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.: 7,582,621

PETITION FOR *INTER PARTES* REVIEW OF PATENT NO. 7,582,621

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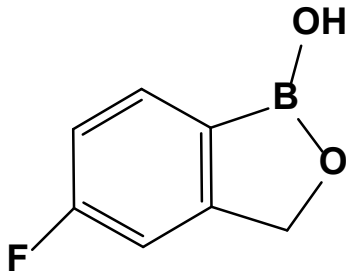
Coalition For Affordable Drugs X LLC ("Petitioner" or "CFAD") respectfully submits this Petition for *Inter Partes* Review ("IPR") of claims 1-12 of U.S. Patent No. 7,582,621 ("the '621 Patent") (Ex. 1001) pursuant to 35 U.S.C. §§ 311-319 and 37 C.F.R. § 42.100 *et seq*.

I. INTRODUCTION

The '621 Patent is directed to methods of treating fungal infections, including ungual and/or periungual infections that affect the hoof, nail, or claw (onychomycosis) with a specific boron-based compound: 1,3-dihydro-5-fluoro-1-hydroxy-2, 1-benzoxaborole, referred to herein as 5-fluoro benzoxaborole. Its chemical structure is:



The claims of the '621 Patent should be invalidated as obvious. The exact claimed compound was disclosed in WO 1995/033754 to Austin et al. ("*Austin*") as a preferred compound for use as a fungicide. Moreover, *Austin* explicitly tests the efficacy of the claimed compound against *Candida albicans*, which is one of the fungal pathogens that cause onychomycosis.

During prosecution, the Examiner rejected the pending claims over U.S.

Patent No. 5,880,188 to Austin et al.[1] in view of a definition of "fungicide" found on a general interest, non-scientific internet website called Answers.com, which defined a fungicide in broad terms of pharmaceutical uses, as well as agricultural uses. The Patent Owner overcame this rejection by arguing that Answers.com taught away from human treatment because the same Internet entry stated that some fungicides were harmful to humans. The Examiner accepted this argument and allowed the claims to issue.

While the Patent Owner's "teaching away" argument may have persuaded the Examiner, it cannot withstand scrutiny in this forum. The fallacy of the argument is exposed in view of how drugs are developed in the pharmaceutical industry. Drug candidates are screened through routine experimentation to determine efficacy and safety before application to humans, thus avoiding the safety fears that the Patent Owner argued to the Examiner. Even more telling, however, is that U.S. Patent Pub. No. 2002/0165121 to Brehove ("*Brehove*") disclosed a pre-existing boron-based industrial fungicide to create a topical pharmaceutical to successfully treat onychomycosis in humans and WO

[1] U.S. Patent No. 5,880,188 is related to WO 1995/033754, which Petitioner relies on in this Petition because the abstract of WO 1995/033754 specifically identifies the compound of claims 1-12 as a preferred compound.

2003/009689 to Freeman et al. ("*Freeman*") also disclosed additional boron-based fungicides for treating onychomycosis in humans.

Claims 1-12 of the '621 Patent are obvious against this real-world backdrop. A person of ordinary skill in the art ("POSITA") would have known that the preferred industrial fungicide disclosed in *Austin* was effective against *Candida albicans* (a known cause of onychomycosis). Accordingly, the *Austin* fungicide would have been an obvious candidate for potential therapeutic use in humans to treat onychomycosis in view of: (1) *Brehove*, which discloses a similar boron-based fungicide that suppresses *Candida albicans* and safely treats onychomycosis in humans; or (2) *Freeman*, which discloses additional boron-based fungicides that effectively suppress species of *Candida* and *Trichophyton rubrum* (a known cause of onychomycosis); or (3) *Freeman* and *Sun*, which discloses a method for topical treatment of onychomycosis, including topical administration to the nail and the surrounding skin. Therefore, Petitioner asserts three grounds for invalidity: (1) claims 1-12 are obvious over *Austin* in view of *Brehove*; (2) claims 1-12 are obvious over *Austin* in view of *Freeman*; and (3) claim 9 is obvious over *Austin* in view of *Freeman* and *Sun*.

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 "First" Petition and a concurrently filed "Second" Petition for *Inter Partes* Review of U.S. Patent No. 7,767,657, which is a continuation-in-part of the '621 Patent (Case Nos. Unassigned).

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

Lead Counsel	Back-Up Counsel
Jeffrey D. Blake, Esq. Reg. No. 53,214 **Merchant & Gould PC** 191 Peachtree Street N.E., Suite 4300 Atlanta, GA 30303 Main Telephone: (404) 954-5100 Main Facsimile: (404) 954-5099 jblake@merchantgould.com	Kathleen E. Ott, Esq. Reg. No. 64,038 Peter A. Gergely, Esq. (*Pro Hac Vice*) Ryan James Fletcher, Ph.D., Esq. (*Pro Hac Vice*) **Merchant & Gould PC** 1801 California Street, Suite 3300 Denver, CO 80202

	Main Telephone: (303) 357-1670 Main Facsimile: (303) 357-1950 kott@merchantgould.com pgergely@merchantgould.com rfletcher@merchantgould.com Brent E. Routman, Esq. (*Pro Hac Vice*) **Merchant & Gould PC** 3200 IDS Center 80 South Eighth Street Minneapolis, MN 55402 Main Telephone: (612) 332-5300 Main Facsimile: (612) 322-9081 broutman@merchantgould.com

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 KerydinIPR@merchantgould.com.

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

Payment of $23,000 for the fees set forth in 37 C.F.R. § 42.15(a)(1-2) 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 ’621 Patent is available for IPR and that

neither Petitioner nor any RPI is barred or estopped from requesting IPR of the '621 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 '621 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 § 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 1-12 of the '621 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 1-12 of the '621 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 '621 Patent is requested in view of the following four publications: (1) WO 1995/033754 to Austin et al. ("*Austin*") (Ex. 1002); (2) U.S. Patent Pub. No. 2002/0165121 to Brehove ("*Brehove*") (Ex. 1003); (3) WO 2003/009689 to Freeman et al. ("*Freeman*") (Ex. 1004); and (4) U.S. Patent No.

6,042,845 to Sun et al. ("*Sun*") (Ex. 1005). None of *Austin*, *Brehove*, *Freeman*, or *Sun* was made of record during prosecution of the '621 Patent.

Each of the publications listed above is available as prior art against the '621 Patent under pre-AIA 35 U.S.C. § 102(b) because each was published more than one year before February 16, 2005, the filing date of the provisional application to which the '621 Patent claims priority. Specifically, (1) *Austin* was published on December 14, 1995; (2) *Brehove* was published on November 7, 2002; (3) *Freeman* was published on February 6, 2003; and (4) *Sun* was published March 28, 2000.

The following combinations of the above-listed publications render claims 1-12 of the '621 Patent obvious under pre-AIA 35 U.S.C. § 103(a):

Ground	Claim Nos.	Proposed Statutory Rejections
1	1-12	Claims 1-12 of the '621 Patent are obvious under 35 U.S.C. §103(a) over *Austin* in view of *Brehove*.
2	1-12	Claims 1-12 of the '621 Patent are obvious under 35 U.S.C. §103(a) over *Austin* in view of *Freeman*
3	9	Claim 9 of the '621 Patent is obvious under 35 U.S.C. §103(a) over *Austin* in view of *Freeman* and *Sun*

Copies of *Austin*, *Brehove*, *Freeman*, and *Sun* are filed herewith. The above grounds for unpatentability are supported by the Declaration of Stephen Kahl, Ph.D. ("Kahl Decl.") (Ex. 1006) and the Declaration of S. Narasimha Murthy, Ph.D. ("Murthy Decl.") (Ex. 1008), which are both filed herewith.

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

The terms of the '621 Patent claims are to be given their broadest reasonable interpretation in light of the specification, as understood by a person of ordinary skill in the art. *See* 37 C.F.R. § 42.100(b). Petitioner submits, for purposes of the IPR only, the constructions given in Section V.C. below. Any claim terms not discussed herein 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)

A detailed explanation of how construed claims 1-12 of the '621 Patent are unpatentable on the statutory grounds identified above, including the identification of where each element of claims 1-12 are found in prior art publications, is set forth below in Section VI.

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

The exhibit numbers of the supporting evidence relied upon to support Petitioner's challenge as to claims 1-12 of the '621 Patent and the relevance of the evidence to the unpatentability arguments raised, including the specific portions of the evidence that support Petitioner's challenge, are set forth in Section VI. Exhibit 1006 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 1008 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 1-12, reasons for combining the references relied upon in this Petition, and the reasons and motivations to pharmaceutically formulate and topically apply the compounds discussed herein.

V. SUMMARY OF THE '621 PATENT

A. Lineage Of The '621 Patent

The '621 Patent, entitled "Boron-Containing Small Molecules," issued September 1, 2009, from U.S. Patent Application No. 11/357,687 ("the '687 Application") filed February 16, 2006, claiming priority to U.S. Provisional Application No. 60/654,060, filed February 16, 2005. (Ex. 1001.)

B. Description Of The Alleged Invention Of The '621 Patent

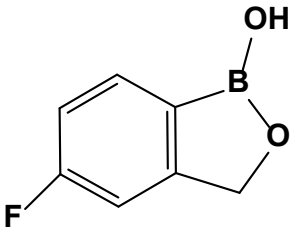
The '621 Patent is directed to boron-based heterocyclic compounds for treating fungal infections, and in particular, topical treatment of onychomycosis and other cutaneous fungal infections. (Ex. 1001, Abstract.) In the background, the '621 Patent cites problems with prior art treatment methods and compounds, such as adverse effects related to long-term oral administration of antifungals (*id.* at Col. 1:28-44), issues with surgical removal of all or part of the nail (*id.* at Col. 1:46-52),

and issues with topical treatments, including maintaining nail contact and nail penetration (*id.* at Col. 1:53-67, Col. 2:12-25).

The '621 Patent claims administration of 1,3-dihydro-5-fluoro-l-hydroxy-2,1-benzoxaborole ("C10 compound"), or a pharmaceutically acceptable salt thereof, sufficient to treat an infection. (*Id.* at Col. 67:34-38.) Preparation and analytical data regarding the C10 compound is described with reference to Examples 5-7 (*id.* at Cols. 55:59-57:18), Example 16, antifungal activity (*id.* at Cols. 59:42-60:42), Example 17, solubility, stability (*id.* at Cols. 60:44-62:29), Examples 18-20, nail penetration (*id.* at Cols. 62:31-67:32), and Figures 1B, 2A-4, 6-7. The '621 Patent admits that formulation of pharmaceutically effective carriers, as well as pharmaceutically acceptable additives and penetration enhancers, were known in the art. (*Id.* at Col. 11:3-57.)

