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 PGR2025-00043
Patent No. 12,071,391

PETITION FOR POST GRANT REVIEW

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10. WO 2011/107855 ("Gandhi") 13

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PETITIONER'S EXHIBIT LIST

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1001	USPN 12,071,391 ("391 patent")
1002	File history of USPN 12,071,391
1003	USPN 9,333,190 ("Ahmad")
1004	WO2017/70651 ("Liu")
1005	EXCERPT OF HANDBOOK OF PHARMACEUTICAL SALTS: PROPERTIES, SELECTION, & USE (P. Heinrich Stahl & Camille G. Wermuth eds., 1st ed., 2002) ("Stahl")
1006	Benameur, H., Capsule Technology, Enteric Capsule Drug Delivery Technology – Achieving Protection Without Coating, 15(5) DRUG DEV. & DELIVERY 34-37 (2015) ("Benameur")
1007	Melgardt de Villiers, *Pharmaceutical Solvents & Solubilizing Agents*, *in* A Practical Guide to Contemporary Pharmacy Practice (3d ed., 2009) ("de Villiers")
1008	Stegemann, S., Hard gelatin capsules today – and tomorrow, CAPSUGEL LIBRARY (2002) ("Stegemann")
1009	Excerpts OF HANDBOOK OF PHARMACEUTICAL EXCIPIENTS (Rowe, R., Sheskey, J. & Owen, S., eds., 5th ed., 2006) (The "HPE")
1010	Cole, E., et al., *Enteric coated HPMC capsules designed to achieve intestinal targeting*, 231 INTL J. PHARMACEUTICS 83-95 (2002) ("Cole")
1011	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")
1012	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")
1013	Fauq, A.H., et al., *A convenient synthesis of (Z)-4-hydroxy-N-desmethyltamoxifen (endoxifen)*, 20 BIOORGANIC MED. CHEM. LETT. 3036-38 (2010) ("Fauq")

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1015	Krahn, F. et al, *Effect of type and extent of crystalline order on chemical and physical stability of carbamazepine*, 53(1) INT'L J. OF PHARMACEUTICS 25-34 (1989) ("Krahn")
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1017	Fan, J. et al., *Pharmacokinetics*, 81 BIOCHEM. PHARMACOLOGY 93-120 (2014) ("Fan")
1018	Urso, R. et al., *A short introduction to pharmacokinetics*, 6 EUR. REV. FOR MED. & PHARMACOLOGICAL SCIS., 33-44 (2002) ("Urso")
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1021	Beasley, D. et al, *The Evolution of Stomach Acidity and Its Relevance to the Human Microbiome*, 10(7) PLOS ONE 1-12 (2015) ("Beasley")
1022	WO 2011/107855 ("Gandhi")
1023	USPN 11,572,334 ("334 patent")
1024	Supporting information to Milroy, L. et al., *A multi-gram-scale stereoselective synthesis of Z-endoxifen*, 28 BIOORGANIC MED. CHEM. LETT. 1352-56 (2018)
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1031	Wieckhusen, D., *The Development of API Manufacturing Processes – Targets aand Strategies*, 60(9) CHIMIA INT'L J. FOR CHEM. 598-604 (2006) ("Wieckhusen")
1032	COULSON & RICHARDSON, COULSON & RICHARDSON'S CHEMICAL ENGINEERING (5th ed. 2002) ("Coulson & Richardson")
1033	Expert Declaration of Jason McConville, Ph.D.
1034	Expert Declaration of Ron Bihovsky, Ph.D.

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I. INTRODUCTION

Intas Pharmaceuticals Limited petitions for post grant review of claims 1-44 of U.S. Patent No. 12,071,391 ("the 391 patent"; Ex. 1001). The claims of the 391 patent are directed to a composition comprising 90% by weight (Z)-endoxifen and an enteric material, and methods of administering such compositions. 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, 90% (Z)-endoxifen formulations, including endoxifen salts, that include an enteric material and other, common, pharmaceutical excipients and additives were well-known in the art. Thus, any claim not anticipated would have been obvious. Indeed, nearly identical claims were found anticipated and/or obvious in a PGR of the 391 patent's grandparent patent, the 334 patent.

II. MANDATORY NOTICES

Real parties-in-interest: Intas Pharmaceuticals Ltd. ("Intas") is the real-party-in-interest. Accord Healthcare, Inc. is a U.S. 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.

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Related matters: PGR2023-00043, filed by Petitioner, addresses claims 1-22 of U.S. Patent No. 11,572,334, the grandparent of the 391 patent. The PTAB found claims 1-22 of the 334 patent unpatentable. *See Intas Pharms. Ltd. v. Atossa Therapeutics*, *Inc.*, PGR2023-00043, Paper 37, *1 (P.T.A.B. January 29, 2025) (hereinafter, "334 FWD"). Petitioners are also at the same time filing a petition for *inter partes* review challenging related U.S. Patent No. 11,261,151, the parent of the 391 patent.

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Service information: Petitioner consents to service by email at: 391PGR@mcandrews-ip.com.

III. GROUNDS FOR STANDING

The 391 patent is available for post grant review because it issued on August 27, 2024, and the date of filing is within the 9-month period provided by 35 U.S.C.

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§ 321(c). Petitioner is not barred or estopped from requesting a post grant review challenging claims 1-44 of the 391 patent on the grounds identified in this Petition.

IV. IDENTIFICATION OF GROUNDS

Petitioner identifies the following grounds of unpatentability:

Ground	Challenged Claims	Basis
1	1-6, 8, 9, 11-15, 20, 23, 26-37, 40-44	Anticipated by Ahmad
2	1-6, 8, 9, 11-16, 20, 23, 26-37, 40-44	Obvious over Ahmad
3	26-29, 33-37, 40, and 41	Obvious over Ahmad in view of Ahmad 2010/Ahmad 2012
4	7	Obvious over Ahmad in view of Benameur
5	10, 12-15, 30, and 31	Obvious over Ahmad in view of de Villiers/Gandhi
6	21-25	Obvious over Ahmad in view of Stegemann/HPE
7	17-19, 38, and 39	Obvious over Ahmad in view of Cole
8	10, 12-15, and 30	Lack of Written Description/Enablement

V. BACKGROUND

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

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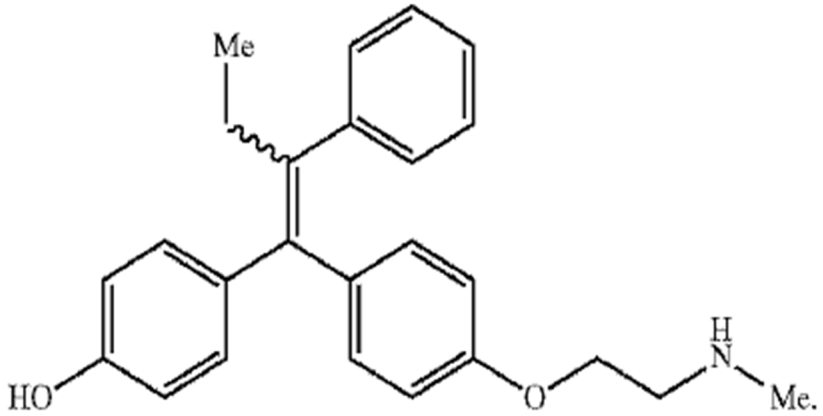

McConville, ¶19;[1] Bihovsky, ¶14;[2] Ex. 1001. A citrate salt of endoxifen is marketed and sold in India by Intas, under the brand name Zonalta for the treatment of manic episodes with or without mixed features of bipolar disorder. Endoxifen has long been known to be an active metabolite of tamoxifen, which has been used in the treatment of breast cancer. McConville, ¶20; Ex. 1001, Fig 1, 1:63-2:6; Ex. 1003, Fig. 3, 1:35-56; Ex. 1004, [0003]. Thus, interest in endoxifen itself as a treatment

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[1] "McConville" refers to Exhibit 1033, the Expert Declaration of Jason McConville, Ph.D. Dr. McConville is an expert in a pharmaceutical and formulation sciences. McConville, ¶¶1-15, Appendix A.

[2] "Bihovsky" refers to Exhibit 1034, the Expert Declaration of Ron Bihovsky, Ph.D. Dr. Bihovsky is an expert in organic chemistry and medicinal chemistry. Bihovsky, ¶¶1-10, Appendix A.

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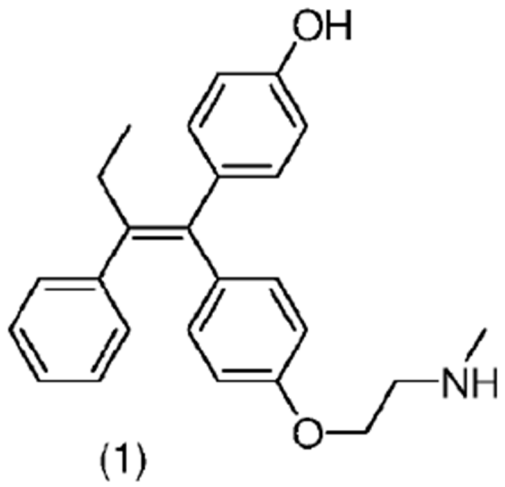
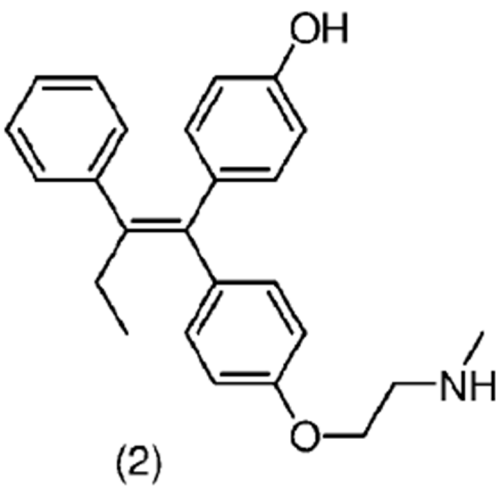
for breast cancer has been contemplated and studied in the prior art. McConville, ¶20; Ex. 1003, 1:64-2:4; Ex. 1004, [0003]; Ex. 1006; Ex. 1007.

"Endoxifen exists as two forms, E and Z, with the Z form more active at the estrogen receptor." Ex. 1004, [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
	

Bihovsky, ¶15; Ex. 1004, Abstract. The (Z)-isomer of endoxifen is known to be more active (McConville, ¶20; Bihovsky, ¶16; Ex. 1004, [0004]), and methods of producing highly pure (Z)-endoxifen are known in the art. *See* Bihovsky, ¶17; Ex. 1004; Ex. 1005.

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Some drugs, including endoxifen, are subject to acid-catalyzed degradation in the acidic conditions of the stomach. McConville, ¶21; Ex. 1003, 18:19-21. To prevent such degradation, enteric materials, such as coatings, capsules, or tablets, may be used to prevent release of the active ingredient in the stomach and instead release the active substance in the intestines. McConville, ¶21; Ex. 1003, 18:19-21; Ex. 1008, 83; Ex 1010, 34. For example, Intas's Zonalta endoxifen product is sold in enteric coated tablets. Enteric materials are well-known in the art. *See* McConville, ¶21; Ex. 1008; Ex. 1010.

VI. THE 391 PATENT

A. Subject Matter of the 391 Patent

The 391 patent is titled "Methods for Making and Using Endoxifen." Ex. 1001, Cover. It was filed on March 30, 2023 as a continuation of Application No. 18/090,757 (now USPN 11,680,036), which is a continuation of Application No. 17/580,428 (now USPN 11,572,334), which 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.*

The 391 patent is directed to compositions including a compound of 90% by weight (Z)-endoxifen and an enteric material, and methods of administering such compositions. Ex. 1001, Abstract, Claims 1, 32; McConville, ¶23; Bihovsky, ¶19. The compound may be in the form of a pharmaceutically acceptable salt of 90% by

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weight (Z)-endoxifen. Ex. 1001, Abstract, 34:2-9, Claims 1, 32; McConville, ¶23; Bihovsky, ¶19. The enteric material may be in the form of a tablet, capsule, and/or coating. Ex. 1001, 4:31-35. The 391 patent also discloses compositions including common pharmaceutical additives, such as, for example, fillers, disintegrants, and/or lubricants. Ex. 1001, 36:65-38:55.

