Filed: February 28, 2017

Filed on behalf of: Otsuka Pharmaceutical Co., Ltd.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ALKERMES PHARMA IRELAND LTD.
and ALKERMES, INC.,
Petitioner,

v.

OTSUKA PHARMACEUTICAL CO., LTD.,
Patent Owner.

Case IPR2017-00287
Patent 9,125,939 B2

PATENT OWNER'S PRELIMINARY RESPONSE

TABLE OF CONTENTS

Page(s)

TABLE OF AUTHORITIES

Page(s)

Cases

Federal Statutes

Regulations

Other Authorities

PATENT OWNER'S EXHIBIT LIST

EXHIBIT	DESCRIPTION
2001	Image of webpage accessed via hyperlink, http://www.prnewswire.com/news-releases/data-demonstrate-aripiprazole-significantly-improved-symptoms-of-acute-mania-in-patients-with-bipolar-disorder-77570072.html, provided by Dr. Frances in Ex. 1002, ¶ 35
2002	Burris et al., *Aripiprazole, a Novel Antipsychotic, Is a High-Affinity Partial Agonist at Human Dopamine D2 Receptors*, 302 J. PHARMACOLOGY & EXPERIMENTAL THERAPEUTICS 381 (2002)
2003	Jordan et al., U.S. Patent Application Publication No. 2002/0173513
2004	Clinical Trial Report, CN138-00ST ("Clinical Trial Report")
2005	Citrome et al., *Pharmacokinetics and Safety of Aripiprazole and Concomitant Mood Stabilizers*, 5 INT'L J. NEUROPSYCHOPHARMACOLOGY, S187, P.4.E. 035
2006	November 15, 2002, Prescription Information of Abilify®
2007	November 15, 2002, Letter from the FDA regarding Approval of Abilify®
2008	Excerpt from Hirose Declaration, Ex. 1076 at 1162

I. Introduction

Patent Owner Otsuka Pharmaceutical Co., Ltd. respectfully submits this preliminary response under 37 C.F.R. § 42.107 to the Petition for *Inter Partes* Review of U.S. Patent No. 9,125,939 ("the '939 patent").

The claims relate to a method of treating bipolar disorder in a patient partially nonresponsive to lithium or valproic acid, divalproex sodium or a salt thereof monotherapy by administering aripiprazole and lithium in a ratio of about 1 part by weight aripiprazole to about 0.01 to 500 parts by weight lithium. Petitioner contends that claims 2, 6, 7, and 9 would have been obvious according to six proposed grounds of unpatentability. The requested grounds, however, fail to demonstrate that trial should be instituted for three independent reasons.

First, negating all six grounds, Petitioner fails to establish that at least three of the documents that it relies on are printed publications as required by § 311(b). Specifically, Petitioner does not establish that the abstracts of Keck (Ex. 1007) and Citrome (Ex. 1008) were publicly available at any date before the '939 patent was filed, let alone as of the critical date. Petitioner also fails to provide sufficient evidence to establish that Otsuka/BMS Press Release (Ex. 1028) was publicly available before the critical date or that it would have been accessible to the interested public.

Second, even if Petitioner's documents constitute printed publications, which Petitioner has not shown, none of its requested grounds establishes a reasonable likelihood that any challenged claim is unpatentable. Every ground relies on the same conclusions that preliminary findings for *specific* atypical antipsychotics would have been extrapolated to *all* atypical antipsychotics, including aripiprazole, and that aripiprazole would have been expected to have the same usefulness *in combination with mood stabilizing drugs* as other antipsychotic medication. The record, however, does not support these conclusions. Instead, Petitioner's own exhibits repeatedly recognize aripiprazole as a novel antipsychotic having a chemical structure and mechanism of action that differed from the marketed typical and atypical antipsychotics at the time.

Moreover, Petitioner and its declarant present no evidence to support why a combination of aripiprazole and lithium would have been reasonably expected to treat bipolar disorder in the *specific claimed population of bipolar disorder patients*, *i.e.*, "in a patient partially nonresponsive to lithium or valproic acid, divalproex sodium or salt thereof monotherapy." Petitioner instead simply references certain examples in the '939 patent specification and alleges that the inventors had a reasonable expectation of success based on the prior art. Petitioner's reasoning is prohibited by law. It cannot rely on the examples in the

'939 patent or the inventors' alleged mindset to evidence what a person of ordinary skill in the art would have known or expected.

Third, Petitioner's grounds simply rehash the arguments that the Office fully vetted and ultimately withdrew during the prosecution of the '939 patent. Although Petitioner relies on facially different documents, the disclosures and arguments based on them mirror the Examiner's efforts. And none of Petitioner's challenges to Patent Owner's showing of unexpected results should undo the careful analysis that this Office already did. As a result, the Board should use its discretion under § 325(d) to deny institution.

Thus, for these and other reasons presented below, Petitioner fails to show a reasonable likelihood of prevailing on any challenged claim. The Board should therefore deny institution of *inter partes* review.

II. Petitioner Has Not Established That Keck, Citrome & BMS/Otsuka Press Release Are Printed Publications As Required by § 311(b)

Petitioner asserts that Keck (Ex. 1007), Citrome (Ex. 1008) and BMS/Otsuka Press Release (Ex. 1028) are prior art (Pet. at 15 n.1, 16, 22 n.2), but fails to establish that any of those exhibits are printed publications as required by 35 U.S.C. § 311(b). The critical date of the '939 patent is May 23, 2002, which Petitioner does not challenge. Petitioner alleges that Keck and Citrome are abstracts from a 2002 Annual Meeting of the American Psychiatric Association

("APA") held during May 18-23, 2002. *Id*. at 15 n.1, 22 n.2. Petitioner also asserts that they were published on or before the first day of the conference, *i.e.*, before the May 23, 2002, critical date. *Id.* Petitioner also argues that BMS/Otsuka Press Release was published on May 22, 2002, one day before the critical date. *Id.* at 16. Despite Petitioner's assertions, however, it has not presented evidence sufficient to establish that Keck, BMS/Otsuka Press Release, and Citrome are printed publications at any date relevant for prior art purposes, let alone as of the critical date. Thus, because all of Petitioner's grounds of unpatentability rely on either Keck or BMS/Otsuka Press Release or Citrome, the Petition must be denied as to all grounds.

A. An IPR Challenge Can Only Rely on Printed Publications

An IPR may only be initiated "on the basis of prior art consisting of patents or printed publications." 35 U.S.C. § 311(b). Whether a document qualifies as a printed publication involves a case-by-case inquiry into the facts and circumstances surrounding the document's disclosure to members of the public. *In re Cronyn*, 890 F.2d 1158, 1161 (Fed. Cir. 1989); *Google Inc. v. ART+COM Innovationpool GmbH*, IPR2015-00789, Paper 8 at 4, 6-10 (P.T.A.B. Sept. 2, 2015). The key inquiry is whether the document was made "sufficiently accessible to the public interested in the art" before the critical date. *Cronyn*, 890 F.2d at 1160.

Petitioner has the burden of proving that a document was published or otherwise sufficiently disseminated to the public. *See, e.g.*, *In re Lister*, 583 F.3d 1307, 1317 (Fed. Cir. 2009) (burden is on the proponent to show document was publicly available); *Coal. for Affordable Drugs IV LLC ("ADROCA") v. Pharmacyclics, Inc.*, IPR2015-01076, Paper 33 at 6 (P.T.A.B. Oct. 19, 2015) ("Petitioner must make a threshold showing that the reference is a prior art 'printed publication[].'"); *Ford Motor Co. v. Versata Dev. Grp., Inc.*, IPR2016-01012, Paper 12 at 6 (P.T.A.B. Nov. 4, 2016). A document is publicly accessible "upon a satisfactory showing that such document has been disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence, can locate it." *SRI Intern., Inc. v. Internet Sec. Sys., Inc.*, 511 F.3d 1186, 1195 (Fed. Cir. 2008). A conclusory assertion without evidence of distribution or dissemination is insufficient to establish that a document is a "printed publication." *ADROCA*, IPR2015-01076, Paper 33 at 7 ("Given his unsupported assertions, we give little to no weight to Dr. Atanackovic's conclusory testimony that NCT00849654 constitutes prior art.'"); *Groupon, Inc. v. Blue Calypso, LLC*, CBM2013-00035, Paper 45 at 18-23 (P.T.A.B. Dec. 17, 2014).

B. Petitioner Provides No Evidence of the Publication, Dissemination, or Public Availability of Keck and Citrome

Petitioner fails to show that Keck and Citrome qualify as prior art printed publications. Petitioner offers no evidence of the publication, dissemination, or public availability to support its assertion that Keck and Citrome were published and distributed before the critical date of the '939 patent.

