

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

INTAS PHARMACEUTICALS LTD.
Petitioner,

v.

ATOSSA THERAPEUTICS, INC.
Patent Owner.

PGR 2023-00043

**PATENT OWNER'S RESPONSE TO PETITION FOR POST-GRANT
REVIEW**

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PATENT OWNER'S UPDATED EXHIBIT LIST

EXHIBIT	DESCRIPTION
2001	Expert Declaration of Stephen Graham Davies, D. Phil. ("Davies Decl.")
2002	Elkins et al., "Characterization of the isomeric configuration and impurities of (Z)-endoxifen by 2D NMR, high resolution LCMS, and quantitative HPLC analysis," J. Pharmaceutical and Biomedical Analysis, 88:174-179 (2014) ("Elkins")
2003	U.S. Patent No. 11,261,151 ("151 patent")
2004	Excerpt of '151 Patent File History - IDS Filings, Receipts, List Considered ("985 File History 1")
2005	Excerpt of '151 Patent File History - Liu ("985 File History 2")
2006	Excerpt of '151 Patent File History - FOA and NOA ("985 File History 3")
2007	Intl. Pub. No. WO 2010/135703A2 by Ahmad et al.
2008	Intl. Pub. No. WO 2009/032699A1 by Bortz et al.
2009	Intl. Pub. No. WO 2009/120999A2 by Kushner et al.
2010	Excerpt of File History for U.S. Patent 9,333,190 - Office Actions, Responses, Declarations, and Allowance ("Ahmad File History")
2011	Ali et al., "Endoxifen is a new potent inhibitor of PKC: A potential therapeutic agent for bipolar disorder," Bioorganic & Medicinal Chem. Letters, 20:2665-2667 (2010) ("Ali")
2012	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, "Impurities: Guideline for Residual Solvents," Step 4 Version (2021) ("ICH Guidelines")
2013	Stephen Graham Davies, D. Phil. <i>Curriculum Vitae</i>
2014	Center for Drug Evaluation and Research, FDA Guidance Document, "Development of New Stereoisomeric Drugs," (1992) ("FDA Guidance")

EXHIBIT	DESCRIPTION
2015	Lv et al., "Synthesis of mixed (E,Z)-, (E)-, and (Z)-norendoxifen with dual aromatase inhibitory and estrogen receptor modulatory activities," J. Med. Chem., 56: 4611-4618 (2013) ("Lv")
2016	Buchanan et al., "Solubilization and Dissolution of Tamoxifen-Hydroxybutenyl Cyclodextrin Complexes," J. Pharm. Sciences, 95(10):2246-2255 (2006) ("Buchanan")
2017	Gupta et al., "Salts of Therapeutic Agents: Chemical, Physicochemical, and Biological Considerations," Molecules, 23:1719 (2018) ("Gupta")
2018	Jacques et al., <i>Enantiomers, Racemates, and Resolutions</i> (1981) ("Jacques")
2019	Declaration of Susan M. Krumplitsch in Support of Motion to Appear <i>Pro Hac Vice</i>
2020	Expert Declaration of Stephen Graham Davies, D. Phil. in Support of Patent Owner's Response ("Davies POR Decl.")
2021	Deposition Transcript of Jason T. McConville, Ph.D. taken on April 12, 2024, in <i>Intas Pharmaceuticals Ltd. v. Atossa Therapeutics, Inc.</i> , PGR2023-00043 ("McConville Tr.")
2022	Excerpt of File History for U.S. Patent 9,333,190 – Original Filed Application, Office Actions, Responses, Appeal of Examiner's Decision, Declarations, and Allowance ("Ahmad File History Excerpt 2")
2023	Prescribing Information for Nolvadex® (tamoxifen citrate tablets)
2024	Prescribing Information for Soltamox® (tamoxifen citrate solution)
2025	Prescribing Information for Evista® (raloxifene hydrochloride tablets)
2026	Prescribing Information for Fareston® (toremifene citrate tablets)

Following the Board's decision granting institution (Paper 11 or "ID"), Patent Owner Atossa Therapeutics, Inc.'s ("Atossa") hereby submits this Response to the Petition for Post-Grant Review ("PGR") of U.S. Patent No. 11,572,334 ("the '334 patent") (EX1001), filed by Intas Pharmaceuticals, Ltd. ("Petitioner" or "Intas").

I. INTRODUCTION

The '334 patent claims a ground-breaking invention: pharmaceutical formulations comprised of at least 90% pure (Z)-endoxifen. (Z)-endoxifen is currently being studied in clinical trials as a preventative and treatment for hormone-dependent breast disorders, such as estrogen receptor (ER)-positive breast cancer and has the potential to revolutionize ER-positive breast cancer chemotherapy and to even prevent breast cancer. The '334 patent describes novel methods for synthesizing and purifying (Z)-endoxifen resulting in highly pure (Z)-endoxifen that can be formulated into oral dosage forms to treat patients. The '334 patent claims enteric coated capsule formulations containing at least 90% (Z)-endoxifen free base, methods of delivering such formulations to a patient resulting in specific pharmacokinetic parameters, and methods of treating hormone-dependent breast and reproductive tract disorders. (EX2020, hereinafter "Davies POR Decl.," at ¶¶ 107-112.) Prior to the '334 patent, it was not known in the art how to make an at least 90% isomerically pure (Z)-endoxifen in an oral pharmaceutical dosage form.

(Z)-endoxifen is a highly unstable compound, as it rapidly interconverts to its inactive isomer (E)-endoxifen, under aqueous or acidic conditions yielding an equilibrium mixture of approximately 60% (Z)-endoxifen and 40% (E)-endoxifen. (EX1001 at 82:11-14 (citing EX2002 (Elkins) (“Conversion [of Z-endoxifen HCL to (E)-endoxifen] is expected to be more rapid in a solution environment.”)); (*see also* Davies POR Decl. at ¶¶ 55-56.) None of the art cited by Petitioner acknowledges the inherent instability of (Z)-endoxifen or the challenges in formulating a stable, isomerically pure pharmaceutical solid oral dosage form.

Petitioner raises six grounds challenging the patentability of the '334 patent, but each fails for a myriad of reasons. (“Pet.,” Paper 1.) Significantly, every ground relies—in whole or in part—on U.S. Patent No. 9,333,190 (“Ahmad,” EX1003), which is fatally flawed. As explained in Patent Owner’s Preliminary Response (“POPR,” Paper 7), Ahmad is not enabled as it does not describe or teach methods sufficient for producing the 90% pure (Z)-endoxifen composition claimed by the '334 patent. As discussed in detail below and in the accompanying declaration of Dr. Davies, the synthetic method described in Ahmad would result in a highly *impure* (Z)-endoxifen mixture. (Davies POR Decl. at ¶¶ 74-77.)

Although the Board acknowledged Atossa’s enablement argument in the ID, it “declined to prematurely address Patent Owner’s enablement arguments.” (ID at

16.) Trial has been instituted and Ahmad remains non-enabling. Petitioner's expert, Dr. McConville, admitted that he did not have the requisite chemistry background to properly evaluate Ahmad's disclosed synthetic pathway. (EX2021, hereinafter "McConville Tr.," at 55:9-57:7; 63:7-64:4; 72:22-75:22.) Petitioner cannot rebut Patent Owner's overwhelming evidence that Ahmad is not enabled. Accordingly, Grounds 1 and 2 fail.

Grounds 3-6, which combine Ahmad with secondary references, do not cure Ahmad's deficiencies and these grounds also fail. Moreover, Petitioner has failed to fully explain why a POSA would combine any of these references and have a reasonable expectation of success in doing so. Moreover, secondary considerations of non-obviousness demonstrate that all claims of the '334 patent are patentable.

With respect to Ground 6, at the institution stage the Board found that Petitioner had *not* shown that it is more likely than not that Claims 18 and 19 are unpatentable over the cited references. (ID at 31.) This remains true at this stage in proceedings, as Dr. McConville admitted that rate of absorption of the drug, a pharmacokinetic component that impacts the claimed parameters, *may change* depending on the formulation administered. (McConville Tr. at 130:19-131:12 (when asked whether the pharmacokinetics of endoxifen free base and citrate forms would be expected to be identical or different, Dr. McConville stated "You would

have to test them. It could be. It could not be.”.) This evidence further supports the Board’s conclusion that the Petition fails to demonstrate unpatentability of claims 18 and 19.

The Board’s decision to institute is based, in part, on an overly broad, *sua sponte* construction of “the compound of Formula (III) is (Z)-endoxifen” to “include the polymorphic salt, free base, co-crystal and solvate forms of (Z)-endoxifen.” (ID at 10 (citing EX1001 at 12:48-59).) As discussed below, the Board’s proposed construction is incongruent with claims themselves and is not an express definition from the specification. Even if, however, the overly broad construction of “compound” is maintained, it does not cure the enablement deficiencies in Ahmad for Grounds 1 and 2, nor does it cure the deficiencies with the remaining grounds.

For these reasons, and further reasons articulated below, Petitioner’s challenges fail, and the Board should find that Petitioner failed to establish that any of the claims of the ’334 patent are unpatentable.

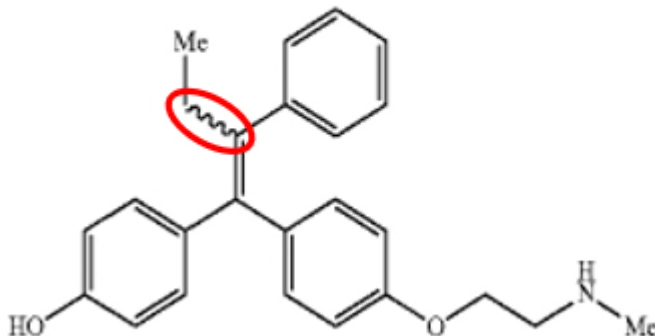
II. SCIENTIFIC BACKGROUND

Estrogen receptor (ER)-positive breast cancer has long been treated with tamoxifen. (EX1001 at 1:63-66.) Tamoxifen acts as a selective ER modulator, binding to estrogen receptors and inhibiting growth and proliferation of cancer cells. (*Id.*) While tamoxifen has long been used in the prevention and treatment of

hormone-sensitive breast cancer and reproductive tract cancers, there is a need for safer and more efficacious treatments. For example, tamoxifen is associated with a host of serious side effects, including increased risk of endometrial cancer and blood clots. (*Id.* at 1:66-2:2.) Tamoxifen is also associated with vasomotor symptoms such as hot flashes and night sweats. (*Id.*) Tamoxifen resistance is well documented, leading to treatment failure and cancer progression. (*Id.* at 2:3-6.)

Endoxifen is the primary metabolite of tamoxifen and it exists in two isomeric forms: (E)-endoxifen and (Z)-endoxifen. (Davies POR Decl. at ¶¶ 49-50.) Isomeric forms, or “stereoisomers,” possess identical constitutions (*i.e.*, atom connectivity) but differ in the arrangement of atoms in space. (*Id.* at ¶ 68.) Accordingly, stereoisomers of a given compound generally are chemically and pharmacologically distinct, often exhibiting separate bioavailability and enzymatic inhibition. (*Id.* at ¶¶ 51-52.) Stereoisomer relationships include enantiomers, which are non-superimposable mirror images of each other that generally possess identical physical and chemical properties, and diastereomers, which are non-mirror images of each other that commonly differ in the arrangement of atoms around a double bond. (*Id.* at ¶ 68.) A pair of diastereomers, like (E)-endoxifen and (Z)-endoxifen, have different chemical and physical properties, and are conventionally represented by a wavy line, as shown in Claims 1 and 15 of the '334 patent. (*Id.*)

Formula (III)



(EX1001 at 98:16-29, 99:12-24.)

Purifying diastereomers is known to be difficult since, by definition, stereoisomers have identical molecular weights and functional groups. (Davies POR Decl. at ¶¶ 69-70.) Accordingly, chemists will utilize chromatography (which is generally limited to small-scale, non-clinical applications where low yield can be tolerated) or crystallization to separate diastereomers. (*Id.* at ¶ 69.) However, crystallization of diastereomers poses significant challenges for novel compounds, if at all achievable, because diastereomers can exhibit similar chemical properties commonly exploited by crystallization techniques, such as solubility. (*Id.* at ¶¶ 53-54, 70.) As such, purifying diastereomers through crystallization requires extensive experimentation to determine probable crystallization parameters, including, but not limited to, type, co-solvent system, dissolution temperature, and crystallization temperature. (*Id.* at ¶ 70.)

Crystallization of diastereomers is also hypersensitive to impurities in a crude product as well as chosen-reagents, as the presence of different solvents can lead to unpredictable formation of solvents rather than the pure diastereomer. (*Id.* at ¶¶ 69, 71.) Diastereomers crystallization is also challenging where the diastereomer can freely isomerize, as is the case for endoxifen, or exist as a eutectic system. (*Id.* at ¶ 72.) As Dr. Davies explains, a eutectic system is “a homogeneous mixture of substances that melts or solidifies at a single temperature which is below that of the melting point of any of the substances individually.” (*Id.*) Accordingly, it is well understood that purifying a eutectic system of diastereomers through crystallization to achieve an isomerically pure composition is difficult, if not impossible to ever achieve. (*Id.*)

(Z)-endoxifen is the active isomer, exhibiting much higher anti-estrogenic activity than the parent compound, tamoxifen. (EX1001 at 2:36-38.) (Z)-endoxifen is currently being evaluated in clinical trials for the prevention and treatment of ER-positive breast cancer. (E)-endoxifen has little or no anti-estrogenic activity. It was known in the art that (Z)-endoxifen is unstable, as (E)-endoxifen and (Z)-endoxifen rapidly interconvert under various commonly used conditions. (*Id.* at ¶ 55.)

