

**UNITED STATES PATENT AND TRADEMARK OFFICE**

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**BEFORE THE PATENT TRIAL AND APPEAL BOARD**

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INTAS PHARMACEUTICALS LTD.  
Petitioner,

v.

ATOSSA THERAPEUTICS, INC.  
Patent Owner.

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PGR 2023-00043

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

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*Patent Owner's Sur-Reply*  
*PGR2023-00043*  
*U.S. Patent No. 11,572,334*

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**PATENT OWNER'S UPDATED EXHIBIT LIST**

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

EXHIBIT	DESCRIPTION
2015	Lv et al., "Synthesis of mixed (E,Z)-, (E)-, and (Z)-norendoxifen with dual aromatase inhibitory and estrogen receptor modulatory activities," J. Med. Chem., 56: 4611-4618 (2013) ("Lv")
2016	Buchanan et al., "Solubilization and Dissolution of Tamoxifen-Hydroxybutenyl Cyclodextrin Complexes," J. Pharm. Sciences, 95(10):2246-2255 (2006) ("Buchanan")
2017	Gupta et al., "Salts of Therapeutic Agents: Chemical, Physicochemical, and Biological Considerations," Molecules, 23:1719 (2018) ("Gupta")
2018	Jacques et al., <i>Enantiomers, Racemates, and Resolutions</i> (1981) ("Jacques")
2019	Declaration of Susan M. Krumplitsch in Support of Motion to Appear <i>Pro Hac Vice</i>
2020	Expert Declaration of Stephen Graham Davies, D. Phil. in Support of Patent Owner's Response ("Davies POR Decl.")
2021	Deposition Transcript of Jason T. McConville, Ph.D. taken on April 12, 2024, in <i>Intas Pharmaceuticals Ltd. v. Atossa Therapeutics, Inc.</i> , PGR2023-00043 ("McConville Tr.")
2022	Excerpt of File History for U.S. Patent 9,333,190 – Original Filed Application, Office Actions, Responses, Appeal of Examiner's Decision, Declarations, and Allowance ("Ahmad File History Excerpt 2")
2023	Prescribing Information for Nolvadex® (tamoxifen citrate tablets)
2024	Prescribing Information for Soltamox® (tamoxifen citrate solution)
2025	Prescribing Information for Evista® (raloxifene hydrochloride tablets)
2026	Prescribing Information for Fareston® (toremifene citrate tablets)
2027	Deposition Transcript of Ron Bihovsky, Pd.D. taken on August 14, 2024, in <i>Intas Pharmaceuticals Ltd. v. Atossa Therapeutics, Inc.</i> , PGR2023-00043

*Patent Owner's Sur-Reply*  
*PGR2023-00043*  
*U.S. Patent No. 11,572,334*

EXHIBIT	DESCRIPTION
2028	Deposition Transcript of Jason T. McConville, Ph.D. taken on August 15, 2024, in <i>Intas Pharmaceuticals Ltd. v. Atossa Therapeutics, Inc.</i> , PGR2023-00043
2029	Supplemental Declaration of Stephen Graham Davies, D. Phil. in Support of Patent Owner's Sur-Reply



## **I. INTRODUCTION**

Atossa's Response ("POR") explains how the cited prior art does not render the challenged claims of the '334 patent anticipated or obvious. In response, Petitioner changes course from the Petition, relying on a new expert and new prior art, adopting the Board's overly broad claim construction, and engaging in a strained, hindsight-driven reading of the cited art. Petitioner's arguments should be rejected and the challenged claims found patentable.

All six grounds rely on Ahmad (EX1003), which does not enable a POSA to make at least 90% (Z)-endoxifen, whether free base or salt. Grounds 1 and 2 rely on Ahmad alone. Petitioner's formulation expert, Dr. McConville, admitted that Ahmad does not contain an enabling example of making at least 90% (Z)-endoxifen in an enteric coated formulation. (EX2028 at 80:9-81:18.) Petitioner's chemistry expert, Dr. Bihovsky, performed experiments to make at least 90% (Z)-endoxifen, but did not follow the synthetic method of Ahmad. Instead, he used Liu (EX1004) as a guide, despite the fact that Liu is not included in any ground. Even in attempting to follow Liu, he made a number of material modifications to Liu's method.

Grounds 3-6 also fail. Petitioner does not identify any specific motivation to combine. Petitioner relies on hindsight, pointing to disclosures in the '334 patent to support its conclusion that a POSA would have a reasonable expectation of success.

Petitioner fails to address all of the indicia of non-obviousness, which further support the patentability of the challenged claims.

The Board's institution decision relied on an overly broad construction of "the compound of Formula (III) is (Z)-endoxifen" to "include the polymorphic salt, free base, co-crystal and solvate forms of (Z)-endoxifen." (POR at 19 (citing ID at 10).) Petitioner fails to address Atossa's arguments regarding this overbroad construction. This term should be limited to (Z)-endoxifen free base—but even under the Board's construction, the challenged claims are not anticipated or obvious.