1. Dr. Frances's Testimony Fails to Establish that Keck and Citrome Were Published

The exhibits themselves provide no support that they were published before the critical date. Both Keck and Citrome are two-page exhibits that include an identical first page stating "New Research Abstracts" for the 2002 Annual Meeting of the APA. Ex. 1007 at 1; Ex. 1008 at 1. The second page of Keck indicates that it is the eighty-sixth page of an unidentified document. Ex. 1007 at 2. Similarly, the second page of Citrome indicates that it is the eighty-seventh page of an unidentified document. Ex. 1008 at 2. The only dates found on either of these documents relate to when the 2002 Annual Meeting and presentations supposedly occurred. Ex. 1007; Ex. 1008. Accordingly, the exhibits themselves fail to provide any indication of when they were published or disseminated to the interested public.

Nevertheless, Petitioner asserts that Keck and Citrome are printed publications that were available at least as early as May 18, 2002, making them

prior art under § 102(b).[1] Pet. at 15 n.1, 22 n.2. As support, Petitioner cites to Dr. Frances's declaration, which states that he has purportedly attended more than 20 Annual Meetings of the APA, and that Abstracts from those meetings are routinely made available in print form to psychiatrists and to the public on or before the first day of the conference. *Id.*; Ex. 1002 ¶ 34 n.3, ¶ 37 n.4. Dr. Frances did not testify that he actually attended the 2002 Annual Meeting or that Keck and Citrome, in particular, were actually distributed to the attendees on or before the first day of the conference. As such, Dr. Frances fails to establish that these exhibits qualify as prior art printed publications. To conclude otherwise would contravene Federal Circuit and Board precedent.

Indeed, the Federal Circuit and Board both require evidence that a document was *actually* published or distributed, rather than an unsupported assertion that it

[1] To the extent Petitioner is arguing that the presentations themselves make Keck and Citrome printed publications, Petitioner is wrong. An IPR may only be initiated "on the basis of prior art consisting of patents or printed publications." 35 U.S.C. § 311(b). Moreover, a presentation at a conference is not necessarily prior art. *In re Klopfenstein*, 380 F.3d 1345, 1349 n.4 (Fed. Cir. 2004). Here, Petitioner provides no evidence that the presentations underlying the abstracts actually occurred.

was. For example, in *Norian Corp. v. Stryker Corp.*, the Federal Circuit upheld the district court's finding that an abstract allegedly distributed at a conference was not a printed publication because, among other things, the co-author of the abstract testified that he had attended the meeting and had taken along a copy of the abstract to be given to a meeting organizer, but could not recall whether he *attended the presentation* and could not recall whether copies of the abstract were *actually available* to hand out. 363 F.3d 1321, 1330 (Fed. Cir. 2004). The Court upheld this finding despite record testimony that presenters at the conference generally provided handouts to attendees. *Id*. By contrast, here Petitioner provides no evidence 1) regarding the APA's practice of distributing conference abstracts; 2) whether the APA even had standard distribution practices; and 3) whether those practices (which have not been shown to exist) were actually followed for the 2002 Annual Meeting. Thus, Dr. Frances's unsubstantiated testimony that the abstracts for the annual meetings are "routinely made available" is insufficient to establish Keck and Citrome as printed publications. Ex. 1002 ¶ 35.

The Board also requires firsthand knowledge of a document's alleged dissemination to the public. For example, the petitioner in *Ford* argued that an article was published during a conference. IPR2016-01012, Paper 12 at 4-5. The Board, however, found that "the only information on the face of Stahl to indicate that it was publicly accessible before the critical date is the header," and that "the

exhibit contains no copyright date, and there is no further indication in Stahl itself as to when and under what circumstances or conditions it may have been disseminated to members of the public." *Id*. at 7. The Board was also unpersuaded by the expert's testimony that the article was allegedly published during the conference because the expert made no showing that he *attended* or *had personal knowledge* of the conference. *Id.* at 8-9.

The Board has similarly held that a petitioner failed to establish that clinical trial protocols were printed publications when petitioner's expert testified only that clinical trial protocols were "typically" widely disseminated, without any firsthand knowledge about the distribution of the protocols at issue. *Boehringer Ingelheim Int'l GmbH v. Biogen Inc.*, IPR2015-00418, Paper 14 at 10-12 (P.T.A.B. July 13, 2015); *see also*, *ADROCA*, IPR2015-01076, Paper 33 at 7 ("Dr. Atanackovic has not attested to any personal knowledge of the public accessibility or dissemination of NCT00849654 in February 2009.").

The situation is no different here. Dr. Frances claims no firsthand knowledge of the 2002 Annual Meeting, or of the Keck and Citrome abstracts themselves. Nor does he provide any support for the APA's allegedly standard distribution practice beyond a generalization from allegedly attending more than 20 annual meetings. Dr. Frances could have attempted to provide specifics, including entries from his calendar, registration packets, and abstracts from other

meetings he attended to support his contention. He did not. Thus, just like the petitioners in *Ford* and *Boehringer*, Petitioner here has failed to provide evidence that Keck and Citrome were actually published or disseminated prior to the critical date (or by any relevant prior art date).

2. Petitioner Did Not Provide the Source of Keck and Citrome

Moreover, Petitioner does not provide any information about where it obtained Keck and Citrome or how Petitioner assembled those exhibits. Dr. Frances did not testify that the exhibits were true and accurate copies of the abstracts obtained from attending the 2002 Annual Meeting. *See* Ex. 1002 ¶ 34 n.3, ¶ 37 n.4. In a similar situation, where the petitioner failed to explain whether the document at issue was an actual copy obtained at a conference, the Board found that the petitioner failed to establish that the document qualified as a prior art printed publication. *Temporal Power, Ltd. v. Beacon Power, LLC*, IPR2015-00146, Paper 10 at 11 (P.T.A.B. Apr. 27, 2015).

Thus, for at least these reasons, Petitioner has not established that Keck and Citrome are prior art printed publications.

C. Petitioner Provides No Evidence of the Publication, Dissemination, or Public Availability of BMS/Otsuka Press Release

Petitioner argues—without any citations to record evidence, including Dr. Frances's declaration—that BMS/Otsuka Press Release from PR Newswire (Ex.

1028) is a press release that was "available to the public at least as early as May 22, 2002," making it § 102(b) prior art. Pet. at 16. Such an unsupported statement, here again, cannot support a finding that BMS/Otsuka Press Release is a prior art printed publication.

1. Petitioner Provides No Evidence Supporting the Publication of BMS/Otsuka Press Release Before the Critical Date

The Board requires petitioners to explain the nature of any alleged publication date, and has held against them when they failed to do so. *See, e.g.*, *ADROCA*, IPR2015-01076, Paper 33 at 7; *LG Elecs., Inc. v. Advanced Micro Devices, Inc.*, IPR2015-00329, Paper 13 at 13 (P.T.A.B. July 10, 2015) ("Petitioner offers no evidence of the nature of this date."); *Square, Inc. v. Unwired Planet, LLC*, CBM2014-00156, Paper 11 at 18 (P.T.A.B. Dec. 24, 2014) ("Petitioner has failed to provide any evidence that would allow us to determine the significance of the ISBN number[,]" which included the alleged publication date.). For example, in *ADROCA*, petitioner and its expert asserted, without evidence, that a copy of a webpage that indicated that it was "updated" on a certain date was a printed publication. IPR2015-01076, Paper 33 at 7. The Board held, however, that the petitioner failed to establish the document at issue was a prior art printed publication because the petitioner provided "no explanation or evidence of what

that ['update'] date means" and offered no "evidence of the website's publishing practices." *Id.*

Here, the facts are analogous. Ex. 1028 has three dates: (1) May 22, 2002, in the header of the document; (2) a 2002 copyright date in the header of the document; and (3) May 23, 2002, indicated as a "Load-Date" on the fourth page of the document, none of which is specified as a publication date. Petitioner makes no attempt to explain what each date means, and provides no evidence relating to the publishing practices of PR Newswire.

Moreover, Petitioner provides no support whatsoever to establish the source, publication, dissemination, or public availability of Ex. 1028. *See* Pet. at 16. While Dr. Frances provides a hyperlink (Ex. 1002 ¶ 35), Petitioner did not incorporate that link into the Petition. *See id*. Indeed, Petitioner does not even cite to Dr. Frances's declaration to support that Ex. 1028 is a printed publication. *See id*. The Board has previously refrained from considering information that was presented only in an expert declaration. *Boehringer*, IPR2015-00418, Paper 14 at 10 (The Board "decline[d] to import the extensive discussion about the public accessibility of the ECOG protocols from Dr. Grossbard's Declaration into the Petition, based solely on the Petition's citation of certain paragraphs within the Declaration."). Thus, the Board should not consider the hyperlink.

Even if it did, however, it would find that the link leads to a document that is different from Ex. 1028. *Compare* Ex. 2001 *with* Ex. 1028. For example, while Ex. 1028 has a header that includes information such as the copyright ownership of PR Newswire, "Distribution," "Section," "Length," and "Dateline," and has the "Classification" section that includes a "Load-Date," the page accessible from the hyperlink does not. Thus, the link itself does not establish the source of Ex. 1028.