C. Construction Of Key Terms In The '621 Claims

Claims 1, 11, and 12 of the '621 Patent recite the following compound: "1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole." 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole is disclosed in *Austin* as 5-fluoro-1,3 dihydro-1-hydroxy-2,1-benzoxaborole. (Ex. 1008 at ¶¶ 39-40, 61, 79.) The compound of Independent claims 1, 11, and 12 has the following structure:



(*Id*. at ¶ 79.) The ’621 Patent discloses this structure at column 32, lines 10-25 as Compound I with a formula of $C_7H_6BFO_2$ and a molecular weight of 151.93 Daltons. (Ex. 1001 at Col. 32:10-25; Ex. 1008 at ¶ 80.)

Claims 1, 11, and 12 of the ’621 Patent recite a “therapeutically effective amount” of the claimed compound. Therapeutically effective amount means “an amount of the claimed compound needed to reach the desired therapeutic result.” (Ex. 1008 at ¶ 81.) This is consistent with how the ’621 Patent defines “therapeutically effective amount.” (Ex. 1001 at Col. 9:53-58.)

Claim 3 recites the term “dermatological diseases.” Dermatological diseases is a broad term that means “diseases of the hair, nail, or skin.” (Ex. 1008 at ¶ 82.) This is consistent with the ’621 Patent’s use of “dermatological diseases” when giving some examples of dermatological diseases of the nail. (Ex. 1001 at Col. 29:33-44.)

Claim 3 recites the term “tinea pedis.” Tinea pedis means and is commonly referred to as athlete’s foot. (Ex. 1008 at ¶ 83.) This is consistent with the ’621 Patent’s use of tinea pedis. (Ex. 1001 at Col. 29:51-57.)

Claim 6 recites the term “tinea unguium.” Tinea unguium is “onychomycosis

caused by a dermatophyte." (Ex. 1008 at ¶ 84.) This is consistent with how the '621 Patent defines tinea unguium. (Ex. 1001 at Col. 28:24-25.)

D. Summary Of The Original Prosecution Of The '621 Patent

The '621 Patent was filed on February 16, 2006, as U.S. Application No. 11/357,687 with 39 claims. (Ex. 1010 at pp. 99-111.) In response to a restriction requirement, Applicants elected claims 27-31 (and new claims 40-42), canceled claims 1-26 and 32-39, and made a species election of 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole. (Ex. 1011.) Applicants further amended claim 27 (issued claim 1) to recite "1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole, or a pharmaceutically acceptable salt thereof or a prodrug thereof." (*Id.* at 3.)

In an Office Action dated August 26, 2008, all pending claims were rejected based on 35 U.S.C. § 112, first paragraph, because Applicants claimed "'treating or preventing infection' without limitation" (Ex. 1012 at p. 5), and "the prodrug of the instant compound" (*id.* at p. 7). The claims were further rejected under 35 U.S.C. § 103(a) over Austin et al. (U.S. Patent No. 5,880,188) in view of a definition for fungicide (Answers.com), which provided that a fungicide can be used for the agricultural or pharmaceutical industries. (*Id.* at pp. 11-12.) The Examiner noted that while "the level of skill in the art is high," due to the unpredictable nature of the pharmaceutical art, the specification failed to provide sufficient support for the broad use of the pharmaceutical compound to treat or prevent infection, or for

formulation of a prodrug thereof, and would result in exhaustive search or undue experimentation by one of skill in the art. (*Id.* at pp. 3-10.)

In response to the rejections under section 112, first paragraph, Applicants did not refute that the level of skill in the art was high, but amended claim 27 without argument, deleting the phrases "or preventing" and "or a prodrug thereof" and adding the phrase "sufficient to treat said infection." (Ex. 1013 at p. 2.) In fact, during prosecution of a related continuation-in-part application (U.S. Application No. 11/505,591), Applicants responded to a similar statement by the Examiner as follows: "As stated by the Examiner, the level of skill in the chemical arts is high. In view of this finding, Applicants submit that the specification, coupled with the knowledge generally known in the art, is sufficient to enable practice of the full scope of the rejected claim." (Ex. 1015 at p. 8.)

In response to the obviousness rejections, Applicants argued that "one of skill in the art would not presumptively consider a compound to be suitable for administration to an animal, especially a human, merely because a compound has been shown to have antifungal effects in paint or aviation fuel." (Ex. 1013 at p. 6.) Moreover, applicants argued that the secondary reference (Answers.com) cited by the Examiner 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.*)

The Examiner accepted Applicants arguments and a Notice of Allowance issued on April 22, 2009. (Ex. 1014.) The '621 Patent issued on September 1, 2009. (Ex. 1001.) After issuance, the Patent Owner filed petitions to extend the patent term adjustment from 267 days to 464 days (Ex. 1016), which was granted (Ex. 1017), and to remove Carolyn Bellinger-Kawahara and Kirk Maples as inventors (Ex. 1018), which was also granted. (Ex. 1019.)

E. The State Of The Art

Fungicides have been simultaneously disclosed for both industrial and pharmaceutical use for more than half a century. The cross-application of fungicides for both industrial and pharmaceutical uses, including use with humans, is neither new nor discouraged. Some representative examples from the past half century include:

- U.S. Patent No. 2,831,866 to W.A. Freeman et al. (Ex. 1020) disclosed pyridyl-4-nitrosopyrazoles for treating fungal infections, e.g., resulting from *Trichophyton rubrum*, in plants and humans. (*Id.* at Col. 1:19-42.)
- U.S. Patent No. 3,093,659 to Bell et al. (Ex. 1021) disclosed fungicides for industrial applications as well as for clinical applications, e.g., treating fungal infections caused by *Trichophyton rubrum* and *Candida albicans*, without irritating effects. (*Id*. at Cols. 2:65-3:19.)
- U.S. Patent No. 3,297,525 to Grier (Ex. 1022) disclosed heterocyclic

compounds for clinical treatment of fungal infections, e.g., caused by *Candida albicans* and *Trichophyton rubrum,* as well as for industrial applications, such as fungicidal additives for paints and other coating compositions and organic films. (*Id.* at Col. 1:18-26, Col.4:20-46, Col. 13:32-38, Col. 18:1-45.)

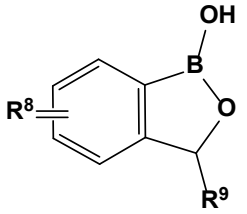
▪ U.S. Patent No. 3,370,957 to Wagner et al. (Ex. 1023) disclosed the use of heterocyclic compounds as effective fungicidal agents for industrial applications, e.g., paint, leather, plastics, and fuel, as well as for medical therapies to treat, for example, mycotic infections such as onychomycosis caused by *Trichophyton rubrum*. (*Id.* at Col. 1:28-32, Col. 3:25-38, Cols. 3:74-4:36, Col. 9:11-24, Col. 13:3-15, 64-70.)

▪ U.S. Patent No. 4,202,894 to Pfiffner (Ex. 1026) disclosed morpholine compounds for use as effective fungicides in agricultural and pharmaceutical applications, including the disclosure that certain compounds were effective against *Candida albicans* and trichophytes. (*Id.* at Cols. 16:24-17:8, Col. 18:42-43, Table III.)

▪ U.S. Patent No. 4,822,822 to Arita et al. (Ex. 1029) disclosed benzylamine derivatives as agricultural, industrial and therapeutic fungicides. (*Id*. at Abstract.) The compounds were described as therapeutic, antimycotic agents for safe treatment of fungal infections in humans and animals with reduced

side-effects, e.g., infections caused by *Candida albicans*, as well as industrial fungicides having effectiveness and a high degree of safety. (*Id.* at Cols. 2:60-4:4, Col. 15:30-66.)

In 1995, *Austin* (Ex. 1002) described the preferred boron-based compound 5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole, which is the compound claimed in the '621 Patent, for use as an industrial fungicide. Oxaboroles of the general formula were described:

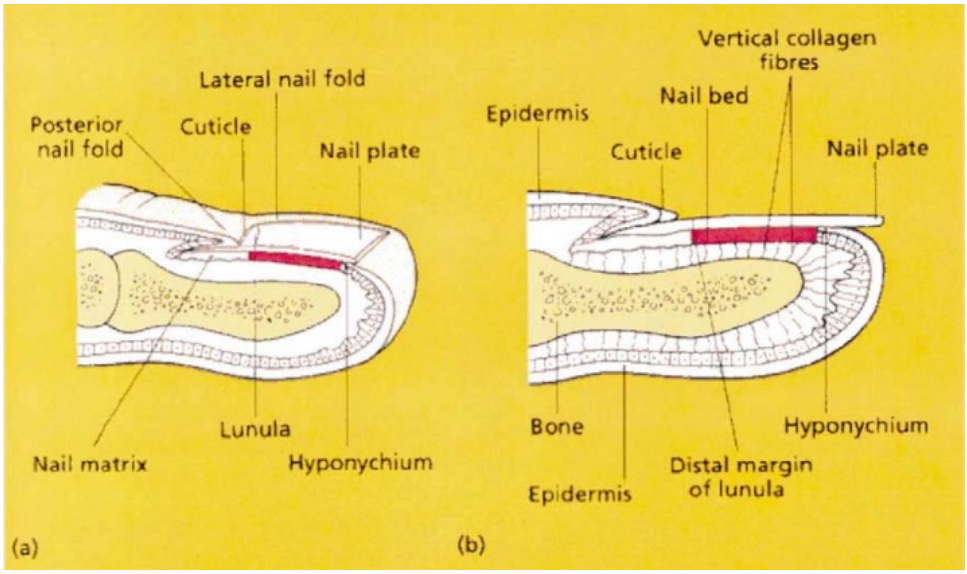


with Example 64 having 5-fluoro at R^8 and hydrogen at R^9. (*Id*. at p. 22, ll. 6-14, p. 23.) As provided in Table 9, Example 64 is highly effective against *Candida albicans*. (*Id.* at p. 37, *see also id.* at p. 36, ll. 1-12.) For example, the oxaboroles disclosed by *Austin* are "particularly effective against micro-organisms such as bacteria, algae, yeasts and particularly fungi, especially fungi which cause degradation of plastics materials" and provide "protection of a medium susceptible to microbial attack by the treatment of the medium with an effective amount of an oxaborole." (*Id.* at p. 1, ll. 35-38, p. 2, ll. 1-4.)

