

Petitioner's Demonstratives

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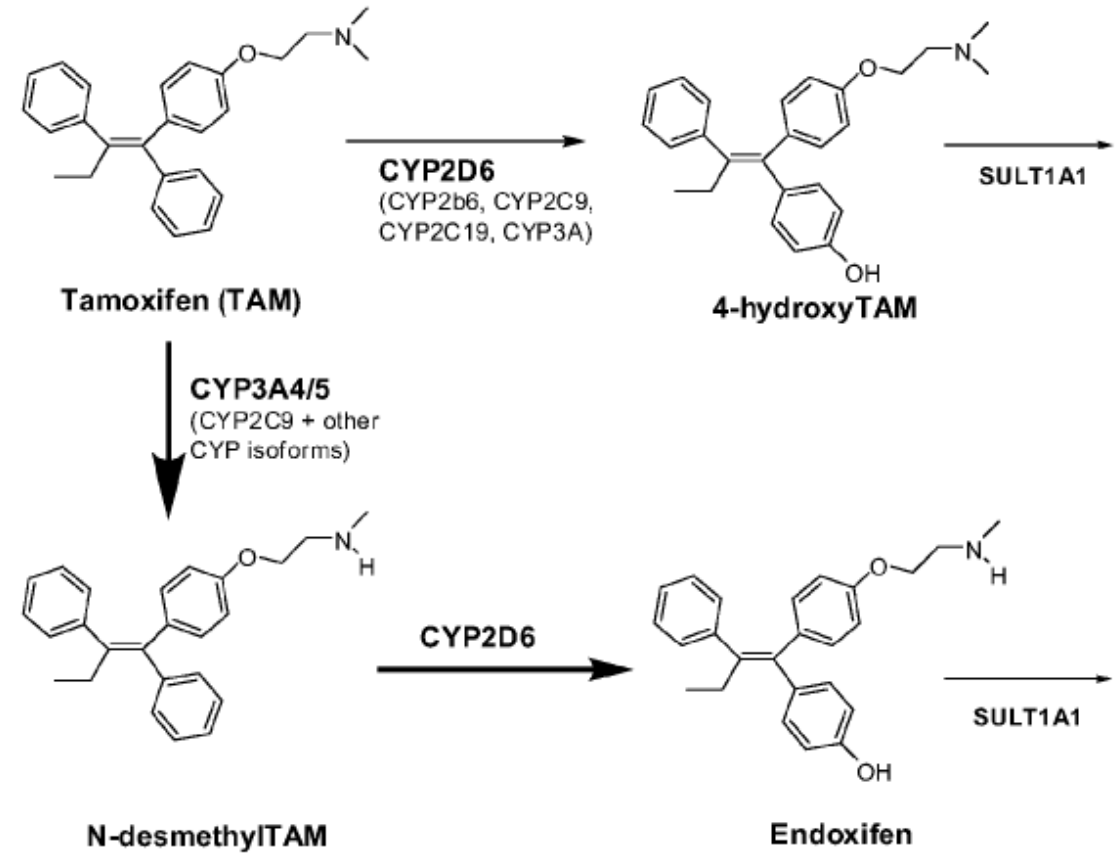
- 1. Background**
- 2. 90% (Z)-endoxifen enabled in prior art (Grounds 1 and 2)**
- 3. Routine formulation modifications (Grounds 3-5)**
- 4. Inherent and known target pharmacokinetic limitations (Ground 6)**
- 5. Objective indicia**

Background

Endoxifen a metabolite of Tamoxifen



Ahmad



Ex. 1003 at Fig. 3

Endoxifen known to be promising for breast cancer

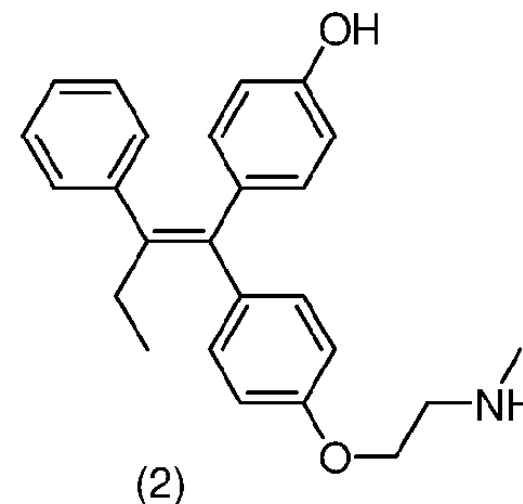
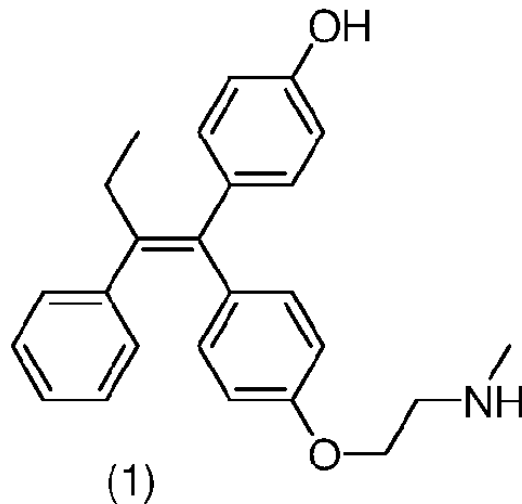
Ahmad 2010

In summary, we 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. Consequently, its activity is not likely to be affected by either CYP2D6 genetic polymorphisms or drug–drug interactions that inhibit CYP2D6 activity. This is a first-in-human study to evaluate the safety, bioavailability, and PK of endoxifen.

Ex. 1006 at 3

(Z)- Isomer known to be more active

Liu



[0004] Endoxifen exists as two forms, E and Z, with the Z form more active at the estrogen receptor. Endoxifen is frequently synthesized as a mixture of E and Z, with a

Ex. 1004 at Abstract, [0004]

Methods of making highly pure (Z)-endoxifen known

Liu

precipitated was collected by filtration and washed with ice-cooled acetone. The solid was dried in vacuo at 35 °C to a constant weight to give 1698 g (34%) of (Z)-endoxifen, with an isomeric purity of 99% (HPLC analysis). ¹H NMR (300 MHz, DMSO-d₆) 0.85 (3H, t, CH₃), 2.28 (3H, s, CH₃-N), 2.43 (2H, q, C=C-CH₂), 2.73 (2H, t, CH₂-N), 3.86 (2H, t, CH₂-O), 6.58 (2H, d, Ar), 6.69-6.77 (4H, m, Ar), 6.98 (2H, d, Ar), 7.10-7.18 (5H, m, Ar), 9.45 (1H, s, Ar-O-H); ¹³C NMR (100 MHz, DMSO-d₆) 13.3, 28.5, 36.1, 50.3, 67.0, 113.3, 115.0, 125.9, 127.8, 129.3, 130.0, 131.3, 133.9, 135.5, 137.9, 139.9, 142.2, 156.1, 156.5; MS (ES-MS) 374.1 (MH⁺), 396.6 (M-Na⁺).

Ex. 1004 at [0076]

Enteric formulations known

Ahmad

When desired, composition containing endoxifen or endoxifen-lipid complex can be encapsulated in enteric-coated capsules to protect it from acids in the stomach. The term “enteric” refers to the small intestine, and enteric coatings prevent release of medication before it reaches the small intestine. Most enteric coatings work by presenting a surface that is stable at acidic pH but breaks down rapidly at higher pH.

Ex. 1003 at 18:19-26

Enteric formulations known

Ahmad 2010

METHODS

Endoxifen synthesis. Synthesis of endoxifen citrate was carried out as described previously in multiple steps starting from 4-bromophenol.¹⁸ Endoxifen citrate was prepared as an enteric-coated tablet for oral administration to human subjects. Enteric-coated tablets (0.5, 1.0, 2.0, or 4 mg (two tablets of 2 mg)) of endoxifen citrate were manufactured in accordance with current good manufacturing practices.

Ex. 1006 at 3

The 334 Patent

U.S. Patent No. 11,572,334



(12) **United States Patent**
Quay et al.

(10) **Patent No.:** US 11,572,334 B2
(45) **Date of Patent:** Feb. 7, 2023

(54) METHODS FOR MAKING AND USING
ENDOXIFEN

(71) Applicant: **Atossa Therapeutics, Inc.**, Seattle, WA (US)

(72) Inventors: **Steven C. Quay**, Seattle, WA (US); **Yao-Lin Sun**, Tainan (TW); **Lung-Hu Wang**, Kaohsiung (TW); **Chang-Jung Wu**, Kaohsiung (TW); **Chuan-Der Huang**, Tainan (TW)

(73) Assignee: **ATOSSA THERAPEUTICS, INC.**,
Seattle, WA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: 17/580,428

(22) Filed: Jan. 20, 2022

(65) **Prior Publication Data**

US 2022/0242816 A1 Aug. 4, 2022

Related U.S. Application Data

(63) Continuation of application No. 16/641,985, filed as application No. PCT/US2018/050272 on Sep. 10, 2018, now Pat. No. 11,261,151.

(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.

(51)	Int. Cl.	
	A61K 31/135	(2006.01)
	C07C 217/18	(2006.01)
	C07C 213/10	(2006.01)
	A61K 9/00	(2006.01)
	A61K 45/06	(2006.01)

(52) U.S. Cl.
CPC C07C 217/18 (2013.01); C07C 218/10
(2013.01); A61K 9/0053 (2013.01); A61K
45/06 (2013.01); C07B 2209/13 (2013.01)

(58) **Field of Classification Search**
CPC A61K 31/135
USPC 514/648
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

FOREIGN PATENT DOCUMENTS		
CN	101891635 A	11/2010
CN	102448467 A	5/2012
CN	104203961 A	12/2014
CN	104352504 A	2/2015

(Continued)

OTHER PUBLICATIONS

Ahamad A., et al., "Endoxifen, A New Cornerstone 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)

(74) *Attorney, Agent, or Firm* — DLA Piper LLP

(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.

22 Claims, 13 Drawing Sheets

Accord Exhibit 1001
Page 1 of 67
BCD2023.00042

Related U.S. Application Data

(63) Continuation of application No. 16/641,985, filed as application No. PCT/US2018/050272 on Sep. 10, 2018, now Pat. No. 11,261,151.

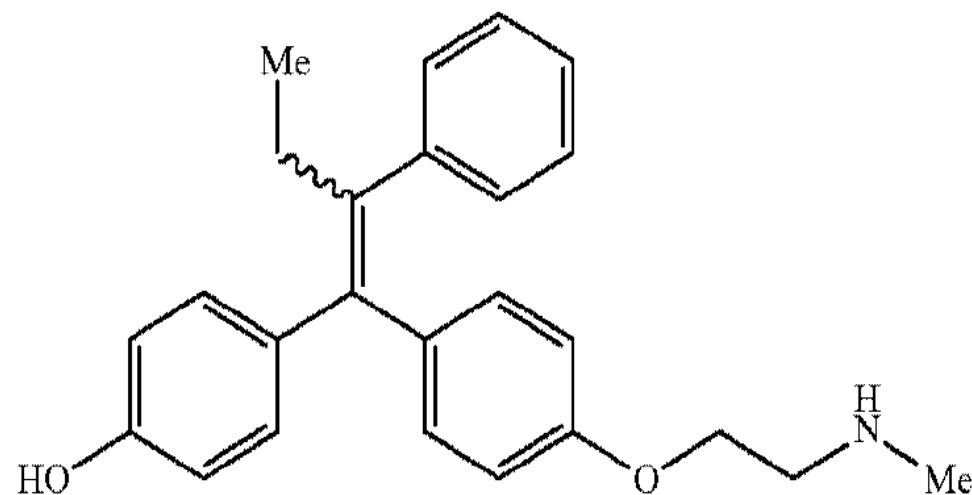
(60) Provisional application No. 62/693,885, filed on Jul. 3, 2018, provisional application No. 62/624,787, filed on Jan. 31, 2018, provisional application No. 62/556,884, filed on Sep. 11, 2017, provisional application No. 62/556,799, filed on Sep. 11, 2017.

