UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

INTAS PHARMACEUTICALS LTD.,
Petitioner,

v.

ATOSSA THERAPEUTICS, INC.,
Patent Owner.

PGR2023-00043
Patent 11,572,334 B2

Before SHERIDAN K. SNEDDEN, TINA E. HULSE, and JAMIE T. WISZ, *Administrative Patent Judges.*

HULSE, *Administrative Patent Judge*.

JUDGMENT
Final Written Decision
Determining All Challenged Claims Unpatentable
35 U.S.C. § 328(a)

I. INTRODUCTION

Intas Pharmaceuticals Ltd. ("Petitioner") filed a Petition requesting post-grant review of claims 1–22 of U.S. Patent No. 11,572,334 B2 (Ex. 1001, "the '334 Patent"), which is owned by Atossa Therapeutics, Inc. ("Patent Owner"). Paper 1 ("Pet."). After considering the Petition, Preliminary Response (Paper 7), and Petitioner's pre-institution Reply (Paper 10), we instituted post-grant review of the challenged claims of the '334 Patent. Paper 11 ("Institution Decision" or "Dec. Inst.").

After institution, Patent Owner filed a Response (Paper 14, "PO Resp."), Petitioner filed a Reply (Paper 16, "Pet. Reply"), and Patent Owner filed a Sur-reply (Paper 21, "PO Sur-reply"). An oral argument was held in this proceeding on October 30, 2024, and a copy of the transcript was entered into the record. Paper 34 ("Tr.").

We have jurisdiction under 35 U.S.C. § 6, and we issue this Final Written Decision under 35 U.S.C. § 328(a) and 37 C.F.R. § 42.73. For the reasons discussed below, we conclude that Petitioner has proven by a preponderance of the evidence that claims 1–22 of the '334 Patent are unpatentable.

A. Real Parties-in-Interest

Petitioner identifies itself and Accord Healthcare, Inc. (a U.S. subsidiary of Petitioner) as the real parties-in-interest to this proceeding. Pet. 1. Petitioner also states that "[o]ther parties who may be interested in the outcome of this PGR include the National Cancer Institute/National Institutes of Health Clinical Center, Eli Lilly and Company, Pfizer Inc., Jina Pharmaceuticals Inc., Cheiljedang Corp., Alchem Laboratories Corporation, and Lambda Therapeutic Research Limited." *Id.*

Patent Owner identifies itself as the real party-in-interest. Paper 5, 1.

B. Related Proceedings

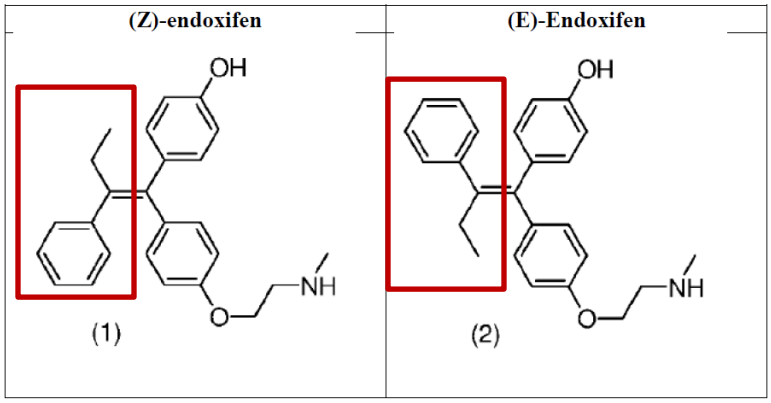
Petitioner states that there are no current related matters. Pet. 1. Patent Owner states that the '334 Patent is not involved in any related litigation matters, but identifies various patent applications related to the '334 Patent. Paper 5, 1.

C. The '334 Patent

The '334 Patent, entitled "Methods for Making and Using Endoxifen," issued on February 7, 2023, and claims the benefit of several continuation and provisional applications, the earliest of which was filed on September 11, 2017. Ex. 1001, codes (54), (63), (64). According to the Abstract, the '334 Patent "provides industrially scalable methods of making (Z)-endoxifen or a salt thereof, crystalline forms of endoxif[e]n, and compositions comprising them," as well as "methods for treating hormone-dependent breast and hormone-dependent reproductive tract disorders." *Id.*, Abstract.

Endoxifen is the active metabolite of tamoxifen, a selective estrogen receptor modulator that is used to treat endocrine responsive breast cancer, i.e., hormone-dependent or hormone-sensitive breast cancer. *Id.* at 1:63–2:9. Endoxifen has two isomers,[1] (E)-endoxifen and (Z)-endoxifen, illustrated below:

[1] An isomer has the same constituent atoms connected to the same atoms, but the three-dimensional spatial arrangement of those atoms differs. Ex. 1020 ¶¶ 20–21.



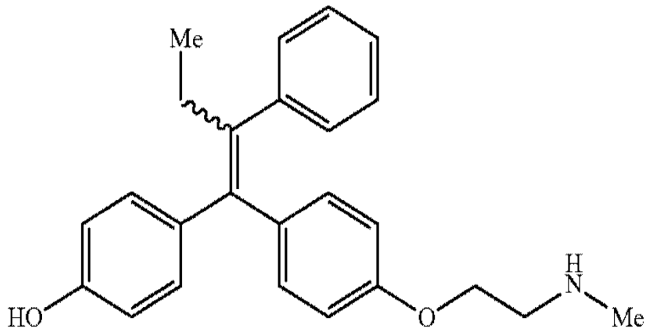
The annotated illustration above depicts the chemical structure of (Z)-endoxifen on the left and (E)-endoxifen on the right with red boxes around the portion of the isomers that have differing spatial orientations. Ex. 1020 ¶ 21.

According to the '334 Patent Specification, "[i]t is widely accepted that (Z)-endoxifen is the main active metabolite responsible for the clinical efficacy of tamoxifen." Ex. 1001, 2:36–38. "Several cytochrome P450 (CYP) mutations have been proposed to cause reduced conversion of tamoxifen to its active metabolite, endoxifen, and reduce tamoxifen efficacy and increase resistance to the drug," but "changes in the CYP genotype do not fully explain the tamoxifen resistance and the reduced endoxifen levels observed in some subjects." *Id.* at 2:7–22. Accordingly, the Specification states that several alternatives to tamoxifen are being developed for treating breast cancer. *Id.* at 2:23–24.

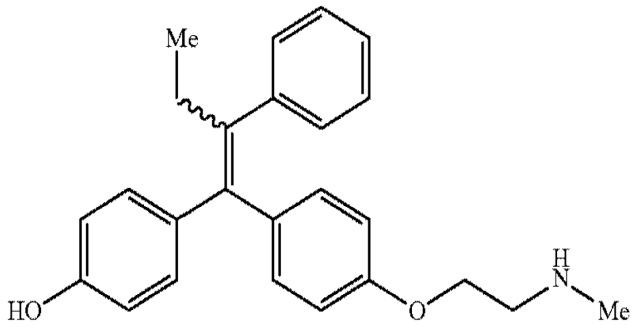
The Specification states that although hydrochloride and citrate salts of endoxifen are known in the art and being evaluated for metastatic cancer, "there remains [an] unmet medical need for new compositions and methods for the treatment and/or prevention of hormone-dependent breast and reproductive tract (gynecologic) disorders." *Id.* at 2:39–53.

D. Illustrative Claim

Petitioner challenges claims 1–22 of the '334 Patent, of which claims 1 and 15 are independent. Claims 1 and 15 are illustrative and are reproduced below:

> 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.

Ex. 1001, 98:13–30.

> 15. A method of delivering (Z)-endoxifen to a subject, the method comprising administering to the subject an oral formulation comprising an endoxifen composition encapsulated in an enteric capsule, wherein the endoxifen composition comprises a compound of Formula (III):
>
> Formula (III)
>
> 
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wherein at least 90% by weight of the compound of Formula (III) is (Z)-endoxifen.

Id. at 99:7–26. Claims 2–14 depend directly or indirectly from claim 1. *Id.* at 98:31–99:6. And claims 16–22 depend directly or indirectly from claim 15. *Id.* at 99:27–100:28.

E. The Asserted Grounds of Unpatentability

Petitioner challenges claims 1–22 of the '334 Patent based on the grounds set forth in the table below.

Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
1, 2, 4, 15, 20–22	102	Ahmad[2]
1, 2, 4, 15, 20–22	103	Ahmad
5–8, 16, 17	103	Ahmad, Cole[3]
3	103	Ahmad, Benameur[4]
9–13	103	Ahmad, Stegemann,[5] HPE[6]
14, 18, 19	103	Ahmad, Ahmad 2010,[7] Ahmad 2012[8]

[2] Ahmad et al., US 9,333,190 B2, issued May 10, 2016. Ex. 1003 ("Ahmad").
[3] Cole, et al., *Enteric coated HPMC capsules designed to achieve intestinal targeting*, 231 INTL. J. PHARMACEUTICS 83–95 (2002). Ex. 1008 ("Cole").
[4] Hassan Benameur, *Capsule Technology: Enteric capsule drug delivery technology – Achieving Protection Without Coating*, 15 DRUG DEVELOPMENT & DELIVERY 34–37 (June 2015). Ex. 1010 ("Benameur").
[5] Stegemann et al., *Hard gelatin capsules today – and tomorrow*, Capsugel Library 3–23 (2d ed., 2002). Ex. 1011 ("Stegemann").
[6] HANDBOOK OF PHARMACEUTICAL EXCIPIENTS (Raymond C. Rowe et al. eds., 5th ed. 2006). Ex. 1012 ("HPE").
[7] Ahmad et al., *Endoxifen, a New Cornerstone of Breast Cancer Therapy: Demonstration of Safety, Tolerability, and Systemic Bioavailability in Healthy Human Subjects*, 88 CLINICAL PHARMACOLOGY & THERAPEUTICS 814–17 (Dec. 2010). Ex. 1006 ("Ahmad 2010").
[8] Ahmad et al., *Endoxifen for breast cancer: Multiple-dose, dose-escalation study characterizing pharmacokinetics and safety in metastatic breast*

Petitioner also relies on the Declarations of Jason McConville, Ph.D. (Exs. 1020, 1031) and Ron Bihovsky, Ph.D. (Ex. 1030). Patent Owner relies on the Declarations of Stephen Graham Davies, D. Phil. (Exs. 2001, 2020, 2029).

II. ELIGIBILITY FOR POST-GRANT REVIEW

Section 6(d) of the Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (Sept. 16, 2011) ("AIA") sets forth the post-grant review provisions, which apply only to patents subject to the first-inventor-to-file provisions of the AIA. AIA § 6(f)(2)(A) (stating the provisions of Section 6(d) "shall apply only to patents described in section 3(n)(1)"). Post-grant reviews are only available for patents that issue from applications "that contain[] or contained at any time . . . a claim to a claimed invention that has an effective filing date . . . on or after" March 16, 2013. AIA § 3(n)(1). Moreover, "[a] petition for a post-grant review may only be filed not later than the date that is 9 months after the date of the grant of the patent or of the issuance of a reissue patent (as the case may be)." 35 U.S.C. § 321(c). Petitioner has the burden of demonstrating eligibility for post-grant review. *See Mylan Pharms. Inc. v. Yeda Res. & Dev. Co.*, PGR2016-00010, Paper 9 at 10 (PTAB Aug. 15, 2016).

