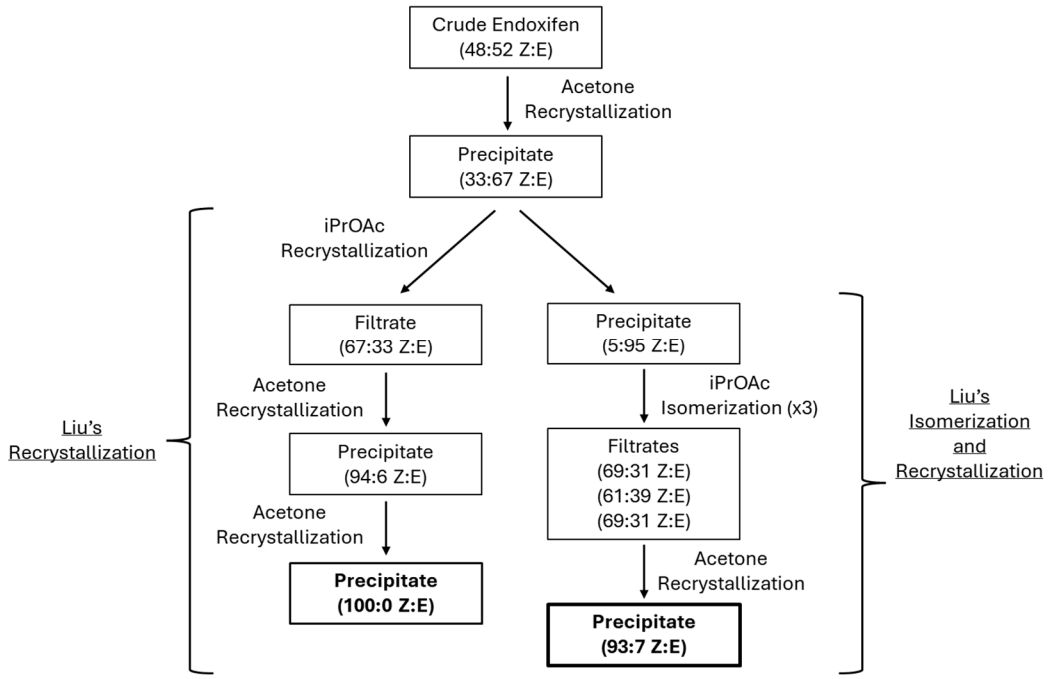
[6] In PGR2023-00043, the Board found that "(Z)-endoxifen" recited in the claims was limited to "its free base form." *Intas v. Atossa*, PGR2023-00043, Paper 37 at *12. Here, the claim does not expressly recite "(Z)-endoxifen" like the claim at issue in the 334 PGR where the Board found that the specification defined "compound of Formula (III)" "broadly". *Id.* However, the construction of "the compound of Formula (III)" and/or "(Z)-isomer" to include or not include salts and solvates is immaterial to the unpatentability of the claim. Indeed, the claims are anticipated by and/or obvious over the cited references whether they are interpreted broadly or more narrowly because Liu (and Ahmad) teach the use of a free base.

A POSA would have understood that Liu's synthesis forms the free base. Bihovsky, ¶¶76-77. Specifically, Liu teaches the use of crystallization procedures to purify (Z)-endoxifen from a mixture of (E)- and (Z)-endoxifen. *Id.*; Ex. 1003 at Abstract. Liu further teaches that the (E)-isomer can be converted to the (Z)-isomer by isomerization, which increases the yield of (Z)-endoxifen. Bihovsky, ¶77; Ex. 1003 at [0073]-[0076]. Liu teaches that his method results in a (Z)-endoxifen crystalline material with "an isomeric purity of 99% (HPLC analysis)." Ex. 1003 at [0076].

Thus, Liu teaches a composition comprising a crystalline form of a compound of Formula (III) wherein at least 90% by weight of the compound of Formula (III) in the composition is the (Z)-isomer. Bihovsky, ¶78; *see also Intas v. Atossa*, PGR2023-00043, Paper 37 at *25 ("Liu teaches a detailed method for synthesizing and purifying (Z)-endoxifen with 99% isomeric purity through recrystallization.").

Further, as evidenced by Dr. Bihovsky's own reproduction of Liu's teachings, Liu provides an enabling disclosure to a POSA. Bihovsky, ¶¶44-73; *Intas v. Atossa*, PGR2023-00043, Paper 37 at *25-28 (discussing Dr. Bihovsky's synthesis of (Z)-

endoxifen following Liu).[7] Specifically, as discussed in more detail above (section VI.B.), Dr. Bihovsky reproduced the synthesis of Liu to form crude endoxifen, and then purified the crude endoxifen to obtain highly pure (Z)-isomer using both the disclosed recrystallization pathway as well as the isomerization and recrystallization pathway, obtaining two separate samples of (Z)-endoxifen with greater than 90% purity (100% and 93% purity, respectively):



Bihovsky, ¶71; *see also id.*, ¶¶44-73.

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[7] Petitioner notes that Patent Owner carries the initial burden to rebut a presumption of enablement and does not waive the right to present further evidence of enablement should Patent Owner make an enablement argument.

> ***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±0.3°, 17.1±0.3° and 21.8±0.3° two theta.***

Liu does not disclose that the (Z)-endoxifen he creates is the claimed "Form I" or provide an XRPD characterization of the resulting crystalline solids. However, Dr. Bihovsky reproduced Liu as described above, and sent the resulting crystals to Dr. Miller for XRPD testing. Bihovsky, ¶74; Miller, ¶¶23-25, 29. Both crystalline solids (*e.g.*, obtained from following Liu's recrystallization and Liu's isomerization/recrystallization procedures) exhibited XRPD patterns consistent with the claims of the 151 patent. Miller, ¶¶23-25, 29, 30. Therefore, Liu inherently teaches the claimed Form I of (Z)-endoxifen. *Id.*, ¶31; Bihovsky ¶¶43.

"[T]he X-ray diffraction pattern is the fingerprint of periodic atomic arrangements in a given material." Ex. 1011 at Abstract. Therefore, the results of Dr. Millers's testing confirm that the resulting (Z)-endoxifen from following Liu's method is the claimed Form I, characterized by the claimed XRPD peaks. Miller, ¶¶29-31.

Thus, Liu inherently teaches the crystalline form of the (Z)-isomer is Form I, characterized by an XRPD comprising major peaks at 16.8±0.3°, 17.1±0.3° and 21.8±0.3° two theta. *Id.*, ¶31.

B. Claims 2-5

As described above, Dr. Bihovsky reproduced Liu and had the resulting crystalline subjected to XRPD analysis by Dr. Miller. Bihovsky, ¶74; Miller, ¶¶23-25, 29. The results confirm the peaks recited in the dependent claims are similarly present in the resulting crystalline solids. Miller, ¶¶32-36.

2. The composition of claim 1, wherein the x-ray powder diffraction pattern further comprises at least one peak selected from 16.0±0.3°, 18.8±0.3° and 26.5±0.3 two theta.

As Dr. Miller explains, XRPD testing confirms the (Z)-endoxifen made by both Liu's recrystallization and isomerization processes comprise each of the listed peaks:

XRPD Results of Liu's Isomerization and Recrystallization Procedure

2-Theta	d(Å)	Intensity (%)
7.0596	12.5113	5.3%
9.2221	9.5818	9.6%
12.2968	7.1921	3.3%
14.1140	6.2699	16.1%
15.1034	5.8613	7.4%
15.9991	5.5351	10.5%
16.7726	5.2815	52.0%
17.0879	5.1848	100.0%
18.1572	4.8818	32.8%
18.4964	4.7930	2.6%
18.8126	4.7132	2.4%
19.7344	4.4951	3.9%
19.8949	4.4592	4.8%
20.1986	4.3928	2.3%
20.7968	4.2678	19.3%
21.2492	4.1779	10.2%
21.6815	4.0956	39.9%
22.4860	3.9508	7.7%
23.1546	3.8382	7.5%
24.3068	3.6588	28.3%
25.2900	3.5188	12.1%
25.7163	3.4614	1.7%
26.4785	3.3635	9.3%
26.8135	3.3222	18.1%

XRPD Results of Liu's Recrystallization Procedure

2-Theta	d(Å)	Intensity (%)
7.092	12.454	7.80%
9.282	9.520	12.90%
12.329	7.173	4.30%
14.160	6.250	18.30%
15.167	5.837	8.50%
16.002	5.534	11.60%
16.803	5.272	51.70%
17.120	5.175	100.00%
18.189	4.873	34.60%
18.576	4.773	3.60%
18.827	4.710	6.60%
19.795	4.481	3.20%
19.929	4.452	4.40%
20.236	4.385	2.60%
20.848	4.258	23.90%
21.133	4.201	5.60%
21.315	4.165	15.40%
21.735	4.086	49.90%
22.532	3.943	8.60%
23.204	3.830	9.60%
23.386	3.801	2.80%
24.355	3.652	30.50%
25.296	3.518	13.70%
25.762	3.455	2.30%
26.513	3.359	10.30%
26.864	3.316	20.80%

Miller, ¶32.