The link, like Ex. 1028, also fails to provide any information as to how and when PR Newswire became aware of the information in Ex. 1028 and uploaded it to its website. A hyperlink, and especially one that provides no further details about a document's potential publication, is insufficient to support a finding of public accessibility. *See Ford*, IPR2016-01012, Paper 12 at 8 (existence of hyperlink was not persuasive of public accessibility before the critical date); *see also*, *Air Liquide Large Indus. U.S., LP v. Praxair Tech. Inc.*, IPR2015-01074, Paper 11 at 6 (P.T.A.B. Oct. 26, 2015) (conference website was insufficient evidence of availability at the website at the critical date).

Furthermore, the Board has held that a website provided as an exhibit did not support the public accessibility of a document prior to the critical date 1) when the petitioner failed to provide any archival evidence of the website, and 2) when the dates on the exhibit were after the critical date. *Google*, IPR2015-00789, Paper 8 at 8 (P.T.A.B. Sept. 2, 2015). The situation here is similar. Petitioner fails to

provide any archival evidence of the hyperlink, and Ex. 1028 itself includes multiple dates, none of which Petitioner explained. At best, the hyperlink supports only that PR Newswire *currently* allows access to subject matter substantially identical to Ex. 1028.

The copyright notice of 2002 likewise fails to provide any evidence as to when BMS/Otsuka Press Release was made accessible to the public. Indeed, the Board recently concluded that "[t]he copyright notice, alone, however, sheds virtually no light on whether the document was publicly accessible as of that date, therefore additional evidence is typically necessary to support a showing of public accessibility." *Microsoft Corp. v. Corel Software, LLC*, IPR2016-01300, Paper 13 at 10-11 (P.T.A.B. Jan. 4, 2017). Here, the copyright of 2002 does not provide any information as to when Ex. 1028 was *actually* published.

2. Petitioner Fails to Establish That Persons Interested in the Art Would Have Been Able to Access BMS/Otsuka Press Release

The mere fact that a document may have existed before the critical date of the patent is insufficient to establish that the document is a prior art printed publication. *In re Bayer*, 568 F.2d 1357, 1360-62 (Fed. Cir. 1978) (holding that an uncatalogued, unshelved thesis is not a "publication" within the meaning of 35 U.S.C. § 102(b)). Separate and apart from Petitioner's failure to provide any support for its assertion that BMS/Otsuka Press Release was published before the

critical date (Pet. at 16.), Petitioner has not shown that it was disseminated or otherwise made available to persons of ordinary skill. *SRI Intern.*, 511 F.3d at 1195.

Petitioner could have attempted to provide evidence demonstrating that persons interested in the art would have been able to locate BMS/Otsuka Press Release before the critical date, but it did not do so. As such, Petitioner cannot establish that BMS/Otsuka Press Release is a prior art printed publication. The Board held against a petitioner in a similar circumstance where the petitioner failed to provide any evidence as to how persons interested in the art would have located the document at issue. *See Cisco Sys., Inc. v. Constellation Techs. L.L.C.*, IPR2014-01085, Paper 11 at 9 (P.T.A.B. Jan. 9, 2015) ("Petitioner's naked assertion that Rosenberg was published is not supported by the record, which fails to identify the circumstances and manner in which persons interested and ordinarily skilled in the subject matter could locate the reference." (citation omitted)). The result should be the same here.

3. Petitioner Does Not Provide the Source of BMS/Otsuka Press Release

To establish that a document is a printed publication, at the very least Petitioner must provide evidence of its source. *See, ResQNet.com, Inc. v. Lansa, Inc.*, 594 F.3d 860, 865 (Fed. Cir. 2010); *Boehringer*, IPR2015-00418, Paper 14 at

10, 14. Both the Federal Circuit and Board have held that a document is not a printed publication when the source was not provided as evidence. For example, the Board in *Boehringer* found that the petitioner had not explained "how or where it obtained the ECOG protocols[,]" and ultimately held that the petitioner failed to establish those protocols were prior art printed publications. IPR2015-00418, Paper 14 at 10, 14. Here, the origin of Ex. 1028 is unclear, and the hyperlink sheds no light on its actual source because it leads to a different document altogether.

For all of these reasons, Petitioner has not met its burden to establish that BMS/Otsuka Press Release is a printed publication, and all of the grounds based on it should be denied.

III. Even If Certain Documents Constitute Printed Publications, Which Petitioner Has Not Shown, Petitioner Fails to Establish a Reasonable Likelihood that Any Claim is Unpatentable

The Petition proposes six grounds of unpatentability based on obviousness. The grounds are largely redundant of one another, each essentially mixing and matching the same documents in different combinations. But no matter how Petitioner combines its selection of documents, none of its proposed grounds establishes a reasonable likelihood that any challenged claim is unpatentable as obvious.

A. Petitioner Fails to Establish the Requisite Motivation to Support Its Proposed Grounds of Unpatentability

Petitioner alleges that a person of ordinary skill in the art would have been motivated to arrive at the challenged claims because one would have generally expected a combination of atypical antipsychotics with mood stabilizers to "provid[e] improved efficacy over either agent alone, especially if the patient did not fully respond to a mood stabilizer monotherapy." Pet. at 25 (citing "Ex. 1002 ¶ 60; Ex. 1009 at 4, 9; see generally Ex. 1002, Appendices A-D"); *see also* Pet. at 31, 33, 35, 37, 39. Petitioner further asserts that a person of ordinary skill in the art would have been motivated to combine lithium and aripiprazole to arrive at the claimed method of treatment. *E.g.*, *id*. at 27. Petitioner's arguments, however, are unsupported by the record.

1. Petitioner Has Not Demonstrated That Atypical Antipsychotics Would Be Added to Mood Stabilizers "Whenever the Mood Stabilizer Was Insufficiently Effective"

To support its alleged motivation, Petitioner relies on Dr. Frances's opinion that "[i]n milder cases . . . mood stabilizers would often be started first as monotherapy, but antipsychotics would be added *whenever the mood stabilizer was insufficiently effective*, such as when the patient has shown an inadequate response

to the monotherapy."[2] Ex. 1002 ¶ 60 (emphasis added). But Petitioner's own documents do not support this. In particular, Expert Consensus states:

[2] More often than not, as in this instance, Dr. Frances fails to provide any citations to support his opinions. Both the Federal Circuit and the Board ascribe "little probative value" to declaration opinions that lack objective support. *DIRECTV, LLC v. Qurio Holdings, Inc.*, IPR2015-02006, Paper 6 at 10-11 (P.T.A.B. Apr. 4, 2016) (quoting *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 294 (Fed. Cir. 1985)). Thus, the Board should not credit Dr. Frances's unsupported testimony. *See, e.g., Gen. Elec. Co. v. TAS Energy Inc.*, IPR2014-00163, Paper 11 at 11 (P.T.A.B. May 13, 2014); *see also, e.g., Praxair Distribution, Inc. v. INO Therapeutics, Inc.*, IPR2015-00522, Paper 12 at 15 (P.T.A.B. July 29, 2015). The Board should also reject Petitioner's and Dr. Frances's general references to ninety pages of appendix material, *i.e.*, "Appendices A-E." *See, e.g., Whole Space Indus. Ltd. v. Zipshade Indus. (B.V.I.) Corp.*, IPR2015-00488, Paper 14 at 13-14 (P.T.A.B. July 24, 2015) (denying consideration of material "not presented and developed in the Petition" as violating "the particularity and specificity required of supporting evidence" and requiring the Board to "sift through" thirty-one pages of a Declaration); *see also, e.g., DIRECTV*, IPR2015-02006, Paper 6 at 10 ("[T]he Petition's consistent citations to

> [i]f the patient has had no response to the first mood stabilizer within 1 to 2 weeks, the experts recommend adding or switching to another top-rated mood stabilizer. In contrast, if the patient is showing a partial response, the experts would simply add a second mood stabilizer [not an atypical antipsychotic] after 2 to 3 weeks.

Ex. 1026 at 18.

Similarly, contrary to Petitioner's assertions, APA Practice Guidelines (Ex. 1009) do *not* indicate that the combination of any atypical antipsychotic with lithium or valproate was generally viewed as more effective than those agents alone. Pet. at 27. Rather, in the short, four-sentence "Combination therapy" section, only two antipsychotics are mentioned: olanzapine and risperidone. Ex. 1009 at 31, right col. The cited studies themselves identify the findings as "preliminary." *See id.* (citing study "307," which is titled "Safety and efficacy of risperidone as combination therapy for the manic phase of bipolar disorder: *preliminary findings* of a randomized double blind study" (emphasis added)). Based on these preliminary studies, APA Practice Guidelines state that the combination of an atypical antipsychotic with a mood stabilizer "*may* be more effective." Ex. 1009 at 15, left col. (emphasis added).

---

large portions of the [Expert] Declaration runs afoul of the particularity and specificity required of supporting evidence under our governing statute and rules.").

