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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

INTAS PHARMACEUTICALS LTD.,
Petitioner

v.

ATOSSA THERAPEUTICS, INC.,
Patent Owner

Case PGR2023-00043

Patent No. 11,572,334

PETITIONER'S REPLY

TABLE OF CONTENTS

I.	Introduction.....	1
II.	A POSA has experience with dosage forms.....	1
III.	The claims are not limited to a free base.....	2
IV.	Ground I: Ahmad is enabled and anticipates the claims	3
A.	Ahmad's teaching of using 90% pure (Z)-endoxifen was in the public's possession.....	3
1.	Liu and Fauq confirm that Ahmad's teaching of 90% pure (Z)-endoxifen was enabled	4
2.	Liu and Fauq are prior art and may be used to show Ahmad is enabled.....	5
3.	Patent Owner's efforts to distinguish Liu are unavailing	7
B.	Patent Owner's cases are inapposite	8
V.	Ground II: It would have been obvious to make a 90% pure (Z)-endoxifen capsule based on Ahmad	10
A.	Petitioner argued in Ground II it would have been obvious to use knowledge such as Liu to form 90% pure (Z)-endoxifen	10
B.	A POSA would have been motivated to form 90% pure (Z)-endoxifen capsules with a reasonable expectation of success	10
VI.	Ground III: It would have been obvious to combine Ahmad with Cole's teaching of an enteric coated capsule	12
VII.	Ground IV: It would have been obvious to combine Ahmad with Benameur's teaching of an enteric capsule	16
VIII.	Ground V: It would have been obvious to combine Ahmad with standard excipients as taught in e.g., the HPE and Stegemann.....	18

IX.	Ground VI: It would have been obvious to determine a dosage amount for Ahmad's (Z)-endoxifen capsules that would result in the claimed pharmacokinetics based on Ahmad 2010 and 2012	20
A.	It would have been obvious to select a dosage form between 0.01 mg and 200 mg (Z)-endoxifen per capsule as shown in Ahmad 2010 and 2012	20
B.	The pharmacokinetic limitations are the inherent result of dosing a patient with 90% (Z)-endoxifen as taught in Ahmad at the dosages taught in Ahmad 2010 and 2012	22
X.	The secondary considerations do not show nonobviousness	24
XI.	Conclusion	25

TABLE OF AUTHORITIES

Cases

<i>Allergan Inc. v. Apotex</i> , 754 F.3d 952 (Fed. Cir. 2014)	19
<i>Amgen Inc. v. Sanofi</i> , 872 F.3d 1367 (Fed. Cir. 2017)	5
<i>Bristol-Myers Squibb Co. v. Ben Venue Lab ’ys, Inc.</i> , 246 F.3d 1368 (Fed. Cir. 2001)	3, 5, 6, 7
<i>Corephotonics, Ltd. v. Apple Inc.</i> , 84 F.4th 990 (Fed. Cir. 2023)	10
<i>Daiichi Sankyo Co. v. Apotex, Inc.</i> , 501 F.3d 1254 (Fed. Cir. 2007)	2
<i>Endo Pharms. Sols., Inc. v. Custopharm Inc.</i> , 894 F.3d 1374 (Fed. Cir. 2018)	23
<i>Galderma Lab ’ys, L.P. v. Tolmar, Inc.</i> , 737 F.3d 731 (Fed. Cir. 2013)	18
<i>Impax Labs., Inc. v. Aventis Pharms., Inc.</i> , 496 F. Supp. 2d 428 (D. Del. 2007).....	8
<i>In re Bass</i> , 314 F.3d 575 (Fed. Cir. 2002)	2
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<i>In re Donohue</i> , 766 F.2d 531 (Fed. Cir. 1985)	6
<i>In re Fulton</i> , 391 F.3d 1195 (Fed. Cir. 2004)	11, 25

Petitioner’s Reply
U.S. Patent No. 11,572,334

In re Huai-Hung Kao,

639 F.3d 1057 (Fed. Cir. 2011)23

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435 F.3d 1381 (Fed. Cir. 2006)2

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No. 2021-2166, 2024 WL 960453 (Fed. Cir. Mar. 6, 2024)19

Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.,

821 F.3d 1359 (Fed. Cir. 2016)10

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853 F.3d 1316 (Fed. Cir. 2017)25

Par Pharm., Inc. v. TWi Pharms., Inc.,

773 F.3d 1186 (Fed. Cir. 2014)23

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480 F.3d 1348 (Fed. Cir. 2007)19