The two isomeric forms of endoxifen, (Z)-endoxifen and (E)-endoxifen, can exist as a free base, a salt, or a solvate. Compounds existing in their free base, salt,

and solvate forms generally possess different physical properties, such as solubility, melting point, and spectroscopic data, since salt or solvate forms would include additional atoms, additional bonds, and different ratios of atoms. (*Id.* at ¶ 63.) As such, formulation scientists often covert the free base form of a compound into a salt or solvate to improve aqueous solubility, bioavailability, and/or pharmacokinetic properties. (*Id.*)

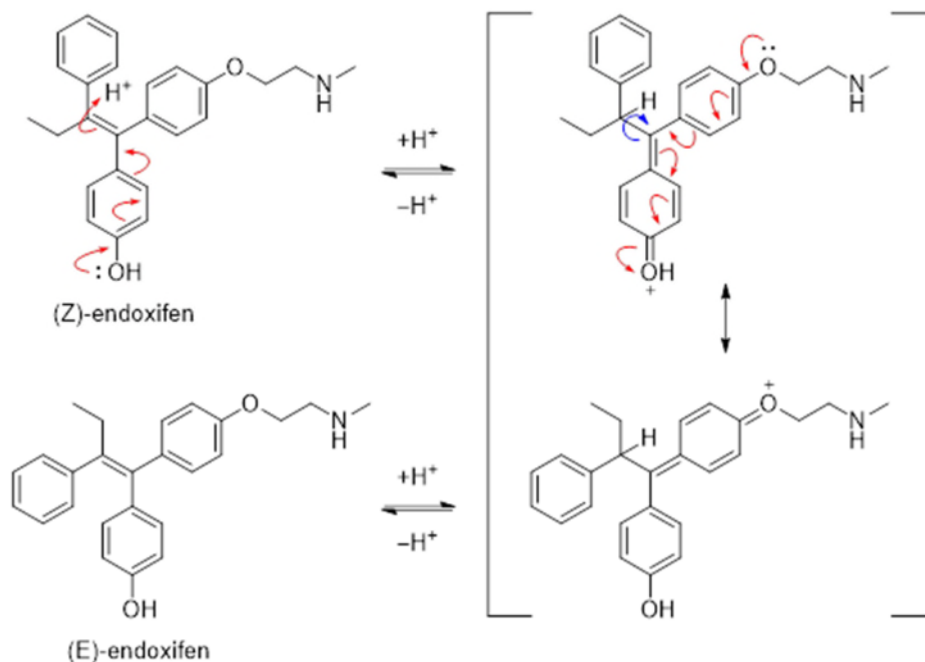
Because separate forms of compounds exhibit different physical properties, it is conventional in the field that the name of a salt or solvate form of a compound recites the identity of the salt or solvate, respectively. (*Id.* at ¶¶ 61-62.) Indeed, Petitioner's own drug label for Zonalta identifies the compound as an endoxifen citrate salt. (*Id.* at ¶ 118.) More so, the Chemical Abstracts Service ("CAS") Number system, which Dr. Davies states a POSA would be readily familiar with, assigns unique identifying CAS numbers to a compound and each of its various forms, *e.g.*, salt, solvate, etc., because each form is understood to be a separate and distinct compound. (*Id.* at ¶ 62.) Importantly, a POSA appreciates that the "active moiety" of a compound, *i.e.*, the core molecule or ion that is responsible for the physiological or pharmacological action of a drug substance, is not equivalent to the chemical name of the compound. (*Id.* at ¶¶ 64-65.) Rather, because of safety concerns involved in pharmaceutical formulation science, chemical nomenclature dictates that

a salt or solvate form of a compound would include each of the salt or solvate atoms, respectively, in its name (*e.g.*, “endoxifen citrate,” which is the citrate salt of endoxifen). (*Id.* at ¶ 65.)

Because of the uncertainty in predicting the outcome of purifying diastereomers, prior to the '334 patent, it was difficult to sufficiently separate the two diastereomers of endoxifen free base to obtain a highly pure (Z)-endoxifen free base composition and the stability of such a composition had not been evaluated. (*Id.* at ¶ 53.) Indeed, it would be impossible to predict the resulting isomeric ratio for a set of crystallization conditions or the particular conditions that would give rise to a highly purified (Z)-endoxifen free base composition. (*Id.* at ¶¶ 55-56.) Moreover, as Dr. Davies explains, acidic conditions, such as the conditions needed to synthesize a citrate salt using citric acid, would result in acid-promoted isomerization of (Z)-endoxifen, as shown in the schematic below. Under these common conditions, either a pure (Z)-endoxifen or a pure (E)-endoxifen composition would be expected to isomerize to a mixture of (Z)-endoxifen and (E)-endoxifen rather than the desired highly pure (Z)-endoxifen. (*Id.* at ¶¶ 57-59.) The '334 patent inventors therefore recognized a need for synthetic and purification methods to obtain a formulation containing highly pure (Z)-endoxifen in an industrially scalable process that is sufficiently stable at ambient temperatures and

humidities for extended periods of time to facilitate the preparation of pharmaceutical compositions that would be suitable for administration to a subject.

(EX1001 at 82:36-41.)



III. THE '334 PATENT

A. Prosecution History

As described in Patent Owner's Preliminary Response, the '334 patent was filed as U.S. Patent Application No. 17/580,428 (the "'428 application") on January 20, 2022, and issued on February 7, 2023. The '334 patent claims the benefits of Provisional Application Nos. 62/693,885, filed Jul. 3, 2018; 62/624,787, filed Jan. 31, 2018; 62/556,884, filed Sept. 11, 2017; and 62/556,799, filed Sept. 11, 2017. (POPR at 8-11.)

During prosecution, the applicant submitted Information Disclosure Statements listing at least 66 U.S. Patent references, 31 foreign patent documents, and 76 non-patent literature documents, all of which were acknowledged by the Examiner during prosecution. (EX1002 at 345-358; *see also* EX2004 ('985 File History 1) at 24.)) Additional references were disclosed in the text of the specification. Eight of the eighteen references cited in the Petition were presented during examination including EX1003 on which all six grounds depend. This includes Ahmad (EX1003), on which every ground depends. (ID at 33.) The Examiner also considered other publications in the same patent family as Ahmad, including PCT Pub. No. WO 2008/070463, to which Ahmad claims priority to. (EX2004 at 25.) The Examiner also considered U.S. Patent Pub. No. 20160346230, which shares the same specification as EX1003 (Ahmad). (*Id.* at 57.)

Similarly, EX1004, EX1005, EX1006, EX1007, and EX1018 were listed on IDS filings. (EX1002 at 346, 349-351.) EX1008 was described in the specification and incorporated by reference. (EX1001 at 11:6-10, 86:55-59.) EX1015 is referenced throughout the specification and in Claims 5-7. (*Id.* at 41:61- 64; 42:10-29, 55:8-56:65, 86:67, 98:38-51.)

The '428 application issued 13 months after it was filed. While the application faced no rejections during prosecution, there is no indication that the Examiner failed

to fully consider the art disclosed by applicants, nor did Petitioner identify any such irregularity in the Petition.

U.S. Patent No. 11,261,151 (the “’151 patent,” EX2003), filed as U.S. Patent Application No. 16/641,985 (the “’985 application”) on September 10, 2018, is the parent of the ’334 patent. The ’151 patent shares a specification with the ’334 patent, includes similar claims directed to (Z)-endoxifen compositions and, as the Board acknowledged, disclosed many of the same references during prosecution that are contained in the Petition, including EX1003 (Ahmad) and Liu (EX1004). (ID at 35.) Although the Board found that the ’151 patent’s prosecution history has limited probative value, (ID at 33), neither Petitioner nor the Board found any indication—like the prosecution history of the ’334 patent—that the Examiner failed to consider any of the art submitted during prosecution of the ’151 patent.

B. Specification

The ’334 patent discloses and teaches methods for generating an at least 90% isomerically pure (Z)-endoxifen composition suitable for oral formulation.

The ’334 patent teaches a synthetic pathway to create this highly pure (Z)-endoxifen. (EX1001 at Examples 1, 4-9; *see also* Davies POR Decl. at ¶¶ 107, 109-110, 112.) The starting isomeric mixture of (E)-endoxifen and (Z)-endoxifen is first subjected to crystallization. (EX1001 at Examples 1, 4, 9.) Because the inventors

determined that (E)-endoxifen is less soluble than (Z)-endoxifen in certain solvents, this solubility difference was used to preferentially crystallize (E)-endoxifen versus (Z)-endoxifen, thereby selectively removing a portion of the (E)-endoxifen and leaving an enriched (Z)-endoxifen component (*e.g.*, a mother liquor or filtrate). For example, the results from Table 2 of Example 1 in the '334 patent show the enrichment of (Z)-endoxifen from a crude (E)-endoxifen and (Z)-endoxifen mixture achieved in a single step using fractional crystallization in isopropanol and ethyl acetate. (*Id.* at Example 1 "A. Fractional Crystallization.") The enriched (Z)-endoxifen component is then subjected to further crystallization to obtain pure (Z)-endoxifen solid as a free base composition. (*Id.* at Example 1 "C. Recrystallization from Mother Liquor.") The (Z)-endoxifen free-base solid compositions described in the '334 patent have increased stability in ambient conditions, with reduced isomeric conversion to the (E)-isomer, which results from the synthetic and purification conditions described therein.

The '334 patent further teaches a synthetic method suitable for industrial scale to make oral formulations comprising the at least 90% isomerically pure (Z)-endoxifen composition. (*Id.* at Examples 4-9.) The '334 patent also teaches product storage stability, (*id.* at Example 11), and impurity-free compositions of (Z)-endoxifen, (*id.* at Example 12). None of these concepts are taught by any of the art

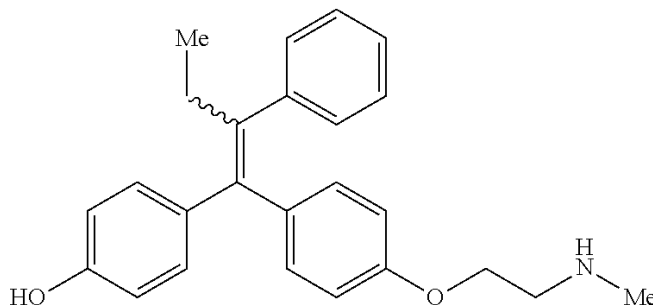
cited in the Petition. (Davies POR Decl. at ¶¶ 111, 189.) The '334 patent further provides data demonstrating the pharmacokinetics of the claimed formulations which have improved bioavailability. (EX1001 at Example 15; Davies POR Decl. at ¶ 111.)

C. Issued Claims

The '334 patent issued with 22 claims. (EX1001 at 98:12-100:28.) The two independent claims—Claims 1 and 15—each recite, in part:

“a compound of Formula (III):

Formula (III)



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

IV. POSA DEFINITION

In the ID, the Board adopted Atossa's POSA definition:

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, and design of pharmaceutical compounds and derivatives thereof as of the date of the claimed

inventions. A POSA would have worked with a team of professionals with training in related disciplines, such as pharmacology, pharmacokinetics, formulation, drug discovery and/or drug development as of the date of the claimed inventions.

(ID at 8.)

This definition reflects the nature of the invention claimed in the '334 patent, including the complicated synthetic pathway and instability of the (Z) and (E) isomers.

While Petitioner's expert, Dr. McConville, has expertise in pharmaceuticals and formulation design, he does not have the requisite chemistry expertise to analyze the synthetic methods in any of the prior art or the '334 patent itself. (McConville Tr. at 16:21-17:7; 18:10-19:6; 58:19-59:19; 60:8-60:20.) For example, when asked if the synthetic pathways disclosed in Ahmad and the '334 patent are the same or different, Dr. McConville testified "I can't recall. I didn't really go through step by step. And even doing so, ***I'm not an expert on that.***" (*Id.* at 62:21-63:16 (emphasis added).) He further testified that one would "ask a chemist" to understand the different impurity profiles between the two synthetic methods. (*Id.*; *see also id.* at 64:1-5; 65:20-66:8; 67:4-13; 72:22-75:6; 78:16-21; 81:1-10; 82:7-88:8; 89:18-90:11; 96:8-20; 99:8-100:7.)

The Petitioner fails to explain how a pharmaceutical formulation expert, such as Dr. McConville, would be able to properly evaluate the synthetic methods disclosed in Ahmad. Petitioner has no direct expert testimony relevant to the chemistry issues demonstrating non-enablement of Ahmad.

V. CLAIM CONSTRUCTION

In the ID, the Board agreed with Atossa that “enteric coating” should be construed as “a capsule with one or more enteric coating agent[s] or an intrinsically enteric capsule that does not need an additional coating to provide the enteric property to control or delay disintegration and absorption of the compositions comprising endoxifen or salts thereof in the gastrointestinal tract and thereby provide a sustained action over a longer period of time.” (ID at 9-10.)

While neither party provided an express construction for “the compound of Formula (III) is (Z)-endoxifen,” the Board *sua sponte* construed the phrase to include “the polymorphic salt, free base, co-crystal and solvate forms of (Z)-endoxifen.” (ID at 10.) The Board invited the parties to address this construction at trial. (*Id.*)

A. Governing Principles

As the Board notes, the standard for claim construction in post grant review proceedings is “the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. § 282(b), including construing the claim

in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent.” 37 C.F.R. § 42.200(b). *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-1313 (Fed. Cir. 2005) (en banc) sets forth the guiding principles for this analysis.