B. Prosecution History

The 391 patent did not face any art-based rejections. Ex. 1002, 282-85. The only rejection the 391 patent faced was an obvious-type double patenting rejection over the 391 patent's parent and grandparent patents. *Id.*, 282-84. In response, Patent Owner filed a terminal disclaimer. *Id.*, 289-91, 302. Thereafter, the Examiner issued a Notice of Allowance, without providing reasons for the allowance. *Id.*, 318-22.

C. Person of Ordinary Skill in the Art

A POSA for purposes of the 391 patent is someone with a graduate degree in organic chemistry, medicinal chemistry, pharmaceutical chemistry, or a related field, and four to six years of experience in the synthesis, purification, analysis, design, and/or formulation of pharmaceutical compounds and derivatives. Bihovsky, ¶21; McConville, ¶25; *see also* 334 FWD at *9 (adopting same definition of a POSA). A POSA would have worked with a team of professionals with training in related disciplines, such as pharmacology, pharmacokinetics,

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formulation, drug discovery and/or drug development as of the date of the claimed inventions. Bihovsky, ¶21; McConville, ¶25. Drs. McConville and Bihovsky meet or exceed the level of skill of a POSA. Bihovsky, ¶22; McConville, ¶26; *see also* 334 FWD at *9-10 (stating Drs. McConville and Bihovsky are POSAs).

D. Claim Construction

For purposes of this PGR, all terms should be given their plain and ordinary meaning, and Petitioner does not contend any claims require construction.

VII. SUMMARY OF THE PRIOR ART

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

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, 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, Abstract. Ahmad teaches the use of the Z-isomer of endoxifen, including at over 90% purity. *Id.*, 12:14-17 ("One object of the present invention is to provide E-endoxifen or (Z)-endoxifen with at least 80% purity, such as at least 90% pure...."); *see also id.*, 2:24-

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40, 3:55-61. Ahmad teaches that purity levels can be accomplished using crystallization or chromatography. *Id.*, 11:17-23. Ahmad discloses that its compositions can be in the form of a pharmaceutically acceptable salt. *Id.*, 2:24-30 ("In some embodiments, the endoxifen...is in the form of a salt."), 8:47-63 (listing salts), 9:1-20 (same).

Ahmad also teaches that "[i]n some embodiments, the composition comprises a tablet or a filled capsule, wherein said tablet or filled capsule optionally comprises an enteric coating material." *Id.*, 4:41-44. Ahmad further teaches that "[w]hen desired, [the] composition containing endoxifen or endoxifen-lipid complex can be encapsulated in enteric-coated capsules to protect it from acids in the stomach." *Id.*, 18:19-26.

Ahmad teaches that the "compositions of the present invention can be employed to treat breast cancer and breast related diseases." *Id.*, 18:47-49. Thus, Ahmad teaches enteric coated formulations of highly pure (Z)-endoxifen, for the treatment of breast cancer and other breast diseases. McConville, ¶30.

B. Other Prior 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, Cover. Thus, Liu is prior art under 35 U.S.C. § 102(a)(1). Liu teaches a method for synthesizing highly-pure (Z)-

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endoxifen. *Id.*, [0046]-[0055]. As discussed in more detail in his declaration, Dr. Bihovsky followed Liu's method and synthesized highly-pure (Z)-endoxifen. *See* Bihovsky, ¶¶42-72.

2. HANDBOOK OF PHARMACEUTICAL SALTS: PROPERTIES, SELECTION, & USE (P. Heinrich Stahl & Camille G. Wermuth eds., 1st ed., 2002) ("Stahl")

Stahl was published and publicly available in 2002 and thus is prior art under 35 U.S.C. §102(a)(1). Ex. 1005. Stahl discloses commonly used pharmaceutical salts. *Id.*, 334-45.

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

Benameur was published and publicly available in June 2015 and thus is prior art under 35 U.S.C. § 102(a)(1). Ex. 1006. Benameur teaches intrinsically enteric capsules that do not require coating. *Id.*, 36.[3]

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[3] 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.

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4. Melgardt de Villiers, *Pharmaceutical Solvents & Solubilizing Agents*, *in* A PRACTICAL GUIDE TO CONTEMPORARY PHARMACY PRACTICE (3d ed., 2009) ("de Villiers")

De Villiers was published and publicly available in 2009 and thus is prior art under 35 U.S.C. §102(a)(1). Ex. 1007. De Villiers discloses various pharmaceutical excipients, including common solvents and liquid vehicles. *Id.*, 190-91.

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

Stegemann was published and publicly available in 2002 and thus is prior art under 35 U.S.C. § 102(a)(1). Ex. 1008.[4] Stegemann teaches "[t]he production process" and the "[u]se of [e]xcipients" for capsules. *Id.*

6. HANDBOOK OF PHARMACEUTICAL EXCIPIENTS (Rowe, R., Sheskey, J. & Owen, S., eds., 5th ed., 2006) (the "HPE")

The HPE was published and publicly available in 2006 and thus is prior art under 35 U.S.C. § 102(a)(1). Ex. 1009. "The *Handbook of Pharmaceutical Excipients* is an internationally acclaimed reference work recognized as one of the

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

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most authoritative and comprehensive sources of information on excipients used in pharmaceutical formulation." *Id.*, Back Cover; McConville, ¶39.

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

Cole was published and publicly available in 2002 and thus is prior art under 35 U.S.C. § 102(a)(1). Ex. 1010. Cole teaches the use of enteric coated capsules. *Id.*, 83. The 391 patent acknowledges Cole, and uses Cole's method. Ex. 1001, 84:61-65.

8. Allen & Ansel, Ansel's Pharmaceutical Dosage Forms & Drug Delivery Systems (10th ed. 2013) ("Ansel")

The Tenth Edition of Ansel was published in 2013 and is therefore prior art under 35 U.S.C. § 102(a)(1). Ex. 1030. Ansel is well known to those of skill in the art as a go-to guide to learn about various pharmaceutical dosage forms and drug delivery systems. *Id.*

9. Shargel, Leon & Yu, Andrew, Applied Biopharmaceutics & Pharmacokinetics (7th ed. 2016) ("Shargel")

Shargel was published and publicly available in 2016 and thus is prior art to the 391 patent under 35 U.S.C. § 102(a)(1). Ex. 1029, iv. Shargel explains that "pharmacokinetics involves the development of pharmacokinetic models that predict drug disposition after drug administration" and is used to "design[] and predict[] optimal dosing regimens for individuals or groups of patients." *Id.*, 4.

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10. WO 2011/107855 ("Gandhi")

International Application WO 2011/107855 ("Gandhi") was filed on March 2, 2011, and published on September 9, 2011. Ex. 1020, Cover. Thus, Gandhi is prior art under 35 U.S.C. § 102(a)(1). Gandhi teaches a "stable, sustained release oral liquid suspension dosage form of pharmaceutical active ingredients...." *Id.*, Abstract.

11. 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 2010 was published and publicly available in 2010 and thus is prior art under 35 U.S.C. § 102(a)(1). Ex. 1011, 814. Ahmad 2010 discloses pre-clinical trials of endoxifen showing that it is likely to be a safe and effective treatment for breast cancers. *Id.*

12. 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 2012 is an abstract of a poster published online on May 20, 2012 and presented on June 4, 2012, and thus is prior art under 35 U.S.C. § 102(a)(1). Ex. 1012, 1. Ahmad 2012 discloses pre-clinical trials of endoxifen showing that it is likely to be a safe and effective treatment for breast cancers. *Id.*, 2.

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VIII. RELATED PROCEEDINGS

As discussed above, PGR2023-00043 found all claims of the 334 patent, the grandparent of the 391 patent, unpatentable over Ahmad, Cole, Benameur, Stegemann, the HPE, Ahmad 2010, and Ahmad 2012. 334 FWD. As discussed in more detail below, collateral estoppel from the PTAB's final written decision in PGR2023-00043 applies to various issues relevant to this IPR. *See MaxLinear, Inc. v. CF CRESPE LLC*, 880 F.3d 1373, 1376 (Fed. Cir. 2018) ("It is well established that collateral estoppel, also known as issue preclusion, applies in the administrative context."); *Papst Licensing GMBH & Co. KG v. Samsung Elecs. Am., Inc.*, 924 F.3d 1243, 1251 (Fed. Cir. 2019) (stating issue preclusion can apply to final PTAB decisions). To invoke collateral estoppel, a party must show:

> (1) the issue is identical to one decided in the first action; (2) the issue was actually litigated in the first action; (3) resolution of the issue was essential to a final judgment in the first action; and (4) [the party against whom collateral estoppel is being asserted] had a full and fair opportunity to litigate the issue in the first action.

Google LLC v. Hammond Develop. Int'l, Inc., 54 F.4th 1377, 1381 (Fed. Cir. 2022).

Here, as discussed in more detail below, many of the claims of the 391 patent present "identical issues of patentability" to those found unpatentable in PGR2023-00043 and therefore require a finding of unpatentability. *MaxLinear*, 880 F.3d at 1377 ("[T]he collateral-estoppel effect of an administrative decision of

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unpatentability generally requires the invalidation of related claims that present identical issues of patentability."); *see also Google*, 54 F.4th at 1381 ("[C]ollateral estoppel may apply even if the patent claims 'use slightly different language to describe substantially the same invention,' so long as 'the differences between the unadjudicated patent claims and adjudicated patent claims do not materially alter the question of invalidity.'").

The issues discussed below in connection with those claims that present "identical issues of patentability" were actually litigated in PGR2023-00043 and necessary to the final judgment, and Atossa had a full and fair opportunity to litigate them. Therefore, collateral estoppel applies to such claims, and the Board should find those claims unpatentable for at least the same reasons as the claims at issue in the 334 FWD. Further, "[i]ssue preclusion applies not only to ultimate determinations in a prior adjudication but to subsidiary determinations if sufficiently 'essential' to the ultimate determinations." *Spence v. Dep. of Veterans Affairs*, 831 F. App'x 949, 955 (Fed. Cir. 2020). Thus, Atossa may not reargue factual findings resolved against it in the 334 PGR.

IX. 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

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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. Med-El Elektromedizinische Gerate GmbH*, IPR2019-01469, Paper 6, *10 (P.T.A.B. Feb. 13, 2020) (precedential).

1. 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"

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

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"

Ahmad, Liu, Ahmad 2010, and Ahmad 2012 were cited by the Examiner. However, the Examiner did not issue any rejection of the present claims over any of those references (or over any references whatsoever). The other references herein were not cited by the Examiner. Thus, the arguments presented here were not presented by the Examiner.

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2. Advanced Bionics Part 2: Whether the 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"

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

The Examiner did not issue a single art-based 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, the Examiner erred in not substantively considering them. *See Carrier Fire & Security America's Corp. v. Sentrilock*, *LLC*, IPR2021-00664, Paper 12, *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, *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").