In 2001, Michael Groziak authored an article entitled "Boron Therapeutics on the Horizon," 8 *Am. J. of Therapeuitcs*, 321-328 (2001). (Ex. 1027.) *Groziak*

detailed how "boron-based agents [were] clearly visible on the therapeutic horizon" and specifically recognized that "[b]oronic acids are fairly common and easily prepared synthetic organic compounds" but that "none to date ha[d] been found to be unusually toxic." (*Id*. at Abstract, p. 322, left col.)

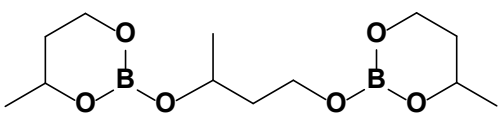
In 2002, Sudaxshina Murdan authored an article entitled "Drug Delivery to the Nail Following Topical Application," 236 *Int'l J. of Pharm.*, 1-26 (2002) (Ex. 1028). In particular, *Murdan* detailed problems and solutions for treating various infections of the human nail unit, the anatomy of which includes:



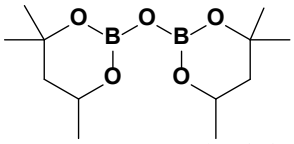
(*Id.* at p. 2.) The nail plate is a hard, rigid, relatively impermeable structure formed by tight layers of dead, flattened, keratinized cells held together by globular, cysteine-rich proteins, and including from 10-30% water. (*See id.* at pp. 2-4.) Due to the relative impermeability of the nail plate, treating infections of the nail bed, such as onychomycosis, had traditionally been challenging. (*See id.* at p. 2.)

Murdan stated that low molecular weight as well as the shape, charge, and hydrophobicity of the drug molecule and its formulation characteristics (e.g., nature of vehicle, pH, drug concentration) could improve results. (*See id.* at p. 9.)

Later in 2002, *Brehove* (Ex. 1003) described use of a boron-based industrial fungicide (referred to as BioBorJF®) for treatment of onychomycosis caused by *Candida albicans* and *Trichophyton rubrum*. (*Id.* at ¶¶ [0005], [0015], [0023] (citing U.S. Patent No. 2,741,548).) BioBorJF® (Ex. 1024) was formulated and introduced in 1965 for disinfection and prevention of microbial growth in jet fuel storage tanks and marine diesel fuels. BioBorJF® is effective against "growth of harmful slime producing fungi" and has the following active ingredients: 2,2'-oxybis (4,4,6-trimethyl-1, 3,2-dioxaborinane) and 2,2-(1-methyltrimethylenedioxy) bis (4-methyl-1,3,2-dioxaborinane). (*Id.*; Ex. 1025.) These compounds have the following structures:



2,2'-(1-methyltrimethylene dioxy) bis (4-methyl-1, 3, 2-dioxaborinane)



2,2'-oxybis (4, 4, 6-trimethyl-1, 3, 2-dioxaborinane)

Brehove noted a report detailing the testing of a dioxiborinane for use as a sedative found it to be "very safe" and that the safety data sheet for BioBorJF® did not suggest otherwise. (Ex. 1003 at ¶ [0015].)

Indeed, *Brehove* tested the active ingredients listed for BioBorJF®, i.e., 2,2'-(1-methyltrimethylene dioxy) bis (4-methyl-1, 3, 2-dioxaborinane) and 2,2'-oxybis (4, 4, 6-trimethyl-1, 3, 2-dioxaborinane), on human subjects for the treatment of onychomycosis and found them to be safe, effective, convenient, and free of toxicity. (*Id.* at ¶¶ [0017]-[0018].) *Brehove* formulated the above dioxaborinanes and topically treated the nails and surrounding skin of human subjects suffering from onychomycosis by "painting the entire toenail and the cuticle for approximately 3 mm beyond the nail." (*Id.* at ¶ [0035].) The dioxaborinanes were found to be particularly effective against *Candida albicans*, and in many cases treatment led to elimination of infection and full recovery of the nail with no side effects or skin irritation. (*Id.* at ¶¶ [0034]-[0035]).

Shortly after *Brehove*, *Freeman* (Ex. 1004) described various phenyl boronic acid derivatives for treating fungal infections including dermatophytoses or onychomycosis of the fingernail and toenails, as well as fungal infections in plants. (*Id.* at ¶ [001].) These compounds were found to be particularly effective against *Trichophyton rubrum*. (*Id.* at ¶ [0034] ("It can be readily seen from the above that PBA exhibited fungicidal effects on *T. rubrum* within the concentration range of 5-10 mg/ml tested").)

By February 16, 2005, the cross-application of fungicides for both industrial and pharmaceutical uses had been known for over a half century, the boron-based

compound of claims 1-12 had been disclosed as a preferred fungicide for suppressing a known cause of onychomycosis, and at least two different publications had disclosed the treatment of onychomycosis by applying formulations containing boron-based compounds to the nail and surrounding skin of humans.

Despite the obviousness of claims 1-12 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* Exs. 1031 ($1300 for 10ml), 1032 ($509.54 for a 30-day supply and $1477.81 for a 90-day supply).) While the Patent Owner can attempt to secure such prices through FDA regulatory exclusivity, it cannot extend those prices with an invalid patent.

VI. PETITIONER HAS A REASONABLE LIKELIHOOD OF PREVAILING

Pursuant to 37 C.F.R. § 42.104(b)(4), there is a reasonable likelihood that at least one claim of the ’621 Patent is unpatentable. In particular, this section provides detailed descriptions and claim charts showing how claims 1-12 of the ’621 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.

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 nonobviousness. *See KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 406-07 (2007) (citing *Graham v. John Deere Co*., 383 U.S. 1, 17-18 (1966)). The scope and content of the prior art, the level of ordinary skill in the art, and the differences between the claimed invention and the art relevant to this Petition are addressed for each statutory ground of rejection upon which this Petition is based.

In assessing obviousness, the U.S. Supreme Court has stated that "[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).

"Although common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *Id*. at 418. The

Court has further stated that "[w]hen there is a design need or a 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." *Id.* at 421. "If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense." *Id*.

A. Each Reference Relied On For Grounds 1-3 Is Prior Art

Each reference applied in Grounds 1-3 is available as prior art against the '621 Patent under pre-AIA 35 U.S.C. § 102(b) as set forth above in Section IV.B.2. None of *Austin*, *Brehove*, *Freeman*, or *Sun* was made of record during prosecution of the '621 Patent.

B. A Person Of Ordinary Skill In The Art

A person of ordinary skill in the art at the time the '621 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. 1006 at ¶ 21; Ex. 1008 at ¶ 34.)

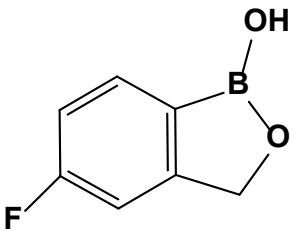
C. Ground 1: Claims 1-12 Are Obvious Over *Austin* In View Of *Brehove*

A person of ordinary skill in the art before February 16, 2005 would have had multiple reasons to combine *Austin* and *Brehove* with a reasonable expectation in successfully arriving at the claimed subject matter. (Ex. 1008 at ¶¶ 61-73, 85-

117.) The combination of *Austin* and *Brehove* discloses all of the limitations of claims 1-12. Petitioner is not aware of any secondary considerations that would render claims 1-12 of the '621 Patent non-obvious. (*Id*. at ¶¶ 85-117.)

1. Claims 1-12 Generally Recite Methods Of Treating Onychomycosis In Humans With 5-Fluoro Benzoxaborole

Independent claim 1 recites a "method of treating an infection in an animal, said method comprising administering to the animal a therapeutically effective amount of 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole, or a pharmaceutically acceptable salt thereof, sufficient to treat said infection." (Ex. 1001 at Col. 67.) 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole has the following structure:



(Ex. 1006 at ¶ 24; Ex. 1008 at ¶ 79.) A short name for 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole is 5-fluoro benzoxaborole. (Ex. 1008 at ¶ 61.)

Claim 2 depends from claim 1 and recites "wherein said infection is a member selected from a systemic infection, a cutaneous infection, and an ungual or periungual infection." (Ex. 1001 at Col. 67.) A "cutaneous infection" is a skin infection. (Ex. 1008 at ¶ 47.) An "ungual" infection is an infection of an animal's

nail, hoof, or claw. (*Id*.)

Claim 3 depends from claim 1 and recites "wherein said infection is a member selected from a" long list of diseases, including "dermatological diseases" and "[t]inea pedis." (Ex. 1001 at Cols. 67-68.) "[D]ermatological diseases" is a broad term that includes onychomycosis. (Ex. 1008 at ¶ 48.) "Tinea pedis" is commonly known as athlete's foot, which is often caused by fungi of the *Trichophyton* genus, including *Trichophyton rubrum*. (*Id*.)

Claim 4 depends from claim 1 and recites "wherein said infection is onychomycosis." (Ex. 1001 at Col. 68.) "[O]nychomycosis" is an infection of the nail that is often caused by three types of fungi: dermatophytes, yeasts, and non-dermatophyte molds. (Ex. 1001 at Col. 28:18-20; Ex. 1008 at ¶ 49.) Dermatophytes refer to the following three fungal genre: *Microsporum*, *Epidermophyton,* and *Trichophyton*. (Ex. 1008 at ¶ 49.) *Trichophyton rubrum* is the most common dermatophyte involved in onychomycosis. (*Id*.) *Candida albicans* is the most commonly isolated yeast species associated with onychomycosis. (*Id*.)

Claim 5 depends from claim 1 and recites "wherein said animal is a member selected from a human, cattle, goat, pig, sheep, horse, cow, bull, dog, guinea pig, gerbil, rabbit, cat, chicken and turkey. (Ex. 1001 at Col. 68.)

Claim 6 depends from claim 4 and recites "wherein said onychomycosis is tinea unguium." (*Id*.) Tinea unguium is onychomycosis caused by a dermatophyte

such as *T. rubrum*. (Ex. 1001 at Col. 28:24-27; Ex. 1008 at ¶ 51.)

Claim 7 depends from claim 1 and recites "wherein said animal is a human." (Ex. 1001 at Col. 68.)

Claim 8 depends from claim 1 and recites "wherein the administering is at a site which is a member selected from the skin, nail, hair, hoof and claw." (*Id*.)

Claim 9 depends from claim 8 and recites "wherein said skin is the skin surrounding the nail, hair, hoof or claw." (*Id*.)

Claim 10 depends from claim 1 and recites "wherein said infection is a fungal infection." (*Id*.)

Like claim 1, claims 11 and 12 are both independent and recite methods of treating or inhibiting fungal infections in humans through administration of 5-fluoro benzoxaborole. (*Id*.) Independent claim 11 recites a "method of treating onychomycosis in a human, said method comprising administering to the human a therapeutically effective amount of 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole, or a pharmaceutically acceptable salt thereof, sufficient to treat said onychomycosis." (*Id*.)