3. The composition of claim 1, wherein the x-ray powder diffraction pattern further comprises at least one peak selected from 12.3±0.3°, 28.0±0.3° and 29.0±0.3° two theta.

As Dr. Miller explains, XRPD testing confirms the (Z)-endoxifen made by both Liu's recrystallization and isomerization processes comprise each of the listed peaks:

XRPD Results of Liu's Recrystallization Procedure

2-Theta	d(Å)	Intensi
7.092	12.454	7.8
9.282	9.520	12.9
12.329	7.173	4.3
14.160	6.250	18.3
15.167	5.837	8.5
16.002	5.534	11.6
16.803	5.272	51.7
17.120	5.175	100.0
18.189	4.873	34.6
18.576	4.773	3.6
18.827	4.710	6.6
19.795	4.481	3.2
19.929	4.452	4.4
20.236	4.385	2.6
20.848	4.258	23.9
21.133	4.201	5.6
21.315	4.165	15.4
21.735	4.086	49.9
22.532	3.943	8.6
23.204	3.830	9.6
23.386	3.801	2.8
24.355	3.652	30.5
25.296	3.518	13.7
25.762	3.455	2.3
26.513	3.359	10.3
26.864	3.316	20.8
28.016	3.182	6.3
28.501	3.129	1.4
28.984	3.078	8.3
30.017	2.975	1.0

XRPD Results of Liu's Isomerization and Recrystallization Procedure

2-Theta	d(Å)	Intensit
7.0596	12.5113	5.3
9.2221	9.5818	9.6
12.2968	7.1921	3.3
14.1140	6.2699	16.1
15.1034	5.8613	7.4
15.9991	5.5351	10.5
16.7726	5.2815	52.0
17.0879	5.1848	100.0
18.1572	4.8818	32.8
18.4964	4.7930	2.6
18.8126	4.7132	2.4
19.7344	4.4951	3.9
19.8949	4.4592	4.8
20.1986	4.3928	2.3
20.7968	4.2678	19.3
21.2492	4.1779	10.2
21.6815	4.0956	39.9
22.4860	3.9508	7.7
23.1546	3.8382	7.5
24.3068	3.6588	28.3
25.2900	3.5188	12.1
25.7163	3.4614	1.7
26.4785	3.3635	9.3
26.8135	3.3222	18.1
27.9493	3.1897	5.2
28.9206	3.0848	7.1
30.7185	2.9082	1.3

Id., ¶33.

4. The composition of claim 1, wherein the x-ray powder diffraction pattern further comprises peaks at 12.3±0.3°, 16.0±0.3°, 18.8±0.3°, 26.5±0.3°, 28.0±0.3° and 29.0±0.3° two theta.

As Dr. Miller explains, XRPD testing confirms the (Z)-endoxifen made by both Liu's recrystallization and isomerization processes comprise each of the listed peaks:

XRPD Results of Liu's Recrystallization Procedure

2-Theta	d(Å)	Intensity (%)
7.092	12.454	7.80%
9.282	9.520	12.90%
12.329	7.173	4.30%
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15.167	5.837	8.50%
16.002	5.534	11.60%
16.803	5.272	51.70%
17.120	5.175	100.00%
18.189	4.873	34.60%
18.576	4.773	3.60%
18.827	4.710	6.60%
19.795	4.481	3.20%
19.929	4.452	4.40%
20.236	4.385	2.60%
20.848	4.258	23.90%
21.133	4.201	5.60%
21.315	4.165	15.40%
21.735	4.086	49.90%
22.532	3.943	8.60%
23.204	3.830	9.60%
23.386	3.801	2.80%
24.355	3.652	30.50%
25.296	3.518	13.70%
25.762	3.455	2.30%
26.513	3.359	10.30%
26.864	3.316	20.80%
28.016	3.182	6.30%
28.501	3.129	1.40%
28.984	3.078	8.30%
30.017	2.975	1.00%

XRPD Results of Liu's Isomerization and Recrystallization Procedure

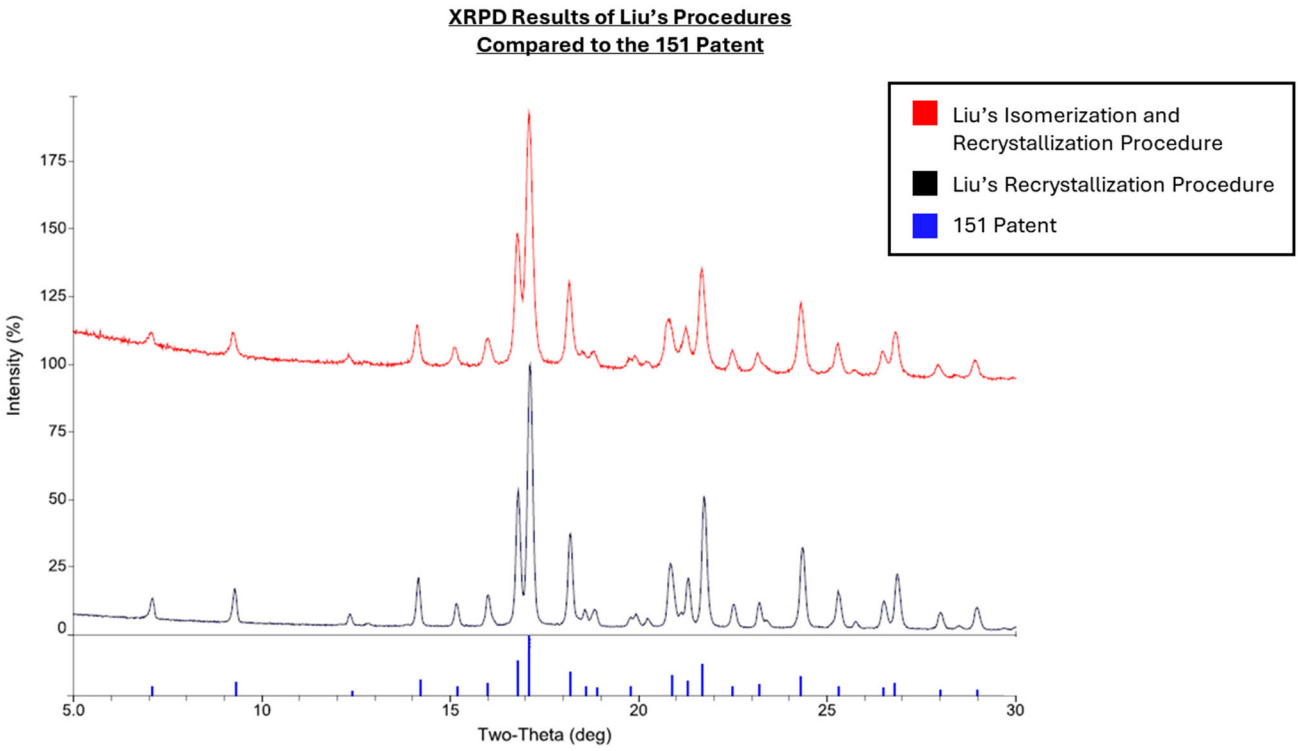
2-Theta	d(Å)	Intensity (%)
7.0596	12.5113	5.3%
9.2221	9.5818	9.6%
12.2968	7.1921	3.3%
14.1140	6.2699	16.1%
15.1034	5.8613	7.4%
15.9991	5.5351	10.5%
16.7726	5.2815	52.0%
17.0879	5.1848	100.0%
18.1572	4.8818	32.8%
18.4964	4.7930	2.6%
18.8126	4.7132	2.4%
19.7344	4.4951	3.9%
19.8949	4.4592	4.8%
20.1986	4.3928	2.3%
20.7968	4.2678	19.3%
21.2492	4.1779	10.2%
21.6815	4.0956	39.9%
22.4860	3.9508	7.7%
23.1546	3.8382	7.5%
24.3068	3.6588	28.3%
25.2900	3.5188	12.1%
25.7163	3.4614	1.7%
26.4785	3.3635	9.3%
26.8135	3.3222	18.1%
27.9493	3.1897	5.2%
28.9206	3.0848	7.1%
30.7185	2.9082	1.3%

Id., ¶34.

5. The composition of claim 1, wherein the crystalline form of the (Z)-isomer is characterized by an x-ray powder diffraction pattern substantially as set forth in FIG. 9 or FIG. 10.

The XRPD data of the crystalline solids obtained following Liu's procedures were substantially as set forth in Fig. 9 or Fig. 10 of the 151 patent—with very close

matches between peaks. *Compare* Ex. 1001 at Figures 9 & 10, *with* Miller, ¶¶35-36. The figure below shows a stick pattern of the Figure 9 and 10 XRPD data reported at Table 8 of the 151 patent in blue for comparison with the XRPD patterns of the two highly-pure endoxifen crystals Dr. Bihovsky synthesized using Liu's teachings. Miller, ¶36. As shown below, the two highly pure endoxifen crystals Dr. Bihovsky synthesized using Liu's teachings exhibit XRPD patterns substantially as set forth in Figure 9/10 and reported at Table 8 in the 151 patent. *Id.*



Id. As Dr. Miller explains, the comparison conclusively demonstrates that the crystalline form of the (Z)-isomer is characterized by an x-ray powder diffraction pattern substantially as set forth in FIG. 9 or FIG. 10. *Id.*, ¶¶35-36.