Ahmad teaches all of the limitations of the independent claims: a composition comprising endoxifen (or a salt thereof) and an enteric material, wherein the endoxifen is at least 90% (Z)-endoxifen. Moreover, forming (Z)-endoxifen at high purities was well-known in the art, as was the use of enteric materials and other

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excipients. This strong evidence of unpatentability (and supporting expert testimony) warrants reconsideration and demonstrates that the Office erred in not considering the cited references and combinations. *See Satco Prods. Inc. v. The Regents of the Univ. of Cal.*, IPR2021-00662, Paper 13, *25 (P.T.A.B. Nov. 8, 2021) (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, *23 (granting institution where "Petitioner shows persuasively" that the art taught the features cited as the basis for allowance). In addition, as discussed above, the grandparent of the 391 patent was found unpatentable over Ahmad. *See* 334 FWD.

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 of any other proceeding involving the 391 patent. Finally, Petitioner's grounds are not redundant or excessive. Although this petition includes 8 grounds of unpatentability, the grounds are not redundant. Instead, the number of grounds is due to the high number of claims (44) addressed in this petition.

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X. GROUND 1: CLAIMS 1, 2, 4-6, 8, 9, 11-15, 20, 23, 26-37, AND 40-44 ARE ANTICIPATED BY AHMAD

A. Claim 1

Claim 1 presents "identical issues of patentability" to claim 1 of the 334 patent that was found unpatentable by the Board. McConville, ¶53; 334 FWD, *31. For example, both claims recite endoxifen in the form of Formula (III), an enteric material, and that at least 90% by weight of the compound of Formula (III) is (Z)-endoxifen. *Compare* Ex. 1001, Claim 1, *with* Ex. 1023, Claim 1. An annotated comparison chart highlighting the similarities of the two claims is below. Although claim 1 of the 334 patent recited an "enteric capsule" and claim 1 of the 391 patent recites an "enteric material," the claims still present identical issues of patentability because "enteric material" is broader than "enteric capsule" and a species anticipates a genus. *See Eli Lilly & Co. v. Barr Lab'ys, Inc.*, 251 F.3d 955, 971 (Fed. Cir. 2001) ("[A] later genus claim limitation is anticipated by, and therefore not patentably distinct from, an earlier species claim."). For at least this reason, the Board should find claim 1 unpatentable over Ahmad.

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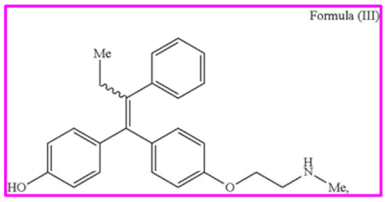
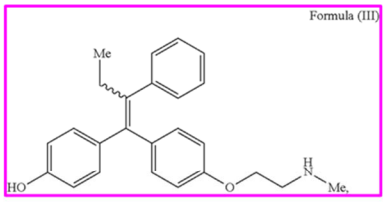
391 Patent	334 Patent (Unpatentable)
1. A composition comprising an endoxifen and an enteric material, wherein: the endoxifen comprises a compound of Formula (III):  or a pharmaceutically acceptable salt thereof, and at least 90% by weight of the compound of Formula (III) is (Z)-endoxifen.	1. An oral formulation comprising an endoxifen composition encapsulated in an enteric capsule, wherein the endoxifen composition comprises a compound of Formula (III):  wherein at least 90% by weight of the compound of Formula (III) is (Z)-endoxifen.

A composition comprising an endoxifen and an enteric material,

Ahmad is titled "Endoxifen compositions and methods" and "provides compositions containing endoxifen." Ex. 1003, Title, Abstract. Ahmad teaches that "[w]hen desired, [the] composition containing endoxifen or endoxifen-lipid complex can be encapsulated in enteric-coated capsules to protect it from acids in the stomach." *Id.*, 18:19-21. Ahmad explains that the "enteric coatings prevent release of medication before it reaches the small intestine." *Id.*, 18:22-24. It further teaches that "[e]nteric coating of capsules filled with compositions containing endoxifen can be done as methods known in the art." *Id.*, 18:27-29. Thus, Ahmad teaches compositions comprising endoxifen and an enteric material. McConville, ¶54.

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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.[5] 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. 1010, 83. Cole teaches numerous enteric polymers, such as, "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.*, 83. Other enteric capsules were also well-known. *See* Ex. 1009, 899 (HPE listing numerous "Enteric formulations/coating agents"); McConville, ¶55.

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[5] Petitioner notes that Patent Owner carries the initial burden to rebut a presumption of enablement and does not waive the right to present further evidence of enablement should Patent Owner make an enablement argument.

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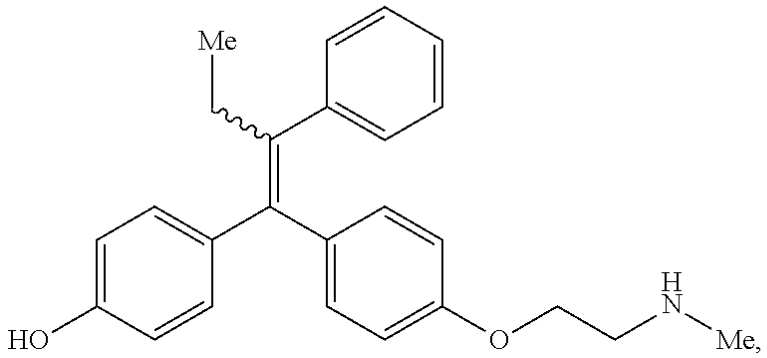
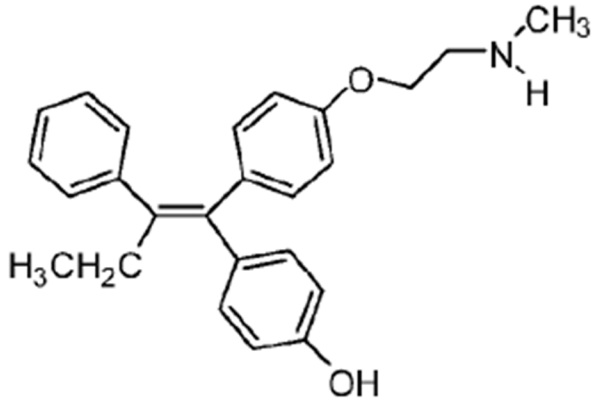
wherein: the endoxifen comprises a compound of Formula (III):

Formula (III)



As discussed, Ahmad's compositions comprise endoxifen. Endoxifen is the compound depicted in Formula III of the 391 patent. McConville, ¶56. Though depicted slightly differently, Ahmad depicts the same chemical structure for endoxifen:



I

Ex. 1003, Cover, Figure 1; McConville, ¶56.

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or a pharmaceutically acceptable salt thereof,

Ahmad teaches that its formulations of (Z)-endoxifen can include a salt of (Z)-endoxifen. McConville, ¶57. For example, Ahmad discloses that "[i]n some embodiments, the endoxifen...is in the form of a salt." Ex. 1003, 2:24-26, Claim 1. Ahmad further provides examples of pharmaceutically acceptable salts. *Id.*, 8:47-63, 9:1-20 (listing salts).

and 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.*, 12:14-17; *id.*, 2:24-40, 3:55-61. Ahmad teaches that this can be accomplished using crystallization or chromatography. *Id.*, 11:17-23. Thus, Ahmad teaches "wherein at least 90% by weight of the compound of Formula (III) is (Z)-endoxifen." McConville, ¶¶58-59; 334 FWD, *20-30.

As detailed above, Ahmad discloses all of the elements of claim 1, and a POSA would at once envisage the claimed invention from Ahmad's teachings. McConville, ¶60. Thus, Ahmad anticipates claim 1.

B. Claim 32

Claim 32 presents "identical issues of patentability" to claim 15 of the 334 patent that was found unpatentable by the Board. McConville, ¶61; 334 FWD, *31.

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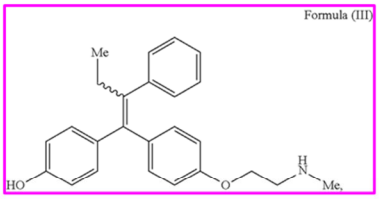
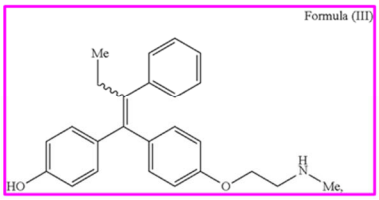
Both claims recite methods of providing endoxifen in the form of Formula (III), an enteric material, and that at least 90% by weight of the compound of Formula (III) is (Z)-endoxifen. *Compare* Ex. 1001, Claim 32, *with* Ex. 1023, Claim 15. An annotated comparison chart highlighting the similarities of the two claims is below. For at least this reason, the Board should find claim 32 unpatentable over Ahmad.

391 Patent	**334 Patent (Unpatentable)**
32. A method comprising administering to a subject a composition comprising an endoxifen and an enteric material, wherein: the endoxifen comprises a compound of Formula (III):  or a pharmaceutically acceptable salt thereof; and 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):  wherein at least 90% by weight of the compound of Formula (III) is (Z)-endoxifen.

> ***32. A method comprising administering to a subject a composition comprising an endoxifen and an enteric material, wherein:***
>
> ***the endoxifen comprises a compound of Formula (III) or a pharmaceutically acceptable salt thereof;***
>
> ***and at least 90% by weight of the compound of Formula (III) is (Z)-endoxifen.***

As discussed above, Ahmad discloses a composition comprising an endoxifen and an enteric material, wherein the endoxifen comprises a compound of Formula

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(III) or a pharmaceutically acceptable salt thereof, and at least 90% by weight of the compound of Formula (III) is (Z)-endoxifen. Claim 32 recites a "method comprising administering to a subject" a composition that is identical to the composition of claim 1. McConville, ¶¶62-63.

Ahmad teaches administering such a composition to a subject. McConville, ¶63. For example, Ahmad discloses "methods for treating and preventing breast cancer and other breast related diseases by administrating novel formulations or compositions comprising a therapeutically effective amount of endoxifen." Ex. 1003, Abstract; *id.*, 19:27-30.

Thus, claim 32 is anticipated by Ahmad.

C. Claim 2

2. The composition of claim 1, wherein the pharmaceutically acceptable salt is selected from the group consisting of an: arecoline, besylate, bicarbonate, bitartarate, butylbromide, citrate, camysylate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynapthanoate, isethionate, malate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, pamaoate (Embonate), pantothenate, phosphate/diphosphate, polygalacuronate, salicylate, stearate, sulfate, tannate, Teoclate, triethiodide, benzathine, clemizole, chloroprocaine, choline, diethylamine, diethanolamine, ethylenediamine, meglumine, piperazine, procaine, aluminum, barium, bismuth, lithium, magnesium, potassium, and zinc salt.

As discussed above, Ahmad discloses that its composition of highly pure (Z)-endoxifen can be in the form of a salt. McConville, ¶64. Ahmad teaches various pharmaceutically acceptable salts, including, for example, citrate, phosphate,

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sulfate, and digluconate. Ex. 1003, 9:1-16. Ahmad further teaches that pharmaceutically acceptable salts may be derived from acids including "hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic, lactic, salicylic, succinic, toluene-psulfonic, tartaric, acetic, citric, methanesulfonic, ethanesulfonic, formic, benzoic, malonic, sulfonic, naphthalene-2-sulfonic, benzenesulfonic acid, and the like." *Id.*, 8:52-59.

Thus, Ahmad anticipates claim 2.

D. Claims 4 and 8

Claims 4 and 8 present "identical issues of patentability" to claims 2 and 4 of the 334 patent that were found unpatentable by the Board. McConville, ¶65; 334 FWD, *31. A comparison chart showing the similarities of the claims is below. For at least this reason, the Board should find claims 4 and 8 unpatentable over Ahmad.

391 Patent	334 Patent (Unpatentable)
4. The composition of claim 1, wherein the composition is a delayed-release formulation.	2. The oral formulation of claim 1, wherein the oral formulation is a delayed-release formulation.
8. The composition of claim 1, wherein the composition comprises an enteric coating.	4. The oral formulation of claim 1, wherein the enteric capsule further comprises an enteric coating.

