



Atossa Therapeutics, Inc. Patent Owner

PGR 2023-0043

Patent No. 11,572,334

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE



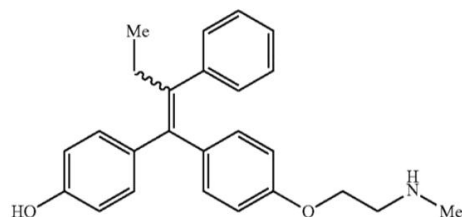
'334 Patent

Methods for Making and Using Endoxifen

- Claims recite:
 - Solid oral dosage formulations of at least 90% pure (Z)-endoxifen
 - Methods of delivering such formulations to patients
- The independent claims depict the **free base** structure of the endoxifen. (Paper 14 at 19-21)


1. An oral formulation comprising an endoxifen composition encapsulated in an enteric capsule, wherein the endoxifen composition comprises a compound of Formula (III):

Formula (III)



wherein at least 90% by weight of the compound of Formula (III) is (Z)-endoxifen.

EX1001 at 98:13-31



 US011572334B2

<p>(12) United States Patent Quay et al.</p> <p>(71) Applicant: Atossa Therapeutics, Inc., Seattle, WA (US)</p> <p>(72) Inventors: Steven C. Quay, Seattle, WA (US); Yao-Lin Sun, Tainan (TW); Lung-Hu Wang, Kaohsiung (TW); Chang-Hung Wu, Kaohsiung (TW); Chuan-Hung Huang, Tainan (TW)</p> <p>(73) Assignee: ATOSSA THERAPEUTICS, INC., Seattle, WA (US)</p> <p>(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.</p> <p>(21) Appl. No.: 17/580,428</p> <p>(22) Filed: Jan. 20, 2022</p> <p>(65) Prior Publication Data US 2022/0242816 A1 Aug. 4, 2022</p> <p>Related U.S. Application Data</p> <p>(63) Continuation of application No. 16/641,985, filed as application No. PCT/US2018/050272 on Sep. 10, 2018, now Pat. No. 11,251,151.</p> <p>(60) Provisional application No. 62/693,885, filed on Jul. 3, 2018, provisional application No. 62/624,787, filed on Jan. 31, 2018, provisional application No. 62/556,884, filed on Sep. 11, 2017, provisional application No. 62/556,799, filed on Sep. 11, 2017.</p> <p>(51) Int. Cl. A61K 31/35 (2006.01) C07C 217/18 (2006.01) C07C 213/10 (2006.01) A61K 9/00 (2006.01) A61K 45/06 (2006.01)</p> <p>(52) U.S. Cl. CPC: C07C 217/18 (2013.01); C07C 213/10 (2013.01); A61K 9/0051 (2013.01); A61K 45/06 (2013.01); C07B 2209/13 (2013.01)</p> <p>(58) Field of Classification Search CPC: A61K 31/35 USPC: 514/648 See application file for complete search history.</p> <p>(56) References Cited U.S. PATENT DOCUMENTS 3,848,030 A 11/1974 Vainbo et al. 4,851,433 A 7/1989 Evans 6,774,122 B2 8/2004 Evans et al. 7,384,418 B2 6/2008 Hung et al. 7,485,623 B2 2/2009 Sun 7,507,769 B2 3/2009 Neisour 7,531,578 B2 5/2009 Forman et al. 7,704,516 B2 4/2010 Evans et al. 7,705,159 B2 4/2010 Macdonald et al.</p>	<p>(10) Patent No.: US 11,572,334 B2 (45) Date of Patent: Feb. 7, 2023</p> <p>7,786,172 B2 8/2010 De et al. 7,968,532 B2 6/2011 Le et al. 8,048,927 B2 11/2011 Le Neutrer 8,058,302 B2 11/2011 Solazzi et al. 8,063,240 B1 11/2011 Koshner et al. 8,119,695 B2 2/2012 Forman et al. 8,379,680 B2 17/2012 Evans et al. 8,436,029 B2 5/2013 Hickey et al. 8,454,943 B2 6/2013 McCook et al. 8,466,139 B2 6/2013 Evans et al. 8,822,511 B2 9/2014 Conbo et al. 8,953,605 B2 3/2015 Conbo et al. 9,073,275 B2 7/2015 Royall et al. 9,090,640 B2 7/2015 Bielech et al. 9,200,045 B2 12/2015 Liu et al. 9,220,080 B2 12/2015 Permal et al. 9,308,181 B2 4/2016 Knak et al. 9,333,190 B2 5/2016 Ahmad et al. 11,281,151 B2* 3/2022 Quay CPC 217/18 2002/0025543 A1 2/2002 Serrano 2003/0021787 A1 1/2003 Hung et al. 2003/0090994 A1 5/2003 Crev. et al. 2004/0059294 A1 5/2004 Hung et al. 2007/0099288 A1 3/2007 Dismore et al. 2007/0161063 A1 7/2007 Love et al. 2007/0190019 A1 8/2007 Cao et al. 2008/0138391 A1 6/2008 Carrara et al. 2008/0110992 A1 12/2008 Singh 2009/0068190 A1 3/2009 Bortz 2009/0098669 A1 4/2009 Vacco 2009/0208944 A1 8/2009 Goetz et al. 2009/0281063 A1 11/2009 Inagi et al. 2009/0291102 A1 11/2009 Fortin 2009/0291134 A1 11/2009 Ahmad et al. (Continued)</p> <p>FOREIGN PATENT DOCUMENTS CN 101801615 A 11/2010 CN 102448467 A 5/2012 CN 104203961 A 12/2014 CN 104332504 A 2/2015 (Continued)</p> <p>OTHER PUBLICATIONS Ahmad A., et al., "Endoxifen, A New Generation of Breast Cancer Therapy: Demonstration of Safety, Tolerability and Systemic Bioavailability in Healthy Human Subjects," Clinical Pharmacology & Therapeutics, Dec. 2010, vol. 88 (6), pp. 814-817. (Continued)</p> <p>Primary Examiner — Raymond J Henley, III (74) Attorney, Agent, or Firm — DLA Piper LLP</p> <p>(57) ABSTRACT The present disclosure provides industrially scalable methods of making (Z)-endoxifen or a salt thereof, crystalline forms of endoxifen, and compositions comprising them. The present disclosure also provides methods for treating hormone-dependent breast and hormone-dependent reproductive tract disorders.</p> <p>22 Claims, 13 Drawing Sheets</p>
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Accord Exhibit 1001
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'334 Patent