As a result, the APA Practice Guidelines later propose future research, specifically directed to how the potential antimanic effect of one atypical antipsychotic might compare to another, and in what circumstances combination therapy may be desirable. *See* Ex. 1009 at 42 ("Do different atypical antipsychotics exert different antimanic effects?" "In what circumstances is combination therapy favored over monotherapy?"). Such aspirational research goals cannot—as a matter of law—support Petitioner's case for motivation, especially where Petitioner has made absolutely no showing to support the conclusion that results with one atypical antipsychotic translate to aripiprazole, an atypical antipsychotic different in structure and receptor-binding profile. *See, e.g.*, *Personal Web Techs., LLC v. Apple, Inc.*, --- F.3d ----, 2017 WL 587132, at *5 (Fed. Cir. Feb. 14, 2017) ("[O]bviousness concerns whether a skilled artisan not only *could have made* but *would have been motivated to make* the combinations or modifications of prior art to arrive at the claimed invention.") (emphases in original); *Star Sci., Inc. v. R.J. Reynolds Tobacco Co.*, 655 F.3d 1364, 1376 (Fed. Cir. 2011) ("[S]peculative and tentative disclosure [in the prior art] of what 'might' or 'may' [result] does not sufficiently direct or instruct one of skill in this art.").

2. Petitioner Does Not Argue and Provides No Evidence that Aripiprazole Was Viewed as Interchangeable With Other Atypical Antipsychotics for Bipolar Disorder

While conceding that at the time of the '939 patent, aripiprazole was "one of the newest atypical antipsychotics on the market" (Pet. at 14), Petitioner neglects to mention aripiprazole was first approved by the FDA a mere six months before the '939 patent's priority date *only* for the short-term treatment of *schizophrenia*. Ex. 2006 at 7; Ex. 2007. Petitioner also fails to address that aripiprazole was known to be unique from all other atypical antipsychotics in chemical structure and mechanism of action. For example, Exhibit 1023—which Petitioner submitted, yet nowhere discusses—states that aripiprazole "is a novel antipsychotic with a mechanism of action that differs from all currently marketed typical and atypical antipsychotics." Ex. 1023 at 1; *see also* Ex. 2002 at 1 ("Aripiprazole is the first next-generation atypical antipsychotic with a mechanism of action that differs from currently marketed typical and atypical antipsychotics."). Even documents Petitioner relies on in its proposed grounds describe aripiprazole's distinctiveness. *See* Ex. 1008 at 2 ("[A]ripiprazole [is] an antipsychotic with a unique pharmacologic profile of dopamine D_2 partial agonism, serotonin $5HT_{1A}$ partial agonism and $5HT_{2A}$ antagonism."); Ex. 1028 at 2.

Furthermore, in prior litigation where aripiprazole and its use for treating schizophrenia were held nonobvious over prior art atypical antipsychotics, the

district court observed that "*[w]ith the exception of aripiprazole*, all FDA-approved atypical antipsychotics are structurally related to either clozapine or risperidone." *Otsuka Pharm. Co., Ltd. v. Sandoz, Inc.*, 3:07-cv-01000, 2010 WL 4596324, at *3 (D.N.J. Nov. 15, 2010) (emphasis added). In affirming the district court's decision, the Federal Circuit reiterated that "[e]very FDA-approved atypical antipsychotic has a chemical structure related either to clozapine or risperidone, *with the sole exception of aripiprazole*." *Otsuka Pharm. Co., Ltd. v. Sandoz, Inc.*, 678 F.3d 1280, 1284 (Fed. Cir. 2012) (emphasis added).

Petitioner has not made any effort to demonstrate that aripiprazole's known differences compared to other atypical antipsychotics would not have impacted what a person of ordinary skill in the art would have thought about its potential interchangeability for olanzapine or risperidone in the treatment of bipolar disorder generally, in the treatment of bipolar disorder in combination therapy, or in the specific patient population of the claims.

The only attempted explanation comes *not* in Petitioner's "detailed explanation" of its proposed grounds but instead in the Frances declaration. Here again, however, Dr. Frances states without citation that "[a] psychiatrist of ordinary skill would have expected aripiprazole to have the same well-established pattern of usefulness in combination with mood stabilizing drugs in the treatment of Bipolar Disorder." Ex. 1002 ¶ 11. This unsupported assertion cannot serve as a

basis to establish a motivation to arrive at the challenged claims. *See In re Magnum Oil Tools Int'l., Ltd.*, 829 F.3d 1364, 1380 (Fed. Cir. 2016) ("To satisfy its burden of proving obviousness, a petitioner cannot employ mere conclusory statements."); *see also, e.g., Praxair*, IPR2015-00522, Paper 12 at 15; *Logic Tech. Dev., LLC v. Fontem Holdings 1 B.V.*, IPR2015-00098, Paper 8 at 10 (P.T.A.B. May 11, 2015); *Gen. Elec. Co.*, IPR2014-00163, Paper 11 at 11; *SAS Institute, Inc. v. ComplementSoft, LLC*, IPR2013-00581, Paper 17 at 3-4 (P.T.A.B. Feb. 25, 2014). Moreover, preliminary data involving only two atypical antipsychotics—olanzapine and risperidone—is the opposite of a "well-established pattern." Ex. 1009 at 31, right col. Thus, Petitioner's asserted motivation is unsupported. As a result, Petitioner fails to establish a reasonable likelihood of prevailing on any challenged claim.

3. Petitioner's Remaining Documents Do Not Cure These Deficiencies

Keck and BMS/Otsuka Press Release do not justify the Petitioner's case of motivation. These exhibits discuss a clinical study involving aripiprazole *monotherapy* compared to *placebo*. Ex. 1007 at 2; Ex. 1028 at 1. That study did not involve administering aripiprazole with another agent, comparing aripiprazole to another agent, or evaluating treatment in a patient population partially nonresponsive to lithium or valproic acid, divalproex sodium or a salt thereof

monotherapy. Indeed, Petitioner and Dr. Frances do not contend that this study would have informed one of ordinary skill on the prospect of *combining* aripiprazole with another agent, much less the claimed combination with lithium for treating the recited patient population.

Tohen indicates that "the combination of lithium or valproate plus olanzapine *may* provide additional efficacy compared with either agent alone." Ex. 1006 at 7 (emphasis added). Here again, Petitioner extrapolates without explanation these preliminary findings concerning olanzapine in combination with a mood stabilizer to *all atypical antipsychotics*, including aripiprazole. *See* Pet. at 31. The Petition provides no basis for broadening Tohen's disclosure to all atypical antipsychotics, let alone to aripiprazole with its distinct chemical structure and mechanism of action. *See* Ex. 1023; *supra* § III.A.2.

Expert Consensus (Ex. 1026) does not even mention the preliminary findings concerning olanzapine and risperidone that were referenced in the short "[c]ombination therapy" paragraph in APA Practice Guidelines (Ex. 1009 at 31). Thus, it lends no support to Petitioner's theory that preliminary findings for certain atypical antipsychotics would have been extrapolated to all atypical antipsychotics, including aripiprazole. *See infra* § IV.C.5.

Citrome summarizes a clinical study assessing the safety of coadministering aripiprazole with lithium or divalproex sodium in patients with schizophrenia or

schizoaffective disorder. Ex. 1008 at 2. The Petition does not contend that a *safety* study involving a *different indication* and *patient population* would have informed one of ordinary skill as to the efficacy of the claimed combination therapy to treat bipolar disorder in a patient partially nonresponsive to lithium or valproic acid, divalproex sodium or a salt thereof monotherapy. *See* Pet. at 38, 40. Indeed, the supposed safety of the combination of lithium and aripiprazole is insufficient to establish any motivation or reasonable expectation of success regarding its *efficacy* in the claimed patient population. Thus, Citrome also provides no basis for Petitioner's asserted motivation. *See infra* § IV.C.3.

B. Petitioner Provides No Basis to Support a Reasonable Expectation of Success

Obviousness requires that one of ordinary skill would have had a reasonable expectation of success in making the claimed invention. *See Broadcom Corp. v. Emulex Corp.*, 732 F.3d 1325, 1335 (Fed. Cir. 2013); *Amgen Inc. v. F. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1362-63 (Fed. Cir. 2009). Here, the Petition mentions the phrase "reasonable expectation of success" in passing but provides no evidence that a combination of aripiprazole and lithium would have been reasonably expected to treat bipolar disorder in the claimed patient population, namely "in a patient partially nonresponsive to lithium or valproic acid, divalproex sodium or a salt thereof monotherapy." As the Federal Circuit has explained, "[i]t is of the

utmost importance that petitioners in the IPR proceedings adhere to the requirement that the initial petition identify with particularity the evidence that supports the grounds for the challenge to each claim." *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1369 (Fed. Cir. 2016) (internal quotations omitted). Nowhere does Petitioner or Dr. Frances account for (1) aripiprazole's distinctive chemical structure and mechanism of action compared to all other marketed antipsychotics at the time (*supra* § III.A.2.), or (2) treating bipolar disorder *in the claimed patient population* using a combination of aripiprazole and lithium. Accordingly, Petitioner fails to carry its burden, and the Petition should be denied.

1. Petitioner Does Not Account for Aripiprazole's Distinctiveness

Aripiprazole is not olanzapine or risperidone. In fact, the record evidence recognizes aripiprazole as distinct from not only those atypical antipsychotics, but *all* marketed typical and atypical antipsychotics at the time of the '939 patent. *Supra* § III.A.2. The question, then, is why would a person of ordinary skill have reasonably expected aripiprazole to be effectively interchangeable with olanzapine or risperidone as a combination therapy for bipolar disorder in the claimed patient population? The Petition does not answer this question. This alone requires denial of the Petition.