4. The composition of claim 1, wherein the composition 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

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until it reaches the intestine. Ex. 1003, 18:22-24. Thus, a POSA would have understood Ahmad to teach a delayed-release formulation. McConville, ¶66; 334 FWD, *31 (finding claim 2 reciting "wherein the oral formulation is a delayed-release formulation" anticipated by Ahmad).

Claim 4 is accordingly anticipated by Ahmad.

8. The composition of claim 1, wherein the composition 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 have understood Ahmad to teach an enteric coating. McConville, ¶67; 334 FWD, *31 (finding claim 4 reciting "wherein the enteric capsule further comprises an enteric coating" anticipated by Ahmad).

Claim 8 is accordingly anticipated by Ahmad.

E. Claims 5 and 6

5. The composition of claim 1, wherein the composition is a tablet.

6. The composition of claim 1, wherein the composition is a capsule.

Ahmad teaches oral administration of highly pure (Z)-endoxifen. For example, Ahmad states that "[e]xemplary routes of administration...can be through the...mouth (oral)...." Ex. 1003, 7:43-45. Ahmad further discloses "[p]harmaceutical preparations that find use with the compositions of the present invention include but are not limited to tablets, capsules, pills." Ex. 1004, 18:1-6; McConville, ¶¶68-69;

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see also 334 FWD, *31 (finding claims 1 and 15 reciting "an enteric ***capsule***" anticipated by Ahmad).

Accordingly, claims 5 and 6 are anticipated by Ahmad.

F. Claims 9, 11-15, 30, and 31

9. The composition of claim 1, wherein the composition is formulated as a suspension.

Ahmad discloses that "[p]harmaceutical preparations that find use with the compositions of the present invention include...suspensions...." Ex. 1003, 18:1-4; McConville, ¶70.

Therefore, claim 9 is anticipated by Ahmad.

11. The composition of claim 9, wherein the suspension comprises a fluid.

As discussed, Ahmad teaches that (Z)-endoxifen can be administered as a suspension. Ahmad further teaches a method including "suspending endoxifen and lipids together in an aqueous solution, e.g., water." Ex. 1003, 16:53-55. A POSA would have understood "an aqueous solution" to be a fluid. McConville, ¶¶71-72. Furthermore, a POSA would have understood that a suspension necessarily includes a fluid. *Id.*

Accordingly, claim 11 is anticipated by Ahmad.

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12. The composition of claim 11, wherein the fluid comprises an alcohol.

14. The composition of claim 9, wherein the suspension comprises an alcohol, a plant oil, a mineral oil, a glycol, an agar, or a mixture thereof.

Ahmad teaches that its composition of (Z)-endoxifen can include an alcoholic vehicle. McConville, ¶73. Ahmad states that "the composition of [the] invention containing endoxifen may also contain one or more nonaqueous vehicles, such as alcoholic vehicles." Ex. 1003, 20:63-65. A POSA would have understood that the "alcoholic vehicle" described by Ahmad would have been used as a fluid with Ahmad's suspension containing (Z)-endoxifen. McConville, ¶73.

As such, claims 12 and 14 are anticipated by Ahmad.

13. The composition of claim 12, wherein the alcohol comprises ethanol.

15. The composition of claim 9, wherein the suspension comprises ethanol, mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, vegetable oil, stearic acid, sodium lauryl sulfate, or a mixture thereof.

31. The method of claim 30, wherein the fluid comprises an alcohol, ethanol, a plant oil, a mineral oil, a glycol, an agar, glycerin, sorbitol, mannitol, polyethylene glycol, vegetable oil, stearic acid, sodium lauryl sulfate, or a mixture thereof.

Ahmad teaches that its composition of (Z)-endoxifen can include an alcoholic vehicle such as ethanol. Ex. 1003, 20:65-67 ("Examples of nonaqueous vehicles include ethyl acetate, ethanol, and isopropanol, preferably ethanol and isopropanol."); McConville, ¶74. Again, a POSA would have understood that the

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"alcoholic vehicle" of ethanol described by Ahmad would have been used as a fluid for the suspension containing (Z)-endoxifen taught by Ahmad. McConville, ¶74.

Ahmad also discloses the use of "sodium lauryl sulfate" as a "pharmaceutically acceptable carrier." Ex. 1003, 8:31-40; McConville, ¶75. A POSA would have understood that a "pharmaceutically acceptable carrier" taught by Ahmad would have been used as a fluid for the suspension containing (Z)-endoxifen. McConville, ¶75.

Accordingly, claims 13, 15, and 31 are anticipated by Ahmad.

G. Claims 20 and 23

20. The composition of claim 1, wherein the composition further comprises hydroxypropylmethyl cellulose.

Ahmad teaches that its compositions can include a gelling agent such as "hydroxypropyl methyl cellulose (HPMC)." Ex. 1003, 21:31-36; McConville, ¶76.

Therefore, claim 20 is anticipated by Ahmad.

23. The composition of claim 1, wherein the composition further comprises a disintegrant.

Ahmad teaches that its disclosure of a "pharmaceutical composition" refers to the combination of an active agent with a carrier. Ex. 1003, 8:15-20; McConville, ¶77. Ahmad further teaches that a "pharmaceutically acceptable carrier" "refers to any of the standard pharmaceutical carriers including…disintigrants [sic] (e.g., potato starch or sodium starch glycolate)...." Ex. 1003, 8:31-38; McConville, ¶77.

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Thus, Ahmad discloses the use of disintegrants and, therefore, claim 23 is anticipated by Ahmad.

H. Claims 26-29 and 33-35

26. The composition of claim 1, wherein the composition comprises from 0.01 mg to 200 mg (Z)-endoxifen.

27. The composition of claim 1, wherein the composition comprises from 1 mg to 20 mg of (Z)-endoxifen.

33. The method of claim 32, comprising administering 1 mg to 20 mg of (Z)-endoxifen.

Ahmad discloses doses of highly pure (Z)-endoxifen within the claimed ranges. McConville, ¶78. For example, Ahmad discloses doses of 1 to 10 mg/day of endoxifen. Ex. 1004, 29:20-31 ("[O]ral doses of endoxifen (1 mg-10 mg/day) with biculatamide [sic] are expected to prevent development of biclutamide-induced [sic] gynecomastia and breast pain."); McConville, ¶78. Although Ahmad does not disclose the exact claimed ranges of claim 26, 27, and 33, it discloses a range that is a species of the claimed broader ranges. *See Titanium Metals Corp. v. Banner*, 778 F.2d 775, 782 (Fed. Cir. 1985); *see also Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006) ("*Titanium Metals* stands for the proposition that an earlier species reference anticipates a later genus claim....."); *ModernaTx, Inc. v. Arbutus Biopharma Corp.*, 18 F.4th 1352, 1364 (Fed. Cir. 2021) ("[A]n anticipating reference need not show that every disclosed compound anticipates; rather it is

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sufficient that it contains a disclosure of 'at least one compound which anticipates.'").

Thus, Ahmad's teaching of a dosage between 1 and 10 mg/day anticipates claims 26, 27, and 33.

> ***28. The composition of claim 1, wherein the composition comprises from 1 mg to 4 mg of (Z)-endoxifen.***
>
> ***29. The composition of claim 1, wherein the composition comprises 8 mg of (Z)-endoxifen.***
>
> ***34. The method of claim 32, comprising administering 1 mg to 4 mg of (Z)-endoxifen.***
>
> ***35. The method of claim 32, comprising administering 8 mg of (Z)-endoxifen.***

Ahmad's teaching of a dose of (Z)-endoxifen between 1 and 10 mg/day also anticipates claims 28, 29, 34, and 35. The claimed dosages overlap with Ahmad's disclosed range, and there is no evidence that there is a "reasonable difference in how the invention operates over the ranges." *UCB*, *Inc. v. Actavis Lab'ys UT*, *Inc.*, 65 F.4th 679, 687 (Fed. Cir. 2023) ("[I]f the prior art discloses an overlapping range, the prior art anticipates the claimed range 'only [] if it describes the claimed range with sufficient specificity such that a reasonable fact finder could conclude that there is no reasonable difference in how the invention operates over the ranges."). Indeed, the claimed dosages are fully encompassed by Ahmad's disclosure and a POSA

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would have expected no difference in how the claimed ranges operate over the ranges disclosed in Ahmad. McConville, ¶79.

Therefore, claims 28, 29, 34, and 35 are anticipated by Ahmad.

I. Claims 36, 37, 40, and 41

36. The method of claim 32, wherein the administering of the composition maintains the subject's plasma endoxifen at a steady state level above 30 nM.

37. The method of claim 32, wherein the administering of the composition maintains the subject's plasma endoxifen at a steady state level from 30 nM to 300 nM.

40. The method of claim 32, 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.

41. The method of claim 32, 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.

Because the composition was known in the art at the time of the invention (*e.g.*, Ahmad), the pharmacokinetics of that composition were inherent in that composition (*e.g.*, in Ahmad's composition). McConville, ¶80. Pharmacokinetics reflect the absorption, distribution, metabolism, and excretion of a particular drug at a certain dosage. *See* Ex. 1029, 4 (explaining pharmacokinetics are used to "design[] and predict[] optimal dosing regimens for individuals or groups of patients."); Ex. 1009, Abstract ("Pharmacokinetics (PK) is the study of the time course of the absorption, distribution, metabolism and excretion (ADME) of a drug...."). In other

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words, as a POSA would have known, the pharmacokinetics are inherent properties of a particular drug. McConville, ¶80. In this way, "[a] single kinetic profile may be well summarized by C_{max}, T_{max}, $t_{1/2}$ and AUC," and that "these parameters[] may well summarize the drug kinetics in the whole population." Ex. 1010, Abstract; *see also* Ex. 1029, 5 ("[R]ecommended dosage regimens produce the desired pharmacologic response in the majority of the anticipated patient population.").

As such, claims 36, 37, 40, and 41 are anticipated by Ahmad. *See King Pharm.*, *Inc. v. Eon Labs*, *Inc.*, 616 F.3d 1267, 1275 (Fed. Cir. 2010) (claim inherently anticipated where drug's bioavailability is natural result of prior art explicated limitations).

J. Claims 42-44

Claims 42-44 present "identical issues of patentability" to claims 20-22 of the 334 patent that were found unpatentable by the Board. McConville, ¶81; 334 FWD, *31. A comparison chart showing the similarities of the claims is below. For at least this reason, the Board should find claims 42-44 unpatentable over Ahmad.

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391 Patent	334 Patent (Unpatentable)
42. The method of claim 32, further comprising treating a hormone-dependent breast disorder or a hormone-dependent reproductive tract disorder in the subject in need thereof.	20. The method of claim 15, further comprising treating a hormone-dependent breast disorder or a hormone-dependent reproductive tract disorder in the subject.
43. The method of claim 42, 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.	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.
44. The method of claim 42, wherein the hormone-dependent breast disorder or the hormone-dependent reproductive tract disorder is tamoxifen-refractory or tamoxifen resistant.	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.

42. The method of claim 32, further comprising treating a hormone-dependent breast disorder or a hormone-dependent reproductive tract disorder in the subject in need thereof.

Ahmad teaches that the "present invention also provides methods of inhibiting hormone-dependent breast carcinoma in a mammal…." Ex. 1003, 5:33-36; *see also id.*, 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 have understood Ahmad to teach a method of treating a patient with the (Z)-endoxifen

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formulation, "further comprising treating a hormone-dependent breast disorder or a hormone-dependent reproductive tract disorder in the subject." McConville, ¶82; *see also* 334 FWD at *31 (finding claim 20 "treating a hormone-dependent breast disorder or a hormone-dependent reproductive tract disorder in the subject" anticipated by Ahmad).

Claim 42 is accordingly anticipated by Ahmad.

