

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

EXPERT DECLARATION OF STEVEN MILLER, Ph.D.

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I, Steven Miller, Ph.D., do hereby declare:

I. Introduction

1. I have been retained to provide my expert opinions on behalf of Intas Pharmaceuticals, Limited, in support of a petition for *inter partes* review of claims 1-21 of U.S. Patent No. 11,261,151 (“the 151 Patent”; Ex. 1001), which challenges the validity of the 151 patent.

2. The opinions set out by this declaration are based on my education, knowledge and experience. I have considered the materials and items identified in this declaration.

II. Education and Professional Background

3. My qualifications and credentials to testify as an expert in this case are set forth in my curriculum vitae (attached as Appendix A).

4. I have significant experience in materials characterization, specifically in regards to analyzing samples through spectroscopic techniques and analyzing the physical structure of molecules using techniques such as X-ray diffraction and spectroscopy. I have more than 20 years of academic and industrial materials development and characterization experience. My research has resulted in more than 15 publications in refereed journals.

5. I obtained a B.A., in Physics, from Rutgers University in 2004. I then obtained an M.S. and then a Ph.D. in Materials Science and Engineering, also from

Rutgers. While at Rutgers, I worked as a teaching assistant, research assistant, post-doctoral assistant, and research associate. I conducted research with the nano-materials and devices group and the composite and optical materials center.

6. Since 2014 I have been the president/owner of H&M Analytical Services, which is a full-service x-ray diffraction and analysis testing lab, which also provides a wide range of other testing and material characterization services. Polymorph identification of pharmaceuticals is a substantial portion of the testing performed by H&M Analytical Services.

7. Since 2018 I have been an Adjunct Professor at Rutgers, teaching Advanced Materials Characterization.

III. Compensation

8. I am being compensated for the time I spend on this matter at my ordinary rate of \$500 per hour for expert services. I am reimbursed for my reasonable expenses incurred in connection with my work on this matter. My compensation does not depend on the opinions I offer or on the outcome of this proceeding or any other proceeding.

IV. Scope of Engagement

9. I was asked by counsel to perform certain experiments to determine the x-ray power diffraction (“XRPD”) patterns of crystals synthesized by Dr. Ron Bihovsky according to the methods taught in International Application No. WO

2017/070651 (“Liu”). I also compared the XRPD patterns of the crystals synthesized by Dr. Bihovsky to the disclosure and claims of the 151 patent.

10. I understand that some of the claims are directed to compositions for use as a pharmaceutical and methods for treating a subject. I am not an expert in pharmaceutical formulations or treating patients, and I have not been asked to offer any opinions outside of my expertise or concerning the ultimate issues of validity of the claims.

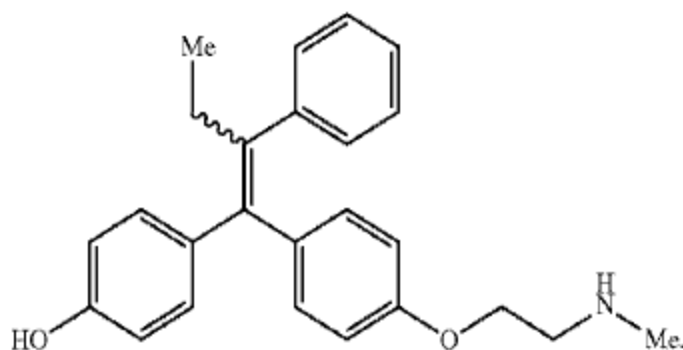
V. Background

11. The claims of the 151 patent are directed to compositions comprising a crystalline form of endoxifen that is at least 90% by weight (Z)-endoxifen having a crystalline Form I, characterized by an x-ray powder diffraction pattern comprising certain peaks.

12. Endoxifen (4-hydroxy-N-desmethyltamoxifen) is a nonsteroidal selective estrogen receptor modulator. I understand that Intas sells endoxifen in India under the brand name Zonalta for the treatment of manic depressive disorder. *See* Ex. 1015.

13. Endoxifen can be depicted as the below chemical structure, which is referred to as Formula (III) in the 151 patent:

Formula (III)



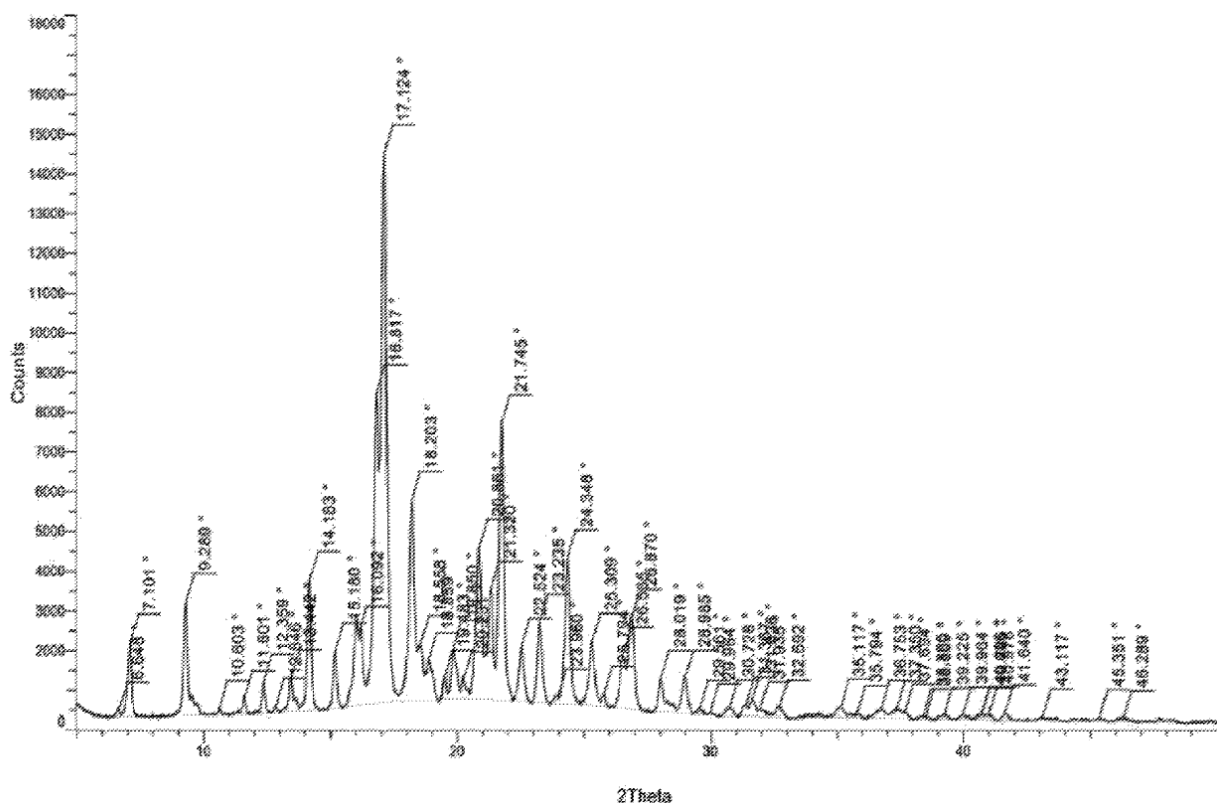
See, e.g., Ex. 1001 at 3:1-15.