Plant Genetic Sys., v. DeKalb Genetics Corp.,

315 F.3d 1335 (Fed. Cir. 2003)5

Schering Corp. v. Geneva Pharms., Inc.,

339 F.3d 1373 (Fed. Cir. 2003)7

Teleflex, Inc. v. Ficosa N. Am. Corp.,

299 F.3d 1313 (Fed. Cir. 2002)6

Therasense, Inc. v. Becton, Dickinson & Co.,

593 F.3d 1325 (Fed. Cir. 2010)24

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PTAB Trial Practice Guide2

PETITIONER'S EXHIBIT LIST

EX.	DESCRIPTION
1001	USPN 11,572,334 ("334 patent")
1002	File history of USPN 11,572,334
1003	USPN 9,333,190 ("Ahmad")
1004	WO2017/70651 ("Liu")
1005	WO 2012/050263 ("Song")
1006	Ahmad, A. et al., Endoxifen, a New Cornerstone of Breast Cancer Therapy: Demonstration of Safety, Tolerability and Systemic Bioavailability in Healthy Human Subjects, 88(6) CLIN. PHARMACOLOGY & THERAPEUTICS 814-817 (2010) ("Ahmad 2010")
1007	Ahmad, A. et al., Endoxifen for breast cancer: Multiple-dose, dose-escalation study characterizing pharmacokinetics and safety in metastatic breast cancer patients, ASCO MEETING LIBRARY, presented June 4, 2012 ("Ahmad 2012")
1008	Cole, E., et al., Enteric coated HPMC capsules designed to achieve intestinal targeting, 231 INTL J. PHARMACEUTICS 83-95 (2002) ("Cole")
1009	Ku, M., et al., Performance qualification of a new hypromellose capsule: Part I. Comparative evaluation of physical, mechanical, and processability quality attributes of Vcaps Plus®, Quali-V® and gelatin capsules, 386 INTL J. PHARMACEUTICS 30-41 (2010) ("Ku")
1010	Benameur, H., Capsule Technology, Enteric Capsule Drug Delivery Technology – Achieving Protection Without Coating, 15(5) DRUG DEV. & DELIVERY 34-37 (2015) ("Benameur")
1011	Stegemann, S., Hard gelatin capsules today – and tomorrow, CAPSUGEL LIBRARY (2002) ("Stegemann")
1012	Excerpts of HANDBOOK OF PHARMACEUTICAL EXCIPIENTS FIFTH EDITION (Rowe, R., Sheskey, J. & Owen, S., eds., 2006) (The "HPE")
1013	Office Action dated 2/25/2020 from prosecution of Application No. 16/641,985

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1014	Prescribing Information for Zonalta
1015	USP 711
1016	Beasley, D. et al, <i>The Evolution of Stomach Acidity and Its Relevance to the Human Microbiome</i> , 10(7) PLoS ONE 1-12 (2015).
1017	Evans, D. et al, <i>Measurement of gastrointestinal pH profiles in normal ambulant human subjects</i> , 29 GUT 1035-41 (1988)
1018	Ahmad, A. et al., <i>Endoxifen, a New Treatment Option for Mania: A Double-Blind, Active-Controlled Trial Demonstrates the Antimanic Efficacy of Endoxifen</i> , Clin Transl Sci (2016) 9, 252–259 (“Ahmad 2016”)
1019	Milroy, L. et al., <i>A multi-gram-scale stereoselective synthesis of Z-endoxifen</i> , Bioorganic Med. Chem. Lett. 28 (2018) 1352-1356 (“Milroy”)
1020	Expert Declaration of Jason McConville, Ph.D.
1021	Ansel, H., et al, PHARMACEUTICAL DOSAGE FORMS AND DRUG DELIVERY SYSTEMS, Seventh Edition (1999)
1022	Fauq, A.H., et al., <i>A convenient synthesis of (Z)-4-hydroxy-N-desmethyltamoxifen (endoxifen)</i> , Bioorganic Med. Chem. Lett. 20 (2010) 3036-3038 (“Fauq”)
1023	Supporting information to Fauq, A.H., et al., <i>A convenient synthesis of (Z)-4-hydroxy-N-desmethyltamoxifen (endoxifen)</i> , Bioorganic Med. Chem. Lett. 20 (2010) 3036-3038
1024	NMR Spectra obtained by Dr. Bihovsky
1025	Supporting information to Milroy, L. et al., <i>A multi-gram-scale stereoselective synthesis of Z-endoxifen</i> , Bioorganic Med. Chem. Lett. 28 (2018) 1352-1356
1026	Majee, S.B. et al., <i>HPMC as Capsule Shell Material: Physicochemical, Pharmaceutical and Biopharmaceutical Properties</i> , 9(10) INT’L J. PHARMACY & PHARMACEUTICAL SCI. 2 (2017)

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1027	Marzorati, M. et al., <i>A novel Hypromellose capsule, with acid resistance properties, permits the targeted delivery of acid-sensitive products to the intestine</i> , 60 LWT – FOOD SCI. & TECH. 544-551 (2015)
1028	Al-Tabakha, M.M., <i>HPMC Capsules: Current Status and Future Prospects</i> , 13(3) J PHARM PHARMACEUTC SCI. 428-442 (2010)
1029	Honkanen, O, <i>Biopharmaceutical Evaluation of Orally and Rectally Administered Hard Hydroxypropyl Methylcellulose Capsules</i> , Division of Biopharmaceutics & Pharmacokinetics, Faculty of Pharmacy, University of Helsinki (March 2004)
1030	Expert Declaration of Ron Bihovsky, Ph.D.
1031	Reply Expert Declaration of Jason McConville, Ph.D.
1032	Additional excerpts of HANDBOOK OF PHARMACEUTICAL EXCIPIENTS FIFTH EDITION (Rowe, R., Sheskey, J. & Owen, S., eds., 2006) (The “HPE”)

I. Introduction

Patent Owner does not dispute that Ahmad teaches every limitation of the independent claims. Instead, it argues *only* that Ahmad does not enable 90% (Z)-endoxifen. But forming 90% pure (Z)-endoxifen was in the public's possession prior to the 334 patent, which confirms Ahmad's enablement and that it anticipates.

Patent Owner's arguments on the formulation claims rely on unsupported assertions that (Z)-endoxifen could interact with capsules, coatings, or excipients. But there is no evidence of such concerns or that the 334 patent overcame them. The pharmacokinetic claims merely recite the inherent result of dosing a patient with a 90% pure (Z)-endoxifen capsule as taught in Ahmad at the dosages taught in Ahmad 2010 and 2012. The claims not anticipated are obvious over Ahmad.

Finally, Patent Owner's secondary considerations do not show non-obviousness. Patent Owner's arguments that a free base embodiment was stable and exhibited good pharmacokinetics is not commensurate with the scope of the claims (which are not limited to the free base and expressly claim pharmacokinetics found in the prior art) and do not show non-obviousness over Ahmad (which teaches using the free base).

