

**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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CASE: PGR2023-00043

Patent No. 11,572,334

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**PATENT OWNER'S PRELIMINARY RESPONSE TO PETITION FOR  
POST-GRANT REVIEW OF U.S. PATENT NO. 11,572,334**

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### PATENT OWNER'S EXHIBIT LIST

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

EXHIBIT	DESCRIPTION
2015	Lv et al., "Synthesis of mixed (E,Z)-, (E)-, and (Z)-norendoxifen with dual aromatase inhibitory and estrogen receptor modulatory activities," J. Med. Chem., 56: 4611-4618 (2013) ("Lv")
2016	Buchanan et al., "Solubilization and Dissolution of Tamoxifen-Hydroxybutenyl Cyclodextrin Complexes," J. Pharm. Sciences, 95(10):2246-2255 (2006) ("Buchanan")
2017	Gupta et al., "Salts of Therapeutic Agents: Chemical, Physicochemical, and Biological Considerations," Molecules, 23:1719 (2018) ("Gupta")
2018	Jacques et al., <i>Enantiomers, Racemates, and Resolutions</i> (1981) ("Jacques")

Patent Owner Atossa Therapeutics, Inc. (“Atossa”) hereby submits this Preliminary Response to the Petition for Post-Grant Review (“PGR”) of U.S. Patent No. 11,572,334 (“the ’334 patent”) (EX1001) filed by Intas Pharmaceuticals Ltd. (“Intas”).

## **I. INTRODUCTION**

Petitioner’s request that the Board institute PGR of claims 1-22 of the ’334 patent should be denied. The Petition is substantively and procedurally flawed—none of the six anticipation and obviousness grounds advanced by Petitioner demonstrate unpatentability. Moreover, the art on which Petitioner relies was considered during prosecution and the Board should exercise its discretion to deny institution under 35 U.S.C. § 325(d). Petitioner also failed to establish that any of the fourteen non-patent publications qualify as prior art.

The inventors of the ’334 patent discovered and claimed pharmaceutical formulations comprising isomerically pure (Z)-endoxifen. (Z)-endoxifen is currently being studied in clinical trials as a preventative and treatment for hormone-dependent breast disorders, such as estrogen receptor (ER)-positive breast cancer and has the potential to revolutionize ER-positive breast cancer chemotherapy and to even prevent breast cancer. The ’334 patent describes a novel synthetic pathway that results in highly pure (Z)-endoxifen that can be

formulated into oral dosage forms to treat patients. The '334 patent claims enteric coated capsule formulations containing at least 90% (Z)-endoxifen free base, methods of delivering such formulations to a patient resulting in specific pharmacokinetic parameters, and methods of treating hormone-dependent breast and reproductive tract disorders. (EX2001 (Davies Decl.) at ¶ 44.)

The invention claimed in the '334 is unexpected and groundbreaking. As of the '334 patent's critical date, endoxifen was only commercially available as a free base mixture of the (E) and (Z) isomers, (Z)-endoxifen HCl, or (Z)-endoxifen citrate salts. (EX1001 at 82:3-5.) Highly pure (Z)-endoxifen free base was not available. As demonstrated in the '334 patent, (Z)-endoxifen free base showed much better stability than (Z)-endoxifen HCl, and further showed increased bioavailability than pharmaceutical compositions comprising endoxifen citrate. (EX1001 at 82:5-13, 36-49.) Further, endoxifen citrate used in oral formulations had not been characterized for isomeric purity (EX1006) and the synthesis of a citrate salt of endoxifen using citric acid would result in acid-promoted isomerization of (Z)-endoxifen to the less active (E)-isomer, resulting in an equilibrated mixture of (E)/(Z)-endoxifen, and therefore would not be desirable for use in pharmaceutical formulations. (See EX2001 (Davies Decl.) at ¶¶ 40, 55, 154, 157.)

(Z)-endoxifen is known to be highly unstable—it rapidly interconverts to its inactive isomer, (E)-endoxifen, under acidic or aqueous conditions, yielding an equilibrium mixture of approximately 60% (Z)-endoxifen and 40% (E)-endoxifen. (EX1001 at 82:11-14 (citing EX2002 (Elkins) (“Conversion [of Z-endoxifen HCL to (E)-endoxifen] is expected to be more rapid in a solution environment.”)); *see also* EX2001 (Davies Decl.) at ¶¶ 50-52.) Prior to the '334 patent, it was not known how to create an oral pharmaceutical dosage form comprising at least 90% (Z)-endoxifen free base.

Petitioner's six grounds and the art cited therein flatly ignore the inherent instability of (Z)-endoxifen and the concomitant problems of formulating a highly pure pharmaceutical solid dosage formulation of (Z)-endoxifen free base. Grounds 1-6 are each based on the primary reference U.S. Patent No. 9,333,190 (EX1003, Ahmad). Ahmad was disclosed during prosecution of the '334 patent and does not even mention the instability of (Z)-endoxifen or its ability to interconvert to the (E)-endoxifen isomer. Ahmad plainly does not disclose a 90% pure oral dosage form of (Z)-endoxifen and does not enable a skilled artisan to create such a dosage form. (EX2001 (Davies Decl.) at ¶¶ 98-111.) Ahmad teaches making solutions of endoxifen solely for toxicity testing but fails to disclose if the endoxifen is a pure isomer or a mixture. (*Id.* at ¶ 63.) Ahmad further discloses using acetic acid to

form solutions and such an acidic solution would produce a mixture of the (Z)- and (E)-isomers—not an at least 90% pure (Z)-endoxifen as claimed by the '334 patent. (*Id.*) Ahmad is the sole reference on which Grounds 1 and 2 are based, and those Grounds necessarily fail.

Grounds 3, 4, and 5 combine Ahmad with generic references describing the use of enteric capsules (Grounds 3 and 4) and excipients (Ground 5). None of these additional references mention (Z)-endoxifen and none cure the deficiencies of Ahmad. (*Id.* at ¶¶ 132-149.)) Ground 6 combines Ahmad with EX1006 (Ahmad 2010) and EX1007 (Ahmad 2012) to address pharmacokinetic limitations, but this combination also fails. Neither of these two additional references explain that endoxifen exists as one of two isomers or that (Z)-endoxifen is the active isomer. Fatally, neither discloses the ratio of (Z)/(E) isomers in the endoxifen formations described therein. (*Id.* at ¶¶ 150-154.) Further compounding the deficiencies of Petitioner's conclusory arguments, Petitioner fails to establish an expectation of success for any of the alleged combinations. (*Id.* at ¶¶ 127-132, 138, 144, 150).

Not only do each of the grounds substantively fail to demonstrate unpatentability, but they also fail procedurally. Institution should be denied under § 325(d). Petitioner's Grounds 1, 2, 3, and 6 rest solely on art that was considered

during prosecution. For example, Grounds 1 and 2 rely exclusively on EX1003 (Ahmad), which was presented during prosecution and considered by the Examiner. Ground 3 combines EX1003 (Ahmad) with EX1008 (Cole) which is incorporated by reference into the specification. (EX1001 at 11:6-10, 86:55-59.) Grounds 4 and 5 combine art that was previously presented to the Examiner with generic enteric capsule and excipient art—none of these are new or novel arguments that merit institution.

Further compounding the Petition's deficiencies, Petitioner fails to make the requisite showing that any of the non-patent publications qualify as prior art. Petitioner failed to authenticate any of EX1006-EX1012, EX1014-EX1019, or EX2021 and failed to demonstrate that any of these exhibits were publicly available as of the critical date of the '334 patent.

Because each of the six Grounds set forth in Intas's Petition suffers from multiple critical defects, the Board should deny institution.

## **II. BACKGROUND OF THE '334 INVENTION**

### **A. The State Of The Art**

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

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

Endoxifen is the primary metabolite of tamoxifen that exists in two isomeric forms: (E)-endoxifen and (Z)-endoxifen. (EX2001 (Davies Decl.) at ¶¶ 44-45.) (Z)-endoxifen is the active isomer, exhibiting much higher anti-estrogenic activity than the parent compound, tamoxifen. (EX1001 at 2:36-38.) (Z)-endoxifen is currently being evaluated in clinical trials for the prevention and treatment of ER-positive breast cancer. (E)-endoxifen has little or no anti-estrogenic activity. It was known in the art that (Z)-endoxifen is unstable, as (E)-endoxifen and (Z)-endoxifen rapidly interconvert under various commonly used conditions. (EX2001 (Davies Decl.) at ¶¶ 47, 50-51.) Prior to the '334 patent, it was difficult to sufficiently separate the two isomers to obtain a highly pure (Z)-endoxifen free base composition and the stability of such a composition had not been evaluated. (*Id.* at ¶¶ 48-51.) The '334 inventors noted that there was a need for synthetic purification methods to obtain a formulation containing highly pure (Z)-endoxifen



in an industrially scalable process that is sufficiently stable at ambient temperatures and humidities for extended periods of time to facilitate the preparation of pharmaceutical compositions that would be suitable for administration to a subject. (EX1001 at 82:36-41.)

**B. The Invention Claimed In The '334 Patent**

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

The '334 patent teaches a synthetic pathway to create this highly pure (Z)-endoxifen. (EX1001 at Examples 1, 4-9; EX2001 (Davies Decl. at ¶¶ 90-93.) The starting isomeric mixture of (E)/(Z)-endoxifen is first subjected to crystallization. (EX1001 at Examples 1, 4, 9.) Because the inventors observed that (E)-endoxifen is much less soluble than (Z)-endoxifen in a variety of solvents, this initial crystallization step results in an enriched (Z)-endoxifen component (*e.g.*, a mother liquor or filtrate). The enriched (Z)-endoxifen component is then subjected to further crystallization to obtain pure (Z)-endoxifen solid as a free base composition. The (Z)-endoxifen free-base solid composition obtained is shown to have increased stability in ambient conditions, with reduced isomeric conversion to the (E)-isomer.