VI. The 151 Patent

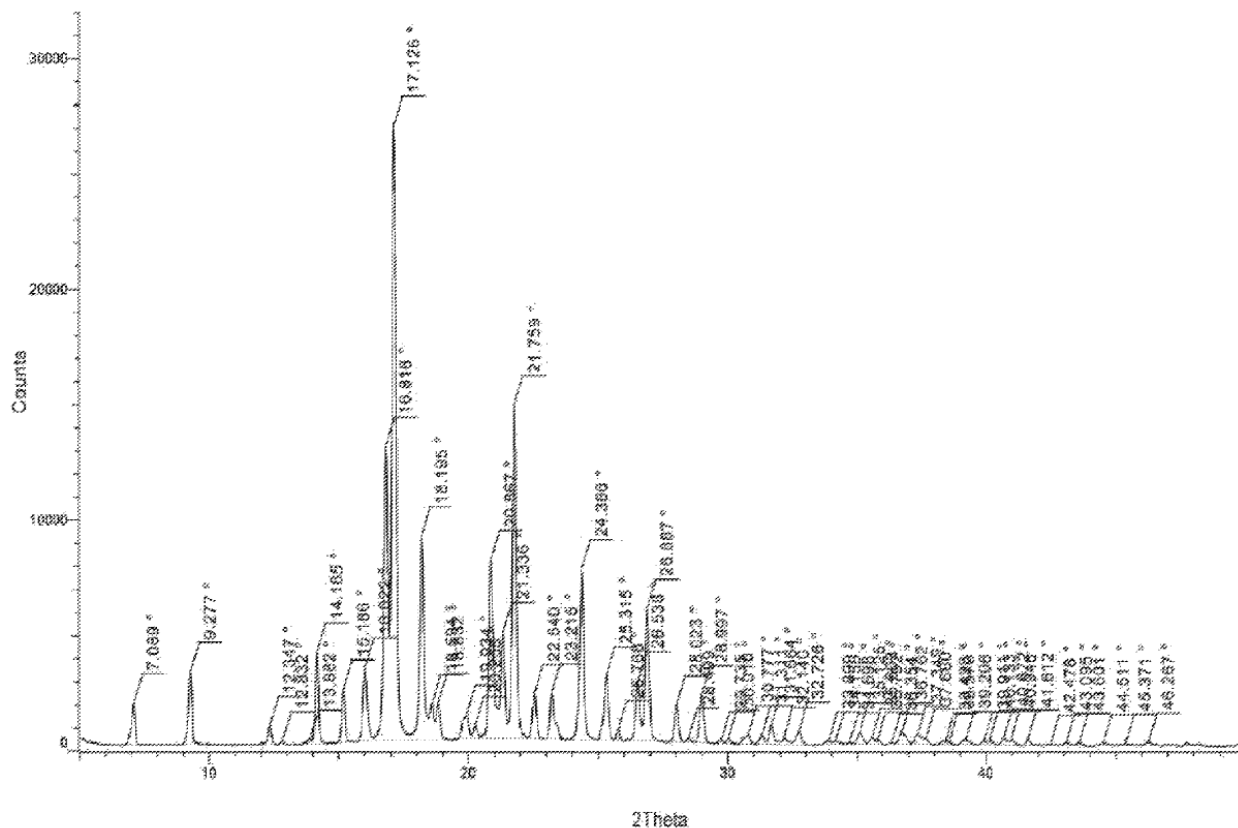
14. The 151 patent is entitled “Methods for Making and Using Endoxifen.” Ex. 1001 at Cover. I understand that the 151 patent is a U.S. National Phase Application of International Application No. PCT/US2018/050272, filed September 10, 2018 and claims priority to Provisional Application No. 62/556,799, dated September 11, 2017. *Id.* Thus, I have been instructed to use September 11, 2017 as the time of invention, and to consider my opinions from the perspective of a person of skill at that time.

15. The 151 patent is directed to compositions of endoxifen that are at least 90% by weight of (Z)-endoxifen in a particular crystalline form (*i.e.*, Form I) and methods of administering such formulations. The 151 patent characterizes Form I by its XRPD pattern. In particular, the 151 patent states that Form I “may be characterized by an x-ray powder diffraction pattern comprising major peaks at $16.8 \pm 0.3^\circ$, $17.1 \pm 0.3^\circ$ and $21.8 \pm 0.3^\circ$ two theta, and optionally further comprising at

least one peak selected from $16.0 \pm 0.3^\circ$, $18.8 \pm 0.3^\circ$ and $26.5 \pm 0.3^\circ$ two theta. In some embodiments, the x-ray powder diffraction pattern further comprises at least one peak selected from $12.3 \pm 0.3^\circ$, $28.0 \pm 0.3^\circ$ and $29.0 \pm 0.3^\circ$ two theta.” *Id.* at 3:20-28. The 151 patent further states that Form I “is characterized by an x-ray powder diffraction pattern substantially as set forth in FIG. 9 or FIG. 10.” *Id.* at 3:32-34. Figures 9 and 10 of the 151 patent are reproduced below.



Id. at Figure 9.