C. Claim 6

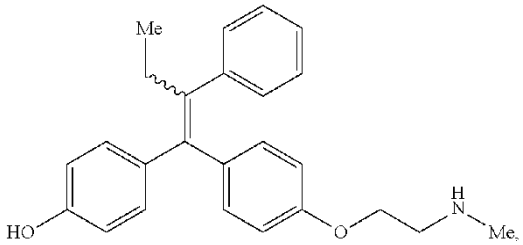
6. The composition of claim 1, wherein greater than 90% by weight of the (Z)-isomer in the composition is crystalline Form I.

As described above, Liu teaches a method a preparing (Z)-endoxifen that results in a (Z)-endoxifen crystalline material with "an isomeric purity of 99% (HPLC analysis)." Ex. 1003 at [0076]. Dr. Bihovsky's experiment following Liu's procedures confirms this. Bihovsky, ¶¶72-73, 81 (obtaining 93% and 100% of (Z)-endoxifen). The samples Dr. Bihovsky synthesized following Liu consisted of greater than 90% (Z)-endoxifen and exhibited XRPD patterns completely consistent with Form I, and did not exhibit any XRPD peaks attributed to forms other than Form I. *Id.*, ¶82. Thus, at least 90% of the (Z)-endoxifen of Liu would be in the claimed Form I. Further, there is no evidence in the 151 patent of achieving 90% Form I other than the XRPD patterns disclosed. *See Constant v. Advanced Micro-Devices, Inc.*, 848 F.2d 1560, 1569 (Fed. Cir. 1988) ("The disclosure in Exhibit 5 is at least at the same level of technical detail as the disclosure in the '491 patent. If [more detail] is essential for an anticipating reference, then the disclosure in the '491 patent would fail to satisfy the enablement requirement of 35 U.S.C. § 112, First ¶."). Therefore, Liu inherently teaches (Z)-endoxifen in the claimed Form I, and "wherein greater than 90% by weight of the (Z)-isomer in the composition is crystalline Form I" as recited in claim 6. Bihovsky, ¶83.

D. Claim 16

16. A method of treating a hormone-dependent breast disorder or a hormone-dependent reproductive tract disorder in a subject, the method comprising administering to the subject a composition comprising a crystalline form of a compound of Formula (III):

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±0.3°, 17.1±0.3° and 21.8±0.3° two theta, thereby treating the hormone-dependent breast disorder or the hormone-dependent reproductive tract disorder.

Liu teaches that (Z)-endoxifen may be used to treat hormone-dependent breast disorders. For example, Liu explains that (Z)-endoxifen is more active at the estrogen receptor, and therefore may be used to treat breast cancer. Ex. 1003 at [0002]-[0004]. Therefore, Liu discloses a method of using highly pure (Z)-endoxifen to "treat[] a hormone-dependent breast disorder or a hormone-dependent reproductive tract disorder in the subject" as recited in claim 16. Bihovsky, ¶84; Miller, ¶37.

As discussed above with respect to claim 1, Liu inherently teaches highly-pure (Z)-endoxifen in the claimed Form I, characterized by an XRPD pattern

"comprising major peaks at 16.8±0.3°, 17.1±0.3° and 21.8±0.3° two theta." Miller, ¶38.

E. Claim 18

18. The method of claim 16, wherein the subject has tamoxifen-refractory or tamoxifen resistant hormone-dependent breast disorder or hormone-dependent reproductive tract disorder.

Tamoxifen has long been used to treat breast cancer. Ex. 1001 at Fig, 1, 1:61-2:6; Ex. 1003, [0003]; Ex. 1004 at Fig. 3, 1:35-56. Liu teaches that endoxifen is a metabolite of tamoxifen, and thus could be used on patients who could not metabolize or had difficulty metabolizing tamoxifen, leading them to be tamoxifen-refractory or tamoxifen-resistant. *See, e.g.*, Ex. 1003, [0003]. For example, Liu describes that "[t]amoxifen's efficacy relies on metabolism in the liver by cytochrome P450 isoforms CYP2D6 and CYP3A4 to transform tamoxifen into the active metabolites, 4-hydroxytamoxifen (afimoxifene) and N-desmethyl-4-hydroxytamoxifen (endoxifen)." *Id.* Liu further teaches that the Z-isomer of endoxifen is "more active at the estrogen receptor." *Id.*, [0004]. Liu also explains that "[g]iving the active (Z)-endoxifen form directly to tamoxifen non-responsive patients has been shown to result in significantly higher endoxifen blood levels compared to giving a similar dose of tamoxifen, and shows evidence of tumor regressions...." *Id.* Liu thus teaches a method of using (Z)-endoxifen to treat tamoxifen-refractory or resistant conditions, such as a hormone-dependent breast

disorder or a hormone-dependent reproductive tract disorder in a subject with tamoxifen-refractory or tamoxifen resistant hormone-dependent breast disorder or hormone-dependent reproductive tract disorder. *Id.*; Bihovsky, ¶86.

X. GROUND 2: CLAIMS 1-21 ARE OBVIOUS OVER LIU AND AHMAD IN VIEW OF THE KNOWLEDGE OF A POSA

A. Claims 1-6

The knowledge within the art at the time of the 151 patent's claimed priority date reinforces that Liu anticipates the 151 patent or, alternatively, renders the 151 patent obvious in view of Liu and the knowledge of a POSA that existed at the time. *See, e.g.*, *Koninklijke Philips v. Google*, 948 F.3d 1330, 1337-38 (Fed. Cir. 2020) (affirming PTAB finding of obviousness based on a single reference in view of the knowledge of a POSA); *Realtime Data, LLC v. Iancu*, 912 F.3d 1368, 1373-74 (Fed. Cir. 2019) (affirming Board's invalidation under § 103 using a single reference where a second reference was used to demonstrate the knowledge of a POSA). In particular, although Liu discloses every element of claims 1-6 of the 151 patent (as discussed above), each of the elements of these claims were also separately known and obvious in view of the knowledge of a POSA.

For example, it was well-known to a POSA that that endoxifen is an active metabolite of tamoxifen, which has been used in the treatment of breast cancer. McConville, ¶67; Bihovsky, ¶89; Ex. 1001 at Fig 1, 1:63-2:6; Ex. 1004 at Fig. 3, 1:35-56; Ex. 1003 at [0003]. It was also well-known that the (Z)-form of endoxifen

is more active at the estrogen receptor. Ex. 1003 at [0004]. Thus, it was known to use (Z)-endoxifen in the treatment of breast cancer. McConville, ¶¶37-38, 67; Ex. 1004 at 1:64-2:4; Ex. 1003 at [0003]. Further, other methods of forming (Z)-endoxifen were known. Bihovsky, ¶¶24-26, 34-35, 95. As discussed above, the claimed XRPD patterns are inherently taught by Liu. Miller, ¶¶24-25, 29-31.

Therefore, arriving at the invention claimed in the 151 patent from Liu would have involved simply utilizing known, conventional, and predictable processes, and a POSA would have had a reasonable expectation of success in doing so. Bihovsky, ¶¶42, 90; McConville, ¶67; *see KSR Int'l Co. v. Teleflex Inc*., 550 U.S. 398, 415-21 (2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results."). Indeed, as discussed above, Liu teaches how to form highly-pure (Z)-endoxifen that exhibits the claimed XRPD pattern. *See, e.g.*, *Apple Inc. v. Corephotonics, Ltd*., 861 F. App'x 443, 449 (Fed. Cir. 2021) ("It is well-established that prior art patents and printed publications…are presumed enabling."). However, to the extent a POSA required other teachings to arrive at the claimed subject matter (which they would not for the reasons discussed herein), 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). *See, e.g.*, *In re Donohue*, 766 F.2d 531, 534 (Fed. Cir. 1985) (additional references may be used "to show that the claimed subject matter, as

disclosed in [the reference], was in the public's possession"); *see also Intas v. Atossa*, PGR2023-00043, Paper 37 at *25-26 (discussing Fauq).

B. Claims 7-9

As discussed, Liu discloses the composition of independent claims 1 and 16. Bihovsky, ¶¶76-79, 84-85; Miller, ¶¶27-31, 37-38. Liu explains that (Z)-endoxifen is more active at the estrogen receptor, and therefore may be used to treat breast cancer. Ex. 1003 at [0002]-[0004]. Ahmad similarly acknowledges that (Z)-endoxifen can be used for treatment of breast cancer. Ex. 1004 at 1:64-66, 10:31-35. Ahmad teaches "compositions of the present invention can be employed to treat breast cancer and breast related diseases," and that "[o]ne object of the present invention is to provide (E)-endoxifen or (Z)-endoxifen with at least 80% purity, such as at least 90% pure...." *Id.* at 18:47-48, 12:14-17. Thus, a POSA in possession of Liu would have been motivated to use the teachings of Ahmad to develop formulations of highly pure (Z)-endoxifen for the treatment of breast cancer and other breast diseases and would have expected success in doing so. McConville, ¶68.