The '334 patent further teaches a synthetic method suitable for industrial scale to make oral formulations comprising the at least 90% isomerically pure (Z)-endoxifen composition. (EX1001 at Examples 4-9.) The '334 patent also teaches product storage stability, *id.* at Example 11, and impurity-free compositions of (Z)-endoxifen, *id.* at Example 12. None of these concepts are taught by any of the art cited in the Petition. The '334 patent further provides data demonstrating the pharmacokinetics of the claimed formulations which have improved bioavailability. (*Id.* at Example 15; EX2001 (Davies Decl. at ¶¶ 90-93.)

### **III. PROSECUTION HISTORY**

#### **A. The '334 Patent Was Substantively Examined**

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

During prosecution, the applicant submitted Information Disclosure Statements listing at least 66 U.S Patent references, 31 foreign patent documents, and 76 non-patent literature documents, all of which were acknowledged by the Examiner during prosecution. (EX1002 at 345-358.) Additional references were disclosed in the text of the specification. Eight of the eighteen references cited in

the Petition were presented during examination including EX1003 on which all six grounds depend.<sup>1</sup> EX1003, EX1004, EX1005, EX1006, EX1007, and EX1018 were listed on IDS filings. (EX1002 at 346, 349-351.) EX1008 was described in the specification and incorporated by reference. (EX1001 at 11:6-10, 86:55-59.) EX1015 is referenced throughout the specification and in claims 5-7. (*Id.* at 41:61-64; 42:10-29, 55:8-56:65, 86:67, 98:38-51.)

The '428 application issued 13 months after it was filed. While the application faced no rejections during prosecution, there is no indication that the Examiner failed to fully consider the art disclosed by applicants, nor did Petitioner identify any such irregularity.

**B. The Parent Patent Of The '334 Patent Overcame Rejections Involving EX1003, EX1004, EX1006, EX1007, and EX1018**

U.S. Patent No. 11,261,151 (the "'151 patent," EX2003) is the parent of the '334 patent. It was filed as U.S. Patent Application No. 16/641,985 (the "'985 application") on September 10, 2018, and is also assigned to Patent Owner. The '151 patent and the '334 patent share the same specification. The '151 patent includes claims to certain compositions comprising crystalline forms of (Z)-

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<sup>1</sup> As discussed below in Section VII, not all of the eighteen art references listed in the Petition predate the '334 patent. EX1014 is undated. EX1019 postdates the priority date to which the '334 patent is entitled.

endoxifen, and methods of treating hormone-dependent breast disorders and reproductive tract disorders with said compositions. (EX2003 at 98:28-100:44.)

During prosecution of the '985 application, Patent Owner disclosed, and the Examiner considered, many of the same references included in the Petition. By explicitly noting that "all references [were] considered except where lined through," the Examiner considered EX1003 (Ahmad). (EX2004 ('985 File History 1) at 24.) The Examiner also considered other publications in the same family as Ahmad. These include PCT Pub. No. WO 2008/070463, the PCT application that EX1003 (Ahmad) claims priority to. (*Id.* at 25.) The Examiner also considered U.S. Patent Pub. No. 20160346230, which also shares the same specification as EX1003 (Ahmad). (*Id.* at 57.)

As with the prosecution of the '334 patent, during prosecution of the parent '151 patent, the Examiner substantively considered EX1006 (*id.* at 59),<sup>2</sup> EX1007 (*id.* at 27), and EX1018 (*id.* at 27). Moreover, Liu (EX1004) was identified by the International Search Report and Written Opinion, (EX2005 ('985 File History 2) at 1), the Intellectual Property Office of Singapore (*id.* at 6-7, 11), the European

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<sup>2</sup> The Examiner first "lined through" EX1006, (EX2004 ('985 File History 1) at 27), because the initially transmitted publication was not legible, as required by 37 C.F.R. § 1.98(a)(2). A legible copy was subsequently provided and reviewed by the Examiner. (*Id.* at 59.)

Patent Office (*id.* at 15-16), and by the Examiner as potential prior art. (*Id.* at 25-26). Patent Owner overcame Liu. (*Id.* at 34.)

#### **IV. CLAIM CONSTRUCTION**

Petitioner asserts that all terms should be given their plain and ordinary meaning but then suggests that the term “enteric capsule” found in claims 1, 3-4, 8, and 14-15 be defined as “a capsule ‘with one or more enteric coating agents,’ or an intrinsically enteric capsule that does not need an additional coating to provide the enteric property.” (Pet. at 9-10) (citing EX1001 at 39:19-30, 40:31-36.) Patent Owner agrees that the plain and ordinary meaning of “enteric capsule” is appropriate, but disagrees with the suggested definition, which omits the following passage from the specification: “to control or delay disintegration and absorption of the compositions comprising endoxifen or salts thereof in the gastrointestinal tract and thereby provide a sustained action over a longer period of time.” (EX1001 at 39:22-26.)

Nevertheless, Petitioner’s proposed construction of “enteric capsule” does not have any impact on its failure to meet its burden at this institution stage. Thus, the Board does not need to construe this or any other claim term in denying the Petition. *See, e.g., Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (noting that “we need only construe terms ‘that

are in controversy, and only to the extent necessary to resolve the controversy”)) (citation omitted); *ClearH20, Inc. v. CEVA Animal Health Inc.*, IPR2020-00039, Paper 21 at 6 (PTAB Mar. 18, 2020) (determining that no express claim construction was necessary in denying institution under § 325(d)). Patent Owner, however, reserves the right to put forth constructions of any particular claim term and to rebut any construction proffered by Petitioner should trial be instituted.

## **V. PERSON OF ORDINARY SKILL IN THE ART**

Petitioner proposes the following definition for a hypothetical POSA:

“... 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. . . . The analysis below would be the same if the level of skill were lower.”

(Pet. at 9.) Petitioner's proposed POSA definition, however, ignores the complex chemistry at the center of the '334 invention and should be rejected. Instead, Patent Owner submits that the hypothetical POSA in the field of the '334 patent would have: a graduate degree in organic chemistry, medicinal chemistry, pharmaceutical chemistry, or a related field, and four to six years of experience in the synthesis, purification, and design of pharmaceutical compounds and derivatives thereof as of the date of the claimed inventions. A POSA would have

worked with a team of professionals with training in related disciplines, such as pharmacology, pharmacokinetics, formulation, drug discovery and/or drug development as of the date of the claimed inventions. (EX2001 (Davies Decl.) at ¶¶ 42-43.)

Patent Owner requests that the Board adopt its definition of a POSA for purposes of this proceeding, as it reflects the nature of the invention: formulations comprising an at least 90% isomerically pure (Z)-endoxifen composition and associated methods of use.

## **VI. DISCRETIONARY DENIAL UNDER § 325(D)**

None of Petitioner's six Grounds raise any new or non-cumulative references and the Board should exercise its discretionary power to deny the Petition pursuant to § 325(d). Petitioner (1) presents the same or substantially the same art that previously was presented to the Office and (2) fails to demonstrate that the Office erred in a manner material to the patentability of challenged claims. *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 at 8 (PTAB Feb. 13, 2020) (precedential).

The *Advanced Bionics* enquiry "reflects a commitment to defer to previous Office evaluations of the evidence of record unless material error is shown." *Id.* at 9.

**A. *Advanced Bionics* Step 1: The Petition Presents The Same Or Substantially The Same Art That Was Considered During Examination**

The first prong of *Advanced Bionics* considers whether the same or substantially the same art or arguments were previously presented. *Id.* at 8. “Previously presented art includes . . . art provided to the Office by an applicant, such as on an Information Disclosure Statement (IDS), in the prosecution history of the challenged patent.” *Id.* at 7-8.

Whether the art is “substantially the same” as previously presented art focuses on (a) the similarities and material differences between the asserted art and the prior art involved during examination, and (b) the cumulative nature of the asserted art and the prior art evaluated during examination. *Merial, Inc., v. Intervet Intl’ B.V.*, IPR2018-00919, Paper 13 at 12 (PTAB Oct. 22, 2018) (citing *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 (PTAB Dec. 15, 2017)).

The Board may also consider the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or Patent Owner distinguishes the prior art. *Id.*; see also *Miltenyi Biomedicine GmbH v. The Trustees of the University of Pennsylvania*, IPR2022-00853, Paper 11 (PTAB Oct. 11, 2022) (explaining that *Becton Dickenson*



“[f]actors (a), (b), and (d) . . . come into play” in the first part of the framework whereas “Factors (c), (e), and (f) of . . . fall within part two of the framework.”).

The first prong of the *Advanced Bionics* test is plainly satisfied here for all six Grounds. As discussed below, the Examiner considered all of the references cited in Grounds 1, 2, 3, and 6. Grounds 4 and 5, which address dependent claims, rely on a combination of references previously considered and cumulative art.

**Ground 1 and 2** rely solely on EX1003, which was presented to and considered by the Examiner during prosecution of the '334 patent. (EX1002 at 346 (cite no. 027) (Examiner noted “all references [were] considered except where lined through”).) EX1003 is cited on the face of the '334 patent. (EX1001 at 1, 18:26-27.) EX1003 was also presented to and considered by the Examiner during prosecution of the parent '151 patent. (EX2004 ('985 File History 1) at 24.)

Petitioner includes EX1004 (Liu), and EX1005 (Song) as background art for Ground 2. Both references are cited in the specification of the '334 patent as references for the synthesis of endoxifen. (EX1001 at 18:30, 18:33-34.) Both references are also included on an IDS submitted during prosecution of the '334 patent. (EX1002 at 349-350.)

