

Filed on behalf of Petitioner COALITION FOR AFFORDABLE DRUGS X LLC

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

COALITION FOR AFFORDABLE DRUGS X LLC,
Petitioner,

v.

ANACOR PHARMACEUTICALS, INC.,
Patent Owner.

Case No.: Unassigned
Patent No.: 7,767,657

**FIRST PETITION FOR *INTER PARTES* REVIEW OF PATENT NO.
7,767,657**

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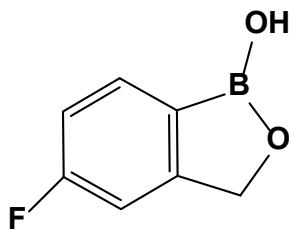
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Coalition For Affordable Drugs X LLC (“CFAD”) respectfully submits this First Petition for *Inter Partes* Review (“IPR”) of all claims of U.S. Patent No. 7,767,657 (“the ‘657 Patent”) (Ex. 1001) pursuant to 35 U.S.C. §§ 311-319 and 37 C.F.R. § 42.100 *et seq.*

I. INTRODUCTION

The ‘657 Patent claims formulations for treating fungal infections of the nails and skin, including onychomycosis, with 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole, the structure of which is:



The claims of the ‘657 Patent are obvious because the claimed compound was disclosed in WO 1995/033754 to Austin et al. (“*Austin*”) as a preferred fungicide effective against *Candida albicans*, which is a fungal pathogen known to cause onychomycosis.

During prosecution of the ‘657 Patent and its parent application, the Patent Owner overcame obviousness rejections by arguing that a general interest, non-scientific internet website called Answers.com taught away from human treatment with an industrial fungicide because it stated that some fungicides were harmful to humans. The Examiner accepted these arguments and allowed the patents to issue.

The fallacy of the Patent Owner's "teaching away" argument is exposed in view of how drugs are developed in the pharmaceutical industry. Drug candidates are screened through routine efficacy and safety protocols before application to humans, thus avoiding the safety fears that the Patent Owner argued to the Examiner. Additionally, U.S. Patent App. Pub. No. 2002/0165121 to Brehove ("*Brehove*") used a boron-based industrial fungicide to suppress *Candida albicans in vitro* and to topically treat onychomycosis in humans.

Claims 1-5, 10-16, and 18-24 of the '657 Patent are thus obvious because a person of ordinary skill in the art ("POSITA") would have known that the preferred industrial fungicide disclosed in *Austin*, which was effective against a known cause of onychomycosis, would have been an obvious candidate for potential therapeutic use in humans in view of *Brehove*, which discloses topical formulations of a similar boron-based industrial fungicide that safely treats onychomycosis.

Claims 6-9 of the '657 Patent, claiming certain formulations, are obvious over *Austin* in view of *Brehove* and one or more of *Chaudhuri*, *Samour*, *Friedman* and *Atlas*, which disclose certain formulations, the preparation of which the '657 admits was well known in the art.

Lastly, claim 17 is obvious over *Austin* in view of *Brehove* and *Shapiro*, the latter disclosing pharmaceuticals to treat onychomycosis and other related diseases.

II. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8(a)(1)

A. Real Party-In-Interest Under 37 C.F.R. § 42.8(b)(1)

Petitioner certifies that CFAD, Hayman Credes Master Fund, L.P. (“Credes”), Hayman Orange Fund SPC – Portfolio A (“HOF”), Hayman Capital Master Fund, L.P. (“HCMF”), Hayman Capital Management, L.P. (“HCM”), Hayman Offshore Management, Inc. (“HOM”), Hayman Investments, L.L.C. (“HI”), nXn Partners, LLC (“nXnP”), IP Navigation Group, LLC (“IPNav”), J. Kyle Bass, and Erich Spangenberg are the real parties-in-interest (collectively, “RPI”). The RPI certifies the following information:

CFAD is a wholly owned subsidiary of Credes. Credes is a limited partnership. HOF is a segregated portfolio company. HCMF is a limited partnership. HCM is the general partner and investment manager of Credes and HCMF. HCM is the investment manager of HOF. HOM is the administrative general partner of Credes and HCMF. HI is the general partner of HCM. J. Kyle Bass is the sole member of HI and sole shareholder of HOM. CFAD, Credes, HOF, and HCMF act, directly or indirectly, through HCM as the general partner and/or investment manager of Credes, HOF and HCMF. nXnP is a paid consultant to HCM. Erich Spangenberg is the Manager and majority member of nXnP. IPNav is a paid consultant to nXnP. Erich Spangenberg is the Manager and majority member of IPNav.

Other than HCM and J. Kyle Bass in his capacity as the Chief Investment Officer of HCM and nXnP, and Erich Spangenberg in his capacity as the Manager/CEO of nXnP, no other person (including any investor, limited partner, or member or any other person in any of CFAD, Credes, HOF, HCMF, HCM, HOM, HI, nXnP, or IPNav) has authority to direct or control (i) the timing of, filing of, content of, or any decisions or other activities relating to this Petition or (ii) any timing, future filings, content of, or any decisions or other activities relating to the future proceedings related to this Petition. All of the costs associated with this Petition will be borne by HCM, CFAD, Credes, HOF and/or HCMF.

B. Related Matters Under 37 C.F.R. § 42.8(b)(2)

Petitioner is aware of a concurrently filed Petition for *Inter Partes* Review (“IPR”) of U.S. Patent No. 7,582,621, upon which the ‘657 Patent claims priority as a continuation-in-part (Case No. Unassigned), and a concurrently filed “Second” Petition for IPR of U.S. Patent No. 7,767,657 (Case No. Unassigned).

C. Lead and Back-Up Counsel Under 37 C.F.R. §§ 42.8(b)(3) & 42.10(a)

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Pursuant to 37 C.F.R. § 42.10(b), a Power of Attorney is provided herewith.

D. Service Information Under 37 C.F.R. § 42.8(b)(4)

Service information for lead and back-up counsel is provided above in the designation of lead and back-up counsel. Petitioner also consents to electronic service by e-mail at Kerydin2IPR@merchantgould.com.

III. PAYMENT OF FEES UNDER 37 C.F.R. § 42.103

Payment of \$27,400 for the fees set forth in 37 C.F.R. § 42.15(a)(1-4) accompanies this Petition. The USPTO is authorized to charge Deposit Account No. 13-2725 for any additional fees that may be due for this Petition.

IV. REQUIREMENTS FOR IPR UNDER 37 C.F.R. § 42.104

A. Grounds for Standing Under 37 C.F.R. § 42.104(a)

Petitioner hereby certifies that the ‘657 Patent is available for IPR and that neither Petitioner nor any RPI is barred or estopped from requesting IPR of the ‘657 Patent because: (1) neither Petitioner nor any RPI are the patent owner; (2) neither Petitioner nor any RPI has filed a civil action challenging the validity of a claim in the ‘657 Patent; (3) neither Petitioner nor any RPI has been served with a complaint alleging infringement of the patent; (4) the estoppel provisions of 35 U.S.C. § 315(e)(1) do not prohibit this IPR; and (5) the patent is not described in Section 3(n)(1) of the Leahy-Smith America Invents Act and so is available for IPR pursuant to 37 C.F.R. § 42.102(a)(2).

B. Identification of Challenge Under 37 C.F.R. § 42.104(b) and Relief Requested

Petitioner requests the cancellation of claims 1-24 of the ‘657 Patent as unpatentable over the prior art for the reasons given herein.

1. Claims for Which IPR Is Requested Under 37 C.F.R. § 42.104(b)(1)

Petitioner requests IPR of claims 1-24 of the ‘657 Patent.

2. Specific Art and Statutory Grounds on Which the Challenge Is Based Under 37 C.F.R. § 42.104(b)(2)

IPR of the ‘657 Patent is requested in view of the following seven publications: (1) WO 1995/033754 (“*Austin*”) (Ex. 1002); (2) U.S. Patent App. Pub. No. 2002/0165121 (“*Brehove*”) (Ex. 1003); (3) U.S. Patent No. 6,143,794 (“*Chaudhuri*”) (Ex. 1004); (4) U.S. Patent No. 6,224,887 (“*Samour*”) (Ex. 1005);

(5) U.S. Patent No. 7,074,392 (“*Friedman*”) (Ex. 1006); (6) U.S. Patent No. 5,498,407 (“*Atlas*”) (Ex. 1007); and (7) U.S. Patent No. 3,816,472 (“*Shapiro*”) (Ex. 1008). None of *Austin*, *Brehove*, *Chaudhuri*, *Samour*, *Friedman*, *Atlas* or *Shapiro* was made of record during prosecution of the ‘657 Patent.

a. Qualifying Prior Art Under 35 U.S.C. § 102(b)

The following publications are prior art against the ‘657 Patent under pre-AIA 35 U.S.C. § 102(b) as each published more than one year before February 16, 2005, the date of the earliest provisional application to which the ‘657 Patent claims priority. (Ex. 1011, ¶ 39.) *Austin* published December 14, 1995; *Brehove* published November 7, 2002; *Chaudhuri* published November 7, 2000; *Samour* published May 1, 2001; *Atlas* published March 12, 1996; and *Shapiro* published June 11, 1974.

b. Qualifying Prior Art Under 35 U.S.C. § 102(e)

Friedman is prior art against the ‘657 Patent under pre-AIA 35 U.S.C. § 102(e)¹ because it was filed on March 27, 2000—almost five years prior to the February 16, 2005 presumed priority date of the ‘657 Patent.

The following combinations of the above-listed publications render claims

¹ A person shall be entitled to a patent unless “(e) the invention was described in . . . (2) a patent granted on an application for patent by another filed in the United States before the invention by the application for patent.” 35 U.S.C. § 102(e).

1-24 of the ‘657 Patent obvious under pre-AIA 35 U.S.C. § 103(a):

Ground	Claim Nos.	Proposed Statutory Rejections
1	1-5, 10-16, 18-24	Claims 1-5, 10-16, and 18-24 of the ‘657 Patent are obvious under 35 U.S.C. § 103(a) over <i>Austin</i> in view of <i>Brehove</i> .
2	6	Claim 6 of the ‘657 Patent is obvious under 35 U.S.C. § 103(a) over <i>Austin</i> in view of <i>Brehove</i> and <i>Chaudhuri</i> .
3	7	Claim 7 of the ‘657 Patent is obvious under 35 U.S.C. § 103(a) over <i>Austin</i> in view of <i>Brehove</i> and <i>Samour</i> .
4	8	Claim 8 of the ‘657 Patent is obvious under 35 U.S.C. § 103(a) over <i>Austin</i> in view of <i>Brehove</i> , <i>Friedman</i> and <i>Atlas</i> .
5	9	Claim 9 of the ‘657 Patent is obvious under 35 U.S.C. § 103(a) over <i>Austin</i> in view of <i>Brehove</i> , <i>Friedman</i> and <i>Samour</i> .
6	17	Claim 17 of the ‘657 Patent is obvious under 35 U.S.C. § 103(a) over <i>Austin</i> in view of <i>Brehove</i> and <i>Shapiro</i> .

Austin, *Brehove*, *Chaudhuri*, *Samour*, *Friedman*, *Atlas* and *Shapiro* are filed herewith. The grounds for unpatentability are supported by the Declarations of Stephen Kahl, Ph.D. (“Kahl Decl.”) (Ex. 1009) and S. Narasimha Murthy, Ph.D. (“Murthy Decl.”) (Ex. 1011) filed herewith.

3. The Construction of the Challenged Claims Under 37 C.F.R. § 42.104(b)(3)

The terms of the ‘657 Patent claims are given their broadest reasonable interpretation in light of the specification, as understood by a POSITA. 37 C.F.R. § 42.100(b). Petitioner submits its claim constructions in Section V.C below. Any undiscussed claim terms should be given their “ordinary meaning” under the

“broadest reasonable construction” standard of § 42.100(b).

4. How the Construed Claims Are Unpatentable Under 37 C.F.R. § 42.104(b)(4)

Section VI below contains a detailed explanation of how the construed claims 1-24 of the ‘657 Patent are unpatentable, including an identification of where each element is found in the prior art.

5. Supporting Evidence Under 37 C.F.R. § 42.104(b)(5)

Section VI also cites the exhibits and evidence relied upon to support the petition, and addresses the relevance of the specific portions of the evidence to the unpatentability arguments. This includes Exhibit 1009, which is a Declaration of Stephen Kahl, Ph.D. under 37 C.F.R. § 42.63(a) attesting to, among other issues, the safety of boron-based compounds and that it would have been obvious to try 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole to treat onychomycosis. Exhibit 1011 is a Declaration of S. Narasimha Murthy, Ph.D. under 37 C.F.R. § 42.63(a) attesting to, among other issues, the obviousness of claims 1-24, the reasons for combining the references, and the reasons to pharmaceutically formulate and topically apply the claimed compound.