Specification

- The specification describes:
 - Product storage stability (Example 11)
 - Compositions with minimal impurities; impurity profile (Table 13, Example 12)
 - Pharmacokinetics resulting in improved bioavailability (Example 15)

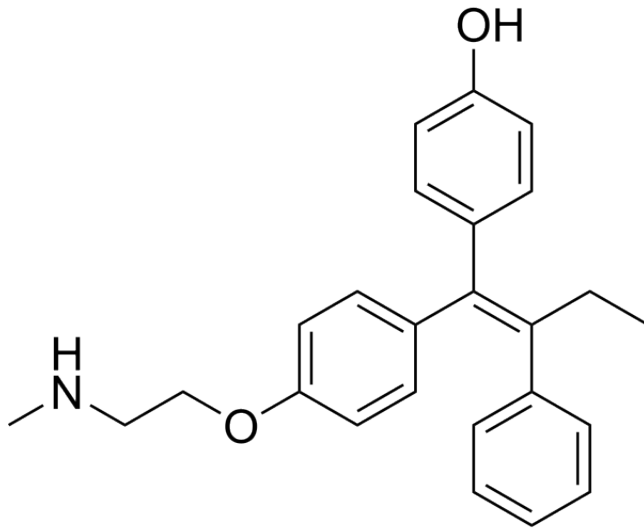
TABLE 13										
Bulk Drug Stability of (Z)-endoxifen Free Base										
Endoxifen	% Purity Storage (5° C.)				% Purity Storage 25° C./60% RH				% Purity Storage 40° C./75% RH	
	0 m	3 m	6 m	9 m	0 m	3 m	6 m	9 m	0 m	3 m
(Free Base)										
(Z)-endoxifen	99.5	99.6	99.5	99.5	99.5	99.6	99.5	99.5	99.5	99.5
(E)-endoxifen	0.19	0.17	0.18	0.19	0.19	0.17	0.18	0.19	0.19	0.17
Water content (Karl Fischer)	0.06	0.05	0.05	0.05	0.06	0.05	0.06	0.07	0.06	0.07
Max Indiv. Impurity	0.11	0.10	0.11	0.11	0.11	0.11	0.11	0.11	0.11	0.11
(Z)-endoxifen USP <921>			13990				14030			13776
Plate Count (cfu/g/mL)										

EX1001 at Table 13

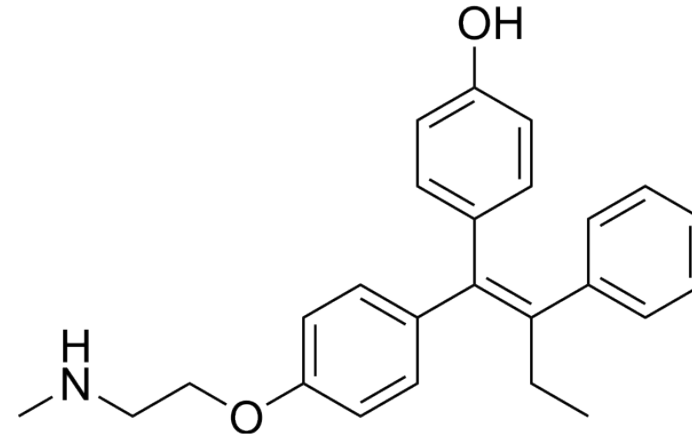
Paper 14 at 13-14.

Technical Overview

Endoxifen Exists In Two Isomeric Forms: (Z) and (E)



(Z)-Endoxifen



(E)-Endoxifen

- (Z)-endoxifen and (E)-endoxifen are diastereomers: the two molecules have the same atom connectivity, but a different arrangement in space. The two molecules are not mirror images of each other. (EX2020 at ¶ 68)
- Diastereomers are difficult to separate and have different chemical and physical properties.
 - (E)-endoxifen is known to be less active than (Z)-endoxifen. (EX2020 at ¶ 68; EX 2021 at 129:3-5)

Paper 7 at 1-3; Paper 14 at 5-6 .