The Petition also cites EX1018 (Ahmad 2106) as background art for Ground 2. EX1018 was also cited during prosecution. (EX1002 at 261.)

While it is true that the '334 patent issued without facing any rejections, during prosecution of the parent '151 patent, the Examiner issued rejections over EX1004 (Liu), focusing on the synthetic method claim of the '151 patent and the synthetic pathway described in Liu. (EX2005 ('985 File History 2) at 25-26.) Patent Owner overcame the rejections over Liu and the parent '151 patent issued. (EX2005 ('985 File History 2) at 34 (referred as "Heinkele"); (EX2006 ('985 File History 3) at 7, 14-16).)

Petitioner should be aware of the parent '151 patent. Not only is the existence of this patent readily discernable, but the Petition itself mistakenly cites a portion of a claim from the '151 patent, attributing it to the challenged '334 patent. The Petition recites a diffraction pattern limitation that does not appear in the '334 patent but does appear in claim 16 of the '151 patent (*See* Pet. at 7-8; EX2003 at 100:22-26.)

The Board has previously rejected institution where the Petitioner failed to discuss the prosecution history of the challenged patent "or its parent application," thus "fail[ing] to point out whether or how the Examiner erred in evaluating the asserted prior art--prior art that is the same art . . . or substantially the same art . . . that the Examiner considered during prosecution." *Merial*, IPR2018-00919, Paper 13 at 25.

Grounds 1 and 2 pass the first prong of the *Advanced Bionics* framework.

**Ground 3** relies on the combination of EX1003 (Ahmad) and EX1008 (Cole). EX1008 describes enteric coated capsule technology. EX1008 is cited in the specification and incorporated by reference. (EX1001 at 11:6-10, 86:55-59.) Specifically, Example 13 describes oral compositions of (Z)-endoxifen, and the specification states that “[t]he capsules are coated with an enteric coating designed to achieve intestinal targeting (upper GI and colon), by the method of Cole et al. (Cole et al., Int’l J. of Pharmaceutics Vol. 231, 83-95 (2002).” (*Id.*)

Further, while the Petitioner argues that “none of the Enteric Capsule Art [included in the Petition]. . . was considered by the Examiner,” (Pet. at 24), there is no basis in the file history to conclude that the Examiner ignored and failed to consider EX1008. Moreover, the Petitioner overlooks the Examiner’s search strategy and results, which included “capsule,” “enteric capsule,” “enteric capsules,” and “enteric” within the same paragraph as “capsule.” (EX1002 at 392.)

Petitioner also argues that because none of the titles of the patents cited on the face of the ’334 patent include the word “capsule” or “enteric capsule,” the Examiner failed to consider any capsule or enteric capsule art. (Pet. at 25.) Petitioner overlooks the following references submitted to the Examiner during prosecution of the ’334 patent that reference enteric capsules: EX1003 (Ahmad) at

4:41-44 (“In some embodiments, the composition comprises a tablet or a filled capsule, wherein said tablet or filled capsule optionally comprises an enteric coating material.”); EX1006 (Ahmad 2010) at 3 (“Endoxifen citrate was prepared as an enteric-coated tablet”); and EX2007 (Intl. Pub. No. WO 2010/135703A2 by Ahmad) at Para. [00155] (“When desired, composition[s] containing endoxifen or endoxifen-lipid complex can be encapsulated in enteric-coated capsules to protect it from acids in the stomach.”). EX2007, a PCT publication in the same family as EX1003 (Ahmad) was explicitly initialed by the Examiner, and thus considered. (EX1002 at 367.)

EX1015 (USP 711) which the Petition cites as background art is cited at least 19 times throughout the specification and there is no indication that it was ignored by the Examiner.

Accordingly, the Enteric Capsule Art cited by Petitioner, including Cole, is cumulative to references submitted during prosecution.

Ground 3 thus passes the first prong of the *Advanced Bionics* framework.

**Ground 4**, which only challenges dependent claims, relies on the combination of EX1003 and EX1010 (Benameur). Benameur is similar to Cole in that it describes enteric capsule technology. EX1010 is merely cumulative of art already considered, including EX1008 (Cole), EX1003 (Ahmad), EX1006 (Ahmad

2010) and other references submitted during prosecution, as discussed above with respect to Ground 3.

Moreover, references added to obviousness combinations “not considered by Examiner solely for ‘additional subject matter of certain dependent claims[] is insufficient to persuade us that exercising our discretion under 35 U.S.C. § 325(d) is inappropriate.’” *Miltenyi*, IPR2022-00853, Paper 11 at 50 (citing *Kayak Software Corp. v. IBM*, CBM2016-00075, Paper 16 at 10 (PTAB Dec. 15, 2016) (informative)).

Ground 4 passes the first prong of the *Advanced Bionics* framework.

**Ground 5**, which also only challenges dependent claims, relies on the combination of EX1003 and EX1011 (Stegemann) and/or EX1012 (the HPE). EX1011 is a document entitled “Hard gelatin capsules today – and tomorrow.” EX1012 appears to be a portion of the index of a publication of pharmaceutical excipients.<sup>3</sup> The Petition relies on EX1011 and EX1012 for the disclosure of “various common excipients for use in capsules” including fillers. (Pet. at 49.)

Similar to the Enteric Coating Art discussed above with respect to Grounds 3 and 4, the Excipient Art (EX1011 and EX1012) is cumulative of at least the following references presented to the Examiner during prosecution: EX1002 at 348

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<sup>3</sup> EX1012 only contains five pages from the index of the publication. There is no substantive text associated with EX1012.

(considered by Examiner), EX2008 at Para. [0051] (“In another embodiment, the excipient may be a filler. Suitable fillers include carbohydrates, inorganic compounds, and polyvinylpyrrolidone. By way of non-limiting example, the filler may be calcium sulfate, both di- and tri-basic, starch, calcium carbonate, magnesium carbonate, microcrystalline cellulose, dibasic calcium phosphate, tricalcium phosphate, magnesium carbonate, magnesium oxide, calcium silicate, talc, modified starches, lactose, sucrose, mannitol, and sorbitol”); EX1002 at 348 (WO2009/120999 considered by Examiner), EX2009 at Para. [0079] (“[t]ablets or capsules can be prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g., pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g., lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g., magnesium stearate, talc or silica); disintegrants (e.g., potato starch or sodium starch glycolate); or wetting agents (e.g., sodium lauryl sulphate).”).

Ground 5 passes the first prong of the *Advanced Bionics* framework.

**Ground 6** combines EX1003 with EX1006 (Ahmad 2010) and EX1007 (Ahmad 2012). All three references were presented to, and considered by, the Examiner during prosecution. (EX1002 at 346, 351.)

Ground 6 therefore also passes the first prong of the *Advanced Bionics* framework.

**B. *Advanced Bionics* Step 2: The Office Made No Material Errors**

Under the second prong of *Advanced Bionics*, “[i]f reasonable minds can disagree regarding the purported treatment of the art or arguments, it cannot be said that the Office erred in a manner material to patentability.” *Advanced Bionics* at 9. Examples of “material error” include “misapprehending or overlooking specific teachings of the relevant prior art where those teachings impact patentability of the challenged claims,” or “an error of law, such as misconstruing a claim term, where the construction impacts patentability of the challenged claims.” *Id.* at 8–9, n.10.

In evaluating whether the Examiner’s analysis constitutes “material error,” the Board considers “(d) the extent of the overlap between the arguments made during examination and the manner in which petitioner relies on the prior art; (e) whether petitioner has pointed out sufficiently how the [E]xaminer erred in its evaluation of the asserted prior art; and (f) the extent to which additional evidence and facts presented in the petition warrant reconsideration of the prior art or arguments.” *Id.* at 9–10 & n.10; *see also Merial*, IPR2018-00919, Paper 13 at 12

(quoting *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 (PTAB Dec. 15, 2017)).

Petitioner bears the “burden of overcoming the deference that is due to a qualified government agency presumed to have properly done its job, which includes one or more Examiners who are assumed to have some expertise in interpreting the references and to be familiar from their work with the level of skill in the art and whose duty it is to issue only valid patents.” *Shire, LLC v. Amneal Pharm., LLC*, 802 F.3d 1301, 1307 (Fed. Cir. 2015) (citation omitted). In *Shire*, the court rejected the primary obviousness reference asserted by defendants because it was “listed on the face of the patents-in-suit and therefore the Examiner is presumed to have considered it.” *Id.*

Petitioner fails to establish that the Office erred in a manner material to the patentability of the challenged claims. Petitioner states that the “Examiner erred in not substantively considering [the references cited in the Petition].” (Pet. at 26.) There is no evidence, however, that the Examiner did not substantively consider the references. The references discussed above were all listed on an IDS and the Examiner noted that “[a]ll references [were] considered except where lined through.” (EX1002 at 345-358, 360-362, 364-365.) This Board has exercised its discretion pursuant to § 325(d) under similar circumstances. In *Biocon Pharma*



*Ltd. v. Novartis Pharmaceuticals Corp.*, IPR2020-01263, Paper 12 at 9 (PTAB Feb. 16, 2021), the Board declined to institute because the Examiner signed an IDS that included the relevant prior art references and “stated that the Examiner considered both prior-art references,” even though one of the references “was ‘not applied by the Examiner.’” The Board “accept[ed] that the Examiner considered [the reference] because it is listed on the IDS and the Examiner signed the IDS with the statement ‘all references considered except where lined through.’” *Id.*

The Notice of Allowance for the ’334 patent states that “[t]he Examiner has conducted a thorough search of the appropriate electronic data bases for the claimed subject matter and did not discover any reference which anticipates the claimed subject matter or would form a basis for concluding that the claimed subject matter would have been obvious. . . . Also, [the] claims . . . are presented in an enabled, definite matter. Accordingly, the Examiner believes the claimed subject matter to be currently in a condition for allowance.” (EX1002 at 388-389.)