V. SUMMARY OF THE ‘657 PATENT

A. Lineage of the ‘657 Patent

The ‘657 Patent issued August 3, 2010 from U.S. Application No. 11/505,591, filed August 16, 2006, (Ex. 1001), which is a continuation-in-part

(CIP) of U.S. Application No. 11/357,687 (now U.S. Patent No. 7,582,621), (Ex. 1018), filed February 16, 2006, and claiming priority to U.S. Provisional Application Nos. 60/654,060, 60/755,227, and 60/746,361, filed February 16, 2005, December 30, 2005 and May 3, 2006, respectively.²

B. Description of the Alleged Invention of the ‘657 Patent

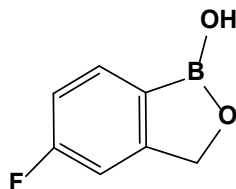
The ‘657 Patent claims topical formulations of a single boron-based compound to treat onychomycosis and other related diseases. (Ex. 1001, Title, Abstract, cols. 323:1-324:49; Ex. 1009, ¶ 23; Ex. 1011, ¶¶ 38, 40-42.) Specifically, the ‘657 Patent claims a pharmaceutical formulation of 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole, or a salt thereof, and a pharmaceutically acceptable excipient for topical administration to an animal suffering from an infection by a microorganism. (Ex. 1001, col. 323:2-8; Ex. 1011, ¶¶ 43-45.) The ‘657 Patent admits that formulation of pharmaceutically effective carriers was well known in the art. (*See* Ex. 1001, cols. 11:21-12:10; Ex. 1011, ¶¶ 49, 195.)

C. Construction of Key Terms in the ‘657 Claims

Claims 1 and 6-11 of the ‘657 Patent recite the following compound: “1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole.” (Ex. 1001, col. 323:2-8, col. 323:24-48; Ex. 1011, ¶¶ 50, 55-60, 117.) *Austin* also discloses 5-fluoro-1,3 dihydro-

² The extent to which the claims of the ‘657 Patent, which is a CIP application, are supported by the U.S. Provisional Applications has not been considered herein.

1-hydroxy-2,1-benzoxaborole, which has the following structure:



(Ex. 1009, ¶¶ 24-25; Ex. 1011, ¶¶ 42-44, 50, 55-60, 75, 78, 82-83, 117; *see also* Ex. 1044, at 3.) The ‘657 Patent discloses this chemical structure, and its formula of $C_7H_6BFO_2$ and molecular weight of 151.93 Daltons. (Ex. 1001, col. 138:10-25; Ex. 1011, ¶ 117.) A short name for 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole is 5-fluoro benzoxaborole. (Ex. 1011, ¶ 50.)

Claims 2 and 3 recite a “lacquer.” (*Id.* ¶¶ 51-52.) While the ‘657 Patent does not define the term “lacquer,” it means a “solution of a solvent and a film-forming polymer containing an active ingredient.” (*Id.* ¶¶ 51-52, 120, 163-64.)

Claim 4 recites the term “emollient,” which means a “material[] used for the prevention or relief of dryness, as well as for the protection of the skin, nail, hair, claw or hoof.” (Ex. 1001, col. 169:64-66; Ex. 1011, ¶¶ 53, 121, 165.)

Claim 4 recites the term “nail penetration enhancer,” which means “an agent that acts to increase the permeability of the skin, nail, hair or hoof to a drug.” (Ex. 1011, ¶ 122; *see id.* ¶¶ 53, 165; Ex. 1001, cols. 11:63-12:10.)

Claims 6-10 recite the term “about,” which is not defined by the ‘657 Patent. (Ex. 1011, ¶¶ 19-20, 123-33.) The term “about” when used with a specified parameter “avoids a strict numerical boundary to the specified parameter,” but suggests a “range [that is] interpreted [based on] its technologic and stylistic context.” *Pall Corp. v. Micron Separations, Inc.*, 66 F.3d 1211, 1217 (Fed. Cir. 1995). When construing “about,” it is appropriate to consider the specification, prosecution history, and other claims. *See id.* It is also appropriate to consider the effects of varying the specified parameter, and extrinsic evidence of meaning and usage in the art. *See id.*; *see also Phillips v. AWH Corp.*, 415 F.3d 1303, 1318-19 (Fed. Cir. 2005) (*en banc*). Case law further provides: (1) “about” does not have a universal meaning³ and may be construed differently in different claims⁴; (2) the term “about” may extend the claimed range to include values that serve the functional purpose of the limitation⁵; (3) “about” has been construed to include a full range of acceptable values when no importance was attributed to the claimed

³ *See Cohesive Techs., Inc. v. Waters Corp.*, 543 F.3d 1351, 1368 (Fed. Cir. 2008).

⁴ *See Abbott Labs. v. Lupin Ltd.*, 753 F. Supp. 2d 382, 418 (D. Del. 2010).

⁵ *Cohesive Techs.*, 543 F.3d at 1370 (“Absent [specification] guidance, we neither can nor should draw a hard and fast numeric line. Rather, we construe ‘about [numeric value]’ to accomplish the function of the [limitation] . . .”).

quantities and the claimed quantities were not added to avoid prior art⁶; (4) when construing “about” it is appropriate to consider acceptable tolerances or quantities based on intrinsic or extrinsic evidence⁷; and (5) in the absence of expert analysis of the specification and comparison to other claims, “about” has been construed according to its plain and ordinary meaning as “approximately” or “reasonably close to.”⁸

Here, the ‘657 Patent is silent with regard to why the particular claimed formulations were chosen, but instead states that the formulations were “well known in the art.” (Ex. 1001, col. 188:29-51; *see also id.* at col. 11:27-35, col. 163:34-43, col. 173:7-9; Ex. 1011, ¶¶ 49, 124-25, 132, 195, 212, 226, 230, 252, 256.) Indeed, the prior art discloses numerous topical formulations for effective treatment of onychomycosis that combine different amounts of various excipients and active agents. The ‘657 Patent does not attribute any importance or unexpected

⁶ *Schreiber Foods, Inc. v. Saputo Cheese USA*, 83 F. Supp. 2d 942, 950 (N.D. Ill. 2000) (construing “about 2 minutes to about 4 minutes” to include 30 seconds to ten minutes, and “about 190 [°]F. to about 205 [°]F.” to include 150° F to 300° F).

⁷ *Abbott Labs.*, 753 F. Supp. 2d at 418 (relying on general tolerances of +/-15%).

⁸ *See Roche Diagnostics Operations, Inc. v. Abbott Diabetes Care*, 667 F. Supp. 2d 429, 441 (D. Del. 2009).

results to the claimed quantities of excipients or active agents in the formulations, nor were the claimed quantities added or limited to avoid prior art. The '657 Patent identifies the purpose of a "pharmaceutically acceptable carrier" as "any formulation or carrier medium that provides the appropriate delivery of an effective amount of a[n] active agent[,] . . . does not interfere with the effectiveness of the biological activity of the active agent, and . . . is sufficiently non-toxic to the host or patient." (Ex. 1001, col. 11:21-27; Ex. 1011, ¶¶ 118, 123, 195, 227.)

Accordingly, the term "about" when used in conjunction with an excipient or active agent should be construed to include a range of acceptable values such that the excipient or active agent serves the functional purpose of the limitation, where the range of acceptable values is determined based on the specification, prosecution history, and prior art. (Ex. 1011, ¶¶ 123-33.)

Claim 6 recites the unit designation "1:10 wt/volume," which is not defined, but means 1 gram solute dissolved in sufficient solvent to form 10 milliliters (mL) of a solution (or composition). (*Id.* ¶¶ 55, 134; *see* Ex. 1037, at 119.)

Claim 10 recites the unit designation "% w/v," which is not defined, but means the percent by weight in grams (g) of a solute in 100 milliliters (mL) of a solution (or composition). (Ex. 1011, ¶¶ 59, 134, 167-68; *see* Ex. 1037, at 119.)

Claim 12 recites a "cosmetically effective amount," and claim 24 recites a "therapeutically effective amount," which both mean "an amount of the claimed

compound needed to reach the desired therapeutic result.” (Ex. 1011, ¶¶ 61, 73, 135, 160, 172, 183; *see* Ex. 1001, col. 10:4-9.)

Claims 14-19 recite “fungus,” “yeast,” and/or “dermatophyte,” as well as a number of specific genera and/or species of the same. “Fungi” encompasses both yeasts and dermatophytes. Dermatophytes refer to the following three genera: *Microsporum*, *Epidermophyton*, and *Trichophyton*. (Ex. 1011, ¶¶ 63-68, 174-78.) Onychomycosis that is caused by a dermatophyte, usually *Trichophyton rubrum* and/or *Trichophyton mentagrophytes*, is referred to as Tinea unguium. (Ex. 1001, col. 132:8-11, col. 139:11-23; Ex. 1011, ¶¶ 68, 178.) *Candida albicans* is a yeast species commonly associated with onychomycosis. (Ex. 1006, col. 1:27-31; Ex. 1011, ¶¶ 87-88, 90, 174-78.)

Claim 20 recites a “cutaneous infection,” which is not defined in the ‘657 Patent, but means an “infection of the skin.” (Ex. 1011, ¶¶ 69, 136, 179.)

Claim 21 recites an “ungual, periungual and subungual infection,” which is an “infection of an animal’s nail, hoof, or claw.” (*Id.* ¶¶ 70, 137, 180; *see* Ex. 1001, col. 1:18-23.)

Claim 22 recites “onychomycosis,” which is “an infection of the nail often caused by dermatophytes, yeasts, and non-dermatophyte molds.” (Ex. 1001, col. 132:2-20, col. 139:11-23; Ex. 1011, ¶¶ 45, 71, 181.)

D. Summary of the Original Prosecution of the ‘657 Patent

The '657 Patent, filed August 16, 2006, is a continuation-in-part of the '621 Patent, filed February 16, 2006. (Ex. 1001; Ex. 1011, ¶ 74; Ex. 1018.)

1. Prosecution History of the '621 Patent

The '621 Patent was filed on February 16, 2006 as U.S. Application No. 11/357,687. (Ex. 1013; Ex. 1018.) In response to a restriction requirement, Applicants elected claims 27-31 and new claims 40-42, and made a species election of 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole. (Ex. 1014, at 6-7.)

In an August 26, 2008 Office Action, all pending claims were rejected based on 35 U.S.C. § 112, ¶ 1, and 35 U.S.C. § 103(a) over U.S. Patent No. 5,880,188 to Austin in view of a definition for “fungicide” from Answers.com indicating that fungicides can be used for both agriculture and pharmacy. (Ex. 1015, at 4-13; *see* Ex. 1009, ¶ 25; Ex. 1011, ¶ 75.) The Examiner noted that while the “level of skill in the art is high,” the claimed subject matter would result in exhaustive search or undue experimentation by one of skill in the art. (Ex. 1015, at 7-8, 10-11.)

In response to the § 112 rejections, Applicants did not dispute that the level of skill in the art was high, but amended claim 27 without argument. (Ex. 1016, at 2.) In response to the obviousness rejections, Applicants argued that Answers.com did not provide motivation and, in fact, taught away from using the claimed compound to treat human infection by stating that “some fungicides are dangerous to human health.” (*Id.* at 6-7; Ex. 1009, ¶ 26; Ex. 1011, ¶ 76.) The Examiner

accepted Applicants' arguments, and a Notice of Allowance issued on April 22, 2009. (Ex. 1017; *see* Ex. 1009, ¶ 27; Ex. 1011, ¶ 77.)

2. Prosecution History of the '657 Patent

The '657 Patent was filed on August 16, 2006 as U.S. Application No. 11/505,591. (Ex. 1001; Ex. 1019.) Upon a restriction requirement, Applicants elected claim 121 (and new claims 193-214), and made a species election of 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole. (Ex. 1020, at 6-7.)

In a January 27, 2009 Office Action, claim 195 was rejected under 35 U.S.C. § 112, ¶ 1, and all claims were rejected under 35 U.S.C. § 103(a) over U.S. Patent No. 5,880,188 to Austin in view of Austin et al. (cited by the Examiner as "CAS:124:234024"). (Ex. 1021, at 4-9; *see* Ex. 1011, ¶ 78.)

In response to the § 112 rejections, Applicants admitted that the level of skill in the chemical arts is high and argued that: (1) the specification, coupled with the knowledge generally known in the art, was sufficient for enablement; and (2) the formulations of the invention could be made based on excipients, additives and methods known in the art. (Ex. 1022, at 8-9; *see* Ex. 1011, ¶ 80.) In response to the § 103(a) rejections, Applicants argued that Answers.com "teaches that compounds that are useful for killing . . . fungi may also harm animals, and thus teaches away from assuming that any fungicide can be used . . . as claimed." (Ex. 1022, at 10-11; *see* Ex. 1009, ¶ 28; Ex. 1011, ¶ 79.) The Examiner issued a Notice

of Allowance on August 7, 2009. (Ex. 1023; *see* Ex. 1009, ¶ 28; Ex. 1011, ¶ 81.)

E. The State of the Art

Fungicides have been simultaneously disclosed for both industrial and human pharmaceutical use for more than 50 years. An overview of the state of the art is discussed in detail in the Declaration of S. Narasimha Murthy, Ph.D. (“Murthy Decl.”) (Ex. 1011). A summary of representative references is as follows:

- *Bell* (Ex. 1025) (disclosing fungicides for industrial applications and clinical applications, including treating infections caused by *Trichophyton rubrum* and *Candida albicans*, without irritating effects).
- *Grier* (Ex. 1026) (disclosing heterocyclic compounds for clinical treatment of fungal infections, e.g., caused by *Candida albicans* and *Trichophyton rubrum*, as well as for industrial applications).
- *Wagner* (Ex. 1027) (disclosing use of heterocyclic compounds as effective fungicidal agents for industrial applications as well as for clinical applications, including treating onychomycosis).
- *Pfiffner* (Ex. 1028) (disclosing morpholine compounds for use as fungicides in agricultural and pharmaceutical applications, with effectiveness against *Candida albicans* and trichophytes).
- *Arita* (Ex. 1029) (disclosing benzylamine derivatives as antimycotic agents for safe treatment of human fungal infections, e.g., caused by *Candida albicans*,

and as industrial fungicides).