II. A POSA has experience with dosage forms

Patent Owner focuses on methods of synthesizing 90% (Z)-endoxifen. But the claims recite *formulations*—not synthetic methods. A POSA therefore should have

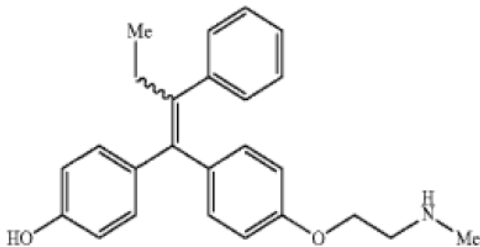
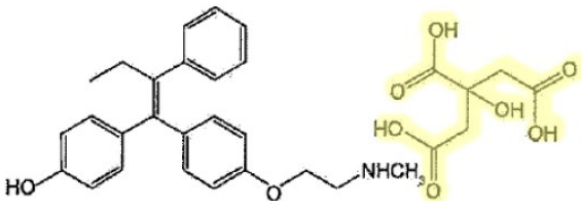
experience in formulating. Pet. 9; *Daiichi Sankyo Co. v. Apotex, Inc.*, 501 F.3d 1254, 1257 (Fed. Cir. 2007).

To be clear, a POSA could consult with a chemist, and an expert in chemistry can offer expert testimony on the enablement issue. *See* PTAB Trial Practice Guide at 34. But because Patent Owner's expert identifies no experience in dosage forms (Ex. 2020 ¶¶ 5-11), his opinions related to *formulating dosage forms* should not be given weight.

III. The claims are not limited to a free base

The claims do not specify a free base and as the Board correctly noted the specification clarifies that the claimed “compound of Formula (III) is (Z)-endoxifen” encompasses the free base *and* salt forms. Paper 11 at 10; Ex. 1001 at 12:48-52. The specification governs. *In re Johnston*, 435 F.3d 1381, 1384 (Fed. Cir. 2006) (specification gave term “broad meaning”); *In re Bass*, 314 F.3d 575, 577 (Fed. Cir. 2002) (“Bass chose to define ‘motorized sports boat’ in the specification. He cannot change or modify that definition on appeal.”).

Patent Owner's attempts to compare the molecular formula to that of endoxifen citrate confirms the point:

Endoxifen (generally)	Endoxifen Citrate
<p data-bbox="649 329 751 346">Formula (III)</p>  <p data-bbox="199 693 563 732">POR 20 (citing claim 1)</p>	 <p data-bbox="820 592 1205 632">POR 22 (citing Ex. 1014)</p>

The claims cover Formula III—regardless of whether it is as a free base or is included as a part of salt. While not necessary to find unpatentability because Ahmad teaches a free base, the Board’s preliminary construction was correct.

IV. Ground I: Ahmad is enabled and anticipates the claims

As Petitioner explained, Ahmad teaches every limitation of claims 1, 2, 4, 15, and 20-22. Pet. 28-36. Patent Owner disputes only whether Ahmad enables 90% (Z)-endoxifen.

A. Ahmad's teaching of using 90% pure (Z)-endoxifen was in the public's possession

Patent Owner primarily relies on the lack of working examples in Ahmad. But “anticipation does not require actual performance of suggestions in a disclosure.” *Bristol-Myers Squibb Co. v. Ben Venue Lab’ys, Inc.*, 246 F.3d 1368, 1379 (Fed. Cir. 2001). “Rather, anticipation only requires that those suggestions be enabling to one of skill in the art.” *Id.*

1. Liu and Fauq confirm that Ahmad's teaching of 90% pure (Z)-endoxifen was enabled

As Patent Owner acknowledges, Ahmad teaches 90% pure (Z)-endoxifen. POR 38; Ex. 1003 at 12:14-17. Patent Owner also acknowledges that Ahmad further teaches a synthetic method for making endoxifen, which “would most likely generate a 1:1 ratio of (E):(Z) isomers.” POR 39. Patent Owner similarly acknowledges that Ahmad teaches the isomers “can be separated to provide the purified preparations of E- and Z-isomer of endoxifen” by crystallization or chromatography. POR 41 (citing Ex. 1003 at 11:19-20). Thus, Ahmad provides significant teachings relevant to obtaining 90% (Z)-endoxifen. Bihovsky¹ ¶¶ 23-24, 32-33; *see also id.* ¶¶ 14-16.

While Patent Owner argues that Ahmad fails to adequately teach these purification methods, it ignores that such techniques were known in the art. For example, Liu teaches how to take a 50/50 E/Z mixture and achieve 90% (Z)-isomer by crystallization as well as isomerization. Ex. 1004 at [0072]-[0075]; Bihovsky ¶¶ 25, 17-20. Fauq teaches how to make highly pure (Z)-endoxifen by chromatography (as does Milroy). Exs. 1022, 1019; Bihovsky ¶¶ 26, 21-22.

¹ “Bihovsky” refers to the Expert Declaration of Ron Bihovsky, Ph.D (Ex. 1030), an expert in organic and medicinal chemistry. *See* Ex. 1030 ¶¶ 1-10, Ex. A.

Following these teachings would not have taken undue experimentation—indeed, Dr. Bihovsky carried out the synthesis and purification of Liu and readily obtained purities in excess of 90%. Bihovsky ¶ 27; § VII.C (Dr. Bihovsky explaining how he carried out Liu's teachings to form (Z)-endoxifen with 100% (crystallization) and 93% (isomerization) isomeric purity respectively). Thus, a POSA would have been able to make Ahmad's invention prior to the 334 patent.

