

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

EXPERT DECLARATION OF JASON McCONVILLE, Ph.D.

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I Jason, McConville, Ph.D., do hereby declare:

I. Introduction

1. I have been retained to provide my expert opinions on behalf of Intas Pharmaceuticals, Limited., in support of a petition for post grant review of claims 1-22 of U.S. Patent No. 11,572,334 (“the 334 patent”; Ex. 1001), which challenges the validity of the 334 patent.

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

II. Education and Professional Background

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

4. I am an Associate Professor of Pharmaceutics at the University of New Mexico College of Pharmacy and an Adjunct Professor at the University of Bonn, in the Department of Pharmaceutical Technology, in Bonn, Germany.

5. I received my Bachelor of Science, with Honours, in Applied Chemistry from Coventry University, in Coventry, United Kingdom in 1994. From 1994 to 1999, I was a Research Technician in Pharmaceutics at the Centre for Drug Formulation Studies at the University of Bath, in Bath, United Kingdom. My main

research project pertained to controlled-release drug delivery, and specifically hydrophilic gel formation and drug release.

6. I subsequently earned my Ph.D. in Pharmaceutics from the University of Strathclyde, in Glasgow, United Kingdom in 2002. My Ph.D. dissertation was titled “Pulsed-Release Drug Delivery and Development of the Time-Delayed Capsule.”

7. After earning my Ph.D., I was a Post-Doctoral Fellow at the University of Texas at Austin College of Pharmacy from 2002 to 2006.

8. In 2006, I joined the faculty at the University of Texas at Austin as an Assistant Professor of Pharmaceutics in the College of Pharmacy. I assumed my present positions at the University of New Mexico and the University of Bonn in 2012.

9. I am a member of several professional societies, including the American Association of Colleges of Pharmacy, the American Association of Pharmaceutical Scientists, and the International Pharmaceutical Excipients Council (IPEC) of the Americas. Additionally, I have served as a scientific advisor to the Respiratory Drug Delivery Conference in Arizona, 2012, as a scientific advisor to the IPEC Americas excipient conference from 2017-2019. Furthermore, in 2017 I also served as a reviewer for the conference proceedings at the 2017 Annual Meeting of the International Pharmaceutical Excipient Council, which included

publications on the use and functionality of a wide range of pharmaceutical excipients. Additionally, I have had a recurring role as scientific advisor to the Drug Delivery to the Lungs conference since 2016.

10. I have taught many courses related to pharmaceutical dosage form, design, and development. For example, I have taught biopharmaceutics and pharmacokinetics to pharmacy students since 2007, in a variety of different core pharmacy courses. As an overview, the course material includes instruction on all main routes of drug delivery and formulation, and includes oral delivery systems such as tablets, capsules formed of film compositions, and oral suspensions. I have also been an advisor to 28 graduate and Pharm.D. students and have been on the dissertation committee for 14 students.

11. I have performed practical-design, development and manufacturing work related to a wide variety of solid oral dosage forms over the last 25-plus years. Further, during my doctoral studies, I worked extensively with delayed drug-release formulations, which included coated capsule formulation designs to delay drug release for targeting to specific parts of the GI tract, such as the distal small intestine or colon. During the course of these studies, I looked extensively at the process of capsule coating, different excipients for capsule filling, and particularly the dissolution performance of delayed release capsules using standardized testing.

12. I have co-authored more than 60 articles, more than 130 abstracts, and many book chapters, including on the topics of oral-dosage design, formulation, and delivery. I have also been a session chair, an invited speaker, or workshop participant on more than 40 occasions, and have served as a Review Panel Member at the National Institutes of Health in 2011, 2017, and 2020.

13. I have acted as the editor of at least four special themed editions for journals, and serve on the editorial boards for journals *Inhalation*, and *Pharmaceutics*, and as an Associate Editor for *Drug Development and Industrial Pharmacy* I have also served, and currently serve, as a reviewer for several leading scientific journals, including *Drug Development and Industrial Pharmacy*, *European Journal of Pharmaceutical Sciences*, *European Journal of Pharmaceutics and Biopharmaceutics*, *International Journal of Pharmaceutics*, *Journal of Controlled Release*, *Journal of Pharmaceutical Sciences*, *Pharmaceutical Research*, and *Molecular Pharmaceutics*.

14. I have received various awards and recognition for my research, including: a research award for a presentation entitled “Design and Evaluation of Pulsatile Drug Delivery Capsule” (University of Strathclyde, Glasgow, May 2001), an outstanding presentation award for “Microwave Dielectric Analysis of Wet Granulations for Erodible HPMC Tablets” (British Pharmaceutical Conference, Glasgow, United Kingdom, September, 2001), a Graduate/Post-Doc Award in

Innovative Aspects of Oral Drug Delivery and Absorption for “Improved Dissolution Rate and Bioavailability through the Formation of a Highly Miscible Binary Mixture” (International Symposium on Controlled Release of Bioactive Materials, Miami, FL, June, 2005), a Best Resident and Research Presentation Award: “Aerosolized Itraconazole (ITZ) as Prophylaxis against Invasive Pulmonary Aspergillosis (IPA) due to *Aspergillus fumigatus*” (American College of Clinical Pharmacy Annual Meeting, 2006), and three research presentation award for novel excipient use presentations from the International Pharmaceutical Excipients Council of the Americas (2009, 2012, and 2014). I have been invited to original papers to renowned pharmaceutical science peer reviewed journals at least 18 times, and have been invited to judge research at international conferences at least 6 times. Additionally, I was selected as Member of the Society for Teaching Excellence at the University of Texas at Austin in 2011, nominated for University of Texas System Regents’ Outstanding Teaching Award in 2012, and an Innovation Award for my work on controlled release thermally gelling polymeric systems.