- *Shapiro* (Ex. 1008) (disclosing antifungal compounds for treatment of fungal infections of the skin, hair and nails, e.g., caused by *Trichophyton rubrum* and *Trichophyton verrucosum*).
- *Austin* (Ex. 1002) (describing the preferred boron-based compound 5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole as highly effective against *Candida albicans* for use as an industrial fungicide).
- *Atlas* (Ex. 1007) (disclosing that synthetic hydrogels were useful for controlled drug delivery and that poly(2-hydroxyethyl methacrylate) was useful in a cosmetic nail polish composition).
- *Mertin* (Ex. 1030) (detailing problems and solutions for treating infections of the human nail unit, including that high-swelling polymers were preferred for therapeutic nail lacquers).
- *Friedman* (Ex. 1006) (disclosing a sustained-release nail varnish for delivery of antifungal agents to treat fungal infections such as onychomycosis).
- *Chaudhuri* (Ex. 1004) (disclosing a topical gel capable of delivering an antifungal through the nail barrier for treating onychomycosis).
- *Groziak* (Ex. 1031) (disclosing that boron-based agents were clearly visible on the therapeutic horizon and that none had been found to be unusually toxic).
- *Samour* (Ex. 1005) (disclosing a nail lacquer formulation with improved

physical properties and diffusion characteristics of active principles for effectively treating onychomycosis in humans).

- *Murdan* (Ex. 1032) (detailing problems and solutions for treating infections of the human nail unit, including that lower molecular weight drug molecules showed improved penetration).

- *Brehove* (Ex. 1003) (describing boron-based industrial fungicides for treating onychomycosis caused by *Candida albicans* and *Trichophyton rubrum*).

- *Freeman* (Ex. 1024) (describing phenyl boronic acid derivatives for treating fungal infections in humans and plants, including onychomycosis).

By February 16, 2005, the cross-application of fungicides for both industrial and pharmaceutical uses had been known for over 50 years, the boron-based compound of claims 1-24 had been disclosed as a preferred fungicide for suppressing a known cause of onychomycosis, and at least two publications had disclosed the treatment of onychomycosis by applying formulations containing boron-based compounds to the nail and surrounding skin of humans.

However, despite the obviousness of claims 1-24 in view of the prior art, the Patent Owner continues to benefit from the privileges of a monopoly. The public has a significant interest in ensuring monopoly privileges are not granted by an invalid patent, particularly where, as here, Kerydin® can cost up to \$500.00 per month or more per patient. (*See* Ex. 1048 (\$1300 for 10ml); Ex. 1049 (\$509.54 for

a 30-day supply and \$1477.81 for a 90-day supply).)

VI. PETITIONER HAS A REASONABLE LIKELIHOOD OF PREVAILING

There is a reasonable likelihood that at least one claim of the ‘657 Patent is unpatentable. 37 C.F.R. § 42.104(b)(4). This section provides detailed descriptions and claim charts showing how claims 1-24 of the ‘657 Patent are obvious under pre-AIA 35 U.S.C. § 103(a), including identifications of where each claim element is found in the prior art. (Ex. 1009, ¶¶ 17-19; Ex. 1011, ¶¶ 17-18, 21-34, 138, 273.)

Underlying factual determinations in an obviousness analysis include (1) the scope and content of the prior art, (2) the level of ordinary skill in the art, (3) the differences between the claimed invention and the prior art, and (4) objective indicia of non-obviousness, *see KSR Int’l Co. v. Teleflex, Inc.*, 550 U.S. 398, 406-07 (2007), which are addressed for each statutory ground of rejection.

In assessing obviousness, “[o]ne of the ways in which a patent’s subject matter can be proved obvious is by noting that there existed at the time of invention a known problem for which there was an obvious solution encompassed by the patent’s claims.” *Id.* at 419-20. “[W]hen a patent ‘simply arranges old elements with each performing the same function it had been known to perform’ and yields no more than one would expect from such an arrangement, the combination is obvious.” *Id.* at 417 (citation omitted). “When there is a design

need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.” *Id.* at 421.

A. Each Reference Relied on for Grounds 1-6 Is Prior Art

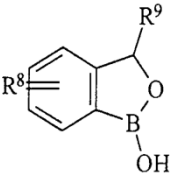
Each reference applied in Grounds 1-6 is prior art against the ‘657 Patent under either pre-AIA 35 U.S.C. § 102(b) or 35 U.S.C. § 102(e). (*See* Section IV.B.2, *supra.*) None of *Austin*, *Brehove*, *Chaudhuri*, *Samour*, *Friedman*, *Atlas* or *Shapiro* was made of record during prosecution of the ‘657 Patent.

B. A Person of Ordinary Skill in the Art

A person of ordinary skill in the art at the time the ‘657 Patent was filed would have had an advanced degree (Master’s or Ph.D.) or equivalent experience in chemistry, pharmacology, or biochemistry, and at least two years of experience with the research, development, or production of pharmaceuticals. (Ex. 1009, ¶¶ 20-22; Ex. 1011, ¶¶ 35-37.)

C. Ground 1: Claims 1-5, 10-16 and 18-24 Are Obvious Over *Austin* in View of *Brehove*

The following claim chart shows the limitations of the above claims and the disclosure of each limitation in the prior art:

7,767,657	<i>Austin</i> in view of <i>Brehove</i>
<p>1. A pharmaceutical formulation, comprising:</p> <p>(a) 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole, or a salt thereof; and</p>	<p><u>Austin</u></p> <ul style="list-style-type: none"> ▪ “The use of oxaboroles and salts thereof as industrial biocides especially fungicides . . . [p]referred compounds are 5- and 6-fluoro or bromo- 1,3-dihydro-1-hydroxy-2,1-benzoxaborole” (Ex. 1002, Abstract.) ▪ “The benzoxaborole derivatives obtained have [the] general formula:” <div style="text-align: center;">  </div> <p>(<i>Id.</i> at 22:5-14.)</p> <ul style="list-style-type: none"> ▪ “Example 64” where “R⁸” is “5-F” and “R⁹” is “H” and “CA” is “<i>Candida albicans</i>” (<i>Id.</i> at 36-37, Table 9.) <p><u>Brehove</u></p> <ul style="list-style-type: none"> ▪ “This invention relates to the treatment of human fingernails and toenails; and more particularly, to topical applications and methods to cure or prevent the spread of nail infections, such as onychomycosis, caused by bacteria, fungi and other pathogens.” (Ex. 1003, ¶ [0003].) ▪ “Onychomycosis is a nail disease of the toes and fingers typically caused by . . . <i>Candida albicans</i>, <i>Trichophyton mentagrophytes</i>, [and] <i>Trichophyton rubrum</i>.” (<i>Id.</i> ¶ [0005].) ▪ “[T]he class of organo-boron compounds have long been known to exhibit biocidal activity.” (<i>Id.</i> ¶ [0007].) ▪ “One formulation is conveniently applied nightly in a petroleum jelly or mineral oil base. Dilute compositions of the active compounds in alcohol or acetone base ha[ve] the ability to deliver concentrated active ingredient as the solvent evaporates. Another formulation is conveniently applied once per week in a cellulose acetate lacquer base. Both formulations are effective in curing the onychomycosis without skin irritation and evident side effects.” (<i>Id.</i> ¶ [0018].)
<p>(b) a pharmaceutically acceptable</p>	<ul style="list-style-type: none"> ▪ See claim element 1(a). <p><u>Brehove</u></p> <ul style="list-style-type: none"> ▪ “One formulation is . . . applied nightly in a petroleum jelly

<p>excipient wherein said pharmaceutical formulation is for topical administration to an animal suffering from an infection by a microorganism.</p>	<p>or mineral oil base. Dilute compositions of the active compounds in alcohol or acetone base . . . deliver concentrated active ingredient as the solvent evaporates. Another formulation is conveniently applied once per week in a cellulose acetate lacquer base. Both formulations are effective in curing the onychomycosis without skin irritation and evident side effects.” (Ex. 1003, ¶ [0018].)</p> <ul style="list-style-type: none"> ▪ 2,2'-(1-methyltrimethylene dioxy) bis-(4-methyl-1, 3, 2-dioxaborinane) and 2,2'-oxybis (4, 4, 6-trimethyl-1, 3, 2-dioxaborinane) were “highly effective in suppressing growth of <i>Candida albicans</i> in vitro.” (<i>Id.</i> ¶¶ [0030], [0033].) ▪ “A male volunteer 58 years old has onychomycosis on both feet. . . . The application [of the above compositions with 25% active ingredients] included painting the entire toenail and the cuticle for approximately 3 mm beyond the nail. . . . In 250 days, the nail is fully-grown, completely free from any [onychomycosis] infection. No skin irritation is observed.” (<i>Id.</i> ¶ [0035].)
<p>2. The formulation of claim 1, wherein said formulation is a member selected from a lacquer, lotion, cream, gel, ointment and spray.</p>	<ul style="list-style-type: none"> ▪ <i>See</i> independent claim 1. <p><u>Brehove</u></p> <ul style="list-style-type: none"> ▪ “Another formulation is conveniently applied once per week in a cellulose acetate lacquer base” and is “effective in curing the onychomycosis without skin irritation and evident side effects.” (Ex. 1003, ¶ [0018].)
<p>3. The formulation of claim 1, wherein said formulation is a lacquer.</p>	<ul style="list-style-type: none"> ▪ <i>See</i> independent claim 1 and dependent claim 2; <i>see, e.g.</i>, Ex. 1003, ¶ [0018] (“Another formulation is conveniently applied once per week in a cellulose acetate lacquer base.”)
<p>4. The formulation of claim 1, wherein said formulation further comprises one or more members selected</p>	<ul style="list-style-type: none"> ▪ <i>See</i> independent claim 1. <p><u>Brehove</u></p> <ul style="list-style-type: none"> ▪ “[T]he composition of the invention contains . . . an active ingredient . . . in combination with a penetration enhancer. As used herein, the term ‘penetration enhancer’ means a chemical compound that increases the permeability of the skin to a drug.” (Ex. 1003, ¶ [0027].)

<p>from an emulsifier, emollient, . . . nail penetration enhancer</p>	<p>▪ “In one embodiment, the composition of the invention contains . . . an active ingredient . . . in combination with at least one member selected from the group consisting of white mineral oil, petroleum jelly and paraffin wax or volatile solvent such as alcohol or acetone. The mineral oil, petroleum jelly and paraffin wax help protect the skin against irritation or drying and serve as a reservoir for the active ingredient permitting extended continuous diffusion and penetration into the nail.” (<i>Id.</i> ¶ [0025].)</p>
<p>5. The formulation of claim 1, wherein said formulation comprises one or more members selected from ethanol and propylene glycol.</p>	<p>▪ See independent claim 1. <u>Austin</u> ▪ “[S]uitable water-miscible organic solvents are . . . alcohols such as ethanol or glycols such as . . . propylene glycol” (Ex. 1002, at 6:34-37.) <u>Brehove</u> ▪ “It is also found by in vivo tests on a volunteer that formulations of the invention achieve efficacy in the treatment of onychomycosis without skin irritation or noticeable side effects. . . . Dilute compositions of the active compounds in alcohol or acetone base . . . deliver concentrated active ingredient as the solvent evaporates.” (Ex. 1003, ¶ [0018].)</p>
<p>10. The formulation of claim 1, wherein said 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole is present in said formulation in a concentration from about 0.5% to</p>	<p>▪ See independent claim 1; see, e.g., Ex. 1002, at 7:5-9 (“The concentration of the oxaborole in the biocide composition is . . . more especially from 10 to 20% by weight relative to the total weight of the biocide composition.”).⁹ <u>Brehove</u> ▪ See Table 1, showing effectiveness against <i>Candida albicans</i> with compound S1 (2,2'-(1-methyltrimethylene dioxy) bis-(4-methyl-1, 3, 2-dioxaborinane)) between 0.1 wt % and 25 wt % in mineral oil; and compound S2 (2,2'-oxybis(4, 4, 6-trimethyl-1, 3, 2-dioxaborinane)) between 0.1 wt % and 25 wt % in mineral oil, as follows:</p>

⁹ As is known, % w/v depends on the density of a solution, e.g., for 5-fluoro benzoxaborole in ethanol, 10-20 wt % is 7.9%-15.8% w/v. (Ex. 1011, ¶¶ 167-69; see also Ex. 1038, at 1038; Ex. 1039, at 835.)