In our Institution Decision, we determined that the challenged claims are eligible for post-grant review. Dec. Inst. 6–7. That is, we found the earliest possible effective filing date of the challenged claims is September 11, 2017, and the Petition was filed less than nine months after the date the patent was granted. *Id.* Patent Owner did not contest these findings during

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cancer patients, 30 J. CLINICAL ONCOLOGY 3089 (2012 ASCO Annual Meeting Abstract) (May 20, 2012). Ex. 1007 ("Ahmad 2012").

trial. We, therefore, maintain that the '334 Patent is eligible for post-grant review. *Id.*

III. ANALYSIS OF GROUNDS

To prevail in this post-grant review of the challenged claims, Petitioner must prove unpatentability by a preponderance of the evidence. 35 U.S.C. § 326(e); 37 C.F.R. § 42.1(d). The petitioner has the burden from the onset to show with particularity why the challenged claims are unpatentable. *See Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016). This burden of persuasion never shifts to the patent owner. *See Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015) (discussing the burden of proof in *inter partes* review).

A. Person of Ordinary Skill in the Art

In determining the level of ordinary skill in the art, we consider the type of problems encountered in the art, the prior art solutions to those problems, the rapidity with which innovations are made, the sophistication of the technology, and the educational level of active workers in the field. *Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.*, 807 F.2d 955, 962 (Fed. Cir. 1986).

Petitioner asserts that a person of ordinary skill in the art ("POSA") would be "someone with a Ph.D. in pharmaceutical sciences or a closely related field and experience in research related to pharmaceutical dosage forms or someone with at least a Bachelor's or Master's degree in pharmaceutical sciences and three to five years of practical experience in formulating drugs." Pet. 9 (citing Ex. 1020 ¶ 27).

Patent Owner argues that Petitioner's definition of a person of ordinary skill in the art "ignores the complex chemistry at the center of the

'334 invention and should be rejected." Prelim. Resp. 12. Patent Owner contends that a person of ordinary skill in the art would have had "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" and "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 12–13 (citing Ex. 2001 ¶¶ 42–43).

As explained in our Institution Decision, we adopted Patent Owner's definition because we do not discern a substantive difference between the parties' respective definitions for the level of ordinary skill in the art—both definitions provide for a highly skilled POSA with experience in formulating drugs. Dec. Inst. 8. Petitioner's counsel confirmed during the hearing that there was no substantive difference between the parties' definitions. Tr. 7:25–8:5. Accordingly, we find the parties' respective definitions to be equivalent and consistent with the level of ordinary skill in the art as reflected by the prior art in this proceeding. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required "where the prior art itself reflects an appropriate level and a need for testimony is not shown" (*quoting Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985))). We, therefore, adopt Patent Owner's definition of a POSA.

Moreover, we find that Dr. McConville, Dr. Bihovsky, and Dr. Davies are all qualified to opine from the perspective of a skilled artisan as all are persons of at least ordinary skill in the art, based on either party's definition.

See Ex. 1020 ¶¶ 3–15; Ex. 2001 ¶¶ 4–11; Ex. 1002 ¶¶ 5–15; Ex. 2036 ¶¶ 5–11, App'x A; *see also Kyocera Senco Indus. Tools Inc. v. Int'l Trade Comm'n*, 22 F.4th 1369, 1376–77 (Fed. Cir. 2022) ("To offer expert testimony from the perspective of a skilled artisan in a patent case—like for claim construction, validity, or infringement—a witness must at least have ordinary skill in the art.").

B. Claim Construction

The Board applies the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. § 282(b). 37 C.F.R. § 42.200(b). Under that standard, claim terms "are generally given their ordinary and customary meaning" as understood by a person of ordinary skill in the art at the time of the invention. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc). Moreover, "claim terms need only be construed 'to the extent necessary to resolve the controversy.'" *See Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

In our Institution Decision, we construed sua sponte the term "the compound of Formula (III) is (Z)-endoxifen," because we disagreed with Patent Owner's argument that the phrase is limited to the free base form of (Z)-endoxifen. Dec. Inst. 10. We preliminarily held that for purposes of the Institution Decision, the construction of "the compound of Formula (III) is (Z)-endoxifen" includes the polymorphic, salt, free base, co-crystal and solvate forms of (Z)-endoxifen. *Id.* (citing Ex. 1001, 12:48–59). During trial, we asked the parties to brief the construction of the term. *See id.*; PO Resp. 19–27; Pet. Reply 2–3; PO Sur-reply 3–4.

Petitioner agrees with the Board's preliminary claim construction, contending that the Specification clarifies that the limitation "compound of Formula (III) is (Z)-endoxifen" encompasses not only the free base, but the salt forms, as well. Pet. Reply 2 (citing Ex. 1001, 12:48–52).

Patent Owner, on the other hand, contends that the Board's construction of "the compound of Formula (III) is (Z)-endoxifen" is overly broad, is not supported by the intrinsic record, and is inconsistent with the way a POSA would interpret the term. PO Resp. 19. Patent Owner further states that "the specification, properly read in conjunction with the claims themselves, supports a narrower construction . . . to include the (Z)-endoxifen free base" and exclude the salt and solvate forms. *Id.*; *see also* PO Sur-reply 3.

That said, the parties both state that it does not matter which construction we apply, as the outcome would be the same regardless. *See* PO Resp. 4; Pet. Reply 3.

Having considered the parties' respective arguments and evidence presented at trial, we find this to be a close case. Despite the ambiguities in the Specification, however, we modify our claim construction in favor of Patent Owner's interpretation.

We begin our analysis with the language of the claims, as defined by the Specification. Claim 1 recites "a compound of Formula (III)" and provides the structure of Formula (III). Ex. 1001, 98:15. Patent Owner contends that because the structure of Formula (III) depicts the free base form of endoxifen and not the salt form, our analysis should end there. PO Resp. 19–20. The Specification suggests otherwise, however, as it expressly defines "'a compound', such as compounds of . . . Formula (III) . . . [to] include the polymorphic, salt, free base, co-crystal, and solvate forms of the

formulas and/or compounds disclosed herein." Ex. 1001, 12:48–52; *see also id.* at 12:52–59 (stating "'compounds of Formula (III)' . . . include . . . the free base of the compounds of Formula (III), and/or the gluconate salts as described herein"). If "the compound of Formula (III)" were limited to the free base form, as shown in the structure of Formula (III), the Specification's definition of "the compound of Formula (III)," which includes the salt and solvate forms of Formula (III), could never be true. Thus, the structure of Formula (III) alone cannot provide the basis for limiting the claims to the free base form.

Nevertheless, although the "compound of Formula (III)" is defined broadly by the Specification, the claim further narrows "the compound of Formula (III)" to "(Z)-endoxifen." *Id.* at 98:29–30. The question, then, is whether "(Z)-endoxifen" should be construed broadly to include the free base and salt form, or if it should be limited to its free base form. Despite various inconsistencies in the Specification, we find on balance that the intrinsic evidence supports limiting the construction of "(Z)-endoxifen" to its free base form.

Patent Owner argues that because the Specification defines "endoxifen" as "4-hydroxy-N-desmethyl-tamoxifen," which lacks any mention of salts or solvates, the claims should be limited to a mixture of (Z)-endoxifen and (E)-endoxifen free base. PO Resp. 20. We disagree. If the use of "endoxifen" alone necessarily connotes the free base form of endoxifen, then the Specification would not have to distinguish "(Z)-endoxifen free base" from "(Z)-endoxifen HCL and (Z)-endoxifen citrate salts." *See, e.g.*, Ex. 1001, 82:3–5 ("Commercially endoxifen is available as an (E)/(Z) isomer free base mixture, as well as ≥98% (Z)-endoxifen HCL and (Z)-endoxifen citrate salts."); *see also id.* at 9:16–17 (stating "the

present disclosure provides a composition comprising (Z)-endoxifen free base or a salt thereof").

When read as a whole, however, we find compelling that the Specification consistently identifies (Z)-endoxifen salts as separate from (Z)-endoxifen. Throughout the Specification—including in the Abstract and the Summary of the Invention—the '334 Patent refers to "(Z)-endoxifen *and salts thereof*," suggesting that references to "(Z)-endoxifen" alone do not include the salt forms unless expressly identified as such. *See, e.g.*, *id.* at Abstract ("The present disclosure provides . . . methods of making (Z)-endoxifen or a salt thereof"), 2:60–62 (Summary of the Invention stating same); 6:4–6 (Summary of the Invention stating "process for manufacturing (Z)-endoxifen or salts thereof").

Moreover, the Specification states that although endoxifen is available commercially as an (E)/(Z) isomer free base mixture, as well as ≥98% (Z)-endoxifen HCL and (Z)-endoxifen citrate salts, "[t]here remains a need for (Z)-endoxifen free base preparations that are sufficiently stable for preparation of pharmaceutical compositions." *Id.* at 82:3–5, 82:37–39. Accordingly, the Specification states, "[p]rovided herein in the present disclosure are preparations of endoxifen free base that are . . . at least 90% (Z)-endoxifen free base." *Id.* at 82:43–45.

Taking the language of the claims and the Specification as a whole, we determine that the intrinsic evidence supports construing the limitation "the compound of Formula (III) is (Z)-endoxifen" to be limited to the (Z)-endoxifen free base form and excludes the salt and solvate forms.

We determine it is unnecessary to expressly construe any other claim terms for purposes of this Decision. *See Wellman*, 642 F.3d at 1361.

C. Ground 1: Alleged Anticipation by Ahmad

Petitioner asserts that claims 1, 2, 4, 15, and 20–22 of the '334 Patent are anticipated by Ahmad. Pet. 28–35. Patent Owner opposes, arguing that Ahmad does not enable the claimed invention. PO Resp. 27–51.

Having considered the arguments and evidence presented at trial, we determine Petitioner has shown by a preponderance of the evidence that those claims are anticipated by Ahmad.

1. Ahmad (Ex. 1003)

Ahmad is a U.S. patent entitled "Endoxifen Compositions and Methods," which issued on May 10, 2016, and claims priority to two provisional applications, the earliest of which was filed on November 22, 2006. Ex. 1003, codes (54), (45), (60). We, therefore, find Ahmad is prior art to the '334 Patent, and Patent Owner does not assert otherwise during trial. *See generally* PO Resp.; PO Sur-reply.

Ahmad describes "compositions containing endoxifen, formulations and liposomes of endoxifen, methods of preparation of such agents and formulations, and use of such agents and formulations for the treatment of breast cancer and other diseases susceptible to endoxifen." Ex. 1003, Abstract. Ahmad explains that "[r]ecently, endoxifen has been shown to be anti-estrogenic in breast cancer cells and to be more potent than Tamoxifen," which is a widely-used, anti-estrogenic drug prescribed for long-term, low-dose therapy of breast cancer. *Id.* at 1:64–66; *see also id.* at 1:36–39.