2. Liu and Fauq are prior art and may be used to show Ahmad is enabled

Patent Owner cannot meaningfully challenge that making 90% pure (Z)-endoxifen was known in the art. Instead, it inaccurately represents the law.

First, Patent Owner states that "Enablement of a prior art patent is determined as of the effective filing date of the patent." POR 45. But "[e]nablement of an anticipatory reference may be demonstrated by a later reference." *Bristol-Myers Squibb*, 246 F.3d at 1379.² Patent Owner's argument that "Liu also postdates Ahmad

² Patent Owner's cases relate to determining enablement of a patent under Section 112, not enablement of prior art. POR 45, 48; *Plant Genetic Sys. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1339 (Fed. Cir. 2003); *Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1374 (Fed. Cir. 2017).

and, at best, is evidence of a dissimilar synthetic method in the art **after** Ahmad's effective filing date" (POR 48) is irrelevant.³

Second, Liu/Fauq do not "supply a missing claim limitation." POR 45 (quoting *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1335 (Fed. Cir. 2002)). *Teleflex* did not address enablement, rather the challenger **admitted** the prior art did not include a limitation but argued it would have been within the skill of a POSA to **add** that limitation. *Id.* That is the **opposite** of the situation here.

Patent Owner **admits** Ahmad teaches 90% (Z)-endoxifen, and the only question is enablement. Liu and Fauq may be used "to show that the claimed subject matter, as disclosed in [Ahmad], was in the public's possession." *In re Donohue*, 766 F.2d 531, 534 (Fed. Cir. 1985); *see also Bristol-Meyers Squibb*, 246 F.3d at 1379-1380.

Patent Owner relies on *Bristol-Meyers Squibb's* statement that it was improper to use a second reference to bring in "specific disclosure" from another reference. POR 46. But there the Court simply found that it was improper to bring

³ That the synthetic pathway of Ahmad and the 334 patent is similarly irrelevant, as a POSA would understand different synthetic pathways can achieve the same results. *Bihovsky* ¶ 33.

in a “specific disclosure” *of a species limitation* (specific premedicant) that was not taught in the anticipatory reference, which taught only a *genus* (premedicants generally). *Bristol-Meyers Squibb*, 246 F.3d at 1380. If Ahmad merely taught the use of endoxifen, it would be inappropriate to turn to a second reference to meet the purity limitation. But here, it is entirely proper to turn to other references to show Ahmad’s teachings of 90% isomeric purity were in the possession of the public prior to the 334 patent.

3. Patent Owner’s efforts to distinguish Liu are unavailing

Patent Owner attempts to distinguish Liu by relying on unclaimed elements. But its arguments fail both as a matter of law and fact.

First, Patent Owner argues that “Liu describes a very different synthetic pathway from both Ahmad and the ’334 patent”; that “Liu does not describe the stability profile of the resulting endoxifen composition”; that “Liu’s method is also inefficient;” and that “Liu would result in endoxifen compositions with different impurity profiles, residual solvents, and stability profiles.” POR 47-48. But the claims do not recite any synthetic pathway, impurity profile, residual solvent or stability profile—rather only a formulation comprising 90% pure (Z)-endoxifen. “An anticipatory reference need only enable subject matter that falls within the scope of the claims at issue, nothing more.” *Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1381 (Fed. Cir. 2003).

Finally, Patent Owner argues that “Liu does not describe a synthetic method to produce an oral pharmaceutical formulation.” POR 47 (citing Davies POR Decl. ¶ 156). To the extent Patent Owner asserts that Liu’s endoxifen cannot be used in an oral formulation, Patent Owner’s argument is not supported by evidence. Dr. Davies offers no such opinion and as Dr. Bihovsky and Dr. McConville explain, it is clear Liu (and Fauq) teach a pathway for making an active pharmaceutical ingredient, which could then be used in an oral formulation. Bihovsky ¶ 31; McConville⁴ ¶ 4.

B. Patent Owner’s cases are inapposite

In *Impax Labs, Inc. v. Aventis Pharms., Inc.*, the district court found a prior art reference not enabling of a method of using a compound to treat a specific disease because that reference disclosed “hundreds to thousands of different compounds and cites numerous medical conditions associated with” them but only mentioned the claimed compound “to exclude it from the claimed invention or to identify it as a ‘raw’ or starting material for the synthesis of other compounds.” 496 F. Supp. 2d 428, 432 (D. Del. 2007). In *Boston Scientific v. Johnson & Johnson*, the Court found that a claim to a genus of analogs that had to have “particular functionality” similar

⁴ “McConville” refers to the Reply Expert Declaration of Jason McConville Ph.D. (Ex. 1031).

to rapamycin was not enabled because the mechanism for the functionality of rapamycin was not known, and if “the mechanism of rapamycin was unknown, surely the mechanism of any ‘similar’ molecules was also unknown” and thus there was “no clear starting point for the modification of rapamycin.” 679 F. Supp. 3d 539, 556 (D. Del. 2010). Neither case held broadly that there is a special rule for organic synthesis, and neither is remotely close to the situation here.

Nor do Patent Owner's cases on enantiomers fare better. In *Forest Laboratories, Inc. v. Ivax Pharmaceuticals, Inc.*, the Federal Circuit found no clear error in a finding of no anticipation of an enantiomer of citalopram because there was evidence that the identified method of separating the enantiomers “was a relatively new and unpredictable technique at the time of the invention [1988]” and “failures of various scientists to resolve citalopram.” 501 F.3d 1263, 1266-67, 1268-69 (Fed. Cir. 2007).

Similarly, in *Sanofi-Synthelabo v. Apotex, Inc.*, the Federal Circuit affirmed a finding that “general statements that these compounds consist of enantiomers” did not enable claims to a “previously unseparated and unknown enantiomer.” 550 F.3d 1075, 1084 (Fed. Cir. 2008).