43. The method of claim 42, 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, hyperplasia, gynecomastia, and breast cancer (among others). *See* Ex. 1003, Abstract, 18:54-60, 29:21-31. Thus, a POSA would have understood 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, ¶83; *see also* 334 FWD at *31 (finding claim 21 "wherein the hormone-dependent breast disorder or the hormone-dependent reproductive tract disorder is..." anticipated by Ahmad).

Therefore, claim 43 is anticipated by Ahmad.

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44. The method of claim 42, 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, ¶84; Ex. 1001, Fig 1, 1:63-2:6; Ex. 1003, Fig. 3, 1:35-56; Ex. 1004, [0003]. It was well-known in the art that endoxifen is a metabolite of tamoxifen, and thus would have been used on patients who could not metabolize or had difficulty metabolizing tamoxifen. As Ahmad notes, "[u]se of endoxifen, e.g., in place of Tamoxifen, avoids several metabolic steps that rely on CYP2D6." Ex. 1003, 2:2-5; 1:64-2:20. A POSA would have understood that endoxifen was expected to be efficacious in patients who were tamoxifen-resistant or tamoxifen-refractory due to metabolic deficiencies, and would have understood Ahmad to teach a method of using its formulation for tamoxifen-refractory or resistant conditions. McConville, ¶84; *see also* 334 FWD at *31 (finding claim 22 "wherein the hormone-dependent breast disorder or the hormone-dependent reproductive tract disorder is tamoxifen-refractory or tamoxifen resistant" anticipated by Ahmad).

Accordingly, claim 44 is anticipated by Ahmad.

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XI. GROUND 2: CLAIMS 1-6, 8, 9, 11-16, 20, 23, 26-37, AND 40-44 ARE OBVIOUS OVER AHMAD IN VIEW OF THE KNOWLEDGE OF A POSA

A. Claims 1, 2, 4-6, 8, 9, 11-15, 20, 23, 26-37, and 40-44

The knowledge within the art at the time of the 391 patent's claimed priority date reinforces that Ahmad anticipates the 391 patent or, alternatively, renders the 391 patent obvious in view of the knowledge of a POSA. *See*, *e.g.*, *Koninklijke Philips v. Google*, 948 F.3d 1330, 1337-38 (Fed. Cir. 2020) (affirming PTAB finding of obviousness based on a single reference in view of the knowledge of a POSA); *Realtime Data*, *LLC v. Iancu*, 912 F.3d 1368, 1373-74 (Fed. Cir. 2019) (affirming Board's invalidation under § 103 using a single reference where a second reference was used to demonstrate the knowledge of a POSA). In particular, although Ahmad discloses every element of claims 1-6, 8, 9, 11-15, 20, 23, 26-37, and 40-44 of the 391 patent, each of the elements of these claims were also separately known and obvious in view of the knowledge of a POSA.

For example, it was well-known to a POSA that endoxifen is an active metabolite of tamoxifen, which had been used in the treatment of breast cancer. McConville, ¶85; Ex. 1001, Fig 1, 1:63-2:6; Ex. 1003, Fig. 3, 1:35-56; Ex. 1004, [0003]. It was also well-known that the (Z)-form of endoxifen is more active at the estrogen receptor. Ex. 1004, [0004]. Thus, it was known to use endoxifen and/or endoxifen salts in the treatment of breast cancer. McConville, ¶85. A POSA would

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have used target pharmacokinetics (such as those of tamoxifen and endoxifen as described by Ahamd 2010 and Ahmad 2012) to develop the claimed compositions before the date of the invention of the 391 patent. McConville, ¶¶49-52, 86; 334 FWD, *48 ("[A] POSA would have been motivated to use the formulation of Ahmad to obtain a pharmacokinetic profile within the ranges recited..., as suggested by Ahmad 2010 with a reasonable expectation of success."). The use of enteric materials, suspensions, oral delivery, and excipients/additives were also well-known in the art. McConville, ¶85; Ex. 1006; Ex. 1007; Ex. 1008; Ex. 1009; Ex. 1010; 334 FWD, *35 ("We credit Dr. McConville's testimony that applying enteric coatings would have been routine...."), *41-43 ("[A] POSA would have had a reason to use the excipients...in light of their well-known uses with a reasonable expectation of success.").

Therefore, arriving at the invention claimed in the 391 patent from Ahmad would have involved simply utilizing known, conventional, and predictable processes, and a POSA would have had a reasonable expectation of success in doing so. McConville, ¶86; *see KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 415-21 (2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

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B. Claim 3

3. The composition of claim 1, wherein the pharmaceutically acceptable salt of the compound of Formula (III) is endoxifen gluconate.

Ahmad teaches a composition of highly pure (Z)-endoxifen as a digluconate salt. Ex. 1003, 9:1-4. It would have been routine for a POSA to formulate the highly pure (Z)-endoxifen composition of Ahmad as a gluconate salt (e.g., to form endoxifen gluconate) rather than a digluconate salt because it would have been easier to synthesize a gluconate salt of endoxifen than a digluconate salt of endoxifen. McConville, ¶87. For example, because (Z)-endoxifen contains a basic amine group and typically forms a monocation (+1) under acidic conditions, it would have been more favorable to form a cation of endoxifen with a charge of +1 to form a monogluconate salt rather than a cation with a charge of +2 to form a digluconate salt, under such conditions. *Id.* This is because forming a digluconate salt would require the protonation of two basic sites to achieve a +2 charge, which may not be feasible under standard conditions if (Z)-endoxifen has only one strongly basic site. *Id.*

Additionally, it would have been obvious to a POSA to formulate endoxifen gluconate given Ahmad's description of endoxifen digluconate. McConville, ¶¶88-91. Indeed, a gluconate salt is simply a salt containing two gluconate anions rather than a single gluconate anion. *Id.* Plus, the use of gluconate salts in pharmaceutical compounds was well-known. McConville, ¶¶105-106. For example, Stahl teaches a

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variety of common, well-known salts for use in pharmaceutical compositions. Ex. 1005, 334-45. Stahl lists gluconate as a common pharmaceutical salt. *Id.*, 334 (D-gluconic acid). Stahl classifies gluconate as "class 1," and explains that "first class salt-formers are those of unrestricted use...because they form physiologically ubiquitous ions, or because the occur as intermediate metabolites in biochemical pathways." Ex. 1005, 331.

It would have been obvious to a POSA to formulate endoxifen gluconate in view of Ahmad's discussion of endoxifen digluconate and the well-known, routine use of gluconate salts in pharmaceutical compositions. McConville, ¶¶105-106. Indeed, "structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a *prima facie* case of obviousness...." *In re Dillion*, 919 F.2d 688, 692 (Fed. Cir. 1990). And as discussed above, the use of single anion salts with endoxifen was well-known. McConville, ¶106; Ex. 1023 (endoxifen citrate); Ex. 1003, 29:3-6 (same); Ex. 1011, 816 (same); Ex. 1028 (endoxifen hydrochloride). A POSA would have had a reasonable expectation of success in formulating a highly pure (Z)-endoxifen composition as an endoxifen gluconate salt because the use of gluconate salts in the pharmaceutical arts was well-known, as was the use of single anion salts with endoxifen. McConville, ¶¶105-106.

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Therefore, it would have been routine and conventional for a POSA to formulate Ahmad's (Z)-endoxifen as a gluconate salt, and a POSA would have had a reasonable expectation of success in doing so. McConville, ¶106; *see In re Dillion*, 919 F.2d at 692 ("[S]tructural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a *prima facie* case of obviousness....").

Accordingly, claim 3 is obvious over Ahmad in view of the knowledge of a POSA.

C. Claim 16

16. The composition of claim 1, wherein the compound of Formula (III) is stable in the composition for at least 10 days at about 25° C.

It would have been obvious to achieve stable formulations of (Z)-endoxifen based on the extensive teachings of the prior art.

A POSA would understand "stable" as used in claim 16 to mean "the continued presence of at least 90% (Z)-endoxifen in a composition...measurable by (Z)-endoxifen conversion to (E)-endoxifen starting from the date of synthesis." Ex. 1001, 81:14-18; McConville, ¶119; Bihovsky, ¶¶74, 78.

Stability does not depend on the synthetic pathway used to generate a molecule (compounds do not remember the way they were made), but rather depends on the composition. Bihovsky, ¶80. And a POSA would have understood highly-

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pure (Z)-endoxifen, such as that taught in Ahmad, to be stable. Bihovsky, ¶¶75, 79. For example, Elkins discusses the results of stability studies of (Z)-endoxifen. Ex. 1026 at 176. Elkins stored (Z)-endoxifen at 5° C and 25° C with a relative humidity of 60% for 12 months. *Id.* at 179. Elkins explains that the (Z)-endoxifen composition slowly degraded from 98% (Z)-endoxifen to 96% (Z)-endoxifen at 25° C with a relative humidity of 60% over 12 months, that (Z)-endoxifen was stable at 5° C, degrading only slightly from 98% to 97. *Id.* Thus, as provided by Elkins, (Z)-endoxifen is stable for significantly longer than the claimed 10 days. *Id.*; Bihovsky, ¶79.

Moreover, a POSA would have understood that it is desirable for a pharmaceutical composition to be stable. McConville, ¶120; Bihovsky, ¶80. As such, a POSA would have been motivated to obtain a composition of (Z)-endoxifen that was stable, which would depend on purity. Bihovsky, ¶¶80-81. To the extent any impurities arose during the course of synthesis that negatively impacted stability, a POSA would have been motivated to use well-known purification techniques to eliminate impurities, with an expectation of success. Bihovsky, ¶¶82-83.

For example, it was well known in the prior art how to purify endoxifen using crystallization (Liu) and chromatography (Fauq). Bihovsky, ¶¶82-83; Ex. 1004; Ex. 1013. If additional purification or optimization were required to improve the stability of (Z)-endoxifen, a POSA would have been able to do so with a reasonable

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expectation of success. Bihovsky, ¶83; *see also* Ex. 1032. A POSA would have also understood how to employ other purification techniques should they be necessary to remove particular impurities. Bihovsky, ¶83. A POSA would have had numerous, well-known purification techniques at their disposal, such as, filtration, centrifugation, extraction, evaporation, drying, and adsorption, among others. *Id.*; Ex. 1032. Thus, if impurities from synthesis caused any issues with stability (of which there is no evidence), a POSA would have been familiar with various techniques for removing them and would have had a reasonable expectation of success in doing so. Bihovsky, ¶83; *see KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 415-21 (2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

The expectation of success is confirmed by Dr. Bihovsky's stability testing of Liu. As mentioned above and discussed in more detail in Dr. Bihovsky's declaration, Dr. Bihovsky synthesized (Z)-endoxifen according to Liu. Bihovsky, ¶¶42-72. Dr. Bihovsky's experiments and NMR data confirm that (Z)-endoxifen synthesized and crystallized according to Liu's teachings provided highly-pure (Z)-endoxifen (NMR of sample 15-35-2P indicates pure (Z)-endoxifen with the presence of 1 weight % of residual acetone; NMR of sample 15-36-1P shows a 93:7 mixture of (Z)- and (E)-

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endoxifen with the presence of 1 weight % of residual acetone). Bihovsky, ¶84.[6] Dr. Bihovsky then tested the stability of the (Z)-endoxifen using a stability testing procedure similar to the bulk stability testing procedure described in the 391 patent (but for 10 days rather than 3-12 months). *Id.*; *see* Ex. 1001 at 82:49-66. Dr. Bihovsky tested the stability of samples of (Z)-endoxifen sealed under nitrogen in sealed ziplock plastic bags. Bihovsky, ¶¶76, 81. He kept one sample of (Z)-endoxifen at 25° C and 60% relative humidity for ten (10) days and another sample at 40° C and 75% relative humidity for ten (10) days. *Id.* Neither sample indicated isomerization of (Z)-endoxifen to (E)-endoxifen after the ten (10) days. *Id.* Therefore, (Z)-endoxifen synthesized according to Liu does not readily convert to

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[6] As discussed the presence of 1 weight % of residual acetone did not harm the stability of (Z)-endoxifen. And, even if the presence of a small amount of acetone did affect the stability of the (Z)-endoxifen, a POSA would have known how to remove the acetone. Bihovksy ¶ 84. For example, the acetone could have been removed by drying the substance in a vacuum. *Id.* Indeed, Dr. Bihovsky dried the (Z)-endoxifen in vacuo at 35° C for 4 days and reduced the amount of residual acetone from 1 weight % to 0.6 weight %. If the amount of residual acetone needed to be reduced further, a POSA would have known how to reduce it. *Id.*

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(E)-endoxifen and is stable. *Id.* This confirms a POSA would have had a reasonable expectation of success view of Ahmad and Liu forming (Z)-endoxifen that is "stable in the composition for at least 10 days at about 25° C." Bihovsky, ¶85.