Ahmad describes methods of preparing a composition containing a therapeutically active amount of endoxifen in its free base or salt form. *Id.* at 2:21–26. Ahmad explains that endoxifen can be purified through crystallization and/or liquid chromatography to produce a purified preparation that contains predominantly E-isomer, predominantly Z-isomer,

or a mixture of E- and Z-isomers of endoxifen. *Id.* at 3:55–61, 11:17–23 ("The separation of E- and Z-isomers of endoxifen in the present invention can be done, e.g., by crystallization, or purification by liquid chromatography (LC), or high pressure liquid column chromatography (HPLC)."). In some embodiments, the composition comprises a tablet or a filled capsule that optionally comprises an enteric coating material. *Id.* at 3:62–4:44.

Ahmad states that "[o]ne object of the present invention is to provide E-endoxifen or Z-endoxifen with at least 80% purity, such as at least 90% pure or at least 95% pure or at least 98% pure or at least 99% pure or at least 100% pure." *Id.* at 12:14–17.

2. Legal Standard

Anticipation requires that "each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.'" *Id.* (citation omitted). Moreover, to anticipate, a prior art reference must "disclose[] 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." *Net MoneyIN, Inc. v. Verisign, Inc.*, 545 F.3d 1359, 1371 (Fed. Cir. 2008).

An 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." *In re Morsa*, 803 F.3d 1374, 1377 (Fed. Cir. 2015) (citing

In re Antor Media Corp., 689 F.3d 1282, 1289–90 (Fed. Cir. 2012)). To determine whether the requisite amount of experimentation is undue, we may consider the so-called *Wands* factors: (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. *See Elan Pharms., Inc. v. Mayo Foundation*, 346 F.3d 1051, 1054–55 (Fed. Cir. 2003) (quoting *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988)).

An anticipatory reference, however, "need not enable the claim in its entirety, but instead the reference need only enable a single embodiment of the claim." *In re Morsa*, 803 F.3d at 1377. Moreover, "a prior art reference must be considered together with the knowledge of one of ordinary skill in the pertinent art." *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994); *see also DeGeorge v. Bernier*, 768 F.2d 1318, 1323 (Fed. Cir. 1985) (finding a reference "need not . . . explain every detail since [it] is speaking to those skilled in the art"). Thus, additional references may be relied upon to show the claimed subject matter was in the public's possession. *In re Donohue*, 766 F.2d 531, 534 (Fed. Cir. 1985) (finding proper the examiner's anticipation rejection that relied upon two additional references to show the subject matter disclosed in the anticipatory reference was in the public's possession).

Moreover, the Federal Circuit has held that in AIA trial proceedings, prior art patents and publications are presumed to be enabled and the patent owner has the burden to prove nonenablement of that prior art. *Apple Inc. v. Corephotonics, Ltd.*, 861 F. App'x 443, 450 (Fed. Cir. 2021) (holding

"regardless of the forum, prior art patents and publications enjoy a presumption of enablement, and the patentee/applicant has the burden to prove nonenablement for such prior art"). As such, *Apple* instructs us that a petitioner need not provide evidence in its petition to show a prior art patent is enabling as part of its burden to prove anticipation. *Id.* at 449–50 (finding the Board erred in shifting the burden to the petitioner to provide evidence in its petition to show prior art patent publication was enabling). Thus, it is Patent Owner's burden to establish by a preponderance of the evidence that Ahmad is not enabling.

Before we turn to the substantive grounds, we must first resolve the parties' disputes over several legal issues regarding enablement. First, Patent Owner asserts that "[w]hile ***the claims*** of a prior art patent are presumed enabled, . . . [t]here is no presumption that every prophetic example in the specification is enabled, especially where that prophetic example is not explicitly claimed." PO Resp. 32 (citations omitted). This is an incorrect statement of the law. The Federal Circuit has clearly stated that "a presumption arises that both the claimed and unclaimed disclosures in a prior art patent are enabled." *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354–55 (Fed. Cir. 2003). Patent Owner may rebut that presumption, but that presumption of enablement exists nonetheless for both the claimed and unclaimed disclosures.

Second, the parties dispute the timeframe by which Ahmad must be enabling. Patent Owner asserts that "[e]nablement of a prior art patent is determined as of the effective filing date of the [prior art] patent." PO Resp. 45. Petitioner disagrees, asserting that a POSA need only have been able to make Ahmad's invention "prior to the 334 patent." Pet. Reply 7.

Patent Owner fails to cite any relevant case law that supports its position. The one case Patent Owner cites relates to enablement of the patent-in-suit under § 112, not that of a prior art reference under § 102. *See* PO Resp. 45 (citing *Plant Genetic Sys., N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1339 (Fed. Cir. 2003)). The Federal Circuit has made clear, however, that "the standard for what constitutes proper enablement of a prior art reference for purposes of anticipation under section 102 . . . differs from the enablement standard under section 112." *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1325 (Fed. Cir. 2005). Thus, we find Patent Owner misstates the law on the timing of enablement of an anticipatory reference.

Whether Petitioner's statement of the law is correct is less clear. In addressing enablement of an anticipatory reference under pre-AIA § 102(b),[9] the Federal Circuit held that the relevant timeframe for determining whether a prior art reference is enabling is one year before the effective filing date of the patent-in-suit. *See Bristol-Myers Squibb Co. v. Ben Venue Lab'ys, Inc.*, 246 F.3d 1368, 1379 (Fed. Cir. 2001) (evaluating whether the disclosure in the anticipatory reference "would have been enabling to one of skill in the art more than one year prior to [the effective filing date of the patent]"); *see also In re Samour*, 571 F.2d 559, 562–63 (CCPA 1978) ("The critical issue under 35 U.S.C. § 102(b) is whether the claimed subject matter was in possession of the public more than one year prior to applicant's filing date not whether the evidence showing such possession came before or after the date of the primary reference."). We are not aware, however, of any controlling case law specifically addressing the timeframe of enablement of

[9] The AIA became effective March 16, 2013.

an anticipatory reference under the current AIA § 102. We note that the reasoning behind the one-year timeframe appears to stem from the one-year bar date of pre-AIA § 102(b). *See Samour*, 571 F.2d at 562 (stating a printed publication that "discloses every material element of the claimed subject matter[] would constitute a bar under 35 U.S.C. § 102(b) to appellant's right to a patent if, more than one year prior to appellant's filing date, it placed [the claimed invention] 'in possession of the public'"); *Bristol-Myers*, 246 F.3d at 1379 (relying on *Samour*). Although AIA § 102(b)(1) provides for a one-year grace period under certain circumstances, that exception does not apply to the facts of this case. *See* 35 U.S.C. § 102(b)(1). Thus, we determine that Ahmad need only be enabling prior to the earliest possible effective filing date of the '334 Patent, i.e., on September 11, 2017, as Petitioner asserts. *See* Pet. 5. We note, however, that our decision would be the same if we applied the *Bristol-Myers* standard of one year prior to the earliest possible effective filing date of the '334 Patent, i.e., September 11, 2016.

Finally, the parties dispute whether additional references, like Liu[10] and Fauq,[11] that post-date Ahmad can be relied upon to show Ahmad is enabled. Patent Owner states that "[p]ost-effective filing date evidence offered to illuminate the post-effective filing date state of the art is improper." PO Sur-reply 12 (arguing it is improper to rely on Liu because Liu postdates Ahmad, citing *Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1374

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[10] Liu et al., WO2017/070651 A1, published Apr. 27, 2017. Ex. 1004 ("Liu").
[11] Fauq et al., *A convenient synthesis of (Z)-4-hydroxy-N-desmethyltamoxifen (endoxifen)*, 20 BIOORG. & MED. CHEM. LETTERS 3036–38 (2010). Ex. 1022 ("Fauq").

(Fed. Cir. 2017)). We disagree. Patent Owner relies on *Sanofi*, a § 112 enablement case, which, as explained above, is inapposite when determining the enablement of a prior art reference under § 102. *See Rasmusson*, 413 F.3d at 1325. Moreover, in *Bristol-Myers*, the Federal Circuit expressly held that "[e]nablement of an anticipatory reference may be demonstrated by a later reference." 246 F.3d at 1379 (citing *Donohue*, 766 F.2d at 532; *Samour*, 571 F.2d at 562)

Having set forth the proper legal standards for anticipation, we apply those legal standards in our analysis below.

3. Analysis

In our Institution Decision, we found Petitioner sufficiently showed that Ahmad discloses each limitation of claims 1, 2, 4, 15, and 20–22. Dec. Inst. 13–17. That is, Ahmad discloses the same chemical structure as Formula (III) and states that an object of the invention is to provide (Z)-endoxifen "with at least 80% purity, such as at least 90% pure." Ex. 1003, Fig. 1, 12:14–17, 2:24–40, 3:55–61. Patent Owner does not dispute those findings. *See* PO Resp. 27–51. We, therefore, maintain that Petitioner has shown by a preponderance of the evidence that Ahmad discloses each limitation of claims 1, 2, 4, 15, and 20–22 for the reasons set forth in our Institution Decision, which we incorporate and adopt here. *See* Dec. Inst. 13–17.

Rather than challenge whether Ahmad discloses each limitation of the challenged claims, Patent Owner asserts that Ahmad does not enable the claimed invention. PO Resp. 27–51. Specifically, Patent Owner asserts that Ahmad does not teach a POSA how to achieve 90% pure (Z)-endoxifen, as required by each of the claims. *Id.* at 28. In response, Petitioner argues that Ahmad is enabling because using 90% pure (Z)-endoxifen was in the

public's possession, as shown, for example, by Liu and Fauq.[12] Pet. Reply 3–9. Having considered the arguments and evidence presented by the parties at trial, we are not persuaded that Ahmad fails to enable the claims.

Patent Owner first broadly asserts that the field of organic chemistry, including the separation and purification of stereoisomers, is unpredictable and difficult, which favors a lack of enablement. PO Resp. 30–32 (citing *Forest Lab'ys, Inc. v. Ivax Pharms., Inc.*, 501 F.3d 1263 (Fed. Cir. 2007) and *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075 (Fed. Cir. 2008)). The cases Patent Owner cites, however, are distinguishable.

In *Forest*, the patent-in-suit claimed a substantially pure enantiomer of a drug. 501 F.3d at 1265–66. That patent, however, issued in 1994, twelve years before the critical date of the '334 Patent. *Id.* The Federal Circuit upheld the district court's findings that, at that time of the invention, chiral high performance liquid chromatography "was a relatively new and unpredictable technique" and noted that several different teams, including the author of the prior art reference, had worked to separate the enantiomers of the claimed drug but failed. *Id.* at 1266.

Similarly, in *Sanofi-Synthelabo*, the patent claimed a particular enantiomer that, in 1985, took months of experimentation to successfully

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[12] In the Petition, Petitioner pre-emptively relied on Liu and Song to argue that Ahmad was enabled because methods of obtaining 90% pure (Z)-endoxifen were known in the art. Pet. 30. Upon realizing that Song erred in its NMR analysis and incorrectly reported its results, Petitioner no longer relied on Song in its Reply. Pet. Reply 4. Petitioner explains, however, that that error "does not demonstrate that a POSA could not follow Liu or other methods of achieving 90% purity." *Id.* at 11 n.5 (citing Ex. 1030 ¶ 30). Because Petitioner was not required to preemptively address enablement in its Petition, *see Apple*, 861 F. App'x at 449–50, we do not fault Petitioner for Song's error.

separate. 550 F.3d at 1081. The prior art reference stated that the invention includes enantiomers, but only disclosed the racemates, and did not describe how to separate the racemates into the claimed dextrorotatory enantiomer. *Id.* at 1083. The Federal Circuit affirmed the district court's finding that because the reference contained no description of how to separate the enantiomers of the compound in question, discovering which method and what combination of variables is required would require undue experimentation. *Id.* at 1085.