Ex. 1001 at Cover

Claims focus on oral formulations – not chemical synthesis

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. **Ex. 1001 at Claim 1**

Prosecution History

Parent claims allowed due to polymorph limitation

Allowable Subject Matter

Claims 1, 5-9, 32-35, 38-43, 46, 47, 49, 52 and 158 are allowed.

As was stated in the 9/7/2021 Office Action, the key to instant claims is the polymorph of Form I. The closest prior art appears to be WO 2014/141292 A2, cited in the IDS, which teaches an endoxifen citrate polymorph (abstract; page 4, 5th full paragraph). (Instant diagramed Formula (III) is (E)/(Z)-endoxifen.) The reference does not teach, show, suggest or make obvious the instant Form I polymorph.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled “Comments on Statement of Reasons for Allowance.”

Ex. 2006 at 16

334 Patent faced no rejections

Application/Control Number: 17/580,428
Art Unit: 1629

Page 2

The present application
first inventor to file provis

Applicant's Preliminary
Statements filed April 21, 2

2022 have been received at

Accordingly, the ap
as reflected by the attached
been considered by the Exa

The reference cited
the patent issued from the p

The following is an

Claim 158 is repres

"An oral formulation

capsule, wherein the endox
omitted] wherein at least 90

The Examiner has c

for the claimed subject mat

subject matter or would for

been obvious. This holds t

application U.S. Patent No.

The Examiner has conducted a thorough search of the appropriate electronic data bases for the claimed subject matter and did not discover any reference which anticipates that claimed subject matter or would form a basis for concluding that the claimed subject matter would have been obvious. This holds true for any double patenting issue involving Applicant's parent application U.S. Patent No. 11,261,151 which contains claims requiring a specific, non-obvious crystalline form of endoxifen. Also, claims 158-179 are presented in an enabled, definite manner.

Ex. 1002 at 388-89

Grounds 1 and 2 – Claims 1, 2, 4, 15, 20-22

No dispute Ahmad teaches every element

POR

VI. GROUND 1 FAILS: AHMAD DOES NOT ANTICIPATE CLAIMS
1, 2, 4, 15, AND 20-22 27

A. Petitioner Cannot Demonstrate That Ahmad Is Enabled 28

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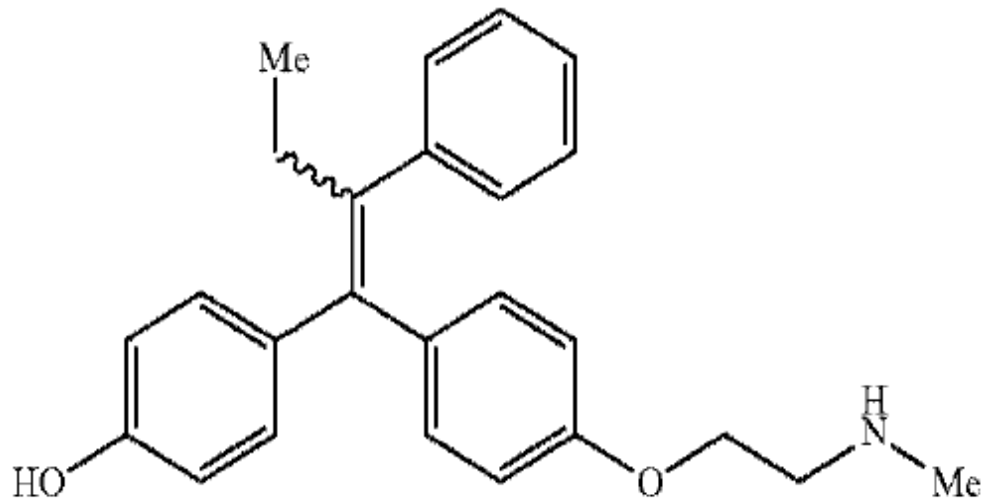
B. Because Ahmad Is Not Enabled, Ahmad Cannot Anticipate
Claims 1, 2, 4, 15 And 20-22 49

POR at TOC

Ahmad teaches enteric coated capsule endoxifen formulations

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.

Ahmad

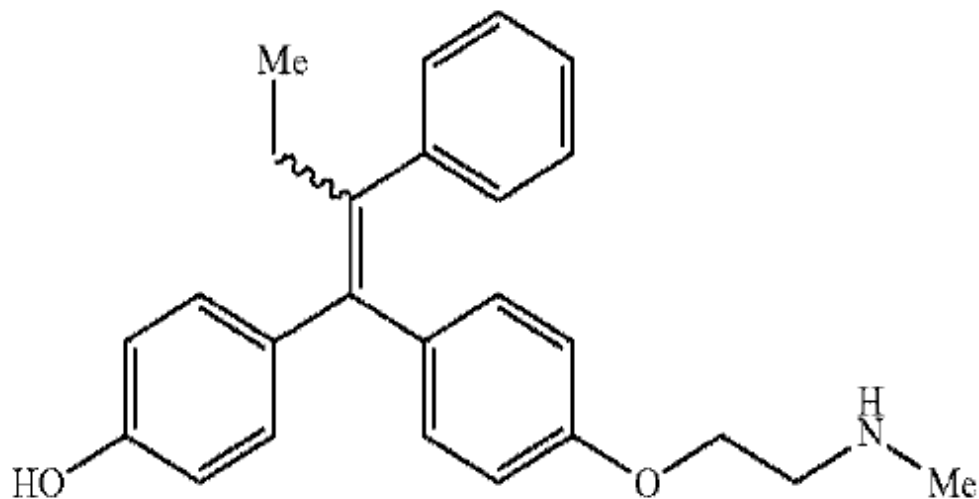
When desired, composition containing endoxifen or endoxifen-lipid complex can be encapsulated in enteric-coated capsules to protect it from acids in the stomach. The term “enteric” refers to the small intestine, and enteric coatings prevent release of medication before it reaches the small intestine. Most enteric coatings work by presenting a surface that is stable at acidic pH but breaks down rapidly at higher pH.

Ex. 1003 at 18:19-26

Ahmad teaches 90% pure (Z)-endoxifen

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.

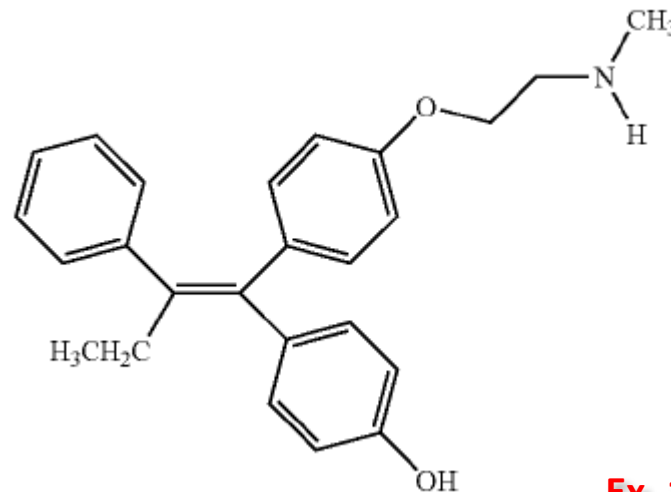
Ahmad

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.

Ex. 1003 at 12:14-17

endoxifen and administering the composition. In some embodiments, the endoxifen is a free base, or is in the form of

Ex. 1003 at 2:24-25



Ex. 1003 at 10:30-52

Ahmad teaches enteric coated capsule that are delayed release

2. The oral formulation of claim 1, wherein the oral formulation is a delayed-release formulation.

4. The oral formulation of claim 1, wherein the enteric capsule further comprises an enteric coating.

Ahmad

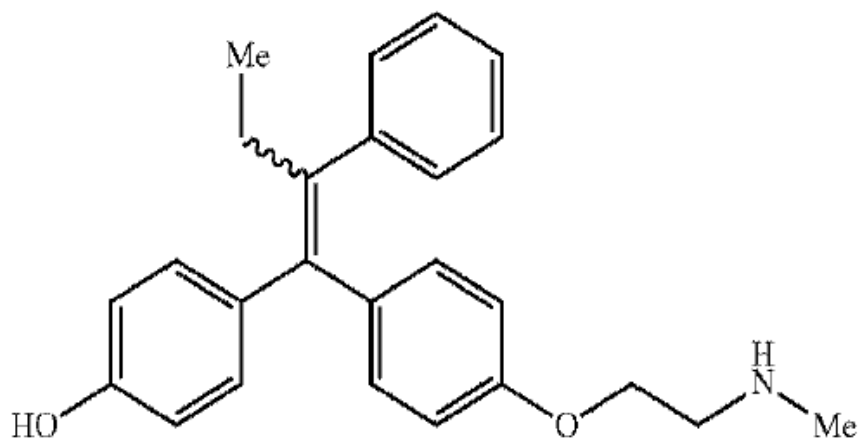
When desired, composition containing endoxifen or endoxifen-lipid complex can be encapsulated in enteric-coated capsules to protect it from acids in the stomach. The term “enteric” refers to the small intestine, and enteric coatings prevent release of medication before it reaches the small intestine. Most enteric coatings work by presenting a surface that is stable at acidic pH but breaks down rapidly at higher pH.

Ex. 1003 at 18:19-26

Ahmad teaches administering (Z) endoxifen

15. A method of delivering (Z)-endoxifen to a subject, the method comprising administering to the subject 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.

Ahmad

The present invention also provides methods of inhibiting hormone-dependent breast carcinoma in a mammal comprising administering any of the above compositions to the mammal.

Ex. 1003 at 5:33-36

Ahmad teaches treating hormone-dependent breast disorders

20. The method of claim 15, further comprising treating a hormone-dependent breast disorder or a hormone-dependent reproductive tract disorder in the subject.

21. The method of claim 20, wherein the hormone-dependent breast disorder or the hormone-dependent reproductive tract disorder is a benign breast disorder, hyperplasia, atypia, atypical ductal hyperplasia, atypical lobular hyperplasia, increased breast density, gynecomastia, ductal carcinoma in situ, lobular carcinoma in situ, breast cancer, precocious puberty, McCune-Albright Syndrome, endometrial cancer, ovarian cancer, uterine cancer, cervical cancer, vaginal cancer, or vulvar cancer.

Ahmad

The present invention also provides methods of inhibiting hormone-dependent breast carcinoma in a mammal comprising administering any of the above compositions to the mammal.

Ex. 1003 at 5:33-36

The compositions of the present invention can be employed to treat breast cancer and breast related diseases. For example, the compositions of the present invention may be administered to a patient diagnosed with benign breast disease. As used herein, the term “benign breast disease”

Ex. 1003 at 18:47-51

Ahmad teaches endoxifen bypasses tamoxifen metabolic issues

22. The method of claim 20, wherein the hormone-dependent breast disorder or the hormone-dependent reproductive tract disorder is tamoxifen-refractory or tamoxifen resistant.

Ahmad

affected by endoxifen are estrogen-regulated genes (8-9). Use of endoxifen e.g., in place of Tamoxifen, avoids several metabolic steps that rely on CYP2D6.

Ex. 1003 at 2:2-5

Ahmad teaches obtaining (Z)-endoxifen by two methods

Ahmad

In some embodiments of the present invention, a mixture of E- and Z-isomers of endoxifen can be separated to provide the purified preparations of E- and Z-isomer of 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).

Ex. 1003 at 11:17-23

Both methods of achieving 90% (Z) achieved in prior art

Liu (Crystallization)

(57) Abstract: Disclosed is a process for preparing (Z)-endoxifen, comprising (i) recrystallizing an input crystalline solid comprising a mixture of (Z)-endoxifen (1) and (E)-endoxifen (2) from a first solvent to provide a first crystalline solid and a first mother liquor, dried in vacuo at 35 °C to a constant weight to give 1698 g (34%) of (Z)-endoxifen, with an isomeric purity of 99% (HPLC analysis). ¹H NMR (300 MHz, DMSO-d₆) 0.85 (3H, t, CH₃),

Ex. 1004 at Abstract, [0076]

Fauq (Chromatography)

romethane to give a clean 1:1 mixture of Z/E isomers that was re-subjected to HPLC separation. In this way, most of the undesired (E)-isomer could be readily converted to the desired (Z)-isomer providing quick access to over 200 mg quantities of pure endoxifen (Z-isomer), a potent antiestrogenic metabolite of tamoxifen traditionally used in breast cancer treatment.