Additionally, Petitioner disregards the thorough prosecution of the parent ’151 patent. The ’151 patent overcame obviousness rejections over EX1004 (Liu). (EX2005 (’985 File History 2) at 34; EX2006 (’985 File History 3) at 7, 16.) As previously noted, the Examiner considered EX1003 (Ahmad). (EX2004 (’985 File History 1) at 24). The Examiner also considered other publications related to

EX1003 (Ahmad) including Intl. Pub. No. WO-2008/070463, (*id.* at 25), and U.S. Patent Pub. No. 2016/0346230 (*id.* at 57).

The addition of the Enteric Capsule Art (EX1008, EX1010) and Excipient Art (EX1011 and EX1012) to Grounds 3, 4, and 5 challenging the dependent claims does not suggest a different result. At best, these references are cumulative of the art considered by the Examiner.

Accordingly, there is no evidence that the Examiner committed material error with respect to any of the rehashed combinations of art proposed by Petitioner. As such, the Board should defer to the Examiner's conclusions that the claims are novel and not obvious and deny institution.

**VII. DISCRETIONARY DENIAL UNDER § 324(A) IS APPROPRIATE BECAUSE PETITIONER FAILED TO ESTABLISH ANY CITED NON-PATENT PUBLICATION QUALIFIES AS PRIOR ART**

The decision to institute a trial is based on “the information presented in the petition filed under Section 321.” 35 U.S.C. § 324(a).<sup>4</sup> § 322(a) sets forth the requirements for a petition filed under § 321. The petition will only be considered if it identifies “in writing, and with particularity, each claim challenged, the grounds on which the challenge to each claim is based, and the evidence that supports the grounds for the challenge to each claim, including (A) copies of

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<sup>4</sup> Petitioner fails to identify any novel or unsettled legal question that is important to other patents or patent applications that might otherwise justify institution. *See* 35 U.S.C. § 324(b).

patents and printed publications that the petitioner relies upon in support of the petition; and (B) affidavits or declarations of supporting evidence and opinions, if the petitioner relies on other factual evidence or on expert opinions.” § 322(a)(3).

The initial burden of production of establishing that an asserted reference is prior art under 35 U.S.C. § 102 falls squarely on Petitioner. *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1379 (Fed. Cir. 2015); *Frontier Therapeutics, LLC v. Medac Gesellschaft Für Klinische Spezialpräparate MBH*, Case IPR2016-00649, Paper 10 (PTAB Sept. 1, 2016) (petitioner bears the burden to make a threshold showing that a reference is “printed publication” prior art). Petitioner, however, has failed to make a threshold showing that any of the non-patent publications cited in the Petition are printed publications that qualify as prior art.

**A. EX1014 Appears To Be An Undated Pharmaceutical Package Insert**

EX1014, which appears to be a pharmaceutical package insert for Zonalta (endoxifen citrate), is undated. Petitioner's expert relies on EX1014 (EX1020 at 6, 8, 31), but fails to address whether the document predates the '334 patent. Petitioner also failed to include any declaration to authenticate EX1014. There is nothing in the record to support a finding that EX1014 was publicly available before the critical date of the '334 patent. *See, e.g., Frontier*, IPR2016-00649,

Paper 10 at 22 (package insert for a pharmaceutical product not sufficiently shown to be printed publication because the conclusory statements of Petitioner's expert without supporting evidence were insufficient to establish public availability). *See also Mylan Pharm., Inc. v. Boehringer Ingelheim GMBH*, IPR2016-01565, Paper 23 (PTAB Aug. 1, 2017) (Petitioner did not provide evidence demonstrating that drug label was publicly available); *Pfizer Inc. v. Biogen Inc.*, IPR2017-01166, Paper 9 (PTAB Nov. 13, 2017) (Petitioner failed to establish that a drug label was a printed publication as the record was devoid of evidence demonstrating the public availability of the label before the critical date). EX1014, and Petitioner's expert's reliance on EX1014, should not be considered in the Board's analysis of the merits of the Petition.

**B. EX1019 Postdates The Critical Date Of The '334 Patent**

On its face, EX1019 appears to be a journal article authored by Milroy et al. EX1019 bears a copyright date of 2018 and states that it was available online on March 13, 2018. (*See* EX1019 at 1.) The critical date of the '334 patent, however, is September 11, 2017. Petitioner offers no evidence that EX1019 was publicly available before September 11, 2017. While the Petition cites EX1019 (Pet. at 37), Petitioner fails to address or explain how a reference that post-dates the '334 patent is relevant to the anticipation and obviousness grounds in the Petition. Petitioner's

expert also relies on EX1019 (EX1020 at 25, 31), without any explanation as to how EX1019 is relevant to the cited grounds. EX1019, and Petitioner's expert's reliance on EX1019, should not be considered in the Board's analysis of the merits of the Petition.

**C. EX1007 Appears To Be An Unauthenticated Web Page**

Petitioner relies on EX1007 in its obviousness combination for ground 6. Petitioner bears the burden to authenticate the evidence on which it relies. Fed. R. Evidence 901 ("the proponent must produce evidence sufficient to support a finding that the item is what the proponent claims it is"). While Petitioner describes EX1007 as originating from "ASCO MEETING LIBRARY, presented June 4, 2012," *see* Pet. Exhibit List, EX1007 appears to be a printout of a web page.

Web pages printouts are not self-authenticating under Fed. R. Evidence 902. *Comcast Cable Communications, LLC v. Rovi Guides, Inc.*, IPR2017-00941, Paper 70 (PTAB Sept. 7, 2018) (excluding web page printout as an exhibit because the petitioner failed to authenticate the document and stating that "to authenticate printouts from a website, various Board panels have required the party proffering the evidence to produce some statement or affidavit from someone with knowledge of the website, such as a web master or someone else with personal knowledge").

Neither Petitioner nor Petitioner's expert offer any evidence to authenticate EX1007. Petitioner failed to submit a declaration from the individual who captured the web page, failed to identify any distinctive characteristics of the web page that would suggest authenticity, and failed to demonstrate that the web page was captured and preserved using a reliable method. Petitioner's expert does not offer any first-hand knowledge of EX1007. *See* EX2021 at 17-18.

EX1007, and Petitioner's expert's reliance on EX1007, should therefore not be considered in the Board's analysis of the merits of the Petition.

**D. Petitioner Did Not Establish That EX1006-EX1011, EX1015-EX1018 Qualify As Publicly Accessible, Printed Publications**

Finally, except for EX1012 and EX1021, Petitioner fails to even attempt to establish that any of the remaining non-patent publications cited—EX1006-EX1011 and EX1015-EX1018—qualify as a printed publication.

Petitioner has the burden to prove that each of these exhibits qualifies as prior art. *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1376 (Fed. Cir. 2016). In *Hulu, LLC v. Sound View Innovations, LLC*, the Board noted that “at the institution stage, the petition must identify, with particularity, evidence sufficient to establish a reasonable likelihood that the reference was publicly accessible before the critical date of the challenged patent and therefore that there is a reasonable likelihood that it qualifies as a printed publication.” IPR2018-01039,

Paper 29 at 2 (PTAB Dec. 20, 2019) (precedential). *See also Acceleration Bay, LLC v. Activision Blizzard Inc.*, 908 F.3d 765, 772 (Fed. Cir. 2018) (“A reference is considered publicly accessible if it was ‘disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art, exercising reasonable diligence, can locate it.’”).

It is a legal determination, based on underlying fact issues, as to whether a reference qualifies as a printed publication. *In re Hall*, 781 F.2d 897, 899 (Fed. Cir. 1986). This analysis must be performed on a case-by-case basis. *In re Lister*, 583 F.3d 1307, 1311 (Fed. Cir. 2009). In a proceeding such as this before the Board, there is no presumption in favor of finding that a reference is a printed publication. *Hulu*, Paper 29 at 16.

Petitioner and Petitioner’s expert failed to explain or offer evidence supporting a finding that any of these non-patent publications qualify as a printed publication. For example, Petitioner failed to include the table of contents, circulation information, or even the journal cover of any of the purported journal articles to demonstrate public accessibility. (*See* EX1006, EX1008, EX1009, EX1010, EX1016, EX1017, EX1018.) It is unclear whether EX1011 is journal article or a book chapter, as there is no identifying information, such as a table of contents or cover page from which EX1011 purportedly came from demonstrating

publication or public accessibility. Similarly, EX1015 has no identifying information, such as a table of contents or publication information, to establish that the document is what Petitioner says it is.

Petitioner has made no effort to support its assertion that any of these references were publicly accessible prior to the critical date of the '334 patent. Therefore, EX1006-EX1011 and EX1015-EX1018, and Petitioner's expert's reliance on said exhibits, should not be considered in the Board's analysis of the merits of the Petition.

## **VIII. EACH OF THE PETITION'S GROUNDS FAILS ON THE MERITS**

As explained below and in EX2001 (Davies Decl.), none of the art cited by Petitioner renders the invention claimed in the '334 patent anticipated or obvious.