<p>about 15% w/v.</p>	<p style="text-align: center;">TABLE I</p> <table border="1" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th style="text-align: center;">Example</th> <th style="text-align: center;">Test Compound</th> <th style="text-align: center;">Wt. % Of S1/S2 In Mineral Oil</th> <th style="text-align: center;">Colonies Of Candida Albicans Observed</th> </tr> </thead> <tbody> <tr> <td></td> <td>Comparative Mineral oil (control)</td> <td style="text-align: center;">0</td> <td style="text-align: center;">1203</td> </tr> <tr> <td></td> <td>1 S1</td> <td style="text-align: center;">0.1</td> <td style="text-align: center;">8</td> </tr> <tr> <td></td> <td>2 S1</td> <td style="text-align: center;">1.0</td> <td style="text-align: center;">2</td> </tr> <tr> <td></td> <td>3 S1</td> <td style="text-align: center;">10</td> <td style="text-align: center;">0</td> </tr> <tr> <td></td> <td>4 S1</td> <td style="text-align: center;">25</td> <td style="text-align: center;">0</td> </tr> <tr> <td></td> <td>5 S1</td> <td style="text-align: center;">50</td> <td style="text-align: center;">0</td> </tr> <tr> <td></td> <td>6 S1</td> <td style="text-align: center;">75</td> <td style="text-align: center;">0</td> </tr> <tr> <td></td> <td>7 S2</td> <td style="text-align: center;">0.1</td> <td style="text-align: center;">11</td> </tr> <tr> <td></td> <td>8 S2</td> <td style="text-align: center;">1.0</td> <td style="text-align: center;">1</td> </tr> <tr> <td></td> <td>9 S2</td> <td style="text-align: center;">10</td> <td style="text-align: center;">0</td> </tr> <tr> <td></td> <td>10 S2</td> <td style="text-align: center;">25</td> <td style="text-align: center;">0</td> </tr> <tr> <td></td> <td>11 S2</td> <td style="text-align: center;">50</td> <td style="text-align: center;">0</td> </tr> <tr> <td></td> <td>12 S2</td> <td style="text-align: center;">75</td> <td style="text-align: center;">0</td> </tr> <tr> <td></td> <td>13 25/75 w/w S1/S2</td> <td style="text-align: center;">25</td> <td style="text-align: center;">0</td> </tr> <tr> <td></td> <td>14 50/50 w/w S1/S2</td> <td style="text-align: center;">25</td> <td style="text-align: center;">0</td> </tr> <tr> <td></td> <td>15 75/25 w/w S1/S2</td> <td style="text-align: center;">25</td> <td style="text-align: center;">0</td> </tr> </tbody> </table> <p>(Ex. 1003, ¶ [0032].)</p> <ul style="list-style-type: none"> ▪ “[T]he active ingredient is between 0.1 wt % and 25 wt % of the composition.” (<i>Id.</i> at Claim 14.) 	Example	Test Compound	Wt. % Of S1/S2 In Mineral Oil	Colonies Of Candida Albicans Observed		Comparative Mineral oil (control)	0	1203		1 S1	0.1	8		2 S1	1.0	2		3 S1	10	0		4 S1	25	0		5 S1	50	0		6 S1	75	0		7 S2	0.1	11		8 S2	1.0	1		9 S2	10	0		10 S2	25	0		11 S2	50	0		12 S2	75	0		13 25/75 w/w S1/S2	25	0		14 50/50 w/w S1/S2	25	0		15 75/25 w/w S1/S2	25	0
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	12 S2	75	0																																																																		
	13 25/75 w/w S1/S2	25	0																																																																		
	14 50/50 w/w S1/S2	25	0																																																																		
	15 75/25 w/w S1/S2	25	0																																																																		
<p>11. The formulation of claim 1, wherein said 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole, or salt thereof, is present in a form which is a member selected from a hydrate with water, a solvate with an alcohol, an adduct with an amino compound, and an adduct with an acid.</p>	<ul style="list-style-type: none"> ▪ See independent claim 1 and dependent claim 5. <p><u>Austin</u></p> <ul style="list-style-type: none"> ▪ “The use of oxaboroles and salts thereof as industrial biocides especially fungicides [p]referred compounds are 5- and 6-fluoro or bromo- 1,3-dihydro-1-hydroxy-2,1-benzoxaborole” (Ex. 1002, Abstract.) ▪ “[S]uitable water-miscible organic solvents are . . . alcohols such as ethanol or glycols such as . . . propylene glycol” (<i>Id.</i> at 6:34-37.) <p><u>Brehove</u></p> <ul style="list-style-type: none"> ▪ “It is also found by in vivo tests on a volunteer that formulations of the invention achieve efficacy in the treatment of onychomycosis without skin irritation or noticeable side effects. . . . Dilute compositions of the active compounds in alcohol or acetone base ha[ve] the ability to deliver concentrated active ingredient as the solvent evaporates.” (Ex. 1003, ¶ [0018].) 																																																																				
<p>12. The formulation of claim 1, wherein said formulation is</p>	<ul style="list-style-type: none"> ▪ See independent claim 1. <p><u>Brehove</u></p> <ul style="list-style-type: none"> ▪ “It is also found by in vivo tests on a volunteer that formulations of the invention achieve efficacy in the treatment 																																																																				

<p>in a cosmetically effective amount.</p>	<p>of onychomycosis without skin irritation or noticeable side effects.” (Ex. 1003, ¶ [0018].)</p> <ul style="list-style-type: none"> ▪ “A male volunteer 58 years old has onychomycosis on both feet. . . . The application [of the above compositions with 25% active ingredients] included painting the entire toenail and the cuticle for approximately 3 mm beyond the nail. . . . In 250 days, the nail is fully-grown, completely free from any [onychomycosis] infection. No skin irritation is observed.” (<i>Id.</i> ¶ [0035].)
<p>13. The formulation of claim 1, wherein a site of said topical administration is skin or nail or hair or skin surrounding the nail or skin surrounding the hair.</p>	<ul style="list-style-type: none"> ▪ <i>See</i> independent claim 1. <p><u>Brehove</u></p> <ul style="list-style-type: none"> ▪ “A male volunteer 58 years old has onychomycosis on both feet. . . . The application [of the above compositions with 25% active ingredients] included painting the entire toenail and the cuticle for approximately 3 mm beyond the nail. . . . In 250 days, the nail is fully-grown, completely free from any [onychomycosis] infection. No skin irritation is observed.” (Ex. 1003, ¶ [0035].)
<p>14. The formulation of claim 1, wherein the microorganism is a fungus or a yeast.</p>	<ul style="list-style-type: none"> ▪ <i>See</i> independent claim 1; <i>see, e.g.</i>, Ex. 1002, at 36-37, Table 9 (“Example 64” where “R⁸” is “5-F” and “R⁹” is “H” and “CA” is “<i>Candida albicans</i>”). <p><u>Brehove</u></p> <ul style="list-style-type: none"> ▪ “Through in vitro microbiological tests it is now found that a topical formulation . . . has powerful potency against <i>Candida albicans</i>.” (Ex. 1003, ¶ [0018].)
<p>15. The formulation of claim 14, wherein said fungus or yeast is a member selected from <i>Candida</i> species </p>	<ul style="list-style-type: none"> ▪ <i>See</i> independent claim 1 and dependent claim 14; <i>see, e.g.</i>, Ex. 1002, at 36-37, Table 9 (“Example 64” where “R⁸” is “5-F” and “R⁹” is “H” and “CA” is “<i>Candida albicans</i>”). <p><u>Brehove</u></p> <ul style="list-style-type: none"> ▪ “Through in vitro microbiological tests it is now found that a topical formulation . . . has powerful potency against <i>Candida albicans</i>.” (Ex. 1003, ¶ [0018].)
<p>16. The formulation of claim 14, wherein said fungus or</p>	<ul style="list-style-type: none"> ▪ <i>See</i> independent claim 1 and dependent claim 14; <i>see, e.g.</i>, Ex. 1002, at 36-37, Table 9 (“Example 64” where “R⁸” is “5-F” and “R⁹” is “H” and “CA” is “<i>Candida albicans</i>”). <p><u>Brehove</u></p>

<p>yeast is a member selected from . . . <i>Candida albicans</i></p>	<p>▪ “Through in vitro microbiological tests it is now found that a topical formulation . . . has powerful potency against <i>Candida albicans</i>.” (Ex. 1003, ¶ [0018].)</p>
<p>18. The formulation of claim 14, wherein said fungus or yeast is a dermatophyte.</p>	<p>▪ See independent claim 1 and dependent claim 14; see, e.g., Ex. 1003, ¶ [0005] (“Onychomycosis is a nail disease of the toes and fingers typically caused by the organisms <i>Candida albicans</i>, <i>Trichophyton mentagrophytes</i>, <i>Trichophyton rubrum</i>, or <i>Epidermophyton floccosum</i> [sic, <i>Epidermophyton floccosum</i>].”).</p>
<p>19. The formulation of claim 14, wherein said fungus or yeast is a member selected from . . . <i>Trichophyton rubrum</i> and <i>Trichophyton mentagrophytes</i>.</p>	<p>▪ See independent claim 1 and dependent claim 14; see, e.g., Ex. 1003, ¶ [0005] (“Onychomycosis is a nail disease of the toes and fingers typically caused by the organisms <i>Candida albicans</i>, <i>Trichophyton mentagrophytes</i>, [and] <i>Trichophyton rubrum</i> . . .”).</p>
<p>20. The formulation of claim 1, wherein the infection is a cutaneous infection.</p>	<p>▪ See independent claim 1. <u>Brehove</u> ▪ “A male volunteer 58 years old has onychomycosis on both feet. . . . The application [of the above compositions with 25% active ingredients] included painting the entire toenail and the cuticle for approximately 3 mm beyond the nail. . . . In 250 days, the nail is fully-grown, completely free from any [onychomycosis] infection. No skin irritation is observed.” (Ex. 1003, ¶ [0035].)</p>
<p>21. The formulation of claim 1, wherein the infection is a member selected from an ungual, periungual and subungual infection.</p>	<p>▪ See independent claim 1. <u>Brehove</u> ▪ “This invention relates to the treatment of human fingernails and toenails; and more particularly, to topical applications and methods to cure or prevent the spread of nail infections, such as onychomycosis, caused by bacteria, fungi and other pathogens.” (Ex. 1003, ¶ [0003].)</p>
<p>22. The</p>	<p>▪ See independent claim 1; see, e.g., Ex. 1003, ¶ [0003] (“This</p>

formulation of claim 1, wherein the infection is onychomycosis.	invention relates to . . . topical applications and methods to cure or prevent the spread of nail infections, such as onychomycosis, caused by bacteria, fungi and other pathogens.”).
23. The formulation of claim 1, wherein the animal is a human.	<ul style="list-style-type: none"> ▪ See independent claim 1; see, e.g., Ex. 1003, ¶ [0003] (“This invention relates to the treatment of human fingernails and toenails; and more particularly, to topical applications and methods to cure or prevent the spread of nail infections, such as onychomycosis . . .”).
24. The formulation of claim 1, wherein said formulation is in a therapeutically effective amount.	<ul style="list-style-type: none"> ▪ See independent claim 1. <p><u>Brehove</u></p> <ul style="list-style-type: none"> ▪ “It is also found by in vivo tests on a volunteer that formulations of the invention achieve efficacy in the treatment of onychomycosis without skin irritation or noticeable side effects.” (Ex. 1003, ¶ [0018].) ▪ “A male volunteer 58 years old has onychomycosis on both feet. . . . The application [of the above compositions with 25% active ingredients] included painting the entire toenail and the cuticle for approximately 3 mm beyond the nail. . . . In 250 days, the nail is fully-grown, completely free from any infection.” (<i>Id.</i> ¶ [0035].)

As shown above, the combination of *Austin* and *Brehove* discloses all of the limitations of claims 1-5, 10-16 and 18-24. (Ex. 1011, ¶¶ 50-54, 59-65, 67-73, 117-22, 135-45, 163-83.) As discussed below, a POSITA would have had several reasons to combine *Austin* and *Brehove* with a reasonable expectation of success in arriving at the claimed subject matter before February 16, 2005. (*Id.* ¶¶ 146-62, 184-85.) Petitioner is not aware of any secondary considerations that would render claims 1-5, 10-16 and 18-24 of the ‘657 Patent non-obvious. (*Id.*)

1. *Austin* Discloses 5-Fluoro Benzoxaborole as an Antifungal Agent

Austin discloses 5-fluoro benzoxaborole as a preferred fungicide, which is the exact same compound recited in claims 1-5, 10-16 and 18-24 of the ‘657 Patent, and identifies a number of organic solvents to form solvates with 5-fluoro benzoxaborole, including “ethanol or glycols such as . . . propylene glycol.” (Ex. 1002, at 6:36-37; Ex. 1009, ¶¶ 24, 32, 34-35; Ex. 1011, ¶¶ 50, 82-83, 85-86, 141, 166, 171.)

Notably, *Austin* discloses that 5-fluoro benzoxaborole has significant antifungal activity against *Candida albicans* (CA), a fungus often associated with onychomycosis, at the lowest concentration tested (5 parts per million). (Ex. 1002, at 36-37, Table 9; Ex. 1009, ¶¶ 32, 35; Ex. 1011, ¶¶ 84-85, 87-88, 174-76.) In a biocide composition, *Austin* identifies a preferred “concentration of the oxaborole . . . more especially from 10 to 20% by weight relative to the total weight of the biocide composition.” (Ex. 1002, at 7:5-9; Ex. 1011, ¶¶ 85, 169.)

2. *Brehove* Discloses the Topical Application of Boron-Based Compound Formulations to Treat Onychomycosis

Brehove discloses the topical application of boron compounds to “treat and prevent the spread of nail infections or onychomycosis caused by bacteria, fungi and other pathogens.” (Ex. 1003, Abstract, ¶ [0003]; Ex. 1009, ¶¶ 36-39; Ex. 1011, ¶¶ 90, 93-95, 97, 143, 180-82.) *Brehove* provides that “[o]nychomycosis is a nail disease of the toes and fingers typically caused by the organisms *Candida albicans*,

Trichophyton mentagrophytes, [and] *Trichophyton rubrum*,” and states that boron-based topical formulations have “powerful potency against *Candida albicans* . . . effectively kill[ing] the most common pathogen causing onychomycosis.” (Ex. 1003, ¶¶ [0005], [0018]; Ex. 1009, ¶ 38; Ex. 1011, ¶¶ 90, 93-94, 97, 143, 174-77.)

Brehove identifies “a fuel additive Biobor® JF containing a combination of 2,2'-(1-methyltrimethylene dioxy) bis-(4-methyl-1, 3, 2-dioxaborinane) and 2,2'-oxybis (4, 4, 6-trimethyl-1, 3, 2-dioxaborinane),” and then utilizes one or more of the active boron-based ingredients of Biobor® JF in topical compositions to treat onychomycosis. (Ex. 1003, ¶ [0015]; Ex. 1009, ¶¶ 37-39; Ex. 1011, ¶¶ 91-92, 94, 144, 170; *see* Ex. 1033; Ex. 1034.)