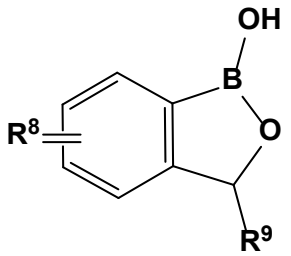
Independent claim 12 recites a "method of inhibiting the growth of a fungus in a human, said method comprising administering to the human a therapeutically effective amount of 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole, or a pharmaceutically acceptable salt thereof." (*Id*.)

Therefore, claims 1-12 of the '621 Patent recite a method of inhibiting or treating onychomycosis in a human through the administration of an effective amount of 5-fluoro benzoxaborole to the nail or skin surrounding the nail of said human. (*Id*. at Cols. 67-68.)

2. *Austin* Discloses 5-Fluoro Benzoxaborole As An Anti-Fungal Agent

Austin discloses 5-fluoro benzoxaborole as a preferred fungicide. (Ex. 1002 at Abstract; Ex. 1006 at ¶¶ 31, 33-34; Ex. 1008 at ¶¶ 61, 90.) Generally, *Austin* discloses that compounds containing an "oxaborole ring" are "particularly effective" against "fungi." (Ex. 1002 at p. 1, ll. 35-40; Ex. 1006 at ¶¶ 31, 33-34; Ex. 1008 at ¶¶ 61, 90.) *Austin's* "preferred" oxaborole ring compounds are "5- and 6-fluoro or bromo- 1,3-dihydro-1-hydroxy-2,1-benzoxaborole." (Ex. 1002 at Abstract; Ex. 1006 at ¶¶ 31, 33-34; Ex. 1008 at ¶¶ 61, 90.) 5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole is the exact same compound recited in claims 1-12 of the '621 Patent. (Ex. 1006 at ¶ 33; Ex. 1008 at ¶¶ 61, 90.)

Austin discloses the preparation of various benzoxaborole derivatives, including 5-fluoro benzoxaborole. (Ex. 1002 at pp. 22-23, Table 5; Ex. 1008 at ¶ 62.) Specifically, *Austin* discloses the preparation of benzoxaborole derivatives having the following general structure where R^8 represents one or more substituents in the phenyl ring:



(Ex. 1002 at pp. 22-23, Table 5, 36; Ex. 1008 at ¶ 62.) *Austin* discloses the elemental analysis of 5-fluoro benzoxaborole in Table 5 at Example 64 where R^8 is 5-F (fluorine at the 5 position of the phenyl ring) and R^9 is H (hydrogen). (Ex. 1002 at pp. 22-23, Table 5; Ex. 1008 at ¶ 62.)

Austin further discloses that 5-fluoro benzoxaborole has significant anti-fungal activity. (Ex. 1002 at pp. 36-37; Ex. 1006 at ¶ 34; Ex. 1008 at ¶ 63.) Specifically, *Austin* discloses anti-fungal activity of 5-fluoro benzoxaborole in Table 9 at Example 64 where R^8 is 5-F and R^9 is H. (Ex. 1002 at p. 37, Table 9; Ex. 1006 at ¶ 34; Ex. 1008 at ¶ 63.) 5-fluoro benzoxaborole is an effective anti-fungal 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 pp. 36-37, Table 9; Ex. 1008 at ¶ 63.) 5-fluoro benzoxaborole is effective at a concentration as low as five (5) parts per million (PPM), which was the lowest concentration tested by *Austin*. (Ex. 1002 at pp. 33, 36-37, Table 9; Ex. 1006, ¶ 34; Ex. 1008 at ¶ 63.) Notably, 5-fluoro benzoxaborole is effective against *Candida albicans,* which is a fungus that often

causes onychomycosis in addition to dermatophytes. (Ex. 1002 at pp. 36-37, Table 9; Ex. 1006 at ¶ 34; Ex. 1008 at ¶ 64.)

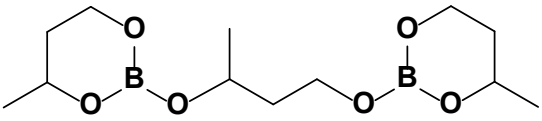
Therefore, *Austin* discloses 5-fluoro benzoxaborole, which is the compound of claims 1-12, as a preferred fungicide to effectively inhibit *Candida albicans*, which is one of the fungi responsible for onychomycosis. (Ex. 1006 at ¶¶ 33-34; Ex. 1008 at ¶¶ 61-66, 90-91.)

3. *Brehove* Discloses The Topical Application Of Boron-Based Compounds To Treat Onychomycosis

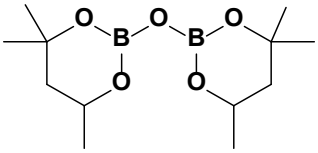
Brehove discloses the topical application of boron compounds to "treat and prevent the spread of nail infections or onychomycosis caused by bacteria, fungi and other pathogens." (Ex. 1003 at Abstract, ¶ [0003]; Ex. 1006 at ¶¶ 36-38; Ex. 1008 at ¶ 67.) *Brehove* further disclosed that "organo-boron compounds have long been known to exhibit biocidal activity." (Ex. 1003 at ¶ [0007]; Ex. 1008 at ¶ 67.) *Brehove* specifically disclosed that boron-based topical formulations have "powerful potency against *Candida albicans* . . . effectively kill[ing] the most common pathogen causing onychomycosis." (Ex. 1003 at ¶ [0018]; Ex. 1008 at ¶ 67.)

The boron-based topical compositions for treating onychomycosis in *Brehove* include: 2,2'-(1-methyltrimethylene dioxy) bis (4-methyl-1,3, 2-dioxaborinane) and/or 2,2'-oxybis (4, 4, 6-trimethyl-1, 3, 2-dioxaborinane), which

have the following structures:



2,2'-(1-methyltrimethylene dioxy) bis (4-methyl-1, 3, 2-dioxaborinane)



2,2'-oxybis (4, 4, 6-trimethyl-1, 3, 2-dioxaborinane)

(Ex. 1003 at ¶¶ [0022], [0030]; Ex. 1006 at ¶¶ 36-38; Ex. 1008 at ¶ 68.) *Brehove* disclosed that topical compositions including these boron-based compounds are "highly effective in suppressing the growth of *Candida albicans* in vitro" at every concentration tested. (Ex. 1003 at ¶¶ [0032]-[0033]; Ex. 1006 at ¶¶ 36-38; Ex. 1008 at ¶ 70.)

The same topical compositions also successfully treated onychomycosis in humans. (Ex. 1003 at ¶¶ [0034]-[0038]; Ex. 1006 at ¶¶ 36-38; Ex. 1008 at ¶ 70.) *Brehove* disclosed the application of the topical compositions to five (5) volunteers suffering from onychomycosis. (Ex. 1003 at ¶¶ [0034]-[0038]; Ex. 1008 at ¶ 71.) In each case, the volunteer applied a topical composition including one or more boron-based compounds directly to the infected nails, and in some instances the cuticles around the nails, to effectively treat the onychomycosis. (Ex. 1003 at ¶¶ [0022], [0030]; Ex. 1008 at ¶ 71.) The topical compositions effectively eradicated the onychomycosis with "[n]o skin irritation . . . and no [evidence of] side effects." (Ex. 1003 at ¶ [0034]; Ex. 1008 at ¶ 71.)

Therefore, *Brehove* disclosed the topical application of boron-based industrial fungicides directly to the nail and surrounding skin of humans to effectively treat onychomycosis typically caused by the organisms *Candida albicans*, *Trichophyton mentagrophytes*, *Trichophyton rubrum*, or *Epidermophyton floccosum*. (Ex. 1006 at ¶¶ 36-38; Ex. 1008 at ¶¶ 66-72, 92.)

4. Summary: Claims 1-12 Are Obvious Over *Austin* And *Brehove*

Reason to Combine the References*:* Given the foregoing, one of ordinary skill in the art would have had several reasons to combine *Austin* and *Brehove* before February 16, 2005 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 responsible for onychomycosis; and (3) *Austin* discloses boron-based compounds that have lower molecular weight than the successful compounds of *Brehove* and are therefore likely to effectively penetrate the nail barrier. (Ex. 1006 at ¶¶ 33-34, 36; Ex. 1008 at ¶¶ 86, 93-96, 116.)

Austin specifically discloses that the compound claimed in the ’621 Patent, 5-fluoro benzoxaborole, is a preferred fungicide to effectively inhibit *Candida albicans*. (Ex. 1006 at ¶ 34; Ex. 1008 at ¶¶ 61, 64, 90.) *Brehove* specifically discloses the topical application of compositions including boron-based compounds directly to the nail and surrounding skin of humans with

onychomycosis to effectively treat onychomycosis typically caused by the organisms *Candida albicans*, *Trichophyton mentagrophytes*, *Trichophyton rubrum*, or *Epidermophyton floccosum*. (Ex. 1006 at ¶ 38; Ex. 1008 at ¶¶ 67-71.)

A person of ordinary skill in the art before February 16, 2005 who was seeking to develop a therapeutic treatment for onychomycosis would have understood that boron compounds were effective fungicides. (Ex. 1008 at ¶ 94.) A person of ordinary skill in the art would have also understood from *Brehove* that known boron-based industrial fungicides had successfully treated onychomycosis with little irritation or side effects. (Ex. 1008 at ¶¶ 92, 94; *see also* Ex. 1006, ¶¶ 28-31.)

A person of ordinary skill in the art would have been further motivated to select 5-fluoro benzoxaborole as disclosed by *Austin* because it is a small molecular weight compound. (Ex. 1008 at ¶ 95.) Penetration of the nail barrier is more effective with smaller molecular weight compounds, which was known in the art. (*Id*.) *Brehove* effectively treated and inhibited onychomycosis in humans with 2,2'-(1-methyltrimethylene dioxy) bis (4-methyl-1,3, 2-dioxaborinane) (molecular weight of 285.9 Daltons) and 2,2'-oxybis (4, 4, 6-trimethyl-1, 3, 2-dioxaborinane) (molecular weight of 269.9 Daltons). (*Id*.; Ex. 1006 at ¶ 38.) 5-fluoro benzoxaborole is a smaller molecular weight compound than either of the effective *Brehove* compounds and would therefore have had a greater likelihood of

successfully penetrating the nail barrier at lower concentrations. (Ex. 1008 at ¶ 95.)