In contrast, here, Ahmad does provide guidance as to which methods can be used to separate the isomers. Specifically, Ahmad teaches that the (E)- and (Z)-isomers of endoxifen can be separated "by crystallization, or purification by liquid column chromatography (LC), or high pressure liquid chromatography (HPLC)." Ex. 1003, 11:19–23. Moreover, Ahmad provides examples of suitable solvents that can be used, and, when a mixture of solvents is used, Ahmad provides examples of ratios that can be used to separate the isomers. *Id.* at 11:24–42. And, unlike the repeated failures of others to separate the enantiomers in *Forest*, 501 F.3d at 1266, here, others, like Liu and Fauq, had successfully purified at least 90% (Z)-endoxifen by the earliest possible effective date of the invention. *See* Ex. 1004 (Liu) ¶ 76; Ex. 1022 (Fauq), Abstract, 3036–38; Ex. 1030 ¶¶ 17–22.

Patent Owner also argues that Ahmad lacks enablement because Ahmad amended its claims during prosecution in response to the examiner's § 103 rejection and submitted a declaration from its co-inventor stating that the oral dosage form administered in Ahmad "was at least 80% Z-endoxifen and was in the form of a citrate salt of endoxifen." PO Resp. 36–37 (citing Ex. 2022, 162–81). Patent Owner asserts that "there is nothing in the specification or file history that demonstrates enablement of anything greater

than 80% purity." *Id.* at 37. We are not persuaded. Statements by a co-inventor regarding his work disclosed in Ahmad offer minimal probative value to the question of whether Ahmad in combination with the knowledge of a POSA enables the claims of the '334 Patent as of September 11, 2016—almost 10 years after the earliest effective filing date of Ahmad. Ex. 1003, code (60) (related provisional application filed Nov. 21, 2006).

Patent Owner next argues that Ahmad does not contain any working examples of the synthetic method that result in a 90% pure (Z)-endoxifen. PO Resp. 38. Moreover, Patent Owner argues that the synthetic pathway of Ahmad is different than that described in the '334 Patent. *Id.* at 39 (citing Ex. 2020 ¶¶ 135–136). Those arguments are both true. But, as Petitioner notes, the Federal Circuit does not require actual performance to be enabling. *See* Pet. Reply 3; *Bristol-Myers*, 246 F.3d at 1379 (finding "anticipation does not require actual performance of suggestions in a disclosure" to be enabling). And, because the '334 Patent claims do not recite a particular synthetic pathway, we agree with Petitioner that any differences between the pathways described in Ahmad and the '334 Patent are inapposite for purposes of enablement. Pet. Reply 6 n.3. We credit the testimony of Dr. Bihovsky that there are a variety of different synthetic and purification approaches for preparing (Z)-endoxifen. Ex. 1030 ¶ 33 (citing Exs. 1003 (Ahmad), 1004 (Liu), 1022 (Fauq)). Moreover, Dr. Bihovsky further explains that each of the prior art methodologies uses one or more purification steps after synthesis to separate the mixture of (E)- and (Z)-endoxifen using crystallization or chromatography, as Ahmad teaches. *Id.* (citing Ex. 1003, 11:19–23). We are persuaded by Dr. Bihovsky's testimony that "[a] POSA would conclude that even if Ahmad produces a different E/Z ratio, purification by standard techniques would still be possible." *Id.*

Patent Owner also argues that purifying (Z)-endoxifen is a technically difficult process and that Ahmad does not substantively describe how to separate (Z)- and (E)-endoxifen isomers beyond generically identifying crystallization, liquid chromatography, and high-pressure liquid chromatography as possible methods. PO Resp. 41. Patent Owner and its expert, Dr. Davies, argue that Ahmad "does not describe any meaningful amounts, ranges, examples, or guidelines to use with any of the three possible purification methods." *Id.* at 42; Ex. 2020 ¶¶ 80, 128. Dr. Davies states that a POSA would understand that "stereoisomers of endoxifen may be separated by solid state techniques, such as fractional crystallization or chromatography, but that the yield of a given isomer is difficult or impossible to predict." Ex. 2020 ¶ 53. Dr. Davies further states that because there are an "almost unlimited number of feasible purification parameter combinations available to a POSA for optimizing compound purification," a POSA would not have arrived at the particular conditions needed for purification without significant and undue experimentation. *Id.*

We identify two problems with Patent Owner's argument and Dr. Davies's opinion. First, the claims do not require a specific yield; they only require a specific purity. *See, e.g.*, Ex. 1001, claim 1. Second, Dr. Davies ignores the state of the art that existed by 2017, including methods taught by Liu and Fauq, which would have provided a POSA reading Ahmad with guidance on how to purify the endoxifen mixture taught by Ahmad to achieve 90% pure (Z)-endoxifen. Ex. 1003, 11:17–42.

Patent Owner argues that Petitioner cannot rely on the additional references to supply a missing claim limitation. PO Resp. 45 (citing *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1335 (Fed. Cir. 2002)). But unlike the prior art in *Teleflex*, which failed to disclose a limitation of

the claims, *see id.*, we find Ahmad discloses each limitation of the claims. *See supra*. Thus, additional references like Liu and Fauq are not impermissibly filling in gaps to supply a missing limitation, and Petitioner may rely on Liu and Fauq to demonstrate the state of the art in 2017.[13] *See* Ex. 1004, code (43); Ex. 1022, 3036; *see also* Ex. 1030 ¶¶ 21, 22.

Liu teaches a detailed method for synthesizing and purifying (Z)-endoxifen with 99% isomeric purity through recrystallization. Ex. 1004 ¶¶ 4, 76; Ex. 1030 ¶¶ 17–20. Specifically, Liu describes a process for preparing a 50:50 mixture of (Z)-endoxifen and (E)-endoxifen and then producing highly pure (Z)-endoxifen (i.e., 99% isomeric purity) from that mixture by crystallization and isomerization. Ex. 1004 ¶¶ 72–76; Ex. 1030 ¶¶ 25, 17–20. Petitioner bolsters its argument regarding Liu with Dr. Bihovsky's testimony stating that he conducted the synthesis and purification of Liu to obtain greater than 90% pure (Z)-endoxifen. Pet. Reply 5 (citing Ex. 1030 ¶ 27).

Petitioner also argues that "Fauq teaches how to make a highly pure (Z)-endoxifen by chromatography (as does Milroy[14])." *Id.* at 4 (citing

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[13] Patent Owner argues that Petitioner impermissibly relies on Fauq because Petitioner raised Fauq for the first time in its Reply. PO Sur-reply 6. We disagree. As explained above, Patent Owner has the burden to prove Ahmad is not enabling, which it raised in its Patent Owner Response. *See Apple*, 861 F. App'x at 449–50 (holding patentee has the burden to prove nonenablement for anticipatory prior art). Petitioner was then entitled to respond to Patent Owner's arguments by raising Fauq in its Reply. *See id.* (finding petitioner did not have to address enablement of an anticipatory reference in the petition).

[14] Milroy et al., *A multi-gram-scale stereoselective synthesis of Z-endoxifen*, 28 BIOORG. & MED. CHEM. LETTERS 1352–56 (2018). Ex. 1019 ("Milroy"). Although we note Petitioner's reference to Milroy here for completeness, we also note that because Milroy post-dates September 11, 2017, Petitioner may

Exs. 1022, 1019; Ex. 1030 ¶¶ 26, 21, 22). Fauq teaches the "synthesis and purification protocols that have resulted in production of pure endoxifen in excess of 200 mg quantities." Ex. 1022, 3036. Specifically, Fauq teaches a four-step synthesis of a mixture of (Z)- and (E)-endoxifen and the use of semi-preparative reverse phase HPLC ["RP-HPLC"] columns to separate the isomers. *Id.*; *see also id.* at 3038 (providing the conditions for the RP-HPLC). Fauq also teaches a protocol for isomerizing (E)-endoxifen to give a 1:1 mixture of Z/E isomers that was resubjected to HPLC separation. *Id.* at Abstract. Fauq explains that "[i]n this way, most of the undesired (E)-isomer could be readily converted to the desired (Z)-isomer providing quick access to over 200 mg quantities of pure endoxifen (Z)-isomer." *Id.*

According to Petitioner and its expert Dr. Bihovsky, following the teachings of Liu and Fauq to purify the (E)/(Z) mixture of isomers of Ahmad would not have taken undue experimentation. Rather, purification using crystallization and chromatography were well-known techniques that were commonly employed and available since before the '334 Patent. Ex. 1030 ¶ 32 (citing Ex. 1004 (Liu); Ex. 1022 (Fauq)).

Patent Owner asserts that because crystallization is unpredictable and highly dependent on purification parameters, a significant amount of experimentation would be needed to determine the proper crystallization conditions required to obtain a specific level of isomeric purity. PO Sur-reply 9 (citing Ex. 2020 ¶ 53). Patent Owner also notes that Dr. Bihovsky chose to follow Liu's synthetic pathway and not Ahmad's, and then

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not rely on Milroy to show that Ahmad is enabled as of 2017. *See Bristol-Myers*, 246 F.3d at 1378 (declining to rely on post-critical date statements to establish enablement of the anticipatory prior art more than one year before the filing date of the patent).

modified several steps of Liu's purification procedure, proving that crystallization would require undue experimentation. *Id.* at 11. Thus, Patent Owner asserts that Dr. Bihovsky's testimony should be disregarded because he did not follow the synthetic methods of Ahmad and the purification methods of Liu. *Id.*

We are not persuaded. We note that Dr. Davies opines that "crystallization of diastereomers poses significant challenges *for novel compounds*" and that determining "the conditions for crystallizing a specific compound *for the first time* are highly unpredictable." Ex. 2020 ¶ 69 (emphasis added). As seen by Liu, however, 90% pure (Z)-endoxifen was not a novel compound and it had been previously purified by crystallization before September 11, 2017. Ex. 1004 ¶ 76. Moreover, although Ahmad and Liu teach different synthetic pathways, Patent Owner notes that Ahmad's synthetic pathway teaches synthesizing a mixture of "roughly equal parts of (E) and (Z)-endoxifen." PO Sur-reply 8. Similarly, Liu teaches a method of synthesizing a 50/50 mixture of (E)/(Z) endoxifen. *See* Ex. 1004 ¶¶ 72–75; Ex. 1030 ¶¶ 25, 17–20; *see also* Ex. 2020 (Dr. Davies) ¶ 87 (stating "Liu provides a process for synthesizing endoxifen and purifying an isomeric mixture of endoxifen to obtain compositions of isomerically purified (Z)-endoxifen, albeit at impracticably low yields"). Thus, the starting mixture of (E)/(Z)-endoxifen for both Ahmad and Liu are roughly the same. *See* Ex. 1030 ¶ 33 ("[A] POSA would expect Ahmad's synthesis to produce an (E)/(Z) ratio similar to the 51:47 ratio obtained by Liu prior to purification.").