Ex. 1022 at Abstract

Law: Additional prior art may demonstrate enablement

Federal Circuit:

“The additional references utilized in this case (viz., Lincoln and Wagner) are not relied upon for suggestion or motivation to combine teachings to meet the claim limitations, as in rejections under 35 U.S.C. § 103.... Such reliance would be pointless, because Nomura alone discloses every element claimed. The purpose of citing Lincoln and Wagner is, instead, to show that the claimed subject matter, as disclosed in Nomura, was in the public's possession. Id. Therefore, the anticipation rejection based on Nomura, Lincoln, and Wagner is proper”

-In re Donohue, 766 F.2d 531, 534 (Fed. Cir. 1985)

Law: Later prior art may demonstrate enablement

Federal Circuit:

“Enablement of an anticipatory reference may be demonstrated by a later reference...We therefore may look to any references that establish that Kris's suggestion of pretreatment **would have been enabling to one of skill in the art more than one year prior to Bristol's earliest filing date of August 3, 1992”**

-Bristol-Myers Squibb Co. v. Ben Venue Lab'ys, Inc., 246 F.3d 1368, 1379 (Fed. Cir. 2001)

Law: Petitioner only required to address enablement on reply

Federal Circuit:

“the Board shifted the burden to Apple to provide evidence before institution (i.e., **in its petition**) that Konno **was enabling** as part of its burden to prove anticipation. **This was error**.... As a result of its error, **the Board refused to consider evidence that Apple introduced with its reply in support of enablement of Konno**—which Apple reasonably introduced after Corephotonics raised the issue of nonenablement... **This too was error** because the Board in effect shifted the burden to Apple to prove enablement before any assertion of nonenablement was raised.”

-Apple Inc. v. Corephotonics, Ltd., 861 F. App'x 443, 449-50 (Fed. Cir. 2021)

Amgen addresses 112 – not prior art

POR at 48

method in the art *after* Ahmad's effective filing date. Post-effective filing date evidence offered to illuminate the post-effective filing date state of the art is improper. *Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1374 (Fed. Cir. 2017). For this additional reason, Liu cannot be used to supply a missing teaching from Ahmad.

PO Sur-Reply at 12

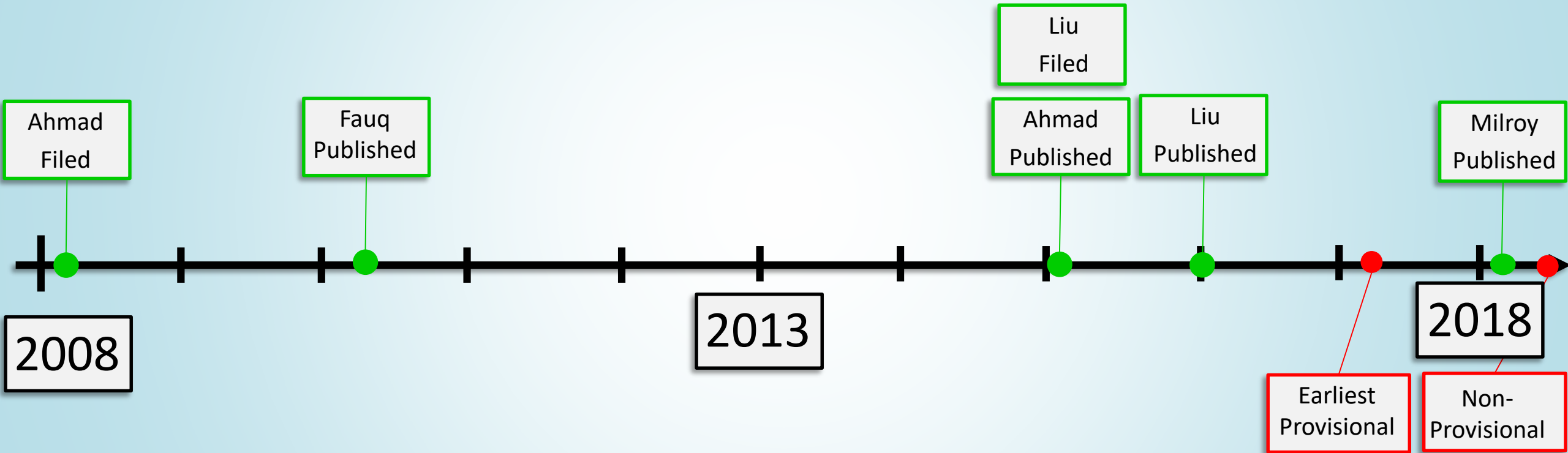
Liu also postdates Ahmad and, at best, is evidence of a dissimilar synthetic method in the art *after* Ahmad's effective filing date. Post-effective filing date evidence offered to illuminate the post-effective filing date state of the art is improper. *Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1374 (Fed. Cir. 2017). Neither

ALZA also addresses 112

PO Sur-Reply at 10-11

Relying on Liu or Fauq as background knowledge to fill in the significant gaps of Ahmad to achieve the claimed invention is not enabling. *ALZA Corp. v. Andrx Pharms., LLC*, 603 F.3d 935, 941 (Fed. Cir. 2010) (a specification that requires a skilled artisan to “engage in an iterative, trial-and-error process to practice the claimed invention” does not provide an enabling disclosure). An enabling disclosure “cannot simply rely on the knowledge of a [POSA] to serve as a substitute for the missing information in the specification.” (*Id.* at 940-941 (internal citations omitted).)

Timeline



Dr. Bihovsky: many ways to achieve 90% (Z)-endoxifen



Dr. Ron Bihovsky

Dr. Bihovsky

Ex. 1022. In sum, the prior art, such as Liu and Fauq, demonstrate that achieving greater than 90% (Z)-Endoxifen as taught by Ahmad would have been well within the skill of a POSA. More specifically, it would have been routine for a POSA to purify the Endoxifen product synthesized according to Ahmad according to the procedures taught by Liu (crystallization) or Fauq (chromatography) to achieve greater than 90% (Z)-Endoxifen. Other approaches were also known to a POSA and also would have been routine. For example, it similarly would have been routine for a POSA to follow Liu's or Fauq's synthesis and purification process in its entirety to achieve greater than 90% (Z)-Endoxifen. My own experiments prove that this is true (Section VII.C.).

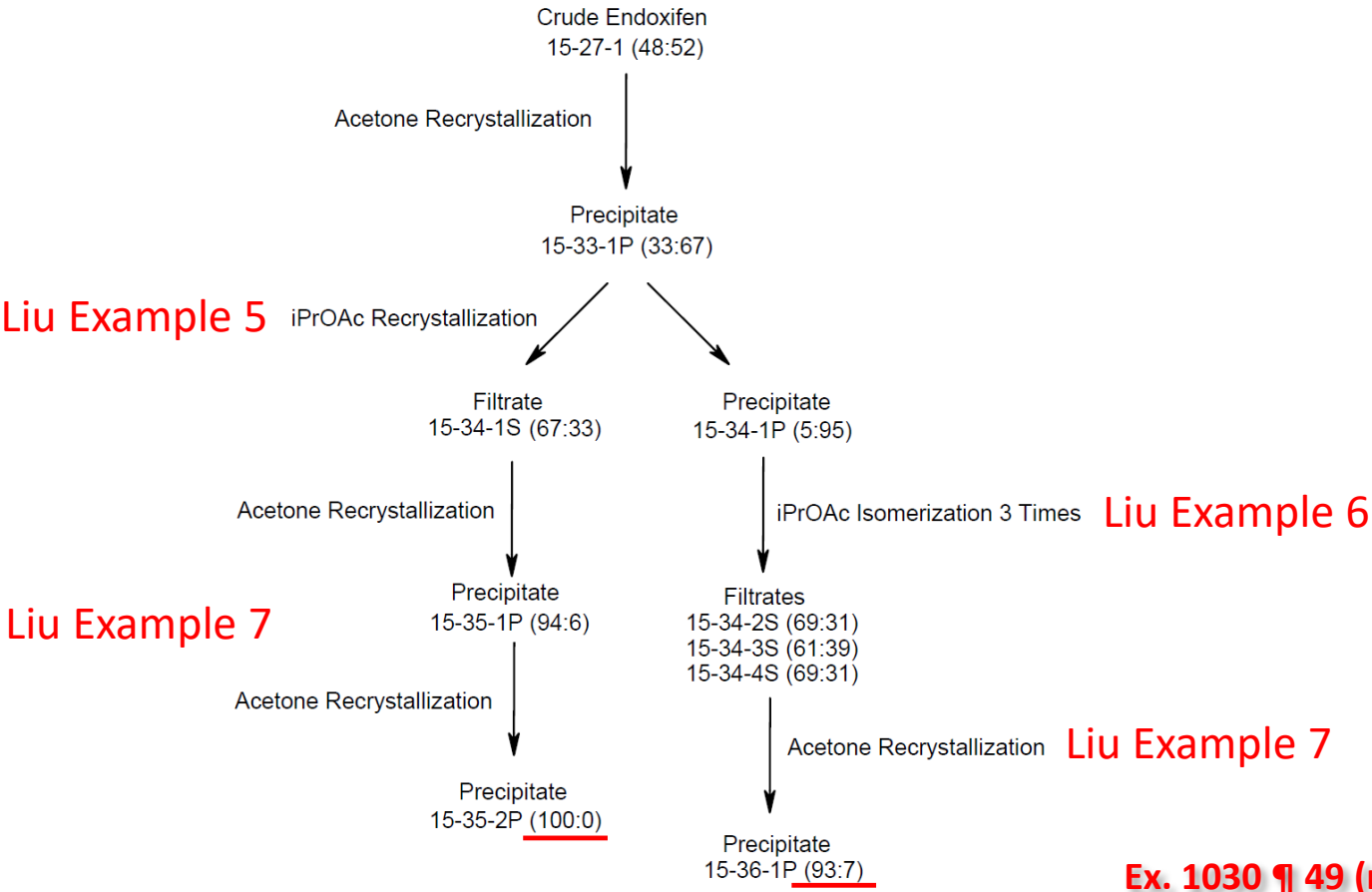
Ex. 1030 ¶ 35

Dr. Bihovsky synthesized 2 90%+ pure samples following Liu



Dr. Ron Bihovsky

Dr. Bihovsky



Dr. Bihovsky: Milroy further shows enablement/RES



Dr. Ron Bihovsky

Dr. Bihovsky

separation of E- and Z- isomers.” *Id.* at 11:24-42. In addition, Milroy, L.-G., et al., *A multi-gram-scale stereoselective synthesis of Z-endoxifen*, 28 BIOORGANIC & MEDICINAL CHEMISTRY LETTERS 1352-1356 (2018) (“Milroy”) (Ex. 1019) have reported a stereoselective multi-gram-scale synthesis of (Z)-Endoxifen with an isomeric purity of >99%. Ex. 1019 at 1354 (“[A]ny trace amounts of the E-isomer were removed by trituration of the crude material.”); *see also* Milroy Supplementary Material (Ex. 1025) at 16 (describing method for synthesizing pure (Z)-Endoxifen and associated NMR data); 7 (Figure S4).

Ex. 1030 ¶ 25

Patent Owner did not antedate Milroy

Sur-Reply

not be “a sufficient dose for—for even one patient”).) Milroy (EX1019), which also postdates the '334 patent, teaches producing (Z)-endoxifen that specifically avoids the use of RP-HPLC, citing a need for a scalable synthesis. (*Id.* at 1353.) A POSA
Sur-Reply at 12

Patent Owner did not antedate Milroy



A multi-gram-scale stereoselective synthesis of Z-endoxifen

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^d Faculty of Science, Division of Pharmacokinetics and Clinical Pharmacology, Department of Pharmaceutical Sciences, Utrecht University, Universiteitsweg 98, 3584 CG Utrecht, The Netherlands



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Ex. 1019

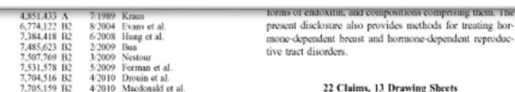
Accord Exhibit 1019
Page 1 of 5
PGR2023-00043



Related U.S. Application Data

(63) Continuation of application No. 16/641,985, filed as application No. PCT/US2018/050272 on Sep. 10, 2018, now Pat. No. 11,261,151.