### **A. Ground 1: Claims 1, 2, 4, 15, 20-22 Are Not Anticipated By Ahmad**

Invalidity under 35 U.S.C. § 102 is an exacting standard. "To anticipate a claim, a prior art reference must disclose every limitation of the claimed invention, either expressly or inherently." *Eli Lilly and Co. v. Los Angeles Biomedical Res. Inst. at Harbor-UCLA Med. Ctr.*, 849 F.3d 1073, 1074-75 (Fed. Cir. 2017) (citation omitted). "To anticipate, a reference must do more than 'suggest' the claimed subject matter." *Id.* (citing *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1055 (Fed. Cir. 2010)). The dispositive anticipation inquiry takes into



account the literal teachings of the prior art reference and inferences the ordinarily skilled person would draw from it. *Id.*

Importantly, to anticipate, a prior art reference must “enable one of ordinary skill in the art to make the invention *without undue experimentation*. . . . In other words, the prior art must enable the claimed invention.” *Impax Labs., Inc. v. Aventis Pharms. Inc.*, 545 F.3d 1312, 1314 (Fed. Cir. 2008) (emphasis added). Undue experimentation is evaluated using the *Wands* factors: “(1) the quantity of experimentation; (2) the amount of direction or guidance present; (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.” *Id.* at 1314-1315 (citing *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988)).

*Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075 (Fed. Cir. 2008) is instructive. There, the patent-in-suit contained claims to the dextrorotatory enantiomer of a specific compound substantially separated from the levorotatory enantiomer. *Id.* at 1082-1083. The asserted anticipatory prior art reference described a racemic mixture of the two enantiomers and contained no examples showing separation of the two, but claimed “both enantiomeric forms or their mixture.” *Id.* at 1083. The district court concluded that the prior art reference was

not enabling, and therefore not anticipatory, as it contained no guidance as to how to separate the two. “Absent such guidance, undue experimentation would be required.” *Id.* at 1084. The Federal Circuit affirmed, finding no clear error in the district court’s analysis. *Id.* at 1085.

***1. Independent Claims 1 and 15***

***a) Ahmad Does Not Contain An Enabling Disclosure Of (Z)-Endoxifen At 90% Or Greater Purity***

Independent claim 1 of the '334 patent recites an “oral formulation comprising an endoxifen composition encapsulated in an enteric capsule . . . ***wherein at least 90% by weight of the compound of Formula III is (Z)-endoxifen.***” (EX1001 at 98:13-31 (emphasis added).) Independent claim 15 recites “[a] method of delivering (Z)-endoxifen to a subject . . . ***wherein at least 90% by weight of the compound of Formula III is (Z)-endoxifen.***” (EX1001 at 99:7-26, emphasis added.) EX1003, however, does not enable a POSA to make 90% pure (Z)-endoxifen. (EX2001 (Davies Decl.) at ¶¶ 98-108.) Because EX1003 does not anticipate independent claims 1 or 15, the challenged dependent claims 2, 4, and 20-22 are also not anticipated and Ground 1 thus fails.

EX1003 states “[o]ne object of the present invention is to provide E-endoxifen ***or*** Z-endoxifen with at least 80% purity, such as at least 90% pure . . .” (EX1003 at 12:14-17, emphasis added.) While EX1003 does state that “a mixture

of E- and Z-isomers of endoxifen can be separated . . . by crystallization, or purification by liquid column chromatography . . . or high-pressure liquid column chromatography,” (*id.* at 11:17-23), EX1003 fails to specifically teach **how** to separate the two isomers to generate 90% pure (Z)-endoxifen. (EX2001 (Davies Decl.) at ¶¶ 98-108.)

Rather than including a specific synthetic pathway and purification steps to generate 90% pure (Z)-endoxifen, EX1003 recites generic lists of solvents, acids, fractional crystallization, and column chromatography conditions. (EX1003 at 11:24-12:13.) For example, EX1003 states:

Suitable solvents that can be employed in present invention for the separation of E- and Z-isomers of endoxifen include but are not limited to hexanes, heptanes, and the like, benzene; toluene; ethyl acetate; acetonitrile; chlorinating solvents such as methylene chloride, chloroform, 1,2-dichloromethane, and the like, ketones, (e.g., acetone, 2-butanone, and the like), ethers such as diethyl ether, diisopropyl ether, methyl butyl ether, and tetrahydrofuran, alcohols such as methanol, ethyl alcohol, and isopropyl alcohol, and the like, and water. A solvent for crystallization can be used as a single solvent, or as mixture of solvents such as hexane-ethyl acetate, chloroform-acetone, chloroform-methanol, dichloromethane-methanol, and the like. When a mixture of two solvents is used in the present invention, examples of ratios of one solvent to another are e.g., in a range such as 9:1 to 1:9, (e.g., 8:2, 7:3; 6:4; 5:5; 4:6; 3:7; 2:8; 1:9, and the like.) However, mixtures for use in the present invention are not limited to these ratios, or to mixtures comprising only two solvents.

(EX1003 at 11:24-42.) Just sorting through the laundry list of solvents would require a POSA to engage in undue experimentation, and this represents just one

step in the synthetic pathway. EX1003 does not describe any meaningful amounts, ranges, examples, or guidelines. (EX2001 (Davies Decl.) at ¶¶ 99-102.)

Even if a POSA attempted to follow the synthesis examples in EX1003 at 22:32-25:67, at best this approach would most likely generate a roughly 1:1 ratio of (E):(Z) isomers, or a 50% pure (Z)-endoxifen mixture. (EX2001 (Davies Decl.) at ¶¶ 109-111.) EX1003 also does not teach the use of a purification method that detects isomeric purity, further limiting the usefulness of the examples in the specification. At best, Ahmad may teach synthesizing a highly impure endoxifen mixture, however, Ahmad does not provide any teachings for subsequent isomeric purification, or any oral formulation thereof, and therefore would not enable a POSA to obtain an isomerically pure (Z)-endoxifen composition suitable for use in an oral formulation. (EX2001 (Davies Decl.) at ¶¶ 105-106.)

The purification of (Z)-endoxifen is a technically difficult and fraught process, in large part because of the instability of the (Z) isomer, which is prone to conversion to (E)-endoxifen. (EX2001 (Davies Decl.) at ¶ 51.) EX1003 does not even mention this instability problem, further compounding the lack of enablement.

Even the claims of EX1003 demonstrate that at most, a POSA might consider generating an 80% pure (Z)-endoxifen in the form of a citrate salt.

(EX1003 at 30:55-61.) As Dr. Davies explains, however, it is unlikely that a POSA would be able to make an 80% (Z)-endoxifen citrate salt composition by following the examples in EX1003 because there is a lack of enabling teaching for doing so. (EX2001 (Davies Decl.) at ¶¶ 105-106.) Even, however, if EX1003 enables the synthesis of 80% Z-endoxifen citrate salt—which it does not—there is no enabling disclosure of 90% (Z)-endoxifen free base. (*Id.* at ¶ 103.)

The Petition does not even try to explain how EX1003 would enable a POSA to synthesize 90% pure (Z)-endoxifen. Instead, the Petition devotes four sentences to this issue and implicitly acknowledges that EX1003 is not enabling and therefore not anticipatory:

Ahmad teaches that “[o]ne object of the present invention is to provide E-endoxifen or Z-endoxifen with at least 80% purity, such as at least 90% pure or at least 95% pure or at least 98% pure or at least 99% pure or at least 100% pure.” . . . Ahmad teaches that this can be accomplished using crystallization or chromatography. . . . Thus, Ahmad teaches “wherein at least 90% by weight of the compound of Formula (III) is (Z)-endoxifen.” To the extent it is argued there is not a specific, enabling disclosure of 90% pure (Z)-endoxifen by Ahmad, forming such pure formulations was known in the art as taught by e.g., Liu and Song.

(*See* Pet. at 29-30.) The Petition identifies no teaching in EX1003 that would allow a POSA to synthesize 90% pure (Z)-endoxifen free base. The Petition’s cursory reference to EX1004 (Liu) and EX1005 (Song) does not supply the missing enabling disclosures. (EX2001 (Davies Decl.) at ¶¶ 112-119.)

**b) The File History Of EX1003 Further Demonstrates That It Does Not Enable A POSA To Make (Z)-Endoxifen At 90% Or Greater Purity**

A review of the file history of EX1003 evinces this enablement deficiency. During prosecution, EX1003 faced numerous rejections. In response, applicants amended the claims to “[a] solid pharmaceutical composition comprising an effective amount of a synthetic preparation of endoxifen, wherein (i) said synthetic preparation of endoxifen is at least 80% Z-endoxifen; (ii) said synthetic preparation of endoxifen is in the form of a salt, wherein said solid pharmaceutical composition is in the form of an enteric-coated tablet or enteric-coated capsule.” (EX2010 (Ahmad File History) at 54.)

After five rounds of rejections, applicants submitted an inventor declaration from co-inventor Sheikh pursuant to 37 C.F.R. §1.132, (EX2010 (Ahmad File History) at 96-98), describing that the endoxifen used in EX1006 (Ahmad 2010) was an **80% (Z)-endoxifen enteric tablet in the form of a citrate salt**. (*Id.* at 96 (emphasis added).) EX1003 issued shortly thereafter with claims to “at least 80% Z-endoxifen . . . in the form of a citrate salt.” (EX1003 at 30:55-64.) There is no basis in the prosecution history of EX1003 to conclude that the inventors themselves ever made a formulation comprising 90% (Z)-endoxifen of any form,

let alone 90% (Z)-endoxifen free base, as contemplated by the '334 patent. (*See, e.g.,* EX1001 at 9:1-2.)

Neither EX1003 nor any references cited in the file history of EX1003 provides sufficient guidance to a POSA as to the solvent ratios, crystallization parameters, or any other reaction conditions that would allow one to practice the claims of the '334 patent without undue experimentation. (EX2001 (Davies Decl.) at ¶¶ 102-106.)

***c) Petitioner's Reliance On EX1004 (Liu) and EX1005 (Song) As Background Art Does Not Enable EX1003***

The Petition seemingly acknowledges the lack of enablement of EX1003 and states that “[t]o the extent it is argued there is not a specific, enabling disclosure of 90% pure (Z)-endoxifen by Ahmad, forming such pure formulations was known in the art as taught by e.g., Liu and Song.” (Pet. at 30.)