The “starting point in construing a claim term must be the words of the claim itself.” *Takeda Pharm. Co. v. Zydus Pharms. USA, Inc.*, 743 F.3d 1359, 1364 (Fed. Cir. 2014) (citing *Phillips*, 415 F.3d at 1314). “Proper claim construction . . . demands interpretation of the entire claim in context, not a single element in isolation.” *Hockerson–Halberstadt, Inc. v. Converse Inc.*, 183 F.3d 1369, 1374 (Fed. Cir. 1999). “While certain terms may be at the center of the claim construction debate, the context of the surrounding words of the claim also must be considered in determining the ordinary and customary meaning of those terms.” *ACTV, Inc. v. Walt Disney Co.*, 346 F.3d 1082, 1088 (Fed. Cir. 2003).

While a patentee may act as their own lexicographer, *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996), without “evidence in the patent specification of an express intent to impart a novel meaning to a claim term, the term takes on its ordinary meaning.” *Optical Disc Corp. v. Del Mar Avionics*, 208 F.3d 1324, 1334-35 (Fed. Cir. 2000). The standard for finding lexicography is exacting. *GE Lighting Solutions, LLC v. AgiLight, Inc.*, 750 F.3d 1304, 1309 (Fed.

Cir. 2014); *see also Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1370 (Fed. Cir. 2005) (declining to find lexicography where the patentee's intent was ambiguous).

Absent clear evidence of lexicography, the term should not be construed more broadly than its ordinary meaning. *Cross Med. Prod., Inc. v. Medtronic Sofamor Danek, Inc.*, 424 F.3d 1293, 1306 (Fed. Cir. 2005). "Broadening of the ordinary meaning of a term in the absence of support in the intrinsic record indicating that such a broad meaning was intended violates the principles articulated in *Phillips*." *Nystrom v. TREX Co.*, 424 F.3d 1136, 1145-46 (Fed. Cir. 2005). "Although . . . each term standing alone can be construed as having varying degrees of breadth, each term must be construed to implement the invention described in the specification." *On Demand Machine Corp. v. Ingram Industries, Inc.*, 442 F.3d 1331, 1340, 1344 (Fed. Cir. 2006). "Care must be taken lest word-by-word definition, removed from the context of the invention, leads to an overall result that departs significantly from the patented invention." *Id.*

Importantly, "[i]t is not necessary that each claim read on every embodiment." *Baran v. Med. Device Techs., Inc.*, 616 F.3d 1309, 1316 (Fed. Cir. 2010); *see also Pacing Techs., LLC v. Garmin Int'l, Inc.*, 778 F.3d 1021, 1026 (Fed. Cir. 2015) ("[W]here the patent describes multiple embodiments, every claim does not need to

cover every embodiment This is particularly true where the plain language of a limitation of the claim does not appear to cover that embodiment.”); *August Tech. Corp. v. Camtek, Ltd.*, 655 F.3d 1278, 1285 (Fed. Cir. 2011) (same).

B. The Board's Construction Of “The Compound of Formula (III) is (Z)-Endoxifen” Is Overbroad

The Board, relying on a single passage in the specification, construed the phrase “the compound of Formula (III) is (Z)-endoxifen” in independent Claims 1 and 15, to include the polymorphic salt, free base, co-crystal and solvate forms of (Z)-endoxifen.¹ This construction is overbroad, not supported by the intrinsic record, and is inconsistent with the way a POSA would interpret the term. The specification, properly read in conjunction with the claims themselves, supports a narrower construction of “the compound of Formula (III) is (Z)-endoxifen” to include the (Z)-endoxifen free base. The appropriate construction excludes the salt and solvate forms.

1. The Claims Themselves Define “The Compound of Formula (III) is (Z)-Endoxifen” As A Free Base

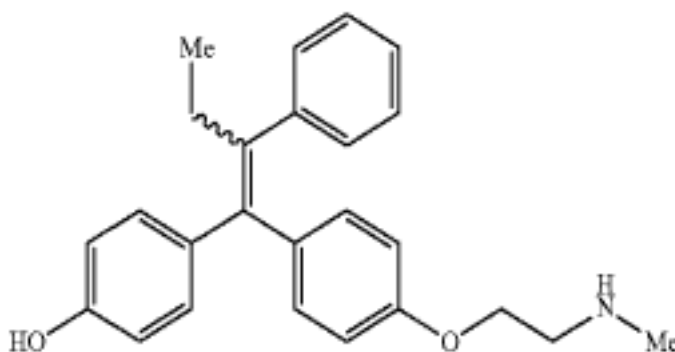
Independent Claims 1 and 15 each recite a molecular structure of an isomeric mixture of (Z)-endoxifen and (E)-endoxifen free base in addition to the claim

¹ The passage from the specification quoted by the Board reads “polymorphic, salt, free base, co-crystal, and solvate forms . . .” (EX1001 at 12:51-52 (emphasis added).) The Board's recitation omits the comma following “polymorphic.”

element “wherein at least 90% by weight of the compound of Formula (III) is (Z)-endoxifen.” This explicit definition of what makes up the “compound of Formula (III)” should govern. Claim 1 states:

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

Formula (III)



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

(EX1001 at 98:13-31.) Further, the wherein clause provides that the compound of Formula (III) is (Z)-endoxifen. The specification defines “endoxifen” as “refer[ring] to 4-hydroxy-N-desmethyl-tamoxifen” (EX1001 at 12:45-46), which lacks any mention of endoxifen salts or solvates.

The molecular structure depicted in Claims 1 and 15 is that of a mixture of (Z)-endoxifen and (E)-endoxifen *free base*, not an endoxifen salt or solvate. (Davies POR Decl. at ¶ 117.) The free base, salt form, and solvate form each have different

chemical formulas and molecular structures. (*Id.*) Dr. McConville agreed. (McConville Tr. at 27:9-11 (“Q: Would a compound and a salt of a compound have the same chemical formula? A. No.”); *id.* at 30:5-7 (“Q. Would a compound and a solvate of a compound have the same chemical formula? A. No.”); *id.* at 34:4-7 (the molecular structure of endoxifen in Claim 1 is not depicted as the salt form); *id.* at 34:22-35:3 (agreeing that the molecular structure in Claim 1 does not include any atoms of a solvate).)

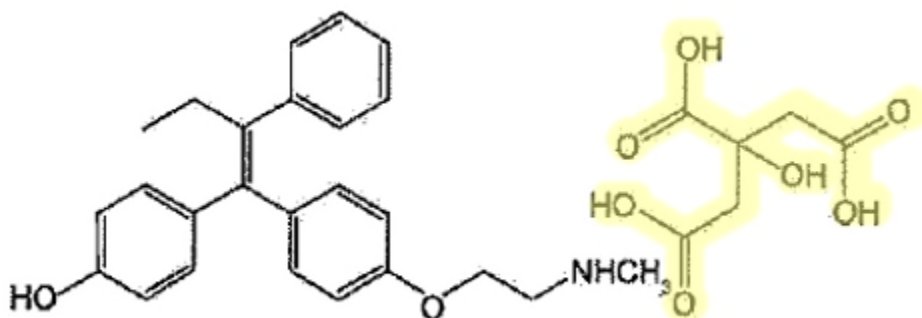
A POSA would understand that the molecular structure in Claims 1 and 15 represents the atoms in an isomeric mixture of (Z)-endoxifen and (E)-endoxifen ***free base***, not salt (or solvate). (Davies POR Decl. at ¶ 117.) If the salt (or solvate) form were intended to be encompassed by Claims 1 and 15, a POSA would expect the molecular structure of the salt (or solvate) form to be depicted. (*Id.*) In fact, both Dr. Davies and Dr. McConville agree that endoxifen in its salt and free base forms have different atoms in addition to the salt atoms themselves, including an extra hydrogen present in the endoxifen (non-salt) portion of the endoxifen citrate salt. (Davies POR Decl. at ¶ 61; *see* McConville Tr. at 34:16-35:3.)

This distinction between endoxifen free base and endoxifen salt is shown in Petitioner’s exhibit, (EX1014), which is an undated drug label for Petitioner’s drug,

Zonalta. Zonalta contains endoxifen citrate salt as the active ingredient. EX1014 at

1. The drug label states:

Endoxifen (4-hydroxy-N-desmethyl tamoxifen) is . . . supplied as a *citrate salt*. The chemical name is (Z)-4-(1-(4-(2-(methylamino)ethoxy) phenyl)-2-phenylbut-1-en-1-yl)phenol Citrate; its empirical formula is C, 65.83; H, 6.24; N, 2.48; O, 25.46. Molecular weight of endoxifen citrate and endoxifen is 565.61 g/mol and 373.26 g/mol respectively. Its structural formula is as follows:



(EX1014 at 2 (highlighting added).)

As Dr. Davies explains, the difference in molecular weights between the endoxifen free base and endoxifen citrate forms is attributed to the citrate salt counterion atoms as highlighted in the molecule above. (Davies POR Decl. at ¶ 118.)

Dr. McConville agreed that the molecular structure depicted in EX1014 is the molecular structure of endoxifen citrate salt, *not* endoxifen free base. (McConville

Tr. 29:15-30:4.) As Petitioner's own drug label shows, if a salt were intended in Claims 1 and 15, a POSA would include the atoms representing the salt in the molecular structure. (Davies POR Decl. at ¶ 118.) This interpretation is consistent with other portions of the '334 patent specification as well, for example, the inventors define "endoxifen" as "refer[ring] to 4-hydroxy-N-desmethyl-tamoxifen" (EX1001 at 12:45-46), which lacks any mention of endoxifen salts or solvates. (Davies POR Decl. at ¶¶ 119-120, 123.) Petitioner's Zonalta label also distinguishes between the molecular weights of endoxifen free base (*i.e.*, 373.26 g/mol) and endoxifen citrate salt (*i.e.*, 565.61 g/mol), further evincing that a POSA recognizes the distinction between a compound in its free base versus salt forms. (*Id.* at ¶ 118.)

"Claim construction begins and ends in all cases with the actual words of the claim." *Becton, Dickinson & Co. v. Tyco Healthcare Grp.*, 616 F.3d 1249, 1254 (Fed. Cir. 2010) (internal citation omitted). This includes the graphical depiction of the molecular structure. *Janssen Products, L.P. v. Lupin Ltd.*, C.A. 10-cv-05954-WHW-CLW, D.I. 477 (Claim Construction Opinion) at 12 (D. Del. 2013). This graphical depiction of the molecular structure of an isomeric mixture of (Z)-endoxifen and (E)-endoxifen free base must control and the "the compound of Formula (III) is (Z)-endoxifen" should be construed to exclude the salt and solvate forms.

2. The Specification Does Not Contain An Express Definition Of “The Compound of Formula (III) is (Z)-Endoxifen”

In addition to the explicit recitation of the molecular structure of a free base in the claims, the specification does not compel a broader construction. The Board characterized the passage from the specification as an “express definition” of the phrase “the compound of Formula (III) is (Z)-endoxifen.” (ID at 10 (citing EX1001 at 12:48-59).) This passage, however, does not reflect definitional intent. The passage instead describes the *scope of potential embodiments* described in the specification. (EX1001 at 12:48-52 (“*Embodiments that reference throughout this specification to ‘a compound’ . . . include the polymorphic, salt, free base, co-crystal, and solvate forms of the formulas and/or compounds disclosed herein.*”) (emphasis added).)

Embodiments in the specification do include free base (Z)-endoxifen, (EX1001 at 18:8), polymorph or crystalline forms of (Z)-endoxifen (*id.* at 18:17-19), salts of (Z)-endoxifen (*id.* at 29:2-10), and solvate forms of (Z)-endoxifen (*id.* at 13:1-6). And where the patentee intended to refer to a salt or solvent form in the specification, the patentee expressly referred to as such. (*Id.* at 12:48-59.) This passage does not reflect an intent to broadly redefine “compound.”

The Board also points to the second sentence in this passage for support of an express definition, but this sentence makes it plain that the passage is referring to the

scope of embodiments. “Thus, the appearances of the phrases ‘a compound’, ‘compound of Formula (I)’, ‘compound of Formula (II)’, ‘**compounds of Formula (III)**’ and ‘compound of Formula (IV)’ **include** Form I of the compound of Formula (IV), **Forms II-III of the compounds of Formula (III)**, the free base of the compound of formula (IV), **the free base of the compounds of Formula (III), and/or the gluconate salts as described herein.**” (*Id.* at 12:52-59 (emphasis added).) Moreover, this sentence refers to the use of the phrase “**compounds of Formula (III)**” whereas the Claims recite to the singular “compound of Formula (III).”

In direct contrast to the specification’s description of “compound” as describing a range of embodiments, the specification expressly defines thirty other terms by using the prefacing phraseology “*As used herein*, the term [] refers to . . .” (EX1001 at 12:12-47, 12:60-16:65 (emphasis added).) The “patentee’s use of the phrases “as used herein” and ‘refer to’ conveys an intent for the sentence [] to be definitional.” *ParkerVision, Inc. v. Vidal*, 88 F.4th 969, 976 (Fed. Cir. 2023) (citing *Kyocera Tools Inc. v. Int’l Trade Comm’n*, 22 F.4th 1369, 1378 (Fed. Cir. 2023)). Importantly, the specification expressly defines “endoxifen”: “As used herein, the term ‘endoxifen’ refers to 4-hydroxy-N-desmethyl-tamoxifen. It is a secondary active metabolite of tamoxifen.” (EX1001 at 12:45-47.) Notably, this express definition lacks any mention of endoxifen salts or solvates.