Here, multiple prior art references demonstrate the (Z)-isomer was both known and had been successfully separated. *See supra*.

V. Ground II: It would have been obvious to make a 90% pure (Z)-endoxifen capsule based on Ahmad

While Ahmad is enabling and thus anticipates, as an alternative Petitioner argued that the claims would have been obvious for the same reasons, incorporating by reference the analysis under Ground I. Pet. 36-37.

A. Petitioner argued in Ground II it would have been obvious to use knowledge such as Liu to form 90% pure (Z)-endoxifen

Patent Owner argues “[n]owhere does Petitioner argue that a POSA would look to Liu, or any other prior art, to supply any missing knowledge regarding the synthesis of a 90% pure (Z)-endoxifen.” POR 53. But Patent Owner itself recognized Petitioner made such an argument. POPR 15 (“Petitioner includes EX1004 (Liu)...as background art for Ground 2.”). The Board agreed. Paper 11 at 20. “It is for the Board to determine what grounds are being articulated in a petition....” *Corephotonics, Ltd. v. Apple Inc.*, 84 F.4th 990, 1002 (Fed. Cir. 2023).

B. A POSA would have been motivated to form 90% pure (Z)-endoxifen capsules with a reasonable expectation of success

Patent Owner repeats its enablement arguments attempting to distinguish Liu based on unclaimed elements. POR 54-55. But like with enablement, a petitioner need only show a reasonable expectation of success in meeting the claim limitations, nothing more. *See Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016).

Patent Owner's other arguments similarly fail. For example, Patent Owner argues that Ahmad does not provide a reasonable expectation of success because it does not provide working examples. POR 59-60. But Petitioner ignores that forming 90% (Z)-endoxifen was known in the art as discussed *supra*. Patent Owner even argues that Ahmad "teaches away from the claimed invention" because it teaches purifying endoxifen with ethyl acetate, which would allegedly lead to (E)-endoxifen. POR 60. But this is both incorrect (as it uses a mixture, *see* Bihovsky ¶¶ 28-29, 34) and in any event is not a teaching away because it "does not criticize, discredit, or otherwise discourage investigation" into forming (Z)-endoxifen from other salts. *In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004).

Dr. Davies avoids even discussing Liu's method, and simply relies on Song's error⁵ and a conclusory (and baseless) argument that "the synthetic methods of

⁵ See POR 57-58; Ex. 2020 ¶ 162. While Patent Owner is correct that Song does not achieve 90% pure (Z)-endoxifen and Petitioner no longer relies on it, as Dr. Bihovsky explains, Song simply erred in his NMR analysis, incorrectly reporting his results, and does not demonstrate that a POSA could not follow Liu or other methods of achieving 90% purity. Bihovsky ¶ 30.

Ahmad and Lui [sic] are different from each other, and Petitioner provides no explanation for how those methods could be combined or modified, especially considering that neither includes the synthetic methods taught in the '334 patent.” Ex. 2020 ¶ 162. That the methods of forming (Z)-endoxifen differ is irrelevant, as the claims recite a formulation, not a method. And it is readily apparent how a POSA would use Ahmad’s or Liu’s teachings of making 90% pure (Z)-endoxifen as taught by Ahmad. *E.g.*, Pet. 37; Bihovsky ¶ 35. As Dr. McConville explained, this “would have been very routine in the art to simply take endoxifen made by the processes discussed above and enclose them in a capsule and use enteric coating to ensure that the drug was released in the intestine rather than the stomach.” Ex. 1020 ¶ 71; *see also* ¶¶ 55, 68; Exs. 1008, 1010. Patent Owner provides no evidence to the contrary.

Thus, claims 1, 2, 4, 15, and 20-22 are obvious, if not anticipated.

VI. Ground III: It would have been obvious to combine Ahmad with Cole’s teaching of an enteric coated capsule

As Petitioner explained, it would have been obvious to use Cole’s enteric coated capsule to make the capsule taught by Ahmad. Pet. 41-46.

There is nothing “hindsight” driven about Petitioner’s combination. Ahmad teaches that enteric capsules should be used to avoid degradation in the stomach. Ex. 1003 at 18:19-24. And Cole teaches a specific enteric coated capsule that avoids releasing drug in the stomach. *See generally* Ex. 1008, *e.g.* at 94; Ex. 1020 ¶ 96.

Thus, a POSA would have been motivated to combine Ahmad with Cole to form an enteric coated (Z)-endoxifen capsule. Ex. 1020 ¶¶ 88-89, 92, 94; McConville ¶¶ 5-7.

Patent Owner's only argument against the combination is alleged "potential interactions between (Z)-endoxifen, HPMC, and the enteric coating material." POR 63. But there is no evidence supporting this argument.

Patent Owner first argues that its expert, "Dr. Davies explained that a POSA would not have a reasonable expectation of success...because a POSA would understand that enteric coatings and pharmaceutical compositions *would* interact." POR 63-64 (citing Ex. 2020 ¶ 166) (emphasis added). But Dr. Davies did not testify that they *would interact*. Rather, he simply said "a POSA must consider potential interactions between enteric coatings and pharmaceutical compositions (*e.g.*, as a result of charge or other effects)...." Ex. 2020 ¶ 166.