## **II. POSA DEFINITION**

The Board's POSA definition reflects the nature of the invention claimed in the '334 patent. (ID at 8.) Dr. Bihovsky testified that Dr. Davies is qualified to serve as an expert. (EX2027 at 53:7-19.) While not explicitly disputing that Dr. Davies is qualified, Petitioner now alleges he does not have sufficient formulation experience to render opinions on Grounds 3-6. (Rep. at 1-2.) Petitioner ignores Dr. Davies' *curriculum vitae*, which lists pharmaceutical companies he founded. (EX2013 at 3-4.) He is familiar with pharmaceutical formulation issues at least through his work with these companies. (EX2029 ¶5.) Petitioner did not cross-examine Dr. Davies and has no basis to attack his formulation knowledge. Dr. Davies is fully qualified to render all of the opinions in his expert declaration, including for Grounds 3-6.

### **III. CLAIM CONSTRUCTION**

#### **A. “Enteric Coating”**

The Board adopted Atossa's construction, which comes from the '334 specification. (ID at 9-10.) Petitioner does not apply this construction instead arguing that this language is “entirely unclear.” (Rep. at 16.) Petitioner's failure to apply this construction further demonstrates the insufficiency of Petitioner's analysis.

#### **B. “The Compound of Formula (III) is (Z)-Endoxifen”**

The Board's *sua sponte* construction includes “the polymorphic salt, free base, co-crystal and solvate forms of (Z)-endoxifen.” (ID at 10.) However, the specification and claims support a construction that includes (Z)-endoxifen free base and excludes the salt and solvate forms. (POR at 16-27.)

The claims depict the molecular structure of (Z)-endoxifen free base and there is no clear evidence of lexicography to support the Board's construction. (POR at 20-27.) Petitioner generically states that “the specification governs.” (Rep. at 2.) But the specification does not provide an express definition. (POR at 24-27.) Petitioner does not rebut this. Petitioner acknowledges that the molecular structures of the free base and salt are different, explicitly demonstrating that the molecular structure of endoxifen citrate includes the citrate atoms. (Rep. at 3.) All experts agree that a free base and corresponding salt and/or solvate have different chemical formulas and

molecular structures. (EX2027 at 24:21-26:22; EX2021 at 27:9-11, 30:5-7, 34:4-7, 34:22-35:3.)

The Board's construction of "the compound of Formula (III)" is overly broad and the phrase should be construed to be directed to the free base and exclude the salt and solvate forms.

#### **IV. THE CHALLENGED CLAIMS ARE PATENTABLE**

##### **A. Ahmad Is Not Enabled**

Atossa has overcome the initial burden of production demonstrating non-enablement. (POR at 34-48.) That burden now shifts, but Petitioner cannot demonstrate enablement.

Ahmad mentions 90% (Z)-endoxifen in a single prophetic sentence: "One object of the present invention is to provide E-endoxifen or Z-endoxifen with at least 80% purity, such as at least 90% pure ..." (EX1003 at 12:14-16.) It is undisputed that Ahmad does not actually teach "at least 90% pure ..." (EX2020 ¶131; EX2027 at 78:12-20; EX2028 at 81:9-19), and Petitioner cites no authority that every prophetic statement in a patent specification is presumed enabled.

At most, Ahmad enables an 80% (Z)-endoxifen citrate salt (Ahmad's claim 1). (EX1003 at 30:55-65; POR at 34-37.) But Ahmad does not teach how to make

this.<sup>1</sup> (EX2020 ¶¶39, 80-81.) Even if Ahmad enables an 80% (Z)-endoxifen citrate salt, Petitioner does not dispute that increasing purity from 80% to 90% is not a trivial endeavor. (EX2020 ¶¶70-72). Petitioner did not explain how a POSA would increase purity to 90% based on Ahmad.

Petitioner acknowledged that the enablement of Ahmad was questionable, arguing that a POSA could rely on Liu and Song for knowledge of “forming such pure formulations” of 90% (Z)-endoxifen. (Pet. at 30.) Petitioner never explained *how* a POSA would rely on Liu or Song to get at least 90% pure (Z)-endoxifen using Ahmad’s teachings. Petitioner identified no passage in Liu or Song that describes making or using a 90% pure (Z)-endoxifen formulation.

Petitioner’s sole expert at the Petition stage, Dr. McConville, opined that “Song also teaches a method of making highly pure (Z)-endoxifen.” (EX1020 ¶37). He is not a chemist (POR at 15, 39), and subsequently admitted he was wrong and agreed that Song teaches making highly pure (E)-endoxifen. (EX2021 at 93:9-94:5; 97:10-17; EX2020 ¶97.) Petitioner submitted a declaration from a different expert, Dr. Bihovsky, a chemist, with the Reply. Dr. Bihovsky agreed that Song teaches

<sup>1</sup> During prosecution, the Ahmad co-inventors declared they made 80% (Z)-endoxifen citrate salt. (POR 34-37.) The prosecution history contains no experimental data or protocol demonstrating *how* they made an 80% citrate salt.

making highly pure (E)-endoxifen.<sup>2</sup> (EX2027 at 100:14-17.) The reliance of Song's inventors and Petitioner's expert on incorrect NMR analyses speaks to the immature state of the (Z)-endoxifen synthesis art prior to the '334 patent's filing.