Brehove further describes a number of topical formulations of the above compounds that are “effective in curing the onychomycosis without skin irritation and evident side effects,” including “[o]ne formulation . . . in a petroleum jelly or mineral oil base”; “[d]ilute compositions of the active compounds in alcohol or acetone base ha[ving] the ability to deliver concentrated active ingredient as the solvent evaporates”; and “[a]nother formulation . . . in a cellulose acetate lacquer base.” (Ex. 1003, ¶ [0018]; Ex. 1011, ¶¶ 95, 145, 163-66, 171-73, 177-79, 183.)

Brehove provides that excipients “mineral oil, petroleum jelly and paraffin wax help protect the skin against irritation or drying and serve as a reservoir for the active ingredient permitting extended continuous diffusion and penetration into the

nail.” (Ex. 1003, ¶ [0025]; Ex. 1011, ¶¶ 96, 165.)

Brehove discloses the application of topical compositions to volunteers suffering from onychomycosis. (Ex. 1003, ¶¶ [0034]-[0038]; Ex. 1009, ¶¶ 37, 39; Ex. 1011, ¶¶ 94, 145, 171-73, 177-79, 183.) In each case, the volunteer applied a topical composition including one or more boron-based compounds directly to the infected nails to effectively treat the onychomycosis. (Ex. 1003, ¶¶ [0030], [0034]-[0038]; Ex. 1011, ¶¶ 94, 97, 145.) The topical compositions effectively eradicated the onychomycosis with “[n]o skin irritation . . . and no [evidence of] side effects.” (Ex. 1003, ¶ [0034]; Ex. 1011, ¶¶ 94, 145, 163-66, 171-72, 177-78, 183.)

3. Summary: Claims 1-5, 10-16 and 18-24 Are Obvious Over *Austin* in View of *Brehove*

Reason to Combine the References with a Reasonable Expectation of Success: Given the foregoing, a POSITA would have had several reasons to combine *Austin* and *Brehove* before February 16, 2005 with a reasonable expectation of success because: (1) both references teach the use of boron-based compounds as fungicides; (2) both references also disclose the use of boron-based compounds to specifically inhibit *Candida albicans*, which is one of the fungi known to cause onychomycosis; and (3) *Austin* discloses the claimed boron-based compound having a lower molecular weight than the successful compounds of *Brehove*, which is therefore more likely to effectively penetrate the nail barrier in

similar topical formulations. (Ex. 1009, ¶¶ 32-33, 40-41; Ex. 1011, ¶¶ 146-62, 184-85.)

Austin specifically discloses that the compound claimed in the '657 Patent, 5-fluoro benzoxaborole, is a preferred fungicide to effectively inhibit *Candida albicans*. (Ex. 1009, ¶¶ 32, 34-35; Ex. 1011, ¶¶ 82-85, 87-89, 139, 141-42.) *Austin* further identifies water-miscible organic solvents for use with 5-fluoro benzoxaborole, including ethanol and propylene glycol, and a preferred concentration of biocide from 10 to 20% by weight relative to the total weight of the composition. (Ex. 1011, ¶¶ 85-86, 166, 169, 171.) *Brehove* discloses topical formulations of boron-based compounds for application directly to the nail and surrounding skin of humans to effectively treat onychomycosis typically caused by the organisms *Candida albicans*, *Trichophyton mentagrophytes*, and *Trichophyton rubrum*. (Ex. 1009, ¶¶ 38-39; Ex. 1011, ¶¶ 94, 145, 171-79, 183.)

A POSITA seeking to develop a therapeutic treatment for onychomycosis before February 2005 would have understood that boron compounds were effective fungicides safely applied to humans. (Ex. 1009, ¶¶ 29-31; Ex. 1011, ¶¶ 89-90, 93-95, 145; *see also* Ex. 1031, at 322 (“Boronic acids are fairly common and . . . none to date has been found to be unusually toxic.”).) A POSITA would have also understood from *Brehove* that boron-based industrial fungicides had successfully treated onychomycosis with little skin irritation or side effects. (Ex. 1009, ¶¶ 33,

39; Ex. 1011, ¶¶ 94, 145, 163-66, 171-72, 177-78, 183.) A POSITA would have further recognized from *Brehove* a number of topical formulations for effective delivery of boron-based fungicides, including compositions in volatile solvents, such as alcohols; emollient-type compositions in petroleum jelly, mineral oil or paraffin wax bases; and lacquer-type compositions in a cellulose acetate lacquer base. (Ex. 1011, ¶¶ 95, 145, 163-66, 171.)

Austin discloses 5-fluoro benzoxaborole, which is a boron heterocycle, and the compounds of *Brehove* are also boron heterocycles. (Ex. 1009, ¶¶ 24, 34-37; Ex. 1011, ¶¶ 82-83, 91.) A POSITA would have expected that 5-fluoro benzoxaborole, which shares similar structural features with the compounds of *Brehove*, would likely share similar functional features. (Ex. 1009, ¶¶ 33, 36; Ex. 1011, ¶¶ 153-56.) Indeed, *Austin* teaches that 5-fluoro benzoxaborole effectively inhibits *Candida albicans* at concentrations as low as 5 parts per million (PPM) of 5-fluoro benzoxaborole, and *Brehove* also discloses the inhibition of *Candida albicans* at concentrations as low as 0.1wt % of boron-based compound. (Ex. 1002, at 32-33, 36-37, Table 9; Ex. 1003, ¶ [0032], Table I; Ex. 1009, ¶¶ 33, 35, 38; Ex. 1011, ¶¶ 142, 160, 170, 174-76.) A POSITA would have expected that 5-fluoro benzoxaborole, which shares functional activity with the compounds of *Brehove*, would likely have had other activities in common as well, such as the inhibition of additional fungi responsible for onychomycosis. (Ex. 1011, ¶¶ 153-56.)

A POSITA would have been further motivated to select 5-fluoro benzoxaborole as disclosed by *Austin* for its relatively small molecular weight. (*Id.* ¶ 149.) Penetration of the nail barrier is more effective with smaller molecular weight compounds, which was known in the art. (Ex. 1032, at 9.) Indeed, *Brehove* effectively treated and inhibited onychomycosis in humans with 2,2'-(1-methyl trimethylene dioxy) bis (4-methyl-1, 3, 2-dioxaborinane) (285.9 Daltons) and/or 2,2'-oxybis (4, 4, 6-trimethyl-1, 3, 2-dioxaborinane) (269.9 Daltons). (Ex. 1011, ¶ 150.) As a smaller molecular weight compound than either of the effective *Brehove* compounds, 5-fluoro benzoxaborole would therefore have had a greater likelihood of successfully penetrating the nail barrier at lower concentrations. (*Id.* ¶¶ 157-58.)

A POSITA would also have had a reasonable expectation of successfully determining a cosmetically or therapeutically effective amount of 5-fluoro benzoxaborole to treat or inhibit onychomycosis. (*Id.* ¶ 160.) The level of one of ordinary skill in the art is high. (*Id.*; Ex. 1022, at 8.) Determining a therapeutically effective amount of 5-fluoro benzoxaborole to treat or inhibit the growth of fungus in a human, i.e., onychomycosis, involves nothing more than routine experimentation. (Ex. 1011, ¶¶ 46-48, 159-61.)

When a patent “simply arranges old elements,” i.e., use of 5-fluoro benzoxaborole in a topical therapeutic composition, “with each [element] performing the same function it had been known to perform,” i.e., inhibiting

Candida albicans, “and yields no more than one would expect from such an arrangement,” i.e., the effective inhibition of onychomycosis, “the combination is obvious.” *KSR*, 550 U.S. at 417. The combination of *Austin* and *Brehove* discloses all of the limitations of claims 1-5, 10-16 and 18-24. (Ex. 1009, ¶¶ 40-41; Ex. 1011, ¶¶ 82-97, 146-62, 184-85.)

D. Ground 2: Claim 6 of the ‘657 Patent Is Obvious Under 35 U.S.C. § 103(a) Over *Austin* in View of *Brehove* and *Chaudhuri*

The following claim chart shows the limitations of the above claim and the disclosure of each limitation in the prior art:

7,767,657	<i>Austin</i> in view of <i>Brehove</i> and <i>Chaudhuri</i>
6. The formulation of claim 1, comprising: about propylene glycol:ethanol in a ratio of about 1:4, and about 1:10 wt/volume of said 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole.	<ul style="list-style-type: none"> ▪ See independent claim 1; see, e.g., Ex. 1002, at 7:5-9 (“The concentration of the oxaborole in the biocide composition is . . . more especially from 10 to 20% by weight relative to the total weight of the biocide composition.”).¹⁰ ▪ <u><i>Austin</i></u> ▪ “suitable water-miscible organic solvents . . . such as ethanol or glycols such as . . . propylene glycol” (<i>Id.</i> at 6:34-37.) ▪ <u><i>Brehove</i></u> ▪ “It is also found by in vivo tests on a volunteer that formulations of the invention achieve efficacy in the treatment of onychomycosis without skin irritation or noticeable side effects. . . . Dilute compositions of the active compounds in alcohol or acetone base . . . deliver concentrated active ingredient as the solvent evaporates.” (Ex. 1003, ¶ [0018].) ▪ See Table 1, compound S1 (2,2’-(1-methyltrimethylene dioxy) bis-(4-methyl-1, 3, 2-dioxaborinane)) is effective at 10 wt % in

¹⁰ For 5-fluoro benzoxaborole in 1:4 propylene glycol to ethanol, 10-20 wt % is 8.3-16.6% w/v. (Ex. 1011, ¶ 191; Ex. 1039, at 835, 1585.)

mineral oil; compound S2 (2,2'-oxybis (4, 4, 6-trimethyl-1, 3, 2-dioxaborinane)) is effective at 10 wt% in mineral oil, as follows:

TABLE I

Example	Test Compound	Wt. % Of S1/S2 In Mineral Oil	Colonies Of Candida Albicans Observed
Comparative	Mineral oil (control)	0	1203
1	S1	0.1	8
2	S1	1.0	2
3	S1	10	0
4	S1	25	0
5	S1	50	0
6	S1	75	0
7	S2	0.1	11
8	S2	1.0	1
9	S2	10	0
10	S2	25	0
11	S2	50	0
12	S2	75	0
13	25/75 w/w S1/S2	25	0
14	50/50 w/w S1/S2	25	0
15	75/25 w/w S1/S2	25	0

(*Id.* ¶ [0032].)

- *See id.* at claim 14 (reciting “wherein the active ingredient is between 0.1 wt % and 25 wt % of the composition.”)

Chaudhuri

- “[S]uitable solvents include pharmaceutically acceptable lower alkanols of one to four carbon atoms (e.g., ethanol . . .) [and] pharmaceutically acceptable dihydroxylalcohols (e.g., . . . propylene glycol . . .).” (Ex. 1004, col. 6:2-7.)
- “The gel formulation according to this invention can also have a composition shown in Table[] B

TABLE B

Ingredients	Wt %
Water	qs
Propylene glycol	5–20
Hydroxypropylcellulose	1–5
Ethanol	20–80
Polyolprepolymer-2	0–10
Sodium laureth sulfate	0–5
Benzyl alcohol	0–10
Lactic acid	0.1–1
Sodium lactate	1.5–15
Povidone	0–5
Antifungal	0.5–15

(*Id.* at cols. 8:57-9:10.)

As shown above, the combination of *Austin*, *Brehove*, and *Chaudhuri* discloses all of the limitations of claim 6. (Ex. 1011, ¶¶ 55, 123, 134, 187-88.) As discussed below, a POSITA would have had several reasons to combine *Austin*, *Brehove*, and *Chaudhuri* with a reasonable expectation of success in arriving at the claimed subject matter. (*Id.* ¶¶ 186, 194-200.) Petitioner is not aware of any secondary considerations that would render claim 6 non-obvious. (*Id.*)

1. *Austin* Discloses 5-Fluoro Benzoxaborole as an Antifungal Agent and *Brehove* Discloses the Topical Application of Boron-Based Compounds to Treat Onychomycosis

Petitioner incorporates its discussion of *Austin* and *Brehove* from Sections VI.C.1-VI.C.3. (*See id.* ¶¶ 189-91.) In particular, *Austin* identifies a preferred concentration from 10 to 20% by weight of biocide, and organic solvents including ethanol and propylene glycol. (Ex. 1002, at 6:34-37, 7:5-9; Ex. 1011, ¶¶ 86, 169, 191.) *Brehove* describes a formulation of 10 wt % active agent in mineral oil for treating onychomycosis that is effective against *Candida albicans*. (Ex. 1003, ¶ [0032], Table 1; Ex. 1011, ¶¶ 170, 191.)

2. *Chaudhuri* Discloses a Formulation of Propylene Glycol:Ethanol in a Ratio of About 1:4 with About 1:10 Wt/Volume of Antifungal

Chaudhuri discloses topical formulations of antifungal drugs for treating onychomycosis in humans, e.g., caused by dermatophytes such as *Trichophyton*

rubrum or *T. mentagrophytes*, and in particular, discloses a stable gel formulation, including an antifungal and one or more pharmaceutically acceptable excipients, which was “capable of delivering the antifungal through the nail barrier.” (Ex. 1004, Abstract, col. 1:21-30, col. 2:8-15; Ex. 1011, ¶¶ 98, 192.)