Hence, one of ordinary skill in the art would have had multiple reasons to combine the teachings of *Austin* and *Brehove* to treat or inhibit the growth of onychomycosis with the preferred 5-fluoro benzoxaborole compound of *Austin* based on the success of *Brehove*. (*Id*. at ¶¶ 93-96, 116.)

Reasonable Expectation of Success: One of ordinary skill in the art before February 16, 2005 would have reasonably expected *Austin's* 5-fluoro benzoxaborole to exhibit the same activity and success of the boron-based compounds in *Brehove* because boron-based compounds were well known biocides, 5-fluoro benzoxaborole shares common structural features with the boron compounds of *Brehove*, 5-fluoro benzoxaborole was disclosed as a preferred fungicide that shares common activity with the boron compounds of *Brehove*, 5-fluoro benzoxaborole has a lower molecular weight than the boron compounds of *Brehove*, and *Brehove* demonstrated the successful application of a boron-based industrial fungicide to a human to effectively treat onychomycosis without any noticeable irritation or side effects. (Ex. 1006 at ¶¶ 28-32; Ex. 1008 at ¶¶ 97-106, 117.)

A person of ordinary skill in the art before February 16, 2005 understood that boron-based compounds were known fungicides. (*See, e.g.*, Ex. 1003 at ¶ [0007] ("organo-boron compounds have long been known to exhibit biocidal

activity"); Ex. 1008 at ¶ 99.) A person of ordinary skill in the art would have understood that boron compounds, including boronic acids and boron heterocycles, under evaluation as boron-based therapeutics before February 16, 2005, were generally safe for human use. (Ex. 1006 at ¶ 30; Ex. 1008 at ¶¶ 66, 69-71; *see also, e.g.*, Ex. 1027 at 322 ("Boronic acids are fairly common and . . . none to date has been found to be unusually toxic.").)

The use of industrial boron-based fungicides to effectively treat humans was known in the art. (Ex. 1008 at ¶¶ 67-73.) In fact, *Brehove* disclosed the use of boron-based fungicides to successfully treat and inhibit onychomycosis in humans without any skin irritation or evident side effects. (*Id*. at ¶¶ 67-73, 103-104.) A person of ordinary skill in the art interested in treating or inhibiting fungal infections such as onychomycosis in humans would have had a reasonable expectation of success in using 5-fluoro benzoxaborole for such a purpose. (*Id*. at ¶¶ 103-106.)

5-fluoro benzoxaborole shares common structural features with the compounds of *Brehove*. *Austin* discloses 5-fluoro benzoxaborole, which is a boron heterocycle. (*Id.* at ¶ 100.) The compounds of *Brehove* are also boron heterocycles. (*Id*.) A person of ordinary skill in the art would have expected that 5-fluoro benzoxaborole, which shares similar structural features with the compounds of *Brehove*, would likely share similar functional features as well. (*Id*.)

5-fluoro benzoxaborole was disclosed as a preferred fungicide that shares common activity with the compounds of *Brehove*. (*Id*. at ¶ 101.) *Austin* teaches that 5-fluoro benzoxaborole exhibits fungicidal activity. (*Id*.) *Austin* specifically identifies 5-fluoro benzoxaborole as one of three preferred compounds. (*Id*.) *Austin* specifically discloses that 5-fluoro benzoxaborole effectively inhibits *Candida albicans*. (*Id*.) *Brehove* also discloses the inhibition of *Candida albicans*. (*Id*. at ¶ 72.) Thus both references disclose the inhibition of *Candida albicans* by boron heterocycles. A person of ordinary skill in the art 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. (*Id*. at ¶ 101.) Therefore, a person of ordinary skill in the art would have been motivated before February 16, 2005 to use the preferred compound of *Austin* to treat onychomycosis as taught by *Brehove*, and would have had a reasonable expectation of success because both compounds inhibit *Candida albicans*. (*Id*. at ¶ 106.)

5-fluoro benzoxaborole has a lower molecular weight than the compounds of *Brehove*. (*Id*. at ¶ 102.) It was well known to a person of ordinary skill in the art before February 16, 2005 that lower molecular weight compounds are more effective at penetrating the nail plate following topical administration. (*Id*.; *see also, e.g.*, Ex. 1028 at 9 ("As expected, molecular size has an inverse relationship

with penetration into the nail plate. The larger the molecular size, the harder it is for molecules to diffuse through the keratin network and [the] lower the drug permeation.").) The compounds of *Brehove* have a higher molecular weight than 5-fluoro benzoxaborole. (Ex. 1008 at ¶ 102.) A person of ordinary skill in the art would have expected that 5-fluoro benzoxaborole would effectively penetrate the nail plate following topical administration because the compounds of *Brehove* were effective at treating and inhibiting onychomycosis following topical application to the nail plate despite having substantially higher molecular weights. (*Id*.)

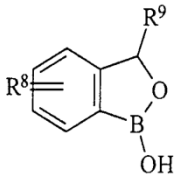
A person of ordinary skill in the art would also have had a reasonable expectation of successfully determining a therapeutically effective amount of 5-fluoro benzoxaborole to treat or inhibit onychomycosis. (*Id*. at ¶ 105.) The level of one of ordinary skill in the art is high. (Ex. 1015 at p. 8.) Determining 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. 1008 at ¶ 105.) *Austin* disclosed that 5-fluoro benzoxaborole effectively inhibits *Candida albicans*, among other fungi, at concentrations as low as 5 ppm. (*Id*. at ¶ 91.) *Brehove* disclosed the effective inhibition of *Candida albicans, in vitro,* at concentrations as low as 0.1% boron-based compound by weight of the composition. (*Id*. at ¶ 70; Ex. 1003 at ¶ [0032],

Table I.) *Brehove* further disclosed the effective inhibition and treatment of onychomycosis via topical application to the nail and surrounding skin of a human with a composition containing as little as 12.5% boron-based compounds by weight of the composition. (Ex. 1008 at ¶ 70; Ex. 1003 at ¶ [0037].) Determining a therapeutically effective amount of 5-fluoro benzoxaborole to treat or inhibit onychomycosis before February 16, 2005 involved nothing more than routine experimentation based on well-established protocols (Ex. 1008 at ¶¶ 105-06.)

Given the foregoing, one of ordinary skill in the art would have had a reasonable expectation of successfully administering a therapeutically effective amount of 5-fluoro benzoxaborole to a human to treat or inhibit a fungal infection, e.g., onychomycosis, based on the success of *Brehove* because boron-based compounds were well known biocides, the preferred 5-fluoro benzoxaborole shares common structural features and common activity with the effective compounds of *Brehove*, 5-fluoro benzoxaborole is more likely to penetrate the nail plate than the higher molecular weight but still effective *Brehove* compounds, and determining a therapeutically effective amount of 5-fluoro benzoxaborole to successfully treat or inhibit onychomycosis is nothing more than routine experimentation based on known protocols. (*Id*. at ¶¶ 106, 117; *see also* Ex. 1006 at ¶¶ 32, 44.)

When a patent "simply arranges old elements," i.e., the addition of 5-fluoro benzoxaborole from an industrial composition to 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 1-12. (Ex. 1008 at ¶¶ 61-73, 86-117.) The following claim chart shows the limitations of these claims, and the disclosure of each limitation in the prior art.

7,582,621	***Austin* in view of *Brehove***
1. A method of treating an infection in an animal, said method comprising administering to the animal a therapeutically effective amount of 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole, or a pharmaceutically acceptable salt thereof, sufficient to treat said infection.	***Austin*** ▪ "[C]ompounds containing an oxaborole ring are particularly effective against micro-organisms such as bacteria, algae, yeasts and particularly fungi." (Ex. 1002 at p. 1, ll. 35-40.) ▪ "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." (*Id*. at Abstract.) ▪ "The benzoxaborole derivatives obtained have the general formula:"  (*Id*. at p. 22, ll. 5-14.) ▪ "Example 64" where "R^8" is "5-F" and "R^9" is "H." (*Id*. at p. 23, Table 5.) ▪ "Example 64" where "R^8" is "5-F" and "R^9" is "H" and "CA" is *Candida albicans*. (*Id*. at pp. 36-37, Table 9.)

	Brehove ▪ "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 at ¶ [0003].) ▪ "Members of the class of organo-boron compounds have long been known to exhibit biocidal activity." (*Id*. at ¶ [0007].) ▪ Compositions containing "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 *Candida albicans* in vitro." (*Id*. at ¶¶ [0018], [0033].) ▪ "2,2′-(1-methyltrimethylene dioxy) bis-(4-methyl-1, 3, 2-dioxaborinane) [ ] and 2,2′-oxybis (4, 4, 6-trimethyl-1, 3, 2-dioxaborinane) [have] powerful potency against *Candida albicans*. That is to say, it is found in accordance with the invention, that active constituents of certain compositions effectively kill the most common pathogen causing onychomycosis." (*Id*. at ¶ [0018].) ▪ "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" and "in 250 days, the nail is fully-grown, completely free from any [onychomycosis] infection." (*Id*. at ¶ [0035].)
2. The method of claim 1, wherein said infection is a member selected from a systemic infection, a cutaneous infection, and an ungual or periungual infection.	▪ *See* independent claim 1. ***Austin*** ▪ "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 at Abstract.) ***Brehove*** ▪ "Onychomycosis is a nail disease of the toes and fingers typically cause by the organisms *Candida albicans, Trichophyton mentagrophytes, Trichophyton*

	rubrum, or *Epidermpophyton floccusum* [sic].” (Ex. 1003 at ¶ [0005].) ▪ “A male volunteer 58 years old has onychomycosis on both feet . . . [t]he application [of the above compositions with 25% active ingredients] included painting the entire toenail and the cuticle for approximately 3 mm beyond the nail” and “in 250 days, the nail is fully-grown, completely free from any infection.” (*Id.* at ¶ [0035]; *see also id*. at ¶¶ [0034], [0036]-[0038].)
3. The method of claim 1, wherein said infection is a member selected from . . . dermatological diseases . . .[2]	▪ *See* independent claim 1 and dependent claim 2 where *Brehove* treats a patient for onychomycosis which is a “dermatological disease.” (*See, e.g.*, Ex. 1003 at ¶ [0035] (“The application included painting the entire toenail and the cuticle for approximately 3 mm beyond the nail” and “in 250 days, the nail is fully-grown, completely free from any [onychomycosis] infection.”).)
4. The method of claim 1, wherein said infection is onychomycosis.	▪ *See* independent claim 1 and dependent claim 2. (*See, e.g.*, Ex. 1003 at ¶ [0035] (“A male volunteer 58 years old has onychomycosis on both feet . . . [t]he application included painting the entire toenail and the cuticle for approximately 3 mm beyond the nail” and “in 250 days, the nail is fully-grown, completely free from any infection.”).)
5. The method of claim 1, wherein said animal is a member selected from a human, cattle, goat, pig, sheep, horse, cow, bull, dog, guinea pig, gerbil, rabbit, cat, chicken and turkey.	▪ *See* independent claim 1 and dependent claim 2. (*See, e.g.*, Ex. 1003 at ¶ [0035] (“A male volunteer 58 years old has onychomycosis on both feet . . . [t]he application included painting the entire toenail and the cuticle for approximately 3 mm beyond the nail” and “in 250 days, the nail is fully-grown, completely free from any infection.”).)
6. The method of	▪ *See* independent claim 1, dependent claim 2, and