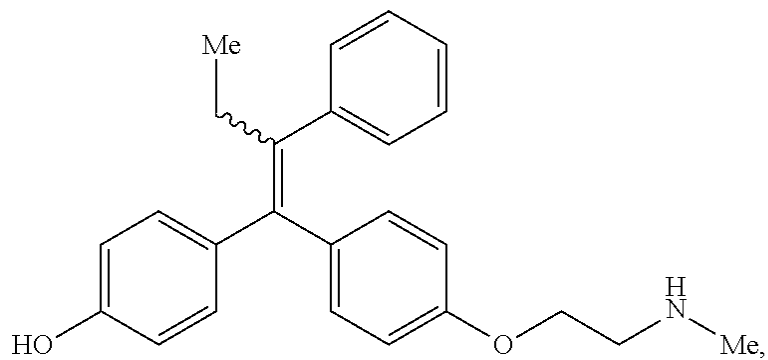
Id. at Figure 10.

16. I understand that the 151 patent contains the following 21 claims:

Independent Claim 1 and Dependent Claims 2-15 and 21

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 $16.8\pm0.3^\circ$, $17.1\pm0.3^\circ$ and $21.8\pm0.3^\circ$ two theta.

2. The composition of claim 1, wherein the x-ray powder diffraction pattern further comprises at least one peak selected from $16.0\pm0.3^\circ$, $18.8\pm0.3^\circ$ and $26.5\pm0.3^\circ$ two theta.

3. The composition of claim 1, wherein the x-ray powder diffraction pattern further comprises at least one peak selected from $12.3\pm0.3^\circ$, $28.0\pm0.3^\circ$ and $29.0\pm0.3^\circ$ two theta.

4. The composition of claim 1, wherein the x-ray powder diffraction pattern further comprises peaks at $12.3\pm0.3^\circ$, $16.0\pm0.3^\circ$, $18.8\pm0.3^\circ$, $26.5\pm0.3^\circ$, $28.0\pm0.3^\circ$ and $29.0\pm0.3^\circ$ 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.

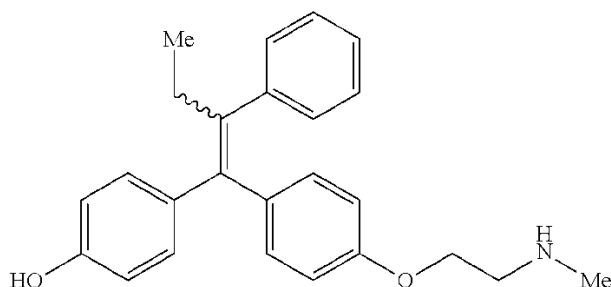
15. The composition of claim 11, having a mean area under the curve extrapolated to time infinity ($AUC_{0-\infty}$) of the compound of Formula (III) of 200 hr*ng/mL to 10000 hr*ng/mL.

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.

Independent Claim 16 and Dependent Claims 17-20

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 $16.8 \pm 0.3^\circ$, $17.1 \pm 0.3^\circ$ and $21.8 \pm 0.3^\circ$ two theta, thereby treating the hormone-dependent breast disorder or the hormone-dependent reproductive tract disorder.

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.

VII. Person of Ordinary Skill in the Art

17. I understand that the content of a patent (including its claims) and prior art should be interpreted the way a person of ordinary skill in the art (or “POSA”) would have interpreted the material at the time of the alleged invention. In my opinion, a POSA for purposes of the 151 patent is 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. 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.

18. I base my opinion on my review of the 151 patent, the problems the 151 patent was attempting to solve, the prior art discussed below, and my general experience with pharmaceutical compounds and the people working in the field. I meet and/or exceed the definition of a POSA. I also note that my opinions would not change if the level of skill in the art were found to be lower.

VIII. Claim Construction

19. I understand that terms should be given their plain and ordinary meaning to a person of skill at the time of invention. I have applied this principle to all terms in the 151 patent addressed below.

IX. Summary of the Prior Art

A. WO 2017/070651 (“Liu”)

20. I understand that International Application No. WO 2017/070651 (“Liu”) was filed on October 24, 2016, and published on April 27, 2017 and is therefore prior art to the 151 patent. Ex. 1002 at Cover.

21. Liu teaches methods for synthesizing and purifying (Z)-endoxifen with a 99% isomeric purity. *See, e.g., id.* at [0076]. In particular, Liu discloses two methods of preparing highly pure (Z)-endoxifen: i) synthesis followed by sequential recrystallizations (“Liu’s Recrystallization Procedure”), *id.*, [0021]-[0045], and (ii) synthesis followed by isomerization and sequential recrystallizations (“Liu’s Isomerization and Recrystallization Procedure”). *Id.*, [0046]-[0055]. Liu does not report any XRPD data of the compounds Liu synthesized. Thus, Liu does not report whether its compounds exhibited the XRPD pattern recited in the claims of the 151 patent (*i.e.*, Form I). However, as I discuss in more detail below, I have confirmed that Liu’s procedure provides (Z)-endoxifen that exhibits an XRPD pattern consistent with Form I as claimed in the 151 patent.

B. General X-Ray Powder Diffraction Art

22. 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. Bunaciu, A. et al., *X-ray Diffraction: Instrumentation and Applications*, 45 CRITICAL REVIEWS IN ANALYTICAL CHEM. 289-99 (May 21, 2015) (“Bunaciu”) discloses that XRPD can

be used to identify a specific polymorph structure. Ex. 1011 at 289. For example, Bunaciu explains that “[i]n 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.” *Id.* Thus, the same (or substantially similar) XRPD patterns for different samples of a substance indicate that the samples have the same polymorph structure. *Id.*

X. X-Ray Powder Diffraction of (Z)-Endoxifen Synthesized in Accordance with Liu’s Procedures

23. Dr. Bihovsky followed the procedures outlined in Liu to obtain highly pure (Z)-endoxifen. I then tested the highly pure (Z)-endoxifen synthesized by Dr. Bihovsky according to Liu to obtain the XRPD patterns of the crystals. I also analyzed the resulting XRPD patterns. The experimental test and analysis conditions used for the XRPD testing is attached to this declaration as Appendix B.

24. The results of my XRPD testing for the resulting (Z)-endoxifen crystals from both Liu’s Recrystallization Procedure and Liu’s Isomerization and Recrystallization Procedure are below. The tables below provide the measured peak positions (*e.g.*, °2-theta), the d-spacing, and the intensity of each measured peak for each solid (*e.g.*, the solids made by Liu’s recrystallization procedure and the solids made by Liu’s isomerization and recrystallization procedure).