7. The composition of claim 1, further comprising a pharmaceutically acceptable carrier or diluent.

Pharmaceutically acceptable carriers and diluents were common excipients employed in virtually all pharmaceutical formulations. McConville, ¶¶69-70. For example, Ahmad teaches that its (Z)-endoxifen compositions can include a "pharmaceutically acceptable carrier or diluent." Ex. 1004, 8:31-38; *see also* 19:56-

58. Ahmad also discloses formulations including substances that can act as a diluent. *See, e.g.*, *id.*, 9:57-61 (sucrose, glucose, lactose, sorbitol, mannitol), 8:37-38 (starch).

Indeed, diluents (also sometimes called fillers) were commonly included in pharmaceutical formulations and are well-known in the pharmaceutical industry and to POSAs. McConville, ¶70; Ex. 1012 at 900 ("Fillers *see* Diluents (tablet/capsule)"). For example, Stegemann teaches that several excipients function as fillers at higher volumes. Ex. 1013 at 7-8 ("Talcum, for instance, serves as a lubricant in concentrations below 5%. At higher concentrations, it is mainly considered a filler…. Starch, which is commonly added to tablets as a disintegrant owing to its macerating properties of 5% to 10%, might be used as a filler in hard gelatin capsules…."); *see also* Ex. 1012 at 897 (listing "Diluents tablet/capsule" including talc, calcium carbonate, sugar spheres, microcrystalline cellulose, kaolin, mannitol, sorbitol, starch, pregelatinized starch, and others).

As taught by these references, the use of a carrier and/or diluent in a pharmaceutical formulation was a routine and common practice. McConville, ¶71. A POSA would have been motivated to use a carrier and/or diluent for its normal use—to make the ingredients easier to process, stabilize the formulation, and/or make the formulation a suitable size for consumption, and would have had a reasonable expectation of success, as carriers and diluents were commonplace excipients in the art. *Id.*; *see also Intas v. Atossa*, PGR2023-00043, Paper 37 at *41-

43 (finding depending claims reciting a filler, a disintegrant, and a lubricant unpatentable because "a POSA would have had a reason to use the excipients...in light of their well-known uses with a reasonable expectation of success").

Accordingly, claim 7 would have been obvious over Liu in view of Ahmad in view of the knowledge of a POSA.

8. The composition of claim 7, wherein the composition is formulated for oral, parenteral, topical, or intraductal delivery.

Ahmad teaches that formulation of highly pure (Z)-endoxifen can be administered via "oral, intravenous, subcutaneous, percutaneous, parenteral, intraperitoneal, rectal, vaginal, and/or topical delivery." Ex. 1004, 4:49-52. Such methods of administration of a composition to a subject 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 administering Liu's (Z)-endoxifen via the routes recited in claim 8. McConville, ¶72.

Accordingly, claim 8 would have been obvious over Liu in view of Ahmad in view of the knowledge of a POSA.

9. The composition of claim 7, wherein the composition is formulated for oral delivery as a tablet, a caplet, a capsule, or a pill.

As discussed, Ahmad teaches oral administration of highly pure (Z)-endoxifen. Ahmad further discloses "[p]harmaceutical preparations that find use with the compositions of the present invention include but are not limited to tablets,

capsules, pills" and that "[f]or the oral mode of administration, preferred forms of endoxifen...include tablets, capsules…." Ex. 1004, 18:1-6. The use of tablets, caplets, capsules, and pills 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 administering Liu's (Z)-endoxifen via the oral delivery routes recited in claim 9. McConville, ¶73.

Accordingly, claim 9 would have been obvious over Liu in view of Ahmad in view of the knowledge of a POSA.

C. Claims 13 and 14

13. The composition of claim 11, wherein the oral dosage form is formulated as an enteric tablet, an enteric caplet, an enteric capsule, a delayed-release tablet, a delayed-release caplet or a delayed-release capsule.

Ahmad teaches that (Z)-endoxifen may be encapsulated in enteric tablets or capsules. For example, Ahmad states that "[i]n some embodiments, the composition comprises a tablet or a filled capsule, wherein said tablet or filled capsule optionally comprises an enteric coating." Ex. 1004 at 4:41-44. Indeed, Ahmad describes that "[w]hen desired, composition containing endoxifen...can be encapsulated in enteric-coated capsules to protect it from acids in the stomach." *Id.* at 18:19-21. Ahmad explains that the "enteric coatings prevent release of medication before it reaches the small intestine." *Id.* at 18:22-24. It further teaches that "[m]ost enteric coatings work by presenting a surface that is stable at acidic pH but breaks down rapidly at higher

pH." *Id.* at 18:24-26. Ahmad suggests that the "[e]nteric coating of capsules filled with compositions containing endoxifen can be done as methods known in the art." *Id.* at 18:27-29. Thus, Ahmad teaches (Z)-endoxifen formulations as an enteric tablet, an enteric capsule, a delayed-release tablet, or a delayed-release capsule. McConville, ¶74.

To the extent it is argued there is not a specific, enabling disclosure of an enteric capsule in Ahmad, such capsules were well known in the art. *Id.*, ¶75. For example, Cole teaches that "[e]nteric coated products are designed to remain intact in the stomach and then to release the active substance in the upper intestine" and that "the reasons for using enteric coated preparations are well documented." Ex. 1008 at 83. Cole notes that (in 2002), "site specific delivery into the upper intestine has been achieved for many years by the use of pH-sensitive coatings…." *Id.* at 84. Cole teaches numerous polymers used to achieve this effect: "[t]he polymers commonly used to achieve enteric properties are anionic polymethacrylates (copolymerisate of methacrylic acid and either methylmethacrylate or ethyl acrylate (Eudragit®), cellulose based polymers, e.g. cellulose acetate phthalate (Aquateric®) or polyvinyl derivatives, e.g. polyvinyl acetate phthalate (Coateric®)." *Id.* at 83. Other enteric capsules were also well known. *See, e.g.*, Ex. 1012 at 899 (HPE listing numerous "Enteric formulations/coating agents"). Thus, Ahmad, in view of the knowledge of a POSA, enables the enteric capsule limitation. McConville, ¶75.

A POSA would have been motivated to use an enteric capsule as taught in Ahmad (and Cole) to the 90% (Z)-endoxifen taught by Liu for the reasons described in Ahmad—to avoid degradation of the (Z)-endoxifen in the acidic conditions of the stomach—and would have had a reasonable expectation of success in doing so as enteric capsules were well known in the art. McConville, ¶76; *see also Intas v. Atossa*, PGR2023-00043, Paper 37 at *35 ("We credit Dr. McConville's testimony that applying enteric coatings would have been routine..., which is consistent with Ahmad's disclosure that the enteric coating 'can be done as methods known in the art.'").

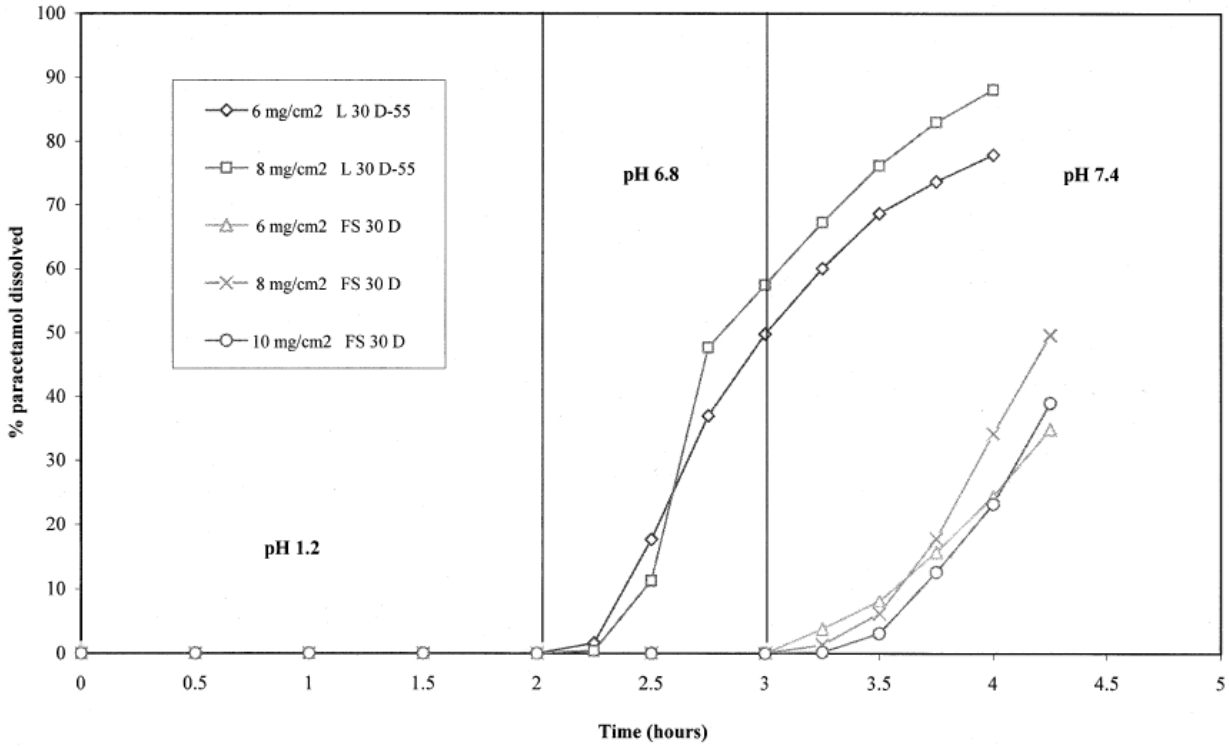
Therefore, claim 13 would have been obvious over Liu and Ahmad and the knowledge of a POSA.