Abandoning Song, Petitioner's Rep. now argues that a POSA would rely on Liu or Fauq, a new reference teaching an entirely different purification protocol. (Rep. at 4-5.) Petitioner impermissibly raises new art and new arguments—both should be disregarded. *Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1366, 1369 (Fed. Cir. 2016) (reply brief and declaration exceeded the proper scope because they cited new prior art references not relied on in the Petition to support unpatentability).

Petitioner states that both references describe known techniques for purification. (Rep. at 4-5.) But Petitioner never explains *how* a POSA would achieve the claimed at least 90% pure (Z)-endoxifen using Ahmad—even relying on background knowledge of Liu or Fauq—without engaging in undue experimentation. The *Wands* factors require no undue experimentation for enablement. (POR at 29-30, 32-34.) Petitioner does not address the *Wands* factors.

<sup>2</sup> Dr. Bihovsky testified he tried Song's (Z)-endoxifen purification procedure first, before Liu, because it seemed “really straightforward.” (EX2027 at 88:5-17; 94:18-95:8.) He began his experiments in June or July 2023 and finished by the end of 2023. (*Id.* at 90:17-92:19.)

## **1. Lack of Working Examples**

Petitioner cannot dispute that Ahmad contains no working example of making a 90% pure (Z)-endoxifen **composition**. (Rep. at 3-4.) Dr. Bihovsky agreed: “I didn’t see any analytical method reported in this patent. So without that, there apparently is not a working example.” (EX2027 at 77:2-78:21.) Dr. Bihovsky further agreed that Ahmad does not teach how to make 90% (Z)-endoxifen free base or salt. (*Id.* at 79:7-17.)

Dr. McConville agreed that Ahmad does not include an enabling example of making an enteric coated 90% (Z)-endoxifen **formulation**. “[Col. 18:1-18] describes what can be made. I – obviously it doesn’t – that’s not an enabling example.” (EX2028 80:9-16.) “Ahmad does not explicitly describe that there because it’s not an enabling example of course.” (EX2028 at 81:17-19.)

Dr. Bihovsky testified that Ahmad’s four-step synthetic pathway in Examples 1-4 does not describe the isomeric purity of the resulting endoxifen. (EX2027 at 74:5-9; EX1003 at 123:11-18.) Petitioner does not dispute that Ahmad’s synthetic pathway most likely results in an impure isomeric E:Z mixture of 5.8:4.2. (EX2020 ¶75; EX2027 at 79:7-17.)

It is undisputed that the lack of any working examples supports a finding of non-enablement. *Takeda Pharm. Co., LTD v. Handa Pharms., LLC*, C.A. No. 11-

00840-JCS, 2013 WL 9853725, at \*72 (N.D. Cal. Oct. 17, 2013) (finding a prior art patent not enabled in part because it “does not contain any working examples regarding how to synthesize solid dexlansoprazole”).

## **2. The Level of Predictability of the Prior Art and Lack of Guidance Provided by Ahmad**

It is undisputed that the field of organic chemistry, including separation and purification of stereoisomers, is unpredictable and requires a significant amount of experimentation. (POR at 30-32.)

It is undisputed that Ahmad's synthetic pathway is entirely different than the '334 patent's synthetic pathway. (POR at 38-40.) Instead, Petitioner mischaracterizes Dr. Davies' analysis of Ahmad's synthetic method. (Rep. at 11-12; EX1030 ¶¶28, 29, 34.) Dr. Davies compared the synthetic pathway of Ahmad to Ali (EX2011), specifically the use of an ethyl acetate/hexane crystallization which resulted in an E:Z ratio of 5.8:4.2. (EX2020 ¶75.) Petitioner does not dispute Dr. Davies' opinion regarding the expected isomeric ratio of Ahmad based on Ali. At most, Ahmad's synthetic pathway teaches synthesizing a highly impure crude endoxifen mixture containing roughly equal parts of (E) and (Z)-endoxifen. Ahmad fails to provide any guidance as to the expected E:Z isomeric ratio at the conclusion of its ethyl acetate crystallization step. Petitioner's experts agreed. (EX2027 at 74:5-18; EX2021 at 73:18-22.)



It is undisputed that Ahmad does not describe how to purify its resulting crude endoxifen mixture or how to perform subsequent isomeric purification. At best, Ahmad generically and prophetically states that a POSA could use crystallization, liquid column chromatography (LC), or high-pressure liquid column chromatography (HPLC) to purify the crude mixture. (EX1003 at 11:21-23.)

With respect to purification, Ahmad does not provide any specific conditions that could be used to obtain at least 90% (Z)-endoxifen. (EX2020 ¶135.) Instead, Ahmad recites a lengthy, generic list of solvents, acids, fractional crystallization and column chromatography conditions that may be used. (EX1003 at 11:24-42.)