**XRPD Results of Liu's
Recrystallization Procedure**

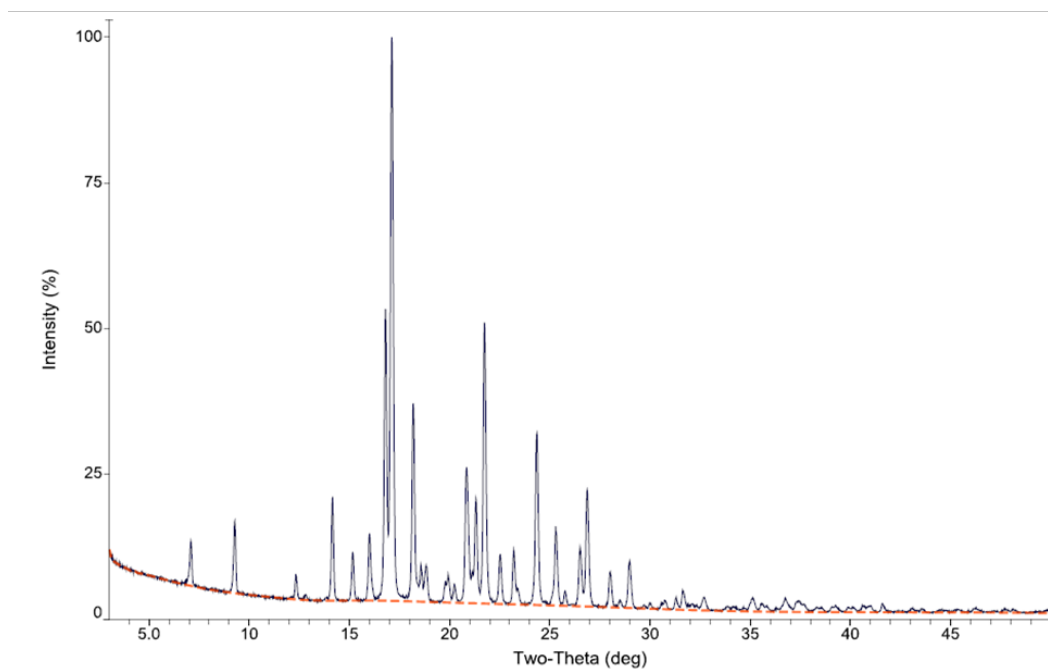
2-Theta	d(Å)	Intensity (%)
7.092	12.454	7.80%
9.282	9.520	12.90%
12.329	7.173	4.30%
14.160	6.250	18.30%
15.167	5.837	8.50%
16.002	5.534	11.60%
16.803	5.272	51.70%
17.120	5.175	100.00%
18.189	4.873	34.60%
18.576	4.773	3.60%
18.827	4.710	6.60%
19.795	4.481	3.20%
19.929	4.452	4.40%
20.236	4.385	2.60%
20.848	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%
28.016	3.182	6.30%
28.501	3.129	1.40%
28.984	3.078	8.30%
30.017	2.975	1.00%
30.577	2.921	1.20%
30.755	2.905	1.50%
31.303	2.855	1.90%
31.633	2.826	2.90%
32.709	2.736	2.10%
35.119	2.553	2.10%
35.617	2.519	1.40%
36.742	2.444	2.10%
37.426	2.401	1.60%
37.690	2.385	1.20%
39.262	2.293	1.20%
40.633	2.219	1.00%
40.984	2.200	1.20%
41.602	2.169	1.40%

**XRPD Results of Liu's Isomerization
and Recrystallization Procedure**

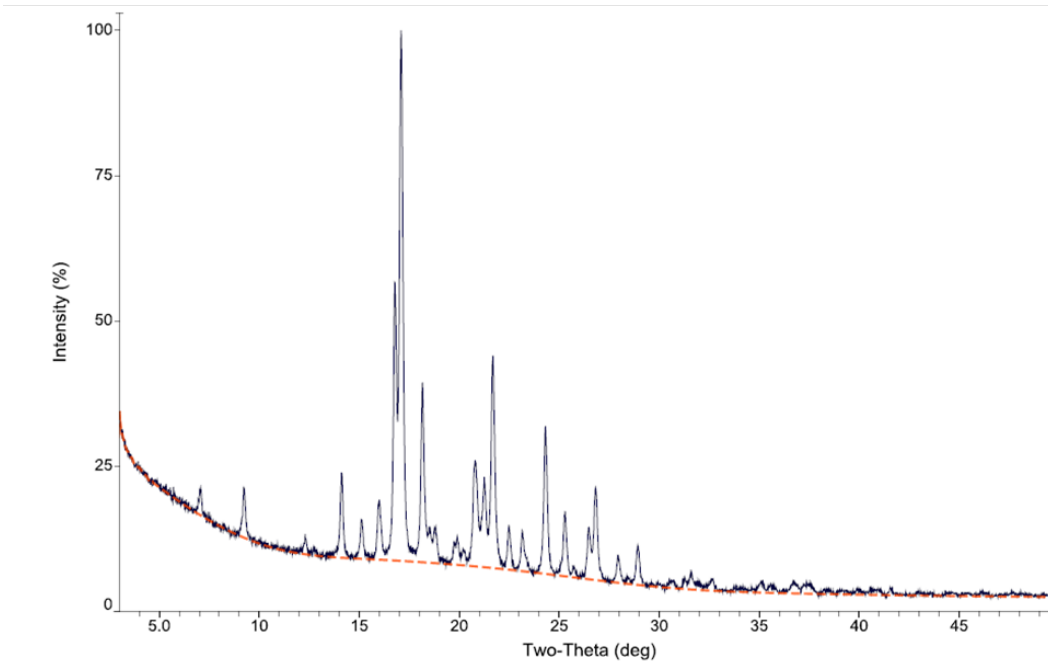
2-Theta	d(Å)	Intensity (%)
7.0596	12.5113	5.3%
9.2221	9.5818	9.6%
12.2968	7.1921	3.3%
14.1140	6.2699	16.1%
15.1034	5.8613	7.4%
15.9991	5.5351	10.5%
16.7726	5.2815	52.0%
17.0879	5.1848	100.0%
18.1572	4.8818	32.8%
18.4964	4.7930	2.6%
18.8126	4.7132	2.4%
19.7344	4.4951	3.9%
19.8949	4.4592	4.8%
20.1986	4.3928	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%
31.2886	2.8565	1.8%
31.6080	2.8284	3.0%
32.5985	2.7446	1.9%
35.0858	2.5556	1.6%
35.1753	2.5493	2.2%
35.6552	2.5160	1.1%
36.7208	2.4454	1.7%
37.5069	2.3960	1.6%

25. The graphs below also provide the results of the XRPD testing of the resulting (Z)-endoxifen crystals from Dr. Bihovsky. The graphs below provide the XRPD patterns in °2-theta as a function of intensity for each of the solids made by Liu's recrystallization procedure and the solids made by Liu's isomerization and recrystallization procedure.

