Filed on behalf of Intas Pharmaceuticals Ltd.

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

INTAS PHARMACEUTICALS LTD.,

Petitioner

v.

ATOSSA THERAPEUTICS, INC.,

Patent Owner

Case PGR2023-00043

Patent No. 11,572,334

PETITION FOR POST GRANT REVIEW

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PETITIONER'S EXHIBIT LIST

EX.	DESCRIPTION
1001	USPN 11,572,334 ("334 patent")
1002	File history of USPN 11,572,334
1003	USPN 9,333,190 ("Ahmad")
1004	WO2017/70651 ("Liu")
1005	WO 2012/050263 ("Song")
1006	Ahmad, A. et al., Endoxifen, a New Cornerstone of Breast Cancer Therapy: Demonstration of Safety, Tolerability and Systemic Bioavailability in Healthy Human Subjects, 88(6) CLIN. PHARMACOLOGY & THERAPEUTICS 814-817 (2010) ("Ahmad 2010")
1007	Ahmad, A. et al., Endoxifen for breast cancer: Multiple-dose, dose-escalation study characterizing pharmacokinetics and safety in metastatic breast cancer patients, ASCO MEETING LIBRARY, presented June 4, 2012 ("Ahmad 2012")
1008	Cole, E., et al., Enteric coated HPMC capsules designed to achieve intestinal targeting, 231 INTL J. PHARMACEUTICS 83-95 (2002) ("Cole")
1009	Ku, M., et al., Performance qualification of a new hypromellose capsule: Part I. Comparative evaluation of physical, mechanical, and processability quality attributes of Vcaps Plus®, Quali-V® and gelatin capsules, 386 INTL J. PHARMACEUTICS 30-41 (2010) ("Ku")
1010	Benameur, H., Capsule Technology, Enteric Capsule Drug Delivery Technology – Achieving Protection Without Coating, 15(5) DRUG DEV. & DELIVERY 34-37 (2015) ("Benameur")
1011	Stegemann, S., Hard gelatin capsules today – and tomorrow, CAPSUGEL LIBRARY (2002) ("Stegemann")
1012	Excerpts of HANDBOOK OF PHARMACEUTICAL EXCIPIENTS FIFTH EDITION (Rowe, R., Sheskey, J. & Owen, S., eds., 2006) (The "HPE")
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1014	Prescribing Information for Zonalta
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1016	Beasley, D. et al, *The Evolution of Stomach Acidity and Its Relevance to the Human Microbiome*, 10(7) PLoS ONE 1-12 (2015).
1017	Evans, D. et al, *Measurement of gastrointestinal pH profiles in normal ambulant human subjects*, 29 GUT 1035-41 (1988)
1018	Ahmad, A. et al., *Endoxifen, a New Treatment Option for Mania: A Double-Blind, Active-Controlled Trial Demonstrates the Antimanic Efficacy of Endoxifen*, Clin Transl Sci (2016) 9, 252–259 ("Ahmad 2016")
1019	Milroy, L. et al., *A multi-gram-scale stereoselective synthesis of Z-endoxifen*, Bioorganic Med. Chem. Lett. 28 (2018) 1352-1356 ("Milroy")
1020	Expert Declaration of Jason McConville, Ph.D.
1021	Ansel, H., et al, PHARMACEUTICAL DOSAGE FORMS AND DRUG DELIVERY SYSTEMS, SEVENTH EDITION (1999)

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I. Introduction

Intas Pharmaceuticals Limited., petitions for post grant review of claims 1-22 of U.S. Patent No. 11,572,334 ("the 334 patent"; Ex. 1001). The claims of the 343 patent are directed to oral formulations of 90% by weight (Z)-endoxifen encapsulated in an enteric capsule, and methods of administering such formulations. Such formulations and methods, however, were disclosed in the art by U.S. Patent No. 9,333,190 ("Ahmad"), which anticipates the independent claims. And, both endoxifen formulations that are 90% Z-isomer and enteric capsules were well-known in the art. Thus, any claim not anticipated would have been obvious.

II. Mandatory notices

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

Related matters: There are no current related matters.

Lead and backup counsel:

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Service information: Petitioner consents to service by email at: 334PGR@mcandrews-ip.com.

III. Grounds for standing

The 334 patent is available for post grant review because it issued on February 7, 2023, and the date of filing is within the 9 month period provided by 35 U.S.C. § 321(c). Petitioner is not barred or estopped from requesting a post grant review challenging claims 1-22 of the 334 patent on the grounds identified in this Petition.

IV. Identification of Grounds

Petitioner identifies the following grounds of unpatentability:

Ground	Challenged Claims	Basis
1	1, 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

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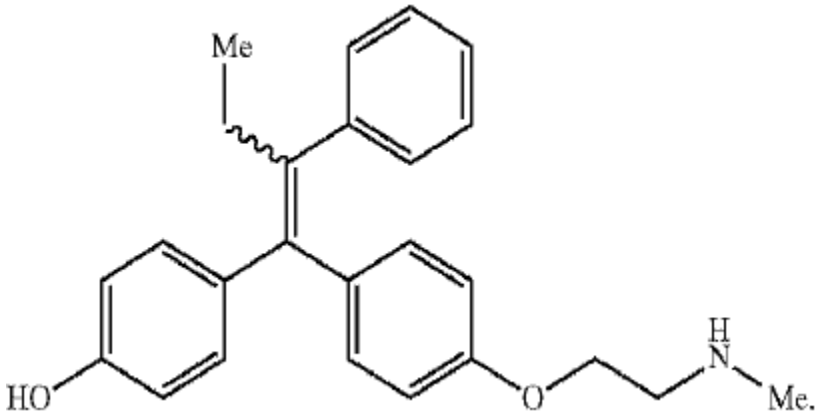
V. Background

Endoxifen (4-hydroxy-*N*-desmethyltamoxifen) is a nonsteroidal selective estrogen receptor modulator, with the following chemical structure:



McConville ¶ 18;[1] Ex. 1001. A citrate salt of endoxifen is marketed and sold in India by Intas, under the brand name Zonalta for the treatment of manic episodes with or without mixed features of bipolar disorder. *See* Ex. 1014. Endoxifen has long been known to be an active metabolite of tamoxifen, which has been used in the treatment of breast cancer. McConville ¶ 19; Ex. 1001 at Fig 1, 1:63-2:6; Ex. 1003 at Fig. 3, 1:35-56; Ex. 1004 at [0003]; Ex. 1005 at [3]. Thus, interest in endoxifen itself as a treatment for breast cancer has been contemplated and studied in the prior art.

[1] "McConville" refers to Exhibit 1020, the Expert Declaration of Jason McConville, Ph.D. Dr. McConville is an expert in a pharmaceutical and formulation sciences. McConville ¶¶ 1-15, Appendix A.

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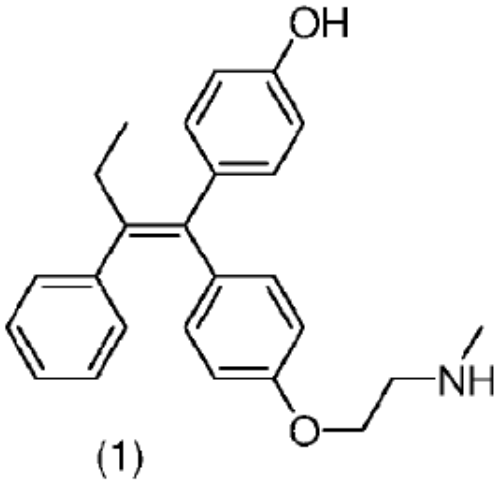
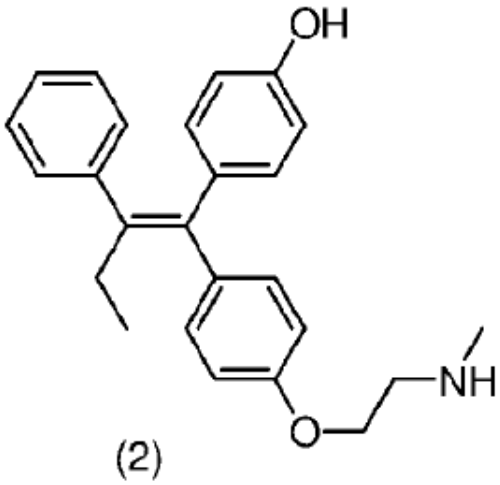
McConville ¶ 19; Ex. 1003 at 1:64-2:4; Ex. 1004 at [0003]; Ex. 1005 at [1]; Ex. 1006; Ex. 1007.