[2] The remainder of “infections” listed in claim 3 can be found at Ex. 1001, Column 67, line 42 to Column 68, line 19.

claim 4, wherein said onychomycosis is tinea unguium.	dependent claim 4. (*See, e.g.*, Ex. 1003 at ¶ [0035] ("A male volunteer 58 years old has onychomycosis on both feet . . . [t]he application included painting the entire toenail and the cuticle for approximately 3 mm beyond the nail" and "in 250 days, the nail is fully-grown, completely free from any infection.").) ***Brehove*** ▪ "Onychomycosis is a nail disease of the toes and fingers typically cause by the organisms *Candida albicans, Trichophyton mentagrophytes, Trichophyton rubrum,* or *Epidermpophyton floccusum* [sic]." (Ex. 1003 at ¶ [0005].)
7. The method of claim 1, wherein said animal is a human.	▪ *See* independent claim 1 and dependent claim 2. (*See, e.g.*, Ex. 1003 at ¶ [0035] ("A male volunteer 58 years old has onychomycosis on both feet . . . [t]he application included painting the entire toenail and the cuticle for approximately 3 mm beyond the nail" and "in 250 days, the nail is fully-grown, completely free from any infection.").)
8. The method of claim 1, wherein the administering is at a site which is a member selected from the skin, nail, hair, hoof and claw.	▪ *See* independent claim 1 and dependent claim 2. (*See, e.g.*, Ex. 1003 at ¶ [0035] ("A male volunteer 58 years old has onychomycosis on both feet . . . [t]he application included painting the entire toenail and the cuticle for approximately 3 mm beyond the nail" and "in 250 days, the nail is fully-grown, completely free from any infection.").)
9. The method of claim 8, wherein said skin is the skin surrounding the nail, hair, hoof or claw.	▪ *See* independent claim 1, dependent claim 2, and dependent claim 8. (*See, e.g.*, Ex. 1003 at ¶ [0035] ("A male volunteer 58 years old has onychomycosis on both feet . . . [t]he application included painting the entire toenail and the cuticle for approximately 3 mm beyond the nail" and "in 250 days, the nail is fully-grown, completely free from any infection.").)
10. The method of claim 1, wherein said infection is a fungal infection.	▪ *See* independent claim 1 and dependent claim 2. (*See, e.g.*, Ex. 1003 at ¶ [0035] ("A male volunteer 58 years old has onychomycosis on both feet . . . [t]he application included painting the entire toenail and the cuticle for approximately 3 mm beyond the nail" and "in 250 days, the nail is fully-grown, completely free

	from any infection.").) ***Brehove*** ▪ "Onychomycosis is a nail disease of the toes and fingers typically cause by the organisms *Candida albicans, Trichophyton mentagrophytes, Trichophyton rubrum,* or *Epidermpophyton floccusum* [sic]." (Ex. 1003 at ¶ [0005].)
11. A method of treating onychomycosis in a human, said method comprising administering to the human a therapeutically effective amount of 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole, or a pharmaceutically acceptable salt thereof, sufficient to treat said onychomycosis.	▪ *See* independent claim 1 and dependent claim 2. (*See, e.g.*, Ex. 1002 at Abstract, p. 1, ll. 35-40 ("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. 1003 at ¶¶ [0003], [0007], [0018], [0033]-[0038].) ***Brehove*** ▪ "A male volunteer 58 years old has onychomycosis on both feet . . . [t]he application included painting the entire toenail and the cuticle for approximately 3 mm beyond the nail" and "in 250 days, the nail is fully-grown, completely free from any infection." (Ex. 1003 at ¶ [0035].)
12. A method of inhibiting the growth of a fungus in a human, said method comprising administering to the human a therapeutically effective amount of 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole, or a pharmaceutically acceptable salt thereof.	▪ *See* independent claim 1 and dependent claim 2. (*See, e.g.*, Ex. 1002 at Abstract, p. 1, ll. 35-40 ("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. 1003 at ¶¶ [0003], [0007], [0018], [0033]-[0038] ***Brehove*** ▪ "A male volunteer 58 years old has onychomycosis on both feet . . . [t]he application included painting the entire toenail and the cuticle for approximately 3 mm beyond the nail" and "in 250 days, the nail is fully-grown, completely free from any infection." (Ex. 1003 at ¶ [0035].)

D. Ground 2: Claims 1-12 Are Obvious Over *Austin* In View Of *Freeman*

A person of ordinary skill in the art would have had multiple reasons to combine *Austin* and *Freeman* with a reasonable expectation of successfully arriving at the claimed subject matter. (Ex. 1008 at ¶¶ 61-65, 74-77, 118-148.) The combination of *Austin* and *Freeman* discloses all of the limitations of claims 1-12. (*Id*.) Petitioner is not aware of any secondary considerations that would render claims 1-12 of the '621 Patent non-obvious.

1. Claims 1-12 Generally Recite Methods Of Treating Onychomycosis In Humans With 5-Fluoro Benzoxaborole

Petitioner incorporates its discussion of claims 1-12 of the '621 Patent from Section VI.C.1.

2. *Austin* Discloses 5-Fluoro Benzoxaborole As An Anti-Fungal Agent

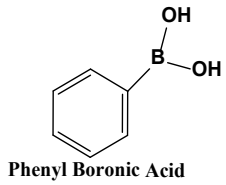
As discussed above, *Austin* discloses 5-fluoro benzoxaborole, which is the compound of claims 1-12, as a preferred fungicide to effectively inhibit *Candida albicans*, which is one of the fungi responsible for onychomycosis. (Ex. 1006 at ¶ 33; Ex. 1008 at ¶¶ 122-23.)

3. *Freeman* Discloses The Topical Application Of Boron-Based Compounds To Treat Onychomycosis

Freeman discloses "method and compositions for treating fungal infections, and more particularly, dermatophytoses or onchomycosis [sic] of the fingernail and

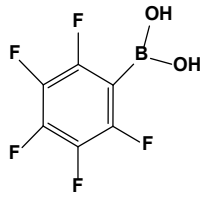
the toenail" with phenyl boronic acid and derivatives thereof. (Ex. 1004 at ¶¶ [001], [0022]; Ex. 1008 at ¶ 75.) *Freeman* recognizes that both "dermatophytes and non-dermatophytes, especially *Candida Sp*., have been identified as etiologic agents of onychomycosis." (Ex. 1004 at ¶ [008]; Ex. 1008 at ¶ 74.) *Freeman* further recognizes that the "dermatophyte species that most often causes onychomycosis in North America" includes "*T. rubrum*." (Ex. 1004 at ¶ [008]; Ex. at 1008 at ¶ 74.)

The topical compositions for treating onychomycosis in *Freeman* include "phenyl boronic acid and derivatives thereof as well as related boronic acid compounds have fungicidal properties . . . [which] have been found to be particularly useful in treating nail fungal infections." (Ex. 1004 at ¶ [0022]; Ex. 1008 at ¶ 75.) Phenyl boronic acid ("PBA") has the following structure:

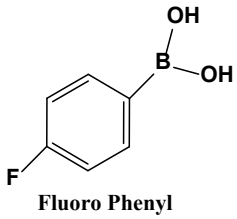


Phenyl Boronic Acid

(Ex. 1004 at ¶¶ [0029]-[0034]; Ex. 1008 at ¶ 75.) *Freeman* also discloses fluoro phenyl boronic acid derivatives of PBA, including the following structures:



Pentafluoro Phenyl Boronic Acid



Fluoro Phenyl Boronic Acid

(Ex. 1004 at ¶ [0062] ("R_1, R_2, R_3, R_4, and R_5" are all fluorine or "R_3" is fluorine and the remaining substituents are hydrogen); Ex. 1006 at ¶ 39; Ex. 1008 at ¶ 75.) *In vitro* tests by *Freeman* show that both PBA and pentafluoro phenyl boronic acid exhibit anti-fungal activity by inhibiting *T. rubrum* within a concentration range of 5-10 mg/ml. (Ex. 1004 at ¶¶ [0034]-[0037]; Ex. 1008 at ¶ 76.)

Freeman discloses the topical administration of compositions containing PBA or its derivatives "in the form of a buffered solution, lotion, or ointment . . . once daily until cure" for the treatment of onychomycosis. (Ex. 1004 at ¶ [0030]; Ex. 1008 at ¶ 76.) Specifically, the *Freeman* formulations are prepared for application to the "skin or nails" for the treatment of onychomycosis. (*Id*. at ¶¶ [0053], [0064]; Ex. 1008 at ¶¶ 76-77.)

Therefore, *Freeman* discloses the topical application of compositions including phenyl boronic acid, or derivatives thereof, directly to the skin or nail of a human with onychomycosis to treat onychomycosis typically caused by *Candida albicans*, *Trichophyton mentagrophytes*, *Trichophyton rubrum*, or *Epidermophyton floccosum*. (Ex. 1008 at ¶ 74-77, 124; *see also* Ex. 1006 at ¶¶ 39-42.)

4. Summary: Claims 1-12 Are Obvious Over *Austin* And *Freeman*

Reason to Combine the References: Given the foregoing, one of ordinary skill in the art would have had multiple reasons to combine *Austin* and *Freeman*

before February 16, 2005 because: (1) both references teach the use of boron-based compounds as fungicides; (2) both references disclose the use of boron-based compounds to specifically inhibit *Candida albicans* or *T. rubrum*, which are fungi responsible for onychomycosis; and (3) *Austin* discloses boron-based compounds that have structural similarity to *Freeman's* preferred compounds for treating and inhibiting onychomycosis in humans. (Ex. 1008 at ¶¶ 65, 74, 77, 125-127.)