15. I am a named inventor on thirteen patents or patent applications.

III. Compensation

16. I am being compensated for the time I spend on this matter at my ordinary rate of \$700 per hour for expert consulting and \$900 per hour for expert

testimony. I am reimbursed for my reasonable expenses incurred in connection with my work on this matter. My compensation does not depend on the opinions I offer or on the outcome of this proceeding or any other proceeding.

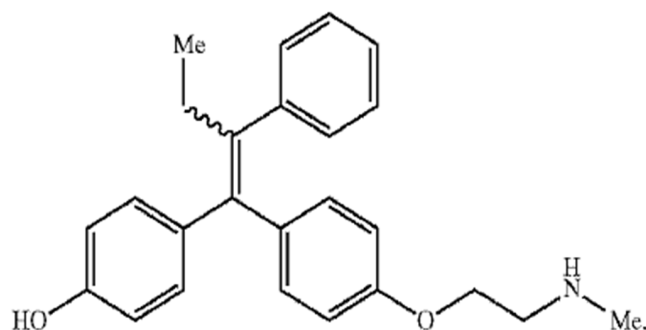
IV. Background

17. The claims of the 334 patent are directed to oral formulations of endoxifen that is 90% by weight (Z)-endoxifen encapsulated in an enteric capsule, and methods of administering such formulations.

18. Endoxifen is the common name given to the compound with the chemical formula 4-hydroxy-*N*-desmethyltamoxifen, a nonsteroidal selective estrogen receptor modulator. I understand that Intas sells endoxifen in India under the brand name Zonalta for the treatment of manic depressive disorder. *See* Ex. 1014.

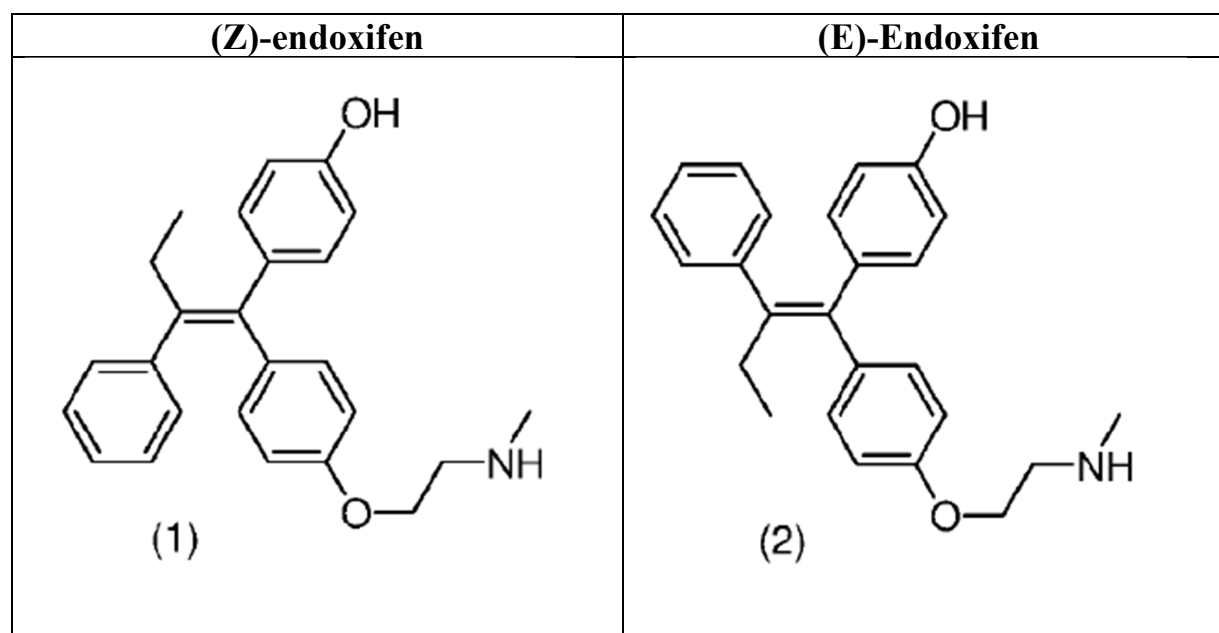
19. Endoxifen has been known for years, and is an active metabolite of tamoxifen, which has long been used to treat breast cancer. *E.g.*, Ex. 1001 at Fig 1, 1:63-2:6; Ex. 1003 at Fig. 3, 1:35-56; Ex. 1004 at [0003]; Ex. 1005 at [3]. Thus, interest in endoxifen itself as a treatment for breast cancer has been contemplated and studied in the prior art. Ex. 1003 at 1:64-2:4; Ex. 1004 at [0003]; Ex. 1005 at [1]; Ex. 1006; Ex. 1007.

20. Endoxifen can be depicted by the following diagram, referred to as Formula III in the 334 patent:



Ex. 1001 at *e.g.* 3:1-15.

21. The wavy line in the above diagram represents that the attached ethyl group (—Me refers to CH₂-CH₃ or an ethyl group) can be positioned in one of two directions, forming what are known as stereoisomers. Stereoisomers are compounds with the same chemical formula, but a different three-dimensional arrangement of atoms. A person of skill understands that this molecule can be found in two isomeric forms, (E) and (Z), as depicted below:



Ex. 1004 at Abstract.

22. It was known in the art that the (Z) isomer was more active at the estrogen receptor, and thus beneficial for the treatment of breast cancer. Ex. 1004 at [0004].