Crystallization is unpredictable and highly dependent on purification parameters including solvent types, solvent ratios, rate of solvent addition, compound concentrations, temperature, agitation, and others. (EX2020 ¶53.) A significant amount of experimentation would be needed to determine the crystallization conditions required to obtain a specific level of isomeric purity. (*Id.* ¶¶53-54, 58, 132.) As Song's errors evidence, the NMR analysis of any resulting products is challenging even for a POSA.

As with crystallization, Ahmad fails to provide any guidance as to the appropriate chromatography conditions for separation of the endoxifen

stereoisomers. Petitioner does not dispute that the yield of a given isomer obtained from chromatography is difficult or impossible to predict. (EX2020 ¶¶53.)

Ahmad does not provide sufficient instruction to employ crystallization or chromatography to achieve 90% pure (Z)-endoxifen without engaging in undue experimentation.

### **3. The State of the Prior Art**

Petitioner ignores that selecting the appropriate solvents and experimental conditions from Ahmad for purification would require undue experimentation. Petitioner instead argues that a POSA would turn to Liu (crystallization) or Fauq (chromatography) to supplement the missing disclosure of Ahmad. Petitioner argues a POSA could prepare crude endoxifen by the synthetic pathway of Ahmad and separate (E) and (Z)-endoxifen by crystallization or chromatography, as in Liu or Fauq, respectively. (Rep. at 4.)

Relying on Liu or Fauq as background knowledge to fill in the significant gaps of Ahmad to achieve the claimed invention is not enabling. *ALZA Corp. v. Andrx Pharms., LLC*, 603 F.3d 935, 941 (Fed. Cir. 2010) (a specification that requires a skilled artisan to “engage in an iterative, trial-and-error process to practice the claimed invention” does not provide an enabling disclosure). An enabling disclosure “cannot simply rely on the knowledge of a [POSA] to serve as a substitute for the

missing information in the specification.” (*Id.* at 940-941 (internal citations omitted).)

Even if this approach was permissible, Petitioner ignores the unpredictability in the art. A POSA would need to carefully evaluate the different impurity profiles and residual solvent contents resulting from different synthetic methods. Dr. Bihovsky agreed that these factors can impact purification. (EX2027 at 83:16-84:7.)

To demonstrate Ahmad's enablement, Petitioner inexplicably argues that a POSA could follow Liu's synthetic pathway and subsequent purification steps. Dr. Bihovsky did not attempt to follow Ahmad's synthetic pathway. (EX2027 at 29:22-30:3; 33:10-16; 74:15-18.) Instead, he attempted to follow Liu's method. He admitted to modifying two steps of Liu's procedure, in addition to performing the reaction on a significantly smaller scale, which the experts agree can necessitate different techniques. (EX2027 at 38:22-39:7; 39:8-21; 40:6-14; 43:15-44:3; EX2029 ¶8.) Dr. Davies subsequently analyzed Dr. Bihovsky's laboratory notebook and determined that Dr. Bihovsky made additional modifications to Liu, including reaction times, temperatures, and reagents used—despite these modifications not being taught or suggested by Liu. (EX2029 ¶¶10, 11, 14, 15, 17, 21, 23.).

Dr. Bihovsky did not follow the synthetic methods of Ahmad and the purification methods of Liu, as Petitioner suggests a POSA would have done. (Rep.

at 4.) That Dr. Bihovsky had to modify Liu further supports a finding that undue experimentation would be required to successfully combine Ahmad with Liu to achieve at least 90% (Z)-endoxifen. Petitioner's position that a POSA could follow the teachings of Liu to supplement the absent disclosure of Ahmad is unfounded.

Liu also postdates Ahmad and, at best, is evidence of a dissimilar synthetic method in the art *after* Ahmad's effective filing date. Post-effective filing date evidence offered to illuminate the post-effective filing date state of the art is improper. *Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1374 (Fed. Cir. 2017). Neither *Donohoe* nor *Bristol-Myers* stand for the proposition that a later prior art reference can fill in the missing gaps of the earlier reference. Liu cannot be used to supply a missing teaching from Ahmad.

Fauq teaches obtaining (Z)-endoxifen using reverse phase high performance liquid chromatography (RP-HPLC). 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. (EX2027 at 102:9-13 (Dr. Bihovsky agreed that the 200 milligrams of (Z)-endoxifen produced by Fauq would not be "a sufficient dose for—for even one patient").) Milroy (EX1019), which also postdates the '334 patent, teaches producing (Z)-endoxifen that specifically avoids the use of RP-HPLC, citing a need for a scalable synthesis. (*Id.* at 1353.) A POSA

would not look to Fauq to produce (Z)-endoxifen for use in an oral formulation due to the insufficient quantities obtained.

Petitioner fails to substantively address any of these arguments. Because undue experimentation would be required for a POSA to make the claimed at least 90% (Z)-endoxifen formulation using Ahmad and background knowledge, Ahmad is not enabled.

**B. Ground 1 Fails**

Ground 1 asserts that Ahmad anticipates Claims 1, 2, 4, 15, and 20-22. Petitioner does not contest that an anticipatory prior art reference must enable a POSA to practice the claimed invention without undue experimentation. *Impax Labs., Inc. v. Aventis Pharms. Inc.*, 545 F.3d 1312, 1314 (Fed. Cir. 2008).