"Endoxifen exists as two forms, E and Z, with the Z form more active at the estrogen receptor." Ex. 1004 at [0004]. These two forms are isomers, meaning that while the constituent atoms are the same, and each atom is connected to the same atom(s), the three-dimensional spatial arrangement of those atoms differs, as depicted below:

(Z)-endoxifen	**(E)-Endoxifen**
	

McConville ¶¶ 20-21; *see also* Ex. 1004 at Abstract. The (Z) isomer is known to be more active (McConville ¶ 22, Ex. 1004 at [0004], and methods of producing highly pure (Z) isomer are known in the art. *See, e.g.*, Exs. 1004, 1005.

Some drugs, including endoxifen, are subject to acid-catalyzed degradation in the acidic conditions of the stomach. McConville ¶ 23; Ex. 1003 at 18:19-21. To

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prevent such degradation, enteric capsules or tablets may be used, which capsules remain intact in the stomach and release the active substance in the upper intestine. McConville ¶ 23; Ex. 1003 at 18:19-21; Ex. 1008 at 83; Ex 1010 at 34. For example, Intas's Zonalta endoxifen product is sold in "Enteric coated tablet(s)." Ex. 1014 at 1. Enteric capsules and tablets are well known in the art. *See, e.g.* McConville ¶ 23; Exs. 1008, 1010.

VI. The 334 patent

A. Subject matter of the 334 patent

The 334 patent is titled "Methods for making and using Endoxifen." Ex. 1001 at Cover. It was filed on January 20, 2022 as a continuation of application No. 16/641,985 (now USPN 11,261,151), and claims priority to provisional application no. 62/556,799, dated September 11, 2017. *Id.* Without conceding that the 334 patent is entitled to such a priority date, Intas uses September 11, 2017 as the date of invention. The 334 patent is directed to oral formulations of 90% by weight (Z)-endoxifen encapsulated in an enteric capsule, and methods of administering such formulations. McConville ¶¶ 24-25. The enteric capsule may be either a capsule made enteric by coating "with one or more enteric coating agent," or an intrinsically enteric capsule that does not need an additional coating to provide the enteric property. Ex. 1001 at 39:19-30, 40:31-36; McConville ¶ 25.

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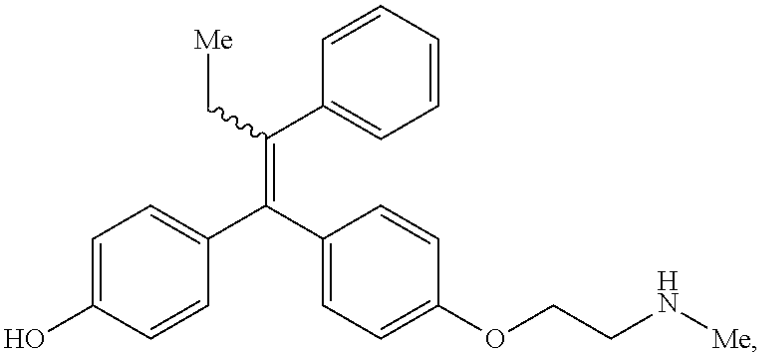
B. Claims of the 334 patent

<u>Independent claim 1 and dependent claims 2-14</u>

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.

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

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

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

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.

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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.

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

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.

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

Independent claim 15 and dependent claims 16-22

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):

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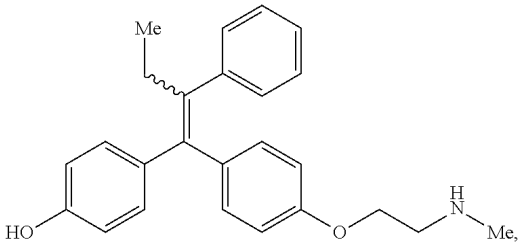
Formula (III)



wherein at least 90% by weight of the compound of Formula (III) in the composition is the (Z)-isomer, and wherein the crystalline form of the (Z)-isomer is Form I, characterized by an x-ray powder diffraction pattern comprising major peaks at 16.8±0.3°, 17.1±0.3° and 21.8±0.3° two theta, thereby treating the hormone-dependent breast disorder or the hormone-dependent reproductive tract disorder.

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.

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.

18. The method of claim 15, further comprising producing an area under curve (AUC0-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 (Cmax) of (Z)-endoxifen in the subject of from 14 ng/mL to 62 ng/mL per 4 mg of (Z)-endoxifen administered.

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,

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> ovarian cancer, uterine cancer, cervical cancer, vaginal cancer, or vulvar cancer.
>
> 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.

C. Prosecution history

The 334 patent did not face a single rejection. The Examiner stated that "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." Ex. 1002 at 388/398.

D. Person of ordinary skill in the art

A POSA for purposes of the 334 patent is someone with a Ph.D. in pharmaceutical sciences or a closely related field and experience in research related to pharmaceutical dosage forms or someone with at least a Bachelor's or Master's degree in pharmaceutical sciences and three to five years of practical experience in formulating drugs. McConville ¶ 27. The analysis below would be the same if the level of skill were lower. *Id.* Dr. McConville meets or exceeds the level of skill of a POSA. *Id.*

E. Claim construction

For purposes of this PGR, all terms should be given their plain and ordinary meaning. The term "enteric capsule" in independent claim 1 means a capsule "with

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one or more enteric coating agent," or an intrinsically enteric capsule that does not need an additional coating to provide the enteric property. McConville ¶¶ 28-29. This is the plain and ordinary meaning of "enteric capsule" and the specification confirms this understanding. *Id.*; Ex. 1001 at 39:19-30, 40:31-36.

VII. Summary of the prior art

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

U.S. Patent No. 9,333,190 ("Ahmad") issued on May 10, 2016, from a PCT application filed November 21, 2007, and claims priority to provisional application No. 60/860,420, filed November 21, 2006. Ex. 1003 at Cover. Thus, Ahmad is prior art under 35 U.S.C. § 102(a)(1) and (2).

Ahmad "provides compositions containing endoxifen, formulations and liposomes of endoxifen, methods of preparation of such agents and formulations, and use of such agents and formulations for the treatment of breast cancer and other breast diseases and diseases susceptible to endoxifen." Ex. 1003 at Abstract. Ahmad teaches the use of the Z-isomer of endoxifen, including at over 90% purity. *Id.* at 12:14-17 ("[o]ne object of the present invention is to provide E-endoxifen or Z-endoxifen with at least 80% purity, such as at least 90% pure...."); *see also id.*at 2:24-40, 3:55-61. Ahmad teaches that purity levels can be accomplished using crystallization or chromatography. *Id.* at 11:17-23.

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Ahmad also teaches that "In some embodiments, the composition comprises a tablet or a filled capsule, wherein said tablet or filled capsule optionally comprises an enteric coating material." *Id.* at 4:41-44. Ahmad further teaches that "When desired, composition containing endoxifen or endoxifen-lipid complex can be encapsulated in enteric-coated capsules to protect it from acids in the stomach" and that "the term 'enteric' refers to the small intestine, and enteric coatings prevent release of medication before it reaches the small intestine." *Id.* at 18:19-24. Ahmad further teaches that "[m]ost enteric coatings work by presenting a surface that is stable at acidic pH but breaks down rapidly at higher pH." *Id.* at 18:24-26.

Ahmad also teaches that the "compositions of the present invention can be employed to treat breast cancer and breast related diseases." *Id.* at 18:47-48. Thus, Ahmad teaches enteric coated formulations of highly pure (Z)-endoxifen, for the treatment of breast cancer and other breast diseases. McConville ¶¶ 30-33.

B. Endoxifen Art

1. WO 2017/070651 ("Liu")

International application WO 2017/070651 ("Liu") was filed on October 24, 2016, and published on April 27, 2017. Ex. 1004 at Cover. Thus, it is prior art under 35 U.S.C. § 102(a)(1).

Liu teaches that "Endoxifen exists as two forms, E and Z, with the Z form more active at the estrogen receptor." *Id.* at [0004]. It further teaches that "Endoxifen

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is frequently synthesized as a mixture of E and Z, with a difficult separation of isomers required to obtain pure Z isomer" and that "[s]ome procedures in the art separate the E and Z isomers via methods which are expensive and difficult to perform on larger scale, such as preparative HPLC." *Id.* "Thus there is a need in the art for a practical, scalable synthesis that gives access to highly pure (Z)-endoxifen." *Id.* Liu thus teaches an efficient method of generating highly pure (Z)-endoxifen through recrystallization. Liu teaches that its method achieved "1698 g (34%) of (Z)-endoxifen, with an isomeric purity of 99% (HPLC analysis)." *Id.* at [0076].

In sum, Liu teaches a method of making highly pure (Z)-endoxifen. McConville ¶¶ 34-35.