**XRPD Results of Liu's
Recrystallization Procedure**



**XRPD Results of Liu's Isomerization
and Recrystallization Procedure**



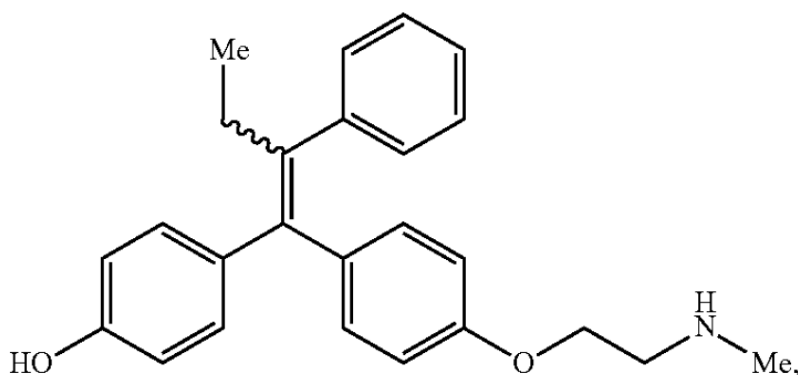
XI. Claims 1-5 and 16 in View of Liu

26. I incorporate by reference Dr. Bihovsky's discussion of the claims in in view of Liu.

A. Independent Claim 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

27. 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. *See id.* at 12:48-52.

28. 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. 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.

wherein the crystalline form of the (Z)-isomer is Form I, characterized by an x-ray powder diffraction pattern comprising major peaks at $16.8 \pm 0.3^\circ$, $17.1 \pm 0.3^\circ$ and $21.8 \pm 0.3^\circ$ two theta.

29. Liu does not disclose that the (Z)-endoxifen created is the claimed “Form I” or provide an XRPD characterization of the resulting crystalline solids. However, as discussed above, Dr. Bihovsky reproduced Liu, and sent the resulting crystals to me for XRPD testing.

30. “[T]he X-ray diffraction pattern is the fingerprint of periodic atomic arrangements in a given material.” Ex. 1011 at Abstract; *see also* Ex. 1031 at 1 (“Every crystalline phase of a given substance produces a characteristic X-ray diffraction pattern.”). As such, an XRPD pattern can be used to identify a particular form of a crystal structure. Therefore, as shown below, the results of my XRPD testing confirm that the resulting (Z)-endoxifen from both Liu’s Recrystallization and Liu’s Isomerization and Recrystallization Procedures are the claimed Form I, characterized by the claimed XRPD peaks. *See* Ex. 1031 at 9 (“The agreement in the 2θ diffraction angles between specimen and references is expected to be within 0.2° for the same crystal form . . .”).

**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%
28.016	3.182	6.30%
28.501	3.129	1.40%
28.984	3.078	8.30%
30.017	2.975	1.00%
30.577	2.921	1.20%
30.755	2.905	1.50%
31.303	2.855	1.90%
31.633	2.826	2.90%
32.709	2.736	2.10%
35.119	2.553	2.10%
35.617	2.519	1.40%
36.742	2.444	2.10%
37.426	2.401	1.60%
37.690	2.385	1.20%
39.262	2.293	1.20%
40.633	2.219	1.00%
40.984	2.200	1.20%
41.602	2.169	1.40%

**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%
31.2886	2.8565	1.8%
31.6080	2.8284	3.0%
32.5985	2.7446	1.9%
35.0858	2.5556	1.6%
35.1753	2.5493	2.2%
35.6552	2.5160	1.1%
36.7208	2.4454	1.7%
37.5069	2.3960	1.6%

31. Thus, Liu inherently teaches that the crystalline form of the (Z)-isomer obtained is Form I, characterized by an XRPD comprising major peaks at $16.8 \pm 0.3^\circ$, $17.1 \pm 0.3^\circ$ and $21.8 \pm 0.3^\circ$ two theta.

B. Dependent Claim 2

32. As discussed above, “[t]he agreement in the 2θ diffraction angles between specimen and references is expected to be within 0.2° for the same crystal form.” *See* Ex. 1031 at 9. The results of the XRPD testing of the crystalline solids of (Z)-endoxifen obtained via Dr. Bihovsky’s synthesis of highly pure (Z)-endoxifen by following both Liu’s Recrystallization and Liu’s Isomerization and Recrystallization Procedures are within 0.2° of the values disclosed in the 151 patent. Therefore, the XRPD testing confirms that the peaks recited in dependent claim 2 are similarly present in Liu’s resulting crystalline solids.

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

**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%
28.016	3.182	6.30%
28.501	3.129	1.40%
28.984	3.078	8.30%
30.017	2.975	1.00%
30.577	2.921	1.20%
30.755	2.905	1.50%
31.303	2.855	1.90%
31.633	2.826	2.90%
32.709	2.736	2.10%
35.119	2.553	2.10%
35.617	2.519	1.40%
36.742	2.444	2.10%
37.426	2.401	1.60%
37.690	2.385	1.20%
39.262	2.293	1.20%
40.633	2.219	1.00%
40.984	2.200	1.20%
41.602	2.169	1.40%

**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%
31.2886	2.8565	1.8%
31.6080	2.8284	3.0%
32.5985	2.7446	1.9%
35.0858	2.5556	1.6%
35.1753	2.5493	2.2%
35.6552	2.5160	1.1%
36.7208	2.4454	1.7%
37.5069	2.3960	1.6%

C. Dependent Claim 3

33. As discussed above, “[t]he agreement in the 2Θ diffraction angles between specimen and references is expected to be within 0.2° for the same crystal form.” *See* Ex. 1031 at 9. The results of the XRPD testing of the crystalline solids of (Z)-endoxifen obtained via Dr. Bihovsky’s synthesis of highly pure (Z)-endoxifen

by following both Liu's Recrystallization and Liu's Isomerization and Recrystallization Procedures are within 0.2° of the values disclosed in the 151 patent. Therefore, the XRPD testing confirms that the peaks recited in dependent claim 3 are similarly present in Liu's resulting crystalline solids.