Austin specifically discloses the compound claimed in the '621 Patent, 5-fluoro benzoxaborole, is a preferred fungicide to effectively inhibit *Candida albicans*. (*Id*. at ¶¶ 122, 126-27.) *Freeman* specifically discloses boron compositions including PBA and derivatives thereof for topical application directly to the nails of humans with onychomycosis to effectively treat onychomycosis typically caused by the organisms *Candida Sp.*, *Trichophyton mentagrophytes*, *Trichophyton rubrum*, or *Epidermophyton floccosum*. (*Id*. at ¶¶ 124, 127.)

A person of ordinary skill in the art before February 16, 2005 who was seeking to develop a therapeutic treatment for onychomycosis would have understood that boron compounds were effective fungicides. (*Id*. at ¶ 126.) A person of ordinary skill in the art would have also understood that boron-based compounds had previously been disclosed for treating fungal infections in humans. (*Id*. at ¶ 127.)

A person of ordinary skill in the art would have been further motivated to

select 5-fluoro benzoxaborole as disclosed by *Austin* because it is structurally similar to PBA and pentafluoro phenyl boronic acid, which *Freeman* disclosed as preferred compounds for treating and inhibiting onychomycosis in humans. (*Id*.) A person of ordinary skill in the art would have had a reasonable expectation that 5-fluoro benzoxaborole would have similar activity to PBA and pentafluoro phenyl boronic acid following topical administration to a human because the compounds are structurally similar. (*Id*.)

Hence, one of ordinary skill in the art would have readily combined the teachings of *Austin* and *Freeman* to treat or inhibit the growth of onychomycosis with the preferred 5-fluoro benzoxaborole compound of *Austin* based on the disclosures of *Freeman*. (*Id*. at ¶¶ 125-28, 147.)

Reasonable Expectation of Success: One of ordinary skill in the art before February 16, 2005 would have reasonably expected 5-fluoro benzoxaborole as disclosed by *Austin* to exhibit the same activity of the boron-based compounds in *Freeman* because, as discussed below, boron-based compounds were known fungicides, 5-fluoro benzoxaborole shares common structural features with the compounds of *Freeman*, 5-fluoro benzoxaborole was disclosed as a preferred fungicide that shares common activity with the compounds of *Freeman*, 5-fluoro benzoxaborole has a similar molecular weight to the compounds of *Freeman*, and *Freeman* disclosed a boron-based compound for human use in order to treat

onychomycosis. (Ex. 1006 at ¶¶ 32, 44; Ex. 1008 at ¶¶ 129-30.)

A person of ordinary skill in the art before February 16, 2005 understood that boron-based compounds were known fungicides. (Ex. 1008 at ¶ 131; *see also, e.g.*, Ex. 1002 at Abstract.) A person of ordinary skill in the art would have understood that boron compounds, including boronic acids and boron heterocycles, under evaluation as boron-based therapeutics before February 16, 2005, were safe for application to a human. (Ex. 1006 at ¶ 30; Ex. 1008 at ¶¶ 66, 69-71; *see also, e.g.*, Ex. 1027 ("Boronic acids are fairly common and . . . none to date has been found to be unusually toxic.").)

The use of boron-based compounds to treat humans was well known in the art. (Ex. 1008 at ¶¶ 74-77.) *Freeman* disclosed the use of structurally similar boron-based compounds for use in treating onychomycosis in humans. (*Id*. at ¶ 132.) A person of ordinary skill in the art interested in treating or inhibiting onychomycosis would have had a reasonable expectation of success in using the boron-based compounds of *Austin* to treat or inhibit onychomycosis in humans. (*Id*. at ¶¶ 131-32.)

5-fluoro benzoxaborole shares common structural features with the compounds of *Freeman*. *Austin* discloses 5-fluoro benzoxaborole, which is a boron heterocycle. (*Id*. at ¶ 100.) The compounds of *Freeman* are cyclic compounds which include boron. (*Id*. at ¶¶ 75, 132.) A person of ordinary skill in the art would

have expected that 5-fluoro benzoxaborole, which shares similar structural features with the compounds of *Freeman*, would likely share similar functional features as well. (*Id*. at ¶ 132.)

5-fluoro benzoxaborole was disclosed as a preferred fungicide that shares common activity with the compounds of *Freeman.* (*Id*. at ¶ 133.) *Austin* teaches that 5-fluoro benzoxaborole is one of three preferred compounds and effectively inhibits *Candida albicans*. (*Id*.) A person of ordinary skill in the art would have expected that 5-fluoro benzoxaborole, which shares functional activity with the compounds of *Freeman* (the inhibition of fungus responsible for onychomycosis), would likely have had other activities in common as well, i.e., the inhibition of additional fungi responsible for onychomycosis. (*Id*.)

5-fluoro benzoxaborole has a relatively low molecular weight. (*Id*. at ¶ 134.) It was well known to a person of ordinary skill in the art before February 16, 2005 that lower molecular weight compounds are more effective at penetrating the nail plate following topical administration. (*See, e.g.*, Ex. 1028 at p. 9, right col.) The compounds of *Freeman* have a similar molecular weight to the 5-fluoro benzoxaborole. (Ex. 1008 at ¶ 134.) For example, 5-fluoro benzoxaborole has a molecular weight of 151.93 Daltons while phenyl boronic acid has a molecular weight of 121.9 Daltons and pentafluoro phenyl boronic acid has a molecular weight of 211.88 Daltons. (*Id*.) A person of ordinary skill in the art would have

expected that 5-fluoro benzoxaborole would effectively penetrate the nail plate following topical administration because *Freeman* discloses similar molecular weight compounds for treating and inhibiting onychomycosis following topical application to the nail plate. (*Id*.)

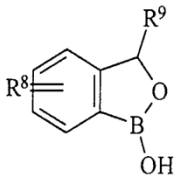
A person of ordinary skill in the art would also have had a reasonable expectation of successfully determining a therapeutically effective amount of 5-fluoro benzoxaborole to treat or inhibit onychomycosis. (*Id*. at ¶ 136.) The level of one of ordinary skill in the art is high. (Ex. 1015 at p. 8.) Determining 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. 1008 at ¶ 136.) *Austin* disclosed that 5-fluoro benzoxaborole effectively inhibits *Candida albicans*, among other fungi, at concentrations as low as 5 ppm. (*Id*. at ¶ 91.) *Freeman* explained "[a]ny number of assays well known in the art may be used to test whether a particular compound suspected of being a fungicide, can be used. These assays are conventional and can be readily adapted . . . by one skilled in the art without undue experimentation." (Ex. 1004 at ¶ [0054].) *Freeman* further disclosed known protocols for determining "suitable" and "safe dosage level[s]." (*Id*. at ¶¶ [0055]-[0058].) *Freeman* disclosed the effective inhibition of *T. rubrum* at concentrations of 5-10 mg/ml of PBA and pentafluoro phenyl boronic acid. (Ex. 1008 at ¶ 76.) Determining a therapeutically

effective amount of 5-fluoro benzoxaborole to treat or inhibit onychomycosis before February 16, 2005 involved nothing more than routine experimentation based on well-established protocols. (*Id*. at ¶ 136.)

Given the foregoing, one of ordinary skill in the art would have had a reasonable expectation of successfully administering a therapeutically effective amount of 5-fluoro benzoxaborole to a human to treat or inhibit a fungal infection, e.g., onychomycosis. (*Id*. at ¶¶ 137, 148; *see also* Ex. 1006 at ¶¶ 32, 44.)

When a patent "simply arranges old elements," i.e., the addition of 5-fluoro benzoxaborole from an industrial composition to a topical therapeutic composition, "with each [element] performing the same function it had been known to perform," i.e., inhibiting *Candida albicans* or *T. rubrum*, "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 *Freeman* discloses all of the limitations of claims 1-12. (Ex. 1008 at ¶¶ 61-66, 74-77, 118-148.) The following claim chart shows the limitations of these claims, and the disclosure of each limitation in the prior art.

7,582,621	***Austin* in view of *Freeman***
1. A method of treating an infection in an animal, said method comprising administering to the	***Austin*** ▪ "[C]ompounds containing an oxaborole ring are particularly effective against micro-organisms such as bacteria, algae, yeasts and particularly fungi." (Ex. 1001at p. 1, ll. 35-40.) ▪ "The use of oxaboroles and salts thereof as industrial

animal a therapeutically effective amount of 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole, or a pharmaceutically acceptable salt thereof, sufficient to treat said infection.	biocides especially fungicides . . . [p]referred compounds are 5- and 6-fluoro or bromo- 1,3-dihydro-1-hydroxy-2,1-benzoxaborole." (*Id*. at Abstract.) ▪ "The benzoxaborole derivatives obtained have the general formula:"  (*Id*. at p. 22, ll. 5-14.) ▪ "Example 64" where "R^8" is "5-F" and "R^9" is "H." (*Id*. at p. 23, Table 5.) ▪ "Example 64" where "R^8" is "5-F" and "R^9" is "H" and "CA" is *Candida albicans*. (*Id*. at pp. 36-37, Table 9.) ***Freeman*** ▪ "The present invention relates to methods and compositions for treating fungal infections, and more particularly, dermatophytoses or onchomycosis of the fingernail and the toenail, as well as fungal infections in plants." (Ex. 1004 at ¶ [001].) ▪ "It has now been discovered that phenyl boronic acid and derivatives thereof as well as related boronic acid compounds have fungicidal properties, and that these compounds are particularly useful in treating fungal infections. These compounds have been found to be particularly useful in treating nail fungal infections." (*Id*. at ¶ [022].) ▪ "The water-soluble PBA [phenyl boronic acid] or derivatives thereof are administered topically in the form of a buffered solution, lotion, or ointment . . . [g]enerally, the compositions are applied topically once daily until cure." (*Id*. at ¶ [030].)
2. The method of claim 1, wherein said infection is a member selected from a systemic infection, a cutaneous	▪ *See* independent claim 1. ***Austin*** ▪ "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-