Purifying Endoxifen Isomers Is Difficult

- Purification of diastereomers, such as (E)- and (Z)-endoxifen, is difficult and unpredictable.
 - Crystallization:
 - Requires extensive experimentation to determine the appropriate experimental conditions, including co-solvent system, dissolution temperature, and crystallization temperature. (EX2001 at ¶ 70)
 - Hypersensitive to impurities in crude product and reagents used. (EX2001 at ¶ 69, 71)
 - Chromatography:
 - Highly dependent on solvent, impurity profile, and scale. (EX2001 at ¶ 69)
 - Typically limited to non-clinical applications because of low yield. (EX2027 at 50:12-21; 55:21-56:6)

Endoxifen Is Known To Be Unstable

- Endoxifen is known to isomerize (convert from one isomer to the other). (EX2020 at ¶ 55)
- A POSA would know that a composition of pure (Z)-endoxifen or (E)-endoxifen will isomerize to a mixture of (Z)-endoxifen and (E)-endoxifen under certain conditions:
 - Acidic conditions (EX2027 at 112:16-113:6)
 - Aqueous conditions (EX2001 at ¶¶ 50-52)
- High temperatures accelerate this isomerization. (EX2028 at 108:6-21)

Compounds, Salts, and Solvates

- A POSA would understand that a compound (or “free base”), a salt of a compound, and a solvate of a compound are separate and distinct.
- Salts and solvates of a compound have additional atoms and additional bonds. (EX2027 at 24:21-26:22; EX2021 at 27:9-11, 30:5-7, 34:4-7, 34:22-35:3)
- A compound, a salt of a compound, and a solvate of a compound have different chemical names and different chemical formulas. (EX2021 at 27:9-11, 30:5-7)
- A compound and its corresponding salts or solvates can also have different physical properties. (EX2020 at ¶ 63)

The Challenged Claims Are Novel

Pharmaceutical Formulations Containing at least 90% Pure (Z)-Endoxifen are not Taught by the Prior Art

- The pharmaceutical formulation claimed by the '334 patent exhibits:
 - Surprising and unexpected stability: minimal conversion from (Z)-endoxifen to (E)-endoxifen and minimal formation of impurities demonstrated. (EX1001 at 83:1-20)
 - Superior bioavailability: improved concentration from oral administration compared to literature values. (EX1001 at 95:50-62)
- There is a long-felt need for new therapeutics to treat hormone-dependent breast and reproductive tract cancers.

Accelerated Stability Test of Solid (Z)-endoxifen Free Base			
	No.		
	1	2	3
Z-endoxifen	1 g	1 g	1 g
Temperature	40° C.	60° C.	80° C.
2 days	E/Z ratio 1/76 (1.27%/97.45%)	1/75 (1.30%/97.43%)	1/76 (1.28%/97.42%)
Total Impurity	1.28%	1.27%	1.30%
7 days	E/Z ratio 1/81 (1.2%/97.11%)	1/83 (1.17%/87.11%)	1/7 2(1.34%/96.92%)
Total Impurity	1.69%	1.72%	1.74%
10 days	E/Z ratio 1/75 (1.29%/97.31%)	1/82 (1.27%/97.48%)	1/77 (1.27%/97.33%)
Total Impurity	1.40%	1.33%	1.40%

EX1001 at 83:1-20

While hydrochloride and citrate salts of endoxifen . . . are known in the art and currently under evaluation for metastatic cancer, there remains unmet medical need for new compositions and methods for the treatment and/or prevention of hormone-dependent breast and reproductive tract (gynecologic) disorders.

EX1001 at 2:39-53

Paper 7 at 58-59.

POSA Definition

Board Adopted Atossa's POSA Definition at Institution

Petitioner Seeks to Modify the POSA Definition

- Atossa and the Board's POSA definition:

- “[A] graduate degree in organic chemistry, medicinal chemistry, pharmaceutical chemistry, or a related field, and four to six years of experience in the synthesis, purification, and design of pharmaceutical compounds and derivatives thereof as of the date of the claimed inventions” and “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.” (Paper 11 at 8)

- Petitioner's new POSA definition:

- Adds an additional requirement that a POSA “should have experience in formulating [dosage forms].” (Paper 16 at 1-2)

Board Adopted Atossa's POSA Definition at Institution

Petitioner's Unsupported Argument that Dr. Davies is not a POSA under Petitioner's POSA definition

- Dr. Davies has experience with formulation and meets Petitioner's requirement (EX2013 at 3):
 - Oxford Asymmetry Limited; Founder and Director (1992 – 1998)
 - MuOx Ltd. (Acquired by Summit Therapeutics plc); Founder and Non-Executive Chairman (*Drug Discovery for Orphan Muscle Diseases*) (2011 – 2014)
 - Summit Therapeutics plc; Non-executive Director (*Drug Development for Duchenne Muscular Dystrophy and Antibiotic against Clostridium difficile*) (2014 – 2018)
- Dr. Bihovsky's experience (EX1030 at ¶ 13):
 - "I understand that the claims are directed to formulations. I am not an expert in formulations ..."

Claim Construction

Claim Construction: “Enteric Capsule”

All claims

- The Board adopted Atossa’s construction of “enteric capsule”:

“a capsule with one or more enteric coating agent[s] or an intrinsically enteric capsule that does not need an additional coating to provide the enteric property to control or delay disintegration and absorption of the compositions comprising endoxifen or salts thereof in the gastrointestinal tract and thereby provide a sustained action over a longer period of time.”

Paper 11 at 9-10

- Petitioner failed to apply this construction

Patent Owner states that “Benameur does not teach that the use of this enteric capsule drug delivery technology would provide a sustained action of (Z)-endoxifen over a longer period of time.” POR 65. But it is entirely unclear what Patent Owner means, as claim 3 does not recite a “sustained action...over a longer period of time” (and longer than what?). Patent Owner also argues that a “POSA would not

Paper 16 at 16

Claim Construction: “The Compound of Formula (III) is (Z)-endoxifen”

All claims

- The Board’s *sua sponte* construction at Institution (Paper 11 at 10):
 - “We construe ‘the compound of Formula (III) is (Z)-endoxifen’ to include the polymorphic salt, free base, co-crystal and solvate forms of (Z)-endoxifen.”