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

**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%
28.016	3.182	6.30%
28.501	3.129	1.40%
28.984	3.078	8.30%
30.017	2.975	1.00%
30.577	2.921	1.20%
30.755	2.905	1.50%
31.303	2.855	1.90%
31.633	2.826	2.90%
32.709	2.736	2.10%
35.119	2.553	2.10%
35.617	2.519	1.40%
36.742	2.444	2.10%
37.426	2.401	1.60%
37.690	2.385	1.20%
39.262	2.293	1.20%
40.633	2.219	1.00%
40.984	2.200	1.20%
41.602	2.169	1.40%

**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%
31.2886	2.8565	1.8%
31.6080	2.8284	3.0%
32.5985	2.7446	1.9%
35.0858	2.5556	1.6%
35.1753	2.5493	2.2%
35.6552	2.5160	1.1%
36.7208	2.4454	1.7%
37.5069	2.3960	1.6%

D. Dependent Claim 4

34. As discussed above, “[t]he agreement in the 2θ diffraction angles between specimen and references is expected to be within 0.2° for the same crystal form.” See Ex. 1031 at 9. The results of the XRPD testing of the crystalline solids of (Z)-endoxifen obtained via Dr. Bihovsky’s synthesis of highly pure (Z)-endoxifen

by following both Liu's Recrystallization and Liu's Isomerization and Recrystallization Procedures are within 0.2° of the values disclosed in the 151 patent. Therefore, the XRPD testing confirms that the peaks recited in dependent claim 4 are similarly present in Liu's resulting crystalline solids.

4. The composition of claim 1, wherein the x-ray powder diffraction pattern further comprises peaks at $12.3\pm0.3^\circ$, $16.0\pm0.3^\circ$, $18.8\pm0.3^\circ$, $26.5\pm0.3^\circ$, $28.0\pm0.3^\circ$ and $29.0\pm0.3^\circ$ two theta.

**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%
28.016	3.182	6.30%
28.501	3.129	1.40%
28.984	3.078	8.30%
30.017	2.975	1.00%
30.577	2.921	1.20%
30.755	2.905	1.50%
31.303	2.855	1.90%
31.633	2.826	2.90%
32.709	2.736	2.10%
35.119	2.553	2.10%
35.617	2.519	1.40%
36.742	2.444	2.10%
37.426	2.401	1.60%
37.690	2.385	1.20%
39.262	2.293	1.20%
40.633	2.219	1.00%
40.984	2.200	1.20%
41.602	2.169	1.40%

**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%
31.2886	2.8565	1.8%
31.6080	2.8284	3.0%
32.5985	2.7446	1.9%
35.0858	2.5556	1.6%
35.1753	2.5493	2.2%
35.6552	2.5160	1.1%
36.7208	2.4454	1.7%
37.5069	2.3960	1.6%

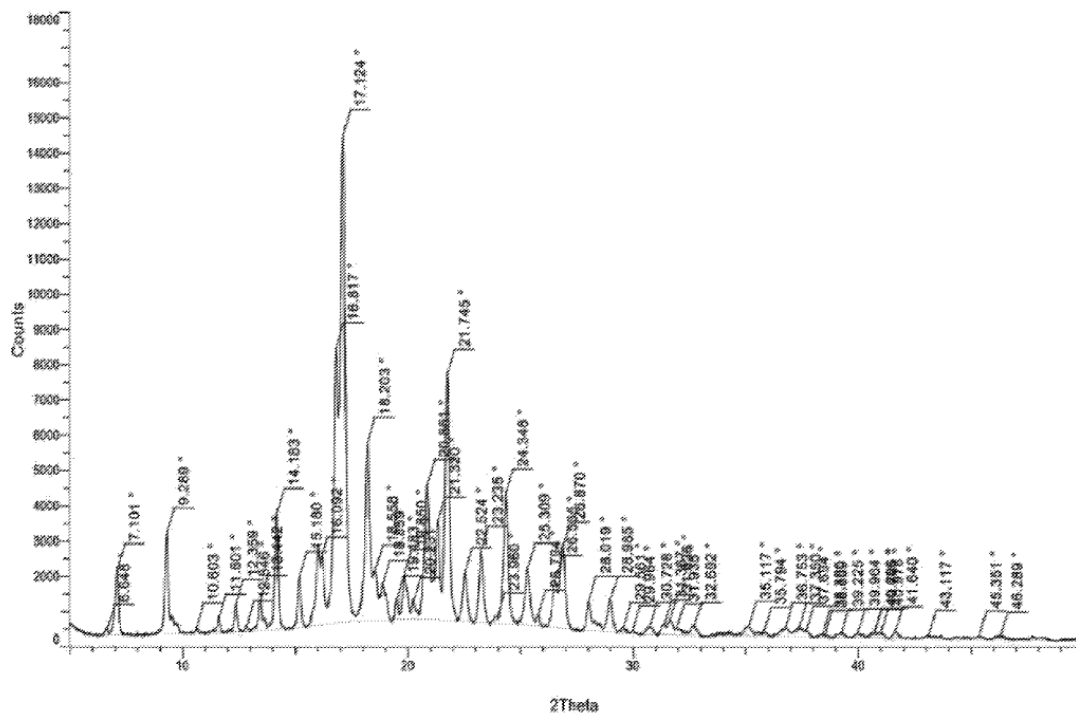
E. Dependent Claim 5

35. As discussed above, “[t]he agreement in the 2θ diffraction angles between specimen and references is expected to be within 0.2° for the same crystal form.” *See* Ex. 1031 at 9. The results of the XRPD testing of the crystalline solids of (Z)-endoxifen obtained via Dr. Bihovsky’s synthesis of highly pure (Z)-endoxifen