(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.



Ex. 1001 at cover

Accord Exhibit 1001
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אחות וריטיות

Ahmad anticipates

Dr. McConville

67. While no specific example in Ahmad describes an enteric coated capsule with 90% (Z)-endoxifen, a person of skill reading Ahmad would understand it to be taught as a combination of beneficial elements that Ahmad teaches, and would envisage the product recited in claim 1.

Ex. 1020 ¶ 67



Ahmad renders claims obvious

Dr. McConville



71. A POSA would have had a reasonable expectation of success in arriving at the claimed invention, as both forming (Z)-endoxifen and enteric capsules were well known in the art as I have described above. This would have been very routine in the art to simply take endoxifen made by the processes discussed above and enclose them in a capsule and use enteric coating to ensure that the drug was released in the intestine rather than the stomach.

Ex. 1020 ¶ 71

Ground 3 – Claims 5-8, 16 and 17

No dispute Ahmad and Cole teach every imitation

5. The oral formulation of claim 1, formulated such that the oral formulation is resistant to dissolution in an acidic environment for at least 2 hours, as measured in a dissolution test performed according to a method of USP 711.

6. The oral formulation of claim 1, formulated such that the oral formulation releases no more than 10% of the (Z)-endoxifen over 2 hours in gastric fluid, as measured in a dissolution test performed according to a method of USP 711.

16. The method of claim 15, further comprising releasing no more than 10% of the (Z)-endoxifen in a stomach of the subject within 2 hours following administration.

Ahmad

When desired, composition containing endoxifen or endoxifen-lipid complex can be encapsulated in enteric-coated capsules to protect it from acids in the stomach. The term “enteric” refers to the small intestine, and enteric coatings prevent release of medication before it reaches the small intestine. Most enteric coatings work by presenting a surface that is stable at acidic pH but breaks down rapidly at higher pH.

Ex. 1003 at 18:19-26

Cole

No release of paracetamol was detected at pH 1.2 over 2 h or at pH 6.8 over the subsequent 1-h period for the capsules coated with Eudragit® FS 30 D. At

Ex. 1008 at 89

No dispute Ahmad and Cole teach every imitation

7. The oral formulation of claim 1, formulated such that the oral formulation releases at least 50% of the (Z)-endoxifen within 8 hours in intestinal fluid, as measured in a dissolution test performed according to a method of USP 711.

17. The method of claim 15, further comprising releasing at least 50% of the (Z)-endoxifen in a small intestine of the subject within 8 hours following administration.

Cole

6 and 8 mg cm⁻² Eudragit® L 30 D-55. At pH 6.8 release of paracetamol was rapid, with very little

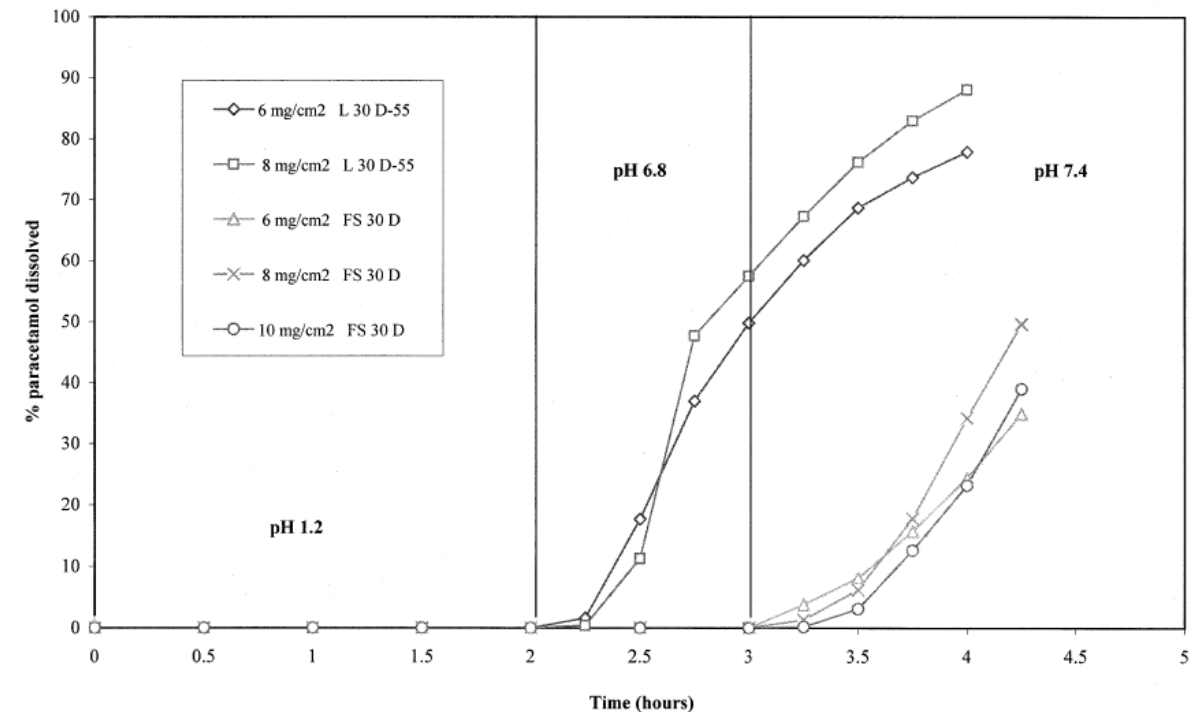


Fig. 4. Dissolution of paracetamol from HPMC capsules coated with Eudragit® L 30 D-55 and Eudragit® FS 30 D. N = 3.

Ex. 1008 at 89, 91

No dispute Ahmad and Cole teach every imitation

8. The oral formulation of claim 1, wherein the enteric capsule comprises hydroxypropylmethyl cellulose.

Ahmad

When desired, composition containing endoxifen or endoxifen-lipid complex can be encapsulated in enteric-coated capsules to protect it from acids in the stomach. The term “enteric” refers to the small intestine, and enteric coatings prevent release of medication before it reaches the small intestine. Most enteric coatings work by presenting a surface that is stable at acidic pH but breaks down rapidly at higher pH.

Ex. 1003 at 18:19-26

Cole

In this paper, we describe the manufacture of two different Eudragit[®] coated HPMC capsules and their in vitro/in vivo performance.

Ex. 1008 at 84

POSA motivated to use Cole with expectation of success



Dr. McConville

92. As I explained above, a POSA would have been motivated to achieve such a formulation, and methods of using such formulations, to ensure that the endoxifen was released in the small intestine, rather than in the stomach where it may be degraded by acid, as taught by Ahmad. As shown in Cole, achieving successful enteric coatings was routine in the art, and thus a POSA would have had more than a reasonable expectation of success in using an enteric coated capsule that could resist drug release in the stomach.

Ex. 1020 ¶ 92

PO's Argument: "potential" interactions

POR

While Petitioner asserts that the active ingredient in Cole is immaterial to the analysis, (*see* Pet. at 41 n.6), Petitioner and Dr. McConville ignore the inherent instability of (Z)-endoxifen and any potential interactions between (Z)-endoxifen, HPMC, and the enteric coating material. Dr. Davies explained that a POSA would not have a reasonable expectation of success in achieving an enteric formulation of at least 90% (Z)-endoxifen based on a combination of Ahmad and Cole because a POSA would understand that enteric coatings and pharmaceutical compositions would interact. (Davies POR Decl. at ¶ 166.)

POR at 63-64

Dr. Davies does not say there *would* be interactions

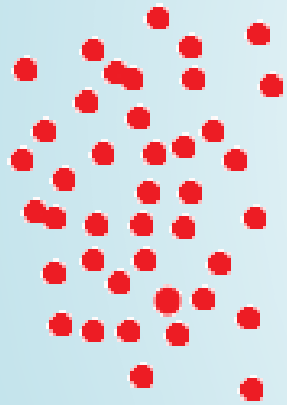
Dr. Davies

intestine rather than the stomach.” (EX1020 (McConville Decl.) at ¶ 71.) I strongly disagree with Dr. McConville’s oversimplification of what a POSA would readily understand to be a highly technical and unpredictable endeavor. As just a few non-limiting examples of the challenges faced, a POSA must consider potential interactions between enteric coatings and pharmaceutical compositions (*e.g.*, as a result of charge or other effects), as well as variations in release profiles for salts versus corresponding free acids or bases of a given oral formulation. (EX2017 (Gupta) at 10.)

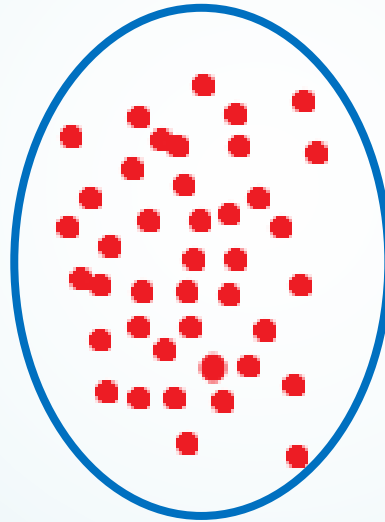
Ex. 2020 ¶ 166

Coating doesn't interact with (Z)-Endoxifen

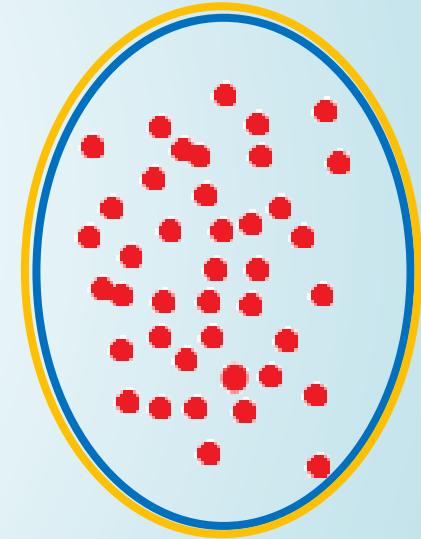
Drug



Capsule



Coating



PO's New Unsupported Sur-Reply Argument: Heat is problem

Sur-Reply

Moreover, Dr. McConville testified that an enteric coating is applied to the outside of a capsule *after* it has been filled with the active ingredient. (EX2028 at 52:8-56:11.) Heat is applied to the filled capsule to dry the coating. A POSA would know that “[t]he high temperatures (>40°C) associated with functional coating application and drying can degrade ... sensitive active [ingredients].” (EX1010 at 2; Pet. at 48.)

Petitioner's argument that one could swap paracetamol for (Z)-endoxifen (Rep. at 13-15) ignores that (Z)-endoxifen is sensitive to heat. (POR at 63-64.) Dr. **Sur-Reply at 19**

HPMC preferred because it is compatible

Majee

CONCLUSION

In spite of gelatin being the most widely used capsule shell material, it has several demerits. The key challenges put forward by gelatin capsules with respect to the phenomenon of cross-linking, variable mechanical strength under altered conditions of processing or storage temperature and relative humidity, preferential compatibility with only certain types of fill materials and excipients have been successfully overcome by hydroxypropylmethyl cellulose, a semi-synthetic alternative exhibiting better physicochemical, pharmaceutical and biopharmaceutical properties as also comparable performance. Studies conducted by various manufacturing companies and research laboratories have reported HPMC capsules to be superior to hard gelatin capsules in terms of mechanical strength and compatibility with a wide range of drugs and excipients possessing reactive functional groups and varying degrees of hygroscopicity. It exhibits better short term stability at

Ex. 1026 at 6

HPMC preferred because it is compatible

Al-Tabakha

The cross-linking of gelatin that affects product dissolution and disintegration has not been observed for HPMC capsules under similar conditions. This makes HPMC capsules compatible with wider range of products except for some oxidizing agent

Ex. 1028 at 439

Honkanen

Another notable difference between HPMC and gelatine capsule shells is that HPMC capsule shells are compatible with most filling materials, since the only incompatibility known for HPMC is the interaction between some oxidizing agents (Harwood, 2000). Gelatine, on the other hand, has chemically reactive

Ex. 1029 at 4

POSA led *toward* HPMC



Dr. McConville

interaction between some oxidizing agents.”) A POSA would have expected HPMC to be compatible with endoxifen due to its general compatibility with most drugs, including moisture sensitive drugs. Rather than being deterred by the “potential” compatibility concerns discussed by Dr. Davies, in reality a POSA would have been motivated to use an HPMC capsule as taught by Cole *because of* its general compatibility.