Paper 11 at 10.

Claim Construction: “The Compound of Formula (III) is (Z)-endoxifen”

- A compound, a salt of a compound, and a solvate of a compound have different atoms and different chemical formulas.
 - Dr. McConville agreed. (EX2021 at 27:9-11, 30:5-7, 34:4-7, 34:22-35:3)
 - Dr. Davies agreed. (EX2020 at ¶ 61 (citing EX2021 at 27:9-11, 30:5-7))
 - Dr. Bihovsky agreed. (EX2027 at 24:21-26:22)
- Endoxifen in its salt and free base forms have different atoms in addition to the salt atoms themselves, including an extra hydrogen present in the endoxifen (non-salt) portion of the endoxifen citrate salt. (EX2021 at 34:16-35:3)
- These three categories are separate and have distinct properties.

63. Compounds and their corresponding salts and solvates can have different physical properties, such as solubility, melting point, and spectroscopic characteristics—among others.

EX2020 at ¶ 63

Paper 14 at 7-9, 21-23; Paper 21 at 3-4.

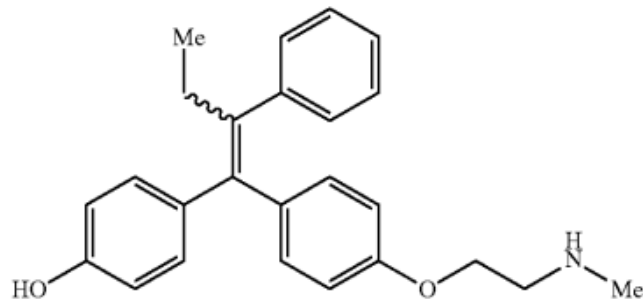
Claim Construction: “The Compound of Formula (III) is (Z)-endoxifen”

- Claims depict molecular structure of free base

What is claimed is:

1. An oral formulation comprising an endoxifen composition encapsulated in an enteric capsule, wherein the endoxifen composition comprises a compound of Formula (III):

Formula (III)



wherein at least 90% by weight of the compound of Formula (III) is (Z)-endoxifen.

EX1001 at 98:13-31

- Specification recognizes the availability of endoxifen salts and the need for endoxifen free base formulations

Commercially, endoxifen is available as an E/Z isomer free base mixture, as well as $\geq 98\%$ (Z)-endoxifen HCl and (Z)-endoxifen citrate salts. Stability of Z-endoxifen HCl salt in aqueous and solid forms has been previously published (Elkins et al. J Pharm Biomed Anal. 2014 January; 88: 174-179). Elkins et al. provide predicted t90 values for 10%

room temperature and 9 days at 45° C. There remains a need for (Z)-endoxifen free base preparations that are sufficiently stable for preparation of pharmaceutical compositions that are suitable for administering to subjects, for example, at ambient temperatures as well as at higher temperature and humidity.

EX1001 at 82:3-8, 37-42

Claim Construction: “The Compound of Formula (III) is (Z)-endoxifen”

- Specification does not contain an express definition of the phrase.
- Specification does contain a list of potential embodiments.
- The scope of potential embodiments does not constitute an express definition.
- There is no evidence of an express intent to act as lexicographer.

Without “evidence in the patent specification of an **express intent** to impart a novel meaning to a claim term, the term takes on its ordinary meaning.” *Optical Disc Corp. v. Del Mar Avionics*, 208 F.3d 1324, 1334-35 (Fed. Cir. 2000).

Claim Construction: “The Compound of Formula (III) is (Z)-endoxifen”

- Specification uses definitional language 30 times, but not with this phrase

As used herein, the term “tamoxifen” **refers** to (Z)-2-[4-(1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethylethanamine. Tamoxifen can also refer to the E-isomer or a combination of the E-isomer and the Z-isomer.

As used herein, the term “dosage form” **means** the form in which the compounds or compositions of the present disclosure are delivered to a patient.

As used herein, the term “endoxifen” **refers** to 4-hydroxy-N-desmethyl-tamoxifen. It is a secondary active metabolite of tamoxifen.

As used herein “primary therapy” **refers** to a first line of treatment upon initial diagnosis of a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both in a subject. Exemplary primary therapies may involve surgery, a wide range of chemotherapies, and radiotherapy.

- In contrast, the passage cited by the Board describes embodiments:

Embodiments that reference throughout this specification to “a compound”, such as compounds of Formula (I), Formula (II), Formula (III) and Formula (IV), include the polymorphic, salt, free base, co-crystal, and solvate forms of the formulas and/or compounds disclosed herein. Thus, the

EX1001 at 12:35-38, 45-59; 13:58-60; 14:44-49

Paper 14 at 26.

Ahmad Does Not Enable 90% (Z)-Endoxifen

Ahmad Does Not Enable 90% (Z)-Endoxifen

- The only description of 90% isomeric purity in Ahmad is a *single* prophetic statement:

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 or at least 95% pure or at least 98% pure or at least 99% pure or at least 100% pure.

EX1003 at 12:14-17

- There are no working examples or specific teachings of at least 90% (Z)-endoxifen anywhere in Ahmad.
 - Dr. Bihovsky agreed. (EX2027 at 77:2-78:21)
 - Dr. McConville agreed. (EX2028 at 81:17-19)
- Among a laundry list of solvents and crystallization conditions, there is no guidance towards which, if any, conditions can be used to obtain at least 90% (Z)-endoxifen.
 - Dr. Bihovsky agreed. (EX2027 at 74:5-18)
 - Dr. McConville agreed. (EX2021 at 73:18-22)

Paper 14 at 41-42; Paper 21 at 4, 7-8, 11.