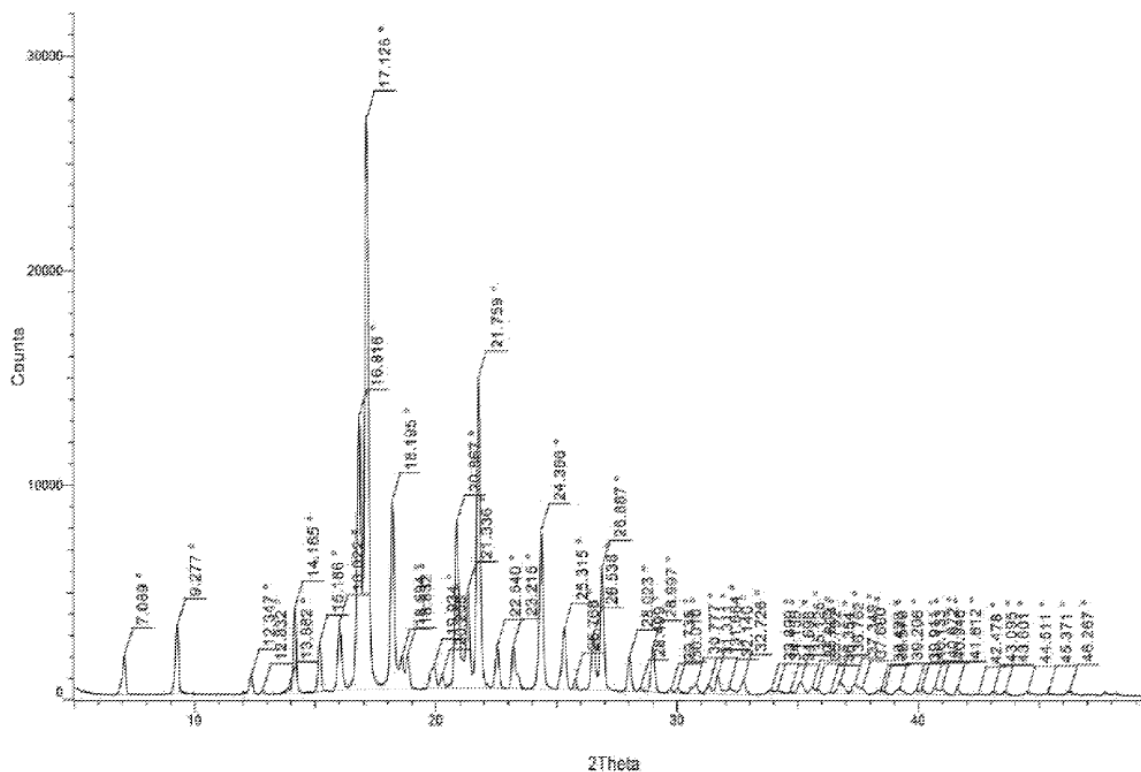
by following both Liu's Recrystallization and Liu's Isomerization and Recrystallization Procedures are within 0.2° of the values disclosed in the 151 patent. Therefore, the XRPD testing confirms that the peaks recited in dependent claim 5 are similarly present in Liu's resulting crystalline solids.

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.

36. The 151 patent's Figures 9 and 10 are reproduced below. Also below is a figure illustrating the XRPD patterns of the crystalline solids obtained by Dr. Bihovsky following Liu's Recrystallization and Liu's Isomerization and Recrystallization Procedures arranged for comparison with a stick pattern of the XRPD pattern data reported at Table 8 of the 151 patent (shown in blue), which corresponds to the XRPD patterns shown in Figures 9 and 10.

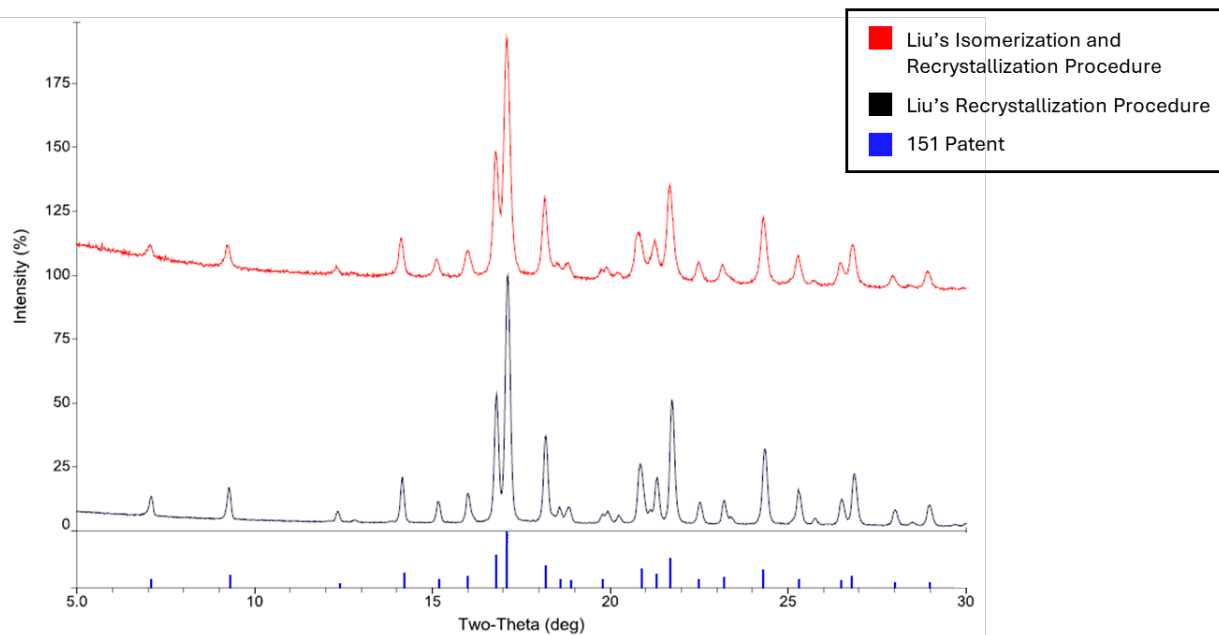


Ex. 1001, Figure 9.



Id., Figure 10.