infection, and an ungual or periungual infection.	1-hydroxy-2,1-benzoxaborole." (Ex. 1001 at Abstract.) ***Freeman*** ▪ "The present invention relates to methods and compositions for treating fungal infections, and more particularly, dermatophytoses or onchomycosis of the fingernail and the toenail, as well as fungal infections in plants . . . [m]any fungal infections, or mycoses, of humans and animals affect only the outer layers of skin." (Ex. 1004 at ¶ [001].) ▪ "'Onychomycosis' has traditionally referred to a nondermatophytic infection of the nail. Onychomycosis is now used as a general term to denote any fungal nail infection. Tinea unguium specifically describes a dermatophytic invasion of the nail plate." (*Id*. at ¶ [005].) ▪ "The dermatophyte species that most often causes onychomycosis in North America and parts of Europe are *T. rubrum*, *T. metagrophytes*, and *Epidermophyton floccosum*. The first two are much more often implicated than *E. floccosum*. Both dermatophytes and non-dermatophytes, especially *Candida Sp.*, have been identified as etiologic agents of onychomycosis." (*Id*. at ¶ [008].)
3. The method of claim 1, wherein said infection is a member selected from . . . dermatological diseases . . . Tinea pedis	▪ *See* independent claim 1 and dependent claim 2. (*See, e.g.*, Ex. 1004 at ¶ [008] ("The dermatophyte species that most often causes onychomycosis in North America and parts of Europe are *T. rubrum*.").) ***Freeman*** ▪ "The dermatophyte *Trichophyton rubrum* is a major cause of tinea pedis and onychomycosis." (*Id*. at ¶ [002].) ▪ "It can be readily seen from the above that PBA exhibited fungicidal effects on *T. rubrum* within the concentration range of 5-10 mg/ml tested." (*Id*. at ¶ [0034].)
4. The method of claim 1, wherein said infection is onychomycosis.	▪ *See* independent claim 1 and dependent claim 2. (*See, e.g.*, Ex. 1004 at ¶ [001] ("The present invention relates to methods and compositions for treating fungal infections, and more particularly, dermatophytoses or

	onchomycosis of the fingernail and the toenail, as well as fungal infections in plants . . . [m]any fungal infections, or mycoses, of humans and animals affect only the outer layers of skin.").)
5. The method of claim 1, wherein said animal is a member selected from a human, cattle, goat, pig, sheep, horse, cow, bull, dog, guinea pig, gerbil, rabbit, cat, chicken and turkey.	▪ *See* independent claim 1 and dependent claim 2. (*See, e.g.*, Ex. 1004 at ¶ [001] ("The present invention relates to methods and compositions for treating fungal infections, and more particularly, dermatophytoses or onchomycosis of the fingernail and the toenail . . . [m]any fungal infections, or mycoses, of humans and animals affect only the outer layers of skin.").)
6. The method of claim 4, wherein said onychomycosis is tinea unguium.	▪ *See* independent claim 1, dependent claim 2, dependent claim 3, and dependent claim 4. (*See, e.g.*, Ex. 1004 at ¶¶ [002], [008], [0034] ("It can be readily seen from the above that PBA exhibited fungicidal effects on *T. rubrum* within the concentration range of 5-10 mg/ml tested.").) ***Freeman*** ▪ "The dermatophyte *Trichophyton rubrum* is a major cause of tinea pedis and onychomycosis." (*Id*. at ¶ [002].) ▪ "Onychomycosis is now used as a general term to denote any fungal nail infection. Tinea unguium specifically describes a dermatophytic invasion of the nail plate." (*Id*. at ¶ [005].)
7. The method of claim 1, wherein said animal is a human.	▪ *See* independent claim 1 and dependent claim 2. (*See, e.g.*, Ex. 1004 at ¶ [001] ("The present invention relates to methods and compositions for treating fungal infections, and more particularly, dermatophytoses or onchomycosis of the fingernail and the toenail, as well as fungal infections in plants . . . [m]any fungal infections, or mycoses, of humans and animals affect only the outer layers of skin.").)
8. The method of claim 1, wherein the administering is at a site which is a member selected from the skin,	▪ *See* independent claim 1 and dependent claim 2. ***Freeman*** ▪"The water-soluble PBA [phenyl boronic acid] or derivatives thereof are administered topically in the form of a buffered solution, lotion, or ointment . . .

nail, hair, hoof and claw.	[g]enerally, the compositions are applied topically once daily until cure." (Ex. 1004 at ¶ [030]; *see also id*. at ¶ [0053].) ▪ "For treating humans and other animals, the compositions are applied topically." (*Id*. at ¶ [0040].) ▪"When applied to the skin or nails, the requisite amounts of PBA compound will depend on the type of application . . . and on any compensation required for penetration into the upper layers of the skin." (*Id*. at ¶ [0064].)
9. The method of claim 8, wherein said skin is the skin surrounding the nail, hair, hoof or claw.	▪ *See* independent claim 1, dependent claim 2, and dependent claim 8. (*See, e.g.*, Ex. 1004 at ¶¶ [030], [0040], [0064] ("When applied to the skin or nails, the requisite amounts of PBA compound will depend on the type of application . . . and on any compensation required for penetration into the upper layers of the skin.").)
10. The method of claim 1, wherein said infection is a fungal infection.	▪ *See* independent claim 1 and dependent claim 2. (*See, e.g.*, Ex. 1004 at ¶ [001] ("The present invention relates to methods and compositions for treating fungal infections, and more particularly, dermatophytoses or onchomycosis of the fingernail and the toenail.").)
11. A method of treating onychomycosis in a human, said method comprising administering to the human a therapeutically effective amount of 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole, or a pharmaceutically acceptable salt thereof, sufficient to treat said onychomycosis.	▪ *See* independent claim 1 and dependent claim 2. (*See, e.g.*, Ex. 1002 at Abstract, p. 1, ll. 35-40 ("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. 1004 at ¶¶ [001]-[002], [005], [008], [0022], [0030] ("The present invention relates to methods and compositions for treating fungal infections, and more particularly, dermatophytoses or onchomycosis of the fingernail and the toenail . . . [m]any fungal infections, or mycoses, of humans and animals affect only the outer layers of skin.").)
12. A method of inhibiting the growth of a	▪ *See* independent claim 1 and dependent claim 2. (*See, e.g.*, Ex. 1002 at Abstract, p. 1, ll. 35-40 ("The use of

fungus in a human, said method comprising administering to the human a therapeutically effective amount of 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole, or a pharmaceutically acceptable salt thereof.	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. 1004 at ¶¶ [001]-[002], [005], [008], [0022], [0030] ("The present invention relates to methods and compositions for treating fungal infections, and more particularly, dermatophytoses or onchomycosis of the fingernail and the toenail . . . [m]any fungal infections, or mycoses, of humans and animals affect only the outer layers of skin.").)

E. Ground 3: Claim 9 Is Obvious Over *Austin* In View Of *Freeman* And *Sun*

A person of ordinary skill in the art would have had multiple reasons to combine *Austin*, *Freeman*, and *Sun* with a reasonable expectation of successfully arriving at the claimed subject matter. (Ex. 1008 at ¶¶ 149-158.) The combination of *Austin*, *Freeman*, and *Sun* discloses all of the limitations of claim 9. (*Id*.) Petitioner is not aware of any secondary considerations that would render claim 9 of the '621 Patent non-obvious.

1. Claim 9 Recites A Method Of Treating Onychomycosis In Humans Via Application Of 5-Fluoro Benzoxaborole To The Skin Surrounding A Nail

Claim 9 depends from claim 8 which in turn depends from Independent claim 1. Petitioner incorporates its discussion of claims 1, 8, and 9 of the '621 Patent from Section VI.C.1.

2. *Austin* Discloses 5-Fluoro Benzoxaborole As An Anti-Fungal Agent And *Freeman* Discloses The Topical Application Of Boron-Based Compounds To Treat Onychomycosis

Petitioner incorporates its discussion of *Austin* and *Freeman* from Section VI.D.

3. *Sun* Discloses The Anti-Fungal Treatment Of Nails Via Topical Application To The Skin Surrounding The Nail

Sun discloses the topical administration of anti-fungal drugs to the nail and surrounding skin of a human to effectively treat onychomycosis. (Ex. 1005 at Abstract; Ex. 1008 at ¶ 78.) Specifically, *Sun* discloses "a method for the treatment of fungal diseases in nails, which comprises the topical administration to the nail of . . . an effective amount of an anti-fungal drug." (Ex. 1005 at Col. 4:15-25; Ex. 1008 at ¶¶ 78, 156.) *Sun* contemplates topical delivery to both the nail plate and the surrounding skin: "topical administration to the nail, and if desired, also to the surrounding skin." (Ex. 1005 at Abstract; Ex. 1008 at ¶¶ 78, 156.) Notably, the target fungal infection in Sun is onychomycosis, "which is usually an infection by *Epidermophyton floccosum*, several species of Trichophyton, or *Candida albicans*." (Ex. 1005 at Col. 4:29-35, 49-53; Ex. 1008 at ¶¶ 78, 156.)

4. Summary: Claim 9 Is Obvious Over *Austin*, *Freeman*, And *Sun*

Reason to Combine the References: Before February 16, 2005 a POSITA would have had a reason to combine the disclosures in *Austin*, *Freeman*, and *Sun*

for all the reasons discussed above as for *Austin* and *Freeman.* In addition, a POSITA would have further motivation to combine *Sun* because like *Freeman*, *Sun* also discloses treating or inhibiting onychomycosis in humans by administering a topical formulation to the skin and nail of a human. (Ex. 1008 at ¶ 157.)

Reasonable Expectation of Success: Before February 16, 2005 a POSITA would have reasonably expected that the administration of a therapeutically effective amount of 5-fluoro benzoxaborole to the skin surrounding the nail of a human would treat or inhibit a fungal infection such as onychomycosis for all the reasons discussed above for *Austin* and *Freeman*. The reasonable expectation of success is demonstrated by the prior art itself: *Freeman.* (*Id*. at ¶ 158.) The combination of *Austin, Freeman*, and *Sun* discloses all of the limitations of claim 9. (*Id*. at ¶¶ 61-66, 74-78, 150-58.) The following claim chart shows the limitations of these claims, and the disclosure of each limitation in the prior art.

7,582,621	***Austin* in view of *Freeman* And *Sun***
9. The method of claim 8, wherein said skin is the skin surrounding the nail, hair, hoof or claw.	▪ *See* independent claim 1, dependent claim 2, and dependent claim 8 from Ground 2. (*See, e.g.*, Ex. 1004 at ¶¶ [030], [0040], [0064] ("When applied to the skin or nails, the requisite amounts of PBA compound will depend on the type of application . . . and on any compensation required for penetration into the upper layers of the skin.").) ***Sun*** ▪ "There is disclosed a method for the treatment of fungal diseases in nails, which comprises the topical

	administration to the nail and, if desired, also to the surrounding skin." (Ex. 1005 at Abstract.)

VII. CONCLUSION

For at least the reasons given above, claims 1-12 of the '621 Patent are unpatentable because they are obvious over the references cited herein. Accordingly, Petitioner respectfully requests IPR of claims 1-12 of the '621 Patent.

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 Petition for *Inter Partes* Review of Patent No. 7,582,621, an accompanying Power of Attorney in *Inter Partes* Review, an Appendix of Exhibits, and supporting Exhibits 1001 - 1032 were provided via UPS, postage prepaid, to the Patent Owner by serving the correspondence address of record for the '621 Patent.

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