14. The composition of claim 11, wherein at least 80% of the compound of Formula (III) in the oral dosage form is released in the intestines of the subject.

As Ahmad teaches, (Z)-endoxifen formulations can be encapsulated in enteric-coated capsules to prevent release of medication before it reaches the small intestine, then trigger release. Ex. 1004, 18:19-24. Ahmad explains that enteric coatings work by breaking down rapidly at the relatively higher pH of the small intestine, rather than the more acidic pH of the stomach. *Id.* at 18:19-26.

As Ahmad suggests, enteric capsules and coatings were known in the art. *Id.* at 18:27-29. As a POSA would have known, many of the enteric capsules and

coatings that were known in the art were specifically designed to prevent release of an active ingredient in the stomach. McConville, ¶¶77-78. Indeed, Cole teaches that at "pH 6.8,[8] release of the paracetamol was rapid…." Ex. 1008 at 89. As seen in Figure 4 of Cole (reproduced below), the enteric coating prevented release in the stomach (0% at pH of 1.2), and released 80% of the active ingredient after about 3.5 to 4 hours in a pH of 7.4.



Ex. 1008, Fig. 4. Thus, a POSA would have understood that "at least 80% of the compound of Formula (III) in the oral dosage form is released in the intestines

[8] The pH of the proximal small intestine has been measured to be about 6.6. Ex. 1017.

of the subject" for Liu's composition formulated according to Ahmad, such as using the coating described by Cole (or another enteric coating known in the art). McConville, ¶79.

A POSA would have been motivated to achieve such a formulation and method of using it to ensure that the endoxifen was released in the small intestine where it could be absorbed into the body and have pharmaceutical effect. *Id.*, ¶80. A POSA would have had a reasonable expectation of success, as this was known in the art (*e.g.*, as is taught in Cole). *Id.*; *see also Intas v. Atossa*, PGR2023-00043, Paper 37 at *35 ("It was known that endoxifen could be susceptible to degradation in the acidic conditions of the stomach, and a POSA would have been motivated to use an enteric capsule to avoid acidic degradation and improve bioavailability.").

Accordingly, claim 14 would have been obvious over Liu and Ahmad in view of the knowledge of a POSA.

D. Claims 10-12 and 15

Because 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 (*e.g.*, in Liu's composition) and cannot demonstrate patentability. *See Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012) ("The initial blood serum concentration resulting from administering a PPI dosage is an inherent property of the formulation, and an obvious formulation cannot become nonobvious

simply by administering it to a patient and claiming the resulting serum concentrations."); *see also In re Huai-Hung Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011) (claimed "food-effect" related serum concentration level is inherent property of drug); *King Pharm., Inc. v. Eon Labs, Inc*., 616 F.3d 1267, 1275 (Fed. Cir. 2010) (drug's bioavailability is natural result of prior art explicated limitations); *see also* McConville, ¶81. Indeed, pharmacokinetics reflect the absorption, distribution, metabolism, and excretion of a particular drug at a certain dosage. *See* Ex. 1027 at 4 (explaining pharmacokinetics are used to "design[] and predict[] optimal dosing regimens for individuals or groups of patients."); Ex. 1009 at Abstract ("Pharmacokinetics (PK) is the study of the time course of the absorption, distribution, metabolism and excretion (ADME) of a drug...."). In other words, as a POSA would have known, the pharmacokinetics are inherent properties of a particular drug. McConville, ¶81. In this way, "[a] single kinetic profile may be well summarized by C_{max}, T_{max}, $t_{1/2}$ and AUC," and that "these parameters[] may well summarize the drug kinetics in the whole population." Ex. 1010 at Abstract; *see also* Ex. 1027 at 5 ("[R]ecommended dosage regimens produce the desired pharmacologic response in the majority of the anticipated patient population."). Moreover, when measuring pharmacokinetic properties, only the pharmacokinetics of the active ingredient of a formulation are measured (*e.g.*, the pharmacokinetics of any impurities are not considered). McConville, ¶81. Therefore, because the claimed

composition was known in the art before the time of the invention, its inherent pharmacokinetics recited in the claims were likewise known in the art prior to the 151 patent. *Id.*

Even if not inherent, a POSA would have known the target pharmacokinetics expected to be efficacious based on the known drug tamoxifen. McConville, ¶¶82-83. Like Liu and Ahmad, Ahmad 2010 and Ahmad 2012 recognize that (Z)-endoxifen may be used to treat breast cancer. Ex. 1006, 814; Ex. 1007, 1. Ahmad 2010 and Ahmad 2012 tested the safety, tolerability, and pharmacokinetics of endoxifen in human subjects. Ex. 1006, 814; Ex. 1007, 1. Ahmad 2010 and 2012 describe the endoxifen pharmacokinetics expected to be efficacious by comparing the pharmacokinetics of endoxifen to the pharmacokinetics of the known anti-cancer drug, tamoxifen. McConville, ¶¶82-83; Ex. 1006, 816 ("On the basis of these results, we expect that multiple daily endoxifen doses of 2.0–4.0 mg will result in endoxifen exposures that would be similar to those found in patients with normal CYP2D6 function who are administered tamoxifen at 20 mg/day. That is, a dose of 4 mg of endoxifen should be appropriate for breast cancer prevention and therapy."); Ex. 1007, 2 ("Multiple daily endoxifen doses of 4.0-8.0 mg resulted in endoxifen exposures that would be sufficient for effective therapy."). The pharmacokinetics described fall within the scope of the claims as outlined below. McConville, ¶82.

Thus, Ahmad 2010 and Ahmad 2012 show that the claimed pharmacokinetic properties would not have been surprising or unexpected, and to the extent the claimed pharmacokinetics were not inherently achieved following Liu, a POSA would have been aware of the target pharmacokinetics expected to be efficacious and would have been motivated to optimize a formulation to achieve them (*e.g.*, as indicated by Ahmad 2010 and Ahmad 2012). McConville, ¶¶82-83; *see also Intas v. Atossa*, PGR2023-00043, Paper 37 at *48 ("[A] POSA would have been motivated to use the formulation of Ahmad to obtain a pharmacokinetic profile within the ranges recited..., as suggested by Ahmad 2010 with a reasonable expectation of success.").[9] For example, a POSA would have increased or decreased the amount of (Z)-endoxifen in the formulation to adjust C_{max}, added an absorption enhancer to the formulation, changed the particle size of the (Z)-endoxifen, and/or added a surfactant

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[9] The Board disagreed with Petitioner's inherency arguments relating to similar pharmacokinetic claims in the 334 PGR. Those determinations by the Board were not essential to the Board's judgment finding the claims of the 334 patent unpatentable, and therefore collateral estoppel does not apply to this issue in this IPR. *See Google*, 54 F.4th at 1381 (stating requirements for collateral estoppel to apply).

to increase solubilization. McConville, ¶83. A POSA would have been aware of the different ways to adjust the pharmacokinetics of a formulation and would have had a reasonable expectation of success in altering the pharmacokinetics of a formulation, as adjusting the pharmacokinetics of a formulation was a routine, commonplace, and straightforward practice in the formulation arts. *Id.*

> ***10. The composition of claim 7, wherein a mean half-life of the compound of Formula (III) in a subject treated with the composition is between 30 hours to 60 hours.***
>
> ***12. The composition of claim 11, wherein a mean half-life of the compound of Formula (III) in the subject is between 40 hours to 55 hours.***

The mean half-life of a compound is an inherent property of that compound. Ex. 1027 at 36 ("The biological half-life of the drug is the time needed for 50% of the drug to be eliminated"); Ex. 1018 at 6. Indeed, the claims recite "a mean half-life ***of the compound of Formula (III)***," meaning a mean half-life of (Z)-endoxifen. Therefore, the claims themselves acknowledge that the half-life is inherent to (Z)-endoxifen. The half-life does not depend on the concentration of (Z)-endoxifen administered. McConville, ¶84. As such, the claimed half-life is merely the inherent property of dosing a patient with the 90% (Z)-endoxifen taught by Liu in a dosage form at 1 to 200 mg as taught by Ahmad. *Id.*; *see* cases cited *supra* this section X.D.