23. Some drugs, including endoxifen, are subject to acid-catalyzed degradation in the low pH acidic conditions of the stomach. *E.g.*, Ex. 1003 at 18:19-21. To prevent such degradation, enteric capsules or tablets may be used, which remain intact in the stomach and release the active substance in the upper intestine where the pH is higher. 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.

V. The 334 patent

24. The 334 patent is titled "Methods for making and using Endoxifen." Ex. 1001 at Cover. It was filed on January 20, 2022, but is 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.* Thus I have been instructed to use September 11, 2017 as the time of invention, and to consider my opinions from the perspective of a person of skill at that time.

25. The 343 patent is directed to oral formulations of endoxifen that are 90% by weight (Z)-endoxifen, encapsulated in an enteric capsule, and methods of

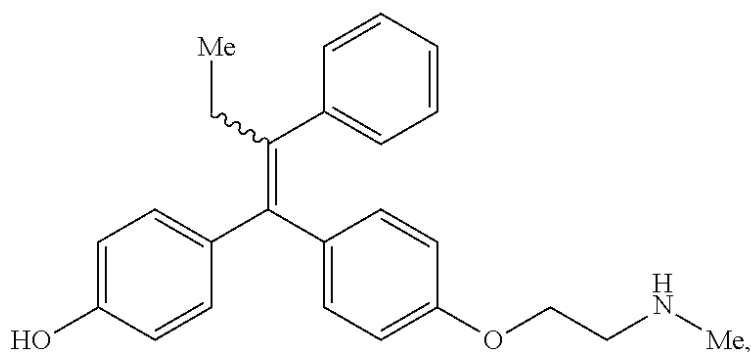
administering such formulations. The enteric capsule may be either a capsule made enteric by coating “with one or more enteric coating agent,” or an intrinsically enteric capsule that does not need an additional coating to provide the enteric property. *Id.* at 39:19-30, 40:31-36.

26. I understand that the 334 patent contains the following 22 claims:

Independent claim 1 and dependent claims 2-14

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.

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.

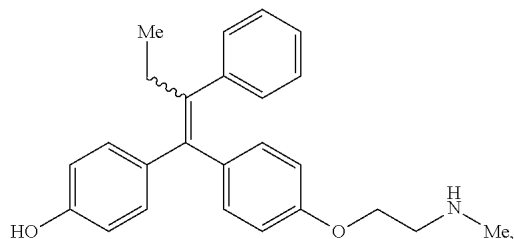
13. The oral formulation of claim 12, wherein the lubricant comprises calcium stearate, magnesium stearate, zinc stearate, mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil, ethyl oleate, ethyl laureate, agar, or combinations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

Formula (III)



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

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 (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.

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.

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.

VI. Person of ordinary skill in the art

27. I understand that the content of a patent (including its claims) and prior art should be interpreted the way a person of ordinary skill in the art (or “POSA”) would have interpreted the material at the time of the alleged invention. In my opinion, a POSA for purposes of the 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. I base this opinion off of my review of the 334 patent, the problems the 334 patent was attempting to solve, the prior art discussed below, and my general experience with pharmaceutical formulation development field and the people working in the field. I meet and/or exceed the definition of a

POSA. I also note that my opinions would not change if the level of skill in the art were found to be lower.

VII. Claim construction

28. I understand that terms should be given their plain and ordinary meaning to a person of skill at the time of invention. I have applied this principle to all terms in the 334 patent.

29. The only term I believe warrants special consideration is the term “enteric capsule” in independent claim 1. In my opinion, this term would be understood by a POSA to mean a capsule with enteric properties, including both a capsule “with one or more enteric coating agent[s],” or an intrinsically enteric capsule that does not need an additional coating to provide the enteric property. The 334 patent describes both of these possibilities as an “enteric capsule,” consistent with how a POSA would view this term. Ex. 1001 at 39:19-30, 40:31-36.

VIII. Summary of the prior art

A. US 9,333,190 (“Ahmad”)

30. I understand that 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) and is therefore prior art to the 334 patent.

31. 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, 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.* at 12:14-17; *see also id.* at 2:24-40, 3:55-61. Ahmad teaches that this purification can be accomplished by using crystallization or chromatography. As I discuss below, achieving such levels of purity was well known in the art as disclosed by several references.

32. 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 18:19-29. 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.*

Ahmad's definition of enteric and description of enteric coatings are standard in the art.

33. Ahmad also teaches that the "compositions of the present invention can be employed to treat breast cancer and breast related diseases." *Id.* at 18:47-66. In sum, Ahmad teaches the use of enteric coated capsules of highly pure (Z)-endoxifen to treat breast cancer and other breast diseases.

B. Endoxifen Art

1. WO 2017/070651 ("Liu")

34. I understand that international application WO 2017/070651 ("Liu") was filed on October 24, 2016, and published on April 27, 2017 (Ex. 1004 at Cover) and is therefore prior art to the 334 patent.

35. Liu teaches an efficient method of generating highly pure (Z)-endoxifen through crystallization. Liu teaches that its method achieved "1698 g (34%) of (Z)-endoxifen, with an isomeric purity of 99% (HPLC analysis)." *Id.* at [0076]. In short, Liu teaches a method of making highly pure (Z)-endoxifen.

2. WO 2012/050263 ("Song")

36. I understand that international application WO 2012/050263 ("Song") was filed on December 16, 2010, and published on April 19, 2012 (Ex. 1005 at Cover) and is therefore prior art to the 334 patent.

37. 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. In short, Song also teaches a method of making highly pure (Z)-endoxifen.

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”)

38. I understand that 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 in 2010 (Ex. 1006) and is therefore prior art to the 334 patent. Ahmad 2010 is cited in the 334 patent as a prior publication. Ex. 1001 at 2:45-46.