There is no use of this definitional language with “compound.” This distinction is key—if the patentee intended to provide an express definition, the patentee knew to use the definitional phrase “as defined herein,” having done so thirty times. This distinction weighs against finding that the patentee expressly defined “compound” as the Board preliminarily concluded in the ID. *See, e.g., Meds. Co. v. Mylan, Inc.*, 853 F.3d 1296, 1306 (Fed. Cir. 2017) (finding no definitional intent where the purported definition did not “accord with the linguistic formula used by the patentee to signal the designation of other defined terms”). In *Meds. Co.*, the Federal Circuit noted that when expressly defining terms, “the patentees use[d] a similar format: the defined term in quotation marks, followed by the terms ‘refers to’ or ‘as defined herein’ . . . Because [the purported definition at issue] departs from this format, . . . [it] lacks the clear expression of intent necessary for a patentee to act as its own lexicographer.” *Id.* (internal citation and some quotation marks omitted); *see also Abbott Labs. v. Andrx Pharms., Inc.*, 473 F.3d 1196, 1210-1211 (Fed. Cir. 2007) (declining to find lexicography where patentee omitted the phrase “as used herein means” because the specification “unambiguously provide[d] definitions of other claim terms” by employing that phrase); *Merck*, 395 F.3d at 1370 (lexicography not found where there was ambiguity).

Respectfully, for all these reasons, the Board erred in construing “the compound of Formula (III)” to include the polymorphic, salt, free base, co-crystal, and solvate forms. Instead, the “the compound of Formula (III)” as claimed should be construed to exclude the salt and solvate forms.

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

Ground 1 challenges the patentability of Claims 1, 2, 4, 15, and 20-22 as anticipated by Ahmad (EX1003). To anticipate, a prior art reference must “enable one of ordinary skill in the art to make the invention *without undue experimentation*. . . . In other words, the prior art must enable the claimed invention.” *Impax Labs., Inc. v. Aventis Pharms. Inc.*, 545 F.3d 1312, 1314 (Fed. Cir. 2008) (emphasis added).

Ahmad contains a single sentence in the specification stating that one object of Ahmad’s invention is to provide “E-endoxifen or Z-endoxifen with at least 80% purity, such as at least 90% pure . . .” (EX1003 at 12:14-16.) This is the only place in the entire patent in which Ahmad references 90% purity. This passage does not specify whether the endoxifen must be a (E) or (Z) isomer, or whether the endoxifen must be a free base, salt, or a solvate. The sole claim in Ahmad is limited to an “at least 80%” pure (Z)-endoxifen citrate composition. (*Id.* at 30:54-65.) During

prosecution, Ahmad never sought claims to any endoxifen purity level greater than “at least 80%,” including 90% isomerically pure (Z)-endoxifen.

Ahmad fails to provide any working examples or specific teachings that would enable a POSA to practice Ahmad’s single claim directed to an 80% pure endoxifen citrate. (Davies POR Decl. at ¶¶ 39, 81.) But even assuming Ahmad enables the synthesis of **80% pure** endoxifen citrate—which it does not—Ahmad does not teach how to achieve **90% pure** (Z)-endoxifen, whether free base or salt. Ahmad simply does not contain an enabling disclosure of (Z)-endoxifen at 90% or greater purity. (See, e.g., POPR at 32-40.) As Dr. Davies explains, an increase from 80% purity to 90% purity is significant and not routine. (Davies POR Decl. at ¶¶ 70-72.)

Because Ahmad does not enable a POSA to practice the claimed invention of the ’334 patent without undue experimentation, Ground 1 fails.

A. Petitioner Cannot Demonstrate That Ahmad Is Enabled

Ahmad fails to teach a synthetic pathway and associated purification steps to generate 90% pure (Z)-endoxifen. At best, Ahmad includes a single sentence describing 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 . . .” (EX1003 at 12:14-17.) Ahmad, however, does not teach **how** to achieve a 90% isomerically pure (Z)-endoxifen. (See POPR at 32-33 (citing EX2001 (Davies Decl.) at ¶¶ 98-108).)

As Dr. Davies describes, a POSA would need to undertake further research and undue experimentation to arrive at the composition claimed in the '334 patent. (Davies POR Decl. at ¶¶ 53-54, 70-72; *see also* POPR at 32.) The Board acknowledged Atossa's enablement arguments but declined to address those arguments at the institution stage. (ID at 15-16.)

1. Enablement Requirement

As the Board and Petitioner acknowledge, an anticipatory reference must be enabling by allowing a person of skill in the art to practice or carry out the method at issue without undue experimentation. (ID at 12.); *see also In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009) (citing *Impax Labs.*, 545 F.3d at 1314). The inquiry as to whether “undue experimentation is needed is not a single, simple factual determination, but rather [] a conclusion reached by weighing many factual considerations.” *Martek Bioscis. Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1378 (Fed. Cir. 2009) (quoting *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988)). Determining what level of experimentation qualifies as “‘undue,’ so as to render a disclosure non-enabling, is made from the viewpoint of persons experienced in the field of the invention.” *Elan Pharms., Inc. v. Mayo Found. for Med. Educ. & Research*, 346 F.3d 1051, 1055 (Fed. Cir. 2003).

The factors that guide the determination of whether or not undue experimentation is required, which are referred to as the “Wands Factors,” include: “(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.” *Amgen*, 987 F.3d at 1084 (quoting *Wands*, 858 F.2d at 736-37); *see also ALZA Corp. v. Andrx Pharms., LLC*, 603 F.3d 935, 941 (Fed. Cir. 2010) (a specification that requires a skilled artisan to “engage in an iterative, trial-and-error process to practice the claimed invention” does not provide an enabling disclosure).

2. The Field Of Organic Chemistry, Including Separation And Purification Of Stereoisomers, Is Difficult, Unpredictable, And Requires Significant Experimentation

The disclosure in Ahmad is insufficient to put a POSA in possession of the invention without engaging in undue experimentation. *See, e.g., Impax Labs, Inc. v. Aventis Pharms., Inc.*, 496 F.Supp.2d 428, 432 (D. Del. 2007), *aff'd* 2008 U.S. App. LEXIS 20841 (Fed. Cir. Oct. 3, 2008). It is well accepted that the synthesis of solid chemical formulations, which falls within the field of organic chemistry, is unpredictable. *See Boston Scientific v. Johnson & Johnson*, 679 F. Supp.2d 539, 557 (D. Del. 2010) (noting that “the chemical arts have long been acknowledged to be

unpredictable”). Organic chemistry is an experimental science, meaning that one cannot predict the outcome of an experiment without actually carrying out the experiment (such as a crystallization or synthesis) in the laboratory. *See Schering Corp. v. Gilbert*, 153 F.2d 428, 433 (2d Cir. 1946) (“Organic chemistry is essentially an experimental science and results are often uncertain, unpredictable and unexpected.”).

The science of separating stereoisomers (*e.g.*, enantiomers and diastereomers) has also been found to be unpredictable and difficult. *See, e.g., Forest Laboratories, Inc. v. Ivax Pharmaceuticals, Inc.*, 501 F.3d 1263 (Fed. Cir. 2007) (affirming the district court’s finding regarding the known difficulty of separating enantiomers and the unpredictability of their properties). In *Forest*, defendants argued that a scientific publication describing the enantiomers of a compound rendered a patent claiming one of the enantiomers obvious. The district court rejected defendants’ argument because the reference did not teach how to obtain the desired enantiomer and was therefore not enabled. *Id.* at 1268-69. The Federal Circuit affirmed.

Similarly, in *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075 (Fed. Cir. 2008), the patent-in-suit contained claims to one enantiomer of a specific compound substantially separated from the other enantiomer. 550 F.3d at 1082-1083. The asserted anticipatory prior art patents described a racemic mixture of the two

enantiomers and contained no examples showing how to separate the two, but claimed “both enantiomeric forms or their mixture.” *Id.* at 1083. The district court found that “[d]iscovering which method and what combination of variables is required [to separate the enantiomers] is sufficiently arduous and uncertain as to require undue experimentation, even by one skilled in the relevant art.” *Id.* at 1085 (citing *Sanofi-Synthelabo v. Apotex, Inc.*, 492 F.Supp.2d 353, 387 (S.D.N.Y. 2007)). The Federal Circuit affirmed the district court’s finding that “the reference patents would not have enabled a person of ordinary skill to obtain [the desired enantiomer] substantially separated from the levorotatory enantiomer.” *Id.*

3. Burden Shifting Framework

While *the claims* of a prior art patent are presumed enabled, (ID at 15-16), this presumption is not immutable and can be overcome by a patent owner. *See, e.g., Cubist Pharms., Inc. v. Hospira, Inc.*, 75 F. Supp. 3d 641, 662 (D. Del. 2014) (finding the disclosure in the prior art patent reference not enabling and therefore not anticipatory); *Sanofi-Synthelabo*, 550 F.3d. at 1085. There is no presumption that every prophetic example in the specification is enabled, especially where that prophetic example is not explicitly claimed. *See Amgen Inc. v. Sanofi*, 987 F.3d 1080, 1085 (Fed. Cir. 2021) (quoting *McRO, Inc. v. Bandai Namco Games Am. Inc.*, 959 F.3d 1091, 1100 (Fed. Cir. 2020)) (although a specification does not need to

“describe how to make and use every possible variant of the claimed invention, when a range is claimed, there must be reasonable enablement of the scope of the range.”).

The patent owner bears the initial burden of producing evidence establishing that the prior art reference is not enabled. *See Raytheon Techs. Corp. v. GE*, 993 F.3d 1374, 1381-82 (Fed. Cir. 2021) (finding the PTAB erred in holding that a challenged prior art reference was enabled because patent owner met its burden of producing evidence of non-enablement).

If, as here, Atossa satisfies its burden of production, the burden shifts to the Petitioner to rebut Atossa's evidence by producing evidence establishing that the challenged claim limitations of the patent-in-suit are enabled by the prior art patent reference. *See id.* (“In contrast, [patent owner] presented ***extensive, un rebutted evidence of non-enablement***. [Patent owner] submitted and relied on [an expert] declaration . . . detailing the unavailability of the revolutionary composite material contemplated by [the prior art reference]. . . . In sum, we conclude that ***[Petitioner] failed to provide an evidence-based case for how the [claimed invention in the challenged patent]. . . is enabled by [the prior art's] disclosure***.”) (emphasis added).

There is no such evidence on which Petitioner can rely. While Dr. McConville testified that he presumed Ahmad was enabled, this presumption was based only the fact that Ahmad is an issued patent. (McConville Tr. at 99:8-100:7.) Dr. McConville

testified that he did not have the chemistry expertise to evaluate Ahmad's synthetic methods. (*Id.* at 100:4-7.) He further testified that he performed no analysis or investigation into whether Ahmad actually enabled a POSA to make the claimed invention. (*Id.*)

4. Atossa Has Met Its Burden Of Producing Evidence Demonstrating That Ahmad Is Not Enabled

a. Ahmad's Prosecution History Evidences The Lack Of Enablement For Any Claim Scope Greater Than 80% Purity (Z)-Endoxifen Citrate Salt

The application that resulted in Ahmad was originally filed with 39 claims. (EX2022 at 46-52.) The as-filed claims included "[Claim] 2. . . . wherein the anticancer drug is endoxifen, and wherein said endoxifen is a free base or in the form of a salt;" "[Claim] 4. . . . wherein said endoxifen is predominantly in a form selected from the group consisting of E-isomer, Z-isomer, and a mixture of E- and Z-isomer;" and "[Claim] 8[:] A method of purifying the endoxifen of claim 5, comprising: crystalizing said endoxifen; and/or chromatographically treating said endoxifen; to produce a purified preparation of endoxifen, wherein said purified preparation of endoxifen contains predominantly E-isomer, predominantly Z-isomer, or a mixture of E-and Z-isomers of endoxifen." (*Id.* at 46-48.) None of the claims specified a purity level for (Z)-endoxifen.

Those claims were cancelled in a preliminary amendment and new claims were added, including Claims 40 and 54. (*Id.* at 53-59.) Claim 40 recited: “A composition comprising an effective amount of a complex comprising endoxifen, wherein said endoxifen is in a free base or is in the form of a salt.” (*Id.* at 54.) Claim 54 recited “A method of claim 51, comprising: a) crystallizing said endoxifen; and/or b) chromatographically treating said endoxifen; to produce a purified preparation of endoxifen, wherein said purified preparation of endoxifen contains predominantly E-isomer, predominantly Z-isomer, or a mixture of E- and Z-isomers of endoxifen.” (*Id.* at 58.)

After the examiner imposed a restriction requirement, Ahmad elected Group 1 drawn to a composition comprising endoxifen, amended Claim 40, and withdrew Claim 54. (*Id.* at 69-75.) Claim 40 was in part amended to “A composition comprising an effective amount of a complex comprising a synthetic preparation of endoxifen, wherein said endoxifen is a free base or is in the form of a salt . . .” (*Id.* at 71.) No purity level limitation was included in pending Claim 40. The examiner rejected the pending claims under § 103, (*id.* at 77, 79-83); Ahmad then attempted to overcome the rejections, (*id.* at 86-95); but the examiner maintained the rejections under § 103, (*see id.* at 97-106).