It is axiomatic that in the anticipation analysis, EX1004 and EX1005 cannot be used to fill in any missing limitations, such as a purity level greater than 80% or the creation of (Z)-endoxifen free base—both absent from EX1003. “Anticipation requires disclosure of all of the limitations of a claim in one place, not by combination of multiple disclosures.” *See, e.g., N. Am. Oil Co., Inc. v. Star Brite Distrib., Inc.*, 46 F. App'x 629, 631 (Fed. Cir. 2002)

Even if EX1004 and EX1005 are evaluated only as providing background knowledge that a POSA would be expected to have, these references do not enable EX1003. (EX2001 (Davies Decl.) at ¶¶ 112-119.) First, the Petition oversimplifies the technical difficulties of purifying (Z)-endoxifen that can be administered in an enteric capsule for therapeutic use. (*Id.*) Neither EX1004 nor EX1005 describe synthetic pathways explicitly suitable for use as pharmaceutical formulations. For example, neither EX1004 nor EX1005 describe whether particular listed solvents are suitable for pharmaceutical manufacturing or whether harmful residual solvents or impurities might remain in the resulting endoxifen. Neither EX1004 nor EX1005 use the same synthetic pathway as either the '334 patent or EX1003. (EX2001 (Davies Decl.) at ¶¶ 69, 124.) For example, EX1004 uses entirely different starting materials than either the '334 patent or EX1003. (*Id.*) And neither EX1004 nor EX1005 describe the stability profile of the resulting endoxifen. (*Id.*) The Petition provides no explanation for how a POSA could use either synthetic method described in the disclosure of EX1003 to create an oral formulation comprising 90% pure (Z)-endoxifen.

Moreover, the Petition fails to identify with any particularity the portions of EX1004 or EX1005 that would enable EX1003. 37 C.F.R. § 42.204(b)(4) and (5) require that the Petition identify “[t]he exhibit number of the supporting evidence



relied upon to support the challenge and the relevance of the evidence to the challenge raised, including identifying specific portions of the evidence that support the challenge.” Instead, the Petition improperly shifts the onus on to Patent Owner and the Board to dig through the references to understand the grounds presented. This is another reason for denial. *Intervet Inc. v. Boehringer Ingelheim Vetmedica Inc.*, IPR2018-01788, Paper 9 at 8 (PTAB Apr. 16, 2019) (denying institution and noting that “[a]brief must make all the arguments accessible to the judges, rather than ask them to play archeologist with the record”).

In sum, EX1003 does not anticipate claims 1, 2, 4, 15, and 20-22 because it does not disclose a 90% pure (Z)-endoxifen composition and does not enable a POSA to synthesize such a composition without engaging in undue experimentation. The Petition’s high level, conclusory statements do not meet Petitioner’s burden of demonstrating anticipation by a preponderance of the evidence.

## **2. *Dependent Claims 2, 4, 20-22***

Dependent claims 2 and 4 depend on claim 1 and dependent claims 20-22 depend on claim 15. Each of these dependent claims requires at least 90% (Z)-endoxifen, which is not enabled by EX1003. Because neither claim 1 nor claim 15

is anticipated by EX1003 (Ahmad), claims 2, 4, and 20-22 are consequently not anticipated. *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1371 (Fed. Cir. 2008) (holding that “unless a reference discloses within the four corners of the document not only all of the limitations claimed but also all of the limitations arranged or combined in the same way as recited in the claim, it cannot be said to prove prior invention of the thing claimed and, thus, cannot anticipate under 35 U.S.C. § 102.”).

**B. Ground 2: Claims 1, 2, 4, 15, 20-22 Are Not Obvious Over Ahmad**

Petitioner next relies on EX1003 (Ahmad) as a single obviousness reference. However, just as EX1003 fails to anticipate the challenged claims, it fails to render them obvious. “Obviousness is a question of law with underlying factual findings related to, among other things, the scope and content of the prior art, whether a person of ordinary skill in the art [] would have had reason to combine or modify the prior art to arrive at the claimed invention, and in so doing, would have had a reasonable expectation of success.” *Grunenthal GmbH v. Alkem Labs. Ltd.*, 919 F.3d 1333, 1341 (Fed. Cir. 2019).

Petitioner uses Ahmad as a standalone reference in its obviousness challenge for Ground 2. But “[i]n the absence of such other supporting evidence to enable a skilled artisan to make the claimed invention, a standalone § 103 reference must

enable the portions of its disclosure being relied upon.” *Raytheon Techs. Corp. v. GE*, 993 F.3d 1374, 1381 (Fed. Cir. 2021) (citing *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 297 (Fed. Cir. 1985)). Therefore, Ahmad’s lack of enablement is also fatal for Ground 2.

Though § 103 “does not require absolute predictability of success’ . . . [w]hat does matter is whether the prior art gives direction as to what parameters are critical and which of many possible choices may be successful.” *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 965 (Fed. Cir. 2014) (citation omitted). A reasonable expectation of success requires more than a trial-by-error process where a POSA “merely var[ies] all parameters or tr[ies] each of numerous possible choices until . . . possibly arriv[ing] at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.” *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1365 (Fed. Cir. 2007) (internal citation omitted).

Petitioner urges the Board to adopt a “trial-by-error” method here, suggesting that a POSA would just modify EX1003 in some unexplained manner to arrive at the claimed invention. But doing so invites only impermissible hindsight bias. *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1070-71 (Fed. Cir. 2012) (“Where, however, a

defendant urges an obviousness finding by merely throwing metaphorical darts at a board in hopes of arriving at a successful result, but the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful, courts should reject hindsight claims of obviousness.”) (internal citation omitted).

***1. Independent Claims 1 and 15***

***a) The Petition Is Silent On How EX1003 Should Be Modified To Arrive At The Claimed 90% (Z)-Endoxifen Composition***

The Petition devotes one paragraph to explaining how EX1003 renders independent claims 1 and 15 obvious. (Pet. at 37.) While Petitioner asserts that “[a] POSA would have had a reasonable expectation of success in arriving at the claimed limitation, as both forming (Z)-endoxifen and enteric capsules were well known in the art,” the Petition fails to explain how a POSA would use EX1003 to get to the 90% (Z)-endoxifen required by independent claims 1 and 15. (EX2001 (Davies Decl.) at ¶¶ 121-122.)

Though a “reference asserted under §103 does not necessarily have to enable its own disclosure, i.e., be ‘self-enabling,’ to be relevant to the obviousness inquiry[,]” thus possibly “furnish[ing] the motivation to combine,” some other reference must enable the claimed limitation. *See Raytheon*, 993 F.3d at 1380. That is, “the evidence of record must still establish that a skilled artisan could have

made the claimed invention.” *Id.* At 1381. The Petition, however, does not formally seek to combine EX1003 with any other reference to meet the 90% (Z)-endoxifen limitation. There is no evidence cited by Petitioner that a POSA would be able to use the synthetic methods described in EX1003 to make a pharmaceutical formulation comprising 90% (Z)-endoxifen free base. (EX2001 (Davies Decl.) at ¶¶ 121-122.)

The Petition cites *Game & Tech Co. v. Activision Blizzard Inc.*, 926 F.3d 1370, 1381 (Fed. Cir. 2019), for the proposition that a single reference can render a patent obvious. (Pet. at 37.) However, the Petition omits the central premise of *Activision*, which is that “a patent can be obvious in light of a single prior art reference *if it would have been obvious to modify that reference to arrive at the patented invention.*” *Activision*, at 1381 (emphasis added). The Petition fails to explain how a POSA could modify EX1003 to arrive at the claimed invention.

As described above in Section VII.A.1.a., a POSA following the synthetic pathway of EX1003 would, at best, arrive at an estimated 1:1 isomeric mixture of (E/Z)-endoxifen. (EX2001 (Davies Decl.) at ¶ 109.) Even giving the Sheikh declaration the greatest benefit of the doubt and assuming it teaches a POSA how to achieve an 80% (Z)-endoxifen citrate salt (although neither the Sheikh declaration nor EX1003 provide any experimental conditions or results

demonstrating 80% isomeric purity of (Z)-endoxifen or methods of making endoxifen citrate salt) (EX2001 (Davies Decl.) at ¶ 106.), it still falls far short of teaching how to achieve an oral formulation comprising greater than 90% (Z)-endoxifen.

EX1003 also fails to acknowledge the importance of an isomerically pure (Z)-endoxifen composition that would equilibrate to a (E)/(Z)-endoxifen mixture at ambient temperatures and humidity. (*Id.* at ¶¶ 107, 130.) Stability is key to pharmaceutical formulations. EX1003 is silent as to stability of the resulting endoxifen citrate salt. More problematic, EX1003 suggests the use of an endoxifen citrate salt oral formulation, the synthesis of which teaches away from an isomerically pure (Z)-endoxifen composition. (EX2001 (Davies Decl.) at ¶¶ 58-61, 110.) As discussed by Dr. Davies, the synthesis of a citrate salt would likely involve dissolving the purified (Z)-endoxifen solid in a citric acid solution, which would promote the acid-promoted isomerization of (Z)-endoxifen to (E)-endoxifen. (EX2001 (Davies Decl.) at ¶¶ 58-61, 110.)

As Dr. Davies explains, EX1003 also teaches away from the '334 patent by describing only methods of purifying endoxifen with ethyl acetate, which would predominantly result in an isomerically enriched (E)-endoxifen solid. (*Id.* at ¶ 58.) EX1003 further teaches away from the '334 patent because it lacks an initial step

for (Z)-endoxifen purification, which would result in a roughly 1:1 isomeric ratio of (E)-endoxifen:(Z)-endoxifen. (*Id.* at ¶ 59.)