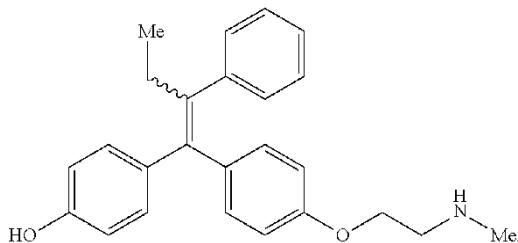
XRPD Results of Liu's Procedures
Compared to the 151 Patent



F. Independent 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 $16.8 \pm 0.3^\circ$, $17.1 \pm 0.3^\circ$ and $21.8 \pm 0.3^\circ$ two theta, thereby treating the hormone-dependent breast disorder or the hormone-dependent reproductive tract disorder.

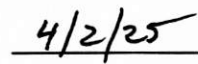
37. Liu teaches that (Z)-endoxifen may be used to treat hormone-dependent breast disorders. For example, Liu explains that (Z)-endoxifen is more active at the estrogen receptor, and therefore may be used to treat breast cancer. Ex. 1003 at [0002]-[0004]. Therefore, Liu discloses a method of using highly 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.

38. And as discussed with respect to claim 1, the (Z)-endoxifen obtained by following both Liu’s Recrystallization and Liu’s Isomerization and Recrystallization Procedures exhibit the claimed XRPD patterns. Thus, Liu inherently discloses (Z)-endoxifen in the claimed Form 1.

39. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

A handwritten signature in cursive script, appearing to read "Steven Miller", is written over a horizontal line.

Steven Miller, Ph.D.

A handwritten date "4/2/25" is written over a horizontal line.

Date

APPENDIX A

Dr. Steven L. Miller, PhD, MBA

H&M Analytical Services
1301 Whitehorse Mercerville Rd., Suite 101
Hamilton, NJ 08619
(609) 758-5700
steve@h-and-m-analytical.com

- Education:** Ph.D., Materials Science and Engineering, *Rutgers University*, 2008.
Thesis Title: "Towards Room Temperature Processed and Completely Flexible Organic Photovoltaics", Thesis Advisor: Prof. Manish Chhowalla
M.S., Materials Science and Engineering, *Rutgers University*, 2006.
B.A., Physics (minor: Mathematics), *Rutgers University*, 2004.
M.B.A., Finance/Accounting, *University of California, Irvine*, 1991.
B.A., Economics, *University of California, Irvine*, 1987.
- Technical Experience:**
- | | |
|--------------|--|
| 2014-Current | President/Owner, H&M Analytical Services, Cream Ridge, NJ |
| 2018-Current | Adjunct Professor, Rutgers University, School of Engineering
Course taught: Advanced Materials Characterization |
| 2012-2014 | Scientist, H&M Analytical Services, Cream Ridge, NJ |
| 2009-2012 | Research Associate, Ceramic, Composite and Optical Materials Center, Materials Science and Engineering, Rutgers University, Piscataway, NJ. |
| 2008-2009 | Post Doctoral Assistant, Ceramic, Composite and Optical Materials Center, Materials Science and Engineering, Rutgers University, Piscataway, NJ. |
| 2004-2007 | Graduate Research Assistant, Nano-Materials and Devices Group, Materials Science and Engineering, Rutgers University, Piscataway, NJ. |
| 2004-2008 | Teaching Assistant, Materials Science and Engineering, Rutgers University, Piscataway, NJ.
Courses: - Materials Processing I
- Photonic, Electronic and Magnetic Applications of Nanostructures and Nanomaterials
- Electron Microscopy |
- Business Experience:** Summary – *Almost twenty years of experience in finance and accounting, including high level management positions. Extensive experience managing budgets, people and projects. Significant achievements/projects included:*
- *Initial public offering for medical equipment leasing company.*
 - *Developed and implemented quality control and peer review standards for the public accounting profession.*
 - *Designed and managed financial reporting system for a start-up company.*
 - *Designed and developed a production planning system for a printed circuit board manufacturing facility.*
- | | |
|-----------|---|
| 2000-2004 | Technical Manager, American Institute of Certified Public Accountants, Jersey City, NJ. |
| 1998-1999 | Audit Manager, Ernst & Young LLP, Iselin, NJ. |
| 1996-1997 | Chief Accounting Officer, Rockford Industries, Inc. Santa Ana, CA. |
| 1991-1996 | Audit Manager, Deloitte & Touche LLP, Costa Mesa, CA. |
| 1990-1991 | Finance Manager, Conservation Technologies, Inc., Irvine, CA. |
| 1985-1988 | Financial Analyst, Xerox Corp., El Segundo, CA. |

- Publications:** A. Chikkam, M. Zamanzadeh, S. Pulagam, P. Mortel, B. Murali, S. Miller, S. Mercurio, "Corrosion Deposits Database - X-Ray Diffraction Analysis of Deposits from Oil and Gas Upstream Well/Production Systems," *AMPP Conference Proceedings*, C2024-20831 (2024)
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A. Du Pasquier, S. Miller, and M. Chhowalla, "On the use of Ga-In eutectic and halogen light source for testing P3HT-PCBM organic solar cells," *Solar Energy Materials and Solar Cells* **90**, 1828 (2006).

A. Du Pasquier, H.E. Unalan, A. Kanwal, S. Miller, and M. Chhowalla, "Conducting and transparent single-wall carbon nanotube electrodes for polymer-fullerene solar cells," *Applied Physics Letters* **87**, 203511 (2005).

Synergistic activities, memberships and awards:

- Founded the Materials Research Society Student Chapter at Rutgers University.
- Former member of the Materials Research Society, American Physical Society, American Association for the Advancement of Science, and Sigma Xi.
- Awarded the Betty Skuze Thompson Prize in physics.
- Supervised/assisted with undergraduate and graduate research projects.
- Established laboratory and protocols for general photovoltaic research at Rutgers University.
- Established TEM sample preparation laboratory and procedures.
- Established and maintained Rutgers FESEM laboratory.

Skills:

Transmission Electron Microscopy, Scanning Electron Microscopy, Electron Energy Loss Spectroscopy, Energy Dispersive Spectroscopy, Wavelength Dispersive Spectroscopy, Optical Microscopy, Atomic Force Microscopy, X-ray Diffractometry, Raman Spectroscopy, UV-Vis Spectroscopy, Fourier Transform Infra-Red Spectroscopy, Thermo Gravimetric Analysis, Profilometry, Electrical Characterization