2. WO 2012/050263 ("Song")

International application WO 2012/050263 ("Song") was filed on December 16, 2010, and published on April 19, 2012. Ex. 1005 at Cover. Thus, it is prior art under 35 U.S.C. § 102(a)(1).

Song discloses "a method of preparing endoxifen by coupling 4,4-hydroxybenzophenone as a starting material with propiophenone," which "can be used to obtain an E/Z-form endoxifen mixture with a high yield compared to the conventional methods of preparing endoxifen, and provide Z-form endoxifen of at least 99% purity in the mixture to have a therapeutic effect." Ex. 1004 at Abstract.

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Song discloses "[a]n endoxifen mixture obtained by the fractional crystallization and mainly consisted of E-form endoxifen is treated according to the following Scheme 3 and converted into a mixture having an E/Z ratio of 1:1" and "Z-form endoxifen is separated by the fractional crystallization" such that "the Z-form endoxifen is obtained with higher yield." *Id.* at [61]. Specifically, Song teaches obtaining endoxifen "having an E/Z ratio of 1/99." *Id.* at [92]-[94], [97]-[98].

In sum, Song also teaches a method of making highly pure (Z)-endoxifen. McConville ¶¶ 36-37.

3. Ahmad, A. et al., *Endoxifen, a New Cornerstone of Breast Cancer Therapy: Demonstration of Safety, Tolerability and Systemic Bioavailability in Healthy Human Subjects*, 88(6) CLIN. PHARMACOLOGY & THERAPEUTICS 814-817 (2010) ("Ahmad 2010")

Ahmad, A. et al., *Endoxifen, a New Cornerstone of Breast Cancer Therapy: Demonstration of Safety, Tolerability and Systemic Bioavailability in Healthy Human Subjects*, 88(6) CLIN. PHARMACOLOGY & THERAPEUTICS 814-817 (2010) ("Ahmad 2010") was published and publicly available in 2010 and thus is prior art under 35 U.S.C. § 102(a)(1). Ex. 1006.

Ahmad 2010 discloses pre-clinical trials of endoxifen showing that it is likely to be a safe and effective treatment for breast cancers. Ahmad 2010 was published by the first named inventor on the Ahmad patent. Compare Ex. 1006 *with* Ex. 1003. Ahmad 2010 teaches that "Endoxifen is an active metabolite of tamoxifen, a drug

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used in the treatment of breast cancer." Ex. 1006 at Abstract. "In order to be clinically effective, tamoxifen must be converted to endoxifen by cytochrome P450 2D6 (CYP2D6)." *Id.* Ahmad 2010 reports on a study "demonstrating that single oral doses of endoxifen are safe and well tolerated and have sufficient bioavailability to reach systemically effective levels in human subjects" for treatment of breast cancer. *Id.* "Furthermore, it was found that endoxifen is rapidly absorbed and systemically available and that it displays dose proportionality in peak drug concentrations in plasma (Cmax) and area under the concentration–time curve extrapolated from 0 to ∞ ($AUC_{0-\infty}$) over the dose range 0.5-4.0 mg." *Id.*

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

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In sum, Ahmad 2010 teaches that endoxifen is likely to be safe and effective for the treatment of breast cancer. McConville ¶¶ 38-39.

4. Ahmad, A. et al., *Endoxifen for breast cancer: Multiple-dose, dose-escalation study characterizing pharmacokinetics and safety in metastatic breast cancer patients*, ASCO MEETING LIBRARY, presented June 4, 2012 ("Ahmad 2012")

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

Ahmad 2012 discloses pre-clinical trials of endoxifen showing that it is likely to be a safe and effective treatment for breast cancers. Ahmad 2012 was presented by the first named inventor on the Ahmad patent. Compare Ex. 1007 *with* Ex. 1003. Ahmad 2012 teaches that "Direct administration of endoxifen would not be subject to pharmacogenetic variations or drug-drug interactions." *Id.* at 1. It disclosed that the group's "preclinical studies (Breast Cancer Treat 122, 579-584, 2010) have validated the concept of using endoxifen for the treatment of breast cancer." *Id*. Ahmad 2012 disclosed test results showing that "the single oral doses tested up to 4 mg of endoxifen were safe, well tolerated and bioavailable" *Id*. Ahmad 2012 concludes that "Multiple daily endoxifen doses of 4.0-8.0 mg resulted in endoxifen exposures that would be sufficient for effective therapy." *Id.* at 2.

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In sum, Ahmad 2012 also teaches that endoxifen is likely to be safe and effective for the treatment of breast cancer. McConville ¶¶ 40-41.

C. Enteric Capsule Art

1. Cole, E., et al., *Enteric coated HPMC capsules designed to achieve intestinal targeting*, 231 INTL J. PHARMACEUTICS 83-95 (2002) ("Cole")

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

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

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Cole "describe[d] the manufacture of two different Eudragit® coated HPMC capsules and their in vitro/in vivo performance." *Id.* at 84. Cole found that no drug "was released over 2 h at pH 1.2 from the capsules coated with 6 and 8 mg cm^{-2} Eudragit® L 30 D-55" while at "pH 6.8 release of paracetamol was rapid…." *Id.* at 89. The 334 patent acknowledges Cole, and uses Cole's method. Ex. 1001 at 86:51-61.

In sum, Cole teaches the effective use of an enteric coating to form capsules that will bypass the stomach and release drug in the intestine. McConville ¶¶ 42-43.

2. Ku, M., et al., *Performance qualification of a new hypromellose capsule: Part I. Comparative evaluation of physical, mechanical, and processability quality attributes of Vcaps Plus®, Quali-V® and gelatin capsules*, 386 INTL J. PHARMACEUTICS 30-41 (2010) ("Ku")

Ku, M., et al., *Performance qualification of a new hypromellose capsule: Part I. Comparative evaluation of physical, mechanical, and processability quality attributes of Vcaps Plus®, Quali-V® and gelatin capsules*, 386 INTL J. PHARMACEUTICS 30-41 (2010) ("Ku") was published and publicly available in February 2010 and is thus prior art under 35 U.S.C. § 102(a)(1). Ex. 1009.

Ku explains how Capsugel "developed a new HPMC capsule, Vcaps Plus® (Hypromellose Shell 2), without a gelling agent or other ingredient in 2006." *Id.* at 32. Vcaps Plus® launched "mid-2007 and the new Shell 2 has since been used

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successfully in over a dozen IND compounds." *Id.* The 334 patent describes the use of Vcaps Plus®. Ex. 1001 at 40:46-55.

In sum, Ku teaches the use of HPMC capsules as an effective alternative to traditional gelatin capsules. McConville ¶¶ 44-45.

3. Benameur, H., Capsule Technology, Enteric Capsule Drug Delivery Technology – Achieving Protection Without Coating, 15(5) DRUG DEV. & DELIVERY 34-37 (2015) ("Benameur")

Benameur, H., *Capsule Technology, Enteric Capsule Drug Delivery Technology – Achieving Protection Without Coating*, 15(5) DRUG DEV. & DELIVERY 34-37 (2015) ("Benameur") was published and publicly available in June 2015 and thus is prior art under 35 U.S.C. § 102(a)(1). Ex. 1010.

Benameur teaches intrinsically enteric capsules that do not require coating. Benameur teaches that the "major hurdle in oral delivery of many sensitive molecules, such as nucleotides, peptides, live biopharmaceutical products, and vaccines, is protecting the active entity from acidic and enzymatic degradation in the GI tract." *Id.* at 35. It further teaches that "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." *Id.* at 34. "ECDDT's intrinsically enteric properties are attained by incorporating pharmaceutically approved enteric polymers in the capsule shell using conventional

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pin-dipping capsule manufacturing processes." *Id.* "By eliminating the preparation and application steps used for enteric coating, ECDDT can offer accelerated development timelines and reduced program risk" and "can also enable the oral delivery of sensitive molecules…which can degrade at the high temperatures or can be sensitive to aqueous coating solution associated with pan and fluid bed coating processes." *Id.* "The 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." *Id.*

Benameur teaches that a "pharmaceutical-grade cellulosic enteric formulation (complying with EP/USP/JP) was prepared using polymer aqueous dispersion or pseudolatex with plasticizer addition to achieve optimal dipping, setting, and film-forming properties for capsule shell production." *Id.* at 35. "Intrinsically enteric size 0 white opaque capsules – equivalent in appearance, dimensions, and mechanical properties to conventional two-piece hard capsules – were then manufactured on a full-scale, commercial hard capsule manufacturing machine." *Id.* "In vivo results (Figure 2) showed that no pellets were released from ECDDT capsules in the

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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." *Id.* at 36.[2]

In sum, Benameur teaches the use of capsules with intrinsic enteric capabilities that do not require an enteric coating. McConville ¶¶ 46-47.