Ex. 1031 ¶ 13

PO's argument: charge “could” impact stability

POR

would interact. (Davies POR Decl. at ¶ 166.) Dr. McConville did acknowledge that HPMC and enteric coatings can be electrostatically charged. (McConville Tr. at 108:14-109:5.) Yet this electrostatic charge could impact the stability of a (Z)-endoxifen free base or salt. (Davies POR Decl. at ¶ 164.) A POSA would also need

POR at 64

No evidence of “charge” problem



Dr. McConville

carry a positive charge. Ex. 2021 at 108:14-17. I did not testify that HPMC carries a positive charge under all conditions. Under certain conditions, such as during capsule filling, it is possible that HPMC could carry a positive triboelectric (*i.e.*, electrostatic) charge. Whether HPMC would actually carry a positive charge is dependent on what surface it is placed on in the dry state. However, this does not seem relevant, since the issue I refer to is concerned with the capsule filling of powders, as powders can sometimes adhere to the sides of a capsule during the filling process, particularly in a low humidity environment. These concerns are well characterized, and capsule filling with powders is well understood in the field.

Ex. 1031 ¶ 12

No evidence of “charge” problem



Dr. McConville

A POSA would understand that capsule filling with powders does not pose a significant problem in the industry, as capsule filling is used routinely for thousands of medications on a daily basis. . In any case, Dr. Davies does not cite to any evidence, I have not seen any evidence, and I am not aware of any reason, that a positive electrostatic charge on HPMC would have been a concern in relation to the stability of endoxifen.

Ex. 1031 ¶ 12

334 patent provides no evidence of problem or solution



Dr. McConville

10. Further, I note that the 334 patent does not say anything about interactions between the enteric coating and endoxifen. If there were any issues related to interactions between the enteric coating and endoxifen, the 334 patent fails to disclose any solutions to such a problem. The 334 patent simply states that “[t]he capsules are coated with an enteric coating designed to achieve intestinal targeting (upper GI and colon), by the method of Cole et al.” Ex. 1001 at 86:55-58. It would have been routine and predictable for a POSA to incorporate (Z)-endoxifen into an enteric coated capsule formulation as was well known in the art.

Ex. 1031 ¶ 14

334 patent provides no evidence of problem or solution



Dr. McConville

14. Further, the 334 patent does not include any disclosure related to issues with compatibility between HPMC and endoxifen. Thus, to the extent that there were any issues with compatibility associated with endoxifen loaded into an HPMC capsule, the 334 patent does not disclose any solutions. The 334 patent simply states that commercial HPMC capsules can be used. *See, e.g.,* Ex. 1001 at

Ex. 1031 ¶ 14

PO's argument: salt impacts “release profiles”

POR

endoxifen free base or salt. (Davies POR Decl. at ¶ 164.) A POSA would also need to consider the variation in release profiles for salts as compared to corresponding free acids or bases of a given oral dosage form. (*Id.* at ¶ 167.)

Further, in light of the inherent instability of (Z)-endoxifen and the interactions between (Z)-endoxifen and the enteric coating material, a POSA would need to engage in undue experimentation to design a solid oral dosage form with the desired characteristics of a delayed release oral formulation (*e.g.*, enteric formulation). (*Id.* at ¶¶ 166-167.)

POR at 64

Release rate depends on coating, not salt form of drug



Dr. McConville

control certain properties of the drug. Notably, Gupta does not say anything about “variations in release profiles for salts versus corresponding free acids or bases” as Dr. Davies alleges. In truth, the degradation of the enteric coating is what would control the release profile of the drug from the capsule, not whether the endoxifen is a salt or a free base. See, e.g., Ex. 1008 at 84 (“As previously mentioned, site specific delivery into the upper intestine has been achieved for many years by the use of pH-sensitive coatings (Healey, 1989). By applying a thicker coating and/or raising the threshold pH at which dissolution of the coating begins, colon specific delivery using enteric polymers has been achieved (Hardy et al., 1987a).”). Thus, the salt form would not have impacted the release rate of the drug from the capsule (though it could potentially affect its absorption *after* release).

Ex. 1031 ¶ 15

Combining Cole and Ahmad routine



Dr. McConville

16. In sum, a POSA would not have been led away from using HPMC capsules and enteric coatings, and it would have been routine to fill an HPMC capsule with (Z)-endoxifen and coat it, as taught in Cole. In other words, a POSA would have been motivated to use HPMC capsules and would have had far more than a reasonable expectation of success in doing so. This is the type of routine work a formulator does every day.

Ex. 1031 ¶ 16

Ground 4 – Claim 3

No dispute Ahmad and Benameur teach every limitation

3. The oral formulation of claim 1, wherein the enteric capsule is uncoated.

Ahmad

When desired, composition containing endoxifen or endoxifen-lipid complex can be encapsulated in enteric-coated capsules to protect it from acids in the stomach. The term “enteric” refers to the small intestine, and enteric coatings prevent release of medication before it reaches the small intestine. Most enteric coatings work by presenting a surface that is stable at acidic pH but breaks down rapidly at higher pH.

Ex. 1003 at 18:19-26

Benameur

Enteric capsule drug delivery technology (ECDDT) was developed to provide oral delivery with full enteric protection and rapid release in the upper gastrointestinal (GI) tract without the use of coatings. ECDDT's intrinsically enteric

Ex. 1010 at 34

POSA motivated to use uncoated capsules



Dr. McConville

101. A POSA would have been motivated to do so to obtain the benefits Benameur highlights, the ability to produce drug without exposing it to the heating necessary for a coating process or to eliminate the need for process development of an enteric coating step. It would have been a routine design choice to use this alternative technology. And it certainly would have been an obvious to try option as only two options for an enteric capsule existed.

Ex. 1020 ¶ 101

Dr. Davies: Benameur doesn't mention endoxifen

Dr. Davies

173. It is my opinion that a POSA would not have been motivated to combine the teachings of Benameur with the endoxifen compositions of Ahmad to reach the claimed invention of the '334 patent, at least because a POSA would not be able to synthesize a composition comprising at least 90% (Z)-endoxifen for the use in an oral formulation from either reference. Further, a POSA would not know how to achieve the desired characteristics of a delayed release oral formulation (e.g., enteric formulation) without undue experimentation. As Dr. McConville acknowledged in his testimony, Benameur does not teach the use of its enteric capsule with endoxifen. (McConville Dep Tr. at 113:11-116:4.) Tellingly, neither the Petition nor Dr. McConville's declaration shed any light on the lack of motivation to combine, beyond conclusory statements. **Ex. 2020 at ¶ 173**

Benameur applicable to endoxifen



Dr. McConville

19. Benameur teaches that “[t]he enteric properties and rapid release of specialized ECDDT capsule shells have been demonstrated to meet pharmacopeia standards for both in vitro and in vivo performance using esomeprazole magnesium trihydrate (EMT) **as a model compound**.” Ex. 1010 at 34. Thus, a POSA would understand that Benameur used EMT as a model drug, and that the **technology taught by Benameur would be applicable to other drugs, such as endoxifen**. Further, Benameur teaches that “EMT was chosen as a model compound due to both market relevancy of Nexium® and the high gastric sensitivity. EMT is known to rapidly degrade in acidic media.” *Id.* at 35. Therefore, **a POSA would have been motivated to incorporate (Z)-endoxifen, another acid labile drug, into a formulation using the enteric technology taught by Benameur**. Dr. Davies does not cite to any evidence that would demonstrate a lack

Ex. 1031 ¶ 19

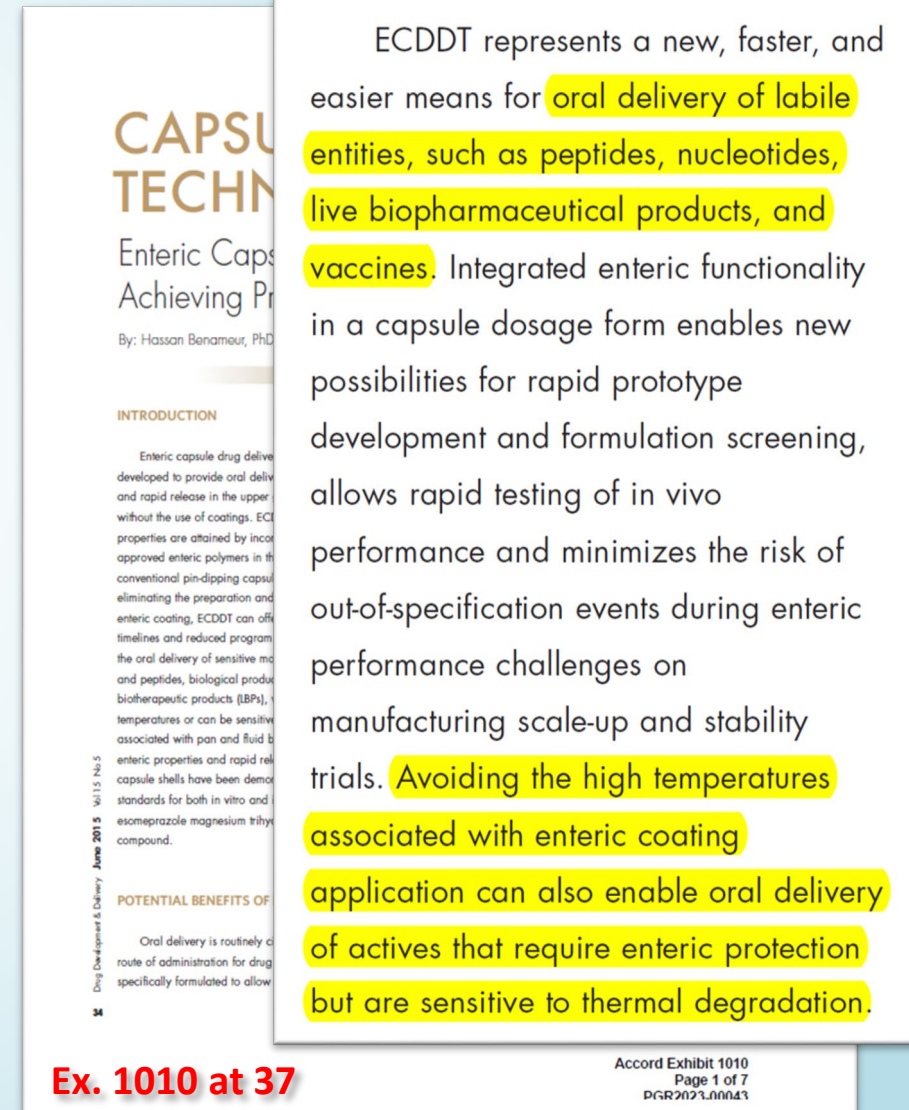
Benameur applicable to endoxifen



Dr. McConville

22. Nothing in Benameur would have indicated to a POSA that its formulation would only be suitable for use with the model compound EMT. To the contrary, Benameur teaches that its formulations are suitable for use in a broad range of active ingredients. For example, Benameur teaches that “ECDDT represents a new, faster, and easier means for oral delivery of labile entities, such as peptides, nucleotides, live biopharmaceutical products, and vaccines.” *Id.* at 37.

Ex. 1031 ¶ 22



Ex. 1010 at 37

POSA would expect success with Benameur

Dr. McConville



102. Benameur's capsules obtained the same results as those discussed above for the enteric coated capsules taught by Cole. Specifically, Benameur teaches "In vivo results (Figure 2) showed that no pellets were released from ECDDT capsules in the stomach and that the capsule quickly opened in the small intestine 30 minutes from gastric emptying to the onset of drug release from the pellet dissolution." Ex. 1010 at 36. Thus, a POSA would have had a reasonable expectation of success in using the capsules described by Benamauer (and sold by Capsugel) in place of an enteric coated capsule as taught by Ahmad.