Ahmad appealed the final rejection under 35 U.S.C. § 103. (*Id.* at 109-130.) Ahmad's brief is silent as to purity level of the claimed endoxifen and whether the claimed composition was in the form of a free base or salt. Ahmad subsequently amended pending Claim 40 to recite: "A solid pharmaceutical composition comprising an effective amount of a synthetic preparation of endoxifen, wherein: i) said synthetic preparation of endoxifen is at least 80% Z-endoxifen; ii) said synthetic preparation of endoxifen is in the form of a salt; wherein said solid pharmaceutical composition is in the form of an enteric-coated tablet or enteric-coated capsule." (*Id.* at 133-151.) Along with the amendment, Ahmad submitted a declaration under 37 C.F.R. § 1.132, which included a copy of Ahmad 2010 (EX1006) and described the results from administering an endoxifen citrate compound to patients. (*Id.* at 145-151.) Nowhere in that declaration did Ahmad describe the purity of the endoxifen solid oral dosage form that was administered.

In the subsequent office action, the examiner maintained the rejection under 35 U.S.C. § 103 over Claim 40. (*Id.* at 153-161.) In response, Ahmad, for the first time, argued that the prior art did not teach a salt form and did not teach 80% purity of (Z)-endoxifen. (*Id.* at 162-167.) The examiner again maintained the rejection, noting that the prior art taught a 75% pure (Z)-endoxifen. (*Id.* at 169-176.) In response, Ahmad's co-inventor submitted a separate declaration under 37 C.F.R. §

1.132, (*id.* at 177-181), describing that the solid oral dosage form administered in Ahmad 2010 (EX1006) “was at least 80% Z-endoxifen and was in the form of a citrate salt of endoxifen.” (*Id.* at 177.) That declaration was silent as to how the dosage form was synthesized and made no claim to synthesizing anything more than “at least 80%.” Moreover, the declaration provided no evidence that the endoxifen citrate was actually “at least 80%” (Z)-endoxifen. Shortly thereafter, pending Claim 40 issued as Claim 1.

Even assuming Ahmad’s claim to “at least 80% (Z)-endoxifen . . . citrate salt” is sufficiently enabled to achieve 80% purity—it is not—there is nothing in the specification or file history that demonstrates enablement of anything greater than 80% purity. There is no evidence of record that Ahmad is enabled such that a POSA could achieve 90% pure (Z)-endoxifen composition, whether free base or salt. *See, e.g., MagSil Corp. v. Hitachi Global Storage Techs., Inc.*, 687 F.3d 1377, 1383-84 (Fed. Cir. 2012) (although claims were construed to cover resistive changes “from 10% up to infinity,” the Federal Circuit held that the claims were not enabled because the “patent specification only disclose[d] enough information to achieve an 11.8% resistive change”).

b. Ahmad Teaches A Different Synthetic Method To Produce An Unknown Mixture Of (Z)-Endoxifen And (E)-Endoxifen Isomers

The challenged claims of the '334 patent recite an endoxifen composition comprising at least 90% by weight of (Z)-endoxifen. While Ahmad's specification contains a single sentence stating that the object of the invention is to provide "E-endoxifen or Z-endoxifen with at least 80% purity, such as at least 90% pure" (EX1003 at 12:14-16), Ahmad does not contain any working examples demonstrating that the synthetic method described therein results in a 90% pure (Z)-endoxifen. (Davies POR Decl. at ¶¶ 80, 131.) Dr. McConville agreed that the passage at 12:14-16 of Ahmad does not contain any description of a synthetic method that could be used to generate 90% pure (Z)-endoxifen, (McConville Tr. at 57:12-17), and testified that the question of whether Ahmad provided such a working example anywhere in the specification "[is] more of a chemistry question, for different experts" (*see id.* at 55:17-56:12).

The lack of any working examples supports a finding of non-enablement. *Cf. Takeda Pharm. Co., LTD v. Handa Pharms., LLC*, C.A. No. 11-00840-JCS, 2013 U.S. Dist. LEXIS 187604, at *238-39 (N.D. Cal. Oct. 17, 2013) (finding a prior art patent not enabled in part because its specification "does not contain any working examples regarding how to synthesize solid dexlansoprazole").

Ahmad's synthetic pathway is entirely different than what is described in the '334 patent. (*See, e.g.*, Davies POR Decl. at ¶¶ 135-136.) When asked whether he compared the synthetic pathways of Ahmad and the '334 patent, Dr. McConville testified that he "didn't think that that was relevant" and "I'm not an expert on that." (McConville Tr. at 63:7-16.) Ahmad's synthetic pathway produces a different (E)/(Z) isomeric ratio than produced by the methods of the '334 patent. As Dr. Davies explains, a POSA following the synthetic pathway described in Ahmad (EX1003) at 22:32-25:67, "would most likely generate a 1:1 ratio of (E):(Z) isomers." (Davies POR Decl. at ¶¶ 77, 139, 183.) This would be, at best, a 50% pure (Z)-endoxifen composition—a far cry from the 90% purity recited in the challenged claims.

As Dr. Davies explains, this 1:1 ratio results, in part, from Ahmad's synthetic approach, which utilizes an ethyl acetate-heptane crystallization of the crude endoxifen product mixture. (EX1003 at 25:5-67 (Example 4); *see also* Davies POR Decl. at ¶ 135.) Because (Z)-endoxifen is more soluble in ethyl acetate than (E)-endoxifen, crystallization in ethyl acetate would result in an endoxifen composition with a higher concentration of (E)-endoxifen than (Z)-endoxifen. (Davies POR Decl. at ¶¶ 76, 135.) Dr. McConville testified that a chemist, not himself, would be best

suited to answer questions about Ahmad's Example 4. (McConville Tr. at 72:8-73:17.)

Thus, at best, Ahmad's synthetic process teaches synthesizing a highly impure crude endoxifen mixture containing roughly equal parts of (E)-endoxifen and (Z)-endoxifen. Ahmad fails to provide guidance as to the isomeric ratio of (Z)-endoxifen to (E)-endoxifen that would be expected at the conclusion of the ethyl acetate crystallization step. Dr. McConville agreed. (*Id.* at 73:18-22.)

Compounding the problem, Ahmad does not describe any method to further purify the crude endoxifen mixture that results from Example 4. There is no teaching on making a (Z)-endoxifen enriched filtrate and subsequently crystallizing the filtrate to result in a highly pure (Z)-endoxifen. (Davies POR Decl. at ¶¶ 77-79.) Dr. McConville testified that he would rely on "somebody that's got expertise in that area, a chemist." (McConville Tr. at 74:8-75:8.) Ahmad does not teach any subsequent isomeric purification, as would be required to produce a purified (Z)-endoxifen, and thus would not enable a POSA to obtain an isomerically pure (Z)-endoxifen composition suitable for use in an oral formulation. (Davies POR Decl. at ¶¶ 39, 112.)

c. Ahmad Does Not Describe How To Separate (Z)-Endoxifen And (E)-Endoxifen Isomers

The purification of (Z)-endoxifen is a technically difficult process, in large part because of the instability of the (Z)-endoxifen isomer, which is prone to conversion to (E)-endoxifen. (Davies POR Decl. at ¶¶ 55-56.) Ahmad is silent on the instability of (Z)-endoxifen, much less how one might prevent it from converting to (E)-endoxifen.

Ahmad provides no substantive instruction on how to separate the two isomers to obtain 90% pure (Z)-endoxifen. Instead, Ahmad generically states that (E)-endoxifen and (Z)-endoxifen isomers “can be separated to provide the purified preparations of E- and Z-isomer of endoxifen.” (EX1003 at 11:19-20.) Ahmad provides three possible methods to separate the two isomers: crystallization, liquid column chromatography (LC), or high-pressure liquid column chromatography (HPLC). (*Id.* at 11:21-23.)

Nowhere does Ahmad describe that any of these three methods would achieve 90% purity or how they might be used—other than in the most general and aspirational sense. Ahmad does not provide sufficient instruction to employ any of these three methods to achieve 90% pure (Z)-endoxifen without engaging in undue experimentation. Instead, Ahmad recites an extensive list of solvents, acids, fractional crystallization and column chromatography conditions that may be used.

(EX1003 at 11:24-42.) This generic list is not limited to the categories of solvents recited: “suitable solvents . . . include but are not limited to . . . A solvent for crystallization can be used as a single solvent, or as a mixture of solvents . . . When a mixture of two solvents is used in the present invention, examples of ratios of one solvent to another are e.g., in a range such as 9:1 to 1:9, (e.g., 8:2, 7:3; 6:4; 5:5; 4:6; 3:7; 2:8; 1:9, and the like.) However, mixtures for use in the present invention are not limited to these ratios, or to mixtures comprising only two solvents.” (*Id.*)

Just sorting through the laundry list of solvents and experimental conditions would require a POSA to engage in undue experimentation, and this represents just a single step in the synthetic pathway. Ahmad does not describe any meaningful amounts, ranges, examples, or guidelines to use with any of the three possible purification methods. (Davies POR Decl. at ¶¶ 80, 128.)

Crystallization: Ahmad does not provide any specific crystallization conditions that could be used to obtain greater than 90% (Z)-endoxifen. (Davies POR Decl. at ¶ 135.) Dr. McConville was unable to identify any such teachings. (McConville Tr. at 85:15-88:13.) As Dr. Davies explains, crystallization is unpredictable and highly dependent on purification parameters including solvent types, solvent ratios, rate of solvent addition, compound concentrations, temperature, agitation, and even others. (Davies POR Decl. at ¶ 53.) A significant

amount of experimentation would be needed to determine the crystallization conditions required to obtain a specific level of isomeric purity. (*Id.* at ¶¶ 53-54, 58, 132.)

Dr. McConville testified that a chemist would be best suited to understand the challenges in crystallization and recrystallization. (McConville Tr. at 83:1-13.) He could not comment on the impact of varying these parameters. (*Id.* at 83:14-85:14.)

Liquid Chromatography (LC) and High-Pressure Liquid Column Chromatography (HPLC): As with crystallization, Ahmad fails to provide any guidance as to the appropriate chromatography conditions that could be used to separate the stereoisomers of endoxifen. As Dr. Davies explains, the yield of a given isomer is difficult or impossible to predict using chromatography. (Davies POR Decl. at ¶ 53.) There is considerable uncertainty involved in selecting the conditions best suited for purifying a given isomer as well as predicting the outcome of any such purification attempt. For example, purifying a composition containing a mixture of stereoisomers may result in only one of the isomers being purified and would require further characterization to determine which isomer was purified. (*Id.* at ¶ 53, 68-70.) Dr. McConville testified that he would rely on a chemist to understand whether Ahmad identified chromatography parameters required to identify 90% (Z)-endoxifen. (McConville Tr. at 90:1-11.) Dr. McConville agreed

that Ahmad provided no chromatography data quantifying the isomeric purity of the endoxifen synthesized. (*Id.* at 90:12-19.)

Notably, the Federal Circuit considered similar facts in the case of an anticipatory prior art patent reference relied upon for teaching stereoisomer purification in *Sanofi-Synthelabo v. Apotex, Inc.*, and found that “[d]iscovering which method and what combination of variables is required [to separate the enantiomers] is sufficiently arduous and uncertain as to require undue experimentation, even by one skilled in the relevant art.” 550 F.3d 1075, 1085 (Fed. Cir. 2008) (citing *Sanofi-Synthelabo v. Apotex, Inc.*, 492 F.Supp.2d 353, 387 (S.D.N.Y. 2007)). For these same reasons, Ahmad is not enabled because it also fails to provide sufficient direction to enable a POSA to produce a 90% pure (Z)-endoxifen stereoisomer.

d. Liu And Song Cannot Supply Limitations Missing From Ahmad

Petitioner argues that, “[t]o the extent it is argued there is not a specific, enabling disclosure of 90% pure (Z)-endoxifen by Ahmad, forming such pure formulations was known in the art as taught by e.g., Liu and Song.” (*See* Pet. at 30.) The Petition, however, fails to identify exactly what teaching(s) from Liu and Song are being relied on to support a finding that Ahmad is enabled.

In response to Patent Owner's argument that Liu and Song "cannot be used to fill in any missing limitations, such as a purity level greater than 80% or the creation of (Z)-endoxifen free base," (see POPR at 37), Petitioner contends that "[c]ontrary to Patent Owner's arguments, additional references may be used "to show that the claimed subject matter, as disclosed in [the anticipatory reference], was in the public's possession." (See Paper 10 at 5 n.3 (citing *In re Donohue*, 766 F.2d 531, 534 (Fed. Cir. 1985) and *Bristol-Myers Squibb Co. v. Ben Venue Lab's, Inc.*, 246 F.3d 1368, 1379 (Fed. Cir. 2001).)

Enablement of a prior art patent is determined as of the effective filing date of the patent. *Plant Genetic Sys., N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1339 (Fed. Cir. 2003). Although the Federal Circuit has recognized the limited exception that a challenger may "use [] additional references to confirm the contents of the allegedly anticipating reference," the Federal Circuit has "made clear that anticipation does not permit an additional reference to supply a missing claim limitation." *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1335 (Fed. Cir. 2002) (citing *Studiengesellschaft Kohle, m.b.H. v. Dart Indus., Inc.*, 726 F.2d 724, 727 (Fed. Cir. 1984) (one cannot rely on additional references "for a very specific teaching" rather than for the light they shed on what the anticipatory reference would have meant to a POSA)).