Therefore, in addition to failing to teach or enable isomerically pure (Z)-endoxifen compositions, EX1003 also fails to disclose methods of endoxifen citrate preparation that would be stable and resistant to acid-promoted isomerization. The Petition is silent on explaining how a POSA would modify EX1003 to overcome these purity and stability issues.

***b) The Petition Is Silent On How The Background Knowledge Of A POSA Could Be Used To Modify EX1003 To Arrive At The Claimed 90% (Z)-Endoxifen***

The only background knowledge the Petition attributes to a POSA are the following: “(Z)-endoxifen was more active at estrogen receptors” (Pet. at 37 (citing EX1004 and Petitioner’s expert declaration at ¶ 62)), “endoxifen could degrade in the acidic conditions of the stomach” (*id.* (citing EX1004, Petitioner’s expert declaration at ¶ 65, EX1014,<sup>5</sup> EX1018, EX1019<sup>6</sup>)), and “forming both Z-endoxifen and enteric capsules were well known.” (*Id.* (citing Petitioner’s expert declaration at ¶ 68)).

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<sup>5</sup> As explained above in Section VII.A, EX1014 is undated and not authenticated and therefore is not available as prior art.

<sup>6</sup> As explained above in Section VII.B, EX1019 postdates the ‘334 patent and is not available as prior art.

Neither the Petition nor Petitioner's expert declaration, however, substantively address the background knowledge a POSA would understand from the state of the art that would allow a POSA to modify EX1003 to get to 90% (Z)-endoxifen.

Petitioner's expert does state that "achieving 90% pure (Z)-endoxifen was disclosed in the art by other references such as Liu and Song. . . . A POSA would thus know how to make 90% pure (Z)-endoxifen." (EX1020 at ¶ 64.) Petitioner's expert, however, fails to explain how this knowledge of benchtop synthesis methods would educate a POSA using EX1003 to get to the claimed invention of a pharmaceutical formulation with 90% (Z)-endoxifen. (EX2001 (Davies Decl.) at ¶¶ 112-119.)

Even if EX1004 (Liu) and EX1005 (Song) are evaluated as background art, a POSA would not be able to use those teachings to arrive at the claimed invention for multiple reasons. EX1004 (Liu) describes a very different synthetic pathway to that of the '334 patent as well as to the synthetic pathway of Ahmad, which includes different starting materials and different crystallization parameters, and further results in impracticably low yields. (EX2001 (Davies Decl.) at ¶¶ 69-70, 112-119.) EX1004 does not describe an oral formulation, and there is no teaching about the stability of the resulting endoxifen compound. (*Id.*) EX1004 is silent on



whether residual solvents or other impurities might be present, which would make the resulting endoxifen product unsuitable for a pharmaceutical formulation. (*Id.*) Finally, the two different synthetic pathways of EX1003 and EX1004 would likely result in two different impurity profiles and two different stability profiles. (EX2001 (Davies Decl.) at ¶¶ 69, 112-119.) The Petition and Petitioner's expert are both silent as to how or why a POSA would be motivated to combine the teachings of these two references.

As explained by Dr. Davies, the teachings of EX1005 (Song) are even more problematic. (EX2001 (Davies Decl.) at ¶¶ 77-87, 112-119.) According to Dr. Davies, EX1005 does not disclose a synthetic method of creating highly pure (Z)-endoxifen as a result of experimental error. (*Id.* at ¶¶ 77-87.) EX1005 relies on incorrect analysis of nuclear magnetic resonance (NMR) spectroscopy data to characterize the final product, and it is more likely that EX1005 describes a method of synthesizing highly pure (E)-endoxifen. (*Id.*) The Petition and Petitioner's expert are both silent as to the specific process and analysis details employed by EX1005. A POSA following the teachings of EX1005 would thus be directed away from the claimed invention.

Thus, even relying on background knowledge in EX1004 and EX1005 regarding creating highly pure (Z)-endoxifen, a POSA would not be motivated to

modify EX1003 to create a pharmaceutical formulation with 90% pure (Z)-endoxifen. Ground 2 fails to render independent claims 1 and 15 obvious. (EX2001 (Davies Decl.) at ¶¶ 127-131.)

## **2. Dependent Claims 2, 4, 20-21**

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

## **C. Ground 3: Claims 5-8, 16, 17 Are Not Obvious Over Ahmad In View Of Cole**

Petitioner’s third ground seeks to combine EX1003 with EX1008 (Cole) to challenge dependent claims 5-8, 16, and 17. Each of these challenged dependent claims includes the requirement that the formulation comprises an endoxifen composition wherein “at least 90% by weight of the compound of Formula (III) is

(Z)-endoxifen” found in independent claims 1 and 15. As described above, EX1003 fails to anticipate or render obvious these independent claims.

Petitioner's Ground 3 fails because Grounds 1 and 2 fail. It is axiomatic that if an independent claim is nonobvious, then the dependent claim is also nonobvious. The Board does not need to consider “arguments that certain dependent claim limitations would have been obvious where the base claim has not been proven invalid.” *SynQor, Inc. v. Artesyn Techs., Inc.*, 709 F.3d 1365, 1375 (Fed. Cir. 2013).

Even putting aside this failure of proof for the independent claims, EX1008 is incorporated by reference into the '334 patent in Example 13. (EX1001 at 86:55-61.) Cole is cited for the following teaching: “The capsules [of Example 13] are coated with an enteric coating designed to achieve intestinal targeting (upper GI and colon), by the method of Cole et al. . . . EUGRADIT L30 D55 is used as an enteric coating for upper gastrointestinal targeted release.” (*Id.*) The Federal Circuit held that it is “hindsight reasoning” to “do no more than piece the invention together using the patented invention as a template.” *Tex. Instruments v. U.S. Int'l Trade Comm'n*, 988 F.2d 1165, 1178 (Fed. Cir. 1993). Petitioner engages in impermissible hindsight analysis when combining EX1008 and EX1003 to arrive at the enteric coating limitation of the dependent claims.

For example, rather than identifying a motivation to combine the references on the basis of the references themselves, Petitioner states that a “POSA would understand Cole to teach that enteric coating capsules, such as those taught in Ahmad, would be ‘formulated such that the oral formulation is resistant to dissolution in an acidic environment for at least 2 hours, as measured in a dissolution test performed according to a method of USP 711.’” (Pet. at 42.) Moreover, the Petition fails to explain why a POSA would have a reasonable expectation of success, beyond the fact that Cole is included in the ’334 patent. (EX2001 (Davies Decl.) at ¶¶ 132-137.) This is impermissible hindsight bias because it uses the ’334 patent as a goalpost.

Further, a POSA would not have a reasonable expectation of success in combining Ahmad with Cole. A POSA would need to engage in undue experimentation to create an oral formulation of at least 90% (Z)-endoxifen with the desired characteristics, such as increased bioavailability. (EX2001 (Davies Decl.) at ¶¶ 133-136.) Developing an oral formulation, especially of a compound like (Z)-endoxifen that is known to interconvert to its inactive isomer, would require significant experimentation to determine a formulation that would result in the desired characteristics (*Id.*) Neither Ahmad nor Cole teach what would have

been expected when formulating endoxifen or provide any reasonable expectation of success for producing enteric formulations comprising endoxifen.

Ground 3 thus fails and challenged claims 5-8, 16, and 17 are not obvious over EX1003 (Ahmad) in view of EX1008 (Cole).

**D. Ground 4: Claim 3 Is Not Obvious Over Ahmad In View Of Benameur**

Petitioner's fourth ground seeks to combine EX1003 with EX1010 (Benameur) to challenge dependent claim 3. As with Ground 3, this challenged dependent claims includes the requirement that the formulation comprises an endoxifen composition comprising "at least 90% by weight of the compound of Formula (III) is (Z)-endoxifen" found in independent claims 1 and 15. As described above, EX1003 fails to anticipate or render obvious these independent claims, and thus claim 3 is also non-obvious.

In addition to the fatal flaw that EX1003 does not invalidate the independent claims, the Petition fails to describe a motivation to combine EX1010, which teaches uncoated enteric capsules with EX1003 to arrive at the uncoated enteric capsule limitation of claim 3.

Again, the Petition engages in hindsight analysis by failing to identify any passage in EX1003 that suggests an uncoated enteric capsule limitation is desired. This is impermissible hindsight in an obviousness analysis. *Innogenetics, N.V. v.*

*Abbott Labs.*, 512 F.3d 1363, 1374 n.3 (Fed. Cir. 2008) (“We must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention”). While Petitioner states that uncoated enteric capsules are desirable because some “sensitive molecules . . . can degrade at the high temperatures or can be sensitive to aqueous coating solution associated with pan and fluid bed coating processes,” (Pet. at 54), there is no teaching in EX1003 that (Z)-endoxifen is sufficiently unstable that it would benefit from such an approach. In short, Petitioner’s argument is untethered from any relevant facts. Further, a POSA would readily understand that the drug formulation process is highly technical and unpredictable and involves significant challenges such as potential chemical interactions between coatings and other formulation components; variability in release properties depending on the characteristics of the compound being formulated; among countless others. (EX2001 (Davies Decl.) at ¶¶ 135, 138-143.)

Ground 4 fails and challenged claim 3 is patentable.

**E. Ground 5: Claims 9-13 Are Not Obvious Over Ahmad In View Of Stegemann And/Or The HPE**

For Ground 5, Petitioner relies on EX1011 (Stegemann) and/or EX1012 (the Handbook of Pharmaceutical Excipients, or HPE) to challenge dependent claims 9-

13, which require fillers, disintegrants, and lubricants. For similar reasons as set forth above, because the independent claims are non-obvious, these dependent claims are non-obvious.