Ahmad is not enabled and does not “teach[] 90% pure (Z)-endoxifen.” (Rep. at 4.) Ahmad’s single prophetic sentence is insufficient. (EX1003 at 12:14-16.) It is undisputed that Ahmad’s synthetic pathway does not describe the isomeric purity of the resulting endoxifen and does not teach how to achieve at least 90% pure (Z)-endoxifen. (EX2027 at 74:5-9; 74:19-75:4; 79:7-17.) Petitioner points to Liu and Fauq without explaining specifically how either reference enables a POSA to make the claimed at least 90% pure (Z)-endoxifen composition.

Ahmad's lack of enablement holds true whether or not the Board applies its proposed broad construction of "the compound of Formula (III) is (Z)-endoxifen." Ahmad does not teach a POSA how to achieve 90% pure (Z)-endoxifen composition, whether free base or citrate salt. Ground 1 fails.

**C. Ground 2 Fails**

Ground 2 asserts that Ahmad alone renders Claims 1, 2, 4, 15, and 20-22 obvious. Petitioner does not dispute that "a standalone § 103 reference must enable the portions of its disclosure being relied upon." *Raytheon Techs. Corp. v. GE*, 993 F.3d 1374, 1381 (Fed. Cir. 2021) (citations omitted). This is "the same standard applied to anticipatory references." *Id.*

Ahmad is not enabled, even if combined with the background knowledge of a POSA supplied by Liu or Fauq. Petitioner does not provide a single example of *how* a POSA would modify Ahmad to achieve at least 90% (Z)-endoxifen; or *why* a POSA would be motivated to modify Ahmad using the teachings of Liu or Fauq.

Petitioner argues that "it is readily apparent how a POSA would use Ahmad's or Liu's teachings of making 90% pure (Z)-endoxifen as taught by Ahmad" (Rep. at 12) but does not explain *how* a POSA would modify Ahmad to make 90% pure (Z)-endoxifen. Petitioner's obviousness challenge fails as a matter of law. *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1380 (Fed. Cir. 2016) ("To satisfy its burden of

proving obviousness, a petitioner cannot employ mere conclusory statements. The petitioner must instead articulate specific reasoning, based on evidence of record, to support the legal conclusion of obviousness.”).

In fact, a POSA could not rely on either Liu or Fauq’s benchtop syntheses to modify Ahmad. (EX2020 ¶¶154-156.) Liu describes a very different synthetic pathway from both the ’334 patent and Ahmad, including different starting materials and crystallization parameters, and results in impracticably low yields. (*Id.* ¶¶87, 154-55.) Liu does not contain any description of the resulting endoxifen’s stability or the presence of any residual solvents or impurities that could render the endoxifen unsuitable for a pharmaceutical formulation. (*Id.* ¶155.) Petitioner does not dispute that the different synthetic pathways of Ahmad and Liu would likely result in different impurity profiles and different stability profiles. (*Id.* ¶87.)

Ahmad’s synthetic method likely results in a composition with more (E)-endoxifen than (Z)-endoxifen. (POR at 57-58.) Petitioner provides no explanation of how a POSA could apply the purification steps of Liu to Ahmad. Dr. Bihovsky did not attempt this combination, instead relying on Liu alone—and even then, he was forced to materially modify Liu’s experimental conditions to achieve the intended result. (EX2027 at 39:9-21; 40:6-14.)

Petitioner also does not articulate *why* a POSA would modify Ahmad. Ahmad fails to appreciate the pH and temperature instability of (Z)-endoxifen and instead specifically directs a POSA to use such destabilizing conditions. Ahmad goes so far as to teach preferred formulation pHs as low as 4.0 (EX1003 at 26:5-21), and provides Examples 5-6 where its endoxifen product is dissolved in glacial acetic acid (*id.*), which promote isomerization from (Z)-endoxifen to a mixture of (Z) and (E)-endoxifen. (EX2020 ¶81.) It is undisputed that exposure of (Z)-endoxifen—even highly pure (Z)-endoxifen—to acidic conditions such as Ahmad's glacial acetic acid would likely lead to isomerization to a roughly 1:1 ratio of (Z):(E). (EX2027 at 112:16-113:6; EX1004 at [0048]; EX2020 ¶63.)

Ahmad teaches that the salt form of endoxifen is preferred (EX1003 at 2:26-27) and claims a citrate salt formulation. (*Id.* at 30:60-62). Synthesis of a citrate salt typically involves dissolving the (Z)-endoxifen solid in a citric acid solution, which would result in the acid-promoted isomerization of even isomerically pure (Z)-endoxifen to a roughly 1:1 mixture of (Z) and (E)-endoxifen citrate salt. (POR 9-10.) Ahmad also teaches that endoxifen preparations should preferentially include a lipid. (EX1003 at 1:18-21; 3:64-4:22.) Ahmad's Examples 7 and 8 describe suspensions of endoxifen complexed with cholesteryl sulfate and soy lecithin.