A POSA also would have been familiar with different ways to improve the stability of a pharmaceutical composition by using formulation strategies and/or packaging solutions amongst others. McConville, ¶120; Ex. 1030, 102-163. Formulation strategies are specific to the type of degradation mechanism and API, but would include for example: use of stabilizers, coatings, pH optimization, solubilization techniques, polymorph selection, lyophilization, etc. McConville, ¶120; Ex. 1030, 102-163. Packaging solutions are dependent on the type of dosage form, but would include for example: desiccants and/or moisture barriers, oxygen scavengers, light-resistant containers, air-tight or inert gas packaging. McConville, ¶120; Ex. 1030, 102-163. Utilizing such techniques to improve the stability of the (Z)-endoxifen composition would have been nothing more than utilizing known, conventional, and predictable processes, and a POSA would have had a reasonable expectation of success in doing so. McConville, ¶120.

Therefore, claim 16 is obvious over Ahmand in view of the knowledge of a POSA.

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XII. GROUND 3: CLAIMS 26-29, 33-37, 40, AND 41 ARE OBVIOUS OVER AHMAD AND AHMAD 2010/2012 IN VIEW OF THE KNOWLEDGE OF A POSA

A. Claims 26-29 and 33-35

Claim 26 presents "identical issues of patentability" to claim 14 of the 334 patent that was found unpatentable by the Board. McConville, ¶92; 334 FWD, *46. A comparison chart showing the similarities of the claims is below. For at least this reason, the Board should find claim 26 unpatentable over Ahmad in view of Ahmad 2010/2012.

391 Patent	334 Patent (Unpatentable)
26. The composition of claim 1, wherein the composition comprises from 0.01 mg to 200 mg (Z)-endoxifen.	14. The oral formulation of claim 1, wherein the endoxifen composition comprises from 0.01 mg to 200 mg (Z)-endoxifen per enteric capsule.

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> ***26. The composition of claim 1, wherein the composition comprises from 0.01 mg to 200 mg (Z)-endoxifen.***
>
> ***27. The composition of claim 1, wherein the composition comprises from 1 mg to 20 mg of (Z)-endoxifen.***
>
> ***28. The composition of claim 1, wherein the composition comprises from 1 mg to 4 mg of (Z)-endoxifen.***
>
> ***29. The composition of claim 1, wherein the composition comprises 8 mg of (Z)-endoxifen.***
>
> ***33. The method of claim 32, comprising administering 1 mg to 20 mg of (Z)-endoxifen.***
>
> ***34. The method of claim 32, comprising administering 1 mg to 4 mg of (Z)-endoxifen.***
>
> ***35. The method of claim 32, comprising administering 8 mg of (Z)-endoxifen.***

Ahmad discloses doses of 1 to 10 mg/day of endoxifen. Ex. 1004, 29:20-31. Similarly, Ahmad 2010 and Ahmad 2012 provide safety data suggesting appropriate dosages 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, 816. Ahmad 2012 teaches that "[m]ultiple daily endoxifen doses of 4.0-8.0 mg resulted in endoxifen exposures that would be sufficient for effective therapy." Ex. 1007, 1-2. Ahmad, Ahmad 2010, and Ahmad 2012 all suggest using dosage forms well within the values recited by claims 26-29 and 33-35. Therefore, at the very least, it would have been obvious for a POSA to try dosages of (Z)-endoxifen in the claimed amounts. McConville, ¶93; 334 FWD, *46 ("[W]e credit the well-supported

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testimony of Dr. McConville that it would have been routine for a POSA to run experiments like those described in Ahmad 2010 and Ahmad 2012 to determine the proper dosage of highly pure (Z)-endoxifen.”).

Thus, claims 26-29 and 33-35 are obvious over Ahmad and Ahmad 2010/2012 in view of the knowledge of a POSA.

B. Claims 36, 37, 40, and 41

Claims 40 and 41 present “identical issues of patentability” to claims 18 and 19 of the 334 patent that were found unpatentable by the Board. McConville, ¶94; 334 FWD, *48-49. A comparison chart showing the similarities of the claims is below. For at least this reason, the Board should find claims 40 and 41 unpatentable over Ahmad in view of Ahmad 2010/2012.

391 Patent	334 Patent (Unpatentable)
40. The method of claim 32, 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.	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.
41. The method of claim 32, 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.	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.

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> ***36. The method of claim 32, wherein the administering of the composition maintains the subject's plasma endoxifen at a steady state level above 30 nM.***
>
> ***37. The method of claim 32, wherein the administering of the composition maintains the subject's plasma endoxifen at a steady state level from 30 nM to 300 nM.***
>
> ***40. The method of claim 32, 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.***
>
> ***41. The method of claim 32, 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.***

The claimed pharmacokinetic properties are merely inherent properties that arise from dosing a patient with 1 to 200 mg of Ahmad's (Z)-endoxifen formulation. McConville, ¶95. Merely claiming such inherent properties of a prior art composition is not enough to render those claims patentable. *See Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012) ("[A]n obvious formulation cannot become nonobvious simply by administering it to a patient and claiming the resulting serum concentrations."); *In re Huai-Hung Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011) (claimed "food-effect" related serum concentration level is inherent property of drug).

Moreover, Ahmad 2010 and Ahmad 2012 show that the claimed pharmacokinetic properties would not have been surprising or unexpected. McConville, ¶95. For example, Ahmad 2010 and 2012 describe the endoxifen

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pharmacokinetics expected to be efficacious by comparing the pharmacokinetics of endoxifen to the pharmacokinetics of the known anti-cancer drug, tamoxifen. McConville, ¶¶95, 97, 99, 101, 103; Ex. 1006, 816 ("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."); Ex. 1007, 2 ("Multiple daily endoxifen doses of 4.0-8.0 mg resulted in endoxifen exposures that would be sufficient for effective therapy."). The pharmacokinetics described in Ahmad 2010 and Ahmad 2012 fall within the scope of the claims.

For example, Ahmad 2010 further teaches that "the estimated steady-state plasma concentration (C^{SS}_{max}) of endoxifen is 55.1 ng/ml when the drug is administered in multiple doses of 4 mg at dose intervals of 24 h...." Ex. 1006, 816. Converting the C^{SS}_{max} from ng/ml to nM yields a C^{SS}_{max} of 147.5 nM.[7] Ahmad 2012 provides steady state plasma levels ranging from 65.5 to 359 nM.[8] Ex. 1012, 2.

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[7] (55.1 ng/ml * 373.5 g/mol) / 1000 = 147.5 nM. *See* Ex. 1019 (providing molecular weight of endoxifen); McConville, ¶97.

[8] After converting from ng/ml to nM. *See supra*, n.8; McConville, ¶97.

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Ahmad 2010 also produced data demonstrating the AUC in subjects treated with 0.5 to 4.0 mg of endoxifen:

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, 815. As shown in the table above, the AUC for 4 mg is well within the claimed range. *Id.*; McConville, ¶101.

And to the extent the claimed pharmacokinetics were not inherently achieved following Ahmad, a POSA would have been aware of the target pharmacokinetics expected to be efficacious and would have been able to optimize a formulation to achieve them (*e.g.*, as indicated by Ahmad 2010 and Ahmad 2012). McConville, ¶¶96, 98, 100, 102, 104. A POSA would have been aware of the different ways to adjust the pharmacokinetics of a formulation and would have had a reasonable expectation of success in altering the pharmacokinetics of a formulation, as adjusting the pharmacokinetics of a formulation was a routine, commonplace, and straightforward practice in the formulation arts. *Id.* For example, a POSA would have increased or decreased the amount of (Z)-endoxifen in the formulation to adjust C_{max}, added an absorption enhancer to the formulation, changed the particle size of

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the (Z)-endoxifen, and/or added a surfactant to increase solubilization. McConville, ¶96.

Therefore, given the teachings of Ahmad 2010 and Ahmad 2012, a POSA would have been aware of the target pharmacokinetics expected to be efficacious for (Z)-endoxifen compositions and would have optimized a formulation to achieve them with a reasonable expectation of success. *Id.*; 334 FWD, *48 ("[A] POSA would have been motivated to use the formulation of Ahmad to obtain a pharmacokinetic profile within the ranges recited..., as suggested by Ahmad 2010 with a reasonable expectation of success.").

Thus, claims 36, 37, 40, and 41 would have been obvious over Ahmad and Ahmad 2010/2012 in view of the knowledge of a POSA.

XIII. GROUND 4: CLAIM 7 IS OBVIOUS OVER AHMAD AND BENAMEUR IN VIEW OF THE KNOWLEDGE OF A POSA

A. Claim 7

Claim 7 presents "identical issues of patentability" to claim 3 of the 334 patent that were found unpatentable by the Board. McConville, ¶107; 334 FWD, *37-39. A comparison chart showing the similarities of the claims is below. For at least this reason, the Board should find claim 7 unpatentable over Ahmad in view of Benameur.

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

7. The composition of claim 1, wherein the composition is uncoated.

As discussed above, Ahmad teaches the use of an enteric coated capsule for its endoxifen formulations. 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 (*e.g.*, Capsugel). McConville, ¶108.

For example, Benameur teaches that "[e]nteric 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." Ex. 1006, 34; McConville, ¶109. Such capsules were commercially available by October 7, 2016.[9]

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[9] 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

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Thus, a POSA would have understood Benameur to teach the alternative use of an uncoated enteric capsule. McConville, ¶110; 334 FWD, *37 ("Benameur teaches the use of an enteric capsule that is uncoated...."). A POSA would have been motivated to do so to obtain the benefits Benameur highlights, such as the ability to produce a 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. McConville, ¶110; Ex. 1006, 34; *see also* 334 FWD, *38 ("[A] POSA would have had a reason to combine Benameur's intrinsic capsules with Ahmad's formulation with a reasonable expectation of success.").

Accordingly, claim 7 would have been obvious over Ahmad and Benameur in view of the knowledge of a POSA.

XIV. GROUND 5: CLAIMS 10, 12-15, 30, AND 31 ARE OBVIOUS OVER AHMAD AND DE VILLIERS/GANDHI IN VIEW OF THE KNOWLEDGE OF A POSA

A. Claim 10

10. The composition of claim 9, wherein the suspension comprises a syrup or an elixir.

Ahmad discloses that its endoxifen compositions can be in the form of a syrup or a suspension. Ex. 1003, 18:4-7. Ahmad does not explicitly disclose that its suspension can comprise a syrup or elixir.

However, a POSA would have understood that a syrup (or an elixir) could have been used in the formulation of a suspension as described by Ahmad.