Ex. 1020 ¶ 102

POSA would expect success with Benameur



Dr. McConville

Thus, to the extent any issues existed with incorporating endoxifen into Benameur's enteric capsules, the 334 patent does not disclose any solutions. I am not aware of any issues that would have needed to be overcome, and a formulation scientist would have understood that Benameur's capsules could be used with Ahmad's (Z)-endoxifen with a very high likelihood of success.

Ex. 1031 ¶ 24

Ground 5 – Claims 9-13

No dispute excipients well known

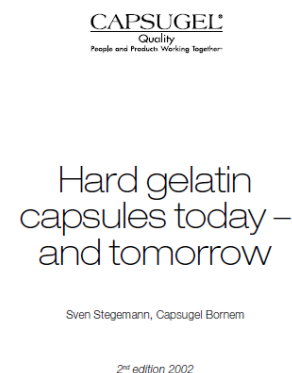
9. The oral formulation of claim 1, wherein the endoxifen composition further **comprises a filler**.

10. The oral formulation of claim 9, wherein the **filler comprises** talc, calcium carbonate, a sugar, a salt, microcrystalline cellulose, methyl cellulose, carboxymethyl cellulose, kaolin, mannitol, silicic acid, sorbitol, starch, pregelatinized starch, or combinations thereof.

11. The oral formulation of claim 1, wherein the endoxifen composition further comprises a **disintegrant**.

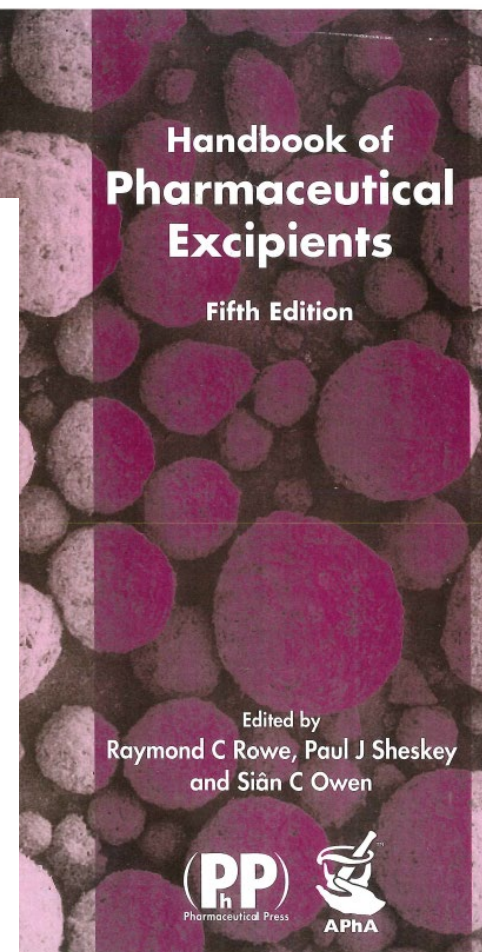
12. The oral formulation of claim 1, wherein the endoxifen composition further comprises a **lubricant**.

13. The oral formulation of claim 12, wherein the **lubricant comprises** calcium stearate, magnesium stearate, zinc stearate, mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil, ethyl oleate, ethyl laureate, agar, or combinations thereof.



Capsugel Library
Ex. 1011

Accord Exhibit 1011
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Exs. 1012, 1032

Accord Exhibit 1012
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POSA would use excipients for standard use

Dr. McConville



107. A POSA would have been motivated to use a filler 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 a POSA would have had a reasonable expectation of success as the use of fillers was routine and common in the industry.

Ex. 1020 ¶ 107

Routine formulation decision

Dr. McConville



108. As discussed above, fillers are a common pharmaceutical excipient. And the specifically recited fillers of claim 10 are well-known and common examples of fillers. *See, e.g.*, Ex. 1011 at 7-8 (teaching use of “[t]alcum,” “microcrystalline cellulose” and “[s]tarch”); Ex. 1012 (HPE) at 900 (“Fillers *see* Diluents (tablet/capsule)”), 897 (listing “Diluents tablet/capsule” including talc, calcium carbonate, sugar spheres, microcrystalline cellulose, kaolin, mannitol, sorbitol, starch, pregelatinized starch, and others). The selection of these fillers would be a routine formulation decision.

Ex. 1020 ¶ 108

Routine formulation decision

Dr. McConville



112. A POSA would have been motivated to use a disintegrant for its normal use, ensure that the active ingredient is made available quickly for dissolution for absorption in the body at the proper location. And a POSA would have had a reasonable expectation of success because the use of disintegrants was well known and routine.

Ex. 1020 ¶ 112

Routine formulation decision

Dr. McConville



116. A POSA would have been motivated to use a lubricant for its normal use, to make processing and manufacturing more efficient. And a POSA would have had a reasonable expectation of success because the use of lubricants was well known and routine.

Ex. 1020 ¶ 116

Routine formulation decision

Dr. McConville



117. As described above, the use of lubricants was common in the pharmaceutical arts. The listed lubricants were well-known. *E.g.* Ex. 1011 at 8; Ex. 1012 at 905 (HPE listing “Lubricants (tablet/capsule)” including calcium stearate, magnesium stearate, zinc stearate, mineral oil, glycerin, polyethylene glycol, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil, and others).

118. The selection of the recited lubricants would have been a routine design choice in making a formulation. Accordingly, the use of these lubricants would have been routine and well known.

Ex. 1020 ¶¶ 117-118

PO's argument: “potential” interactions

Dr. Davies

178. Oral formulations are known to have variable compatibilities (*e.g.*, chemical stabilities and chemical interactions) with pharmaceutical excipients, and those interactions depend on the oral formulation used (*e.g.*, a salt oral formulation or a free base oral formulation). (EX2017 (Gupta) at 9.) Dr. McConville testified, and I agree, that a POSA would consider potential interactions between (Z)-endoxifen and any excipients when formulating drug product. (McConville Dep Tr. at 120:16-20.)

Ex. 2020 ¶ 178

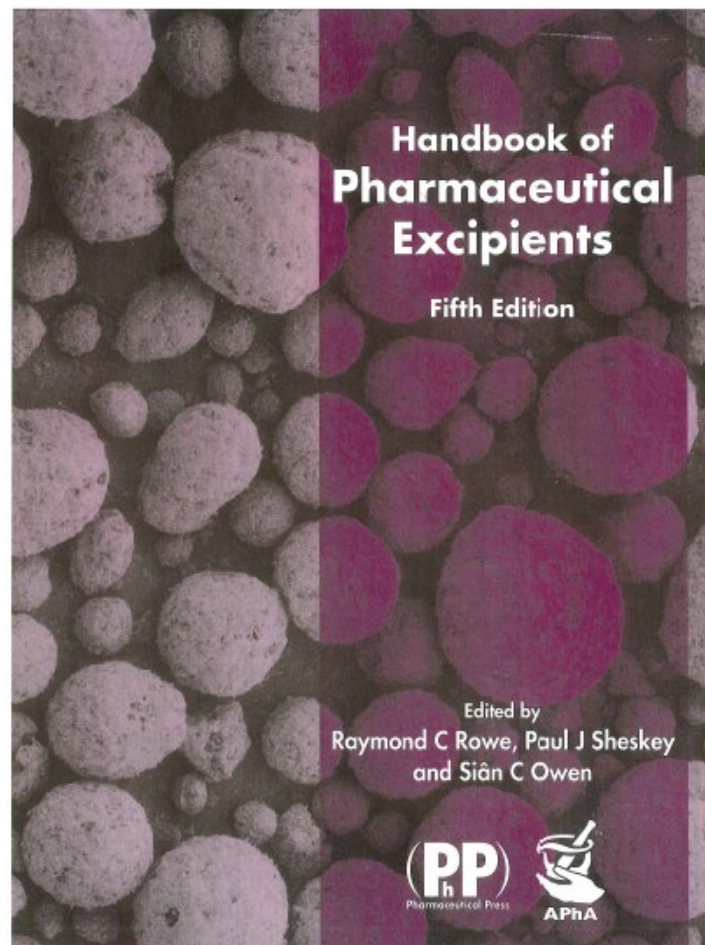
Excipients Predictable

Dr. McConville



30. A POSA would have understood that incompatibilities between an API and certain excipients are possible. This basic fact does not somehow negate the motivation a POSA would have to combine Ahmad with Stegemann and the HPE incorporated the claimed well-known excipients into endoxifen formulations. To the contrary, a POSA would have looked to the HPE as a general guide on pharmaceutical excipients, including assessing the likelihood of issues related to incompatibilities between certain excipients and an API. Thus, a POSA would have been able to predictably select excipients that would not have any undesirable interactions between the excipients and endoxifen. From there, it would have been routine practice for a POSA to run conventional experiments to ensure that there were in fact no interactions between the excipients and endoxifen. **Ex. 1031 ¶ 30**

POSA knows how to look for incompatibilities



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Talc

1 Nonproprietary Names

BP: Purified talc
JP: Talc
PhEur: Talcum
USP: Talc

2 Synonyms

Altaic; ESS3b; hydrous magnesium calcium silicate; hydrous magnesium silicate; Luzemas Pharma; magnesium hydrogen metasilicate; Magal Omanthus; Magal Star; powdered talc; purified French chalk; Purtaic; soapstone; steatite; Superiore.

3 Chemical Name and CAS Registry Number

Talc [14807-96-6]

4 Empirical Formula and Molecular Weight

Talc is a purified, hydrated, magnesium silicate, approximating to the formula $Mg_3(Si_2O_5)_4(OH)_4$. It may contain small, variable amounts of aluminum silicate and iron.

5 Structural Formula

See Section 4.

6 Functional Category

Anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant.

7 Applications in Pharmaceutical Formulation or Technology

Talc was once widely used in oral solid dosage formulations as a lubricant and diluent, see Table 1,¹¹⁻¹³ although today it is less commonly used. However, it is widely used as a dissolution retardant in the development of controlled-release products.¹⁴⁻¹⁶ Talc is also used as a lubricant in tablet formulations,¹⁷ in a novel powder coating for extended-release pellets,¹⁸ and as an adsorbent.¹⁹

In topical preparations, talc is used as a dusting powder, although it should not be used to dust surgical gloves; see Section 14. Talc is a natural material; it may therefore frequently contain microorganisms and should be sterilized when used as a dusting powder; see Section 11.

Talc is additionally used to clarify liquids and is also used in cosmetics and food products, mainly for its lubricant properties.

Table 1 Uses of talc.

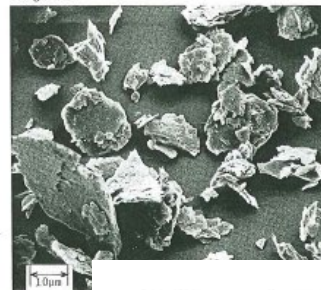
Use	Concentration (%)
Dusting powder	90.0-99.0
Glidant and tablet lubricant	1.0-10.0
Tablet and capsule diluent	5.0-30.0

8 Description

Talc is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

SEM: 1

Excipient: Talc (Purtaic)
Manufacturer: Charles B. Crystal Co., Inc.
Lot No.: 1102A-2
Magnification: 1200x
Voltage: 10 kV



9 Pharmac

See Table II.

10 Typical

Acidity/alkalinity

dispersion.

Hardness (Moh)

Moisture content: talc absorbs insignificant amounts of water at 25°C and relative humidities up to about 90%.

Particle size distribution: varies with the source and grade of material. Two typical grades are: ≥99% through a 74 µm (#200 mesh) or ≥99% through a 44 µm (#325 mesh).

Refractive index: $n_D^{25} = 1.54-1.59$

Solubility: practically insoluble in dilute acids and alkalis, organic solvents, and water.

Specific gravity: 2.7-2.8

Specific surface area: 2.41-2.42 m²/g

768 Talc

Table II: Pharmacopeial specifications for talc.