For example, in a case involving a method of treatment for narcolepsy where a patient was given GHB in a dose that was reduced by at least 5% from a typical effective dose when the patient received a concomitant administration of valproate, the Board denied institution, concluding *inter alia* that Petitioner had not established a reasonable expectation of success. *Par Pharm. Inc. v. Jazz Pharm. Ireland Ltd.*, IPR2016-00002, Paper 12 at 4, 13-14 (P.T.A.B. Apr. 12, 2016). Specifically, although the prior art suggested that valproate might intensify the effect of GHB, thus producing an expectation that a lower dose would still be efficacious, the record evidence also showed that the body eliminated GHB through alternative pathways not inhibited by valproate. *Id*. at 13. Petitioner did not provide any evidence that valproate alone could have "predictably" compensated for the GHB lost through these alternative routes. *Id*. at 13-14.

Likewise, here, Petitioner does not demonstrate that one would have—or even could have—*predictably* translated preliminary findings for olanzapine or risperidone in combination with mood stabilizers to the claimed combination of aripiprazole and lithium. In fact, Petitioner's own declarant admits that drug interactivity is highly unpredictable. *See* Ex. 1004 at Appendix A ¶ 20.

2. Petitioner Does Not Account for the Claimed Patient Population

a. The Preamble Is Limiting

Under well-settled legal principles and as confirmed by the prosecution history, "treating bipolar disorder in a patient partially nonresponsive to lithium or valproic acid, divalproex sodium or a salt thereof monotherapy" limits each challenged claim. Petitioner does not argue otherwise. Indeed, it proposes a construction for the recited patient population. Pet. at 10.

Thus, to carry its burden, the Petition must identify, with particularity, evidence that a person of ordinary skill in the art would have reasonably expected a combination of aripiprazole and lithium administered in the claimed amounts to be effective to "treat[] bipolar disorder in a patient partially nonresponsive to lithium or valproic acid, divalproex sodium or a salt thereof monotherapy." *See DePuy Spine, Inc v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) ("[T]he 'predictable result' discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically combined, but also that the combination would have worked for its intended purpose."). This it does not do.

b. Petitioner Fails to Provide Any Evidence that a Combination of Aripiprazole and Lithium Would Have Been Reasonably Expected to Treat Bipolar Disorder in the Claimed Patient Population

For each proposed ground, Petitioner's *only* evidence for a reasonable expectation of success is Dr. Frances's testimony, which has *no* citations to any record evidence and essentially mimics the language of the Petition. *Compare, e.g.*, Pet. at 33 *with* Ex. 1002 ¶ 92, Pet. at 27 *with* Ex. 1002 ¶ 64, Pet. at 31-32 *with* Ex. 1002 ¶ 74, Pet. at 36 *with* Ex. 1002 ¶ 74, Pet. at 38 *with* Ex. 1002 ¶ 82, Pet. at 40 *with* Ex. 1002 ¶¶ 86-87. As such, Petitioner fails to meet its burden to identify with particularity evidence to support its obviousness challenge. *Intelligent Bio-Sys.*, 821 F.3d at 1369.

Further, Petitioner's unsupported contention that one of ordinary skill would have understood all atypical antipsychotics in combination with mood stabilizers to be "generally more effective than monotherapy" (Pet. at 27) on its face fails to account for "patients partially nonresponsive to lithium or valproic acid, divalproex sodium or a salt thereof monotherapy." The same holds true for Petitioner's generic assertion that "aripiprazole, which was new to the market, was safe and effective in treating bipolar disorder." Pet. at 27. Notably, Petitioner does not address the recognized uncertainty inherent in successfully treating bipolar disorder in patients who are refractory to first-line treatment. *See* Ex. 1026 at 8

("[T]here are many situations for which *there are no well-controlled data*, such as key drug-drug comparisons or *the management of illness that is refractory to first-line treatments*." (emphasis added)). And Petitioner likewise ignored its own document's disclosure that results regarding aripiprazole in bipolar disorder generally were equivocal at the time. Ex. 1028 at 1 ("In a second placebo-controlled study . . . aripiprazole did not show statistical separation from placebo.").

The Board has previously denied institution under similar circumstances, specifically where a petitioner failed to adequately account for a particular patient population. *Phigenix, Inc. v. Genentech, Inc.*, IPR2014-00842, Paper 10 at 15-16 (P.T.A.B. Dec. 9, 2014). There, the claims related to a "tumor characterized by overexpression of ErbB2 receptor *and that does not respond, or responds poorly*, to treating with an anti-ErbB antibody [HERCEPTIN®]." *Id*. at 5. The prior art taught that some patients failed to respond to HERCEPTIN®, and that HERCEPTIN® increased the effectiveness of chemotherapy in patients who responded to HERCEPTIN® and chemotherapy. *Id*. at 15. The petitioner attempted to take this disclosure a step further, arguing it suggested that "patients *unresponsive* to HERCEPTIN® would respond to the HERCEPTIN® antibody, if administered with chemotherapy." *Id*. at 15-16 (emphasis added). But petitioner's assertion failed to account for the claimed patient population, and the Board thus

concluded that it had not established a reasonable expectation of success. *Id.* at 16. The result should be no different here.

Moreover, the Board routinely denies petitions for failing to sufficiently address a claim element. For example, in *Intelgenx Corp v. ICOS Corp.*, the Board denied institution of *inter partes* review on a claim directed to "[a] method of treating sexual dysfunction" comprising administering a compound in "one or more unit dose containing about 1 to about 20 mg, up to a maximum total dose of 20 mg per day." IPR2016-00678, Paper 13 at 3 (P.T.A.B. Sept. 1, 2016). The petitioner alleged that one of ordinary skill would have reasonably expected doses in the claimed range to provide "therapeutic efficacy for treating sexual dysfunction." *Id.*, Paper 1 at 28. But the petitioner failed to provide any evidence to account for the "up to a maximum total dose of 20 mg per day" limitation. Citing this failure alone, the Board observed that "all patent claim terms are presumed to have meaning" and necessarily denied institution for failing to establish a reasonable likelihood of prevailing on any challenged claim. *Id.*, Paper 13 at 6-7; *see also*, *e.g.*, *Jiawei Tech. (HK) Ltd. v. Richmond*, IPR2014-00937, Paper 22 at 7-8 (P.T.A.B. Dec. 16, 2014) (denying institution where petitioner's explanation for how a skilled artisan would have arrived at the challenged claims glossed over a claim limitation).

Similarly, here, the preamble is limiting, and Petitioner fails to explain with any particularity how an ordinary artisan would have reasonably expected a combination of aripiprazole and lithium to treat bipolar disorder in the claimed patient population.

3. Petitioner's Allegation of Reasonable Expectation of Success Impermissibly Relies on the '939 Patent Specification

In a footnote, Petitioner attempts to justify its deficient analysis by pointing to the '939 patent specification and what the *inventors* reasonably expected. Pet. at 27-28 n. 4.[3] This is legally improper. 35 U.S.C. § 103(a) ("Patentability shall not be negatived by the manner in which the invention was made."); *see KSR Int'l v. Teleflex Inc.*, 550 U.S. 398, 421 (2007) (warning against a "temptation to read into the prior art the teachings of the invention in issue" and instructing courts to "guard against slipping into use of hindsight"); *Life Techs. v. Clontech Labs., Inc.*, 224 F.3d 1320, 1325 (Fed. Cir. 2000) ("[T]he path that leads an inventor to the invention is expressly made irrelevant to patentability by statute.").

[3] Patent Owner disagrees with Petitioner's characterization of the '939 patent in this footnote.

IV. Petitioner's Grounds Should Be Denied as Redundant to the Art and Arguments Previously Considered and Overcome During Prosecution

A. The Board Should Deny Institution Where the Same or Substantially the Same Prior Art or Arguments Were Previously Presented

Under 35 U.S.C. § 325(d), the Board has discretion to deny petitions that raise the same or substantially the same prior art or arguments that were previously presented to the Office, including during prosecution. This discretion gives the Office control over its own resources and ensures that post-grant proceedings are not tools for harassment. *See Apotex Inc. v. OSI Pharms., Inc.*, IPR2016-01284, Paper 8 at 7 (P.T.A.B. Jan. 9, 2017) (citing H.R. REP. No. 112-98, pt.1 at 48 (2011); *Lower Drug Prices for Consumers, LLC v. Forest Labs. Holdings Ltd.*, IPR2016-00379, Paper 14 at 2, 6-12 (P.T.A.B. July 1, 2016) ("readjudicating substantially the same prior art and arguments as those presented during prosecution would not be an efficient use of Board resources"); *see also Mylan Pharms. Inc. v. Yeda Research & Dev. Co.*, PGR2016-00010, Paper 9 at 6-10 (P.T.A.B. Aug. 15, 2016) (denying institution of PGR where Office already considered the issue of whether the application was a pre-AIA or AIA application).