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McConville, ¶111. For example, de Villiers lists common liquid vehicles that would have been used for suspensions. Ex. 1007, 191, Table 15.1 (listing common liquid vehicles). As shown below, de Villiers specifically lists syrups and elixirs as common vehicles. *Id.* Therefore, it would have been routine and within the skill of a POSA to have formulated a suspension of highly-pure (Z)-endoxifen as taught by Ahmad with a syrup or elixir vehicle as taught by de Villiers. McConville, ¶112. Formulating a suspension of highly-pure (Z)-endoxifen as taught by Ahmad with a syrup or elixir vehicle as taught by de Villiers would have been nothing more than a routine design choice for a POSA. McConville, ¶112; *see also Bial-Portela & CA S.A. v. Alkem Lab'ys Ltd.*, 2022 WL 4244989, at *20 (D. Del. Sept. 15, 2022) (stating "in view of the ranges disclosed in the HPE, an artisan of ordinary skill would be able to "select the right excipients..." without undue experimentation).

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Table 15.1 USP AND NF EXCIPIENTS CATEGORIZED AS SOLVENTS AND VEHICLES

SOLVENT	VEHICLE
Acetone	FLAVORED AND/OR SWEETENED
Alcohol	Aromatic Elixir
Alcohol, Diluted	Benzaldehyde Elixir, Compound
Amylene Hydrate	Dextrose
Benzyl Benzoate	Peppermint Water
Butyl Alcohol	Sorbitol Solution
Canola Oil	Syrup
Caprylocaproyl Polyoxylglycerides	OLEAGINOUS
Corn Oil	Alkyl (C12-15) Benzoate
Cottonseed Oil	Almond Oil
Diethylene Glycol Monoethyl Ether	Canola Oil
Ethyl Acetate	Corn Oil
Glycerin	Cottonseed Oil
Hexylene Glycol	Ethyl Oleate
Isopropyl Alcohol	Isopropyl Myristate
Lauroyl Polyoxylglycerides	Isopropyl Palmitate
Linoleoyl Polyoxylglycerides	Mineral Oil
Methyl Alcohol	Mineral Oil, Light
Methylene Chloride	Octyldodecanol
Methyl Isobutyl Ketone	Olive Oil
Mineral Oil	Peanut Oil
Oleoyl Polyoxylglycerides	Safflower Oil
Peanut Oil	Sesame Oil
Polyethylene Glycol	Soybean Oil
Polyethylene Glycol Monomethyl Ether	Squalane
Propylene Glycol	STERILE
Sesame Oil	Sodium Chloride Injection, Bacteriostatic
Stearoyl Polyoxylglycerides	Water for Injection, Bacteriostatic
Water for Injection	SOLID CARRIER
Water for Injection, Sterile	Sugar Spheres
Water for Irrigation, Sterile	
Water, Purified	

From the United States Pharmacopeial Convention Inc. USP 30/ NF 25. 2006: Front Matter—NF: Excipients. Rockville, MD: Author, 2007, with permission.
Source: 2007 USP 30/ NF 25. Rockville, MD: The United States Pharmacopeial Convention Inc., 2006: Front Matter—NF: Excipients.

Thus, claim 10 is obvious over Ahmad and de Villiers in view of the knowledge of a POSA.

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B. Claims 12-15 and 31

12. The composition of claim 11, wherein the fluid comprises an alcohol.

13. The composition of claim 12, wherein the alcohol comprises ethanol.

14. The composition of claim 9, wherein the suspension comprises an alcohol, a plant oil, a mineral oil, a glycol, an agar, or a mixture thereof.

15. The composition of claim 9, wherein the suspension comprises ethanol, mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, vegetable oil, stearic acid, sodium lauryl sulfate, or a mixture thereof.

31. The method of claim 30, wherein the fluid comprises an alcohol, ethanol, a plant oil, a mineral oil, a glycol, an agar, glycerin, sorbitol, mannitol, polyethylene glycol, vegetable oil, stearic acid, sodium lauryl sulfate, or a mixture thereof.

As discussed above, Ahmad teaches that its composition of (Z)-endoxifen can include an alcoholic vehicle. Ex. 1003, 20:63-65. De Villiers likewise teaches that alcohols are common vehicles for suspensions. Ex.1007, 190 ("[S]olvent-vehicles frequently used as ingredients in drug products and compounded preparations include alcohol...."). De Villiers teaches that ethanol is a common alcohol used in pharmaceutical preparations. *Id.*, 195 ("[ethanol] is used as a solvent-vehicle for the preparation of pharmaceutical dosage forms for internal or external use").

Ahmad further teaches the use of "sodium lauryl sulfate" as a "pharmaceutically acceptable carrier." Ex. 1003, 8:31-40. de Villiers additionally teaches the use of sorbitol, mineral oil, plant oils, and vegetable oils as vehicles. *Id.*, 190.

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Table 15.1 USP AND NF EXCIPIENTS CATEGORIZED AS SOLVENTS AND VEHICLES

SOLVENT	VEHICLE
Acetone	FLAVORED AND/OR SWEETENED
Alcohol	Aromatic Elixir
Alcohol, Diluted	Benzaldehyde Elixir, Compound
Amylene Hydrate	Dextrose
Benzyl Benzoate	Peppermint Water
Butyl Alcohol	Sorbitol Solution
Canola Oil	Syrup
Caprylocaproyl Polyoxylglycerides	OLEAGINOUS
Corn Oil	Alkyl (C12-15) Benzoate
Cottonseed Oil	Almond Oil
Diethylene Glycol Monoethyl Ether	Canola Oil
Ethyl Acetate	Corn Oil
Glycerin	Cottonseed Oil
Hexylene Glycol	Ethyl Oleate
Isopropyl Alcohol	Isopropyl Myristate
Lauroyl Polyoxylglycerides	Isopropyl Palmitate
Linoleoyl Polyoxylglycerides	Mineral Oil
Methyl Alcohol	Mineral Oil, Light
Methylene Chloride	Octyldodecanol
Methyl Isobutyl Ketone	Olive Oil
Mineral Oil	Peanut Oil
Oleoyl Polyoxylglycerides	Safflower Oil
Peanut Oil	Sesame Oil
Polyethylene Glycol	Soybean Oil
Polyethylene Glycol Monomethyl Ether	Squalane
Propylene Glycol	STERILE
Sesame Oil	Sodium Chloride Injection, Bacteriostatic
Stearoyl Polyoxylglycerides	Water for Injection, Bacteriostatic
Water for Injection	SOLID CARRIER
Water for Injection, Sterile	Sugar Spheres
Water for Irrigation, Sterile	
Water, Purified	

From the United States Pharmacopeial Convention Inc. USP 30/ NF 25. 2006: Front Matter—NF: Excipients. Rockville, MD: Author, 2007, with permission.
Source: 2007 USP 30/ NF 25. Rockville, MD: The United States Pharmacopeial Convention Inc., 2006: Front Matter—NF: Excipients.

Id. It would have been routine and within the skill of a POSA to have formulated a suspension of highly-pure (Z)-endoxifen as taught by Ahmad with an alcohol, ethanol, of sorbitol, mineral oil, plant oils, and/or vegetable oils, as taught

by de Villiers. McConville, ¶¶113-118. Formulating a suspension of highly-pure (Z)-endoxifen as taught by Ahmad with the claimed vehicles would have been nothing more than a routine design choice for a POSA. *Id.*

Therefore, claims 12-15 and 31 are obvious over Ahmad and de Villiers in view of the knowledge of a POSA.

C. Claim 30

30. A method of making the composition of claim 9, the method comprising suspending the endoxifen and the enteric material in a fluid.

Ahmad teaches an enteric coating to prevent release of medication before it reaches the small intestine. McConville, ¶143. Ahmad does not explicitly disclose the use of an enteric material in a suspension, but does describe the use of suspensions of endoxifen and the use of enteric materials. *Id.* Gandhi teaches the use of a "rate controlling polymer" in an oral suspension of an active ingredient to create a "stable, sustained release oral liquid suspension dosage." Ex. 1022, Abstract. Gandhi describes "sustained-release dosage forms" as a dosage designed to release "an active agent over an extended period of time." *Id.*, 4:15-16. Although Gandhi does not explicitly refer to its "rate controlling polymer" as an enteric material, a POSA would have understood the "rate controlling polymers" described by Gandhi to be enteric materials. McConville, ¶144; Ex. 1022, 4:16-18 (synonymizing "sustained-release" with "controlled-release" and "delayed release"). Indeed, both Gandhi and the 391 patent describe the same substances for use as a "rate controlling

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polymer" or "enteric material." *Compare* Ex. 1022, 7:20-8:22 (listing EUDRAGIT L and S as hydrophobic rate controlling polymers), *with* Ex. 1001, 39:22-51 (describing EUDRAGIT L and S copolymers as "pH dependent polymers" that "target upper small intestines and colon").

A POSA would have been motivated to formulate a suspension of (Z)-endoxifen, as described by Ahmad, with an enteric material, as described by Gandhi, to ensure that the endoxifen was released in the small intestine where it would be absorbed into the body and have pharmaceutical effect. McConville, ¶145. Indeed, as discussed above, Ahmad describes the use of enteric materials for its (Z)-endoxifen formulations. A POSA would have had a reasonable expectation of success as this is taught in Gandhi. *Id.*

Accordingly, claim 30 would have been obvious over Ahmad and Gandhi in view of the knowledge of a POSA.

XV. GROUND 6: CLAIMS 21-25 ARE OBVIOUS OVER AHMAD AND STEGEMANN/HPE IN VIEW OF THE KNOWLEDGE OF A POSA

A. Claims 21-25

Claims 21-25 present "identical issues of patentability" to claims 9-13 of the 334 patent that were found unpatentable by the Board. McConville, ¶121; 334 FWD, *40-43. For example, the claims from both patents recite common, well-known pharmaceutical excipients. *Compare* Ex. 1001, Claims 21-25, *with* Ex. 1023, Claims 9-13. A comparison chart showing the similarities of the claims is below. For at least

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these reasons, the Board should find claims 21-25 unpatentable over Ahmad and Stegemann/the HPE in view of the knowledge of a POSA.

391 Patent	**334 Patent (Unpatentable)**
21. The composition of claim 1, wherein the composition further comprises a filler.	9. The oral formulation of claim 1, wherein the endoxifen composition further comprises a filler.
22. The composition of claim 21, wherein the filler comprises a sugar, salt, talc, calcium carbonate, microcrystalline cellulose, methyl cellulose, carboxymethyl cellulose, kaolin, mannitol, silicic acid, sorbitol, starch, pregelatinized starch, or combinations thereof.	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.
23. The composition of claim 1, wherein the composition further comprises a disintegrant.	11. The oral formulation of claim 1, wherein the endoxifen composition further comprises a disintegrant.
24. The composition of claim 1, wherein the composition further comprises a lubricant.	12. The oral formulation of claim 1, wherein the endoxifen composition further comprises a lubricant.
25. The composition of claim 24, 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.	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.

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21. The composition of claim 1, wherein the composition further comprises a filler.

22. The composition of claim 21, wherein the filler comprises a sugar, salt, talc, calcium carbonate, microcrystalline cellulose, methyl cellulose, carboxymethyl cellulose, kaolin, mannitol, silicic acid, sorbitol, starch, pregelatinized starch, or combinations thereof.

A filler (also sometimes called a diluent) is a common pharmaceutical excipient that increases the volume of a pharmaceutical formulation. McConville, ¶122. It helps make ingredients easier to process, stabilizes the formulation, and makes the formulation a suitable size for consumption. *Id.*; Ex. 1020, 184.

Fillers were well-known in the pharmaceutical industry. McConville, ¶¶123, 125. For example, Stegemann teaches that several excipients function as fillers at higher volumes. Ex. 1008, 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. 1009, 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). In addition, Ahmad teaches formulations including substances that can

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act as a filler/diluent. *See*, *e.g.*, Ex. 1003, 9:57-61(sucrose, glucose, lactose, sorbitol, mannitol), 8:37-38 (starch).