(EX1003 at 26:25-50.) Of Ahmad's 15 examples, there are no examples of a solid oral dosage form of endoxifen, whether free base or salt.

Further complicating any motivation to modify Ahmad in light of background knowledge, Petitioner's cited references contain errors that would render any such modification less likely to be successful. Song (EX1005) erroneously claimed to purify (Z)-endoxifen but actually made highly purified (E)-endoxifen. (POR at 55; EX2027 at 88:18-90:16). A POSA following the teachings of Song would be directed squarely *away* from the claimed invention. Fauq (EX1022) incorrectly describes that its (Z)-endoxifen hydrochloride salt exists in equilibrium with (E)-endoxifen. (EX1022 at 3; EX2027 at 103:2-104:1 (“[T]here’s an error here...”)).

Claims cannot be found obvious by “focus[ing] on what a skilled artisan would have been *able* to do, rather than what a skilled artisan would have been *motivated* to do at the time of the invention.” *Polaris Industries, Inc. v. Arctic Cat, Inc.*, 882 F.3d 1056, 1068 (Fed. Cir. 2018) (emphasis in original). Evidence relevant to teaching away should not be “outright discard[ed].” *Id.* at 1069. “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 lead in a direction divergent from the path that was taken by applicant.” *Id.* (citation omitted). Ignoring such teachings “invite[s] the ‘distortion caused by hindsight bias’

into the fold.” *Id.* at 1068. “[E]ven if a reference is not found to teach away, its statements regarding preferences are relevant to a finding regarding whether a skilled artisan would be motivated to combine that reference with another reference.” *Id.* Liu, Fauq, and Song do not support Petitioner’s obviousness argument.

Ahmad—even combined with the POSA’s background knowledge of Liu or Fauq—does not render the challenged claims obvious. Ground 2 thus fails.

**D. Ground 3 Fails**

Petitioner argues that a POSA would be motivated to combine the enteric paracetamol capsule of Cole with Ahmad. (Rep. at 12.) Ahmad, however, fails to teach a formulation comprising an endoxifen composition wherein “at least 90% by weight of the compound of Formula (III) is (Z)-endoxifen” as required by independent Claims 1 and 15. (POR at 14.) Petitioner’s Ground 3 fails for that reason alone.

Petitioner argues that a POSA would be motivated to combine Ahmad with Cole because Ahmad states that “compositions containing endoxifen or endoxifen-lipid complex can be encapsulated in enteric-coated capsules.” (Rep. at 12 (citing EX1003 at 18:19-21).) The ’334 patent states that commercial HPMC capsules can

be used and does not disclose any incompatibility between HPMC and endoxifen. (EX1031 ¶14.) This is textbook hindsight analysis.

Moreover, Dr. McConville testified that an enteric coating is applied to the outside of a capsule *after* it has been filled with the active ingredient. (EX2028 at 52:8-56:11.) Heat is applied to the filled capsule to dry the coating. A POSA would know that “[t]he high temperatures (>40°C) associated with functional coating application and drying can degrade ... sensitive active [ingredients].” (EX1010 at 2; Pet. at 48.)

Petitioner’s argument that one could swap paracetamol for (Z)-endoxifen (Rep. at 13-15) ignores that (Z)-endoxifen is sensitive to heat. (POR at 63-64.) Dr. McConville did not investigate the thermal stability of (Z)-endoxifen. (EX2028 at 56:12-19.) He testified that “it is possible” that (Z)-endoxifen would isomerize to a mixture of (E) and (Z)-endoxifen when heated. (*Id.* at 108:6-21.) He agreed that a POSA would consider the stability of the active ingredient during formulation (*id.* at 15-21), and a POSA would want to avoid conditions that would promote isomerization to a mixture of (E) and (Z)-endoxifen. (*Id.* at 109:17-22.) He did not identify any prior art teaching of how to avoid formulation conditions that could promote isomerization. (*Id.* at 113:10-114:4.)

In light of the inherent instability of (Z)-endoxifen, including when exposed to heat and electrical charge (POR at 63-64), a POSA would need to engage in undue experimentation to design the claimed dosage form. Ground 3 thus fails.

**E. Ground 4 Fails**

Petitioner fails to adequately explain how a POSA would be motivated to combine Benameur with Ahmad with a reasonable expectation of success. Benameur describes enteric capsules for esomeprazole oral formulations. (EX2021 at 113:11-116:4.) Esomeprazole and endoxifen are unrelated and do not share similar properties—esomeprazole does not isomerize to a less active stereoisomer in acidic conditions, unlike (Z)-endoxifen. (EX2028 63:21-64:5.) Ignoring that Ahmad does not teach how to make compositions comprising at least 90% (Z) endoxifen, Petitioner also failed to identify any suggestion in Ahmad to use the enteric capsule of Benameur. Instead, Petitioner generically argues that a POSA would be motivated to use *any* enteric capsule to protect *any* active ingredient from the acidic environment of the stomach. (Pet. at 47-48; Rep. 16-17.) This conclusory analysis is insufficient. *ActiveVideo Networks, Inc. v. Verizon Commc'ns, Inc.*, 694 F.3d 1312, 1328 (Fed. Cir. 2012) (“generic” analysis that “bears no relation to any specific combination of prior art elements” is insufficient to supply a motivation to combine).