In formulation, *Chaudhuri* describes a “therapeutically effective amount” of antifungal compound (e.g., butenafine), “[p]referably . . . about 1% to about 10% by weight and more preferably about 2% to about 8% by weight.” (Ex. 1004, col. 5:11-21, 28-30; Ex. 1011, ¶¶ 99, 193.) In Table B, *Chaudhuri* discloses compositions with propylene glycol between 5-20 wt %, ethanol between 20-80 wt %, and antifungal between 0.5-15 wt %.¹¹ (Ex. 1004, cols. 8:60-9:11; Ex. 1011, ¶¶ 99, 193.) Thus, *Chaudhuri* describes a topical formulation for treatment of onychomycosis with propylene glycol to ethanol in a ratio of about 1:4 (i.e., ratios of propylene glycol:ethanol from about 5:20 wt % to about 20:80 wt %) and about 1:10 wt/volume of antifungal (i.e., about 0.4-12.4 % w/v). (Ex. 1011, ¶¶ 100, 193.)

3. Summary: Claim 6 Is Obvious Over *Austin* in View of *Brehove* and *Chaudhuri*

Reason to Combine the References and Reasonable Expectation of

¹¹ For antifungal in 1 part propylene glycol to 4 parts ethanol, 0.5-15 wt % converts to 0.4-12.4 % w/v (presuming that 1.93 mL propylene glycol plus 10.13 mL ethanol is about 12.06 mL 1:4 propylene glycol:ethanol). (Ex. 1011, ¶ 193 n.7.)

Success: As admitted in the ‘657 Patent, preparation of the claimed formulations was “well known in the art.” (Ex. 1001, col. 188:29-51; Ex. 1011, ¶¶ 124, 195.) The ‘657 Patent does not describe any new or unexpected results attributable to the pharmaceutical formulation, nor was the formulation limited to avoid prior art. Before February 16, 2005, a POSITA would have had a reason to combine the disclosures in *Austin*, *Brehove* and *Chaudhuri* for all the reasons discussed above for *Austin* and *Brehove*. (Ex. 1011, ¶ 194.) A POSITA would have had further motivation to combine *Chaudhuri* because it describes topical formulations for effectively delivering antifungal compounds (e.g., butenafine) of higher molecular weight (e.g., 317.47 Daltons) than 5-fluoro benzoxaborole (151.93 Daltons) through the nail barrier to treat onychomycosis. (*Id.* ¶¶ 197-98; Ex. 1040, at 1.) A POSITA would have reasonably expected that a formulation shown to effectively deliver a higher molecular weight antifungal agent through the nail barrier would be likely to effectively deliver 5-fluoro benzoxaborole to treat onychomycosis for all of the reasons discussed above for *Austin* and *Brehove*. (*Id.* ¶¶ 196-98.)

E. Ground 3: Claim 7 of the ‘657 Patent Is Obvious Under 35 U.S.C. § 103(a) Over *Austin* in View of *Brehove* and *Samour*

The following claim chart shows the limitations of the above claim and the disclosure of each limitation in the prior art:

7,767,657	<i>Austin</i> in view of <i>Brehove</i> and <i>Samour</i>
7. The formulation	▪ See independent claim 1; see, e.g., Ex. 1002, at 7:5-9 (“The

<p>of claim 1, comprising: about 70% ethanol; about 20% poly(vinyl methyl ether-alt-maleic acid monobutyl ester) and about 10% of said 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole.</p>	<p>concentration of the oxaborole in the biocide composition is . . . more especially from 10 to 20% by weight relative to the total weight of the biocide composition.”).</p> <p><u>Austin</u></p> <ul style="list-style-type: none">▪ “[S]uitable water-miscible organic solvents are . . . ethanol or glycols such as . . . propylene glycol . . .” (<i>Id.</i> at 6:32-38.) <p><u>Brehove</u></p> <ul style="list-style-type: none">▪ “It is also found by in vivo tests on a volunteer that formulations of the invention achieve efficacy in the treatment of onychomycosis without skin irritation or noticeable side effects. . . . Dilute compositions of the active compounds in alcohol or acetone base . . . deliver concentrated active ingredient as the solvent evaporates.” (Ex. 1003, ¶ [0018].) <p><u>Samour</u></p> <ul style="list-style-type: none">▪ “A nail lacquer effective for the treatment or prevention of fungal infections, such as, onychomycosis, includes . . . antifungal agent in a clear, stable, film-forming lacquer vehicle . . .” (Ex. 1005, Abstract.)▪ “Typically, amounts of active antifungal agent in the range of from about 0.5 to 20 percent by weight, preferably from about 1 to 10 percent, by weight, of the total composition (including solvents, film-forming polymer, enhancer, etc.) will suffice for compositions for treatment as well as compositions for prevention.” (<i>Id.</i> at col. 12:9-14.)▪ “Film-forming polymers useful in the present invention are commercially available, such as . . . acrylic copolymers . . . under the tradename Eudragit, e.g., Eudragits E, RS, RL,; the methylvinyl ether copolymers . . . under the tradename Gantrez, e.g., Gantrez ES-335I, Gantrez ES-425, ES-435 Particularly good results have been obtained with . . . Gantrez ES-425.” (<i>Id.</i> at cols. 7:54-8:7.)▪ “[S]atisfactory results are obtained when the amount of film-forming polymer is in the range of from about 10 to about 70 percent, preferably from about 15 to about 50 percent, especially from about 20 to 40 percent by weight of the total nail lacquer composition.” (<i>Id.</i> at col. 8:39-44.)▪ “Solvents which may be used in the nail lacquer compositions . . . may be selected from among the usual physiologically safe organic solvents for lacquer compositions
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	<p>. . . . As examples of such solvents mention may be made of lower alkanols, e.g., ethanol” (<i>Id.</i> at col. 9:31-49.)</p> <ul style="list-style-type: none">▪ See Example 7, No. 318A, a lacquer formulation including 71% ethanol, 24% film-forming polymer (Eudragit RL), and 5% active ingredient (econazole). (<i>See id.</i> at col. 22:20-36.)
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As shown above, the combination of *Austin*, *Brehove*, and *Samour* discloses all of the limitations of claim 7. (Ex. 1011, ¶¶ 56, 117-19, 202-03.) A POSITA would have had several reasons to combine *Austin*, *Brehove*, and *Samour* with a reasonable expectation of success in arriving at the claimed subject matter. (*Id.* ¶¶ 201, 211-16.) Petitioner is not aware of any secondary considerations that would render claim 7 of the ‘657 Patent non-obvious. (*Id.*)

1. *Austin* Discloses 5-Fluoro Benzoxaborole as an Antifungal Agent and *Brehove* Discloses the Topical Application of Boron-Based Compounds to Treat Onychomycosis

Petitioner incorporates its discussion of *Austin* and *Brehove* from Sections VI.C.1-VI.C.3 and VI.D.1. (*See id.* ¶¶ 204-06.)

2. *Samour* Discloses a Formulation of About 70% Ethanol; About 20% Poly(Vinyl Methyl Ether-Alt-Maleic Acid Monobutyl Ester) and About 10% Antifungal

Samour discloses a nail lacquer effective for treating onychomycosis in humans, caused by dermatophytes, molds and *Candida*, including dermatophytes *Trichophyton rubrum* and *T. mentagrophytes*; and in particular, discloses “improvements in the physical properties (e.g., durability, water-resistance, flexibility) of water-insoluble adherent films . . . of [a] nail lacquer composition, as

well as improved diffusion characteristics of active principle(s) included in the lacquer composition from the resulting film.” (Ex. 1005, Abstract, col. 1:23-35, col. 3:59-65; Ex. 1011, ¶¶ 101, 207.)

Samour provides that “amounts of active antifungal agent [e.g., econazole] . . . range . . . from about 0.5 to 20 percent by weight, preferably from about 1 to 10 percent, by weight.” (Ex. 1005, col. 12:9-14, col. 16:40-62; Ex. 1011, ¶¶ 102, 208.)

Samour describes “[f]ilm-forming polymers . . . such as . . . methylvinyl ether copolymers sold . . . under the tradename . . . Gantrez ES-425 [i.e., poly(vinyl methyl ether-alt-maleic acid monobutyl ester)].” (Ex. 1005, col. 7:54-62; Ex. 1011, ¶¶ 103, 208; Ex. 1035, at 5.) *Samour* provides that “satisfactory results are obtained when the amount of film-forming polymer is . . . preferably from about 15 to about 50 percent, especially from about 20 to 40 percent by weight of the total nail lacquer composition.” (Ex. 1005, col. 8:39-44; Ex. 1011, ¶¶ 103, 208.)

When a plasticizer is present, *Samour* provides that it will be “especially, from about 4 to 8 percent, based on the total weight of the composition.” (Ex. 1005, col. 9:18-23; Ex. 1011, ¶ 104.) *Samour* also identifies a number of “physiologically safe organic solvents,” including ethanol; and in Example 7, discloses a lacquer formulation including 71% ethanol, 24% film-forming polymer (Eudragit RL), and 5% active ingredient (econazole). (Ex. 1005, col. 9:31-49, col. 22:20-36; Ex. 1011, ¶¶ 105-06, 209.)

Accordingly, *Samour* describes a topical formulation for treatment of onychomycosis with about 70% ethanol (i.e., Example 7, 71% ethanol), about 20% poly(vinyl methyl ether-alt-maleic acid monobutyl ester) (i.e., between 20 and 40% Gantrez ES-425), and about 10% antifungal (i.e., antifungal from about 0.5-20% by weight, preferably from about 1-10% by weight). (Ex. 1011, ¶¶ 107, 210.)

3. Summary: Claim 7 Is Obvious Over *Austin* in View of *Brehove* and *Samour*

Reason to Combine the References and Reasonable Expectation of

Success: As admitted in the ‘657 Patent, preparation of the claimed formulations was “well known in the art.” (Ex. 1001, col. 188:29-51; Ex. 1011, ¶¶ 124, 195, 212.) The ‘657 Patent does not describe any new or unexpected results attributable to the pharmaceutical formulation, nor was the formulation limited to avoid prior art. A POSITA would have had a reason to combine the disclosures in *Austin*, *Brehove* and *Samour* for all the reasons discussed above as for *Austin* and *Brehove*. (Ex. 1011, ¶ 211.) A POSITA would have had further reason to combine because *Samour* describes topical lacquer formulations with improved physical properties (e.g., durability, water-resistance, flexibility), as well as improved diffusion characteristics of active antifungals (e.g., econazole) having higher molecular weight (e.g., 361.68 Daltons) than 5-fluoro benzoxaborole (151.93 Daltons) for treating onychomycosis in humans. (*Id.* ¶¶ 213-14.) A POSITA would have

reasonably expected that an improved lacquer formulation for topical delivery of higher molecular weight antifungal agents to the nail of a human would be likely to effectively deliver 5-fluoro benzoxaborole to treat or inhibit onychomycosis for all the reasons discussed above for *Austin* and *Brehove*. (*Id.* ¶¶ 201, 215-16.)

F. Ground 4: Claim 8 of the ‘657 Patent Is Obvious Under 35 U.S.C. § 103(a) Over *Austin* in View of *Brehove*, *Friedman* and *Atlas*

The following claim chart shows the limitations of the above claim and the disclosure of each limitation in the prior art:

7,767,657	<i>Austin</i> in view of <i>Brehove</i> , <i>Friedman</i> and <i>Atlas</i>
8. The formulation of claim 1, comprising: about 56% ethanol; about 14% water; about 15% poly(2-hydroxyethyl methacrylate); about 5% dibutyl sebacate and about 10% of said 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole.	<ul style="list-style-type: none"> ▪ See independent claim 1; see, e.g., Ex. 1002, at 7:5-9 (“The concentration of the oxaborole in the biocide composition is . . . more especially from 10 to 20% by weight relative to the total weight of the biocide composition.”). ▪ <u><i>Brehove</i></u> ▪ “Dilute compositions of the active compounds in alcohol or acetone base ha[ve] the ability to deliver concentrated active ingredient as the solvent evaporates.” (Ex. 1003, ¶ [0018].) ▪ <u><i>Friedman</i></u> ▪ “The most common organisms involved in the fungal infections of the nail are <i>Trichophyton rubrum</i>, <i>Trichophyton mentagrophytes</i>, <i>Epidermophyton floccosum</i>, . . . [and] <i>Candida albicans</i>” (Ex. 1006, col. 1:27-31.) ▪ “The present invention provides a pharmaceutical sustained release preparation in a varnish or spray form for local treatment of the nail and surrounding tissues comprising: (a) an antifungal agent; (b) a keratolytic agent; (c) a humectant; (d) water; (e) a polymeric film-forming agent; (f) at least one additional excipient; and (g) a solvent system including at least one volatile solvent.” (<i>Id.</i> at col. 3:32-59.) ▪ “In a preferred embodiment the concentration of the polymeric film-forming agent in the varnish solution is less than about 7.5% (w/w).” (<i>Id.</i> at col. 5:27-29.)