Ahmad Only Claims 80% (Z)-Endoxifen Citrate Salt

- All that is presumed enabled in Ahmad is the claim. So at best, Ahmad enables an 80% (Z)-endoxifen citrate salt:

1. A solid pharmaceutical composition comprising an effective amount of a synthetic preparation of endoxifen, wherein:
i) said synthetic preparation of endoxifen is at least 80% Z-endoxifen;
ii) said synthetic preparation of endoxifen is in the form of a citrate salt;
wherein said solid pharmaceutical composition is in the form of an enteric-coated tablet or enteric-coated capsule.

EX1003 at 30:55-64

- There is no presumption that every prophetic statement in the specification is enabled. *Amgen Inc. v. Sanofi*, 987 F.3d1080, 1085 (Fed. Cir. 2021).

Paper 14 at 28, 32, 41-42; Paper 21 at 4-8.

Admissions of Petitioner's Chemistry Expert: Dr. Bihovsky

- He did not attempt to follow Ahmad's synthetic pathway. (EX2027 at 29:22-30:3; 33:10-16; 74:15-18)
- Ahmad does not teach how to make 90% (Z)-endoxifen free base or salt, nor are there working examples. (EX2027 at 77:2-78:21; 79:7-17)
- Ahmad's four-step synthetic pathway in Examples 1-4 does not describe the isomeric purity of the resulting endoxifen. (EX2027 at 74:1-9)

Paper 14 at 2-3, 20-21, 47; Paper 21 at 1, 7, 11, 23.

Admissions of Petitioner's Formulation Expert: Dr. McConville

- He does not have the requisite chemistry background to properly evaluate Ahmad's disclosed synthetic pathway. (EX2021 at 55:9-57:7; 63:7-64:4; 72:22-75:22)
- Liu describes a different synthetic pathway from both Ahmad and the '334 Patent. (EX2021 at 65:7-11)
- Ahmad does not contain an enabling example of making at least 90% (Z)-endoxifen in an enteric coated formulation. (EX2028 at 80:9-81:18)

Paper 14 at 2-3, 20-21, 47; Paper 21 at 1.

Burden of Demonstrating Enablement Shifts to Petitioner

- Atossa met its initial burden of producing evidence that Ahmad is not enabled to produce 90% (Z)-endoxifen free base or citrate salt.
- During prosecution, Ahmad's claims were limited to at least 80% (Z)-endoxifen citrate salt.
 - **Declaration from co-inventor of Ahmad (EX2022):** the solid oral dosage form administered in Ahmad 2010 (EX1006) was at least 80% (Z)-endoxifen citrate salt.
 - No evidence in declaration of how the dosage form was prepared; no evidence of or claims to higher isomeric purity.
- No evidence of record that Ahmad enables a POSA to achieve 90% (Z)-endoxifen in free base or salt form. (EX2027 at 77:2-78:21; 79:7-17)

Paper 14 at 32-34, 36-37; Paper 21 at 13-14.

Ahmad Does Not Teach How to Purify (Z)-Endoxifen After Synthesis of a Crude Endoxifen Mixture

- Ahmad provides a synthetic pathway that results in a crude endoxifen mixture.
 - It is undisputed that Ahmad likely results in a roughly 1:1 ratio of (Z) endoxifen:(E)-endoxifen.
- Ahmad does not disclose the isomeric ratio of the endoxifen synthesized. (EX2027 at 74:1-9)
- Ahmad does not teach how to purify the crude mixture to achieve 90% pure (Z)-endoxifen.
- Ahmad does not teach or appreciate the instability of (Z)-endoxifen.
 - Ahmad Examples 5 and 6 describe solubilizing endoxifen in acetic acid, which promotes isomerization to a roughly 1:1 ratio of (Z)-endoxifen:(E)-endoxifen. (EX2020 at ¶¶ 75, 77; EX2027 at 112:16-113:6)
 - Ahmad teaches preferred formulation pHs as low as 4.0, which promotes isomerization to a roughly 1:1 ratio of (Z)-endoxifen:(E)-endoxifen. (EX1003 at 26:5-21)

Paper 7 at 32-35; Paper 14 at 38-44; Paper 21 at 4-5, 16.

Ahmad Does Not Teach How to Make 90% (Z)-Endoxifen

- Ahmad does not provide any specific conditions to purify (Z)-endoxifen.
 - “The separation of E- and Z-isomers of endoxifen in the present invention can be done, e.g., by crystallization, or purification by liquid column chromatography (LC), or high pressure liquid column chromatography (HPLC).” (EX1003 at 11:19-23)
- Ahmad lists 19 solvents which may be suitable for use in separation of isomers, with no guidance towards any specific solvents, combinations of solvents, amounts, or conditions.
- A POSA would understand that purification is unpredictable and can be impacted by solvent, concentration, temperature, etc. (EX2027 at 83:16-84:7)

Paper 7 at 32-35, 53; Paper 14 at 31-32, 38-44; Paper 21 at 8.

Liu Cannot Cure the Deficiencies of Ahmad

- Petitioner did not include Liu in any ground and Liu cannot be used to supply the teachings missing from Ahmad.
 - Liu post-dates Ahmad – enablement is determined as of the filing date of Ahmad.
 - Liu uses a different synthetic pathway than Ahmad and has no description of stability or suitability as a pharmaceutical formulation. (EX2027 at 83:8-84:7)
 - A POSA would have no expectation of success in combining the methods of Ahmad with Liu.