Dr. Davies's main argument is that a POSA would not have expected the purification method of Liu to work with the synthetic endoxifen mixture of Ahmad given the differences in stability and impurity profiles that would

result from using the synthetic pathway of Liu versus that of Ahmad. *See* Ex. 2020 ¶¶ 144–145. But Dr. Davies fails to explain why the purification methods taught by Liu would not work, even if the initial mixture of (E)/(Z)-endoxifen had a different stability and impurity profile. *See id.* At best, Dr. Davies generically testifies that "crystallization *can be* greatly impacted by impurities present in a crude product and crystallization parameters for the same diastereomer *may differ* based on the synthetic process used." *Id.* ¶ 71 (emphasis added). We are not persuaded that the hypothetical impact of any impurities is sufficient to show that the specific crystallization methods taught by Liu would be insufficient to purify the mixture of Ahmad.

Patent Owner also criticizes Dr. Bihovsky for altering the methods of Liu. PO Sur-reply 11. According to Patent Owner, Dr. Bihovsky performed the reaction on a significantly smaller scale and changed the reaction times, temperatures, and reagents. *Id.* (citing Ex. 2029 ¶¶ 10, 11, 14, 15, 17, 21, 23). Moreover, Patent Owner asserts, these modifications prove that undue experimentation would have been required to combine Ahmad with Liu to achieve the claimed invention. *Id.* at 11–12.

We are not persuaded. When asked whether anything Dr. Bihovsky did was beyond the level of ordinary skill, Dr. Davies testified that "a person of ordinary skill could do those types of experiments with those modifications." Ex. 1033, 28:17–23. Dr. Davies simply testified that he was "not sure they'd be motivated to do so." *Id.* "A skilled artisan possesses ordinary creativity and is not an automaton." *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 421 (2007). Thus, we are not persuaded that we should disregard Dr. Bihovsky's testimony because he modified the methods of Liu in a way that was within the level of ordinary skill in the art.

Regarding purification by chromatography, Patent Owner asserts that "Ahmad fails to provide any guidance as to the appropriate chromatography conditions for separation of the endoxifen stereoisomers." PO Sur-reply 9–10 (citing Ex. 2020 ¶ 53). According to Patent Owner, a POSA "would understand that RP-HPLC and other chromatography methods are limited in scale and generally not practical for the manufacture of active pharmaceutical ingredients." *Id.* at 12 (citing Ex. 2027, 102:9–13). Patent Owner asserts that a POSA "would not look to Fauq to produce (Z)-endoxifen for use in an oral formulation due to the insufficient quantities obtained." *Id.* at 12–13.

We are not persuaded. None of the '334 Patent claims except claim 14 requires a particular quantity of (Z)-endoxifen. *See* Ex. 1001, 98:13–100:28. And claim 14 recites the "oral formulation of claim 1, wherein the endoxifen composition comprises from 0.01 mg to 200 mg (Z)-endoxifen per enteric capsule." *Id.* at 99:4–6 (claim 14). Fauq teaches a method of obtaining "over 200 mg quantities of pure [Z-]endoxifen" using RP-HPLC. Ex. 1022, 3038. Thus, although Patent Owner makes much of Dr. Bihovsky's testimony that 200 mg of Z-endoxifen would not be "a sufficient dose for even one patient," claim 14 proves otherwise. Moreover, we note that Dr. Davies does not address Fauq in his third declaration, which Patent Owner submitted after Petitioner's Reply. *See generally* Ex. 2029; *see also* Ex. 1033, 72:24–73:3. Dr. Bihovsky's testimony and opinions regarding Fauq are, therefore, unrebutted by Patent Owner's expert. *See* Ex. 1030 ¶¶ 21, 22, 26.

In sum, we find that Patent Owner has not shown by a preponderance of the evidence that a POSA reading Ahmad would have been unable to make 90% pure (Z)-endoxifen. That is, we find Ahmad's guidance that (Z)-

endoxifen can by purified by crystallization or HPLC coupled with Liu and Fauq's detailed conditions for purifying (Z)-endoxifen provide sufficient guidance to a POSA to produce 90% (Z)-endoxifen in Ahmad without undue experimentation. *See* Ex. 1030 ¶¶ 23–26.

Our enablement findings above are consistent with the *Wands* factors, analyzed below.

a. The relative skill of those in the art

As explained above, a POSA is a highly skilled Ph.D. in the pharmaceutical sciences or the equivalent. *See supra*. We, therefore, find this factor weighs in favor of enablement. *In re Paulsen*, 30 F.3d at 1480 (finding prior art reference enabling where the level of skill in the art was "quite advanced" at the time the patent-in-suit was filed).

b. The breadth of the claims

The claims are limited to an oral formulation of 90% pure (Z)-endoxifen free base. As such, we find the breadth of the claims is relatively narrow. We, therefore, find this factor weighs in favor of enablement.

c. The amount of direction or guidance presented and the presence or absence of working examples

Ahmad states that the E- and Z-isomers of endoxifen can be separated by crystallization or purification by liquid column chromatography or HPLC. Ex. 1003, 11:17–23. Ahmad does not, however, provide working examples of any purification method to achieve 90% pure Z-endoxifen free base. Although Ahmad provides some guidance, the lack of working examples on balance weighs against enablement.

d. The predictability or unpredictability of the art, the nature of the invention, state of the prior art, and quantity of experimentation

Although, generally speaking, organic chemistry may be considered unpredictable, references such as Liu and Fauq taught how to make at least

90% pure (Z)-endoxifen using crystallization and HPLC, as suggested by Ahmad. Thus, we are persuaded that it would have been within the level of ordinary skill in the art to employ the methods of Liu and Fauq to purify the approximately 1:1 (E)/(Z) endoxifen mixture of Ahmad to produce 90% pure (Z)-endoxifen as of September 11, 2017. Accordingly, these factors weigh in favor of enablement. *See Wands*, 858 F.2d at 740 (finding no undue experimentation where "[t]here was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known").

2. Conclusion

Having considered the parties' respective arguments, we find on balance that Patent Owner has not satisfied its burden to prove that Ahmad is not enabling. That is, Patent Owner has not shown that a person of ordinary skill in the art would not have been able to make the claimed invention set forth in Ahmad without undue experimentation. Thus, because it is undisputed that Ahmad discloses each limitation of the claims, we find that Petitioner has shown by a preponderance of the evidence that claims 1, 2, 4, 15, and 20–22 are anticipated by Ahmad.[15]

[15] In light of our determination that claims 1, 2, 4, 15, and 20–22 are anticipated by Ahmad, we need not consider Ground 2 of Petitioner's argument that the same claims are unpatentable as obvious over Ahmad. Pet. 36–41. That said, we note that "it is well settled that a disclosure that anticipates under § 102 also renders the claim invalid under § 103, for anticipation is the epitome of obviousness." *Realtime Data, LLC v. Iancu*, 912 F.3d 1368, 1373 (Fed. Cir. 2019) (internal quotations omitted).

D. Unpatentability over Ahmad and Cole

Petitioner asserts that dependent claims 5–8, 16, and 17 are unpatentable as obvious over Ahmad in view of Cole. Pet. 41–46. Patent Owner opposes. PO Resp. 61–64.

We incorporate here our findings and discussion of Ahmad.

1. Cole (Ex. 1008)

Cole is an article entitled, "Enteric coated HPMC capsules designed to achieve intestinal targeting," which on its face indicates it was published in the *International Journal of Pharmaceutics* in 2002. Ex. 1008, 83. We, therefore, find Cole is prior art to the '334 Patent, and Patent Owner does not assert otherwise during trial. *See generally* PO Resp.; PO Sur-reply.

Cole describes manufacturing experiments in which hydroxypropyl methylcellulose (HPMC) capsules containing paracetamol are coated with enteric polymers Eudragit L 30 D-55 and Eudragit FS 30 D, "which are designed to achieve enteric properties and colonic release, respectively." Ex. 1008, 83. Accordng to Cole, "[e]nteric coated products are designed to remain intact in the stomach and then to release the active substance in the upper intestine." *Id.* Cole explains that "site specific delivery into the upper intestine has been achieved for many years by the use of pH-sensitive coatings." *Id.* at 84. Cole reports that capsules coated with Eudragit L 30 D-55 disintegrated relatively rapidly within the small intestine and capsules coated with Eudragit FS 30 D disintegrated further down the GI tract, towards the distal small intestine and proximal colon. *Id.* at 93.

2. Legal Standard

A patent claim is unpatentable under 35 U.S.C. § 103 if the differences between the claimed invention and the prior art are such that the claimed invention, as a whole, would have been obvious before the effective

filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. *KSR*, 550 U.S. at 406. The question of obviousness is resolved on the basis of underlying factual determinations, including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

In analyzing the obviousness of a combination of prior art elements, it can be important to identify a reason that would have prompted one of skill in the art "to combine . . . known elements in the fashion claimed by the patent at issue." *KSR*, 550 U.S. at 418. A precise teaching directed to the specific subject matter of a challenged claim is not necessary to establish obviousness. *Id.* Rather, "any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.* at 420. Accordingly, Petitioner must show that "a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016) (quotations and citations omitted).

3. Analysis

Dependent claims 5–8, 16, and 17 each depend from claim 1 or claim 15 and recite additional limitations related to the enteric coating of the formulations of claims 1 and 15. Ex. 1001, claims 5–8, 16, 17. We found in our Institution Decision that Petitioner showed that Cole teaches the additional limitations of those claims (Dec. Inst. 26; Pet. 41–46) and Patent Owner does not dispute those teachings. *See generally* PO Resp.; PO Sur-

reply. We, therefore, find that Petitioner has demonstrated that the combination of Ahmad and Cole teaches each limitation of claims 5–8, 16, and 17, for the reasons stated in the Petition, which we adopt. Pet. 41–46; *see also* Ex. 1020 ¶¶ 85–97. That is, Cole teaches the requisite release profiles of claims 5–7, 16, and 17 and the hydroxypropylmethyl cellulose (HPMC) limitation of claim 8. *See* Ex. 1008, 84, 89, 91, Fig. 4 (showing 50% release in pH 6.8 around 2.5–3 hours); Ex. 1020 ¶¶ 85–97.

Petitioner argues that a POSA would have been motivated to use Cole's enteric coating with a reasonable expectation of success to achieve the formulation of the claims "to ensure that the endoxifen was released in the small intestine, rather than in the stomach where it may be degraded by acid, as taught by Ahmad." Pet. 42–45; Ex. 1020 ¶¶ 89, 91, 94. Moreover, a POSA would have been motivated to use an HPMC capsule, as taught by Cole, "to achieve the benefits of HPMC capsules over gelatinous capsules . . . and as a matter of routine design choice." Pet. 46 (citing Ex. 1008, 93, 94); Ex. 1020 ¶ 97.