Test	JP 2001	PhEur 2005	USP 28
Identification	+	+	+
Characters	+	+	+
Acid-soluble substances	≤2.0%	—	≤2.0%
Acidity or alkalinity	—	+	—
Production	—	+	—
pH	—	7.0-9.0	—
Water-soluble substances	—	≤0.2%	≤0.1%
Aluminum	—	≤2.0%	—
Calcium	—	≤0.9%	—
Iron	—	≤0.25%	—
Lead	—	≤10 ppm	—
Magnesium	—	17.0-19.5	—
Loss on ignition	≤5.0%	≤7.0%	≤6.5%
Microbial contamination	—	+	≤500/g
Aerobic bacteria	—	≤10 ³ /g	—
Fungi	—	≤10 ² /g	—
Acid and alkali-soluble substances	≤4.0 mg	—	≤2.0%
Water-soluble iron	+	—	+
Arsenic	—	≤4 ppm	≤3 ppm
Heavy metals	—	—	≤0.004%
Lead	—	—	≤0.001%

11 Stability and Storage Conditions

Talc is a stable material and may be sterilized by heating at 160°C for not less than 1 hour. It may also be sterilized by exposure to ethylene oxide or gamma irradiation.¹⁰

Talc should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Incompatible with quaternary ammonium compounds.

ever, intranasal or intravenous abuse of products containing talc can cause granulomas in body tissues, particularly the lungs.¹¹⁶⁻¹¹⁸ Contamination of wounds or body cavities with talc may also cause granulomas; therefore, it should not be used to dust surgical gloves. Inhalation of talc causes irritation and may cause severe respiratory distress in infants.¹¹⁹ see also Section 15.

Although talc has been extensively investigated for its carcinogenic potential, and it has been suggested that there is an increased risk of ovarian cancer in women using talc, the evidence is inconclusive.^{120,121} However, talc contaminated with asbestos has been proved to be carcinogenic in humans, and asbestos-free grades should therefore be used in pharmaceutical products.¹²²

Also, long-term toxic effects of talc contaminated with large quantities of hexachlorophene caused serious irreversible neurotoxicity in infants accidentally exposed to the substance.¹²³

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Talc is irritant if inhaled and prolonged excessive exposure may cause pneumoconiosis.

In the UK, the occupational exposure limit for talc is 1 mg/m³ of respirable dust long-term [8-hour TWA].¹²⁴ Eye protection, gloves, and a respirator are recommended.

16 Regulatory Status

Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (buccal tablets; oral capsules and tablets; rectal and topical preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

17 Related Substances

12 Incompatibilities

Incompatible with quaternary ammonium compounds.

Following this process, the talc is finely powdered, treated with dilute hydrochloric acid, washed with water, and then dried. The processing variables of agglomerated talc strongly influence its physical characteristics.¹¹³⁻¹¹⁵

14 Safety

Talc is used mainly in tablet and capsule formulations. Talc is not absorbed systemically following oral ingestion and is therefore regarded as an essentially nontoxic material. How-

1. Greenwood S, Brooks S. Pharmacological and cosmetic uses of talc. *Drug Dev Ind Pharm* 1990; 16: 2409-2429.
2. Dawoodbhui S, Suryanarayan ER, Woodruff CW. Optimization of tablet formulations containing talc. *Drug Dev Ind Pharm* 1991; 17: 1343-1371.
3. Wang DP, Yang MC, Wong CY. Formation development of oral controlled release pellets of diclofenac sodium. *Drug Dev Ind Pharm* 1997; 23: 1013-1017.
4. Fashti RA, McPhillips AM, Uzaize SA, Sale AM. Potential use of magnesium stearate and talc as dissolution retardants in the development of controlled release drug delivery systems. *Pharm Ind* 1994; 56: 579-585.

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Ex. 1032 at 1, 7, 8

Excipients Predictable

Dr. McConville



31. I understand that Petitioners argued that formulation sciences were unpredictable. I disagree that such a broad statement can be made. At the relevant time period of 2017, formulating enteric capsules with standard excipients was routine and highly predictable. Most excipients had been used for decades, and any potential issues were well-known. In particular, selecting fillers and lubricants was quite routine. I also note that the claims recite a broad group of well-known fillers and lubricants—there is no indication for example that the inventors had to discover a particular species of excipient that was compatible with (Z)-endoxifen. Rather, they simply disclosed that such standard excipients could be used—which would have been highly predictable and standard to a POSA. **Ex. 1031 ¶ 31**

Law: Mere Possibility of Failure Does Not Defeat Obviousness

Federal Circuit:

“But such a mere possibility of failure, in this context, does not mean that there is no reasonable expectation of success.”

In re Samuels, No. 2021-2166, 2024 WL 960453, at *2 (Fed. Cir. Mar. 6, 2024)

“[O]nly a reasonable expectation of success, not a guarantee, is needed.”

Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1364 (Fed. Cir. 2007)

Ground 6 – Claims 14, 18, and 19

Known to dose endoxifen within claimed range

14. The oral formulation of claim 1, wherein the endoxifen composition comprises from 0.01 mg to 200 mg (Z)-endoxifen per enteric capsule.

Ahmad

Example 15

Endoxifen Prevents Development of Bicalutamide-Induced Gynecomastia and Breast Pain

Bicalutamide (CasodexR) is used for treating prostate cancer in men. There is growing evidence that IGF-1 may be involved in prostate cancer promotion and progression. It is also known that anti-estrogen agents such as Tamoxifen decrease IGF-1 levels and prevent bicalutamide-induced gynecomastia in prostate cancer patients (22). Since, endoxifen is an active metabolite of the Tamoxifen anti-estrogen, the silastic slow-release capsules containing endoxifen for implant or oral doses of endoxifen (1 mg-10 mg/day) with bicalutamide are expected to prevent development of bicalutamide-induced gynecomastia and breast pain.

Ex. 1003 at 29:15-31

Known to dose endoxifen within claimed range

Ahmad 2010

In our study, we observed that endoxifen is rapidly absorbed and displays dose-proportional PK with respect to $C_{\max}$ and $AUC_{0-\infty}$. After a single dose of 4 mg, a $C_{\max}$ of 15.1 ng/ml was observed. Therefore, in the multiple-dose study, the $C_{\max}^{SS}$ at steady state ($C_{\max} \times$ accumulation index, 15.1×3.65) with a 4-mg once-daily dosage is expected to be 55.1 ng/ml. 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. 1006 at 816

Ahmad 2012

respect to $C_{\max}$ and AUC (see Table below). **Conclusions:**

Multiple daily endoxifen doses of 4.0-8.0 mg resulted in endoxifen exposures that would be sufficient for effective therapy. The favorable safety and multiple-dose PK profile of endoxifen warrants further evaluation of safety and efficacy of endoxifen in breast cancer patients.

Ex. 1007 at 2

POSA knew to dose within 0.01 to 200 mg



Dr. McConville

effective therapy.” Ex. 1007 at 2-3. While Ahmad 2010 and 2012 do not disclose whether the endoxifen is (E), (Z), or a mix, a POSA would understand that the (Z) form is more active and thus preferred, and would understand to use highly pure (Z) form. Thus, a POSA would have understood that the formulations of Ahmad should include from 0.01 mg to 200 mg (Z)-endoxifen per enteric capsule, specifically around the range of 4 to 8 mg.

Ex. 1020 ¶ 121

Claims not limited to “safe and efficacious dose”

POR at 70

As explained above, prior to the '334 patent, it was difficult to sufficiently separate the two stereoisomers to obtain a highly pure (Z)-endoxifen. The '334 patent inventors noted the need for synthetic purification methods to obtain a formulation containing highly pure (Z)-endoxifen in an industrially scalable process that is sufficiently stable at ambient temperatures and humidities for extended periods of time for patients. (EX1001 at 82:36-41.) Thus, a POSA would not be motivated to apply the dosing information of Ahmad 2010 and Ahmad 2012 (*i.e.*, administering an unknown mixture of (Z)-endoxifen and (E)-endoxifen) to a highly pure (Z)-endoxifen formulation because a POSA would not have an understanding as to whether the Ahmad 2010/Ahmad 2012 dosing information is appropriate for a safe and effective use of a 90% pure (Z)-endoxifen composition.

14. The oral formulation of claim 1, wherein the endoxifen composition comprises from 0.01 mg to 200 mg (Z)-endoxifen per enteric capsule.

Efficacy of (Z)-endoxifen would not lead POSA away



Dr. McConville

34. A POSA would have understood that highly pure (Z)-endoxifen would likely be more active than (E)-endoxifen, but that would not have led a POSA to expect that the dosage amount would be dramatically different from other endoxifen formulations. A POSA would have done pharmacokinetic testing (like that done in Ahmad 2010 and 2012) to determine the ideal dosing range, but it would have been readily apparent to a POSA to test dosages similar to Ahmad 2010 and 2012 (perhaps slightly broader), and in any event well within the range of 0.01 to 200 mg.

Ex. 1031 ¶ 34

Shocking if dose outside of range



Dr. McConville

35. Indeed, it would have been shocking if the efficacious and safe dosage amount was outside of this incredibly broad range. I also note that the 334 patent does not show the full claimed range is efficacious and safe. Thus, the 334 patent appears to do no more than claim a broad range that a POSA would have understood to experiment within to determine the ideal dosing regimen.

Ex. 1031 ¶ 35

Pharmacokinetic Claims

18. The method of claim 15, further comprising producing an area under curve (AUC_{0-inf}) of (Z)-endoxifen in the subject of from 200 hr*ng/mL to 10,000 hr*ng/mL per 4 mg of (Z)-endoxifen administered.

19. The method of claim 15, further comprising producing a maximum blood plasma concentration (C_{max}) of (Z)-endoxifen in the subject of from 14 ng/mL to 62 ng/mL per 4 mg of (Z)-endoxifen administered.

Inherent result of *90% (Z) capsule* taught in Ahmad



Dr. McConville

122. The area under the curve (AUC) is a measurement of the actual body exposure to drug after administration of a dosage of the drug.

123. This limitation would have been the inherent result of dosing the formulations of Ahmad within the dosing ranges taught by Ahmad 2010 and Ahmad 2012 addressed above. For example, Ahmad 2010 produced data demonstrating the AUC 0.5 to 4.0 mg:

Ex. 1020 ¶¶ 122-123

Inherent result of 90% (Z) capsule taught in Ahmad



Dr. McConville

36. I want to clarify that I did not opine (and do not opine) that a 90% (Z)-endoxifen capsule would have the exact same pharmacokinetic results as a (E)/(Z)-endoxifen citrate tablet. A POSA would expect these two formulations to have *different* pharmacokinetics, mainly because of the difference in dosage form (tablet v. capsule). Rather, I opined that the pharmacokinetic limitations in the 334 patent are the inherent and natural result of dosing a patient with a 90% (Z)-endoxifen capsule as taught in Ahmad. In other words, the 334 patent simply claims the results of dosing a patient with 90% (Z)-endoxifen capsules, which was known in the art.

Ex. 1031 ¶ 36

334 patent merely recites results of “neat” administration



Dr. McConville

37. Indeed, there is nothing unique that the 334 patent teaches in order to obtain such pharmacokinetics (*e.g.*, use of particular excipients to modify the release rate). Rather, the 334 patent teaches the use of “neat” (Z)-endoxifen (*i.e.*, with no excipients). Ex. 1001 at 88:15-18 (“DRCaps capsules manually filled with 1, 2, or 4 mg of (Z)-endoxifen neat in compliance with GMP requirements were used.”). Then routine pharmacokinetic tests were performed. *Id.* at 89:26-27 (“AUC(inf) was measured on Day 1 blood draw samples”); 90:25-27 (“Area under the concentration-time curve from time 0 to infinity (AUC_{0-inf}) was also determined for the first dose, on Day 1”); 90:61-63 (same). And the results were disclosed. Ex. 1001 at 92:10-25 (Table 17 displaying results for 4 mg from 736 to 4624 hr*ng/mL); *see also* 11:46-50 (“Subjects were dosed on day 1 and plasma endoxifen levels were measured as shown in Table 17.”). **Ex. 1031 ¶ 37**

PO's Unsupported Sur-Reply Argument

PO Sur-Reply

in the '334 patent. It is undisputed that the synthetic pathways of Ahmad and the '334 patent are dissimilar, and the resulting products would have different impurity profiles—assuming a POSA could even make 90% (Z)-endoxifen by following Ahmad. (EX2029 ¶27.) These different impurities could impact the resulting pharmacokinetics. (EX2029 ¶28-29.) Dr. McConville did not address this.