Patent Owner's argument is also baseless. The coating is applied to the *exterior* of the capsule, and thus does not interact with the active ingredient inside the capsule. McConville ¶¶ 8-10. There could not have been any concern or challenge in using an enteric coating with a capsule containing (Z)-endoxifen. *Id.*

Similarly, Dr. Davies did not testify that there would have been challenges with using HPMC capsules and (Z)-endoxifen, but only that "the HPMC of Cole carries a positive charge" and that a "POSA would understand that charged

formulation components can have unpredictable effects.” Ex. 2020 ¶ 164. But again, Dr. Davies has no expertise in formulation sciences, and cites no evidence. Rather, the evidence shows HPMC capsules are in fact known for their *improved compatibility* with a wide range of actives over gelatin capsules because they *don’t* interact with most actives. McConville ¶¶ 11, 13; Ex. 1026 at 6; Ex. 1027 at 549; Ex. 1028 at 439; Ex. 1029 at 4.

The only citation Dr. Davies provides is a *misrepresentation* of Dr. McConville’s testimony. Dr. McConville testified that HPMC “*can*” carry a positive charge, not that it *does*. Ex. 2021 at 108:14-17. But while HPMC *can* carry electrostatic charge during filling (due to friction), that can easily be avoided, and there is no evidence that it leads to degradation of any active ingredient, let alone (Z)-endoxifen. McConville ¶ 12. Thus, a POSA would not have been led away from using (Z)-endoxifen in an HPMC capsule, and a POSA would have had far more than a reasonable expectation of success in combining Ahmad and Cole. McConville ¶ 16.

Indeed, the 334 patent does not mention *any* issues with interactions between HPMC capsules or enteric coatings and (Z)-endoxifen or how one would avoid any such issues. Rather, the 334 patent simply states that capsules can be used. McConville ¶ 14. If degradation from such interactions was a problem, the 334 patent doesn’t provide a solution.

Patent Owner argues a POSA “would also need to consider the variation in release profiles for salts as compared to corresponding free acids or bases of a given oral dosage form.” POR 64. But first, the claims cover both the free acids and bases, so this distinction is irrelevant. *See* § III. Second, whether the free base or salt is used would not significantly affect the release from the capsule, which is dependent on the degradation of the enteric coating and the capsule, not on the active ingredient used. McConville ¶ 15.

While Cole does not specifically use (Z)-endoxifen, as Dr. McConville explains, Cole uses paracetamol, a common model drug, and a formulator would have understood that Cole could be used with other actives. Ex. 1020 p. 37 n.3; McConville ¶ 7. And Cole’s successful release of drug in the small intestine (i.e., bypassing the acidic conditions of the stomach) would have been a strong motivator for a POSA seeking to formulate with endoxifen to use Cole for the same purpose, and would have provided far more than a reasonable expectation of success. Ex. 1020 ¶¶ 89, 92, 94, 97; McConville ¶ 16.

For these reasons, claims 5-8, 16, and 17 would have been obvious.

VII. Ground IV: It would have been obvious to combine Ahmad with Benameur's teaching of an enteric capsule

As Petitioner explained, it would have been a routine and obvious modification of Ahmad to use the intrinsically enteric capsule of Benameur instead of Ahmad's teaching of an enteric coated tablet. Pet. 46-48.

Patent Owner's only response is that "Benameur describes enteric capsule drug delivery technology for uncoated oral formulations of esomeprazole" and that "esomeprazole is unrelated to endoxifen." POR 65 (citing Ex. 1010 at 1). But Benameur itself teaches that it used "esomeprazole magnesium trihydrate (EMT) *as a model compound*" which was chosen due to its "high gastric sensitivity." Ex. 1010 at 34. Thus, the technology would have been highly relevant to a POSA developing a formulation for (Z)-endoxifen which was known to be acid-sensitive. Ex. 1020 ¶¶ 100-102; McConville ¶¶ 17-19.

Patent Owner states that "Benameur does not teach that the use of this enteric capsule drug delivery technology would provide a sustained action of (Z)-endoxifen over a longer period of time." POR 65. But it is entirely unclear what Patent Owner means, as claim 3 does not recite a "sustained action...over a longer period of time" (and longer than what?). Patent Owner also argues that a "POSA would not extrapolate the results from Benameur to an unrelated compound." POR 65 (citing Ex. 2020 ¶¶ 172-173). But again, the release of drug from an enteric capsule depends

on the degradation of the capsule—not on the solubility of the active. McConville ¶¶ 20-22. Benamuer plainly teaches a delayed gastric release using a *model* drug, which a POSA would understand would apply equally when (Z)-endoxifen was used. *Id.*

Patent Owner argues that Dr. McConville “testified that ‘of course’ a POSA would have to test the pharmacokinetics of (Z)-endoxifen....” POR 65-66. But that has no bearing on whether a POSA would have been motivated to combine Ahmad and Benamuer with a reasonable expectation of success. McConville ¶ 23.

Finally, Patent Owner repeats its unsupported argument that the “inherent instability of (Z)-endoxifen” would somehow prevent a reasonable expectation of success in placing the (Z)-endoxifen of Ahmad in the capsule of Benamuer. POR 66 (citing Ex. 2020 ¶ 172). But again, there is no evidence supporting this claim, and Dr. Davies states only that “a POSA would not know how to achieve the desired characteristics of a delayed release oral formulation (e.g., enteric formulation) without undue experimentation” because “Benamuer does not teach the use of its enteric capsule with endoxifen.” Ex. 2020 ¶ 173. That conclusory testimony, from an expert with no identified experience in formulation sciences, again fails to show any lack of a reasonable expectation of success. As Dr. McConville explains, a POSA/formulation scientist would have understood that Benamuer’s capsules would

likely be successfully used with (Z)-endoxifen and exhibit the same release rate. Ex. 1020 ¶ 102; McConville ¶ 24.

VIII. Ground V: It would have been obvious to combine Ahmad with standard excipients as taught in e.g., the HPE and Stegemann

As Petitioner explained, it would have been readily apparent to a POSA to use standard excipients in formulating Ahmad's (Z)-endoxifen capsules. Pet. 49-54.