Patent Owner argues that Petitioner's arguments are driven by hindsight and fail to explain why a POSA would have had a reasonable expectation of success. PO Resp. 62–63. Specifically, Patent Owner and Dr. Davies argue that Cole studies paracetamol and does not mention endoxifen. *Id.* at 63; Ex. 2020 ¶ 164. Patent Owner further argues that a POSA would not have had a reasonable expectation of success given the various complications that would arise due to interactions between the enteric coating and pharmaceutical compositions, particularly given the instability of (Z)-endoxifen. PO Resp. 63–64; Ex. 2020 ¶¶ 164, 166, 167.

We find Petitioner has the better position. Ahmad itself provides the reason to combine Ahmad's formulation with Cole's enteric coating, stating

the well-known purpose of applying enteric coatings "to protect it from acids in the stomach" and to "prevent release of medication before it reaches the small intestine." Ex. 1003, 18:19–24. It was known that endoxifen could be susceptible to degradation in the acidic conditions of the stomach, and a POSA would have been motivated to use an enteric capsule to avoid acidic degradation and improve bioavailability. Ex. 1031 ¶ 6 (citing Ex. 1019, 1353). We credit Dr. McConville's testimony that applying enteric coatings would have been routine (Ex. 1020 ¶ 71; Ex. 1031 ¶ 5), which is consistent with Ahmad's disclosure that the enteric coating "can be done as methods known in the art." Ex. 1003, 18:27–29. Similarly, the '334 Patent states that "enteric tablets, enteric caplets, or enteric capsules of the present disclosure may be prepared by techniques known in the art." Ex. 1001, 39:28–30.

Moreover, the fact that Cole uses paracetamol as a model drug and not endoxifen is of no concern to our obviousness analysis. We credit the formulation expertise of Dr. McConville, who explains that "[i]n the case of an enteric coated capsule, it is the degradation of the enteric coating and the capsule that will control the release of the drug, not the nature of the drug itself." Ex. 1031 ¶ 7 (citing Ex. 1008, 84). Thus, a POSA would have understood that the capsule in Cole would have the same benefits for use with other drugs, such as endoxifen. *Id.*

Patent Owner and Dr. Davies identify certain complications that may plague enteric-coated endoxifen formulations and HPMC capsules, such as "potential interactions between enteric coatings and pharmaceutical compositions" and "variations in release profiles." PO Resp. 63–64; Ex. 2020 ¶¶ 164, 166. But we are not persuaded by that argument, because we agree with Dr. McConville that Patent Owner and Dr. Davies fail to cite any credible evidence of such complications between enteric coatings and

endoxifen, and the '334 Patent itself says nothing about any such interactions. Ex. 1031 ¶¶ 8, 10.

Having considered the arguments and evidence presented by the parties, we find that the combination of Ahmad and Cole teaches each limitation of claims 5–8, 16, and 17 and that a POSA would have had a reason to use the enteric coating and HPMC capsules of Cole with the (Z)-endoxifen formulation of Ahmad to reach the claimed invention with a reasonable expectation of success. *See* Ex. 1020 ¶¶ 84–97; Ex. 1031 ¶¶ 5–16.

We consider Petitioner's remaining obviousness grounds before addressing Patent Owner's evidence of objective indicia of nonobviousness, and—after considering all the *Graham* factors together—making our final determination of obviousness of the claims. *See, e.g.*, *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1328 (Fed. Cir. 2016) ("[T]he strength of *each* of the *Graham* factors must be weighed in every case and must be weighted en route to the final determination of obviousness or non-obviousness.").

E. Unpatentability over Ahmad and Benameur

Petitioner asserts that dependent claim 3 is unpatentable as obvious over Ahmad in view of Benameur. Pet. 46–48. Patent Owner opposes. PO Resp. 64–66.

We incorporate here our findings and discussion of Ahmad.

1. Benameur (Ex. 1010)

Benameur is an article entitled, "Enteric Capsule Drug Delivery Technology – Achieving Protection Without Coating," which on its face indicates it was published in the journal *Drug Development & Delivery* in June 2015. Ex. 1010, 34. We, therefore, find Benameur is prior art to the

'334 Patent, and Patent Owner does not assert otherwise during trial. *See generally* PO Resp.; PO Sur-reply.

Benameur describes the use of enteric capsule drug delivery technology (ECDDT), which "was developed to provide oral delivery with full enteric protection and rapid release in the upper gastrointestinal (GI) tract without the use of coatings." Ex. 1010, 34. According to Benameur, "[t]he major hurdle in oral delivery of many sensitive molecules, such as nucleotides, peptides, live biopharmaceutical products, and vaccines, is protecting the active entity from acidic and enzymatic degradation in the GI tract." *Id.* at 35. ECDDT can be used for oral delivery of such sensitive molecules to provide full enteric protection and rapid release in the upper GI tract without coating and is a new, faster, and easier means for oral delivery of labile entities, such as peptides, nucleotides, live biopharmaceutical products, and vaccines. *Id.* at 35, 37.

2. Analysis

Claim 3 depends from claim 1 and further recites that the "enteric capsule is uncoated." Ex. 1001, 98:34–35 (claim 3). We found in our Institution Decision that Petitioner showed Benameur teaches the additional limitation of claim 3 (Dec. Inst. 26–27; Pet. 47) and Patent Owner does not dispute that teaching. *See generally* PO Resp.; PO Sur-reply. We, therefore, find that Petitioner has demonstrated that the combination of Ahmad and Benameur teaches the additional limitation of claim 3 for the reasons stated in the Petition, which we adopt. Pet. 47; *see also* Ex. 1020 ¶¶ 98–100. That is, Benameur teaches the use of an enteric capsule that is uncoated, as required by claim 3. *See* Ex. 1010, 34–35.

Petitioner asserts that "[i]t would have been a routine and obvious modification of Ahmad to instead use an uncoated enteric capsule, as had

been developed in the art by e.g., Capsugel." Pet. 46 (citing Ex. 1020 ¶ 98). Petitioner notes that such capsules were commercially available by October 7, 2016. *Id.* at 47 n.8. Petitioner and Dr. McConville further argue that a POSA would have understood Benameur's uncoated enteric capsule to be a beneficial alternative to the enteric coated capsules taught by Ahmad because uncoated enteric capsules would eliminate the coating process and be a routine design choice while obtaining the same results as the enteric coated capsules taught by Cole. *Id.* at 48; Ex. 1020 ¶¶ 99–101.

We are persuaded that Petitioner has shown that a POSA would have had a reason to combine Benameur's intrinsic capsules with Ahmad's formulation with a reasonable expectation of success. Pet. 48; Ex. 1020 ¶ 102. Patent Owner's arguments do not persuade us otherwise. Patent Owner argues that Benameur relates to formulations of a different drug, esomeprazole, and that a POSA would not extrapolate the results from Benameur to an unrelated compound that is inherently unstable like (Z)-endoxifen. PO Resp. 65–66; Ex. 2020 ¶¶ 172–173. As Petitioner notes, Benameur identifies esomeprazole as a "model compound." Ex. 1010, 34. Given this disclosure, we credit the testimony of Dr. McConville, who explains that a POSA would understand Benameur's teachings with a model drug would be applicable to (Z)-endoxifen, because it is the dissolution of the enteric capsule that controls the time-release characteristics of the formulation, not the nature of the active ingredient. Ex. 1031 ¶¶ 20–22. Dr. McConville also notes that Benameur teaches that its formulations can be used with a broad range of active ingredients, "such as peptides, nucleotides, live biopharmaceutical products, and vaccines." *Id.* ¶ 22 (citing Ex. 1010, 37). Thus, we are persuaded that a POSA would have found Benameur's ECDDT capsules to be an effective alternative to the enteric

coated capsules taught in Ahmad and would have had a reasonable expectation of success in combining them.

F. Unpatentability over Ahmad and Stegemann and/or the HPE

Petitioner asserts that dependent claims 9–13 are unpatentable as obvious over Ahmad in view of Stegemann and/or the HPE. Pet. 49–54. Patent Owner opposes. PO Resp. 66–68.

We incorporate here our findings and discussion of Ahmad.

1. Stegemann (Ex. 1011)

Stegemann is an article entitled, "Hard gelatin capsules today – and tomorrow," which on its face indicates it was published in 2002 in *Capsugel Library*. Ex. 1011, 2. We, therefore, find Stegemann is prior art to the '334 Patent, and Patent Owner does not assert otherwise during trial. *See generally* PO Resp.; PO Sur-reply.

Stegemann provides an overview of hard gelatin capsules used as a dosage form, including their usage, manufacture, and compatibility with various drug substances. *See generally* Ex. 1011, 2. Stegemann explains that "[t]he capsule is one of the oldest dosage forms in pharmaceutical history, known to the ancient Egyptians," with the first patent for a gelatin capsule granted in 1834. *Id.* at 3. According to Stegemann, there are many benefits to using gelatin capsules, including increased control of GI transit time, enhanced bioavailability, and the ability to develop oral dosage forms of drug actives with low melting points, low doses, and instability when exposed to oxygen, light, or humidity. *Id.* at 14, 18–19, 21. Stegemann notes that diluents, lubricants, and disintegrants are all excipients used in the manufacture of hard gelatin capsules and provides examples of the most common excipients used for drug formulations in hard gelatin capsules. *Id.* at 7–8.

2. The HPE (Ex. 1012)

The HPE is an excerpt from the *Handbook of Pharmaceutical Excipients*, and indicates on its face that the fifth edition was published in 2006. Ex. 1012, 2.[16] We, therefore, find the HPE is prior art to the '334 Patent, and Patent Owner does not assert otherwise during trial. *See generally* PO Resp.; PO Sur-reply.

The HPE "is an internationally acclaimed reference work recognized as one of the most authoritative and comprehensive sources of information on excipients used in pharmaceutical formulation." Ex. 1012, 8. The HPE provides information on the uses, chemical and physical properties, licensing, and safety of excipients. *Id.*

3. Analysis

Dependent claims 9–13 depend, either directly or indirectly, from claim 1 and further recite additional components of the endoxifen composition, including a filler (claims 9, 10), disintegrant (claim 11), and a lubricant (claims 12, 13). Ex. 1001, 98:54–99:3.

We found in our Institution Decision that Petitioner showed that Stegemann and/or HPE teaches the additional limitations of those claims (Dec. Inst. 27–28; Pet. 49–53) and Patent Owner does not dispute those teachings. *See generally* PO Resp.; PO Sur-reply. We, therefore, find that Petitioner has demonstrated that the combination of Ahmad and Stegemann and/or HPE teaches each limitation of claims 9–13, for the reasons stated in the Petition, which we adopt. Pet. 49–53; *see also* Ex. 1020 ¶¶ 104–118. For example, regarding the filler limitation of claims 9 and 10, Stegemann

[16] We cite to the page number of the exhibit rather than the page number of the HPE.

and the HPE teach the use of talcum, microcrystalline cellulose, and starch as fillers. Ex. 1011, 7–8; Ex. 1012, 3, 6. Regarding the disintegrant limitation of claim 11, Stegemann and the HPE both list disintegrants, including corn starch. Ex. 1011, 8; Ex. 1012, 3–4. And regarding the lubricant limitations of claims 12 and 13, Stegemann and the HPE teach the use of magnesium stearate and stearic acid as examples of lubricants in capsules. Ex. 1011, 8; Ex. 1012, 7.