D. Excipient Art

1. Stegemann, S., *Hard gelatin capsules today – and tomorrow*, CAPSUGEL LIBRARY (2002) ("Stegemann")

Stegemann, S., *Hard gelatin capsules today – and tomorrow*, CAPSUGEL LIBRARY (2002) ("Stegemann") was published and publically available in 2002 and thus is prior art under 35 U.S.C. § 102(a)(1). Ex. 1011.[3]

Stegemann teaches that the "capsule is one of the oldest dosage forms in pharmaceutical history, known to the ancient Egyptians." *Id.* at 3. "It was in 1931 that Arthur Colton, on behalf of Parke, Davis & Co., succeeded in designing a machine which simultaneously manufactured both bodies and caps and fitted them together to form a hard gelatin capsule." *Id.* According to Stegemann, "[i]t is

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[2] Such capsules are sold as Vcaps Enteric. https://www.capsugel.com/biopharmaceutical-products/vcaps-enteric-capsules. These capsules were released October 7, 2016. https://www.capsugel.com/news/capsugel-launches-vcaps-enteric-capsules-for-enteric-protection-and-delayed.

[3] Available from https://www.capsugel.com/knowledge-center/hard-gelatin-capsules-today-and-tomorrow

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amazing to realise that a machine originally built in 1931 still represents the basic design of today's machinery" and "[o]nly minor modifications have been made to it since that time, in the interests of improved product quality and greater technical efficiency." *Id.*

Stegemann teaches both "The production process" and "Use of Excipients" for capsules. Table 4 displays "Excipients used in formulations of immediate release hard gelatin capsules":[4]

[4] While this table is for immediate-release hard gelatin capsules, a POSA would understand that the same excipients are used for a delayed-release capsule where the delay is produced by a coating or the capsule material itself, rather than the excipients internal to the capsule. McConville ¶¶ 48-49.

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Diluents

→ Improved plug formation and compression

- Mannitol
- Microcrystalline cellulose
- Lactose
- Starch 1500
- Corn starch

Lubricants

→ Improved flow properties and reduced powder adhesion to metal parts

- Magnesium stearate
- Glyceryl monostearate
- Stearic acid

Glidants

→ Improved powder flow properties

- Aerosil
- Talcum

Disintegrants

→ To ensure disintegration of powder mixture

- Croscaramellose
- Corn starch
- Crospovidone
- Starch 1500
- Sodium glycyl starch
- Alginic acid

Wetting agents

→ Improved water penetration into powder mixture

- Sodium lauryl sulphate
- Tween 80

Table 4: Excipients used in formulations of immediate-release hard gelatin capsules.

Id. at 8.

2. HANDBOOK OF PHARMACEUTICAL EXCIPIENTS FIFTH EDITION (Rowe, R., Sheskey, J. & Owen, S., eds., 2006) (the "HPE")

The HANDBOOK OF PHARMACEUTICAL EXCIPIENTS FIFTH EDITION (Rowe, R., Sheskey, J. & Owen, S., eds., 2006) (the "HPE"), Fifth Edition was published and publicly available in 2006 and thus is prior art under 35 U.S.C. § 102(a)(1). Ex. 1012.

"The *Handbook of Pharmaceutical Excipients* is an internationally acclaimed reference work recognized as one of the most authoritative and comprehensive sources of information on excipients used in pharmaceutical formulation" which is "Jointly published by the American Pharmacists Association and the Pharmaceutical Press, the publications department of the Royal Pharmaceutical Society of Great Britain." Ex. 1012 at Back Cover; McConville ¶¶ 50-51.

3. Ansel, H., ET AL, PHARMACEUTICAL DOSAGE FORMS AND DRUG DELIVERY SYSTEMS, SEVENTH EDITION (1999) ("Ansel")

Ansel, H.., et al, PHARMACEUTICAL DOSAGE FORMS AND DRUG DELIVERY SYSTEMS, SEVENTH EDITION (1999) ("Ansel"), was published and publicly available in 1999 and thus is prior art under 35 U.S.C. § 102(a)(1). Ex. 1012. Ansel is a well-known reference for developing and manufacturing pharmaceutical dosage forms and drug delivery systems.

VIII. Discretionary Denial

A. 325(d) based on prosecution activity

The Board engages a two-step inquiry in determining whether it should deny institution based on prosecution activity: (1) whether the same or substantially the same art or arguments previously were presented to the Office (*Becton, Dickinson* factors (a), (b), and (d), and if so, (2) whether Petitioner demonstrates material error by the office (*Becton, Dickinson* factors (c), (e), and (f)). *Advanced Bionics, LLC v.*

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Med-El Elektromedizinische Gerate GmbH, IPR2019-01469, Paper 6 at *10 (P.T.A.B. Feb. 13, 2020) (precedential), citing *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 (P.T.A.B. Dec. 15, 2017).

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

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

Ahmad and the Endoxifen Art are listed on the 334 patent as references considered. Ex. 1001 at (56). However, none of the Enteric Capsule Art or Excipient Art was considered by the Examiner. While Cole is described in the specification of the 334 patent (*Id.* at 86:58-60), it is not listed as a reference considered. *Id.* at (56). Thus, only Grounds 1, 2 and 6 present the same art considered by the examiner, and Grounds 3-5 do not. *See Thorne Research, Inc., v. Trustees of Dartmouth College*, IPR2021-00491, Paper 18 at *8 (PTAB Aug. 12, 2021) ("The fact that one piece of art from the combination was previously presented and/or argued to the Office alone is insufficient to satisfy the first prong of Advanced Bionics two-part test concerning whether the art previously presented to the Office was the same or substantially the same or whether the same or substantially the same arguments previously were presented to the Office.")

Thus, this factor is neutral or at best weighs slightly in favor of discretionary denial.

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

As described above, none of the Enteric Capsule Art or Excipient Art was listed as a cited reference. Nor to the best of Petitioner's knowledge was any similar art listed. *Id.* at (56). For example, none of the cited articles contain the word "enteric" or "capsule" and most, if not all, seem to focus on endoxifen or related compounds, rather than capsule technology. *See Id.* Further, based on a review of the titles of the cited patent references, none contain "enteric" or "capsule."[5] Thus, to the best of Petitioner's knowledge, the Enteric Capsule Art is not cumulative with any art cited by the Examiner. This factor weighs against denial, or is at worst neutral.

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

As described above, the Examiner did not issue any rejection against the claims. *See* §VI.C. Thus, no arguments whatsoever were presented, and the Petition presents entirely new arguments regarding the prior art (as well as new prior art on enteric capsules). Based on these factors above, Petitioner presents entirely new arguments, as well as significant new art, and thus the Board need not reach the

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[5] *See* https://patents.google.com/patent/US11572334B2/en?oq=11572334 at "Patent Citations (79)."

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second factor. However, for completeness, Petitioner addresses the remaining factors.

Advanced Bionics Part 2: Whether Office erred

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

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

As described above, the Examiner did not issue a single rejection of the claims. Thus, none of the references in the Petition were discussed by the examiner or were the basis for rejection. Because these references are highly relevant as described above and below, the Examiner erred in not substantively considering them. *See Carrier Fire & Security America's Corp. v. Sentrilock, LLC*, IPR2021-00664, Paper 12 at *21-23 (P.T.A.B. Sept. 16, 2021) ("The prosecution history provides little insight into the Examiner's evaluation of the prior art. As Patent Owner acknowledges, the Examiner 'issued no rejections,'…."); *Samsung Electronics Co., Ltd., et al. v. Evolved Wireless LLC,* IPR2021-00943, Paper 9 at *10-12 (P.T.A.B. Dec. 1, 2021) (declining to issue discretionary denial where "the references were not used in a rejection or discussed by the Examiner in any Office Action"); *Satco Products Inc. v. The Regents of the Univ. of California*, IPR2021-00662, Paper 13 at *25 (P.T.A.B. Nov. 8, 2021) ("the record does not establish that the Examiner evaluated these references in the same way as a reference used to reject

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a claim. And we are not persuaded that the Examiner evaluated these references sufficiently such that a trial would duplicate what occurred during prosecution").

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

As discussed above, and more fully below, Ahmad teaches all of the limitations of the independent claims: an oral formulation comprising endoxifen composition which is 90% (Z)-endoxifen, encapsulated in an enteric capsule. *See* § VII.A., *supra*. Moreover, forming endoxifen form (Z) at high purities was well-known in the art (*see* § VII.B., *supra*) as was the use of enteric capsules (*see* § VII.C., *supra*).