Petitioner and Dr. McConville engage in impermissible hindsight by relying on the '334 specification for the knowledge that endoxifen could be loaded into enteric coated capsules without an impact on stability. (EX1031 ¶24.) This hindsight taints Petitioner's motivation to combine.

Finally, Petitioner ignores the Board's construction of "enteric capsule" which includes the requirement of "provid[ing] a sustained action over a longer period of time." (ID at 9-10.) Petitioner instead argues that it is "entirely unclear" what this language means and fails to explain how the combination of Benameur and Ahmad meet this requirement. (Rep. at 16). Ground 4 fails.

**F. Ground 5 Fails**

Petitioner's only motivation to combine the excipients of Stegemann and/or the HPE with Ahmad to arrive at the claimed formulations with a reasonable expectation of success is that the recited excipients were "well known commonly used excipients." (Rep. at 18.) This lack of specificity is fatal. *In re Magnum Oil*, 829 F.3d at 1380 (Petitioner must "articulate specific reasoning, based on evidence of record, to support the legal conclusion of obviousness").

In creating a highly pure and stable (Z)-endoxifen formulation, a POSA would not simply choose excipients because they were well known or commonly used. Petitioner does not dispute that (Z)-endoxifen is an inherently unstable compound

under various commonly used conditions. (EX2020 ¶¶55, 85.) Dr. McConville agreed that a POSA would consider potential interactions between (Z)-endoxifen and excipients when formulating drug product. (EX2021 at 120:16-20.) He admitted that neither Stegemann nor the HPE listed incompatibilities for endoxifen. (EX2021 at 119:4-17; 123:16-124:4.) He testified that if a particular compound was not listed, a POSA would look for incompatibilities associated with the relevant class of compounds (EX2028 at 70:2-71:11), but he could not identify the relevant compound class for endoxifen. (*Id.* at 71:12-21.)

Dr. McConville relied on the '334 patent that “does not disclose any challenges associated with incorporating these common excipients into an endoxifen formulation.” (EX1031 ¶27.) “[O]bviousness determinations cannot rely on hindsight,” *KSR Int’l Co. v. Teleflex, Inc.*, 550 U.S. 398, 415, 419 (2007), and Petitioner cannot look to the '334 patent for excipient compatibility to support a motivation to combine.

Ground 5 fails.

## **G. Ground 6 Fails**

### **1. Claim 14 Is Not Obvious**

As with Grounds 3-5, Claim 14 of Ground 6 is non-obvious because independent Claims 1 and 15 are non-obvious. Claim 14 is also non-obvious over

Ahmad in view of Ahmad 2010 and Ahmad 2012. It is undisputed that (a) Ahmad does not disclose the isomeric purity of the endoxifen made by Ahmad's synthesis (EX2027 at 74:1-9.); and (b) that Ahmad 2010 and Ahmad 2012 do not specify the (E)/(Z) ratio of the endoxifen formulation tested. (EX2028 at 27:2-7.)

A POSA would know that the (Z) isomer is the more active endoxifen isomer. (EX2021 at 129:3-5). Petitioner identifies no teaching suggesting a POSA would understand that the dosing ranges for an undisclosed mixture of (E)/(Z) isomers would be appropriate for an at least 90% (Z)-endoxifen formulation. Instead, Petitioner generically argues that a POSA would have tested the dosage ranges of Ahmad 2010 and Ahmad 2012. This level of generality is insufficient to establish obviousness of Claim 14.

## **2. Claims 18 and 19 Are Not Inherently Obvious**

Ground 6 also challenges Claims 18 and 19 as obvious over the same combination of art. The Petition alleges that the pharmacokinetic limitations—area under curve ( $AUC_{0-inf}$ ) for Claim 18 and maximum blood plasma concentration ( $C_{max}$ ) for Claim 19—would be the “inherent result of dosing the formulations of Ahmad within the dosage ranges taught by Ahmad 2010 and 2012.” (Pet. at 55-56.) The Reply alleges these pharmacokinetic limitations “are simply the inherent and natural result of administering the formulation of claim 14.” (Rep. at 22.) But claims

18 and 19 depend on claim 15, not 14, and each recite pharmacokinetic parameters “per 4mg of (Z)-endoxifen administered.” (EX1001 at 99:7-100:12.)

Petitioner points to pharmacokinetic data in the '334 patent to argue that Claims 18 and 19 would be the natural result of providing a formulation of Ahmad to a patient using the dosing regimens of Ahmad 2010 and Ahmad 2012. But Petitioner did not perform any analysis evaluating whether the pharmacokinetics of a 90% (Z) endoxifen made according to Ahmad would fall within the ranges claimed in the '334 patent. It is undisputed that the synthetic pathways of Ahmad and the '334 patent are dissimilar, and the resulting products would have different impurity profiles—assuming a POSA could even make 90% (Z)-endoxifen by following Ahmad. (EX2029 ¶27.) These different impurities could impact the resulting pharmacokinetics. (EX2029 ¶28-29.) Dr. McConville did not address this.