Patent Owner first argues that there was a "complete lack of explanation as to why a POSA would be motivated to combine these references with any reasonable expectation of success." POR 66-67. But as Petitioner explained, backed by evidence, each of the recited excipients were well known commonly used excipients, and a POSA would have been motivated to use them for their normal use. Pet. 49-54 (citing Ex. 1010 ¶¶ 104-118). In other words, the "inactive ingredients in the claimed formulations [were] routine and obvious, and, therefore, non-inventive." *Galderma Lab'ys, L.P. v. Tolmar, Inc.*, 737 F.3d 731, 736 (Fed. Cir. 2013).

Patent Owner argues only that there would not have been a motivation to use these standard excipients for their standard use because of alleged "unpredictable interactions between endoxifen and the various listed excipients." POR 67. But like with its other arguments, Patent Owner cite no evidence, other than the conclusory testimony of an expert who does not formulate. POR 67 (citing Ex. 2020 ¶¶ 178-179).

Nor does Dr. Davies even testify that there were any such concerns. Rather, he offers only vague testimony that “[o]ral formulations are known to have variable compatibilities and chemical interactions) with pharmaceutical excipients, and those interactions depend on the oral formulation used (*e.g.*, a salt oral formulation or a free base oral formulation.)” Ex. 2020 ¶¶ 178-179. But this general teaching that a POSA would think about drug-excipient interactions does not negate the motivation to use such standard excipients. McConville ¶¶ 25-27. To the contrary identifying and avoiding incompatibilities was routine to a POSA. *Id.* ¶¶ 28-29. For example, the HPE teaches incompatibilities, allowing formulators to select excipients that are unlikely to have negative interactions. *Id.* ¶ 30; Ex. 1032 at *e.g.*, 348, 768.

And “such a mere possibility of failure, in this context, does not mean that there is no reasonable expectation of success.” *In re Samuels*, No. 2021-2166, 2024 WL 960453, at *2 (Fed. Cir. Mar. 6, 2024); *see also Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007) (“[O]nly a reasonable expectation of success, not a guarantee, is needed.”).

Nor was the formulation of enteric capsules in 2017 unpredictable. McConville ¶ 31. Patent Owner relies on *AstraZeneca Pharms. L.P. v. Anchen Pharms., Inc.*, but that case simply held that “at the relevant time [1997] the field of formulation was complex and could be unpredictable.” 2012 U.S. Dist. LEXIS 43989, at *73, *131 (D.N.J. Mar. 28, 2012). *Allergan Inc. v. Apotex* is similarly

unhelpful to Patent Owner, as there the Federal Circuit **reversed** a finding of non-obviousness, noting “it does not matter whether hair growth is *generally* an unpredictable endeavor—the question is more narrowly whether the success of using selective PGF analogs to treat hair loss would be reasonably unpredictable.” 754 F.3d 952, 965-66 (Fed. Cir. 2014).

As Dr. McConville explains selecting and utilizing standard excipients for their standard functions would have been highly routine and highly predictable at the time of invention. Ex. 1020 ¶¶ 107, 108, 112, 116, 118; McConville ¶ 31. Thus, a POSA would have had far more than a reasonable expectation of success in arriving at the invention of the excipient claims.

IX. Ground VI: It would have been obvious to determine a dosage amount for Ahmad's (Z)-endoxifen capsules that would result in the claimed pharmacokinetics based on Ahmad 2010 and 2012

A. It would have been obvious to select a dosage form between 0.01 mg and 200 mg (Z)-endoxifen per capsule as shown in Ahmad 2010 and 2012

As Petitioner explained, Ahmad, Ahmad 2010 and Ahmad 2012 all suggest using dosage forms well within the incredibly broad range recited by claim 14. Pet. 54-56. For example, Ahmad teaches using 1-10mg. Ex. 1003 at 29:20-31. Ahmad 2010 tests between 0.5 and 4.0 mg (Ex. 1006 at 2) and Ahmad 2012 tests between 2 and 8 mg (Ex. 1007 at 2). Specifically, Ahmad 2010 reports that “we expect that multiple daily endoxifen doses of 2.0-4.0mg 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.⁶ That is, a dose of 4 mg of endoxifen should be appropriate for breast cancer prevention and therapy.” Ex. 1006 at 3. Similarly, Ahmad 2012 concludes 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 at 2. Thus, a POSA would have been motivated to select endoxifen amounts well within the range of 0.01 to 200 mg. Ex. 1020 ¶¶ 120-121; McConville ¶¶ 32-33.

Patent Owner’s only argument is that “(Z)-endoxifen is the more active isomer of endoxifen” and that a “POSA would not have an understanding as to whether the Ahmad 2010/Ahmad 2012 dosing information is appropriate for a safe and effective use of a 90% pure (Z)-endoxifen.” POR 69-70. But the claims do not recite a safe and efficacious dosing range and while the (Z)-isomer was known to be more active, it would not have led a POSA away from at least testing with these general dosage ranges and determining the most safe and efficacious dosages. Ex. 1020 ¶ 121;

⁶ As explained in the Petition, endoxifen is an active metabolite of tamoxifen generated by the CYP2D6 enzyme, and thus was understood to provide an alternative to tamoxifen for individuals who have impaired CYP2D6 enzyme activity. Pet. 13-14.

McConville ¶ 34.⁷ It would have taken only routine experimentation, such as that done in Ahmad 2010 and Ahmad 2012, to confirm. McConville ¶ 35.