This strong evidence of unpatentability (as well as supporting expert testimony) warrants reconsideration, and demonstrates that the Office erred in not considering the cited references and combinations. *See Satco*, IPR2021-00662, Paper 13 at *25 (noting "the close relevance and applicability" of the art demonstrated "it was error to not apply those references against the claims during prosecution"); *Carrier Fire*, IPR2021-00664, Paper 12 at *23 (granting institution where "Petitioner shows persuasively" that the art taught the features cited as the basis for allowance).

B. Other bases for discretionary denial

There is no pending litigation between Patent Owner and Petitioner or to the best of Petitioner's knowledge any potential party-in-interest. Petitioner is not aware

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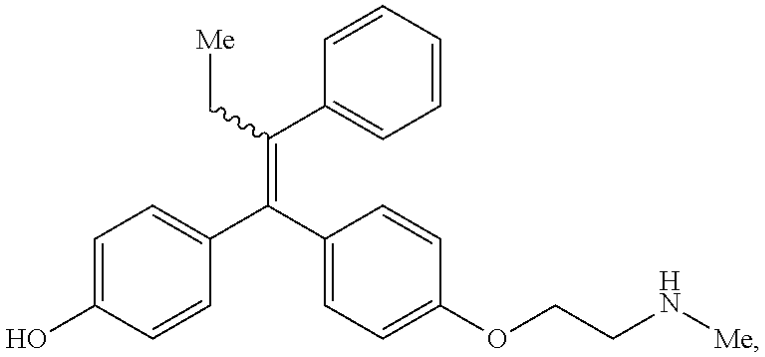
of any other proceeding involving the 334 patent. Finally, Petitioner's grounds are not redundant or excessive. *See* § IV.

IX. Ground 1: Claims 1, 2, 4, 15, and 20-22 are anticipated by Ahmad

A. Independent Claim 1

1. An oral formulation comprising an endoxifen composition…wherein the endoxifen composition comprises a compound of Formula (III):

Formula (III)



Ahmad teaches oral formulations comprising endoxifen, which is the compound depicted in Formula III of the 334 patent. McConville ¶ 53. Ahmad is titled "Endoxifen compositions and methods" and "provides compositions containing endoxifen." Ex. 1003 at Title, Abstract. Though depicted slightly differently, Ahmad depicts the same chemical structure for endoxifen:

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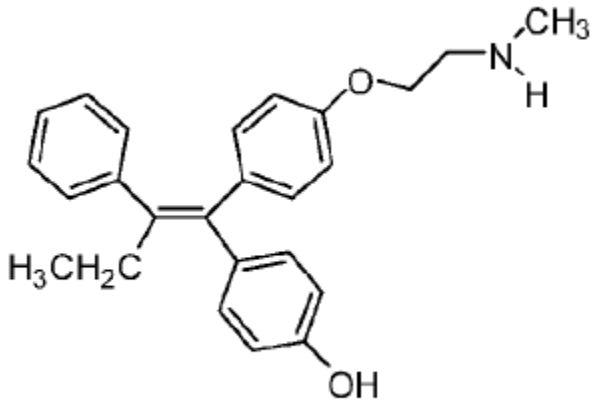

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Ex. 1003 at Cover, Figure 1; McConville ¶ 54.

Ahmad teaches that its formulations may be administered orally. *E.g.*, Ex. 1003 at 7:43-48. For example, it teaches that "[p]harmaceutical preparations that find use with the compositions of the present invention include but are not limited to tablets, capsules, pills…" and that "[f]or the oral mode of administration, preferred forms of endoxifen or endoxifen lipid complex include tablets, capsules…." *Id.* at 18:1-6. Thus, Ahmad teaches "An oral formulation comprising an endoxifen composition…wherein the endoxifen composition comprises a compound of Formula (III)." McConville ¶¶ 58-61.

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

Ahmad teaches that "[o]ne object of the present invention is to provide E-endoxifen or Z-endoxifen with at least 80% purity, such as at least 90% pure or at least 95% pure or at least 98% pure or at least 99% pure or at least 100% pure." *Id.*

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at 12:14-17; *see also id.* at 2:24-40, 3:55-61. Ahmad teaches that this can be accomplished using crystallization or chromatography. *Id.* at 11:17-23. Thus, Ahmad teaches "wherein at least 90% by weight of the compound of Formula (III) is (Z)-endoxifen." McConville ¶¶ 62-64.

To the extent it is argued there is not a specific, enabling disclosure of 90% pure (Z)-endoxifen by Ahmad, forming such pure formulations was known in the art as taught by e.g., Liu and Song. *See* §VII.B. *supra*; Ex. 1004 at [0076]; Ex. 1005 at [92]-[94], [97]-[98]; McConville ¶ 59.

encapsulated in an enteric capsule

Ahmad teaches that its formulations may be encapsulated in enteric capsules: "[i]n some embodiments, the composition comprises a tablet or a filled capsule, wherein said tablet or filled capsule optionally comprises an enteric coating." Ex. 1003 at 4:41-44. Ahmad further teaches that "[w]hen desired, composition containing endoxifen or endoxifen-lipid complex can be encapsulated in enteric-coated capsules to protect it from acids in the stomach." *Id.* at 18:19-21. Ahmad explains that the "enteric coatings prevent release of medication before it reaches the small intestine." *Id.* at 18:22-24. It further teaches that "[m]ost enteric coatings work by presenting a surface that is stable at acidic pH but breaks down rapidly at higher pH." *Id.* at 18:24-26. It finally notes that "[e]nteric coating of capsules filled with compositions containing endoxifen can be done as methods known in the art." *Id.* at

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18:27-29. Thus, Ahmad teaches its formulations "encapsulated in an enteric capsule." McConville ¶¶ 65-66.

To the extent it is argued there is not a specific, enabling disclosure of an enteric capsule, such capsules were well known in the art. For example, Cole teaches that "[e]nteric coated products are designed to remain intact in the stomach and then to release the active substance in the upper intestine" and that "the reasons for using enteric coated preparations are well documented." Ex. 1008 at 83. Cole notes that (in 2002), "site specific delivery into the upper intestine has been achieved for many years by the use of pH-sensitive coatings…" *Id.* at 84. Cole teaches numerous polymers used to achieve this effect: "The polymers commonly used to achieve enteric properties are anionic polymethacrylates (copolymerisate of methacrylic acid and either methylmethacrylate or ethyl acrylate (Eudragit®), cellulose based polymers, e.g. cellulose acetate phthalate (Aquateric®) or polyvinyl derivatives, e.g. polyvinyl acetate phthalate (Coateric®)." *Id.* at 83. Other enteric capsules were also well known. *See, e.g.* Ex. 1012 at 899 (HPE listing numerous "Enteric formulations/coating agents"); McConville ¶ 67-68. Thus, Ahmad, in view of the knowledge of a POSA, enables the enteric capsule limitation. McConville ¶ 67-68.

As detailed above, Ahmad discloses all of the elements of Claim 1, and a person of skill in the art would at once envisage the claimed invention from Ahmad's teachings. McConville ¶ 67. Thus, Ahmad anticipates claim 1. *See Hayward Indus.*,

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Inc. v. Pentair Water Pool & Spa, Inc., 814 F. App'x 592 (Fed. Cir. 2020) ("A prior art reference, however, does not need to include an 'express discussion of the actual combination to anticipate,' but may instead teach that the disclosed elements may be combined such that one of skill in the art could implement the combination.") (citing *Blue Calypso, LLC v. Groupon, Inc*., 815 F.3d 1331, 1344 (Fed. Cir. 2016)).

B. Dependent Claim 2

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

As described above, Ahmad discloses an enteric coated capsule such that the capsule does not release drug throughout its time in the stomach, and delays release until it reaches the intestine. Ex. 1003 at 18:22-24. Thus, a POSA would understand Ahmad to teach a delayed-release formulation. McConville ¶ 72-73. Claim 2 is accordingly also anticipated.

C. Dependent Claim 4

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

As described above, Ahmad discloses an enteric coated capsule such that the capsule does not release drug throughout its time in the stomach. Thus, a POSA would understand Ahmad to teach an enteric coating. McConville ¶ 74. Claim 4 is accordingly therefore also anticipated and/or obvious.

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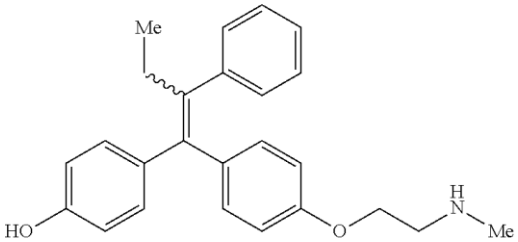
D. Independent Claim 15

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.