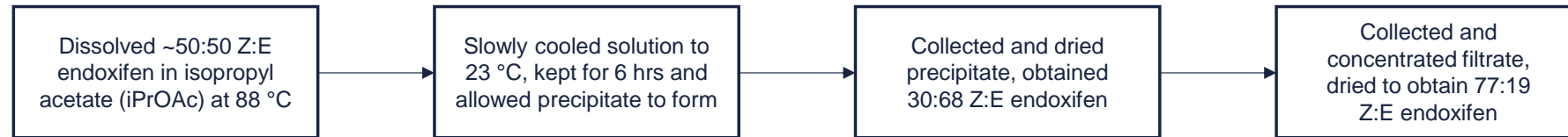
Paper 14 at 46-49, 52-55; Paper 21 at 10-12, 15.

Dr. Bihovsky's Experiments Do Not Demonstrate Enablement of Ahmad

- Petitioner's expert, Dr. Bihovsky, performed experiments to try to demonstrate enablement of Ahmad.
- Dr. Bihovsky did not carry out the synthetic method of Ahmad followed by the purification of Liu, as Petitioners suggest a POSA would have done.
 - Dr. Bihovsky did not attempt to carry out the method of Ahmad. (EX2027 at 29:22-30:3; 32:19-33:16)
 - Dr. Bihovsky only attempted to replicate Liu because, compared to Ahmad, Liu was "more economical" and "had the fewest number of steps . . . the most practical synthesis". (EX2027 at 62:18-63:16; 65:16-66:5; 79:18-80:22)

Dr. Bihovsky's Experimental Work Differed From Liu

Liu Example 5: Recrystallization of ~50:50 E:Z Endoxifen Mixture

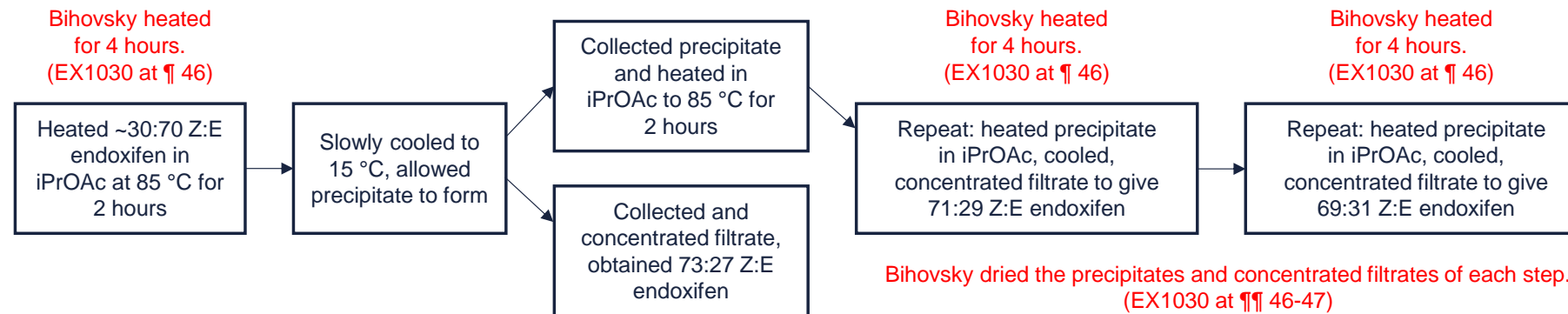


Dr. Bihovsky performed his experiments on a scale over 1000 times smaller than Liu and used endoxifen starting material with a different Z:E ratio than Liu. (EX2027 at 38:22-39:7; EX2029 at ¶¶ 16, 17, 21; EX1030 at ¶¶ 40-41)

- Impact of Dr. Bihovsky's changes:
 - **Scale:**
 - "A POSA would know that reactions on a small scale are not useful models to predict the same reactions on a large scale." (EX2029 at ¶ 8)
 - **Starting material with a different Z:E ratio:**
 - "And when you're crystalizing stuff on a large scale, that's very different to on a small scale ... a large scale acting very differently with impurity profiles, isomer ratios than you would have on a small scale." (EX1033 at 74:20-75:2).

Dr. Bihovsky's Experimental Work Differed From Liu

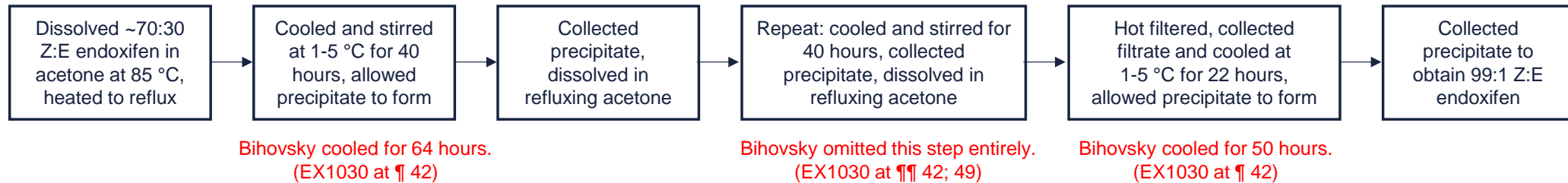
Liu Example 6: Isomerization of E-Enriched Endoxifen to Z-Enriched Endoxifen