39. Ahmad 2010 teaches that “Endoxifen is an active metabolite of tamoxifen, a drug 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 (C_{max}) and area under the concentration–time curve extrapolated from 0 to ∞ (AUC_{0– ∞}) 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.* In short, Ahmad 2010 teaches that the use of endoxifen is likely to be safe and effective for the treatment of breast cancer.

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”)

40. I understand that 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”) was

presented June 4, 2012 (Ex. 1007) and is therefore prior art to the 334 patent.

Ahmad 2012 is cited in the 334 patent as a prior publication. Ex. 1001 at 2:46-47, 96:3-4.

41. Ahmad 2012 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." Ex. 1007 at 2. 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.* at 2. 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.* In short, Ahmad 2012 also teaches that the use of endoxifen is likely to be safe and effective for the treatment of breast cancer.

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")

42. I understand that Cole, E., et al., Enteric coated HPMC capsules designed to achieve intestinal targeting, 231 INTL J. PHARMACEUTICS 83-95 (2002) ("Cole") was published in 2002 (Ex. 1008) and is therefore prior art to the 334 patent.

43. 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. I agree with Cole’s summary. Cole “describe[d] the manufacture of two different Eudragit® coated HPMC capsules and their in vitro/in vivo performance.” *Id.* 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.* In short, Cole teaches the effective use of an enteric coating to form capsules that will bypass the stomach and release drug in the intestine.

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”)

44. I understand that 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 in February 2010 (Ex. 1009) and is therefore prior art to the 334 patent.

45. 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. Ku explains that Vcaps Plus® launched “mid-2007 and the new Shell 2 has since been used successfully in over a dozen IND compounds.” *Id.* The 334 patent describes the use of Vcaps Plus®. Ex. 1001 at 40:46-55. In short, Ku teaches the use of HPMC capsules as an effective alternative to traditional gelatin capsules

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

46. I understand that Benameur, H., Capsule Technology, Enteric Capsule Drug Delivery Technology – Achieving Protection Without Coating, 15(5) DRUG DEV. & DELIVERY 34-37 (2015) (“Benameur”) was published in June 2015 (Ex. 1010) and is therefore prior art to the 334 patent. Ex. 1010 includes a duplicate version of the Benameur article that was procured from <https://archive.org/web/> and reflects that the Benameur article was captured by <https://archive.org/web/> on July 19, 2015. I have confirmed that the Benameur article is present at <https://archive.org/web/> with a capture date of July 19, 2015.

47. Benameur describes an intrinsically enteric capsule that does not require coating. It 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. “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.” *Id.* at 36.¹ In sum, Benameur teaches the use of capsules with intrinsic enteric capabilities that do not require an enteric coating.

D. General Capsule Formulation Art

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

48. Stegemann, S., *Hard gelatin capsules today – and tomorrow*, CAPSUGEL LIBRARY (2002) (“Stegemann”) was published in 2002 (Ex. 1011)² and therefore is prior art to the 334 patent.

49. Stegemann describes capsules and their history, as well as summarizes some of the basic mechanisms of manufacturing capsules known to those of skill in the art. Table 4 displays “Excipients used in formulations of immediate release hard gelatin capsules.” While this table is for immediate-release hard gelatin capsules, a POSA would understand that the same excipients would be used for a

¹ I understand that such capsules are sold as Vcaps Enteric. <https://www.capsugel.com/biopharmaceutical-products/vcaps-enteric-capsules>. I further understand from Capsugel’s website that these capsules were released October 7, 2016. <https://www.capsugel.com/news/capsugel-launches-vcaps-enteric-capsules-for-enteric-protection-and-delayed>

² Available from <https://www.capsugel.com/knowledge-center/hard-gelatin-capsules-today-and-tomorrow>

delayed-release capsule wherein the delay is achieved via application of a coating to the outside of a capsule or by the capsule material itself, rather than the excipients contained within the capsule.

Diluents

→ Improved plug formation and compression

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

Lubricants

→ Improved flow properties and reduced powder adhesion to metal parts

- Magnesium stearate
- Stearic acid
- Glyceryl monostearate

Glidants

→ Improved powder flow properties

- Aerosil
- Talcum

Disintegrants

→ To ensure disintegration of powder mixture

- Croscarmellose
- Crospovidone
- Sodium glycyll starch
- Corn starch
- Starch 1500
- 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”)**

50. I understand that the HANDBOOK OF PHARMACEUTICAL EXCIPIENTS FIFTH EDITION (Rowe, R., Sheskey, J. & Owen, S., eds., 2006) (“HPE”), Fifth Edition was published in 2006 (Ex. 1012) and is therefore prior art to the 334 patent.

51. The HPE is well known to those of skill in the art as a go to guide to learn about various excipients and their uses. For example, the index provides a list of excipients by category, directing those in the art to information about how to use that excipient for its intended purpose.

IX. Motivation to Combine the References

52. I have been informed that a claim is not novel if the elements of the claim were known in one or more prior art references and a POSA would have had a motivation to combine these references and a reasonable expectation of success at arriving at the claimed invention. I have also been informed that the motivation to combine can be found in the knowledge of a POSA and the state of the art. At least for the reasons set forth below, it is my opinion that a POSA would have been motivated to independently arrive at the claimed invention. Further, a POSA would have had a reasonable expectation of success at least because (i) the therapeutic advantages of Z-endoxifen over tamoxifen were well-known; and (ii) the

advantages of coated and uncoated capsules were well established. The claims do nothing to improve upon the then state of the art.