Further, there is nothing surprising about the claimed half-life. McConville, ¶85. For example, Ahmad 2010 provides the pharmacokinetics for tamoxifen dosed

at 20 mg, as well as endoxifen at dosages of 0.5, 1, 2, and 4 mg. Ex. 1006 at Abstract. As shown below, Ahmad 2010 discloses mean half-lives of endoxifen between 52.1 and 58.11 hours. *Id.* at Table 1.

Table 1 Endoxifen doses and pharmacokinetic parameters

Dose	C_{max} (ng/ml)	$AUC_{0-\infty}$ (ng·h/ml)	$t_{1/2}$ (h (CV%))	Vz (l)	Cl (l/h)
Endoxifen 0.5 mg	1.38 ± 0.25	99.9 ± 13.6	58.11 (18.0)	427 ± 101	5.1 ± 0.7
Endoxifen 1.0 mg	3.98 ± 1.7	239 ± 70	54.1 (10.6)	346 ± 88	4.5 ± 1.1
Endoxifen 2.0 mg	6.79 ± 1.85	401 ± 113	55.4 (16.3)	428 ± 133	5.4 ± 1.8
Endoxifen 4.0 mg	15.1 ± 4.24	801 ± 262	52.1 (12.9)	406 ± 119	5.5 ± 1.9
Tamoxifen 20 mg	0.417 ± 0.013	381 ± 47.6	1,051 (16.4)[a]	Fixed	Fixed

Data are given as mean values ± SD except for $t_{1/2}$ (coefficient of variation percentage); $n = 8$ subjects/treatment group. Fixed—could not be estimated from data for tamoxifen, and therefore, values fixed at Vz = 400 l and Cl = 5.0 l/h.

$AUC_{0-\infty}$, area under the concentration–time curve extrapolated from 0 to ∞; C_{max}, peak drug concentrations in plasma; CI, confidence interval; CV, coefficient of variation; $t_{1/2}$, half-life.

[a]Apparent $t_{1/2}$ estimated from terminal exponential phase of the concentration-vs.-time curve.

Id. Therefore, the half-life range recited in claims 10 and 12 of the 151 patent would not have been surprising or unexpected to a POSA. McConville, ¶85.

Even if the claimed half-life range was not inherent in Liu in view of Ahmad's composition, a POSA would have been aware of the target pharmacokinetics expected to be efficacious for (Z)-endoxifen compositions and would have been motivated to optimize a formulation to achieve them with a reasonable expectation of success (*e.g.*, as taught by Ahmad 2010 and Ahmad 2012). McConville, ¶86; *see also Intas v. Atossa*, PGR2023-00043, Paper 37 at *48 ("[A] POSA would have been motivated to use the formulation of Ahmad to obtain a pharmacokinetic profile within the ranges recited..., as suggested by Ahmad 2010 with a reasonable expectation of success.").

Therefore, claims 10 and 12 would have been obvious over Liu and Ahmad in view of the knowledge of a POSA.

> ***11. The composition of claim 1, formulated as an oral dosage form comprising 1 mg to 200 mg per unit dose of the composition, and wherein daily administration of the oral dosage form achieves in a subject treated with the composition one or more of:***
>
> ***a steady state plasma level of the compound of Formula (III) within 7 to 21 days;***
>
> ***a steady state plasma level of the compound of Formula (III) ranging from 25 nM to 300 nM;***
>
> ***a steady state plasma level of the compound of Formula (III) greater than 30 nM; or***
>
> ***maximal plasma levels of the compound of Formula (III) within 2 to 10 hours after administering.***

The prior art taught dosing patients with endoxifen well within the range of 1 mg to 200 mg, and a POSA would have been motivated to dose patients with such amounts. *See* Ex. 1004; Ex. 1006; Ex. 1007; McConville, ¶87, 101; *see also* Claim 19 *infra*. Like the claimed half-life, the pharmacokinetics recited in claim 11 are merely the inherent properties of dosing a patient with the 90% (Z)-endoxifen taught by Liu in a dosage form at 1 to 200 mg as taught by Ahmad. McConville, ¶¶87, 91; cases *supra* Section X.D

Moreover, the pharmacokinetics recited in claim 11 of the 151 patent would not have been surprising or unexpected to a POSA. McConville, ¶88. For example, Ahmad 2010 and Ahmad 2012 teach endoxifen tablets with pharmacokinetics within

the ranges recited in claim 11. For example, Ahmad 2010 teaches that "the estimated steady-state plasma concentration (C^{SS}_{max}) of endoxifen is 55.1 ng/ml when the drug is administered in multiple doses of 4 mg at dose intervals of 24 h...." Ex. 1006 at 816. Converting the C^{SS}_{max} from ng/ml to nM yields a C^{SS}_{max} of 147.5 nM.[10] The steady state plasma level of the endoxifen disclosed by Ahmad 2010 is therefore within the claimed range of 25 nM to 300 nM. McConville, ¶88. The steady state plasma level of the endoxifen disclosed by Ahmad 2010 is also greater than 30 nM, as recited in claim 11. *Id.* Further, Ahmad 2010 teaches that "time to peak (T_{max}) values were between 4.5 and 6 h" for endoxifen doses of 0.5, 1, 2, and 4 mg. Ex. 1006 at 815. Thus, Ahmad 2010 teaches that maximal plasma levels are reached "within 2 to 10 hours after administering" as recited in claim 11. McConville, ¶88.

Ahmad 2012 further suggests that the claimed pharmacokinetics are not surprising or unexpected. McConville, ¶89. For example, as reflected in the table of Ahmad 2012 reproduced below, Ahmad 2012 provides steady state plasma levels ranging from 65.5 to 359 nM[11] and average time to peak of 5 hours. Ex. 1007 at 2.

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[10] (55.1 ng/ml * 373.5 g/mol) / 1000 = 147.5 nM. *See* Ex. 1019 (providing molecular weight of endoxifen); McConville, ¶88 n.4.

[11] After converting from ng/ml to nM. *See supra*, n.10.

Parameters (units)	Mean ± SD		
	2 mg	4 mg	8 mg
T_{max} (h)*	5 (3.0-12.0)	5 (4.0-6.0)	5 (4.0-6.0)
$C_{min\ ss}$ (ng/mL)	15.7±6.4	44.0±11.6	80.4±26.7
$C_{max\ ss}$ (ng/mL)	24.5 ±7.3	75.9 ±18.5	134.1±32.1
AUC_{tau} (ng.h/mL)	445.3 ±146.2	1363.3±396.3	2322.6±619.8
PTF (%)	50.8±19.0	56.5 ±17.9	57.6 ±14.6
$C_{av\ ss}$ (ng/mL)	18.6 ±6.1	56.8 ±16.5	96.8±25.8

*Data presented as median (range)

Id.

Even if the claimed pharmacokinetics were not inherent in Liu in view of Ahmad's composition, a POSA would have been aware of the target pharmacokinetics expected to be efficacious for (Z)-endoxifen compositions and would have been motivated to optimize a formulation to achieve them with a reasonable expectation of success (*e.g.*, as taught by Ahmad 2010 and Ahmad 2012). McConville, ¶90; *see also Intas v. Atossa*, PGR2023-00043, Paper 37 at *48 ("[A] POSA would have been motivated to use the formulation of Ahmad to obtain a pharmacokinetic profile within the ranges recited..., as suggested by Ahmad 2010 with a reasonable expectation of success."). For example, as discussed above, a POSA would have increased or decreased the amount of (Z)-endoxifen in the formulation, added an absorption enhancer, changed the particle size of the (Z)-endoxifen, and/or added a surfactant to increase solubilization. McConville, ¶90.

As such, claim 11 would have been obvious over Liu and Ahmad in view of the knowledge of a POSA.

15. The composition of claim 11, having a mean area under the curve extrapolated to time infinity ($AUC_{0\text{-}inf}$) of the compound of Formula (III) of 200 hr*ng/mL to 10000 hr*ng/mL.

AUC is a measurement of the exposure to drug in the body after dosing. McConville, ¶92. Similar to the claims discussed above, the pharmacokinetics recited in claim 15 are merely the inherent property of dosing a patient with the 90% (Z)-endoxifen taught by Liu in a dosage form at 1-200 mg as taught by *e.g.*, Ahmad. *See* cases *supra* Section X.D.