As taught by these references, the use of a filler in the formulation was a routine and common practice in the formulation arts. McConville, ¶¶124-125. A POSA would have been motivated to use a carrier and/or diluent 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 would have had a reasonable expectation of success, as carriers and diluents were commonplace excipients in the art. *Id.*; 334 FWD, *43 ("[W]e are persuaded that a POSA would have had a reason to use the excipients identified in Stegemann and the HPE in the endoxifen formulation of Ahmad in light of their well-known uses with a reasonable expectation of success.").

Accordingly, claims 21 and 22 would have been obvious over Ahmad in view of Stegemann and/or the HPE.

23. The composition of claim 1, wherein the composition further comprises a disintegrant.

As discussed above, Ahmad teaches that its compositions can include "disintigrants [sic] (e.g., potato starch or sodium starch glycolate)...." Ex. 1003, 8:31-38. Moreover, disintegrants were well-known in the pharmaceutical industry. McConville, ¶126. A disintegrant is a common pharmaceutical excipient that

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increases dissolution of a formulation once it is in a proper medium. *Id.* It helps "ensure that the active ingredient is made available quickly and absorbed by the body in the proper location." *Id.*; *see also* Ex. 1020, 184.

Similar to Ahmad, 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

Ex. 1008, 8; *see also* Ex. 1009, 897-98 (listing disintegrants); Ex. 1020, 184 (same); McConville, ¶127.

As taught by these references, the use of a disintegrant in the formulation was a routine and common practice in the formulation arts. McConville, ¶128. A POSA would have been motivated to use a disintegrant for its normal use—to ensure that the active ingredient is made available quickly and absorbed by the body in the proper location. *Id.* A POSA would have had a reasonable expectation of success as disintegrants were commonly used excipients. *Id.*; 334 FWD, *43 ("[W]e are persuaded that a POSA would have had a reason to use the excipients identified in Stegemann and the HPE in the endoxifen formulation of Ahmad in light of their well-known uses with a reasonable expectation of success.").

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Accordingly, claim 23 would have been obvious over Ahmad in view of Stegemann and/or the HPE.

> ***24. The composition of claim 1, wherein the composition further comprises a lubricant.***
>
> ***25. The composition of claim 24, 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.***

A lubricant is a common pharmaceutical excipient that decreases the friction between pharmaceutical formulations and the tableting equipment contact surface. McConville, ¶129. Lubricants "help[] make processing and manufacturing more efficient." *Id.*

Lubricants were well-known in the pharmaceutical industry. *Id.*, ¶¶130, 132. For example, Stegemann teaches the use of lubricants in capsules:

Lubricants

→ Improved flow properties and reduced powder adhesion to metal parts

- Magnesium stearate
- Glyceryl monostearate
- Stearic acid

Ex. 1008, 8; *see also* Ex. 1009, 905 (listing "Lubricants (tablet/capsule)"). Ahmad likewise discloses the use of compounds that have lubricating properties. *See*, *e.g.*, Ex. 1003, 13:15-25 (stearic acid).

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As taught by these references, the use of a lubricant in the formulation was a routine and common practice in the formulation arts. McConville, ¶¶131-133. A POSA would have been motivated to use a lubricant for its normal use—to make processing and manufacturing more efficient. *Id.*; 334 FWD, *43 ("[W]e are persuaded that a POSA would have had a reason to use the excipients identified in Stegemann and the HPE in the endoxifen formulation of Ahmad in light of their well-known uses with a reasonable expectation of success.").

Thus, claims 24 and 25 would have been obvious over Ahmad and Stegemann/the HPE in view of the knowledge of a POSA.

XVI. GROUND 7: CLAIMS 17-19, 38, AND 39 ARE OBVIOUS OVER AHMAD AND COLE IN VIEW OF THE KNOWLEDGE OF A POSA

A. Claims 17-19, 38, and 39

Claims 17-19, 38, and 39 present "identical issues of patentability" to claims 5-7 of the 334 patent that were found unpatentable by the Board. McConville, ¶134; 334 FWD, *33-36. For example, the claims from both patents recite properties of enteric/delayed-release drugs. *Compare* Ex. 1001, Claims 17-19, 38, 39, *with* Ex. 1023, Claims 5-7. A comparison chart showing the similarities of the claims is below. For at least this reason, the Board should find claims 17-19, 38, and 39 unpatentable over Ahmad and Cole in view of the knowledge of a POSA.

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391 Patent	334 Patent (Unpatentable)
17. The composition of claim 1, formulated such that the composition 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.	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.
18. The composition of claim 1, formulated such that the composition 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.	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.
19. The composition of claim 1, formulated such that the composition 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.	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.
38. The method of claim 32, further comprising releasing no more than 10% of the (Z)-endoxifen in a stomach of the subject within 2 hours following the administering of the composition.	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.
39. The method of claim 32, further comprising releasing at least 50% of the (Z)-endoxifen in a small intestine of the subject within 8 hours following the administering of the composition.	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.

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17. The composition of claim 1, formulated such that the composition 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. McConville, ¶135; Ex. 1003, 18:19-21. Like Ahmad, Cole teaches enteric coated capsules. Cole further teaches that "[n]o paracetamol[10] 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. 1010, 89. Thus, Cole teaches that its enteric coating prevents drug release for at least two hours under strongly acidic conditions. McConville, ¶136. While Cole does not explicitly disclose that the method used was USP 711, a POSA would have recognized that USP 711 was the most common method for dissolution testing, and would have understood from Cole's methodology that it was using USP 711. *Id.*

Thus, a POSA would have understood Cole to teach that enteric coated capsules, such as those taught in Ahmad, "formulated such that the oral formulation

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[10] 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, ¶136 n.8.

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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." *Id.*, ¶137. This resistance to dissolution would have been 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. *Id.* And a POSA would have had a reasonable expectation of success in achieving this release rate, as is taught by Cole. *Id.*; 334 FWD, *36 ("[W]e find that...a POSA would have had a reason to use the enteric coating and HPMC capsules of Cole with the (Z)-endoxifen formulation of Ahmad to reach the claimed invention with a reasonable expectation of success.").

Therefore, claim 17 would have been obvious over Ahmad and Cole in view of the knowledge of a POSA.

> ***18. The composition of claim 1, formulated such that the composition 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.***
>
> ***38. The method of claim 32, further comprising releasing no more than 10% of the (Z)-endoxifen in a stomach of the subject within 2 hours following the administering of the composition.***

As discussed above, a POSA would have understood that an 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. McConville, ¶¶138-139. The pH of the human stomach is 1.5. Ex. 1021, 8. Thus, the conditions described above in Cole

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(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, ¶¶138-139.

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. *Id.*, ¶140. And a POSA would have had a reasonable expectation of success in achieving this release rate as taught by Cole. *Id.*; 334 FWD, *36 ("[W]e find that...a POSA would have had a reason to use the enteric coating and HPMC capsules of Cole with the (Z)-endoxifen formulation of Ahmad to reach the claimed invention with a reasonable expectation of success.").

Accordingly, claims 18 and 38 would have been obvious over Ahmad and Cole in view of the knowledge of a POSA.

> ***19. The composition of claim 1, formulated such that the composition 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.***
>
> ***39. The method of claim 32, further comprising releasing at least 50% of the (Z)-endoxifen in a small intestine of the subject within 8 hours following the administering of the composition.***

As Ahmad teaches, the purpose of its enteric coating is to prevent release of medication before it reaches the small intestine. McConville, ¶141. Cole teaches that

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at "pH 6.8,[11] release of the paracetamol was rapid…." Ex. 1010, 89; *see also id.*, 91, Fig. 4 (showing 50% release in pH 6.8 by about 2.5-3 hours). Thus, a POSA would have understood that Ahmad's formulation coated according to Cole would have been 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 method of USP 711." McConville, ¶141.

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 would be absorbed into the body and have pharmaceutical effect. *Id.* ¶142. A POSA would have had a reasonable expectation of success as this is taught in Cole. *Id.*; 334 FWD, *36 ("[W]e find that...a POSA would have had a reason to use the enteric coating and HPMC capsules of Cole with the (Z)-endoxifen formulation of Ahmad to reach the claimed invention with a reasonable expectation of success.").

Accordingly, claims 19 and 39 would have been obvious over Ahmad and Cole in view of the knowledge of a POSA.

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

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XVII. GROUND 8: LACK OF WRITTEN DESCRIPTION SUPPORT/ENABLEMENT OF CLAIMS 10, 12-15, AND 30

A. Claims 10, 12-15, and 30

10. The composition of claim 9, wherein the suspension comprises a syrup or an elixir.

12. The composition of claim 11, wherein the fluid comprises an alcohol.

13. The composition of claim 12, wherein the alcohol comprises ethanol.

14. The composition of claim 9, wherein the suspension comprises an alcohol, a plant oil, a mineral oil, a glycol, an agar, or a mixture thereof.

15. The composition of claim 9, wherein the suspension comprises ethanol, mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, vegetable oil, stearic acid, sodium lauryl sulfate, or a mixture thereof.

30. A method of making the composition of claim 9, the method comprising suspending the endoxifen and the enteric material in a fluid.

To the extent Patent Owner argues any of the above claims are not anticipated and/or obvious, the claims lack written description support and/or are not enabled by the 391 patent specification. For example, although the 391 patent mentions syrups, elixirs, alcohols, etc., nowhere does the 391 patent specification disclose ***a suspension that comprises*** such substances. Instead, the 391 patent specification states that the disclosed compositions can be in the form of a syrup, elixir, or suspension, but does not disclose ***a suspension that comprises*** a syrup or elixir as recited in claim 10. Ex. 1001, 36:12-16. Similarly, the 391 patent specification generally mentions agars, mineral oil, etc., but fails to disclose ***a suspension that comprises*** such substances. *See*, *e.g.*, *id.*, 38:3-12 (listing claimed substances as

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lubricants). Similarly, the 391 patent specification fails to describe a formulation in which the enteric material is suspended in a fluid with the endoxifen.

Rather than describing the invention in sufficient detail so "that one skilled in the art can clearly conclude that the inventor invented the claimed invention as of the filing date sought," *Lockwood v. Am. Airlines*, *Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997), as to "the full scope of the claimed invention" as of the filing date, *Juno Therapeutics*, *Inc. v. Kite Pharma*, *Inc.*, 10 F.4th 1330, 1336 (Fed. Cir. 2021), Patent Owner appears to have cobbled the claims together from disparate disclosures in the specification. *See*, *e.g.*, *Novozymes A/S v. DuPont Nutrition Bioscis. APS*, 723 F.3d 1336, 1349 (Fed. Cir. 2013) (finding patent invalid for a lack of written description support where patentee sought to "derive written description support from an amalgam of disclosures plucked selectively from the . . . application"). "An applicant is [only] entitled to claims as broad as the prior art ***and his disclosure*** will allow." *Gentry Gallery*, *Inc. v. Berkline Corp.*, 134 F.3d 1473, 1480 (Fed. Cir. 1998) (citing *In re Rasmussen*, 650 F.2d 1212, 1214 (C.C.P.A. 1981)).

For at least these reasons, claims 10, 12-15, and 30 are invalid under 35 U.S.C. § 112 for a lack of written description support/enablement.

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XVIII. CONCLUSION

Petitioner has established it is more likely than not that each of claims 1-44 of the 391 patent is unpatentable, and therefore respectfully requests that the Board institute post grant review of those claims.

Respectfully submitted,

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Dated: April 3, 2025

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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 13,848 words, as determined by Microsoft Word.

Dated: April 3, 2025

By: /*Alejando Menchaca*/
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Lead Counsel for Petitioner
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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 this Federal Express to the Patent Owner at the following correspondence address of record for U.S. Patent No. 12,071,391:

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