Petitioners do not escape § 325(d) simply by raising new art or combinations of art. Rather, the relevant inquiry is whether petitioner presents substantially the same issues. *See Neil Ziegmann, N.P.Z., Inc. v. Stephens*, IPR2015-01860, Paper

11 at 2, 10 (P.T.A.B. Feb. 24, 2016); *PRISM Pharma Co. v. Choongwae Pharma Corp.*, IPR2014-00315, Paper 14 at 12-13 (P.T.A.B. July 8, 2014) (informative decision). Indeed, recently the Board concluded that it could exercise its discretion under § 325(d) even where the exact combination of prior art and an altogether new reference were not considered during prosecution. *Kayak Software Corp. v. Int'l Bus. Machs. Corp.*, CBM2016-00075, Paper 16 at 7-12 (P.T.A.B. Dec. 15, 2016). In such a situation where there were no "clear errors" made during prosecution, and petitioner did not identify any circumstances of material change, such as changed claim constructions or new evidence regarding priority dates, the Board chose to use its discretion under § 325(d). *Id*. at 11.

Here, Petitioner makes the same arguments that the Examiner made and ultimately withdrew based on identical or cumulative disclosures. Moreover, Petitioner does not identify any clear errors or material changes that should preclude the Board from exercising its discretion.

B. Summary of the Prosecution of the '939 Patent

Applicant filed U.S. Patent Application No. 10/556,600 ("the '600 application"), which led to the '939 patent on November 14, 2005. The '600 application is a national stage application under § 371 that claims the benefit of priority of U.S. Provisional Application No. 60/473,378, filed on May 23, 2003.

The Office issued a first Office Action on the merits on April 30, 2009. Ex. 1076 at 928-50. At the time, original claim 12 recited:

> [a] method of treating a mood disorder in a patient comprising separate administration of a first amount of a carbostyril derivative and a second amount of mood stabilizer, wherein the administration is effective to treat the mood disorder in the patient.

Id. at 88-89. Original dependent claim 13 limited the carbostyril derivative to aripiprazole or a metabolite thereof; and claim 15 specifically listed lithium among other mood stabilizers.

The Examiner rejected the pending claims, including claims 12, 13, and 15, *inter alia*, as being obvious over Kowatch et al. (*CNS Spectrum* (April 2003) 8(4):273-80, Ex. 1010, "Kowatch"). *Id*. at 944-45. The Examiner also rejected claim 14, directed to specific metabolites, as being obvious over Kowatch in combination with U.S. Patent Application Publication No. 2002/0173513 (Ex. 2003, "Jordan"). *Id*. at 944-46.

In making its rejections, the Examiner stated that Kowatch discloses "that Lithium is a well known mood stabil[i]zer and compositions containing Lithium are used for treating bipolar disorder, acute mania." *Id.* at 944. In addition, the Examiner stated that Kowatch "also discloses atypical antipsychotics such as Aripiprazole . . . is effective in treating bipolar disorder." *Id*. Further, the Examiner pointed out that Kowatch also taught that the combination of lithium and

an atypical antipsychotic, specifically olanzapine and quetiapine, "decreases bipolar symptoms and improve[s] overall response rates" compared to monotherapy. *Id*. at 944-45. Based on these disclosures, the Examiner concluded that

> [i]t would have been obvious to a person of ordinary skill in the art at the time of invention to combine atypical antipsychotic agent, aripiprazole with lithium because Kowatch teaches that the combination of atypical antipsychotic with lithium gives better overall response in the method of treating bipolar disorder. It is generally considered *prima faci[e]* obvious to combine compounds each of which is taught by the prior art to be useful for the same purpose, in order to form a composition which is used for the very same purpose i.e. for treating bipolar disorder.

Id. at 945. Regarding the rejection of claim 14, the Examiner stated that Jordan discloses that carbostyril derivatives, including aripiprazole and one of its metabolites, dehydroaripirazole, "are useful in treating bipolar disorders." *Id*. at 946.

After an extensive examination spanning six years, the Examiner allowed the claims that ultimately issued. Ex. 1076 at 967-69, 970, 1022, 1047-48, 1049, 1051, 1077, 1096-97, 1099, 1106, 1126, 1144, 1149, 1176, 1197, 1199, 1224, 1243, 1258, 1219, 1224, 1258, 1279, 1291-99. Over the course of prosecution, the Examiner repeatedly rejected—as admitted by Petitioner—"claims substantially corresponding to claims 2, 6, 7, and 9." Pet. at 7; *see e.g.*, Ex. 1076 at 1053-58,

1107-12, 1150-53, 1200-02, 1259-60 (claims 29-30, 34-35, 43, 44, 46). Contrary to Petitioner's assertions, however, those rejections were *not* limited to Kowatch. *See* Pet. at 7. In fact, Applicant submitted and specifically referred to the results of Tohen (Ex. 1006), which are disclosed in Kowatch. Ex. 1076 at 987, 1268, *see also* 956 (Tohen considered by Examiner); Ex. 1010 at 8. The Examiner then used that disclosure in support of an obviousness rejection, stating that Tohen "disclose[s] that response rate was significantly higher in the combination treatment with atypical antipsychotic (olanzapine) and valproate or lithium," and that the study "include[d] patients partially nonresponsive to valproate or lithium." Ex. 1076 at 1133, *see also* 1231. The Examiner additionally cited Clinical Trial Report, CN138-00ST (Ex. 2004, "Clinical Trial Report") to assert "that aripiprazole is useful in treating acute mania episode." *Id*. at 1180. Moreover, Applicant submitted Citrome et al., *Pharmacokinetics and Safety of Aripiprazole and Concomitant Mood Stabilizers*, 5 INT'L J. NEUROPSYCHOPHARMACOLOGY, S187, P.4.E. 035 (Ex. 2005, "Citrome S187"), which is identical in content to Petitioner's Citrome (Ex. 1008) except for the conference details.[4] *Id.* at 1046. The Examiner considered that abstract (*id*.), but did not apply it against the claims.

[4] Just as was noted during prosecution, Patent Owner makes no admission that Citrome S187 is prior art or a printed publication. *See* Ex. 1076 at 1044.

Throughout prosecution, Applicant repeatedly argued that the Office had not established a *prima facie* case of obviousness against any of the pending claims. Ex. 1076 at 970, 1051, 1106, 1149, 1199, 1258. For example, in its last response, Applicant urged the Examiner to consider the prior art as a whole (as must be done). *Id*. at 1268. Applicant asserted that Kowatch discloses nothing more than results from multiple studies using *certain* atypical antipsychotics in combination with lithium or valproate in *specific* patient populations that differed from one another, none of which included the combination of aripiprazole and lithium. *Id*. at 1268-69. Thus, Applicant asserted that "[i]t remains unclear what basis the Office uses to extrapolate from Kowatch's combination summary to the presently pending claims" absent hindsight. *Id*. at 1269.

As part of its case in support of patentability, Applicant submitted a declaration from Dr. Hirose, an inventor of the '939 patent, which included data from experiments in a mouse model for mania. *Id*. at 1156, 1160-64. Applicant asserted that the observed results were "unpredictable from the disclosure of the prior art references, which fail to teach or suggest a synergistic effect achieved by an atypical antipsychotic and mood stabilizer." *Id*. at 1156. In two subsequent Office Actions, the Examiner raised several questions about the Hirose data. *Id*. at 1184-86, 1229-30. And Applicants addressed each point. *Id*. at 1207-08, 1266, 1279-80. Thereafter, based on both Applicant's arguments and Dr. Hirose's

declaration, the Examiner allowed the claims. *Id*. at 1282 ("Office agreed to consider the data and arguments"), 1296.

C. Petitioner Relies on the Same or Cumulative Documents and Uses Them in the Same Way the Examiner Did

Petitioner's six grounds of alleged unpatentability are based on either identical disclosures (Tohen and Citrome) or disclosures that are cumulative (Keck, BMS/Otsuka Press Release, APA Practice Guidelines, Expert Consensus) of the art raised, considered, and rejected by the Examiner during prosecution. Moreover, Petitioner relies on these identical or substantially similar disclosures to support its alleged obviousness case in the same way that the Examiner did.

1. Keck and BMS/Otsuka Press Release are Cumulative of Clinical Trial Report

Keck and the BMS/Otsuka Press Release serve as Petitioner's secondary documents in Grounds 1-4 and 6. Petitioner relies on Keck for the proposition that "aripiprazole was effective and well-tolerated in the treatment of acute mania in patients with bipolar disorder," and that "there was no significant changes in weight for patients taking aripiprazole compared to placebo." Pet. at 26, *see also* 14-15; Ex. 1002 ¶ 34. Petitioner relies on the BMS/Otsuka Press Release for the very same points. Pet. at 26, *see also* 15-16; Ex. 1002 ¶ 35.

The Examiner relied on Clinical Trial Report to reject the claims, asserting that it "teaches that aripiprazole is useful in treating acute mania episode." Ex.