53. At least as early as December 2010, Tamoxifen was a crucial element of the treatment regimen for patients with hormone receptor–positive breast cancer. Ex. 1006 at 814; see also Ex. 1004 at [0003]. Tamoxifen, when orally administered, was extensively metabolized by cytochrome P450 (CYP) enzymes into active metabolites, including afimoxifene (4-hydroxy tamoxifen) and endoxifen (4-hydroxy N-desmethyl tamoxifen). Ex. 1006 at 814; see also Ex. 1004 at [0003]. Some patients did not respond to tamoxifen treatment because they do not produce adequate amounts of afimoxifen and endoxifen, sometimes due to low levels of the metabolizing enzymes. Ex. 1006 at 814; Ex. 1004 at [0003]. Separately, coadministration of antidepressants significantly affected survival in women receiving tamoxifen for breast cancer because of drug–drug interactions. Ex. 1006 at 814 (“CYP2D6 is inhibited by specific selective serotonin reuptake inhibitors that are frequently used to prevent the hot flushes experienced by up to 45% of patients taking tamoxifen.”). Studies revealed that after a single dose of 4 mg, a C_{max} of 15.1 ng/ml was observed. Ex. 1006 at 816. Based on the results of this study, there was a reasonable expectation of success that that multiple daily endoxifen doses of 2.0–4.0 mg would result in endoxifen exposures that would be similar to those found in patients with normal CYP2D6 function who were

administered tamoxifen at 20 mg/day. Ex. 1006 at 816. That is, a dose of 4 mg of endoxifen would be appropriate for breast cancer prevention and therapy. *Id.* A single daily dose is a most preferred dosing regimen because it improves patient compliance.

54. Z-Endoxifen was known to be more active at the estrogen receptor. Ex. 1004 at [0004]. Accordingly, a POSA would be motivated to create a dosage form comprising a high percentage of Z-endoxifen. Prior art references Liu and Song described methods of formulating pure forms of Z-endoxifen. *See* Ex. 1004 at [0076]; Ex. 1005 at [92]-[94], [97]-[98] and Ahmad disclosed compositions comprising endoxifen where over 90% by weight of the claimed formula (III) was Z-endoxifen.

55. Z-endoxifen degraded in the acidic conditions of the stomach (*see, e.g.,* Ex. 1019) and enteric-coated dosage forms were the preferred means to prevent drug release in the acidic conditions of the stomach. *See* Ex. 1003 at 18:19-21. Relatedly, it was well known that gastric emptying occurred within 2 hours. *See* Ex. 1008 at 91. Enteric coating HPMC capsules to obtain the desired release was an industrially viable process. *Id.* at 93. Separately, capsule forms that did not require coating and provided a delayed-release were also known. Ex. 1010. The ability of the coated or uncoated capsules to resist degradation in an acidic environment for the duration of the gastric emptying time would have been

confirmed using industry-standard USP tests. Finally, excipients were routinely used to improve the solubility, flowability, and bulk of active ingredients. (Ex. 1021 at 184-185.)

56. Accordingly, to improve the manufacturability, bioavailability and solubility of Z-endoxifen and to achieve the therapeutic C_{max} values with once-a-day dosing in patients with suboptimal response to tamoxifen (Ex. 1006), a POSA would have been motivated to include the pure form of Z-endoxifen manufactured using well-known methods (Ex. 1004 and Ex. 1005) in uncoated capsules (Ex. 1010) or coated capsules (Ex. 1006.) In doing so, a POSA would have independently arrived at the claimed invention.

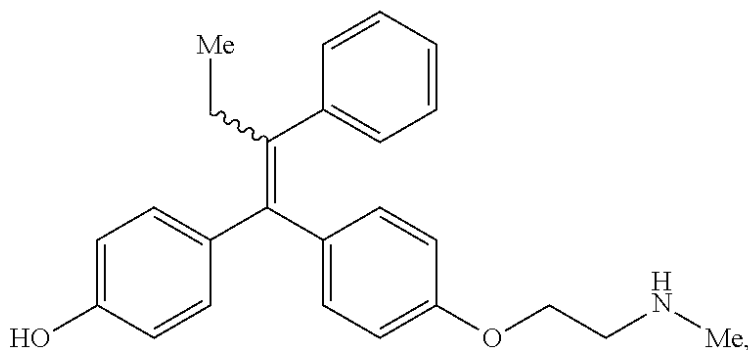
X. Grounds 1 and 2: Claims 1, 2, 4, 15, and 20-22

A. Independent Claim 1

57. Below I address the limitations of independent claim 1, each of which is disclosed by Ahmad and/or well known in the art.

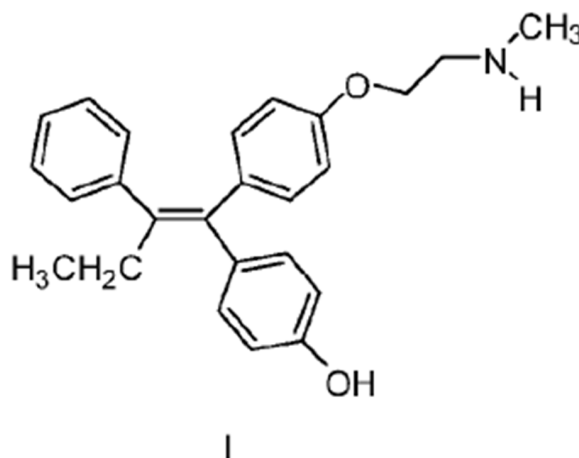
1. An oral formulation comprising an endoxifen composition...wherein the endoxifen composition comprises a compound of Formula (III):

Formula (III)



58. Ahmad teaches oral formulations comprising endoxifen, which is the compound depicted in Formula III of the 334 patent.