In re Donohue, 766 F.2d 531 (Fed. Cir. 1985), cited by Petitioner, does not compel a different result. In *Donohue*, the Federal Circuit accepted the use of a later prior art reference to show enablement of an earlier anticipatory reference, where the later reference was used only “to show that the claimed subject matter, as disclosed in [the anticipatory reference], was in the public’s possession.” *Id.* at 534. Similarly, *Bristol-Myers Squibb Co. v. Ben Venue Lab’s, Inc.*, 246 F.3d 1368, 1378-80 (Fed. Cir. 2001) does not support Petitioner’s argument. Similar to *Donohue*, the Federal Circuit noted that a later reference may be used to demonstrate that the earlier reference was in the public’s possession, but that it was impermissible to turn to other prior art references where the anticipatory reference did not contain a specific disclosure. *Id.* at 1378-80. Neither *Donohue* nor *Bristol-Myers* stand for the proposition that a later prior art reference can fill in the missing gaps of the earlier reference.

Petitioner is improperly attempting to use Liu and Song to supply missing claim limitations from Ahmad to enable the claimed limitation “wherein at least 90% by weight of the compound of Formula (III) is (Z)-endoxifen.” Ahmad does not disclose a synthetic pathway or purification steps sufficient to produce at least 90% by weight of (Z)-endoxifen. (Davies POR Decl. at ¶¶ 75, 77, 80; *see* McConville Tr. at 55:17-56:12 (“[T]hat’s more of a chemistry question, for different experts.”).)

And, as explained by Dr. Davies, Song teaches a method of making highly pure (E)-endoxifen, **not** (Z)-endoxifen. (Davies POR Decl. at ¶ 97.) Dr. McConville agreed with Dr. Davies' analysis of Song. (McConville Tr. at 93:9-94:5 ("And [Dr. Davies] indicates that Song had some errors in the NMR interpretation. And so as a result obviously, you know, Song is not to be relied upon in my opinion because I agree with Dr. Davies in that respect.").) Song, therefore, cannot support a finding that Ahmad enables a POSA to make a composition "wherein at least 90% by weight of the compound of Formula (III) is (Z)-endoxifen." If anything, Song teaches the opposite and creates confusion in the art as a result of its numerous and undisputed technical errors.

Liu describes a very different synthetic pathway from both Ahmad and the '334 patent. (Davies POR Decl. at ¶¶ 87, 144, 154-55; *see* McConville Tr. at 65:7-11.) For example, Liu describes different starting materials, including zinc bromide, 2-phenoxyethyl bromide, and phosphorous tribromide. (EX1004 (Liu) at ¶ 62.) Liu also describes different crystallization parameters used for purification. (Davies POR Decl. at ¶ 87.) Liu does not describe the stability profile of the resulting endoxifen composition. And Liu does not describe a synthetic method to produce an oral pharmaceutical formulation. (McConville Tr. at 95:15-96:7; *see* Davies POR Decl. at ¶ 156.) Liu's method is also inefficient, resulting in a low yield of 34% after

a series of recrystallizations. (Davies POR Decl. at ¶ 87 (citing EX1004 (Liu) at ¶¶ 73-76).) Even if Liu could be relied on to support enablement of Ahmad—it cannot—it is unclear exactly what teachings of Liu would be relevant and Petitioner makes no attempt to explain which teachings would be relevant.

These significant differences between the synthetic pathways of Ahmad, the '334 patent, and Liu would result in endoxifen compositions with different impurity profiles, residual solvents, and stability profiles. (Davies POR Decl. at ¶¶ 87-88; *see* McConville Tr. at 63:3-6 (“It seems reasonable, yes [that different synthetic pathways can result in different impurity profiles.]”).) Dr. McConville agreed that “it is essential to know the exact composition of pharmaceutical formulations [] throughout the entire lifecycle of the product and also exact characterization of residual solvents is essential.” (McConville Tr. at 71:5-16.) A POSA creating an oral solid dosage form would be concerned about Liu’s unknown impurity profile, unknown residual solvents, and unknown stability profile.

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

Petitioner argues that “[if] there is not a specific, enabling disclosure of 90% pure (Z)-endoxifen by Ahmad, forming such pure formulations was known in the art as taught by e.g., Liu and Song.” (Pet. at 30.) Petitioner, however, fails to provide *any* explanation for how Liu’s method of making (Z)-endoxifen supports a finding that the pharmaceutical formulation claimed by Ahmad is enabled. Petitioner’s argument fails and neither Liu nor Song support the conclusion that Ahmad is enabled.

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

“A patent claim is invalid as anticipated only if each and every element of the claim is expressly or inherently disclosed in a single prior art reference.” *Guangdong Alison Hi-Tech Co. v. Int’l Trade Comm’n*, 936 F.3d 1353, 1363-64 (Fed. Cir. 2019) (citations omitted). In the ID, the Board acknowledged that the alleged anticipatory reference “must also be enabling, which requires that the reference ‘teach a skilled artisan—at the time of filing—to make or carry out what it discloses in relation to the claimed invention without undue experimentation.” (ID at 12 (internal citations omitted).) “A prior art reference cannot anticipate a claimed invention ‘if the allegedly anticipatory disclosures cited as prior art are not enabled,’” meaning that the prior art reference must “enable the portion of the disclosure alleged to anticipate

the claimed invention.” *In re Antor Media Corp.*, 689 F.3d 1282, 1287, 1290 (Fed. Cir. 2012).

1. Independent Claims 1, 15

Petitioner alleges Ahmad anticipates Claims 1 and 15 because the specification describes that one object of Ahmad’s 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.” (EX1001 at 12:14-17.) Ahmad’s sole claim only recites “at least 80% Z-endoxifen . . . in the form of a citrate salt.” (*Id.* at 30:55-65.)

For all of the reasons discussed above, Ahmad does not enable, and therefore does not anticipate, the endoxifen composition recited in the challenged claims. This holds true whether or not the Board applies its proposed broad construction of “the compound of Formula (III) is (Z)-endoxifen.” As discussed in detail above, there is no teaching in Ahmad that would allow a POSA to achieve 90% pure (Z)-endoxifen composition, whether free base or citrate salt. And because the Petition improperly points to Liu and Song to support a finding of enablement—without explaining how either reference does so—Liu and Song cannot be used to demonstrate that the ’334 patent’s pathway for generating (Z)-endoxifen was public knowledge at the time the ’334 patent was filed. Moreover, Ahmad’s Claim 1 is limited to, *at most*, an 80%

(Z)-endoxifen citrate salt. Ahmad does not anticipate a 90% pure (Z)-endoxifen, whether free base or salt form.

2. Dependent Claims 2, 4, 20-22

Dependent Claims 2 and 4 depend on Claim 1 and dependent Claims 20-22 depend on Claim 15. Each of these dependent Claims requires at least 90% (Z)-endoxifen, which is not enabled by Ahmad. Because neither Claim 1 nor Claim 15 is anticipated by Ahmad, Claims 2, 4, and 20-22 are consequently not anticipated. *See Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1371 (Fed. Cir. 2008) (holding that “unless a reference discloses within the four corners of the document not only all of the limitations claimed but also all of the limitations arranged or combined in the same way as recited in the claim, it cannot be said to prove prior invention of the thing claimed and, thus, cannot anticipate under 35 U.S.C. § 102”).

Ground 1 thus fails.

VII. GROUND 2 FAILS: CLAIMS 1, 2, 4, 15, AND 20-22 ARE NON-OBVIOUS OVER AHMAD ALONE

Petitioner also asserts that “to the extent Ahmad’s teachings are not anticipatory, they would have rendered the claimed limitation obvious.” (Pet. at 36.) Petitioner’s argument that Ahmad, as a standalone reference, renders Claims 1, 2, 4, 15, and 20-22 obvious fails.

A. Ahmad Is Not Enabled And This Fatal Deficiency Is Not Remedied By Combining Ahmad With The Knowledge Of A POSA

The Federal Circuit has held that “a standalone § 103 reference must enable the portions of its disclosure being relied upon.” *Raytheon Techs. Corp. v. GE*, 993 F.3d 1374, 1381 (Fed. Cir. 2021) (citing *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 297 (Fed. Cir. 1985); *In re Hoeksema*, 399 F.2d 269, 274 (C.C.P.A. 1968)). In *Ashland Oil*, the Federal Circuit instructed that “[t]he test of whether a particular compound described in the prior art may have been relied upon to show that the claimed subject matter at issue would have been obvious is whether the prior art provided an enabling disclosure with respect to the disclosed prior art compound.” 776 F.2d at 297. The Federal Circuit further instructed that this enablement requirement is “the same standard applied to anticipatory references.” *Raytheon*, 993 F.3d at 1381.

Petitioner relies on Ahmad’s disclosure and knowledge of a POSA *only* for:

- 1) the higher activity of the Z-isomer as compared to the E-isomer (citing EX1020 (McConville Decl.) and EX1004 (Liu) at ¶ 4); and

2) endoxifen's sensitivity to the acidic environment of the stomach (citing EX1020 (McConville Decl.), Ahmad 2010 (EX1006), the Zonalta drug label (EX1014), Ahmad 2016 (EX2018), and Milroy² (EX1019)).

(*See* Pet. at 37; *see also* ID at 19.)

Petitioner asserts that “[a] POSA would have a reasonable expectation of success in arriving at the claimed invention, as both forming (Z)-endoxifen and enteric capsules were well known in the art.” (Pet. at 37.) Petitioner does not argue that other prior art or specific knowledge of a POSA regarding synthesis of a 90% pure (Z)-endoxifen composition is necessary. Petitioner has not identified any other teaching or knowledge that a POSA would rely on in combination with Ahmad to come up with the invention recited in the challenged claims of the ’334 patent.

Nowhere 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. Although Petitioner did not advance this argument relying on Liu, the Board referred to this argument in the ID. (*See* ID at 20 (“[A] POSA would have had reason to use 90% (Z)-endoxifen as taught by Amahd with a reasonable expectation of success because it was known to be more active at estrogen receptors

² On its face, Milroy bears a publication date of 2018, *after* the September 11, 2017 priority date of the ’334 patent. Thus, the teachings of Milroy would not be available to a POSA as of the priority date of the ’334 patent.

and ***forming 90% pure (Z)-endoxifen was well known in the art, as evidenced at least by Liu.***” (citing EX1020 (McConville Decl.) at ¶¶ 54, 62, 68) (emphasis added)).) Neither Liu nor Paragraph 54 of Dr. McConville’s Declaration is referenced anywhere in the two paragraphs in the Petition setting forth Petitioner’s obviousness argument for Claims 1 and 15. (*See* Pet. at 37). Petitioner did not address the knowledge of a POSA with respect to synthesizing 90% pure (Z)-endoxifen. Similarly, Petitioner did not advance an obviousness ground combining Ahmad and Liu. The burden of persuasion remains on Petitioner to demonstrate unpatentability and the Board cannot “raise . . . unpatentability theories never presented by the petitioner and not supported by record evidence.” *In re Magnum Oil Tools Int’l, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016); *see also Sanofi-Aventis Deutschland GmbH v. Mylan Pharms. Inc.*, 66 F.4th 1373 (Fed. Cir. 2023) (reversing PTAB’s obviousness determination that relied on an argument not advanced by Petitioner).

Even if, assuming *arguendo*, that Liu or Song are evaluated as supplying background knowledge, a POSA could not rely on teachings from either of these benchtop synthesis methods to modify Ahmad in order to arrive at the claimed invention of the ’334 patent. (Davies POR Decl. at ¶¶ 154-156.) Liu describes a very different synthetic pathway to that of the ’334 patent as well as to the synthetic

pathway of Ahmad, which includes different starting materials and different crystallization parameters, and further results in impracticably low yields. (*Id.* at ¶¶ 87, 154-55.) Liu does not describe an oral formulation, and there is no teaching about the stability of the resulting endoxifen compound. Liu is also silent as to the presence of any residual solvents or impurities which could make the resulting endoxifen product unsuitable for a pharmaceutical formulation. (*Id.* at ¶ 155.) Finally, the two different synthetic pathways of Ahmad and Liu would likely result in different impurity profiles and different stability profiles. (*Id.* at ¶ 87.)

Song is even more problematic. As Dr. Davies explains, Song does not disclose a synthetic method of creating highly pure (Z)-endoxifen as a result of experimental error. (*Id.* at ¶ 97.) Song relies on incorrect analysis of nuclear magnetic resonance (NMR) spectroscopy data to characterize the final product, and it is more likely that Song describes a method of synthesizing highly pure (E)-endoxifen. (*Id.* at ¶¶ 98-104.) Dr. McConville agreed with Dr. Davies' analysis and conceded that "Song is not to be relied upon." (McConville Tr. at 93:9-94:5.) A POSA following the teachings Song would thus be directed away from the claimed invention.

For all the reasons discussed above, Ahmad—even combined with the background knowledge of a POSA—does not enable the POSA to make the 90% isomerically pure (Z)-endoxifen composition claimed in the '334 patent.

B. Petitioner Fails To Explain How A POSA Would Modify Ahmad And Why A POSA Would Have A Reasonable Expectation Of Success

Petitioner is obligated to demonstrate “that a skilled artisan would have had reason to combine the teaching of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success from doing so.” *PAR Pharm., Inc. v. TWi Pharms., Inc.*, 773 F.3d 1186, 1193 (Fed. Cir. 2014) (internal quotation marks omitted). Where a single prior art reference is relied on to render a claim obvious, there must be a motivation to modify its teachings to achieve the claimed invention based on the knowledge of a POSA, the reference itself, or from the nature of the problem to be solved to support the obviousness conclusion. *See SIBIA Neurosciences, Inc. v. Cadus Pharm. Corp.*, 225 F.3d 1349, 1356 (Fed. Cir. 2000); *see also Game & Tech Co. v. Activision Blizzard Inc.*, 926 F.3d 1370, 1381 (Fed. Cir. 2019) (“[A] patent can be obvious in light of a single prior art reference *if it would have been obvious to modify that reference to arrive at the patented invention.*”) (emphasis added) (citation omitted).