Additionally, Ahmad 2010 suggests that the inherent pharmacokinetics of the composition of Liu are within the range recited in claim 15. For example, Ahmad 2010 produced data demonstrating the AUC in subjects treated with from 0.5 to 4.0 mg of endoxifen:

Table 1 Endoxifen doses and pharmacokinetic parameters

Dose	C_{max} (ng/ml)	$AUC_{0-\infty}$ (ng·h/ml)	$t_{1/2}$ (h (CV%))	Vz (l)	Cl (l/h)
Endoxifen 0.5 mg	1.38 ± 0.25	99.9 ± 13.6	58.11 (18.0)	427 ± 101	5.1 ± 0.7
Endoxifen 1.0 mg	3.98 ± 1.7	239 ± 70	54.1 (10.6)	346 ± 88	4.5 ± 1.1
Endoxifen 2.0 mg	6.79 ± 1.85	401 ± 113	55.4 (16.3)	428 ± 133	5.4 ± 1.8
Endoxifen 4.0 mg	15.1 ± 4.24	801 ± 262	52.1 (12.9)	406 ± 119	5.5 ± 1.9
Tamoxifen 20 mg	0.417 ± 0.013	381 ± 47.6	1,051 (16.4)[a]	Fixed	Fixed

Data are given as mean values ± SD except for $t_{1/2}$ (coefficient of variation percentage); $n = 8$ subjects/treatment group. Fixed—could not be estimated from data for tamoxifen, and therefore, values fixed at Vz = 400 l and Cl = 5.0 l/h.

$AUC_{0-\infty}$, area under the concentration–time curve extrapolated from 0 to ∞; C_{max}, peak drug concentrations in plasma; CI, confidence interval; CV, coefficient of variation; $t_{1/2}$, half-life.

[a]Apparent $t_{1/2}$ estimated from terminal exponential phase of the concentration-vs.-time curve.

Ex. 1006 at 815. As shown above, the AUC for 1, 2, and 4 mg are well within the claimed range. *Id.*

Even if the claimed pharmacokinetics were not inherent in Liu in view of Ahmad's composition, a POSA would have been aware of the target pharmacokinetics expected to be efficacious for (Z)-endoxifen compositions and would have been motivated to optimize a formulation to achieve them with a reasonable expectation of success (*e.g.*, as taught by Ahmad 2010 and Ahmad 2012). McConville, ¶¶93-94; *see also Intas v. Atossa*, PGR2023-00043, Paper 37 at *48 ("[A] POSA would have been motivated to use the formulation of Ahmad to obtain a pharmacokinetic profile within the ranges recited..., as suggested by Ahmad 2010 with a reasonable expectation of success."). For example, as discussed above, a POSA would have increased or decreased the amount of (Z)-endoxifen in the formulation, added an absorption enhancer, changed the particle size of the (Z)-endoxifen, and/or added a surfactant to increase solubilization. McConville, ¶94.

Therefore, claim 15 would have been obvious over Liu and Ahmad in view of the knowledge of a POSA.

E. Claim 21

21. The composition of claim 1, wherein the composition is stable for at least 9 months at 5° C. and 60% relative humidity or at 25° C. and 60% relative humidity.

A POSA would understand "stable" as used in claim 21 to mean "the continued presence of at least 90% (Z)-endoxifen in a composition...measurable by (Z)-endoxifen conversion to (E)-endoxifen starting from the date of synthesis." Ex.

1001, 82:15-19; Bihovsky, ¶91, McConville, ¶95. A POSA would have understood that the stability of a composition is dependent on the chemical structure of the composition, but does not depend on the synthetic method used to form it. Bihovsky, ¶92. Indeed, the 151 patent itself explains that a drug's stability depends on its crystal structure. Ex. 1001, 30:16-22; *see also* Ex. 1020 at Abstract ("The energies of activation for chemical degradation correlate well with the content in free enthalpy of the respective crystalline phases and their correspondent physical stability."); Ex. 1021 at 4 ("Material properties depend on the crystal structure.").

As shown herein, the (Z)-endoxifen disclosed by Liu is the same composition claimed in the 151 patent. And as discussed above, Liu teaches (Z)-endoxifen with the same crystalline structure (*e.g.*, Form I) as claimed. Therefore, because the chemical structure of the claimed composition and the composition taught by Liu is the same, Liu inherently discloses that its (Z)-endoxifen is "stable for at least 9 months at 5° C. and 60% relative humidity or at 25° C. and 60% relative humidity" as recited in claim 21 of the 151 patent. Bihovsky, ¶92. As such, Liu inherently teaches the claimed stability. *Id.*

Moreover, Elkins discusses the results of stability studies of (Z)-endoxifen. Ex. 1026 at 176. Elkins stored (Z)-endoxifen at 25° C with a relative humidity of 60% for 12 months. *Id.* at 179. Elkins explains that the (Z)-endoxifen composition slowly degraded from 98% (Z)-endoxifen to 96% (Z)-endoxifen at 5° C and 25° C

with a relative humidity of 60% over 12 months. *Id.* Elkins also states that (Z)-endoxifen was stable at 5° C, degrading only slightly from 98% (Z)-endoxifen to 97% (Z)-endoxifen. *Id.* Thus, as provided by Elkins, (Z)-endoxifen is stable for "at least 9 months at 5° C. and 60% relative humidity or at 25° C. and 60% relative humidity," as claimed and such stability certainly would not have been surprising to a POSA. Bihovsky, ¶93.

Dr. Bihovsky's experiments and NMR data confirm that (Z)-endoxifen synthesized and crystallized according to Liu's teachings provided stable highly-pure (Z)-endoxifen. Bihovsky, Appendix B, ¶94. Indeed, Dr. Bihovsky's NMR indicates pure (Z)-endoxifen with the presence of 1 weight % of residual acetone. Bihovsky, ¶97.[12] Dr. Bihovsky also tested the stability of the (Z)-endoxifen he

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[12] The presence of 1 weight % of residual acetone would not have changed the stability of (Z)-endoxifen. *Id.* And, even if the presence of a small amount of acetone did affect the stability of the (Z)-endoxifen, a POSA would have known how to remove the acetone. *Id.* For example, the acetone could have been removed by drying the substance in a vacuum. *Id.* Dr. Bihovsky dried the (Z)-endoxifen I synthesized in vacuo at 35° C for 4 days and reduced the amount of residual acetone

synthesized, albeit for 10 days. Bihovsky, ¶94; *see also* Ex. 1001 at 83:29-47. Dr. Bihovsky sealed samples of (Z)-endoxifen under nitrogen in capped vials inside plastic bags and kept one sample of (Z)-endoxifen at 25° C and 60% relative humidity for ten (10) days and another sample of (Z)-endoxifen at 40° C and 75% relative humidity for ten (10) days. *Id.* Neither sample indicated isomerization of (Z)-endoxifen to (E)-endoxifen after the ten (10) days. *Id.* Therefore, the (Z)-endoxifen synthesized according to Liu does not readily convert to (E)-endoxifen and is stable. *Id.* As such, and as shown by Elkins, a POSA would have understood (Z)-endoxifen synthesized according to Liu would have been stable for 9 months. *Id.*

If not inherent in Liu, a POSA would have understood that it was desirable for a pharmaceutical composition to be stable. McConville, ¶96; Bihovsky, ¶94. As such, a POSA would have been motivated to obtain a composition of (Z)-endoxifen that was stable. Bihovsky, ¶94. To the extent any impurities arose during the course of synthesis that negatively impacted stability, a POSA would have been motivated to use well-known purification techniques to eliminate impurities. For example, it

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from 1 weight % to 0.6 weight %. *Id.* If the amount of residual acetone needed to be reduced further, a POSA would have known how to reduce it. *Id.*

was well known in the prior art how to purify endoxifen using crystallization (Liu) and chromatography (Fauq). Ex. 1004; Ex. 1013. Indeed, Dr. Bihovsky's experiments and NMR data confirm that (Z)-endoxifen synthesized and crystallized according to Liu's teachings provided high purity (Z)-endoxifen. Bihovsky, ¶97.

If additional purification or optimization were required to improve the stability of (Z)-endoxifen, a POSA would have been motivated to do so with a reasonable expectation of success. Bihovsky, ¶¶95-96. For example, crystallization and chromatography were both well-known techniques to a POSA. *Id.*, ¶¶95-96; *see also* Ex. 1029. A POSA would have also understood how to employ other purification techniques should they have been necessary to remove particular impurities. Bihovsky, ¶96. A POSA would have had numerous, well-known purification techniques at their disposal, such as, filtration, centrifugation, extraction, evaporation, drying, and adsorption, among others. *Id.*; Ex. 1029. Thus, if impurities from Liu's synthesis caused any issues with stability (which there is no evidence of), a POSA would have been familiar with various techniques for removing them and would have had a reasonable expectation of success in doing so. Bihovsky, ¶¶96-98; *see KSR Int'l Co. v. Teleflex Inc*., 550 U.S. 398, 415-21 (2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

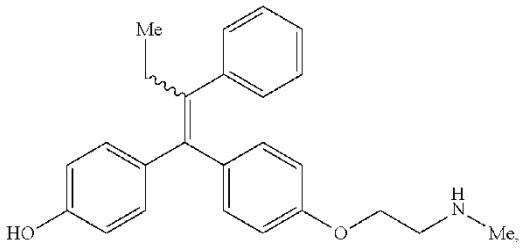
Likewise, a POSA would have been motivated to obtain a stable formulation of (Z)-endoxifen. McConville, ¶96. A POSA would have been familiar with different ways to improve the stability of a pharmaceutical composition by using formulation strategies (such as stabilizers, coatings, pH optimization, solubilization techniques, polymorph selection, lyophilization etc.) and/or packaging solutions (such as desiccants and/or moisture barriers, oxygen scavengers, light-resistant containers, air-tight or inert gas packaging) amongst others. *Id.*; *see also* Ex. 1030 at 102-163. Utilizing such techniques to improve the stability of the (Z)-endoxifen composition would have been nothing more than utilizing known, conventional, and predictable processes, and a POSA would have had a reasonable expectation of success in doing so. McConville, ¶96.