Petitioner asserts that the claims recite "various common excipients for use in capsules" that were "well-known as disclosed for example in Stegemann and the HPE" and therefore obvious to combine with Ahmad. Pet. 49–54 (citing Ex. 1020 ¶¶ 103–118). For each of the claims, Petitioner asserts that the use of the excipient was a routine and common practice in the formulation arts and that a POSA would have been motivated to use the excipient for its normal use. *See* Pet. 50–54; Ex. 1030 ¶¶ 106–118. Petitioner further asserts that a POSA would have had a reasonable expectation of success, as the use of the excipients was commonplace in the art. *See* Pet. 50–54; Ex. 1030 ¶¶ 106–118.

Patent Owner argues that Petitioner fails to explain why a POSA would have been motivated to combine the references with a reasonable expectation of success. PO Resp. 66–67. Patent Owner asserts that none of the references describes oral formulations comprising endoxifen, and that 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 67 (citing Ex. 2020 ¶¶ 178–179).

Again, we find Petitioner has the better position, as we are not persuaded by Patent Owner and Dr. Davies's unsupported assertions. That

Stegemann and the HPE do not refer to endoxifen does not negate the fact that the claimed excipients are well-known compounds with well-known purposes, regardless of the active ingredient. Ex. 1031 ¶ 27. Tellingly, the '334 Patent does not disclose any challenges associated with incorporating the common excipients into an endoxifen formulation. *Id.* Indeed, the Specification states that choosing excipients is well within the skill of a person of ordinary skill in the art:

> One of skill in the art will further recognize that the compositions disclosed herein may comprise one or more excipients known in the art and disclosed herein in any combination appropriate for a desired formulation or preparation. . . . One of skill in the art will be able to select suitable excipients necessary for the preparation of the formulations and appropriate dosage forms compatible with the route of administration based on his or her skill and knowledge in the art and the disclosures made herein.

Ex. 1001, 42:44–55. Given the high level of ordinary skill in the art, we credit the testimony of Dr. McConville, who notes that the HPE generally lists known incompatibilities and that a POSA would have been able to identify known issues and run tests to ensure that there were no negative interactions between the drug and the excipients. Ex. 1031 ¶¶ 29–30. Moreover, we are not persuaded by Patent Owner's broad assertion that formulation sciences were unpredictable, as the *AstraZeneca* case that Patent Owner cites for support relates to the state of the art in 1997. PO Resp. 68 (citing *AstraZeneca Pharms. LP v. Anchen Pharms., Inc.*, 2012 WL 1065458, at *22–*24 (D.N.J. Mar. 29, 2012)). We are persuaded by Dr. McConville's testimony that at the relevant time period of 2017, "formulating enteric capsules with standard excipients was routine and highly predictable," as most excipients had been used for decades and any

potential issues were well known, as evidenced by the list in the HPE. Ex. 1031 ¶ 31.

Having considered the arguments and evidence presented at trial, we are persuaded that a POSA would have had a reason to use the excipients identified in Stegemann and the HPE in the endoxifen formulation of Ahmad in light of their well-known uses with a reasonable expectation of success. *See KSR*, 550 U.S. at 417 ("[A] court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions.")

G. Unpatentability over Ahmad, Ahmad 2010, and Ahmad 2012

Petitioner asserts that dependent claims 14, 18, and 19 are unpatentable as obvious over Ahmad in view of Ahmad 2010 and Ahmad 2012. Pet. 54–57. Patent Owner opposes. PO Resp. 69–74.

We incorporate here our findings and discussion of Ahmad.

1. Ahmad 2010 (Ex. 1006)

Ahmad 2010 is an article entitled, "Endoxifen, a New Cornerstone of Breast Cancer Therapy: Demonstration of Safety, Tolerability, and Systemic Bioavailability in Healthy Human Subjects," that on its face indicates it was published in the journal *Clinical Pharmacology & Therapeutics* in December 2010. Ex. 1006, 814. We, therefore, find Ahmad 2010 is prior art to the '334 Patent, and Patent Owner does not assert otherwise during trial. *See generally* PO Resp.; PO Sur-reply.

According to Ahmad 2010, endoxifen is an active metabolite of tamoxifen, which is a drug used in the treatment of breast cancer and is extensively metabolized by cytochrome P450 (CYP) enzymes into its active metabolites. Ex. 1006, 814. Certain genetic polymorphisms and drugs that interfere with cytochrome P450 2D6 (CYP2D6) inhibit metabolism of

tamoxifen and render it less effective in treating breast cancer. *Id.* Ahmad 2010's authors sought to substitute endoxifen for tamoxifen and administered single escalating oral doses of endoxifen to humans to evaluate the safety, tolerability, and pharmacokinetics (PK) of the drug. *Id.* at 814, 816. Ahmad 2010 reports that "single oral doses of endoxifen are safe and well tolerated and have sufficient bioavailability to reach systemically effective levels in human subjects." *Id.* at 814. As shown below in Table 1, Ahmad 2010 produced pharmacokinetic data from subjects treated with 0.5 to 4.0 mg endoxifen:

Table 1 Endoxifen doses and pharmacokinetic parameters

Dose	C_{max} (ng/ml)	$AUC_{0-\infty}$ (ng·h/ml)
Endoxifen 0.5 mg	1.38 ± 0.25	99.9 ± 13.6
Endoxifen 1.0 mg	3.98 ± 1.7	239 ± 70
Endoxifen 2.0 mg	6.79 ± 1.85	401 ± 113
Endoxifen 4.0 mg	15.1 ± 4.24	801 ± 262
Tamoxifen 20 mg	0.417 ± 0.013	381 ± 47.6

Table 1 shows that 4.0 mg endoxifen results in a C_{max} value of 15.1 ng/ml and an AUC (area under the curve) of 801 ng·h/ml. Ahmad 2010 states that "multiple daily endoxifen doses of 2.0–4.0 mg will result in endoxifen exposures that would be similar to those found in patients with normal CYP2D6 function who are administered tamoxifen at 20 mg/day" and "a dose of 4 mg of endoxifen should be appropriate for breast cancer prevention and therapy." *Id.* at 816.

2. Ahmad 2012 (Ex. 1007)

Ahmad 2012 is a printout from the *Journal of Clinical Oncology*'s web page of an abstract allegedly from the 2012 ASCO Annual Meeting entitled "Endoxifen for breast cancer: Multiple-dose, dose-escalation study characterizing pharmacokinetics and safety in metastatic breast cancer

patients." Ex. 1007, 1.[17] Ahmad 2012 states on its face that it was "[p]ublished online May 20, 2012." We, therefore, find Ahmad 2012 is prior art to the '334 Patent, and Patent Owner does not assert otherwise during trial. *See generally* PO Resp.; PO Sur-reply.

Ahmad 2012 reports that preclinical studies show that single oral doses of endoxifen tested up to 4 mg are safe, well tolerated, and bioavailable in humans. Ex. 1007, 1. Ahmad 2012 discusses results of a multiple-dose escalating study conducted in three cohorts, each of which included six patients, for a total of 18 metastatic breast cancer patients. *Id.* In the study, "Endoxifen at 3 dose levels (2, 4, or 8 mg) was given once daily for 28 days" and was found to be safe up to 8 mg. *Id.* at 1–2. Ahmad 2012 finds that "[m]ultiple daily endoxifen doses of 4.0-8.0 mg resulted in endoxifen exposures that would be sufficient for effective therapy." *Id.* at 2.

3. Analysis

Dependent claim 14 depends from claim 1 and further recites the amount of 0.01 mg to 200 mg (Z)-endoxifen per enteric capsule. Ex. 1001, 99:4–6. Petitioner asserts that Ahmad teaches oral doses of endoxifen at 1 to 10 mg/day, and Ahmad 2010 and 2012 teach administering 4 to 8 mg doses of endoxifen. Pet. 54–55 (citing Ex. 1003, 29:20–31; Ex. 1006, 816; Ex. 1007, 1–2; Ex. 1020 ¶¶ 120–121). Petitioner notes that although Ahmad 2010 and 2012 do not disclose whether the endoxifen is (E), (Z), or a mix of isoforms, a POSA would have understood that "the (Z) form is more active and thus preferred, and would understand to use highly pure (Z) form" and that "the formulations of Ahmad should include from 0.01 mg to 200 mg

[17] We cite to the page number of the exhibit rather than the page number of Ahmad 2012.

(Z)-endoxifen per enteric capsule." *Id.* at 55 (citing Ex. 1020 ¶¶ 120–121). Thus, Petitioner argues claim 14 would have been obvious over Ahmad in view of Ahmad 2010 and Ahmad 2012.

Patent Owner argues that before the '334 Patent, it was difficult to separate the two isomers to obtain highly pure (Z)-endoxifen and there was a need for methods to obtain 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." PO Resp. 70 (citing Ex. 1001, 82:36–41). Thus, according to Patent Owner, a POSA would not have been motivated to apply the dosing methodologies of Ahmad 2010 and Ahmad 2012 because a POSA would not have known whether such dosing information of an unknown mixture of (E)/(Z) endoxifen would be appropriate for highly pure (Z)-endoxifen. *Id.*

We find Petitioner has the better position. Claim 14 recites a very broad range of 0.01 mg to 200 mg (Z)-endoxifen. And Ahmad, Ahmad 2010, and Ahmad 2012 each recites endoxifen dosages well within that range, albeit in unknown (E)/(Z) endoxifen amounts. *See* Ex. 1003, 29:20–31; Ex. 1006, 816; Ex. 1007, 1–2. Dr. McConville explains that despite the unknown mixture, a POSA reading Ahmad 2010 and 2012 would have expected the appropriate dosage of (Z)-endoxifen to fall within the range of 0.01-200 mg given (Z)-endoxifen is more active. Ex. 1031 ¶ 33. Moreover, we credit the well-supported testimony of Dr. McConville that it would have been routine for a POSA to run experiments like those described in Ahmad 2010 and Ahmad 2012 to determine the proper dosage of highly pure (Z)-endoxifen. *Id.* ¶¶ 33–34 (citing Ex. 1006, 814; Ex. 1007, 1).

Dependent claims 18 and 19 depend from claim 15 and further recite specific pharmacokinetic limitations per 4 mg of (Z)-endoxifen

administered. *See* Ex. 1001, 100:4–11. Petitioner argues that those limitations "would have been the inherent results of dosing the formulations of Ahmad within the dosing ranges taught by Ahmad 2010 and Ahmad 2012." Pet. 55; Pet. Reply 22. Petitioner asserts that merely reciting the natural and inherent results of an otherwise obvious formulation cannot lead to patentability. Pet. Reply 23 (citing *Endo Pharms. Sols., Inc. v. Custopharm Inc.*, 894 F.3d 1374, 1381 (Fed. Cir. 2018)).