B. The pharmacokinetic limitations are the inherent result of dosing a patient with 90% (Z)-endoxifen as taught in Ahmad at the dosages taught in Ahmad 2010 and 2012

The Board and Patent Owner misunderstood Petitioner's argument. Petitioner did not argue that the results *of Ahmad 2010* are the inherent result of dosing a patient with 90% (Z)-endoxifen. Rather, Petitioner argued (and argues) that the pharmacokinetic limitations "would have been the inherent results of dosing the formulations of *Ahmad* within the dosing ranges taught by Ahmad 2010 and Ahmad 2012." Pet. 55; Ex. 1020 ¶ 123.⁸ Simply stated, the formulation of claim 14 is obvious as described above; the pharmacokinetic limitations of claims 18 and 19 are simply the inherent and natural result of administering the formulation of claim 14.

⁷ Indeed, it would have been shocking to a POSA if the appropriate dosing range fell outside of that incredibly broad range. McConville ¶ 35. And the 334 patent itself does not show that the full claimed range is "efficacious and safe." *Id.*

⁸ Petitioner could arguably have argued inherent anticipation, but in any event "anticipation is the ultimate of obviousness." *In re Baxter Travenol Labs*, 952 F.2d 388, 391 (Fed. Cir. 1991).

McConville ¶ 36. It is well established that merely reciting the natural and inherent results of an otherwise obvious formulation cannot lead to patentability. *E.g., Endo Pharms. Sols., Inc. v. Custopharm Inc.*, 894 F.3d 1374, 1381 (Fed. Cir. 2018).

Indeed, the 334 patent simply fills a capsule with “neat” (Z)-endoxifen (i.e., no excipients), and measures the resulting pharmacokinetics. *See* McConville ¶ 37. A POSA would have obtained similar results using the 90% pure (Z)-endoxifen capsules taught by Ahmad at the dosages taught by Ahmad 2010 and 2012, because this is simply the inherent result of dosing a patient with 90% pure (Z)-endoxifen capsules. Ex. 1020 ¶ 123, 126; McConville ¶ 38. *See King Pharms., Inc. v. Eon Labs, Inc.*, 616 F.3d 1267, 1275-76 (Fed. Cir. 2010) (relying on challenged patent’s specification to confirm limitation met because it “is the ‘natural result’ flowing from the prior art’s explicitly explicated limitations”); *see also In re Huai-Hung Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011) (same).

Because Petitioner has shown that the pharmacokinetic “limitation[s] at issue necessarily must be present, or the natural result of the combination of elements explicitly disclosed by the prior art,” it has shown the claims are obvious. *Par Pharm., Inc. v. TWi Pharms., Inc.*, 773 F.3d 1186, 1195–96 (Fed. Cir. 2014).

Ahmad 2010 and Ahmad 2012 further show that there was nothing surprising or novel about the claimed pharmacokinetic data, and that the target pharmacokinetic data was known. Thus, to the extent any modifications to a formulation were

necessary (e.g., modifying the formulation to increase or decrease the release rate), it would have been routine to do so. Pet. 53; Ex. 1020 ¶¶ 124, 127. Such modifications would have been well within the skill of a POSA, requiring only the same kind of routine experimentation performed in Ahmad 2010 and 2012. *Id.*; McConville ¶ 39. Thus, even without inherency, the claims would have been obvious.

X. The secondary considerations do not show nonobviousness

First, Patent Owner's asserted secondary considerations are not commensurate with the claim scope because they rely on the assumption that the claims recite a "free base," which is allegedly an improvement over prior art using the salt form. But as the Board correctly determined (§ III, *supra*), the claims cover both the free base and the salt and thus the "evidence of non-obviousness fails because it is not commensurate in scope with the claims which the evidence is offered to support." *Therasense, Inc. v. Becton, Dickinson & Co.*, 593 F.3d 1325, 1336 (Fed. Cir. 2010) (citation omitted). Moreover, any alleged improvement in bioavailability is similarly not commensurate with the scope of the claims, which *expressly* recite a broad range of pharmacokinetics covering the prior art. *See id.*; McConville ¶ 40.

Second, even assuming the claims recite a free base, there is no evidence that the stability data or bioavailability described in the 334 patent was unexpected or

even better than the prior art. *Id.* Patent Owner provided no comparison between the free base described in the 334 patent and prior art free bases, such as those taught in Liu. *In re Baxter Travenol Labs*, 952 F.2d 388, 392 (Fed. Cir. 1991) (“[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art.”).

And regarding bioavailability, the 334 patent compares its data to only an unclear average of numerous prior art formulations (including various dosage forms, salts, strengths, etc.). McConville ¶ 41. There is no comparison, for example, to prior art free base formulations. *Id.*

Finally, there is no evidence of long-felt need for a free base. Patent Owner did not show, for example, that existing endoxifen products were insufficient to meet any need. *Id.*; see *Novartis AG v. Torrent Pharms. Ltd.*, 853 F.3d 1316, 1331 (Fed. Cir. 2017). Patent Owner points to prior related compounds that are sold commercially as salts. POR 76. But this is not a teaching away from a free base. *In re Fulton*, 391 F.3d at 1201. Nor does it demonstrate any long-felt need for a free base. McConville ¶ 42.

Thus, there is no evidence suggesting the non-obviousness of the claims.

XI. Conclusion

Petitioner has established that each of claims 1-22 of the 334 patent is unpatentable.

Petitioner's Reply
U.S. Patent No. 11,572,334

Respectfully submitted,

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CERTIFICATE OF WORD COUNT

I certify under 37 CFR § 42.24 that this **PETITIONER'S REPLY** contains
5,578 words, as determined by Microsoft Word.

Dated: July 17, 2024

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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 Reply and Exhibits 1022-1032 were sent to counsel for Patent Owner at the following email addresses:

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