59. 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:



Ex. 1003 at Cover, Figure 1.

60. 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.

61. Thus, Ahmad teaches “An oral formulation comprising an endoxifen composition...wherein the endoxifen composition comprises a compound of Formula (III).”

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

62. 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.* at 12:14-17; *see also id.* at 2:24-40, 3:55-61. Ahmad teaches that this endoxifen purity can be accomplished using crystallization or chromatography. *Id.* at 11:17-23.

63. Thus, Ahmad teaches “wherein at least 90% by weight of the compound of Formula (III) is (Z)-endoxifen.”

64. I also note that achieving 90% pure (Z)-endoxifen was disclosed in the art by other references such as Liu and Song. Ex. 1004 at [0076]; Ex. 1005 at [92]-[94], [97]-[98]. A POSA would thus know how to make 90% pure (Z)-endoxifen.

encapsulated in an enteric capsule

65. 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 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 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 18:27-29.

66. As described above, a POSA would understand that an “enteric capsule” includes capsules with enteric coatings, which thus bypass the stomach, releasing their contents in the small intestine. Thus, Ahmad teaches its formulations “encapsulated in an enteric capsule.”

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.

68. Forming enteric coated capsules was 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.” *Id.* at 83. Cole accurately 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. 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. Each of these coatings, as well as others were well known. *See, e.g.* Ex. 1012 at 900 (HPE index listing “Enteric formulations/coating agents”). Thus, a POSA would be well aware of how to make an enteric coated capsule as taught in Ahmad.

69. A POSA would have been motivated to use a highly pure form of (Z)-endoxifen, such as 90% (Z)-endoxifen (as taught by Ahmad), because it was known that this form at higher purities was more active at estrogen receptors. *See, e.g.*, Ex. 1004 at [0004]. Thus, while Ahmad discloses various purity levels as well as the use of (E)-endoxifen, a POSA would have selected highly pure (Z)-endoxifen as a better candidate for treatment of breast cancer.

70. 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. *See, e.g.*, Ex. 1019 (“Our finding suggested that Z-endoxifen is unstable to the acidic conditions of the silica gel column chromatography but, in our hands, stable to the basic cleavage and mildly acidic work-up conditions.”) Thus, POSA would have been motivated to use an enteric capsule to avoid acidic degradation and improve bioavailability. I note for example, that the Zonalta endoxifen tablet sold by Intas is an enteric tablet. Ex. 1014. I also note that Ahmad 2010, Ahmad 2012, and Ahmad 2016 use enteric tablets. *See* Exs. 1006, 1007, and 1018. Thus, a POSA would have understood the need for the use of an enteric formulation for endoxifen. A capsule specifically would have been a routine design alternative to a tablet, and is generally simpler and cheaper to manufacture than a tablet.

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.

B. Dependent Claim 2

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

72. As described above, Ahmad discloses an enteric coated capsule such that the capsule does not release drug in the stomach, and delays release until it reaches the intestine. Ex. 1003 at 18:22-24. A POSA would understand Ahmad discloses a delayed-release formulation.

73. It also would have been routine to use known coatings to delay release further, i.e., such that the capsule releases drug further into the GI tract. This use of known coatings to delay release was well known in the art and would have been routine.

C. Dependent Claim 4

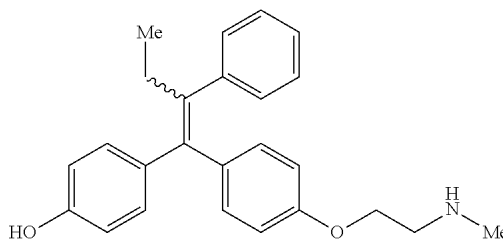
4. The oral formulation of claim 1, wherein the enteric capsule further comprises an enteric coating

74. As described above, Ahmad discloses an enteric coated capsule such that the capsule does not release drug in the stomach. Thus, a POSA would understand Ahmad to teach an enteric coating. As I described above, the use of enteric coatings was well known in the art as described by e.g., Cole and the HPE. See Ex. 1008, Ex. 1012. As I explained for claim 1, a POSA would have been motivated to use an enteric coating to avoid acidic degradation of the endoxifen in the stomach, and allow it to be absorbed in the small intestine.

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.

75. Claim 15 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. Thus I incorporate my analysis provided above for 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

76. 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:-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.”

77. I also note that Ahmad 2010 and Ahmad 2012 disclose using endoxifen for breast cancer. *See* Exs. 1006 and 1007. And that it was well known that endoxifen was an active metabolite of tamoxifen, which was used to treat breast cancer, thus this would have been a known use for endoxifen formulations such as those taught in Ahmad. *See* Exs. 1006 and 1007.

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.

78. 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...”

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.

79. As I described above, 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. 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 1:64-2:21.

80. Thus, a POSA would understand Ahmad to teach a method of using its formulation for tamoxifen-refractory or resistant conditions, because it may be effective in patients who do not adequately metabolize tamoxifen and thus are tamoxifen-refractory or resistant.

81. Other references in the art also taught that the use of endoxifen could bypass the metabolic pathways necessary for tamoxifen to be effective. For example, Liu taught that “[s]ome patients do not respond to tamoxifen treatment because they do not produce adequate amounts of afimoxifen and 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]. Song taught that “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. 1005 at [3]. Ahmad 2012 “propose[d] 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. 1006 at 816. Finally, Ahmad 2012 taught that “Direct administration of endoxifen would not be subject to pharmacogenetic variations or drug-drug interactions.” Ex. 1007 at 2.

82. Thus, it was known in the art that endoxifen could potentially be used to treat patients for whom tamoxifen was not adequately converted to the active metabolite endoxifen.