Dr. McConville similarly does not address the differences in dosing regimes and formulations between the cited art and the '334 patent. He “assumed” that mixtures of (E) and (Z)-endoxifen would all have the same pharmacokinetics, regardless of the percentage of each isomer. (EX2028 at 101:21-102:3; 120:16-121:3.) He did not perform any analysis (*Id.* at 94:9-96:5.) and did not know whether pharmacokinetics would be impacted if (E) and (Z)-endoxifen have different solubilities. (*Id.* at 99:6-12 (“[] I don’t know for sure. This is something that would



have to be tested.”.) He similarly testified that absorption “could be [different]” between endoxifen free base and its salts and that a POSA would need to perform a comparative study. (EX2021 at 43:5-16; EX1031 ¶36.) A POSA would understand that pharmacokinetics are directly impacted by compound solubility, which in turn depends on its isomeric content and form (e.g., free base versus salt). (EX2020 ¶183.)

There is no basis with which to conclude that a 90% (Z)-endoxifen made by Ahmad—even if it did teach how to make such a composition—would have the same pharmacokinetics as claimed in the ’334 patent. Petitioner asks the Board to assume the claimed values are the natural result of dosing with Ahmad but offers no evidence. Ground 6 thus fails.

## **V. SECONDARY CONSIDERATIONS**

Secondary considerations support the non-obviousness of the challenged claims. (POR at 75-77.)

### **A. Unexpected Results**

Petitioner does not dispute that ’334 patent Example 11 demonstrates the surprising and unexpected stability of the resulting (Z)-endoxifen free base (EX1001 at 82:42-49.) While Petitioner faults Patent Owner for not comparing the stability

data of the '334 patent formulation with Liu, there is no evidence that Liu ever created any solid oral enteric formulation of 90% (Z)-endoxifen.

Example 11 does compare the stability of the claimed at least 90% (Z)-endoxifen formulation with an E/Z isomer free base mixture and reported 98% (Z)-endoxifen salts. (EX1001 at 82:3-83:50.)

It is undisputed that the '334 patent describes oral formulations comprising endoxifen free base surprisingly exhibited superior bioavailability as compared to oral formulations of endoxifen citrate. (POR at 76.) Petitioner complains that the claimed composition is not compared to prior art free base formulations (Rep. at 25) but ignores the lack of prior art free base formulations for comparison.

### **B. Teaching Away**

Petitioner does not dispute that other drugs in this class of “selective estrogen receptor modulator” (SERM) compounds are formulated as salts, including Petitioner’s endoxifen tablet. (POR at 75-76.) Petitioner does not dispute that the art taught away from formulating SERMs, including endoxifen, as a free base—as SERM salt forms were industry standard. (*Id.*)

### **C. Long-Felt Need**

It is undisputed that other FDA-approved SERM drugs, formulated as salts, have been marketed for decades. Regardless, a significant unmet medical need

remained for new compositions and methods for the prevention and treatment of hormone-dependent breast and reproductive tract disorders, including cancers. (EX1001 at 2:50-54.) It is undisputed that the claimed at least 90% (Z)-endoxifen compositions achieve superior bioavailability compared to EX1006 and EX1007, (see EX1001 at 95:49-96:24), demonstrating superior suitability of the claimed compositions. Atossa's ability to raise over \$200 million to develop the claimed invention further reflects the market's long-felt need for a superior treatment option.

These secondary indicia are commensurate with the '334 patent claims and there is a sufficient nexus between the claims and unexpected results and long-felt need. *Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1332-33 (Fed. Cir. 2019) (nexus is presumed when the patentee's "objective evidence is tied to a specific product and that product embodies the claimed features, and is coextensive with them") (cleaned up); *Amgen Inc. v. Sandoz Inc.*, 66 F.4th 952, 964-65 (Fed. Cir. 2023) (affirming nonobviousness in part because of a long-felt need for the claimed compound).

## **VI. CONCLUSION**

For all the reasons above, and in Atossa's Preliminary Response and POR, Petitioner fails to show that any challenged claim is unpatentable.

*Patent Owner's Sur-Reply*  
*PGR2023-00043*  
*U.S. Patent No. 11,572,334*

Dated: September 6, 2024

Respectfully Submitted,

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**CERTIFICATE OF WORD COUNT**

The undersigned hereby certifies that the foregoing Patent Owner's Sur-Reply to Petition for Post-Grant Review complies with the type-volume limitations of 37 C.F.R. § 42.24(b). Excluding the items listed 37 C.F.R. § 42.24(a) as not included in the word count, and using the word count function of Microsoft Word, which was used to prepare the paper, the Patent Owner's Response contains 5,588 words.

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**CERTIFICATE OF SERVICE**

The undersigned hereby certifies that on this 6th day of September 2024, a true copy of the foregoing materials was served on Petitioner INTAS PHARMACEUTICALS LTD. by emailing a copy to counsel of record for Petitioner at the email addresses listed below:

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