While claim 15 is independent, it recites a "method of delivering (Z)-endoxifen to a subject, the method comprising administering to the subject" a formulation that is identical to the oral formulation of claim 1. Ex. 1001 at Claims 15 and 1; McConville ¶ 75; Ex. 1003 at 18:1-7 (administering orally). Thus claim 15 is anticipated for the same reasons as claim 1.

E. Dependent Claim 20

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

Ahmad teaches that its formulations may be used to treat hormone-dependent breast disorders. For example, Ahmad states that the "present invention also provides methods of inhibiting hormone-dependent breast carcinoma in a mammal…." Ex. 1003 at 5:33-36; *see also id.* at 18:47-52, 28:37-38 (teaching

treatment of breast cancer and "other estrogen-sensitive conditions" such as benign breast disease). Thus, a POSA would understand Ahmad to teach a method of treating a patient with the (Z)-endoxifen formulation, "further comprising treating a hormone-dependent breast disorder or a hormone-dependent reproductive tract disorder in the subject." McConville ¶ 76. Claim 20 is accordingly also anticipated by Ahmad.

F. Dependent Claim 21

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.

As described above, Ahmad teaches the use of its formulations for benign breast disorder. *See* Ex. 1003 at 18:54-60 (teaching treatment of benign breast disorders such as hyperplasia). Thus, a POSA would understand Ahmad to teach a method of treating a patient with the (Z)-endoxifen formulation, "wherein the hormone-dependent breast disorder or the hormone-dependent reproductive tract disorder is a benign breast disorder [or] hyperplasia…." McConville ¶ 78. Claim 21 is accordingly also anticipated.

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G. Dependent Claim 22

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.

Tamoxifen had long been used to treat breast cancer. McConville ¶ 19; Ex. 1001 at Fig 1, 1:63-2:6; Ex. 1003 at Fig. 3, 1:35-56; Ex. 1004 at [0003]; Ex. 1005 at [3]. It was well-known in the art that endoxifen is a metabolite of tamoxifen, and thus could be used on patients who could not metabolize or had difficulty metabolizing tamoxifen, leading them to be tamoxifen-refractory or tamoxifen-resistant.

For example, Ahmad teaches that "Endoxifen is generated via CYP3A4-mediated N-demethylation and CYP2D6 mediated hydroxylation of Tamoxifen." Ex. 1003 at 1:57-59. As Ahmad notes, "[u]se of endoxifen, e.g., in place of Tamoxifen, avoids several metabolic steps that rely on CYP2D6." Ex. 1003 at 2:2-5; *see also id.* at 1:64-2:20. A POSA would understand therefore that endoxifen would be expected to be efficacious in patients who were tamoxifen-resistant or tamoxifen-refractory due to metabolic deficiencies. McConville ¶¶ 79-80. In other words, a POSA would understand Ahmad to teach a method of using its formulation for tamoxifen-refractory or resistant conditions. *Id.*

Accordingly, claim 22 is anticipated by Ahmad.

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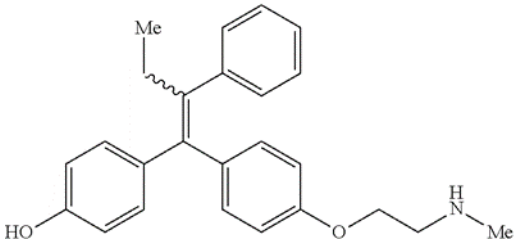
X. Ground 2: Claims 1, 2, 4, 15, and 20-22 are obvious over Ahmad

As explained above, Ahmad teaches the limitations of claims 1, 2, 4, 15 and 20-22, the analysis of which is incorporated by reference. To the extent Ahmad's teachings are not anticipatory, they would have rendered the claimed invention obvious.

A. Independent Claims 1 and 15

1. An oral formulation comprising an endoxifen composition…wherein the endoxifen composition comprises a compound of Formula (III):

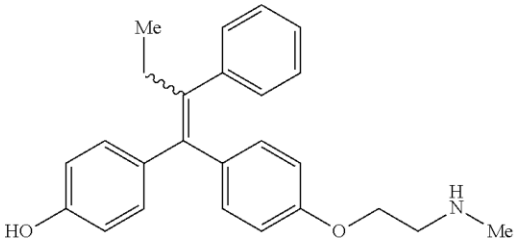
Formula (III)



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

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.

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As explained above, Ahmad teaches all of the limitations of independent claims 1 and 15. To the extent claims 1/15 are not anticipated by Ahmad, it would have been obvious to make the invention based on Ahmad's teachings.

A POSA would have been motivated to use 90% (Z)-endoxifen as taught by Ahmad, because it was known that this form was more active at estrogen receptors. McConville ¶ 62; Ex. 1004 at [0004]. And a POSA would have been motivated to use an enteric capsule as taught by Ahmad, because it would have been understood that endoxifen could degrade in the acidic conditions of the stomach, and as such was typically provided with an enteric coating. McConville ¶ 65; Ex. 1006 (clinical tests using enteric tablets); Ex. 1014 (Intas' Zonalta uses an "enteric coated tablet"); Ex. 1018 at 253 (using "enteric coated tablets" for study); Ex. 1019 at 1353 (noting Z-endoxifen is unstable in acidic conditions). 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. McConville ¶ 68; *supra*. Thus, to the extent Ahmad is not anticipatory, it alone renders claims 1/15 obvious. *See Game & Tech. Co. v. Activision Blizzard Inc.*, 926 F.3d 1370, 1381 (Fed. Cir. 2019).

B. Dependent Claim 2

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

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As explained above, Ahmad teaches a delayed-release formulation in the form of an enteric coating. Motivated as detailed above for claims 1/15, it would have been routine in the art to further add delayed release elements to the coating to ensure release later in the GI tract. McConville ¶¶ 72-73. Thus, to the extent claim 2 is not anticipated by Ahmad, it would have been obvious over Ahmad.

C. Dependent Claim 4

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

As described above, Ahmad discloses an enteric coated capsule such that the capsule does not release drug throughout its time in the stomach. Thus, a POSA would understand Ahmad to teach an enteric coating. McConville ¶ 74. Enteric coatings were also well known in the art. *See id.*; Ex. 1008. Thus, it would have been obvious to use an enteric coating to form the enteric capsule of claim 1. Accordingly, to the extent not already anticipated by Ahmad, claim 4 would have been obvious over Ahmad.

D. Dependent Claims 20 and 21

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

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puberty, McCune-Albright Syndrome, endometrial cancer, ovarian cancer, uterine cancer, cervical cancer, vaginal cancer, or vulvar cancer.

As explained above, Ahmad teaches that the use of its endoxifen formulations for breast cancer and other hormone-dependent breast disorders. To the extent not anticipated by Ahmad, it would have been obvious to use an enteric coated (Z) endoxifen formulation as taught by Ahmad to treat hormone-dependent breast disorders or a hormone-dependent reproductive tract disorder in the subject. It was known in the art that hormone-dependent breast disorders (such as cancer) could be treated by tamoxifen. *See, e.g.*, Ex. 1004 at [0004]; Ex. 1006 at 814; McConville ¶ 76-78.

E. Dependent Claim 22

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.

To the extent Ahmad does not explicitly teach a method of treatment of a tamoxifen-refractory or resistant condition, it would have been obvious to use an endoxifen composition for such purpose. It was well known in the art that endoxifen was the active metabolite of tamoxifen and that some individuals could not adequately metabolize tamoxifen, therefore the use of endoxifen could be effective for those who did not respond to tamoxifen.

For example, Liu taught that "[s]ome patients do not respond to tamoxifen treatment because they do not produce adequate amounts of afimoxifen and

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endoxifen, sometimes due to low levels of the metabolizing enzymes" but that "[g]iving the active (Z)-endoxifen form directly to tamoxifen non-responsive patients has been shown to result in significantly higher endoxifen blood levels compared to giving a similar dose of tamoxifen, and shows evidence of tumor regressions as shown in a phase I study." Ex. 1004 at [0003].

Other references such as Song and Ahmad 2010 and 2012 also teach this possibility. *See* Ex. 1005 at [3] ("tamoxifen can be converted into its active metabolite, endoxifen, by a metabolic enzyme, CYP2D6, present in the liver and endoxifen offers anti-hormone effects. However, there are about 30% of patients with estrogen receptor-positive breast cancer who are genetically deficient in CYP2D6. In case of them, even if tamoxifen is administered, the tamoxifen is not converted into its active form, endoxifen, and, therefore, therapeutic effects cannot be offered."); Ex. 1006 at 816 ("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."); Ex. 1007 at 1 ("Direct administration of endoxifen would not be subject to pharmacogenetic variations or drug-drug interactions").