XI. Ground 3: Claims 5-8, 16, and 17

83. I incorporate by reference my discussion of the independent claims in Grounds 1 and 2. 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, as I discuss below.

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.

84. Claim 5 further recites that the formulation is resistant to dissolution in an acidic environment for at least 2 hours, as measured by USP 711.

85. 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 preparing such enteric coated capsules. Cole further teaches that “[n]o paracetamol³ was released over 2 h at pH 1.2 from the capsules coating with 6 and 8 mg cm⁻² Eudragit® L 30 D-55.” Ex. 1008 at 89. A pH of 1.2 is very acidic. In other words, Cole teaches enteric coatings that are resistant to dissolution in an acidic environment for at least 2 hours.

86. Although, Cole does not explicitly state that its dissolution test is performed “according to a method of USP 711,” the test conditions set forth in

³ 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.

Cole are materially the same as the conditions set forth in USP 711. Specifically, Cole states that the enteric capsules were subject to “2 h of exposure in 0.1 N hydrochloric acid (pH 1.2)” (Ex. 1008 at 86) and “no paracetamol was released over 2 h at pH 1.2.” Id. at 89. USP 711 provides an acid stage that is similar. *See* Ex. 1015 at 6 (“After 2 hours of operation in 0.1 N hydrochloric acid withdraw an aliquot of the fluid, and proceed immediately to the buffer stage.”).

87. To the extent there is any ambiguity in Cole, a POSA would understand that either this method or a similar method was used, and that the same results would have been found using the USP 711 method for delayed release dosage forms. USP 711 is by far the most common method of dissolution testing, and the absence of any specific protocol would lead a POSA to understand that USP 711 was likely used, and if not USP 711, then a very similar method such that the results would be effectively the same.

88. Based on the above, 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.”

89. 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, which is the purpose of an enteric coating as Ahmad discloses.

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 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.

90. 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.

91. The pH of the human stomach is approximately 1.5. *See, e.g.* 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. 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.”

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.

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.

93. As Ahmad teaches, the purpose of its enteric coating is to prevent release of medication before it reaches the small intestine, and enteric coatings work by breaking down rapidly at higher pH. Ex. 1003 at 18:19-26. For example, Cole teaches that at “pH 6.8,⁴ release of the paracetamol was rapid....” Ex. 1008 at 89. Thus, a POSA would understand Cole to teach that such formulations release at

⁴ The pH of the proximal small intestine has been measured to be about 6.6. Ex. 1017.

least 50% of the (Z)-endoxifen within 8 hours in the small intestine. *See* Ex. 1008 at 91 Fig. 4 (showing 50% release in pH 6.8 around 2.5-3 hours). Thus, a POSA would understand Cole to teach that enteric coating capsules, such as those taught in Ahmad, would be “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” and release “at least 50% of the (Z)-endoxifen in a small intestine of the subject within 8 hours following administration.”

94. 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 may be absorbed into the body and have pharmaceutical effect. As evidenced by Cole, a POSA would have had a reasonable expectation of success in doing so as it was well known how to coat a capsule to bypass the stomach.

D. Dependent Claim 8

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

95. HPMC capsules have long been used for pharmaceutical formulations. For example, Cole teaches that HPMC capsules had been available commercially since at least 1992. Ex. 1008 at 84. Ku also teaches that “the new HPMC capsule is satisfactorily qualified and has since been used successfully for nearly 20

investigational new drug (IND) compounds.” Ex. 1009 at Abstract. I note that this was in 2010, the number would have been much higher by the time of invention. 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.

96. 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.” *Id.* at 93. Cole 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.

97. It would have been a routine design choice to make the enteric coated capsules of Ahmad and to use an HPMC capsule, such as Vcaps Plus®. Ex. 1009. 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. *Id.* Further, HPMC is a vegetarian friendly choice, is of non-bovine origin, and may be preferable for those who object to the use of gelatinous capsules. And a POSA would have had a reasonable expectation of success in

using an HPMC capsule as they were well known in the art and had been demonstrated to be successful, e.g. by Cole and Ku.

XII. Ground 4: Claim 3

98. I incorporate by reference my discussion of independent claim 1 in Grounds 1 and 2. The additional limitation of claim 3, that the enteric capsule is uncoated, would have been a routine alternative to the enteric coated capsules disclosed in Ahmad.

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

99. Intrinsically enteric capsules that do not require coating were commercially available before the 334 patent. These capsules were developed as an alternative to enteric coatings to avoid the necessity of exposing the capsule to the coating process. For example, 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. 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.* I understand that such capsules were commercially available by October 7, 2016, according to Capsugel’s website.⁵

100. Based on the above, a POSA would understand Benameur to teach the alternative use of an uncoated enteric capsule instead of the more traditional enteric coated capsule.

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

⁵ 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>

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.

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.

XIII. Ground 5: Claims 9-13

103. I incorporate by reference my discussion of the independent claims in Ground 1. 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.

A. Dependent Claim 9

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

104. A filler (also sometimes called a diluent) is a commonly used pharmaceutical excipient that increases the volume of a pharmaceutical formulation. Ex. 1021 at 184 ("A diluent or filler may be added to the formulation

to produce the proper capsule fill volume.”). It helps make the ingredients easier to process, can stabilize the formulation, and can make the formulation a suitable size for consumption. *Id.*

105. Fillers are well known in the pharmaceutical industry. *Id.* 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....”). The HPE index directs one looking for “Fillers” to “Diluents” (Ex. 1012 at 900), which then lists a number of options. *Id.* at 897. See also Ex. 1021 at 184.

106. As taught by these Stegemann and the HPE, the use of a filler in the formulation was a routine and common practice in the formulation arts. See also Ex. 1021 at 184.