We are not persuaded by Petitioner's inherent obviousness argument. Petitioner and Dr. McConville appear to assume—without supporting evidence—that the recited pharmacokinetic properties of claims 18 and 19 would necessarily be the natural result of administering the 90% (Z)-endoxifen formulation of Ahmad. As Patent Owner notes, however, the synthetic pathways of Ahmad and the '334 Patent are different, and the resulting products would have different impurity profiles, which would impact the pharmacokinetics of the formulation. PO Sur-reply 24 (citing Ex. 2029 ¶¶ 28–29). Dr. Bihovsky agrees that differing impurities could exist. Ex. 2027, 82:3–8. During his cross-examination, Dr. McConville could not answer whether differences in impurity profiles would impact pharmacokinetics. Ex. 2028, 105:22–107:9. Dr. Davies, on the other hand, testified that "a POSA would presume that different compounds, even stereoisomers, present distinct pharmacokinetic profiles." Ex. 2020 ¶ 183. Thus, it is unclear whether the different chemical impurities of the formulation of Ahmad would impact its pharmacokinetic properties. In other words, Petitioner has not shown by a preponderance of the evidence that the pharmacokinetic properties recited in claims 18 and 19 are the natural result of administering the 90% (Z)-endoxifen formulation of Ahmad. Inherency "may not be established by probabilities or possibilities"

and "[t]he mere fact that a certain thing *may* result from a given set of circumstances is not sufficient." *Endo Pharms.*, 894 F.3d at 1381. Although we agree that the claimed ranges are broad, we find Petitioner has failed to show that administering the 90% (Z)-endoxifen formulation of Ahmad would necessarily fall within those ranges.

Alternatively, Petitioner contends that Ahmad 2010 shows that administering 4 mg endoxifen produces pharmacokinetic properties within the recited ranges of the claims. Pet. 55–56. As such, Petitioner and Dr. McConville note that because the pharmacokinetic data of patients taking endoxifen in Ahmad 2010 is similar to that of patients taking tamoxifen, Ahmad 2010 concludes that "a dose of 4 mg of endoxifen should be appropriate for breast cancer prevention and therapy." *See* Ex. 1020 ¶¶ 124, 126; Ex. 1006, 816. Thus, because Ahmad 2010 teaches that the pharmacokinetic data it obtained is expected to be effective, we are persuaded that a POSA "would have been motivated to obtain similar pharmacokinetic data using the capsules disclosed in Ahmad" and a POSA "would have had a reasonable expectation of success in doing so through routine skill and optimization." Pet. 56–57 (citing Ex. 1020 ¶¶ 124, 127); *see also* Pet. Reply 23–24 (citing Ex. 1031 ¶ 39).

We note that Patent Owner does not address Petitioner's alternative argument, focusing only on the inherent obviousness argument. *See generally* PO Resp.; PO Sur-reply. Absent opposition from Patent Owner, we are persuaded that Petitioner has shown that a POSA would have been motivated to use the formulation of Ahmad to obtain a pharmacokinetic profile within the ranges recited in claims 18 and 19, as suggested by Ahmad 2010 with a reasonable expectation of success.

We now consider Patent Owner's evidence of objective indicia of nonobviousness before making our final determination of obviousness.

H. Objective Indicia of Nonobviousness

As an initial matter, we note that Patent Owner's evidence of objective indicia of nonobviousness apply only to claims 3, 5–14, and 16–19, as we have found that claims 1, 2, 4, 15, and 20–22 are anticipated by Ahmad. *Cohesive Techs., Inc. v. Waters Corp.*, 543 F.3d 1351, 1364 ("[O]bviousness requires analysis of secondary considerations of nonobviousness, while secondary considerations are not an element of a claim of anticipation.").

"Objective indicia of nonobviousness can serve as an important check against hindsight bias and 'must always when present be considered.'" *Merck & Cie v. Gnosis S.P.A.*, 808 F.3d 829, 837 (Fed. Cir. 2015). Patent Owner argues that unexpected results, teaching away, and long-felt need support the nonobviousness of the claims. We consider Patent Owner's evidence for each asserted indicia below.

1. Unexpected Results

Patent Owner asserts that the claimed compositions "exhibit unexpected stability as compared to the endoxifen hydrochloride salt." PO Resp. 75 (citing Ex. 2020 ¶¶ 189–190). Patent Owner contends that Example 11 of the '334 Patent demonstrates surprising stability of the (Z)-endoxifen free base for "at least 9 months under conditions of ambient and high temperature and humidity." *Id.* (quoting Ex. 1001, 82:42–49); *see also* Ex. 1001, 85:18–27.

Patent Owner also asserts that the '334 Patent shows the superior bioavailability of the oral free base formulation over endoxifen citrate. PO Resp. 76 (citing Ex. 1001, 95:49–96:24; Ex. 2020 ¶ 190). Patent Owner

explains that this superior bioavailability was unexpected because a POSA would have expected the citrate salt formulations to have increased aqueous solubility and efficacy. *Id.* (citing Ex. 2016, 5).

"To be particularly probative, evidence of unexpected results must establish that there is a difference between the results obtained and those of the closest prior art, and that the difference would not have been expected by one of ordinary skill in the art at the time of the invention." *Bristol-Myers Squibb Co. v. Teva Pharms USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014). Patent Owner compares the stability and bioavailability results to endoxifen citrate. Petitioner asserts that endoxifen citrate is not the closest prior art and that Patent Owner should have compared its results to (Z)-endoxifen free base formulations like Liu. Pet. Reply 25. Even if endoxifen citrate were the closest prior art, we agree with Petitioner that Patent Owner fails to show that a POSA would not have expected a difference between endoxifen free base and citrate salt formations at the time of the invention. *See id.* at 24–25; Ex. 1031 ¶ 41. Patent Owner also fails to explain why any alleged increase in stability and bioavailability is not just a "predictable result but to an unexpected extent" that amounts to a difference in degree rather than a difference in kind. *See UCB, Inc. v. Actavis Labs. UT, Inc.*, 65 F.4th 679, 693 (Fed. Cir. 2023) (stating "[a] difference of degree is not as persuasive as a difference in kind—i.e., if the range produces a new property dissimilar to the known property, rather than producing a predictable result but to an unexpected extent." (internal quotations omitted)). In other words, although Patent Owner may have shown that the stability and bioavailability profiles of (Z)-endoxifen free base differ from those of the citrate salt, Patent Owner has not shown that those differences were sufficiently unexpected to support a finding of nonobviousness.

We, therefore, find that Patent Owner's arguments and evidence of unexpected results carry little weight.

2. Teaching Away

Patent Owner argues that because other FDA-approved selective estrogen receptor modulators ("SERMs") such as Tamoxifen, Raloxifene, and Toremifene, and Petitioner's Zonalta, are all formulated as salts, the art "taught away from formulating a SERM, such as endoxifen, as a free-base—as opposed to one of the SERM salt form that were standard in the industry. PO Resp. 75–76.

We are not persuaded. "A reference may be said to teach away when a person of ordinary skill, upon reading the reference would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *Galderma Lab'ys, L.P. v. Tolmar, Inc.*, 737 F.3d 731, 738 (Fed. Cir. 2013) (quoting *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1327 (Fed. Cir. 2009)). Moreover, "[a] reference does not teach away . . . if it merely expresses a general preference for an alternative invention but does not criticize, discredit, or otherwise discourage investigation into the invention claimed." *Id.*

Patent Owner has not identified any evidence of discouragement or leading in a direction divergent from producing endoxifen free base. At best, Patent Owner's evidence of other SERMs shows that the salt form may have been standard, but that evidence does not teach away from investigating other compositions, like the free base form. *See id.* at 739 (rejecting argument that the prior art taught away from the claimed 0.3% adapalene compositions simply because the prior art showed 0.1% adapalene was the standard concentration of adapalene).

We, therefore, find Patent Owner's arguments and evidence of teaching away carry no weight.

3. Long-Felt but Unsolved Need

Patent Owner also argues that 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." PO Resp. 77 (citing Ex. 1001, 2:50–54). Thus, Patent Owner asserts that its claimed compositions satisfy the need for new pharmaceutical compositions with superior bioavailability. *Id.*; Ex. 2020 ¶ 188.

Petitioner argues that there is no evidence of a long-felt need for a free base form of (Z)-endoxifen. Pet. Reply 25; Ex. 1031 ¶ 42. Petitioner asserts that Patent Owner has failed to show that existing endoxifen products were insufficient to meet any need or that the commercially available salts taught away from a free base. Pet. Reply 25.

We find Petitioner has the better position. Patent Owner relies on the self-serving statements of the '334 Patent that there was a "need" for (Z)-endoxifen free base formulations. *See* PO Resp. 77 (citing Ex. 1001, 2:50–54). Patent Owner offers no objective evidence that there was a long-felt need specifically for endoxifen free base formulations. And Patent Owner offers little explanation for why—other than the generic search for new treatments—a long-felt need existed for (Z)-endoxifen free base formulations.

We, therefore, find Patent Owner's arguments and evidence of long-felt but unresolved need carry little weight.

I. Conclusion as to Obviousness

Having considered Patent Owner's arguments and evidence of secondary considerations as a whole against Petitioner's arguments and evidence of obviousness, we determine that Patent Owner's relatively weak evidence of unexpected results, teaching away, and long-felt need does not outweigh the strong evidence of obviousness set forth above. *Asyst Techs., Inc. v. Emtrak, Inc.*, 544 F.3d 1310, 1316 (Fed. Cir. 2008) ("[A]s we have often held, evidence of secondary considerations does not always overcome a strong prima facie showing of obviousness."); *see also Leapfrog Enters., Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157, 1162 (holding substantial evidence of commercial success, praise, and long-felt did not outweigh the strength of the prima facie obviousness showing).

Thus, we find Petitioner has shown by a preponderance of the evidence that claims 3, 5–14, and 16–19 are unpatentable as obvious over the cited prior art.

IV. CONCLUSION[18]

For the foregoing reasons, we determine that Petitioner has established by a preponderance of the evidence that claims 1–22 of the '334 Patent are unpatentable.

In summary:

Claim(s)	35 U.S.C. §	Reference(s)/Basis	Claim(s) Shown Unpatentable	Claim(s) Not shown Unpatentable
1, 2, 4, 15, 20–22	102	Ahmad	1, 2, 4, 15, 20–22	
1, 2, 4, 15, 20–22	103	Ahmad[19]		
5–8, 16, 17	103	Ahmad, Cole	5–8, 16, 17	
3	103	Ahmad, Benameur	3	
9–13	103	Ahmad, Stegemann, the HPE	9–13	
14, 18, 19	103	Ahmad, Ahmad 2010, Ahmad 2012	14, 18, 19	
Overall Outcome			1–22	

[18] Should Patent Owner wish to pursue amendment of the challenged claims in a reissue or reexamination proceeding subsequent to the issuance of this decision, we draw Patent Owner's attention to the April 2019 *Notice Regarding Options for Amendments by Patent Owner Through Reissue or Reexamination During a Pending AIA Trial Proceeding*. *See* 84 Fed. Reg. 16,654 (Apr. 22, 2019). If Patent Owner chooses to file a reissue application or a request for reexamination of the challenged patent, we remind Patent Owner of its continuing obligation to notify the Board of any such related matters in updated mandatory notices. *See* 37 C.F.R. § 42.8(a)(3), (b)(2).

[19] We need not reach this ground because all asserted claims in this ground have been found unpatentable under anticipation.

V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 1–22 of U.S. Patent No. 11,572,334 B2 are held unpatentable; and

FURTHER ORDERED that, because this is a Final Written Decision, the parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirement of 37 C.F.R. § 90.2.

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