1076 at 1180. Clinical Trial Report discloses the design and results of a Phase III study comparing aripiprazole against the typical antipsychotic haloperidol in acute mania. Ex. 2004 at 1. The conclusions of the study indicate that aripiprazole was found to be superior to haloperidol, and that it was safe and better tolerated than haloperidol. *Id*. at 9. The number of patients with significant weight gain was similar between the two treatment groups. *Id*.

Thus, Keck and BMS/Otsuka Press Release, which Petitioner has not established are printed publications, are cumulative to the Clinical Trial Report on the very same points for which both Petitioner and the Examiner relied on them.

2. Tohen is Tohen

Petitioner relies on Tohen as its primary document in Ground 2 and as a secondary document in Grounds 4 and 6. As mentioned, Applicant raised and the Examiner considered and applied Tohen's disclosure against the pending claims. Specifically, the Examiner rejected the claims over Kowatch, which summarizes the results of Tohen. Ex. 1010 at 8, right-hand col. Applicant noted Tohen's disclosures. Ex. 1076 at 987, 1268. And the Examiner specifically referred to Tohen itself in rejecting the claims. *Id*. at 1133, 1231.

In Grounds 2, 4, and 6, Petitioner relies on Tohen for its disclosure that compared with the use of valproate or lithium alone, "the addition of olanzapine provided superior efficacy in the treatment of manic and mixed bipolar episodes,"

and that from this disclosure a person of ordinary skill would have understood that a combination of lithium and an atypical antipsychotic was effective in treating bipolar disorder in patients partially non-responsive to lithium or valproate monotherapy. Pet. at 31. Petitioner therefore concludes that a person of ordinary skill seeking to improve monotherapy with a mood stabilizer would have been motivated to vary the olanzapine and lithium combination of Tohen by substituting olanzapine with aripiprazole. *Id*.

That sequence of argumentation is identical to the Examiner's. First, the Examiner stated that Tohen discloses that "response rate was significa[n]tly higher in the combination treatment with atypical antipsychotic (olanzapine) and valproate or lithium." Ex. 1076 at 1133. Second, the Examiner pointed out that Tohen includes patients partially nonresponsive to valproate or lithium. *Id*. And finally, based on these disclosures, the Examiner concluded that one of ordinary skill in the art would have been motivated to administer a combination of atypical antipsychotic agent, aripiprazole and lithium with a reasonable expectation of success for treating bipolar disorder in the claimed patient population. *Id*. at 1134, *see also* 1231-32.

3. Citrome is Almost Citrome S187

Petitioner relies on Citrome as its primary document in Grounds 5 and 6, although it is not readily apparent that Citrome is actually the base document. Pet.

at 37-41. While Petitioner has not established that Citrome is a printed publication, and Patent Owner makes no admission that Citrome S187 (Ex. 2005) is prior art to the challenged claims, *ResQNet.com*, 594 F.3d at 866, the substance of Citrome (Ex. 1008) was submitted to the Office by Applicant as Citrome S187 and considered by the Examiner. Ex. 1076 at 1046.

Petitioner relies on Citrome for its disclosure that lithium and aripiprazole were co-administered to patients with schizoaffective disorder and schizophrenia. Pet. at 38. Petitioner further relies on Citrome for its doses allegedly falling within the scope of the claims, as well as for the proposition that a person of ordinary skill in the art would have expected co-administration of lithium and aripiprazole to be safe. *Id*. Petitioner also contends that "[a]lthough the patient population in Citrome was suffering from schizophrenia and schizoaffective disorder, [it] demonstrate[s] that the ordinarily-skilled artisan had already employed a combination of aripiprazole and lithium to treat *mania*." Pet. at 38 n.5 (emphasis added). Petitioner cites absolutely no evidence to support this latter contention. Citrome itself says *nothing* about mania, let alone treating it. *See* Ex. 1008. And neither of the paragraphs of Dr. Frances's declaration that Petitioner cites, 37 and 81, says anything about mania or the treatment of it. Given that the Citrome study was an open-label study with only thirteen patients and no control groups, it could not have established that the co-administration of lithium with aripiprazole was

effective to treat the schizoaffective and schizophrenic patients in the trial, let alone any mania (not even mentioned as being observed in the first place). *See also supra* § III.A.3.

Thus, the Examiner correctly gave Citrome little weight in assessing the claims during prosecution.

4. APA Guidelines are Cumulative of Kowatch

Petitioner relies on the APA Guidelines as its primary document in Ground 1 and as a secondary document in Grounds 4 and 5. Referring only to pages 4, 9, 10, and 25 (*i.e.*, pages 10, 15, 16, and 31 according to the pagination in the footer) of the fifty-plus pages of the APA Guidelines, Petitioner relies on those discrete disclosures for the propositions that 1) lithium plus an antipsychotic or valproate plus an antipsychotic is a "first-line" treatment for "more severe manic or mixed episodes"; 2) those combination treatments *may* be more effective than any of the agents alone; and 3) atypical antipsychotics are preferred over typical psychotics because of their more benign side effect profile. Pet. at 18-19; Ex. 1002 ¶ 28.

APA Guidelines is cumulative of Kowatch, which the Examiner extensively considered during prosecution. Regarding Petitioner's first point, Kowatch states that "[c]urrent clinical practice is to treat mood episodes in children and adolescents with bipolar disorders, *much as one would adults with these disorders, using mood stabilizers* [lithium] *and antipsychotics*." Ex. 1010 at 3 (emphasis

added). Kowatch further states that "atypical antipsychotics are very powerful psychotropics that have recently been found to be efficacious in the treatment of adults with schizophrenia and acute bipolar mania." *Id*. at 7.

Regarding the second point, Kowatch states that "[t]here is emerging data from adult and child studies that the addition of an atypical antipsychotic to a mood stabilizer may decrease bipolar disorder symptoms and improve overall response rates." *Id*. at 8. Moreover, Kowatch summarizes the results of studies with lithium and valproate tested in combination with atypical antipsychotics, olanzapine (Tohen) and quetiapine. *Id*. The Tohen study demonstrated that the "response rate was significantly higher in the combination group." *Id*. In the quetiapine study, Kowatch states that "[t]he findings of this study indicate that quetiapine in combination with valproate was more effective for the treatment of adolescent bipolar mania than valproate alone." *Id*.

And finally, the Clinical Trial Report disclosed that aripiprazole was safe and well tolerated in the patient population tested. Ex. 2004 at 9. Thus, Petitioner's reliance on only certain disclosures of the APA Guidelines is entirely cumulative of documents already extensively considered by the Examiner.

Moreover, Petitioner's arguments about the APA Guidelines directly mirror those the Examiner made regarding Kowatch and Tohen. Specifically, Petitioner states that the APA Guidelines taught that lithium, valproate, and antipsychotic

medications had shown efficacy in the treatment of patients with acute mania, and that the combination therapy was "already viewed as more effective than either agent alone," "especially if the patient did not fully respond to a mood stabilizer monotherapy." Pet. at 25. From this, Petitioner concludes that a person of ordinary skill in the art would have looked to use a combination therapy of lithium and an atypical antipsychotic. *Id*. at 25-26.

The Examiner made the exact same findings and drew a similar conclusion regarding Kowatch (and Tohen). In particular, the Examiner stated that Kowatch "taught that addition of atypical antipsychotic, olanzapine, quetiapine to a mood stabilizer such as lithium decreases bipolar symptoms and improve overall response rates than monotherapy." Ex. 1076 at 1129 (emphasis in original). The Examiner thus concluded that it would have been obvious to use lithium and aripiprazole to treat bipolar disorder "because Kowatch teaches that addition of a[n] atypical antipsychotic to lithium gives better overall response in the method of treating bipolar disorder i.e. one can treat patients more effectively than monotherapy." *Id*. at 1130 (emphasis in original). Petitioner's current arguments are no different.

5. Expert Consensus Adds Nothing to the Art the Examiner Considered

Petitioner relies on only five discrete disclosures from over 100 pages of Expert Consensus to support one of its unpatentability challenges (Ground 3). Pet. at 19-20, 23 (Ground 3 only); Ex. 1002 ¶¶ 29-30. Petitioner asserts that Expert Consensus recommended antipsychotics as first line in the treatment of mania or depression with psychosis, and as potential adjuncts in non-psychotic episodes. *E.g.*, Ex. 1002 ¶ 29. Dr. Frances relies on Expert Consensus for the teaching that atypical antipsychotics, such as olanzapine and risperidone, were generally preferred over conventional antipsychotics. *Id*. Petitioner further points out that if treatment with the combination of a mood stabilizer and antipsychotic was not providing the desired therapeutic result, Expert Consensus recommended substituting the antipsychotic before substituting the mood stabilizer. *Id.* (Patent Owner notes that Expert Consensus actually says that "it *may be appropriate* to change the antipsychotic earlier than the mood stabilizer." Ex. 1026 at 19 (emphasis added).) Finally, Petitioner notes that the combination treatment of mood stabilizer and atypical antipsychotics are either the treatment of choice or an alternative treatment for different types of mania. Ex. 1002 ¶¶ 29-30.

Petitioner's laser focus on only five isolated parts of Expert Consensus fails to provide a fair characterization of the document and its purpose. When

considered in its entirety, one quickly realizes that Expert Consensus is not only cumulative to other documents considered during prosecution, but it is *not* actually supportive of Petitioner's positions.