	<ul style="list-style-type: none">▪ “In a preferred embodiment the weight ratio of the plasticizer to the polymer is in the range from about 0.04:1 to about 0.3:1.” (<i>Id.</i> at col. 5:62-64.)▪ “The hydrophobic methacrylic polymers are preferably Eudragit S, Eudragit L, Eudragit RS, and Eudragit RL manufactured by Rohm Pharma, but hydrophobic methacrylic polymers from other sources can also be used. The polymers provide a uniform film, retard the release rate of the drugs (agents), and can be mixed in regulated amounts to attain the desired drug release characteristics.” (<i>Id.</i> at col. 9:8-15.)▪ “In a preferred embodiment the at least one additional excipient is selected from a group consisting of plasticizers. In a preferred embodiment the plasticizer is selected from the group consisting of dibutyl sebacate. . . .” (<i>Id.</i> at col. 5:49-55.)▪ “In a preferred embodiment the concentration of the plasticizer in the varnish solution is from about 0.1% to about 2% (w/w).” (<i>Id.</i> at col. 5:56-58.)▪ “In a preferred embodiment the alcohol is selected from the group consisting of ethanol In a preferred embodiment the volatile solvent is present in an amount . . . from about 60% to about 90% (w/w), relative to the total weight of the composition.” (<i>Id.</i> at col. 6:1-9.)▪ “Preferably the water concentration in the varnish solution is less than about 5% (w/w), more preferably 0.5-4.5% (w/w) and most preferably 1-4.5% (w/w).” (<i>Id.</i> at col. 8:56-58.) <p><u>Atlas</u></p> <ul style="list-style-type: none">▪ “[H]ydrogels are used . . . for controlled drug delivery. Poly-HEMA (poly 2 hydroxylthyl [sic] methacrylate) is the most widely used hydrogel.” (Ex. 1007, Abstract.)▪ “[B]iocompatibility of hydrogels is attributed to their ability to simulate natural tissue due to their high water content and their special surface properties.” (<i>Id.</i> at col. 1:14-16.)▪ “P-HEMA hydrogels fibers we have described are biocompatible . . . and can be appropriately combined with traditional cosmetic[s] . . . applied [to the] skin and nail” (<i>Id.</i> at col. 1:21-25.)▪ “The percentage of fibers added range from 0.5% to 15% for different types of products The hydrogel fibers may be efficiently utilized as low as 1% due to their high swelling
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	<p>and storage properties.” (<i>Id.</i> at col. 2:45-50.)</p> <ul style="list-style-type: none">▪ “The P-HEMA hollow fibers will act as a reservoir and matrix for diffusion-controlled delivery to skin and nails. P-HEMA fibers are combined with water along with active ingredients, humectant, protein or ethyl alcohol containing perfume and other ingredients required to be applied to skin and allowed to be absorbed.” (<i>Id.</i> at col. 2:58-64.)▪ Example 4 provides P-HEMA in a nail polish composition. (<i>Id.</i> at cols. 3:57-4:7.)
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As shown above, the combination of *Austin*, *Brehove*, *Friedman* and *Atlas* discloses all of the limitations of claim 8. (Ex. 1011, ¶¶ 217-19.) As discussed below, a POSITA would have had several reasons to combine *Austin*, *Brehove*, *Friedman* and *Atlas* with a reasonable expectation of success in arriving at the claimed subject matter. (*Id.* ¶¶ 123-33, 229-37.) Petitioner is not aware of any secondary considerations that would render claim 8 non-obvious. (*Id.*)

1. *Austin* Discloses 5-Fluoro Benzoxaborole as an Antifungal Agent and *Brehove* Discloses the Topical Application of Boron-Based Compounds to Treat Onychomycosis

Petitioner incorporates its discussion of *Austin* and *Brehove* from Sections VI.C.1-VI.C.3 and VI.D.1. (*See id.* ¶¶ 220-22.)

2. *Friedman* Discloses a Formulation of About 56% Ethanol; About 14% Water; About 15% Methacrylic Polymer; About 5% Dibutyl Sebacate and About 10% Antifungal

Friedman discloses a “sustained release” nail varnish for delivery of antifungal agents to fingernails or toenails for treating fungal infections caused by “*Trichophyton rubrum*, *Trichophyton mentagrophytes* . . . [and] *Candida albicans*”

to effectively treat onychomycosis. (Ex. 1006, Abstract, col. 1:28-30, col. 3:32-59; Ex. 1011, ¶¶ 109, 223.) *Friedman* describes a number of methacrylic polymers (e.g., Eudragits) for use as film-forming polymers, but notes that methacrylic polymers from other sources can also be used; *Friedman* also provides that the concentration of the film-forming polymer in the varnish solution is “less than about 7.5% (w/w).” (Ex. 1006, col. 5:27-29, col. 9:3-15; Ex. 1011, ¶¶ 110, 224.)

Friedman describes plasticizers, such as dibutyl sebacate, with a concentration of plasticizer in the varnish solution from “about 0.1% to about 2% (w/w)” and a preferable weight ratio of plasticizer to polymer of “about 0.04:1 to about 0.3:1” (i.e., 1:3). (Ex. 1006, col. 5:51-58, 62-64; Ex. 1011, ¶¶ 111, 225.) At the described concentrations, each excipient in the varnish formulation serves its functional purpose, whether as film-forming agent, plasticizer, solvent, or hydrate.

Suitable volatile solvents include “ethanol,” preferably from “about 60% to about 90% (w/w), relative to the total weight of the composition.”¹² (Ex. 1006, col. 6:1-9; Ex. 1011, ¶¶ 112, 225.) *Friedman* discloses the concentration of water in the nail varnish is “less than about 5% (w/w), more preferably 0.5-4.5% (w/w) and most preferably 1-4.5% (w/w).” (Ex. 1006, col. 8:56-61; Ex. 1011, ¶¶ 112, 225.)

¹² 60% to about 90% (w/w) ethanol corresponds to 47.4% to about 71.1% (w/v) ethanol. (Ex. 1011, ¶ 225 n.8.)

3. *Atlas* Discloses Poly(2-Hydroxyethyl Methacrylate) in a Cosmetic Nail Lacquer

Atlas discloses that hydrogels may be used for controlled drug delivery and that poly(2-hydroxyethyl methacrylate) (i.e., P-HEMA) was the “most widely used hydrogel.” (Ex. 1007, Abstract; Ex. 1011, ¶¶ 113, 228; Ex. 1036, at 4.) *Atlas* also provides that the “biocompatibility of hydrogels is attributed to their ability to simulate natural tissue due to their high water content,” and that hydrogels exhibit “high swelling” properties. (Ex. 1007, col. 1:14-16, col. 2:48-50; Ex. 1011, ¶ 228.) In Example 4, *Atlas* discloses P-HEMA in a cosmetic nail polish composition, also stating that the “P-HEMA hollow fibers will act as a reservoir and matrix for diffusion-controlled delivery to skin and nails” and may be “combined with water along with active ingredients, humectant, protein or ethyl alcohol containing perfume and other ingredients required to be applied to skin and allowed to be absorbed.” (Ex. 1007, col. 2:58-64, cols. 3:57-4:7; Ex. 1011, ¶¶ 113-14, 228.)

4. Summary: Claim 8 Is Obvious Over *Austin* in View of *Brehove*, *Friedman* and *Atlas*

Reason to Combine the References and Reasonable Expectation of

Success: As admitted in the ‘657 Patent, preparation of a formulation including “56% ethanol; 14% water; 15% poly(2-hydroxyethyl methacrylate); 5% dibutyl sebacate; 10% compound is well known in the art.” (Ex. 1001, col. 188:29-51; Ex. 1011, ¶ 230.) The ‘657 Patent does not provide any guidance as to why the

claimed quantities were chosen, and does not attribute any significance or unexpected results to the claimed quantities. Nor was the formulation limited to avoid prior art. (Ex. 1011, ¶ 230.)

A POSITA would have had a reason to combine the disclosures in *Austin*, *Brehove*, *Friedman* and *Atlas* for all the reasons discussed above for *Austin* and *Brehove*. (*Id.* ¶ 229.) As was known in the art before February 16, 2005, “high-swelling polymers” were “preferred” for pharmaceutical lacquer formulations. (*Id.* ¶ 232; Ex. 1030, at 245.) One would have had reason to substitute P-HEMA for the methacrylic polymers of *Friedman* because P-HEMA was a well-known hydrogel, capable of “diffusion-controlled delivery” of active ingredients to skin and nails, and hydrogels were known to have “high water content” and “high swelling . . . properties,” as taught by *Atlas*. (*See* Ex. 1007, Abstract, col. 1:14-16, col. 2:48-50, 58-64; Ex. 1011, ¶¶ 232-33, 236.)

A POSITA would have had further reason to combine *Friedman* because like *Brehove*, *Friedman* discloses treating or inhibiting onychomycosis by administering a topical sustained release nail varnish to the nail of a human. (Ex. 1011, ¶¶ 223, 231, 233.) *Friedman* describes preferred pharmaceutical formulations for the sustained release nail varnish with a ratio of plasticizer (e.g., dibutyl sebacate) to film-forming polymer (e.g., methacrylic polymer) of 1:3, which corresponds to the claimed ratio (5% dibutyl sebacate:15% P-HEMA). (*Id.*

¶ 231.) *Friedman* describes quantities of film-forming polymer, dibutyl sebacate and water that serve their respective functional purposes in the varnish formulation. The *Friedman* varnish formulation also serves the functional purpose of the pharmaceutical formulation of claim 8. (*Id.*; see also Ex. 1001, col. 11:22-27.) Moreover, *Friedman* provides for delivery of higher molecular weight compounds, e.g., miconazole nitrate (479.14 Daltons) and clotrimazole (344.84 Daltons), in a formulation including ethanol, water, methacrylic polymers, and dibutyl sebacate. (Ex. 1006, col. 13:1-38; Ex. 1011, ¶¶ 223, 226-27, 231, 233-34.)

A POSITA would have reasonably expected that a sustained-release system that delivered antifungal agents having higher molecular weights than 5-fluoro benzoxaborole to the nail of a human would be likely to effectively deliver 5-fluoro benzoxaborole to treat onychomycosis for all the reasons discussed above for *Austin* and *Brehove*. (Ex. 1011, ¶¶ 229, 235-37.) A POSITA would further have reasonably expected that P-HEMA, a methacrylic polymer, could be substituted for the film-forming methacrylic polymers of *Friedman* because it was known for its “high swelling” properties, use in controlled drug delivery, and use in topical cosmetic compositions to the skin and nails. (*Id.* ¶ 236.)

G. Ground 5: Claim 9 of the ‘657 Patent Is Obvious Under 35 U.S.C. § 103(a) Over *Austin* in View of *Brehove*, *Samour* and *Friedman*

The following claim chart shows the limitations of the above claim and the

disclosure of each limitation in the prior art:

7,767,657	<i>Austin in view of Brehove, Samour and Friedman</i>
<p>9. The formulation of claim 1, comprising: about 55% ethanol; about 15% ethyl acetate; about 15% poly(vinyl acetate); about 5% dibutyl sebacate and about 10% 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole.</p>	<ul style="list-style-type: none"> ▪ <i>See</i> independent claim 1; <i>see, e.g.</i>, Ex. 1002, at 7:5-9 (“The concentration of the oxaborole in the biocide composition is . . . more especially from 10 to 20% by weight relative to the total weight of the biocide composition.”). ▪ <u>Brehove</u> ▪ “Many suitable film-forming polymers are known. Among those film formers considered to be suitable are polymers and copolymers of vinyl acetate” (Ex. 1003, ¶ [0026].) ▪ <u>Friedman</u> ▪ “In a preferred embodiment the plasticizer is selected from . . . dibutyl sebacate” (Ex. 1006, col. 5:51-55.) ▪ “In a preferred embodiment the concentration of the plasticizer in the varnish solution is from about 0.1% to about 2% (w/w).” (<i>Id.</i> at col. 5:56-58.) ▪ <u>Samour</u> ▪ “[W]ater-insoluble, film-forming polymers which may be used in the nail lacquer compositions of this invention, include . . . polyvinyl acetate” (Ex. 1005, col. 6:23-25.) ▪ “[S]atisfactory results are obtained when the amount of film-forming polymer is in the range of from about 10 to about 70 percent, preferably from about 15 to about 50 percent, especially from about 20 to 40 percent by weight of the total nail lacquer composition.” (<i>Id.</i> at col. 8:39-44.) ▪ “Solvents which may be used in the nail lacquer compositions of this invention . . . may be selected from among the usual physiologically safe organic solvents for lacquer compositions [and] may be made of lower alkanols, e.g., ethanol . . . [and] lower alkyl esters of lower carboxylic acids, e.g., ethyl acetate” (<i>Id.</i> at col. 9:31-43.) ▪ “When the additional plasticizer is present it [is] . . . most usually in the range of from about 0.5 to about 20 percent, preferably from about 2 to 10 percent, especially, from about 4 to 8 percent, based on the total weight of the composition.” (<i>Id.</i> at col. 9:18-23.) ▪ “Typically, amounts of active antifungal agent . . . rang[ing]

	<p>. . . preferably from about 1 to 10 percent, by weight, of the total composition (including solvents, film-forming polymer, enhancer, etc.) will suffice for compositions for treatment as well as compositions for prevention.” (<i>Id.</i> at col. 12:9-14.)</p> <ul style="list-style-type: none">▪ See Table 1, MC 16074B, a lacquer formulation including 6% SPE (2-nonyl-1,3-dioxolane), 6% propylene glycol, 34% ethanol, 25% ethyl acetate, 24% film-forming polymer (Amphomer LV-7), and 5% active ingredient (econazole).▪ See Table 1, MC 16074C, a lacquer formulation including 6% SPE (2-nonyl-1,3-dioxolane), 6% propylene glycol, 49% ethanol, 10% ethyl acetate, 24% film-forming polymer (Amphomer LV-7), and 5% active ingredient (econazole).▪ See Table 1, MC 18236B, a lacquer formulation including 6% SPE (2-nonyl-1,3-dioxolane), 6% propylene glycol, 56% ethanol, 24% film-forming polymer (Amphomer), and 8% active ingredient (econazole). (<i>Id.</i> at Table. 1.)
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As shown above, the combination of *Austin*, *Brehove*, *Samour* and *Friedman* discloses all of the limitations of claim 9. (Ex. 1011, ¶¶ 239-40.) As discussed below, a POSITA would have had several reasons to combine *Austin*, *Brehove*, *Samour* and *Friedman* with a reasonable expectation of success in arriving at the claimed subject matter. (*Id.* ¶¶ 238, 251-59.) Petitioner is not aware of any secondary considerations that would render claim 9 non-obvious. (*Id.*)

1. *Austin* Discloses 5-Fluoro Benzoxaborole as an Antifungal Agent and *Brehove* Discloses the Topical Application of Boron-Based Compounds to Treat Onychomycosis

Petitioner incorporates its discussion of *Austin* and *Brehove* from Sections VI.C.1-VI.C.3 and VI.D.1. (See also *id.* ¶¶ 241-43.)