Accordingly, it was well known in the art that endoxifen could be used for patients who were intractable to or could not be effectively treated by tamoxifen. McConville ¶¶ 79-82.

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Accordingly, if not anticipated, claim 22 would have been obvious over Ahmad, in view of the knowledge of a POSA as demonstrated by the Endoxifen Art.

XI. Ground 3: claims 5-8, 16, and 17 would have been obvious over Ahmad in view of Cole

As described above, independent claim 1 is anticipated by and/or obvious over Ahmad. Such discussion is incorporated by reference into Ground 3. The limitations not expressly disclosed in Ahmad are merely the routine results of the use of its enteric coated formulations, as shown by for example Cole.

A. Dependent Claim 5

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.

As Ahmad teaches, the purpose of the enteric coating is to prevent release of drug in the stomach (at low pH), i.e., is resistant to dissolution in an acidic environment. Ex. 1003 at 18:19-21. As explained above, Cole teaches a method of such enteric coated capsules. Cole further teaches that "[n]o paracetamol[6] was released over 2 h at pH 1.2 from the capsules coating with 6 and 8 mg cm^{-2} Eudragit®

[6] Paracetamol is the sample active ingredient used in Cole. A POSA would understand that the identity of the active ingredient is immaterial as to whether it is released from a capsule, because it is entirely contained in the capsule until the capsule breaks open. McConville ¶ 85 n.3.

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L 30 D-55." Ex. 1008 at 89. Thus, Cole teaches that its enteric coating prevents drug release for at least two hours under strongly acidic conditions. McConville ¶¶ 85-86. While Cole does not disclose explicitly that the method used was USP 711, a POSA would recognize that USP 711 is the most common method for dissolution testing, and would understand from Cole's methodology that it was using USP 711. McConville ¶ 86-87.

Thus, a POSA would understand Cole to teach that enteric coating capsules, such as those taught in Ahmad, would be "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." McConville ¶ 88. This resistance to dissolution would be the purpose of enteric coating, and a POSA would have been motivated to achieve such a formulation 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. *Id.* ¶ 89. And a POSA would have had a reasonable expectation of success in achieving this release rate, as is taught by Cole. *Id.*

Claim 5 is accordingly obvious over Ahmad in view of Cole.

B. Dependent Claims 6 and 16

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

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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.

As described above for claim 5, a POSA would understand that the enteric coating, such as that disclosed in Cole, would resist degradation in acid and thus would not release the (Z)-endoxifen over at least 2 hours. The pH of the human stomach is 1.5. Ex. 1016 at 8. Thus, the conditions described above in Cole (using a pH of 1.2) show that its enteric coatings would not release any drug for 2 hours in gastric fluid or in the stomach. McConville ¶¶ 90-92.

Accordingly, a POSA would understand Cole to teach that enteric coating capsules, such as those taught in Ahmad, would be "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" and a method of using them would comprise "releasing no more than 10% of the (Z)-endoxifen in a stomach of the subject within 2 hours following administration."

Again, 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. McConville ¶ 91. And a POSA would have had a reasonable

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expectation of success in achieving this release rate as taught by Cole. *Id.* Accordingly, claims 6 and 16 would have been obvious over Ahmad in view of Cole.

C. Dependent Claims 7 and 17

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.

As Ahmad teaches, the purpose of its enteric coating is to prevent release of medication before it reaches the small intestine, then trigger release. Ahmad teaches that enteric coatings work by breaking down rapidly at the relatively higher pH of the small intestine. Ex. 1003 at 18:19-26. For example, Cole teaches that at "pH 6.8,[7] release of the paracetamol was rapid…." Ex. 1008 at 89; *see also* Ex. 1008 at 91 Fig. 4 (showing 50% release in pH 6.8 by about 2.5-3 hours). Thus, a POSA would understand that Ahmad's formulation coated according to Cole would be made "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

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

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method of USP 711" and release "at least 50% of the (Z)-endoxifen in a small intestine of the subject within 8 hours following administration." McConville ¶ 93.

A POSA would have been motivated to achieve such a formulation and method of using it to ensure that the endoxifen was released in the small intestine where it could be absorbed into the body and have pharmaceutical effect. *Id.* ¶ 94. A POSA would have had a reasonable expectation of success as this is taught in Cole. *Id.*

Accordingly, claims 7 and 17 would have been obvious over Ahmad in view of Cole.

D. Dependent Claim 8

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

Cole teaches that HPMC capsules had been available commercially since at least 1992. Ex. 1008 at 84; *see also* Ex. 1009 at Abstract (reporting in 2010 that "the new HPMC capsule is satisfactorily qualified and has since been used successfully for nearly 20 investigational new drug (IND) compounds."). Ku studied the HPMC capsule, compared it to traditional gelatin capsules and concluded that "Comparisons to gelatin and HPMC capsule containing carrageenan showed the new HPMC capsule is superior in terms of mechanical strength, hygroscopicity and compatibility with a wide range of drugs." Ex. 1009 at 40.

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Cole uses HPMC capsules, and "demonstrate[d] that the enteric coating of HPMC capsules is an industrially viable process" because it is a "good substrate for adhesion of the coating material, which results in all around uniform film, providing gastric integrity." Ex. 1008 at 93. It concludes that "Enteric coated HPMC capsules can thus be considered to provide a good container for drugs during the early development phase providing the possibility of drug release either in the small intestine or towards the colon." *Id.* at 94. In short, Cole and Ku teach that HPMC capsules are effective. McConville ¶¶ 95-96.

Thus, it would have been obvious for a POSA making the enteric coated capsules of Ahmad to use an HPMC capsule, such as Vcaps Plus®. A POSA would have been motivated to do so to achieve the benefits of HPMC capsules over gelatinous capsules, as described in Ku, and as a matter of routine design choice. McConville ¶ 97.

XII. Ground 4: claim 3 would have been obvious over Ahmad in view of Benameur

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

As discussed above, claim 1 is anticipated and/or obvious over Ahmad, which teaches the use of an endoxifen formulation encapsulated in an enteric coated capsule. It would have been a routine and obvious modification of Ahmad to instead use an uncoated enteric capsule, as had been developed in the art by e.g., Capsugel. McConville ¶ 98.

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Benameur teaches that the "major hurdle in oral delivery of many sensitive molecules, such as nucleotides, peptides, live biopharmaceutical products, and vaccines, is protecting the active entity from acidic and enzymatic degradation in the GI tract." Ex. 1010 at 35. It further teaches that "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." *Id.* at 34. Instead, "ECDDT's intrinsically enteric properties are attained by incorporating pharmaceutically approved enteric polymers in the capsule shell using conventional pin-dipping capsule manufacturing processes." *Id.* "By eliminating the preparation and application steps used for enteric coating, ECDDT can…enable the oral delivery of sensitive molecules…which can degrade at the high temperatures or can be sensitive to aqueous coating solution associated with pan and fluid bed coating processes." *Id.* "The enteric properties and rapid release of specialized ECDDT capsule shells have been demonstrate to meet pharmacopeia standards for both in vitro and in vivo performance using esomeprazole magnesium trihydrate (EMT) as a model compound." *Id.* Further, such capsules were commercially available by October 7, 2016.[8]

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[8] Such capsules are sold as Vcaps Enteric. https://www.capsugel.com/biopharmaceutical-products/vcaps-enteric-capsules. These capsules were released October 7, 2016.

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Thus, a POSA would understand Benameur to teach the alternative use of an uncoated enteric capsule rather than an enteric coated capsule as taught by Ahmad. McConville ¶¶ 99-100. 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, and as a routine design choice. *Id.* ¶ 101.

As Benameur teaches, its capsules obtained the same results as those discussed above for the enteric coated capsules taught by Cole. *See* § XI. *supra*. 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 find these capsules an effective alternative to the coated capsules taught in Ahmad, and would have had a reasonable expectation of success in using Benameur/Capsugel's intrinsic capsules with the formulation of Ahmad. McConville ¶ 102.

Accordingly, Claim 3 would have been obvious over Ahmad in view of Benameur.

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https://www.capsugel.com/news/capsugel-launches-vcaps-enteric-capsules-for-enteric-protection-and-delayed

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XIII. Ground 5: claims 9-13 would have been obvious over Ahmad in view Stegemann and/or the HPE

Claims 9-13 recite various common excipients for use in capsules. Each of these was well-known as disclosed for example in Stegemann and the HPE. McConville ¶ 103. Thus, these claims would have been obvious over Ahmad in view of Stegemann and/or the HPE.

A. Dependent Claim 9

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

A filler (also sometimes called a diluent) is a common pharmaceutical excipient that increases the volume of a pharmaceutical formulation. McConville ¶ 104. It helps make the ingredients easier to process, stabilizes the formulation, and makes the formulation a suitable size for consumption. *Id.*; Ex. 1021 at 184.