Therefore, claim 21 would have been obvious over Liu in view of the knowledge of a POSA.

F. Claim 16

16. A method of treating a hormone-dependent breast disorder or a hormone-dependent reproductive tract disorder in a subject, the method comprising administering to the subject a composition comprising a crystalline form of a compound of Formula (III):

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±0.3°, 17.1±0.3° and 21.8±0.3° two theta, thereby treating the hormone-dependent breast disorder or the hormone-dependent reproductive tract disorder.***

As discussed above, although Liu discloses every element of claim 16 of the 151 patent (as discussed above), the elements of 16 were also separately known and obvious in view of the knowledge of a POSA. For example, it was known to use (Z)-endoxifen in the treatment of breast cancer and methods of forming highly-pure (Z)-endoxifen were known. McConville, ¶97; Bihovsky, ¶¶88-90; Ex. 1003 at 1:64-2:4; Ex. 1004 at [0003]. And as discussed above, the claimed XRPD patterns are inherently taught by Liu. Miller, ¶¶29-31. Therefore, arriving at the invention claimed in the 151 patent from Liu would have involved simply utilizing known, conventional, and predictable processes, and a POSA would have had a reasonable expectation of success in doing so. Bihovsky, ¶¶88-90; McConville, ¶97; *see KSR Int'l Co. v. Teleflex Inc*., 550 U.S. 398, 415-21 (2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

Accordingly, claim 16 would have been obvious over Liu in view of Ahmad in view of the knowledge of a POSA.

G. Claims 17 and 18

17. The method of claim 16, wherein the subject has prostate cancer and wherein the subject further has or is at risk of having gynecomastia.

Ahmad teaches (Z)-endoxifen can be used in patients with prostate cancer and patients with gynecomastia. Ex. 1004, 5:37-43 ("The present invention further provides methods of inhibiting a cancer in a mammal, said cancer including...prostate cancer in a mammal...."), 29:15-31 ("Endoxifen Prevents Development of Bicalutamide-Induced Gynecomastia and Breast Pain"). Ahmad further recognizes that, in patients with prostate cancer, "silastic slow-release capsules containing endoxifen for implant or oral doses of endoxifen (1 mg-10 mg/day) with biculatamide [prostate cancer treatment] are expected to prevent development biclutamide-induced gynecomastia and breast pain." *Id.*, 29:28-31. Thus, a POSA would have been motivated to use the highly pure (Z)-endoxifen of Liu in patients with prostate cancer who have or at risk of having gynecomastia to simultaneously treat both conditions. McConville, ¶98.

Accordingly, claim 17 would have been obvious over Liu and Ahmad in view of the knowledge of a POSA.

18. The method of claim 16, wherein the subject has tamoxifen-refractory or tamoxifen resistant hormone-dependent breast disorder or hormone-dependent reproductive tract disorder.

As discussed, it was well-known to a POSA that endoxifen is an active metabolite of tamoxifen, which has been used in the treatment of breast cancer, and that endoxifen can be used to treat tamoxifen-refractory or tamoxifen resistance hormone-dependent breast disorders or reproductive tract disorders. McConville, ¶99; Ex. 1001 at Fig 1, 1:63-2:6; Ex. 1003 at Fig. 3, 1:35-56; Ex. 1004 at [0003]. For example, Liu explains that "Giving the active (Z)-endoxifen form directly to tamoxifen non-responsive patients has been shown to result in significantly higher endoxifen blood levels compared to giving a similar dose of tamoxifen, and shows evidence of tumor regressions...." Ex. 1003, [0003]. Thus, claim 18 would have been obvious over Liu in view of the knowledge of the POSA.

Similarly, Ahmad teaches that "[e]ndoxifen is generated via CYP3A4-mediated N-demethylation and CYP2D6 mediated hydroxylation of Tamoxifen." Ex. 1004 at 1:57-59. As Ahmad notes, "[u]se of endoxifen, e.g., in place of Tamoxifen, avoids several metabolic steps that rely on CYP2D6." *Id.* at 2:2-5; *see also id.* at 1:64-2:20. A POSA would have therefore understood that endoxifen was expected to be efficacious in patients who were tamoxifen-resistant or tamoxifen-refractory due to metabolic deficiencies. McConville, ¶100. In other words, a POSA

would have understood both Liu and Ahmad to teach a method of using (Z)-endoxifen for tamoxifen-refractory or resistant conditions. *Id*.

Accordingly, claim 18 would have been obvious over Liu and Ahmad in view of the knowledge of a POSA.

H. Claims 19 and 20

19. The method of claim 16, wherein the composition comprises 0.01 mg to 200 mg of the (Z)-isomer.

The claimed dosing range would have been readily apparent to a POSA based on what was known in the art. McConville, ¶101. First, Ahmad teaches in its examples that "oral doses of endoxifen (1 mg-10 mg/day) with biculatamide [sic] are expected to prevent development of biclutamide-induced [sic] gynecomastia and breast pain." Ex. 1004 at 29:20-31. Further, Ahmad 2010 and Ahmad 2012 provide safety data suggesting appropriate dosages of endoxifen. For example, Ahmad 2010 teaches that "a dose of 4 mg of endoxifen should be appropriate for breast cancer prevention and therapy." Ex. 1006 at 816. Similarly, Ahmad 2012 confirmed that 4 mg doses "were safe, well tolerated and bioavailable" and that "[m]ultiple daily endoxifen doses of 4.0-8.0 mg resulted in endoxifen exposures that would be sufficient for effective therapy." Ex. 1007 at 1-2. Ahmad, Ahmad 2010, and Ahmad 2012 all suggest using dosage forms well within the incredibly broad range recited by claim 19. Thus, a POSA would have understood that the formulations of Liu in view of Ahmad should include dosages from 0.01 mg to 200 mg of the more active,

(Z)-endoxifen. McConville, ¶101. Indeed, at the very least, it would have been obvious for a POSA to try dosages in the range of 0.01 mg to 200 mg of (Z)-endoxifen. *Id.*; *see also Intas v. Atossa*, PGR2023-00043, Paper 37 at *35 (crediting Dr. McConville's testimony stating that "a POSA reading Ahmad 2010 and 2012 would have expected the appropriate dosage of (Z)-endoxifen to fall within the range of 0.01-200 mg given (Z)-endoxifen is more active").

Thus, claim 19 would have been obvious over Liu and Ahmad in view of the knowledge of a POSA.

20. The method of claim 16, wherein a steady state plasma level of the compound of Formula (III) is achieved within 7 to 21 days of the first administration of the composition to the subject, and wherein the steady state plasma level of the compound of Formula (III) in the subject is greater than 30 nM.

Similar to that discussed above, claim 20 merely recites inherent properties of dosing a patient with the 90% (Z)-endoxifen taught by Liu in a dosage form at 1-200 mg as taught by Ahmad. *See* McConville ¶102; cases *supra* Section X.D.

Moreover, Ahmad 2010 suggests that the claimed, inherent pharmacokinetics would not have been unexpected or surprising to a POSA. McConville, ¶103. For example, Ahmad 2010 teaches that "the estimated steady-state plasma concentration (C^{SS}_{max}) of endoxifen is 55.1 ng/ml when the drug is administered in multiple doses of 4 mg at dose intervals of 24 h," which gives a C^{SS}_{max} greater than 30 nM (147.5 nM). Ex. 1006 at 816. As discussed above, a POSA would have understood that one

way to adjust the steady state plasma level of (Z)-endoxifen would be to adjust the concentration and/or purity of (Z)-endoxifen given to the patient—increasing the steady state plasma level by increasing the concentration and/or purity of (Z)-endoxifen administered to the patient, or decreasing the steady state plasma level by decreasing the concentration and/or purity of (Z)-endoxifen administered to the patient. McConville, ¶103.

Thus, claim 20 would have been obvious over Liu and Ahmad in view of the knowledge of a POSA.

XI. CONCLUSION

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

Respectfully submitted,

McANDREWS, HELD & MALLOY, LTD.

Dated: April 3, 2025

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CERTIFICATE OF WORD COUNT

I certify under 37 CFR § 42.24 that this **PETITION FOR INTER PARTES REVIEW** contains fewer than 13,690 words, as determined by Microsoft Word.

Dated: April 3, 2025

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CERTIFICATE OF SERVICE

Under 37 C.F.R. §§ 42.6(e)(4) and 42.105, the undersigned certifies on this date, a true and correct copy of this Federal Express to the Patent Owner at the following correspondence address of record for U.S. Patent No. 11,261,151:

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