Served on behalf of Petitioner COALITION FOR AFFORDABLE DRUGS X LLC

By: Jeffrey D. Blake, Esq.
MERCHANT & GOULD P.C.
191 Peachtree Street N.E., Suite 4300
Atlanta, GA 30303
jblake@merchantgould.com
Main Telephone: (404) 954-5100
Main Facsimile: (404) 954-509

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 IPR2015-01776 (Patent 7,582,621 B2)

PETITIONER'S RESPONSE TO PATENT OWNER'S IDENTIFICATION OF NEW ARGUMENTS AND EVIDENCE IN PETITIONER'S REPLY

I. "*Austin* alone provides a reasonable expectation of success"

As argued by Petitioner, *Austin* discloses tavaborole as a preferred, low molecular weight (MW) compound with strong antifungal activity against *Candida albicans*, a known cause of onychomycosis. (Paper 1 at 1, 18-19, 28-29; Ex. 1002, at 37, Abstract; Ex. 1008 ¶¶61, 63-65, 95, 102, 134; Ex. 2032 at 128:8-18, 507:21-508:25). In view of overwhelming evidence establishing low MW as the primary factor predictive of nail penetration, Petitioner stated that *Austin* alone would furnish a reasonable expectation of successfully treating onychomycosis. (Ex. 1028 at 9; Ex. 2041 at 62, 251; Ex. 2032 at 507:16-508:19, 514:13-516:2; Ex. 1064 ¶¶[0001], [0006], [0017].) However, Petitioner does not argue that claims 1-12 of U.S. Patent No. 7,582,621 are unpatentable over *Austin* alone (Paper 1 at 3, 8); the claims are unpatentable based on a 35 U.S.C. § 103 combination of references (Paper 24 at 4, 15-16; Paper 47 at 1-3, 21-23, 28).

II. Antifungal activity against *C. albicans* is predictive of activity against dermatophytes

As argued by Petitioner, *Austin* and *Brehove* disclose boron heterocycles with strong *in vitro* activity against *C. albicans* (Paper 1 at 28-29; Ex. 1002 at 37, Table 9; Ex. 1008 ¶¶63-65, 67) and *Brehove* discloses *in vivo* treatment of onychomycosis, typically caused by dermatophytes and *C. albicans* (Paper 1 at 29-32; Ex. 1003 ¶[0005]; Ex. 1006 ¶32; Ex. 1008 ¶¶70-72). Based on similar

structural features and shared activity against *C. albicans*, Petitioner argued that tavaborole would be expected to share other activities with *Brehove*'s compounds, "such as the **inhibition of additional fungi responsible for onychomycosis**." (Paper 1 at 35; Ex. 1008 ¶¶100-01; Ex. 2032 at 566:15-567:7.) Petitioner argued similarly with respect to *Freeman*. (Paper 1 at 45-48; Ex. 1008 ¶¶73-74, 76-77, 133.) Dr. Murthy confirmed that most antifungals exhibit broad spectrum activity against different fungi, including dermatophytes and *Candida* species. (Ex. 2032 at 531:8-535:21.) In response, PO argued that antifungal activity against *C. albicans* was not predictive of activity against dermatophytes (Paper 32 at 11, 44-46; Ex. 2035 ¶¶63-64, 114, 123, 132). In rebuttal, Petitioner cited prior art showing that activity against *C. albicans* was indeed predictive of activity against dermatophytes, which are more sensitive to antifungals. (Paper 47 at 2, 16-17; Ex. 2070 at 422, 425; Ex. 1044 ¶¶89-93; Ex. 1065 at 5-6; Ex. 1046 at 238:22-239:12.)

III. Nail penetration is inversely related to molecular weight

Petitioner never argued that nail penetration was based on molecular weight ***alone***. Rather, Petitioner argued that nail penetration is inversely related to molecular weight, as shown by *Murdan* (citing *Mertin & Lippold*). (Paper 1 at 32, 35-36; Ex. 1008 ¶¶95, 102; Ex. 2032 at 513:11-516:2; Ex. 1028 at 9-10.) In response, PO argued that nail penetration was unpredictable and required test data for numerous other factors. (Paper 32 at 47-49; Ex. 2036 ¶¶22-29.) In rebuttal,

Petitioner cited prior art evidence, PO's expert paper and PO's exhibits, which establish molecular weight as the primary factor predictive of nail penetration. (Paper 47 at 17-21; Ex. 2041 at 62, 251; Ex. 1065 at 3; Ex. 1066 at 8.)

IV. Topical administration minimizes toxicity concerns

Petitioner argued that boron compounds were generally safe and that topical formulations could avoid the unacceptable risks associated with oral administration. (Paper 1 at 10, 19-20, 48; Ex. 1028 at 2; Ex. 1006 ¶¶30, 44; Ex. 1008 ¶135.) In response, PO argued that boron compounds were toxic. (Paper 32 at 11-17; Ex. 2034 ¶¶68, 96.) In rebuttal, Petitioner noted that PO's exhibits were directed to high-dose oral and/or intravenous administration of boron (Paper 47 at 3-10, 23; Ex. 1043 ¶¶12-23, 26), which is inapplicable to topical administration of boron (Ex. 2033 at 406:7-408:20; Ex. 1044 ¶46; Ex. 1028 at 21; Ex. 1050 at 2, 9).

V. Structural differences between *Austin* and *Freeman*

Petitioner never argued that the compounds of *Austin* and *Freeman* are **not** structurally similar. Rather, Petitioner argued that the boron-containing cyclic compounds of *Austin* and *Freeman* **are** structurally similar, which accounts for their similar biological activity. (Paper 1 at 48-51; Ex. 1008 ¶133.) In rebutting PO's boron "promiscuity" arguments, Petitioner argued that the non-selective binding of boron is minimized where boron is confined within a 5-membered ring, as in tavaborole. (Paper 47 at 12-13; Ex. 2034 ¶36; Ex. 1043 ¶24.)

Respectfully submitted,

MERCHANT & GOULD, P.C.

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By: _____

Jeffrey D. Blake, Esq. Reg. No. 58,884
Kathleen E. Ott, Esq. Reg. No. 64,038
Peter A. Gergely, Esq. (*Pro Hac Vice*)
Ryan J. Fletcher, Esq., Ph.D. (*Pro Hac Vice*)
Brent E. Routman, Esq. (*Pro Hac Vice*)
Merchant & Gould P.C.
191 Peachtree Street N.E., Suite 4300
Atlanta, GA 30303
Main Telephone: (404) 954-5100
Main Facsimile: (404) 954-5099

Counsel for Petitioner

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