Fillers are well known in the pharmaceutical industry. *Id.* ¶ 105. For example, Stegemann teaches that several excipients function as fillers at higher volumes. Ex. 1011 at 7-8 ("Talcum, for instance, serves as a lubricant in concentrations below 5%. At higher concentrations, it is mainly considered a filler… And besides being an excellent filler, microcrystalline cellulose also serves as a disintegrant… Starch, which is commonly added to tablets as a disintegrant owing to its macerating properties of 5% to 10%, might be used as a filler in hard gelatin capsules…."); *see also* Ex. 1012 (HPE) at 900 ("Fillers *see* Diluents (tablet/capsule)"), 897 (listing

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"Diluents tablet/capsule" including talc, calcium carbonate, sugar spheres, microcrystalline cellulose, kaolin, mannitol, sorbitol, starch, pregelatinized starch, and others).

As taught by these references, the use of a filler in the formulation was a routine and common practice in the formulation arts. McConville ¶ 106. A POSA would have been motivated to use a filler for its normal use, to make the ingredients easier to process, stabilizes the formulation, and makes the formulation a suitable size for consumption, and would have had a reasonable expectation of success, as fillers were a commonplace excipient in the art. ¶ 107.

Accordingly, claim 9 would have been obvious over Ahmad in view of Stegemann and/or the HPE.

B. Dependent Claim 10

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

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,

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starch, pregelatinized starch, and others); Ex. 1021 at 184 (listing "lactose, microcrystalline cellulose and starch"). Accordingly, the selection of these fillers would be an obvious and routine formulation decision. McConville ¶ 108.

Claim 10 is accordingly obvious over Ahmad in view of Stegemann and/or The Pharmaceutical HPE.

C. Dependent Claim 11

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

A disintegrant is a common pharmaceutical excipient that increases dissolution of a formulation once it is in a proper medium. McConville ¶ 109. It helps "ensure that the active ingredient is made available quickly and absorbed by the body in the proper location." *Id.*; *see also* Ex. 1021 at 184.

Disintegrants are well known in the pharmaceutical industry. *Id.* ¶ 110. Ahmad teaches that "pharmaceutically acceptable carrier" "refers to any of the standard pharmaceutical carriers including…disintigrants [sic] (e.g., potato starch or sodium starch glycolate…." Ex. 1003 at 8:31-38. Similarly, Stegemann teaches use of the following ingredients as disintegrants:

Disintegrants

→ To ensure disintegration of powder mixture

- Croscaramellose
- Crospovidone
- Sodium glycyl starch
- Corn starch
- Starch 1500
- Alginic acid

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Ex. 1011 at 8. *See also* Ex. 1012 at 897-98 (listing disintegrants); Ex. 1021 at 184 (same).

As taught by these references, the use of a disintegrant in the formulation was a routine and common practice in the formulation arts. McConville ¶ 111. A POSA would have been motivated to use a disintegrant for its normal use, ensure that the active ingredient is made available quickly and absorbed by the body in the proper location, and would have had a reasonable expectation of success as disintegrants were commonly used excipients. *Id.* ¶ 112.

Accordingly, claim 11 would have been obvious over Ahmad in view of Stegemann and/or the HPE.

D. Dependent Claim 12

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

A lubricant is a common pharmaceutical excipient that decreases the friction between pharmaceutical formulations and the tableting equipment contact surface. McConville ¶ 113. Lubricants "help[] make processing and manufacturing more efficient." *Id.*

Lubricants are well known in the pharmaceutical industry. *Id.* ¶ 114. For example, Stegemann teaches the use of lubricants in capsules:

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Lubricants

→ Improved flow properties and reduced powder adhesion to metal parts

- Magnesium stearate
- Glyceryl monostearate
- Stearic acid

Ex. 1011 at 8. *See also* Ex. 1012 at 905 (listing "Lubricants (tablet/capsule)").

As taught by these references, the use of a lubricant in the formulation was a routine and common practice in the formulation arts. McConville ¶ 115. A POSA would have been motivated to use a lubricant for its normal use, to make processing and manufacturing more efficient. *Id.* at 116. Accordingly, claim 12 would have been obvious over Ahmad in view of Stegemann and/or the HPE.

E. Dependent Claim 13

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

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; *see also* 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).

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Accordingly, the use of these lubricants would have been routine and well known. McConville ¶¶ 117-18.

Accordingly, claim 13 would have been obvious over Ahmad in view of Stegemann and/or the HPE.

XIV. Ground 6: claims 14, 18 and 19 would have been obvious over Ahmad in view of Ahmad 2010 and Ahmad 2012

A. Dependent Claim 14

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

The recited dosing range would have been readily apparent to a POSA based on what was known in the art. First, Ahmad teaches in its examples that "oral doses of endoxifen (1 mg-10 mg/day) with biculatamide [sic] are expected to prevent development of biclutamide-induced [sic] gynecomastia and breast pain." Ex. 1003 at 29:20-31. Further, Ahmad 2010 and Ahmad 2012 provide safety data suggesting the appropriate dosage of endoxifen. For example, Ahmad 2010 teaches that "a dose of 4 mg of endoxifen should be appropriate for breast cancer prevention and therapy." Ex. 1006 at 816. Similarly, Ahmad 2012 confirmed that 4 mg doses "were safe, well tolerated and bioavailable" and that "Multiple daily endoxifen doses of 4.0-8.0 mg resulted in endoxifen exposures that would be sufficient for effective therapy." Ex. 1007 at 1-2.

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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. McConville ¶ 121. 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, e.g., 4 to 8 mg. *Id.* ¶¶ 120-21.

Accordingly, claim 14 would have been obvious over Ahmad in view of Ahmad 2010 and Ahmad 2012.

B. Dependent Claim 18

18. The method of claim 15, further comprising producing an area under curve ($AUC_{0\text{-}inf}$) 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

AUC is a measurement of the exposure to drug in the body after dosing. McConville ¶ 122.

The recited AUC limits 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 in subjects treated with from 0.5 to 4.0 mg:

Table 1 Endoxifen doses and pharmacokinetic parameters

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

Ex. 1006 at 815. As shown above, the AUC for 4 mg is well within the recited range. Accordingly, a POSA would understand that the method of using the formulations of Ahmad with 4 mg of endoxifen would result with an AUC within the recited range. McConville ¶ 123.

Further, Ahmad 2010 teaches that the data it obtained is expected to be effective, and thus a POSA would have been motivated to obtain similar pharmacokinetic data using the capsules disclosed in Ahmad. McConville ¶ 124. And a POSA would have had a reasonable expectation of success in doing so through routine skill and optimization. *Id.*

C. Dependent Claim 19

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

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 C_{max} achieved from 0.5 to 4.0 mg:

Table 1 Endoxifen doses and pharmacokinetic parameters

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

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

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

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

Ex. 1006 at 815. As shown above, the Cmax for 4 mg is within the recited range. Accordingly, a POSA would understand that a method of using the formulations of Ahmad with 4 mg of endoxifen would result in a Cmax in the recited range. McConville ¶ 126.

Further, Ahmad 2010 teaches that the data it obtained is expected to be effective, and thus a POSA would have been motivated to obtain similar pharmacokinetic data using the capsules disclosed in Ahmad. McConville ¶ 127. And a POSA would have had a reasonable expectation of success in doing so through routine skill and optimization. *Id.*

XV. Conclusion

Petitioner has established it is more likely than not that each of claims 1-22 of the 334 patent is unpatentable, and therefore respectfully requests that the Board institute post grant review of those claims.

Respectfully submitted,

McANDREWS, HELD & MALLOY, LTD.

Dated: August 18, 2023 By: /*Alejandro Menchaca*/
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Atossa Therapeutics, Inc. Exhibit 2018
Intas Pharms Ltd. v. Atossa Therapeutics, Inc.
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CERTIFICATE OF WORD COUNT

I certify under 37 CFR § 42.24 that this **PETITION FOR POST GRANT REVIEW** contains fewer than 11,643 words, as determined by Microsoft Word.

Dated: August 18, 2023

By: */Alejandro Menchaca/*
Alejandro Menchaca *for Petitioner Intas Pharmaceuticals Ltd.*.

CERTIFICATE OF SERVICE

Under 37 C.F.R. §§ 42.6(e)(4) and 42.105, the undersigned certifies on this date, a true and correct copy of the Petition for Post Grant Review of U.S. Patent No. 11,572,334 (PGR2023-00043), including Exhibits 1001-1021, were served, via Federal Express to the Patent Owner at the following correspondence address of record for U.S. Patent No. 11,572,334:

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