The patent itself cannot be used as a roadmap to modify the prior art to achieve the claimed invention and this hindsight reconstruction must be avoided. *In re*

Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig., 676 F.3d 1063, 1070-71 (Fed. Cir. 2012) (“Where, however, a defendant urges an obviousness finding by merely throwing metaphorical darts at a board in hopes of arriving at a successful result, but the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful, courts should reject hindsight claims of obviousness.”) (internal citation and quotation marks omitted).

A reasonable expectation of success requires more than a trial-by-error process where a POSA “merely . . . var[ies] all parameters or tr[ies] each of numerous possible choices until . . . possibly arriv[ing] at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.” *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1365 (Fed. Cir. 2007) (internal citation omitted).

The references relied upon by Petitioner contain contrary and even erroneous teachings, which ultimately would have served to confuse a POSA seeking to produce a pure (Z)-endoxifen composition rather than providing a reasonable expectation of success. For example, Song (EX1005) erroneously claims to teach a method of purifying (Z)-endoxifen, which according to Dr. Davies and Dr. McConville, actually resulted in highly purified (E)-endoxifen (Davies POR Decl.

at ¶ 103; McConville Tr. at 93:15-94:5), and Ahmad's few examples teach producing a composition with more (E)-endoxifen than (Z)-endoxifen. (Davies POR Decl. at ¶ 76.) Further, the synthetic methods of Ahmad and Lui are different from each other (Davies POR Decl. at ¶¶ 135, 154), 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. In view of these various inconsistent and erroneous teachings, Dr. Davies concludes that "a POSA would not have had a reasonable expectation of success in producing the 90% pure (Z)-endoxifen of the '334 patent from Ahmad (EX1003)—even, or especially, in light of the teachings of Song (EX1005) and Liu (EX1004)." (Davies POR Decl. at ¶ 162.)

C. Ahmad Does Not Render Claims 1, 2, 4, 15 And 20-22 Obvious

1. Independent Claims 1, 15

As discussed above, the Petition devotes only two paragraphs to explaining how Ahmad renders independent Claims 1 and 15 obvious. (Pet. at 37.) Petitioner asserts "[a] POSA would have been motivated to use 90% (Z)-endoxifen as taught by Ahmad because it was known that this form was more active at estrogen receptors." (*Id.*) While it is true that the (Z)-isomer is more active, Petitioner provides no explanation for *why* a POSA would be motivated to specifically increase purity from "at least 80%" to "at least 90%" purity. Even if a POSA was motivated

to achieve at least 90% purity, Petitioner provides no explanation as to *what* a POSA would modify to achieve the claimed 90% (Z)-endoxifen composition. As with Ground 1, this fact holds true whether or not the Board applies its proposed broad construction of “the compound of Formula (III) is (Z)-endoxifen.” Ahmad fails to suggest how a POSA would modify the teachings to achieve 90% pure (Z)-endoxifen composition, whether free base or citrate salt. The Board declined to address this argument at the institution stage, stating “we find those issues are better evaluated once the record has been fully developed at trial for the same reasons stated with respect to Ground 1.” (ID at 20.)

Petitioner also states that “[a] POSA would have had a reasonable expectation of success in arriving at the claimed limitation, as both forming (Z)-endoxifen and enteric capsules were well known in the art.” (Pet. at 37.) The Petition fails to explain *how* a POSA would use Ahmad to get to the 90% (Z)-endoxifen required by independent Claims 1 and 15. (Davies POR Decl. at ¶¶ 151, 161.)

Ahmad would not provide a POSA with a reasonable expectation of success in achieving a 90% (Z)-endoxifen composition for multiple reasons. First, A POSA following the synthetic method set forth in Ahmad would, at best, achieve an estimated 1:1 isomeric mixture of (E)-endoxifen and (Z)-endoxifen because Ahmad lacks an initial step for (Z)-endoxifen purification. (*Id.* at ¶ 77.)

Second, Ahmad fails to appreciate the importance of an isomerically pure (Z)-endoxifen composition that would equilibrate to a mixture of (E)-endoxifen and (Z)-endoxifen at ambient temperatures and humidity. (*Id.* at ¶¶ 56, 81.) Ahmad is silent as to the stability of the resulting endoxifen citrate salt. Having not appreciated the significance of these instability issues, Ahmad cannot contemplate methods for preventing the conversion of (Z)-endoxifen to a mixture of (E)-endoxifen and (Z)-endoxifen, as taught only in the '334 patent. Instead, Ahmad does the opposite by dissolving its endoxifen product in acid, which according to Dr. Davies “promotes undesirable isomerization from (Z)-endoxifen to an equilibrated mixture of (E)-endoxifen and (Z)-endoxifen.” (Davies POR Decl. at ¶ 81.) Thus, if anything, Ahmad teaches away from a formulation of highly pure (Z)-endoxifen.

Third, Ahmad describes only methods of purifying endoxifen with ethyl acetate, which would result in an isomerically enriched (E)-endoxifen solid. (*Id.* at ¶¶ 76-77.) This teaches away from the claimed invention.

Fourth, Ahmad teaches that a preferred embodiment is endoxifen in the form of a salt, (EX1003 at 2:26-27), and claims a citrate salt oral formulation, (*id.* at 30:60-62). The synthesis of a citrate salt would likely involve dissolving the purified (Z)-endoxifen solid in a citric acid solution, which would promote the acid-promoted isomerization of (Z)-endoxifen to (E)-endoxifen. (Davies POR Decl. at ¶ 76.)

The Petition is silent on **how** a POSA would modify Ahmad to overcome any of these issues.

2. Dependent Claims 2, 4, 20-22

As with Ground 1, each of these dependent claims requires at least 90% (Z)-endoxifen, which is not rendered obvious by Ahmad. Because neither Claim 1 nor Claim 15 is obvious in light of Ahmad, Claims 2, 4, and 20-22 are similarly not obvious in light of Ahmad (EX1003). “A fortiori, dependent claim 3 [is] nonobvious (and novel) because it contain[s] all the limitations of claim 1,” which was held to be nonobvious, “plus a further limitation.” *See, e.g., Hartness Int’l, Inc. v. Simplimatic Eng’g Co.*, 819 F.2d 1100, 1108 (Fed. Cir. 1987); *In re Fine*, 837 F.2d 1071, 1076 (Fed. Cir. 1988) (holding that a claim that depends from a non-obvious independent claim is non-obvious because it contains all the limitations of the independent claim, plus a further limitation).

Ground 2 thus fails.

VIII. GROUND 3 FAILS: CLAIMS 5-8, 16, AND 17 ARE NON-OBVIOUS OVER AHMAD IN VIEW OF COLE

Ground 3 challenges the patentability of Claims 5-8, 16, and 17 as obvious by Ahmad in view of Cole (EX1008). The combination of Ahmad and Cole, however, fails to render the challenged claims obvious for at least two reasons.

First, as explained in Patent Owner's Preliminary Response and as detailed above, Ahmad fails to teach a formulation comprising an endoxifen composition wherein "at least 90% by weight of the compound of Formula (III) is (Z)-endoxifen" as required by independent Claims 1 and 15. (*See* POPR at 32-37; Davies POR Decl. at ¶ 136.) Because it is axiomatic that a dependent claim is non-obvious if the independent claim it depends therefrom is non-obvious, Petitioner's Ground 3 fails for the same reason that Grounds 1 and 2 fail. *See SynQor, Inc. v. Artesyn Techs., Inc.*, 709 F.3d 1365, 1375 (Fed. Cir. 2013).

Second, and once again, there is a failure to establish motivation or any reasonable expectation of success in combining Ahmad with Cole to achieve an oral formulation of at least 90% (Z)-endoxifen with the desired characteristics. *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007) (obviousness requires "a showing that the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention"). For example, the Petitioner and the ID fail to explain why a POSA would have a reasonable expectation of success in creating enteric formulations comprising at least 90% (Z)-endoxifen beyond the fact that Cole is incorporated by reference in the '334 patent. (ID at 26; *see* Davies POR Decl. at ¶¶ 163-168.) Further, there is no basis for Petitioner's hindsight-driven contention—which was relied on in the ID,

(*see ID at 26*)—that a POSA would have been motivated to combine Ahmad's formulation with Cole's enteric coating to achieve the claimed dissolution profile. *See, e.g., Amerigen Pharm. Ltd. v. UCB Pharma GmbH*, 913 F.3d 1076, 1089 (Fed. Cir. 2019) (“[W]orking backwards from [a] compound, with the benefit of hindsight, once one is aware of it does not render it obvious.”).

As explained above, Ahmad fails to enable a synthetic pathway to generate 90% pure (Z)-endoxifen, whereas Cole does not even mention “endoxifen.” (Davies POR Decl. at ¶ 164.) Dr. McConville agreed that Cole describes enteric coated paracetamol, (McConville Tr. at 100:19-22), and does not mention or refer to endoxifen, (*id.* at 101:21-102:20). Specifically, Cole does not describe whether an enteric coated endoxifen capsule would provide a sustained action over a longer period of time. (Davies POR Decl. at ¶¶ 164, 166.)

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

would interact. (Davies POR Decl. at ¶ 166.) Dr. McConville did acknowledge that HPMC and enteric coatings can be electrostatically charged. (McConville Tr. at 108:14-109:5.) Yet this electrostatic charge could impact the stability of a (Z)-endoxifen free base or salt. (Davies POR Decl. at ¶ 164.) A POSA would also need to consider the variation in release profiles for salts as compared to corresponding free acids or bases of a given oral dosage form. (*Id.* at ¶ 167.)

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

For at least these reasons, challenged Claims 5-8, 16, and 17 are not obvious over EX1003 (Ahmad) in view of EX1008 (Cole).

Ground 3 thus fails.

IX. GROUND 4 FAILS: THE COMBINATION OF AHMAD AND BENAMEUR DOES NOT RENDER CLAIM 3 OBVIOUS

Ground 4 challenges the patentability of Claim 3 as obvious by Ahmad (EX1003) in view of Benameur (EX1010). As with Ground 3, challenged Claim 3 cannot be obvious because Ahmad fails to anticipate or render obvious the independent Claim 1 on which Claim 3 depends.

Additionally, the combination of Ahmad and Benameur does not render Claim 3 obvious because there is no motivation to combine these references to achieve an uncoated enteric capsule of the claimed formulation. Claim 3 recites “[t]he oral formulation of claim 1, wherein the enteric capsule is uncoated,” (EX1001 at 98:34-35), while Claim 1 requires “[a]n oral formulation comprising an endoxifen composition encapsulated in an enteric capsule” (*see id.* at 98:13-31). In the ID, the Board construed “enteric capsule” to mean:

[A] capsule with one or more enteric coating agent[s] or an intrinsically enteric capsule that does not need an additional coating to provide the enteric property to control or delay disintegration and absorption of the compositions comprising endoxifen or salts thereof in the gastrointestinal tract and thereby provide a sustained action over a longer period of time.

(*See ID* at 9-10.)

Benameur describes enteric capsule drug delivery technology for uncoated oral formulations of esomeprazole. (EX1010 (Benameur) at 1.) Esomeprazole is unrelated to endoxifen, and Dr. McConville testified that he was unsure of the positive or negative charge of the esomeprazole tested in Benameur. (McConville Tr. at 112:4-113:1.) 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. A POSA would not extrapolate the results from Benameur to an unrelated compound. (Davies POR Decl. at ¶¶ 172-73.) Dr. McConville testified

that “of course” a POSA would have to test the pharmacokinetics of (Z)-endoxifen to determine this. (McConville Tr. at 114:19-116:4.)

The Petitioner and the Board fail to identify any teaching in Ahmad that suggests the desirability of using an uncoated capsule. Not only is motivation to combine lacking, but Petitioner also failed to adequately explain why a POSA would have a reasonable expectation of success, given the inherent instability of (Z)-endoxifen. (Davies POR Decl. at ¶ 172.) POSA would not consider combining Ahmad and Benameur to attain the desired highly pure (Z)-endoxifen formulation that is effective for oral formulations.

Accordingly, for at least these reasons, Claim 3 is patentable and non-obvious over Ahmad (EX1003) in view of Benameur (EX1010).

X. GROUND 5 FAILS: CLAIMS 9-13 ARE NON-OBVIOUS OVER AHMAD IN VIEW OF STEGEMANN AND/OR THE HPE

Ground 5 challenges the patentability of Claims 9-13 as obvious by Ahmad (EX1003) in view of Stegemann (EX1011) and/or the Handbook of Pharmaceutical Excipients (EX1012). At the outset, these challenged claims cannot be obvious because, as explained above, the independent claim they rely on is non-obvious. *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992).

Beyond this fatal flaw, these challenged claims are also non-obvious because there is a complete lack of explanation as to why a POSA would be motivated to

combine these references with any reasonable expectation of success. *In re Magnum Oil*, 829 F.3d at 1380 (Petitioner must “articulate specific reasoning, based on evidence of record, to support the legal conclusion of obviousness”). Neither reference describes oral formulations comprising endoxifen, as conceded by Dr. McConville, (McConville Tr. at 119:4-17; 123:16-124:4), or provides a motivation to combine the gel capsules or pharmaceutical excipients with an endoxifen composition comprising at least 90% (Z)-endoxifen. (Davies POR Decl. at ¶¶ 176, 179.)