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.

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

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.

C. Dependent Claim 11

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

109. A disintegrant is a common pharmaceutical excipient that promotes disintegration, and increases the dissolution rate of a formulation once it is in a suitable medium. It helps ensure that the active ingredient is made available quickly for dissolution for absorption in the body at the proper location. *See* Ex.

1021 at 184 (“Disintegrants are frequently included in a capsule formulation to assist the break-up and distribution of the capsule contents in the stomach.”).

110. Disintegrants are well known in the pharmaceutical industry. Ex. 1012 at 897; Ex. 1021 at 184. Ahmad teaches that “pharmaceutically acceptable carrier” “refers to any of the standard pharmaceutical carriers including...disintegrants [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

- | | |
|------------------------|----------------|
| • Croscarmellose | • Corn starch |
| • Crospovidone | • Starch 1500 |
| • Sodium glycol starch | • Alginic acid |

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

111. The use of a disintegrant in the formulation was a routine and common practice in the formulation arts.

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.

D. Dependent Claim 12

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

113. A lubricant is a common pharmaceutical excipient that decreases the friction between pharmaceutical formulations and the tableting equipment contact surface. It helps make processing and manufacturing more efficient.

114. Lubricants are well known in the pharmaceutical industry. Stegemann, for example, describes lubricants for use in capsules:

Lubricants

- Improved flow properties and reduced powder adhesion to metal parts
- Magnesium stearate ● Glyceryl monostearate
- Stearic acid

Ex. 1011 at 8. The HPE also teaches lubricants for use in tablets and capsules. Ex. 1012 at 905 (listing “Lubricants (tablet/capsule)”).

115. The use of a lubricant in the formulation was a routine and common practice in the formulation arts.

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.

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

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.

XIV. Ground 6: Claims 14, 18 and 19

119. I incorporate by reference my discussion of independent claims in Ground 1.

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

120. A POSA would have understood that the formulations should contain from 0.1 to 200 mg of (Z)-endoxifen. For example, Ahmad teaches in its examples that “oral doses of endoxifen (1 mg-10 mg/day) with bicutamide [sic] are

expected to prevent development of bicalutamide-induced [sic] gynecomastia and breast pain.” Ex. 1003 at 29:20-31. Thus, a POSA would understand that the formulations would need to be sized such that 1 to 10 mg per day could be given, which would have been well within the recited range (which is incredibly broad).

121. 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 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.

B. Dependent Claim 18

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

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:

Table 1 Endoxifen doses and pharmacokinetic parameters

Dose	C_{max} (ng/ml)	$AUC_{0-\infty}$ (ng-h/ml)	$t_{1/2}$ (h (CV%))	V_z (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. Ahmad 2010 also noted that “endoxifen is rapidly absorbed and displays a dose-proportional PK with respect to C_{max} and $AUC_{0-\infty}$.” *Id.* Accordingly a POSA would understand that a method of treating patients with the formulations of Ahmad of endoxifen would result in an AUC within the recited range.

124. Further regarding AUC, Ahmad 2010 also teaches that “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. Thus, a POSA would understand that the AUC observed in Ahmad 2010 was expected to be beneficial, and would have been motivated to ensure that the formulations disclosed in Ahmad provided similar data. A POSA would have had a reasonable expectation of success in doing so and it would have taken only routine experimentation to ensure the proper release of endoxifen.

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

125. C_{max} is a measurement of the highest blood plasma concentration of drug.

126. The C_{max} 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} for doses from 0.5 to 4.0 mg:

Table 1 Endoxifen doses and pharmacokinetic parameters

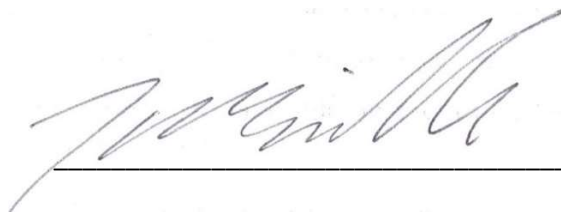
Dose	C_{max} (ng/ml)	$AUC_{0-\infty}$ (ng-h/ml)	$t_{1/2}$ (h (CV%))	V_z (l)	Cl (l/h)
Endoxifen 0.5 mg	1.38 ± 0.25	99.9 ± 13.6	58.11 (18.0)	427 ± 101	5.1 ± 0.7
Endoxifen 1.0 mg	3.98 ± 1.7	239 ± 70	54.1 (10.6)	346 ± 88	4.5 ± 1.1
Endoxifen 2.0 mg	6.79 ± 1.85	401 ± 113	55.4 (16.3)	428 ± 133	5.4 ± 1.8
Endoxifen 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 noted above, Ahmad 2010 teaches the desirability of a 4 mg dose. Ex. 1006 at 816 (“a dose of 4 mg of endoxifen should be appropriate for breast

cancer prevention and therapy.”). And a 4 mg dose results in a Cmax within the claimed range. Ahmad 2010 also noted that “endoxifen is rapidly absorbed and displays a dose-proportional PK with respect to Cmax and AUC_{0-∞}.” *Id.* Accordingly a POSA would understand that a method of treating patients with the formulations of Ahmad of endoxifen would result in an Cmax within the recited range.

127. As discussed above for AUC, a POSA also would have been motivated to ensure the Cmax obtained from the formulations of Ahmad matched the data provided in Ahmad 2010, which was expected to be efficacious. And again, a POSA would have had a reasonable expectation of success in doing so using routine skill.

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

A handwritten signature in black ink, appearing to read 'J. McConville', is written over a horizontal line.

Jason McConville, Ph.D.