2. *Samour* Discloses a Formulation of About 55% Ethanol; About 15% Ethyl Acetate; About 15% Poly(Vinyl Acetate) and About

10% Antifungal

Samour discloses a nail lacquer effective for treating onychomycosis in humans caused by dermatophytes, molds and *Candida*, including dermatophytes *Trichophyton rubrum* and *T. mentagrophytes*, and in particular, discloses “improvements in the physical properties (e.g., durability, water-resistance, flexibility) of water-insoluble adherent films of . . . [a] nail lacquer composition, as well as improved diffusion characteristics of active principle(s) included in the lacquer composition from the resulting film.” (Ex. 1005, Abstract, col. 1:23-35, col. 3:59-65; Ex. 1011, ¶¶ 101, 244.)

Amounts of active antifungal agent (e.g., econazole) range “from about 0.5 to 20 percent by weight, preferably from about 1 to 10 percent, by weight, of the total composition . . . for compositions for treatment as well as compositions for prevention.” (Ex. 1005, col. 12:9-14, col. 16:40-62; Ex. 1011, ¶¶ 102, 245.)

Samour describes water-insoluble, film-forming polymers for use in nail lacquer compositions, including polyvinyl acetate, and provides that “satisfactory results are obtained” when the amount of film-forming polymer is “preferably from about 15 to about 50 percent, especially from about 20 to 40 percent by weight of the total nail lacquer composition.” (Ex. 1005, col. 6:23-25, col. 8:34-44; Ex. 1011, ¶¶ 103, 246-47.) *Samour* also identifies a number of organic solvents, including “ethanol . . . [and] ethyl acetate.” (Ex. 1005, col. 9:31-43; Ex. 1011, ¶¶ 105, 246.)

Samour discloses lacquer formulations: (1) MC 16074C, with 49% ethanol, 10% ethyl acetate, 24% film-forming polymer (Amphomer LV-7), 5% active ingredient (econazole); (2) MC 18236B, with 56% ethanol, 24% film-forming polymer (Amphomer), 8% active ingredient (econazole); and (3) MC 16074B, with 34% ethanol, 25% ethyl acetate, 24% film-forming polymer (Amphomer LV-7), 5% active ingredient (econazole). (Ex. 1005, Table 1; Ex. 1011, ¶¶ 106, 247.)

Thus, *Samour* describes a topical formulation for treatment of onychomycosis with about 55% ethanol (e.g., MC 18236B, 56% ethanol); about 15% ethyl acetate (e.g., MC 16074C, 10% ethyl acetate; MC16074B, 25% ethyl acetate); about 15% poly(vinyl acetate) (e.g., film-forming agents in the range of about 15 to about 50 percent, especially from about 20 to 40 percent by weight); and about 10% antifungal (i.e., antifungal from about 0.5 to 20 percent by weight, preferably from about 1 to 10 percent, by weight). (Ex. 1011, ¶¶ 108, 248.)

3. *Friedman* Discloses a Formulation Including About 5% Dibutyl Sebacate

Friedman discloses a “sustained release” nail varnish for delivery of antifungal agents to treat fungal infections of the nail, such as onychomycosis caused by “*Trichophyton rubrum*, *Trichophyton mentagrophytes* [and] *Candida albicans*.” (Ex. 1006, Abstract, col. 1:28-30; Ex. 1011, ¶ 249.)

Friedman describes plasticizers, such as dibutyl sebacate, and provides that

the concentration of the plasticizer in the varnish solution is from “about 0.1% to about 2% (w/w),” which allows the dibutyl sebacate to serve the functional purpose of a plasticizer. (Ex. 1006, col. 5:51-58; Ex. 1011, ¶¶ 227, 250.) *Friedman* further provides that “[p]lasticizers are added to the varnish solution in order to enhance the plasticity of the film formed and to modify the sustained release characteristics of the polymer.” (Ex. 1006, col. 9:44-46; Ex. 1011, ¶ 255.)

4. Summary: Claim 9 Is Obvious Over *Austin* in View of *Brehove*, *Samour* and *Friedman*

Reason to Combine the References and Reasonable Expectation of

Success: As admitted in the ‘657 Patent, preparation of a formulation including “55% ethanol; 15% ethyl acetate; 15% poly(vinyl acetate); 5% dibutyl sebacate; 10% compound . . . is well known in the art.” (Ex. 1001, col. 188:29-51.) The ‘657 Patent does not provide any guidance as to why the claimed quantities were chosen, does not attribute any new or unexpected results to the claimed quantities, and did not limit the formulation to avoid prior art. (Ex. 1011, ¶ 252.)

A POSITA would have had reason to combine the disclosures of *Austin*, *Brehove*, *Samour* and *Friedman* for all of the reasons discussed above for *Austin* and *Brehove*. (*Id.* ¶¶ 251, 252, 257.) In addition, a POSITA would have had reason to combine *Samour*, which describes topical lacquer formulations of volatile solvents, film-forming agents, and plasticizers, with improved physical properties

(e.g., durability, water-resistance, flexibility) and improved diffusion characteristics for active principles, with *Friedman*, which describes the particular plasticizer dibutyl sebacate. (*Id.* ¶¶ 101, 111, 253, 255.) As plasticizers were known to modify the sustained release characteristics of a polymer, and dibutyl sebacate was a known plasticizer used in the “sustained release” nail lacquer formulation of *Friedman*, a POSITA would have had reason to modify the sustained release characteristics of the *Samour* formulation by substituting dibutyl sebacate as a plasticizer. (*Id.* ¶¶ 255-56, 259.)

Moreover, a POSITA would have reasonably expected that an improved lacquer formulation for topical delivery of antifungal agents having higher molecular weights than 5-fluoro benzoxaborole to the nail of a human, e.g., econazole (381.68 Daltons), miconazole nitrate (479.14 Daltons) and clotrimazole (344.84 Daltons), would be likely to effectively deliver 5-fluoro benzoxaborole to treat onychomycosis for all the reasons discussed above for *Austin* and *Brehove*. (*Id.* ¶¶ 254, 258; Ex. 1005, Table 1; Ex. 1006, col. 13:1-38; Exs. 1041-43.)

H. Ground 6: Claim 17 of the ‘657 Patent Is Obvious Under 35 U.S.C. § 103(a) Over *Austin* in View of *Brehove* and *Shapiro*

The following claim chart shows the limitations of the above claim and the disclosure of each limitation in the prior art:

7,767,657	<i>Austin</i> in view of <i>Brehove</i> and <i>Shapiro</i>
17. The	▪ <i>See</i> independent claim 1 and dependent claim 14; <i>see, e.g.</i> ,

<p>formulation of claim 14, wherein said fungus or yeast is a member selected from <i>Trichophyton concentricum</i>, <i>Trichophyton violaceum</i>, <i>Trichophyton schoenleinii</i>, <i>Trichophyton verrucosum</i>, <i>Trichophyton soudanense</i>, <i>Microsporium gypseum</i>, <i>Microsporium equinum</i>, <i>Candida guilliermondii</i>, <i>Malassezia globosa</i>, <i>Malassezia obtuse</i>, <i>Malassezia restricta</i>, <i>Malassezia slooffiae</i> and <i>Aspergillus flavus</i>.</p>	<p>Ex. 1002, at 36-37, Table 9 (“Example 64” where “R⁸” is “5-F” and “R⁹” is “H” and “CA” is “<i>Candida albicans</i>”).</p> <p><u>Brehove</u></p> <ul style="list-style-type: none"> ▪ “Onychomycosis is a nail disease of the toes and fingers typically caused by the organisms <i>Candida albicans</i>, <i>Trichophyton mentagrophytes</i>, <i>Trichophyton rubrum</i>, or <i>Epidermpophyton floccusum</i> [sic, <i>Epidermophyton floccosum</i>].” (Ex. 1003, ¶ [0005].) ▪ “This invention relates to the treatment of human fingernails and toenails; and more particularly, to topical applications and methods to cure or prevent the spread of nail infections, such as onychomycosis, caused by bacteria, fungi and other pathogens.” (<i>Id.</i> ¶ [0003].) <p><u>Shapiro</u></p> <ul style="list-style-type: none"> ▪ “The compounds of this invention can be used to treat diverse types of fungal infections. . . . Thus, the compounds of this invention can be used for the treatment of ringworm infections of the skin, hair and nails, namely: . . . <i>Tinea unguium</i> (onychomycosis) when caused by one or more of the following genera of fungi: <i>Trichophyton rubrum</i> . . . <i>Trichophyton mentagrophytes</i> . . . <i>Trichophyton verrucosum</i> . . . [and] <i>Microsporium gypseum</i>.” (Ex. 1008, cols. 1:65-2:14.)
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As shown above, the combination of *Austin*, *Brehove* and *Shapiro* discloses all of the limitations of claim 17. (Ex. 1011, ¶¶ 66, 261-62.) As discussed below, a POSITA would have had several reasons to combine *Austin*, *Brehove*, and *Shapiro* with a reasonable expectation of success in arriving at the claimed subject matter. (*Id.* ¶¶ 260, 268-72.) Petitioner is not aware of any secondary considerations that

would render claim 17 of the '657 Patent non-obvious. (*Id.*)

1. *Austin* Discloses 5-Fluoro Benzoxaborole as an Antifungal Agent and *Brehove* Discloses the Topical Application of Boron-Based Compounds to Treat Onychomycosis

Petitioner incorporates its discussion of *Austin* and *Brehove* from Sections VI.C.1-VI.C.3. In particular, *Austin* discloses that 5-fluoro benzoxaborole is an effective antifungal agent against each of the five (5) fungi tested: *Aspergillus niger* (AN); *Aureobasidium pullulans* (AP); *Candida albicans* (CA); *Gliocladium roseum* (GR); and *Penicillium pinophylum* (PP). (Ex. 1002, at 36-37, Table 9; Ex. 1011, ¶¶ 263-64.) *Brehove* describes a formulation of 10 wt % active agent in mineral oil for treating onychomycosis that is effective against *Candida albicans*. (Ex. 1003, ¶ [0032], Table 1; Ex. 1011, ¶ 265.)

2. *Shapiro* Discloses Compositions of Antifungal Compounds for Treating Diverse Types of Fungal Infections

Shapiro discloses antifungal compounds for treatment of a number of infections of the skin, hair and nails, including Tinea unguium (onychomycosis), “caused by one or more of the following genera of fungi: *Trichophyton rubrum* . . . *Trichophyton mentagrophytes* . . . *Trichophyton verrucosum* . . . [and] *Microsporium gypseum*.” (Ex. 1008, col. 2:3-14; Ex. 1011, ¶¶ 115, 266.) Thus, *Shapiro* describes antifungal compounds that have cross-activity against microorganisms that cause onychomycosis (e.g., *Trichophyton rubrum* and

Trichophyton mentagrophytes) and microorganisms that cause other diseases of the skin (e.g., *Trichophyton verrucosum* and *Microsporum gypseum*). (Ex. 1011, ¶¶ 116, 267.)

3. Summary: Claim 17 Is Obvious Over *Austin* in View of *Brehove* and *Shapiro*

Reason to Combine the References and Reasonable Expectation of

Success: Before February 16, 2005 a POSITA would have had a reason to combine the disclosures in *Austin*, *Brehove* and *Shapiro* for all the reasons discussed above as for *Austin* and *Brehove*. (*Id.* ¶¶ 268, 271.) In addition, a POSITA would have been further motivated to combine *Shapiro* because like *Brehove*, *Shapiro* also discloses treating or inhibiting onychomycosis in humans with pharmaceutical drug formulations. (*Id.* ¶¶ 269-70.) More specifically, *Shapiro* describes antifungal compounds that exhibit cross-activity against a number of different fungi, including cross-activity between fungi linked to onychomycosis and fungi linked to other fungal infections of the skin, hair and nails, such as *Trichophyton verrucosum* and *Microsporum gypseum*. (*Id.* ¶ 272.)

VII. CONCLUSION

For at least the reasons given above, claims 1-24 of the '657 Patent are unpatentable because they are obvious over the references cited herein.

Accordingly, Petitioner respectfully requests IPR of claims 1-24 of the '657 Patent.

First Petition For *Inter Partes* Review
Patent No. 7,767,657

Respectfully submitted,

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CERTIFICATE OF SERVICE ON PATENT OWNER

Pursuant to 37 C.F.R. § 42.6(e), the undersigned certifies that on August 20, 2015, a complete and entire copy of this First Petition for *Inter Partes* Review of Patent No. 7,767,657, an accompanying Power of Attorney in First Petition for *Inter Partes* Review of Patent No. 7,767,657, an Appendix of Exhibits for First Petition for *Inter Partes* Review of Patent No. 7,767,657, and all supporting Exhibits 1001-1050 were provided via UPS, postage prepaid, to the Patent Owner by serving the correspondence address of record for the '657 Patent.

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