Indeed, the Petitioner and the Board conclude—without explanation or evidence in support thereof—that a POSA would have been motivated to use each recited excipient of Stegemann and/or the HPE “for its normal use” with a reasonable expectation of success because these excipients were normally used in the art. *See In re Magnum Oil*, 829 F.3d at 1380 (“To satisfy its burden of proving obviousness, a petitioner cannot employ mere conclusory statements.”). But this circular reasoning ignores that (Z)-endoxifen is an inherently unstable compound under various commonly used conditions. (Davies POR Decl. at ¶¶ 55, 85.) A POSA would not simply choose listed excipients based on their “normal” or “predictable” use when creating a highly pure and stable (Z)-endoxifen formulation because of the unpredictable interactions between endoxifen and the various listed excipients. (*Id.*

at ¶¶ 178-79.) Dr. McConville agreed that a POSA would consider potential interactions between (Z)-endoxifen and any excipients when formulating drug product. (McConville Tr. at 120:16-20.)

Formulation science is unpredictable, *AstraZeneca Pharms. LP v. Anchen Pharms., Inc.*, 2012 U.S. Dist. LEXIS 43989, at *131 (D.N.J. 2012) *aff'd*, 498 Fed. Appx. 999 (Fed. Cir. 2013), and a POSA would require additional motivation beyond mere conclusory statements to combine Ahmad's formulation with the various excipients listed in Stegemann and/or the HPE to achieve the claimed highly pure (Z)-endoxifen. *See Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 965 (Fed. Cir. 2014) (prior art must guide artisans to "which of many possible choices may be successful"). Dr. McConville testified that "well, there's a few moving parts to this" when asked to describe how a POSA would determine which excipients to use in a 90% (Z)-endoxifen composition. (McConville Tr. at 119:19-120:15.)

For at least these reasons, challenged Claims 9-13 as non-obvious over Ahmad (EX1003) in view of Stegemann (EX1011) and/or the Handbook of Pharmaceutical Excipients (EX1012).

Ground 5 thus fails.

XI. GROUND 6 FAILS: THE COMBINATION OF AHMAD, AHMAD 2010, AND AHMAD 2012 DOES NOT RENDER CLAIMS 14, 18, OR 19 OBVIOUS

A. Claim 14 Is Not Obvious Over Ahmad, Ahmad 2010, And Ahmad 2012

Like Grounds 3-5 above, challenged Claim 14 of Ground 6 is non-obvious because independent Claims 1 and 15 are non-obvious and not anticipated. *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008). Beyond this, Claim 14 is also non-obvious over Ahmad in view of Ahmad 2010 (EX1006) and Ahmad 2012 (EX1007) because it would not have been obvious to a POSA to apply the dosing information taught by Ahmad 2010 and Ahmad 2012 to achieve a 90% pure (Z)-endoxifen formulation. As with the other grounds, this conclusion is true whether or not the Board applies its proposed broad construction of “the compound of Formula (III) is (Z)-endoxifen.” There is no combination of Ahmad, Ahmad 2010, or Ahmad 2012 that would render the dosing limitation of Claim 14 obvious, whether the 90% pure (Z)-endoxifen composition is free base or salt.

(Z)-endoxifen is the more active isomer of endoxifen. (ID at 28; *see* McConville Tr. at 129:3-5.) Dr. McConville testified that neither Ahmad 2010 nor Ahmad 2012 specifies the isomeric purity of the endoxifen citrate compound that was administered to patients. (McConville Tr. at 126:4-17; 138:14-22; 141:5-15.)

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

For at least these reasons, challenged Claim 14 is non-obvious over Ahmad (EX1003) in view of Ahmad 2010 (EX1006) and Ahmad 2012 (EX1007).

B. The Board Correctly Concluded That Petitioner Did Not Meet Its Burden To Establish That Claims 18 And 19 Are Obvious

Ground 6 also challenges Claims 18 and 19 as obvious over Ahmad (EX1003) in view of Ahmad 2010 (EX1006) and Ahmad 2012 (EX1007). However, Neither Ahmad 2010 nor Ahmad 2012 describe pharmacokinetic properties of a 90% (Z)-endoxifen formulation. Petitioner simply ignores that the claimed 90% (Z)-endoxifen composition of the '334 patent and the prior art formulations of an

unknown and uncharacterized mixture of (E)-endoxifen citrate and (Z)-endoxifen citrate are not identical. Moreover, Petitioner's obviousness attack on Claims 18 and 19 fails even under the Board's proposed broad construction of "the compound of Formula (III) is (Z)-endoxifen."

As pointed out in Patent Owner's Preliminary Response, Petitioner argues that the pharmacokinetic limitations of Claims 18 and 19—area under curve (AUC_{0-inf}) for Claim 18 and maximum blood plasma concentration (C_{max}) for Claim 19—would be the "***inherent result*** of dosing the formulations of Ahmad within the dosage ranges taught by Ahmad 2010 and 2012." (See POPR at 53 (citing Pet. at 55-56) (emphasis added).) "Inherent obviousness is present 'only when the limitation at issue is the '*natural result*' of the combination of prior art elements. (ID at 29 (citing *Par Pharm.*, 773 F.3d at 1195 (emphasis in original)).) The Board further determined that the Petition "has not explained sufficiently why a POSA would understand the recited pharmacokinetic profiles of the 90% pure (Z)-endoxifen of the claims would be the "natural result" of the use of Ahmad 2010's unknown mixture of endoxifen [citrate]." (ID at 29.)

Petitioner provides no evidence to support the allegation that the pharmacokinetic data reported in Ahmad 2010 would be the "natural result" of administering the claimed 90% endoxifen composition of the '334 patent. This

allegation is undermined by data in Ahmad 2010 and 2012, data in the '334 patent, and Dr. McConville's testimony.

First, a comparison of the pharmacokinetic data in Ahmad 2010 and Ahmad 2012 demonstrates that there is not one "natural result" of administering an endoxifen citrate formulation with an unknown ratio of (Z) and (E) isomers. Ahmad 2010 reports the following data for a 4.0 mg endoxifen citrate dosage form:

Table 1 Endoxifen doses and pharmacokinetic parameters

Dose	C_{max} (ng/ml)	$AUC_{0-\infty}$ (ng-h/ml)	$t_{1/2}$ (h (CV%))	V_z (l)	CI (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 \pm 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 $V_z = 400$ l and $CI = 5.0$ 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.

^aApparent $t_{1/2}$ estimated from terminal exponential phase of the concentration-vs.-time curve.

(EX1006 (Ahmad 2010) at 4 (highlighting added).)

Focusing AUC and C_{max} , Ahmad 2012 reports very different pharmacokinetic data for a 4 mg endoxifen citrate dosage form:

Parameters (units)	Mean \pm SD		
	2 mg	4 mg	8 mg
T _{max} (h)*	5 (3.0-12.0)	5 (4.0-6.0)	5 (4.0-6.0)
C _{min ss} (ng/mL)	15.7 \pm 6.4	44.0 \pm 11.6	80.4 \pm 26.7
C _{max ss} (ng/mL)	24.5 \pm 7.3	75.9 \pm 18.5	134.1 \pm 32.1
AUC _{tau} (ng.h/mL)	445.3 \pm 146.2	1363.3 \pm 396.3	2322.6 \pm 619.8
PTF (%)	50.8 \pm 19.0	56.5 \pm 17.9	57.6 \pm 14.6
C _{av ss} (ng/mL)	18.6 \pm 6.1	56.8 \pm 16.5	96.8 \pm 25.8

*Data presented as median (range)

(EX1007 (Ahmad 2012) at 2 (highlighting added).)

The C_{max} data in Ahmad 2012 does not fall within the range recited by Claim 19. Even Petitioner's own evidence demonstrates that the pharmacokinetic results reported in Ahmad 2010 are not the "natural result" of administering a 4 mg endoxifen citrate dosage form with an unknown mixture of (Z) and (E) isomers.

Second, Table 22 of the '334 patent compares data of a different pharmacokinetic parameter (C_{ss}, average concentration at steady state) between the claimed 90% pure (Z)-endoxifen and "published literature" that includes Ahmad 2010 and Ahmad 2012. (EX1001 at 95:49-96:12.) Table 22 demonstrates that the pharmacokinetic profile of the claimed invention is not identical to the pharmacokinetic profile of the formulations tested in EX1006 and EX1007. The claimed invention demonstrates **a much greater** bioavailability. (See *id.* at 95:59-62

(showing the claimed formulation exhibited 154%, 204%, and 150% higher average drug concentration at steady state than the Ahmad 2010 and Ahmad 2012 formulations).)

Finally, a POSA would not expect different isomers and different formulations to exhibit identical pharmacokinetic properties. Dr. McConville testified that absorption rate, a pharmacokinetic component, “could vary, possibly, depending on the solubility – well dissolution, let’s say, the ionization state of the molecule in the gut. . . . There’s many factors that affect absorption.” (McConville Tr. at 41:14-19). He further explained that absorption “could be [different]” between endoxifen free base and endoxifen citrate and that a POSA would need to perform a comparative study to evaluate this. (*Id.* at 43:1-16.)

The Federal Circuit has cautioned that inherency “must be carefully circumscribed in the context of obviousness,” and “may not be established by probabilities or possibilities.” *Par Pharm.*, 773 F.3d at 1195. Given this evidence, Petitioner’s attempt to rely on inherency must fail and the Board was correct in finding that Petitioner had failed to carry its burden of proving that challenged Claims 18 and 19 are obvious over Ahmad (EX1003) in view of Ahmad 2010 (EX1006) and Ahmad 2012 (EX1007).

Ground 6 thus fails.

XII. SECONDARY CONSIDERATIONS

Secondary indicia of non-obviousness, including unexpected results, teaching away, and long felt need, further support a conclusion that the challenged claims are valid and non-obvious and that Grounds 2-6 fail.

Regarding unexpected results, the claimed compositions of 90% isomerically pure (Z)-endoxifen produced according to the methods of the '334 patent exhibit unexpected stability as compared to the endoxifen hydrochloride salt. (Davies POR Decl. at ¶¶ 189-90.) Example 11 demonstrates the surprising stability of the resulting (Z)-endoxifen free base with stability of at least 90% (Z)-endoxifen for “at least 9 months under conditions of ambient and high temperature and humidity.” (EX1001 at 82:42-49.) The bulk drug stability of (Z)-endoxifen is shown to be stable for at least 9 months at 5°C and 25°C at 60% relative humidity (RH) which is predictive of long-term stability (at least 18 months) at ambient temperatures. (*Id.* at 85:18-27.) The Petition ignores unexpected results wholly, and never addresses whether this stability was predicted or expected.

Other drugs in this class of compounds (known as “selective estrogen receptor modulators” or SERMs) are standardly formulated as salts, (*see* Davies POR Decl. at ¶ 191), for example:

- Tamoxifen: commercially available as Nolvadex (tamoxifen citrate salt tablets), (*see* EX2023), and Soltamox (tamoxifen citrate solution), (*see* EX2024);
- Raloxifene: commercially available as Evista (raloxifene hydrochloride salt tablets), (*see* EX2025); and
- Toremifene: commercially available as Fareston (toremifene citrate salt tablets), (*see* EX2026.)

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

In addition to this teaching away, the results of superior bioavailability of the oral free base formulations of the '334 patent were unexpected. A POSA would have expected the citrate salt oral formulations to demonstrate increased aqueous solubility and efficacy. (EX2016 (Buchanan) at 5.) However, as shown in the '334 patent, oral formulations comprising the free base of endoxifen surprisingly exhibited superior bioavailability as compared to oral formulations of endoxifen citrate. (EX1001 at 95:49-96:24; *see* Davies POR Decl. at ¶ 190.)

Regarding long-felt need, the '334 patent discusses the unmet medical need for new compositions and methods for the prevention and treatment of hormone-dependent breast and reproductive tract disorders, including cancer. (EX1001 at 2:50-54.) This unmet need is clear, especially in light of the other FDA-approved SERM drugs that have been on the market for decades, as well as Petitioner's own endoxifen citrate formulation. The enteric oral formulations comprising at least 90% (Z)-endoxifen compositions described in the '334 patent achieve superior bioavailability as compared to EX1006 and EX1007, (*see* EX1001 at 95:49-96:24), demonstrating the superior suitability of the claimed compositions for use as new pharmaceutical compositions for treatment and/or prevention of hormone-dependent breast and reproductive tract disorders. Petitioner similarly ignores long-felt need and never addresses the improved bioavailability shown in the '334 patent. (Davies POR Decl. at ¶ 188.)

These secondary indicia are commensurate with the '334 patent claims and there is a sufficient nexus between the claims of the '334 patent and the unexpected results and long felt need.

XIII. CONCLUSION

For all the reasons set forth above and in Patent Owner's Preliminary Response (Paper 7), Intas's Petition (Paper 1) fails to show that any challenged claim is unpatentable over the art cited in the instituted Grounds.

Patent Owner's Response
PGR2023-00043
U.S. Patent No. 11,572,334

Dated: April 24, 2024

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CERTIFICATE OF WORD COUNT

The undersigned hereby certifies that the foregoing Patent Owner's Response to Petition for Post-Grant Review complies with the type-volume limitations of 37 C.F.R. § 42.24(b). Excluding the items listed 37 C.F.R. § 42.24(a) as not included in the word count, and using the word count function of Microsoft Word, which was used to prepare the paper, the Patent Owner's Response contains 16,353 words.

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that on this 24th day of April 2024, a true copy of the foregoing materials was served on Petitioner INTAS PHARMACEUTICALS LTD. by emailing a copy to counsel of record for Petitioner at the email addresses listed below:

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