- Impact of Dr. Bihovsky's changes (EX2029 at ¶ 20):
 - **Heating time:**
 - “[Dr. Bihovsky carries out Liu’s example 6] [o]n a smaller scale, which is not representative of the large-scale reaction and for different time.” (EX1033 at 68:4-6)
 - **Drying the precipitates and concentrated filtrates of each step:**
 - “[E]ven slight changes in methodology can lead to different results [...] different synthetic pathways can result in different stability and impurity profiles.” (EX2029 at ¶ 27; EX2027 at 83:16-84:7)

Dr. Bihovsky's Experimental Work Differed From Liu

Liu Example 7: Recrystallization of (Z)-enriched endoxifen



- Impact of Dr. Bihovsky's changes:
 - **Omission of Steps:**
 - "It is my opinion that a POSA would expect that variations in synthetic procedure can lead to different outcomes." (EX2029 at ¶ 25)
 - **Cooling Time:**
 - "Well, he didn't follow them in the sense that the scale is 1000 to 2000 times smaller, so any cooling processes and recrystallizations are going to be different." (EX1033 at 64:16-19)

Each Of The Grounds Fails

Ground 1 Fails

Claims 1, 2, 4, 15, 20-22 are Not Anticipated over Ahmad

- An anticipatory reference must be enabling

“A prior art reference cannot anticipate a claimed invention ‘if the allegedly anticipatory disclosures cited as prior art are not enabled.’” *In re Antor Media Corp.*, 689 F.3d 1282, 1287, 1290 (Fed. Cir. 2012).

- Ahmad does not enable 90% (Z)-endoxifen regardless of whether (Z)-endoxifen is construed to be a free base or a salt. (EX2027 at 77:2-78:21; 79:7-17)
 - Ahmad contains a *single* prophetic sentence referencing 90% (Z)-endoxifen

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 or at least 95% pure or at least 98% pure or at least 99% pure or at least 100% pure.

EX1003 at 12:14-17

Paper 14 at 27, 49-51; Paper 21 at 4, 13-14.

Ground 1 Fails

Claims 1, 2, 4, 15, 20-22 are Not Anticipated over Ahmad

- The Petition fails to explain how Liu and/or Song enable Ahmad's 90% (Z)-endoxifen.
- Petitioner's Reply fails to explain how Liu and/or Fauq enable Ahmad's 90% (Z)-endoxifen.

"Anticipation requires disclosure of all of the limitations of a claim in one place, not by combination of multiple disclosures." *N. Am. Oil Co., Inc. v. Star Brite Distrib., Inc.*, 46 F. App'x 629, 631 (Fed. Cir. 2002).

- Petitioner fails to provide expert testimony explaining how Liu, Song and/or Fauq enable Ahmad's 90% (Z)-endoxifen.
- Dependent claims not anticipated because independent claims 1 and 15 are not anticipated.

Paper 7 at 37-40; Paper 14 at 44-49; Paper 21 at 4-6, 10, 12-15.

Ground 2 Fails

Claims 1, 2, 4, 15, 20-22 Not Obvious over Ahmad

- A single obvious reference must be enabling

“In the absence of such other supporting evidence to enable a skilled artisan to make the claimed invention, a standalone § 103 reference **must enable** the portions of its disclosure being relied upon.” *Raytheon Techs. Corp. v. GE*, 993 F.3d 1374, 1381 (Fed. Cir. 2021) (citing *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 297 (Fed. Cir. 1985)).

- Petitioner relies on Ahmad and a POSA’s knowledge for:
 - Higher activity of (Z) isomer of endoxifen
 - Endoxifen is sensitive to the acidic environment of the stomach

Paper 1 at 37; Paper 7 at 40-48; Paper 14 at 51-61; Paper 21 at 14-18.

Ground 2 Fails

Claims 1, 2, 4, 15, 20-22 Not Obvious over Ahmad

- Petition did not rely on Liu for knowledge of a POSA
- Petition did not include obviousness ground combining Ahmad and Liu

Ground	Challenged Claims	Basis
1	1, 2, 4, 15, and 20-22	Anticipated by Ahmad
2	1, 2, 4, 15, and 20-22	Obvious over Ahmad
3	5-8, 16 and 17	Obvious over Ahmad in view of Cole
4	3	Obvious over Ahmad in view of Benameur
5	9-13	Obvious over Ahmad in view of Stegemann and/or the HPE
6	14, 18, and 19	Obvious over Ahmad in view of Ahmad 2010 and Ahmad 2012

Paper 1 at 2

- Even if Liu supplies background knowledge to a POSA, it does not cure Ahmad's enablement deficiencies

Paper 7 at 40-48; Paper 14 at 51-61; Paper 21 at 14-18.

Ground 2 Fails

Claims 1, 2, 4, 15, 20-22 Not Obvious over Ahmad

- Petitioner does not explain how a POSA would modify Ahmad or why a POSA would have a reasonable expectation of success.
- The patent at issue cannot be used as a road map.
- A reasonable expectation of success requires more than trial and error.



Paper 7 at 40-48; Paper 14 at 51-61; Paper 21 at 14-18.

Ground 3 Fails

Claims 5-8, 16-17 Not Obvious Over Ahmad in View of Cole

- Petitioner fails to identify any reasonable expectation of success.
 - Petitioner ignores inherent instability of (Z)-endoxifen, including thermal instability. (EX2028 at 56:12-19; 108:6-21)
 - Undue experimentation would be required to achieve the claimed invention.
- Instead, Petitioner relies on impermissible hindsight. (EX1031 at 6 (“The 334 patent does not say anything about interactions between the enteric coating and endoxifen.”); *id.* at 10 (“[T]he 334 patent explicitly states that HPMC . . . is compatible with (Z)-endoxifen.”))