Again, setting aside this fundamental flaw, the Petition's motivation to combine EX1003 with EX1011 and/or EX1012 and any explanation of a POSA's reasonable expectation of success are conclusory. For example, the Petition states "the selection of these fillers would be an obvious and routine formulation decision." (Pet. at 51). Especially in dealing with an unstable compound such as (Z)-endoxifen, a POSA would need more of a motivation to combine than just a listing of certain excipients in the index of a textbook, (EX1012). Additionally, oral formulations are known to have unpredictable and variable compatibilities when formulated with pharmaceutical excipients (*e.g.*, varying chemical stabilities and chemical interactions) and those interactions further depend on the oral dosage forms used (*e.g.*, a salt or a free base). (EX2001 (Davies Decl.) at ¶¶ 144-149.)

Ground 5 fails and challenged claims 9-13 are not unpatentable over the combination of EX1003 and EX1011 and/or EX1012.

**F. Ground 6: Claims 14, 18, and 19 Are Not Obvious Over Ahmad In View Of Ahmad 2010 And Ahmad 2012**

Finally, the Petition asserts that dependent claims 14, 18, and 19 are obvious in view of EX1003 (Ahmad) and EX1006 (Ahmad 2010) and EX1007 (Ahmad

2012). Again, “dependent claims are nonobvious if the independent claims from which they depend are nonobvious[.]” *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992); *see also Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008) (holding that “if claim 1 is not obvious then claims 6-8 also cannot be obvious because they all depend from a nonobvious claim”) (internal citation omitted). Thus claims 14, 18, and 19 are not obvious because claims 1 and 15 are non-obvious and not anticipated.

The Petition relies on EX1006 and EX1007 for their teachings about certain dosing and pharmacokinetic properties of an endoxifen composition. As explained above in Section VII.A.1.a), the formulation that was administered in EX1006 is, at best, an 80% (Z)-endoxifen citrate salt. Neither EX1006 nor EX1007 describe the dosing parameters or pharmacokinetic properties of a 90% (Z)-endoxifen free base formulation. (EX2001 (Davies Decl.) at ¶¶ 150-154.)

With respect to the dosing limitation of claim 14, while EX1006 and EX1007 suggest appropriate doses of “endoxifen”—as the Petition acknowledges, neither document on its face discloses whether the “endoxifen” is (Z), (E), or a mixture of both isomers. Thus, a POSA would understand that any dosing information gleaned from these two references may not be immediately applicable to a 90% pure (Z)-endoxifen formulation. (*Id.*)



With respect to the pharmacokinetic properties of claims 18 and 19, the Petition states that these values “would be the inherent result” of dosing the formulation of EX1003 with the dosing ranges taught by EX1006 and EX1007. (Pet. at 55-56.) The Petition appears to make an inherent obviousness argument without stating as much. If so, the Federal Circuit has admonished that “the concept of inherency must be limited when applied to obviousness, and is present only when the limitation at issue is the ‘*natural result*’ of the combination of prior art elements.” *Par Pharm., Inc. v. TWi Pharm., Inc.*, 773 F.3d 1186, 1195 (Fed. Cir. 2014) (quoting *In re Oelrich*, 666 F.2d 578, 581 (C.C.P.A. 1981)). Indeed, inherency “must be carefully circumscribed in the context of obviousness[] [and] . . . may not be established by probabilities or possibilities.” *Id.*, at 1188. The Petition’s attempt to rely on inherency must fail because it presents no evidence demonstrating that different isomers or different formulations would have similar pharmacokinetic profiles, and to the contrary, the ’334 patent demonstrates the oral formulations comprising the free base of (Z)-endoxifen exhibited superior bioavailability as compared to oral formulations of endoxifen citrate. (EX2001 (Davies Decl.) at ¶¶ 150-154.)

A POSA would not have had a reasonable expectation of success for producing the oral formulations of the ’334 patent comprising at least 90% (Z)-

endoxifen free base in view of the prior teachings of superior solubility and efficacy for tamoxifen citrate oral formulations (EX2016 (Buchanan) at 5) as well as prior teachings of oral formulations of endoxifen citrate (EX1006 and EX1007). Despite the lack of expectation of success, the '334 patent establishes that oral formulations comprising the free base of (Z)-endoxifen surprisingly exhibited superior bioavailability as compared to oral formulations of endoxifen citrate. (EX2001 (Davies Decl.) at ¶¶ 150; EX1001 at 95:49-96:24.)

Accordingly, the Petition's inherency argument is thus further undermined by the data in the '334 patent itself. Table 22, (EX1001 at 95:49-96:24), presents pharmacokinetic data of the claimed 90% (Z)-endoxifen, ***compared to*** the data from EX1006 and EX1007. As demonstrated in Table 22, the pharmacokinetic profile of the claimed invention is not identical to the pharmacokinetic profile of the formulations tested in EX1006 and EX1007. The claimed invention demonstrates a much greater bioavailability. (See EX1001 at 95:59-62 (showing the claimed formulation exhibited 154%, 204%, and 150% higher average drug concentration at steady state than the Ahmad formulations).)

The Petition states that a "POSA would have been motivated to obtain similar pharmacokinetic data using the capsules disclosed in Ahmad," and that there would be "reasonable expectation of success" through "routine skill and

optimization.” (Pet. at 56-57) (citing to Petitioner’s expert declaration at ¶127). This again is hindsight bias. A POSA would not look at the pharmacokinetic data of the ’334 patent and try to reverse engineer the pharmacokinetic profile to “obtain similar pharmacokinetic data using the capsules disclosed in Ahmad.” (Pet. at 56-57.) “We must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention.” *Innogenetics*, 512 F.3d at 1374 n.3.

Ground 6 thus also fails and challenged claims 14, 18, and 19 are not obvious in light of EX1003, EX1006, and EX1007.

#### **IX. PETITIONER FAILS TO ADEQUATELY ADDRESS SECONDARY INDICIA OF NON-OBVIOUSNESS**

Even if Petitioner’s Grounds 2-6 were sufficient to establish obviousness—they are not—secondary indicia of non-obviousness support a conclusion that the challenged claims are valid and non-obvious. Petitioner ignores the unexpected results and long felt need of the invention claimed in the ’334 patent. As the Board has repeatedly held, “petitions may be denied if they do not address known evidence of secondary considerations.” *Stryker Corp. v. KFx Medical, LLC*, IPR2019-00817, Paper 10 at 28-29 (PTAB Sept. 16, 2019) (collecting cases).

Regarding unexpected results, the claimed methods of synthesizing endoxifen and purifying (Z)-endoxifen resulted in isomerically purified (Z)-endoxifen compositions with unexpected stability as compared to the hydrochloride salt. (EX2001 (Davies Decl.) at ¶ 157.) Example 11 demonstrates surprising stability of the resulting (Z)-endoxifen free base with stability of at least 90% (Z)-endoxifen for “at least 9 months under conditions of ambient and high temperature and humidity.” (EX1001 at 82:42-49.) The bulk drug stability of (Z)-endoxifen is shown to be stable for at least 9 months at 5°C and 25°C at 60% relative humidity (RH) which is predictive of long-term stability (at least 18 months) at ambient temperatures. (EX1001 85:18-27.) Petitioner ignores unexpected results wholly, and never addresses whether this stability was predicted or expected.

The results of superior bioavailability of the oral formulations of the '334 patent were also unexpected due to the prior teachings of the FDA-approved, tamoxifen citrate oral formulations, and endoxifen citrate oral formulations. (EX1006 and EX1007). The citrate salt oral formulations would have been contemplated by a POSA to increase its aqueous solubility and efficacy. (EX2016 (Buchanan) at 5.) However, as shown in the '334 patent, oral formulations comprising the free base of endoxifen surprisingly exhibited superior

bioavailability as compared to oral formulations of endoxifen citrate. (EX1001 at 95:49-96:24; EX2001 (Davies Decl.) at ¶ 157.)

Regarding long-felt need, the '334 patent discusses the unmet medical need for new compositions and methods for the prevention and treatment of hormone-dependent breast and reproductive tract disorders, including cancer. (EX1001 at 2:50-54.) The enteric oral formulations comprising at least 90% (Z)-endoxifen compositions described in the '334 patent achieve superior bioavailability as compared to EX1006 and EX1007, (EX1001 at 95:49-96:24), demonstrating their ability for use as new compositions for treatment and/or prevention of hormone-dependent breast and reproductive tract disorders. Petitioner similarly ignores long-felt need and never addresses the improved bioavailability shown in the '334 patent. (EX2001 (Davies Decl.) at ¶ 156.)

These secondary indicia are commensurate with the '334 patent and there is a sufficient nexus between the claims of the '334 patent and the unexpected results and long felt need. Petitioner's failure to even address secondary indicia is another indication of the futility of the Petition.

## **X. CONCLUSION**

Because each of Intas's unpatentability arguments is fatally deficient, Atossa respectfully requests the Board deny institution.

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

Dated: November 30, 2023

Respectfully Submitted,

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**CERTIFICATE OF WORD COUNT**

The undersigned hereby certifies that the foregoing Patent Owner's Preliminary Response to Petition for Post-Grant Review complies with the type-volume limitations of 37 C.F.R. § 42.24(b). Excluding the items listed 37 C.F.R. § 42.24(a) as not included in the word count, and using the word count function of Microsoft Word, which was used to prepare the paper, the Patent Owner's Preliminary Response contains 12,684 words.

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**CERTIFICATE OF SERVICE**

The undersigned hereby certifies that on this 30th day of November 2023, a true copy of the foregoing materials were 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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