Sur-Reply at 24

Paragraphs 28 and 29 do not address pharmacokinetics

Dr. Davies

28. It is therefore my opinion that following the synthetic method of Ahmad and subsequently applying the purification method of Liu would lead to a different isomeric ratio than following the synthetic and purification methods of Liu. Because of the different impurity profiles and different residual solvent contents in the synthetic product of Ahmad and the synthetic product of Liu, a POSA would not have a reasonable expectation of success in combining the methods of these references as Petitioner suggests. Dr. Bihovsky's laboratory work does not contradict my opinion. Indeed, Dr. Bihovsky's laboratory work confirms my opinion, because Dr. Bihovsky himself had to modify several aspects of the methods disclosed in Liu in order to achieve the results reported in his expert declaration.

Ex. 2029 ¶ 28

Paragraphs 28 and 29 do not address pharmacokinetics

Dr. Davies

29. For at least the reasons I discuss above, it is my opinion that Dr. Bihovsky's laboratory notebook contradicts his opinions and testimony that he reproduced the teachings of Liu to obtain 93% and 100% (Z)-endoxifen. Dr. Bihovsky's experimental work does not demonstrate that a POSA at the time of the '334 Patent's filing would be able to combine the teachings of Ahmad and Liu to achieve greater than 90% (Z)-endoxifen as Petitioner alleges. Accordingly, my opinion remains that Ahmad is not enabled and does not anticipate or render obvious the claims of the '334 Patent.

Ex. 2029 ¶ 29

Pharmacokinetic target known

18. The method of claim 15, further comprising producing an area under curve (AUC_{0-inf}) of (Z)-endoxifen in the subject of from 200 hr*ng/mL to 10,000 hr*ng/mL per 4 mg of (Z)-endoxifen administered.

19. The method of claim 15, further comprising producing a maximum blood plasma concentration (C_{max}) of (Z)-endoxifen in the subject of from 14 ng/mL to 62 ng/mL per 4 mg of (Z)-endoxifen administered.

Ahmad 2010

Table 1 Endoxifen doses and pharmacokinetic parameters

Dose	C_{max} (ng/ml)	$AUC_{0-\infty}$ (ng·h/ml)
Endoxifen 0.5 mg	1.38 ± 0.25	99.9 ± 13.6
Endoxifen 1.0 mg	3.98 ± 1.7	239 ± 70
Endoxifen 2.0 mg	6.79 ± 1.85	401 ± 113
Endoxifen 4.0 mg	15.1 ± 4.24	801 ± 262
Tamoxifen 20 mg	0.417 ± 0.013	381 ± 47.6

Ex. 1006 Table 1

Pharmacokinetic target known

Ahmad 2010

Table 1 Endoxifen doses and pharmacokinetic parameters

Dose	$C_{\max}$ (ng/ml)	$AUC_{0-\infty}$ (ng·h/ml)
Endoxifen 0.5 mg	1.38 ± 0.25	99.9 ± 13.6
Endoxifen 1.0 mg	3.98 ± 1.7	239 ± 70
Endoxifen 2.0 mg	6.79 ± 1.85	401 ± 113
Endoxifen 4.0 mg	15.1 ± 4.24	801 ± 262
Tamoxifen 20 mg	0.417 ± 0.013	381 ± 47.6

In our study, we observed that endoxifen is rapidly absorbed and displays dose-proportional PK with respect to $C_{\max}$ and $AUC_{0-\infty}$. After a single dose of 4 mg, a $C_{\max}$ of 15.1 ng/ml was observed. Therefore, in the multiple-dose study, the $C_{\max}^{ss}$ at steady state ($C_{\max} \times$ accumulation index, 15.1×3.65) with a 4-mg once-daily dosage is expected to be 55.1 ng/ml. 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.

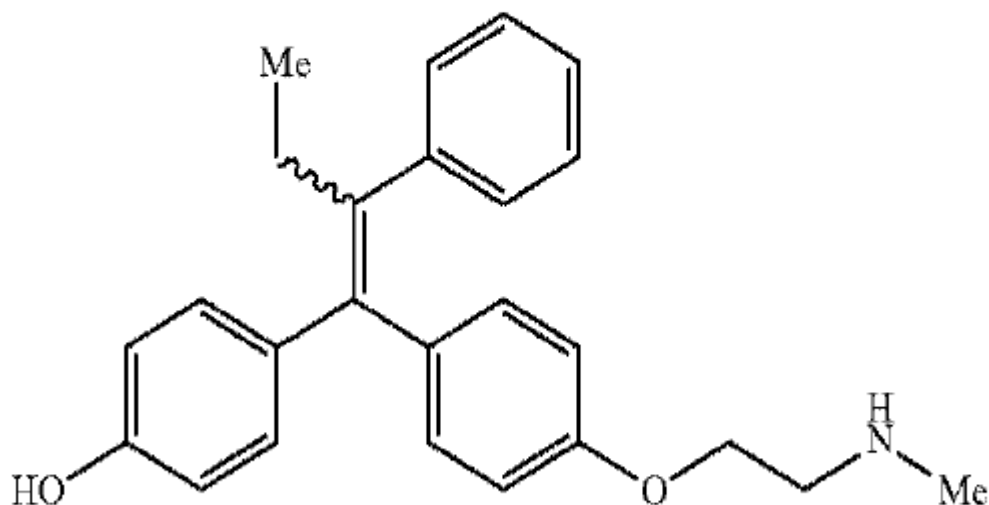
Ex. 1006 Table 1, p. 816

Objective Indicia

Claims *not* limited to free base

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. **Ex. 1001 at Claim 1**

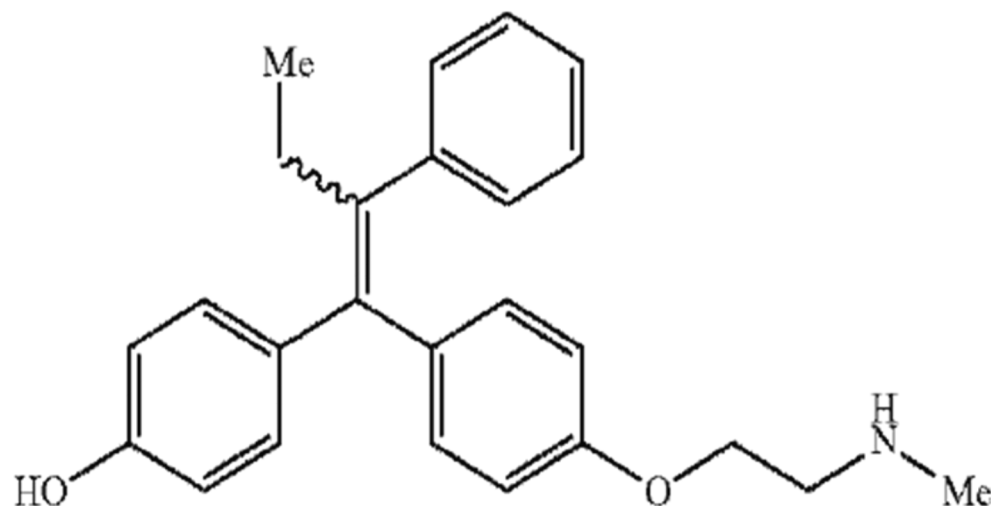
Embodiments that reference throughout this specification to “a compound”, such as compounds of Formula (I), Formula (II), Formula (III) and Formula (IV), include the polymorphic, salt, free base, co-crystal, and solvate forms of the formulas and/or compounds disclosed herein. Thus, the appearances of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

Ex. 1001 at 12:48-59

Claims *not* limited to method, purity, stability

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.

Ex. 1001 at Claim 1

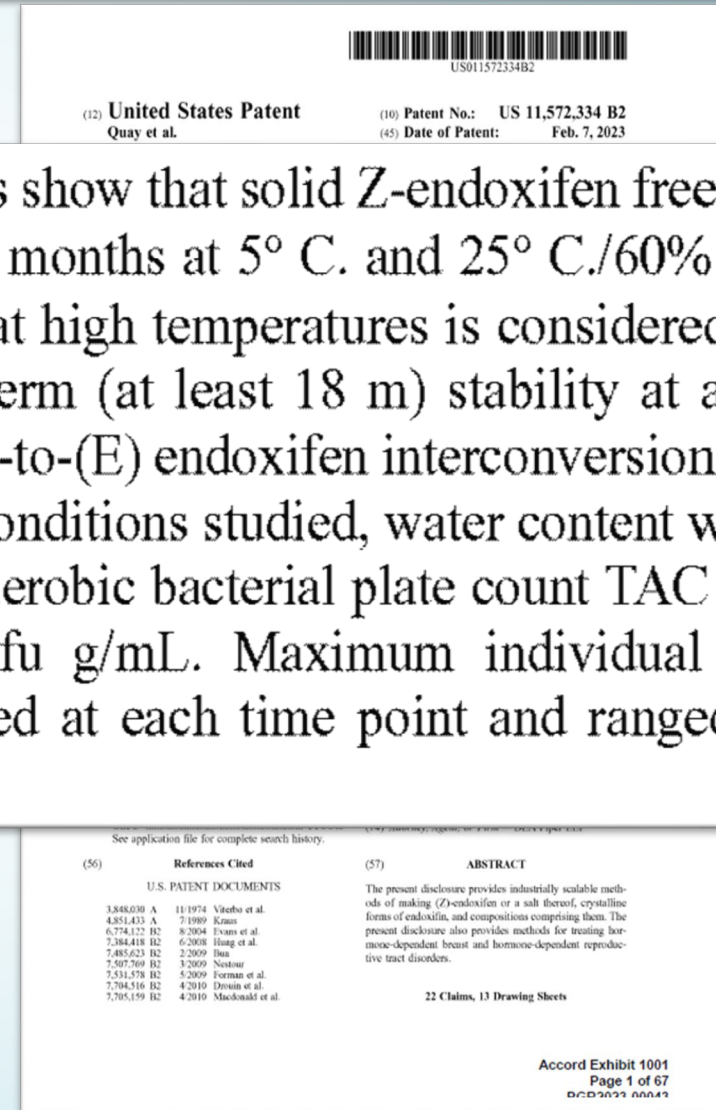
No evidence of improved stability over prior art



Dr. McConville

41. Putting aside that the claims do not appear to be limited to a free base, let alone a free base made by any particular synthetic method, I do not see any evidence that the free base made by the 334 patent's synthetic method has improved stability. Patent Owner has presented no evidence comparing the stability of the free base made according to its method to prior art free bases (such as those taught in Ahmad and Liu).

Ex. 1031 ¶ 41



Ex. 1001 at 85:18-27

Expressly claimed pharmacokinetics achieved by prior art

18. The method of claim 15, further comprising producing an area under curve (AUC_{0-inf}) of (Z)-endoxifen in the subject of from 200 hr*ng/mL to 10,000 hr*ng/mL per 4 mg of (Z)-endoxifen administered.

19. The method of claim 15, further comprising producing a maximum blood plasma concentration (C_{max}) of (Z)-endoxifen in the subject of from 14 ng/mL to 62 ng/mL per 4 mg of (Z)-endoxifen administered.

Ahmad 2010

Table 1 Endoxifen doses and pharmacokinetic parameters

Dose	C_{max} (ng/ml)	$AUC_{0-\infty}$ (ng·h/ml)
Endoxifen 0.5 mg	1.38 ± 0.25	99.9 ± 13.6
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Endoxifen 4.0 mg	15.1 ± 4.24	801 ± 262
Tamoxifen 20 mg	0.417 ± 0.013	381 ± 47.6

Ex. 1006 Table 1

Patent Owner: Other drugs use salts

POR

Other drugs in this class of compounds (known as “selective estrogen receptor modulators” or SERMs) are standardly formulated as salts, (*see* Davies POR Decl.

• • •

(EX1014.) The art thus taught away from formulating a SERM, such as endoxifen, as a free base—as opposed to one of the SERM salt forms that were standard in the industry. (Davies POR Decl. at ¶¶ 191-92.)

POR at 75-76

Law: Use of alternatives not “teaching away”

Federal Circuit:

“The prior art's mere disclosure of more than one **alternative does not constitute a teaching away** from any of these alternatives because **such disclosure does not criticize, discredit, or otherwise discourage** the solution claimed in the '198 application.”

-In re Fulton, 391 F.3d 1195, 1201 (Fed. Cir. 2004)