Hindsight

“[W]orking backwards from that compound, with the benefit of hindsight, once one is aware of it does not render it obvious.”

Amerigen Pharm. Ltd. v. UCB Pharma GmbH,
913 F.3d 1076, 1089 (Fed. Cir. 2019)

Paper 7 at 48-51; Paper 14 at 61-64; Paper 21 at 18-20.

Ground 4 Fails

Claim 3 Not Obvious Over Ahmad in View of Benameur

- Petitioner Fails to Identify Any Reasonable Expectation of Success
 - Petitioner ignores inherent instability of (Z)-endoxifen.
 - Benameur teaches uncoated enteric capsules, but Ahmad is silent as to whether uncoated enteric capsules are desired.
- No motivation to combine Ahmad with Benameur
 - Petitioner's generic argument is insufficient. *ActiveVideo Networks, Inc. v. Verizon Commc'ns, Inc.*, 694 F.3d 1312, 1328 (Fed. Cir. 2012)
- Petitioner again relies on impermissible hindsight. (EX1031 at 15 (“[T]he 334 patent does not disclose anything regarding any of the potential issues with enteric capsules [identified by] Dr. Davies . . . [it] simply states that the endoxifen could be loaded neat into enteric capsules.”))



Hindsight

“[G]eneric analysis that “bears no relation to any specific combination of prior art elements” is insufficient to supply a motivation to combine. *ActiveVideo Networks, Inc. v. Verizon Commc'ns, Inc.*, 694 F.3d 1312, 1328 (Fed. Cir. 2012)

Paper 7 at 51-52; Paper 14 at 64-66; Paper 21 at 20-21.

Ground 5 Fails

Claims 9-13 Not Obvious Over Ahmad in View of HPE or Stegemann

- Petitioner fails to identify any reasonable expectation of success.
 - Petitioner ignores inherent instability of (Z)-endoxifen.
 - A POSA would not simply choose from a list of excipients because they are well known. Dr. McConville agreed a POSA would consider potential interactions between (Z)-endoxifen and excipients. (EX2021 at 120:16-20)
- No Motivation to Combine Ahmad with Either HPE or Stegemann
 - Dr. McConville agreed that “neither [HPE nor Stegemann] describe[] oral formulations comprising endoxifen.” (EX2021 at 119:4-17; 123:16-124:4)
 - Petitioner again relies on impermissible hindsight. (EX1031 at 17 (“[T]he 334 patent does not disclose any challenges associated with incorporating these common excipients into an endoxifen formulation.”))



Paper 7 at 52-53; Paper 14 at 66-68; Paper 21 at 21-22.

Ground 6 Fails

Claims 14, 18, 19 Not Obvious Over Ahmad in View of Either Ahmad 2010 or Ahmad 2012

- Ahmad does not describe the E/Z ratio of the endoxifen synthesized. (EX2028 at 27:2-7). Dr. McConville agrees that neither Ahmad 2010 nor Ahmad 2012 specifies the isomeric purity of the endoxifen citrate compound. (EX2021 at 126:4-17; 138:14-22; 141:5-15; EX2028 at 27:2-7)

Claim 14 - Dosing

- Petitioner identifies no teaching that a dosing range for an unspecified (E)/(Z) mixture is applicable to a 90% pure (Z)-endoxifen.
- Petitioner's generic argument is insufficient.

Claims 18, 19 - Pharmacokinetics

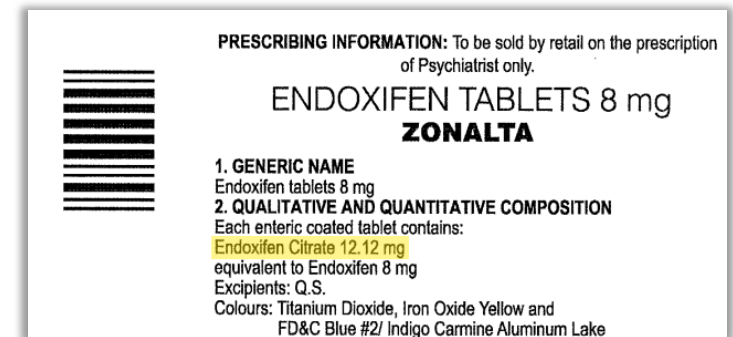
- Different impurity profiles of Ahmad's synthetic process could impact pharmacokinetic values. (EX2028 at 101:21-102:3; 120:16-121:3)
- Dr. McConville assumed (but did not test) whether different ratios of (E)/(Z)-endoxifen have different pharmacokinetic values.
- Petitioner's inherency argument fails.

Paper 7 at 53-57; Paper 14 at 69-74; Paper 21 at 22-25.

Secondary Considerations

Secondary Considerations of Non-Obviousness Have Nexus to '334 Claims

- The claimed formulation exhibits unexpected stability (EX1001 at Example 11)
- The claimed formulation exhibits unexpected superior bioavailability (EX1001 at Example 15)
- There is a long-felt need for new compositions to prevent and treat hormone-dependent breast and reproductive tract disorders, including cancer.
- Prior art, including Petitioner's Zonalta endoxifen tablet, teaches away from formulating an endoxifen compound as a free base.
- All other drugs in the SERM class are formulated as salts or solvates, in contrast to the '334 patent.



EX1014

Paper 7 at 57-59; Paper 14 at 75-77; Paper 21 at 25-27.