The Expert Consensus is exactly what its title suggests—a compilation of survey results from experts in the field. Because it is not an analysis of clinical trial results but instead relies on input from 58 practitioners, the Consensus authors caution of its limitations. Notably, it states that "[w]e have relied on expert opinion precisely because we are asking crucial questions that are not yet well answered by the literature." Ex. 1026 at 12. And further notes that history teaches that expert opinion "at any given time can be very wrong." *Id*.

Contrary to Petitioner's assertions that Expert Consensus somehow conveys that atypical antipsychotics are well-established treatments for bipolar disorder, it instead refers to divalproex and lithium as "the cornerstone choices among this class for both acute and preventive treatment of mania." *Id*. at 5. The report further notes that "[r]egardless of which is selected first, if monotherapy fails, the next recommended intervention is to use these agents [lithium or divalproex] in combination." *Id*. And while experts who were polled supported the use of atypical antipsychotics, "they still hesitate to recommend them over traditional mood stabilizers for monotherapy in mania." *Id*. at 11. In fact, the Expert Consensus notes only that adding an antipsychotic "*may* also be helpful in other

types of mania," but again, that is not the recommended preferred initial treatment. *Id*. at 16-17. Indeed, what the panel actually recommended is that antipsychotics should be reserved for "more severe cases," noting that this recommendation "is the same as in the last survey and is consistent with clinical tradition rather than clear-cut data." *Id*. at 11. Consistently, the authors state that "[e]xperts reserve strongest support for initial strategies and individual medications for which there are high-quality research data, or for which there are longstanding patterns of clinical usage." *Id*. at 5.

Thus, considered as a whole, Expert Consensus does not paint the picture that Petitioner hopes that it would. Indeed, unlike Kowatch, which was extensively considered during prosecution, there is *no* section in Expert Consensus that discusses clinical trials of using a mood stabilizer *and* an atypical antipsychotic in any form of bipolar disorder. *See* Ex. 1026 at 10-11 (discussing only clinical trials using atypical antipsychotics as monotherapy); *supra* § III.A.3. Thus, Petitioner fails to establish that Expert Consensus is somehow closer prior art than Kowatch, which the Examiner deemed to be "the closest prior art." Ex. 1076 at 1296.

6. Conclusion

As shown, Petitioner's cited documents and arguments are all but identical to the disclosures and arguments presented and correctly withdrawn by the Office during examination. On that basis alone, the Board would be well within its

discretion to deny institution here. And Petitioner's additional allegations regarding side effects and unexpected results do not establish any clear error or raise material changes that warrant institution.

D. Petitioner's "Side Effects" Arguments Are Irrelevant

Petitioner focuses on aripiprazole's favorable side effect profile to support motivation. *E.g.*, Pet. at 26-27. That focus, however, does not preclude the Board from exercising its discretion under § 325(d). Petitioner notes that atypical antipsychotics generally were known to have "benign" side effect profiles. *Id*. at 25. The only additional benefit Petitioner identifies for aripiprazole is related to weight gain. *Id*. at 26. But the Examiner considered the Clinical Trial Report, which stated that "aripiprazole was safe and better tolerated than haloperidol," and that "the number of patients with significant weight gain was similar between the two treatment groups." Ex. 2004 at 9. Moreover, side effects are largely irrelevant where Petitioner—like the Examiner—made no effort to demonstrate that aripiprazole is interchangeable based on its *efficacy* with an atypical antipsychotic in the claimed method. *Supra* § III.A.2. *See Daiichi Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1353-54 (Fed. Cir. 2010).

E. Petitioner's Arguments Regarding Dr. Hirose's Declaration Are Irrelevant and Do Not Undermine the Examiner's Conclusions Regarding Patentability

Petitioner asserts that the experimental evidence Applicant submitted during prosecution cannot support the nonobviousness of the challenged claims. Pet. at 41-49 (citing Ex. 1004). Those arguments, however, should not keep the Board from using its discretion to deny institution. The Examiner carefully considered Dr. Hirose's declaration and Applicant's arguments regarding it. And Petitioner fails to establish (indeed does not even contend) that the data itself or the calculations are wrong. Rather, Petitioner's expert Dr. Au quibbles with the experimental design, raising issues that are irrelevant or easily dismissed. In fact, Dr. Au's own opinions demonstrate that a person of ordinary skill would have struggled to have any expectation, let alone a reasonable expectation of success, about the claimed method of treatment, making the submission of any data unnecessary.

1. The Hirose Data

In support of the patentability of the pending claims, Applicant submitted a declaration from Dr. Hirose, one of the inventors on the '939 patent. Ex. 1076 at 1160-64. Dr. Hirose tested the co-administration of aripiprazole and lithium or olanzapine and lithium in a well-known and accepted animal model for the manic condition associated with bipolar disorder. *Id*. at 1161; Ex. 1004 ¶ 44. In that

model, mice are given methamphetamine, which stimulates their locomotion. That locomotion may be potentiated by an active agent, thus providing insight on a compound's potential effect in mania. *E.g.*, Ex. 1004 ¶ 45.

To generate the data in his declaration, Dr. Hirose relied on a testing paradigm where the active agents (aripiprazole, olanzapine, and lithium) were given together at doses that when given alone generated no response, *i.e.*, a sub-therapeutic dose. Ex. 1076 at 1208, *see also* 1265-66. Specifically, mice were administered either 1) vehicle 1 + 2 + 3; 2) vehicle 1 + 2 + methamphetamine; 3) vehicle 2 + aripiprazole + methamphetamine; 4) vehicle 1 + LiCl (e.g., "lithium") + methamphetamine; or 5) aripiprazole + LiCl + methamphetamine. *Id*. at 1162. The same experimental setup was used for an olanzapine arm. *Id*. Those groups and their results are reproduced from the prosecution file history in Ex. 2008 with experiment numbers for clarity.

In the table, "###" indicates that the all vehicle groups (1 and 6) showed a statistically significant difference in locomotor count from the methamphetamine groups in both the aripiprazole (2) and olanzapine (7) arms. *Id*. That means that the dose of methamphetamine administered actually increased locomotor counts to an extent beyond that attributed to chance.

To analyze the rest of the treatment groups, the data was analyzed using a two-tailed Dunnett's test. *Id*. Such a test, as noted by Dr. Au, appropriately

compares each of several experimental treatments against one control. Ex. 1004 ¶ 86. Thus, Group 3 was compared against Group 2; Group 4 was compared against Group 2; and Group 5 was compared against Group 2. As indicated by "**," the last comparison was the only group to separate from the control (Group 2). The differences between the first two comparisons were not statistically significantly different. This makes sense because of the experimental design: individual doses of aripiprazole and lithium were administered that were *not* supposed to be effective, *i.e.*, were not supposed to suppress locomotion. Ex. 1076 at 1208, *see also* 1265-66. Only when used in combination did they display a positive effect by suppressing the methamphetamine-induced locomotion.

Analogous comparisons were done in the olanzapine arm: Group 8 was compared to Group 7; Group 9 was compared to Group 7; and Group 10 was compared to Group 7. None of those groups showed a difference from the control (Group 7) that was statistically significant.

The Examiner considered the Hirose data and initially raised several questions. *Id*. at 1184-85. Contrary to Petitioner's assertions, Applicant responded to each of those points. *Id*. at 1207-08. In a subsequent Office Action, the Examiner asked additional questions about the data. *Id*. at 1229-30. In a final response, Applicant again addressed each of the Examiner's concerns. *Id*. at 1265-67, 1269-70. Based on the experimental paradigm and statistical analysis used,

Applicant ultimately asserted that "at the very least [the declaration] provides the Office with a barometer of the combination of aripiprazole + lithium and olanzapine + lithium in the same environment, whereas Kowatch cannot nor even tries to do so." *Id*. at 1270. After considering Applicant's arguments and participating in an interview, the Examiner allowed the claims based on both Applicant's arguments and the data. *Id*. at 1296.

2. The Results Do Not Change by Expressing Them as % Suppression or by Normalizing Them

Dr. Au criticizes Applicant for conducting its analysis on the raw locomotor count values instead of expressing the results as a % suppression value. Ex. 1004 ¶¶ 65-67, Appendix C. While a % suppression value may lead to a simpler presentation of the data, it is a mathematical fact that the statistical analysis will come out the same way whether raw data or % suppression values are used.

Dr. Au also asserts that Applicant should have normalized the effects of the tested drugs against the methamphetamine baseline, again suggesting that by not doing so, the results would have come out differently. *Id*. But even Dr. Au's own analysis—which is not the one Applicant did or was required to do by the Examiner—demonstrates that the statistical analysis is the same regardless of whether raw data (*i.e.*, "uncorrected counts") or normalized data (*i.e.*, "corrected

Net-counts") are used. Ex. 1004 at Appendix C, Tables B & C (p-value is 0.45 for both the uncorrected, col. 5, and corrected counts, col. 6).

3. The Data was Sufficiently Explained

Dr. Au also contends that the apparent differences between the two methamphetamine control groups and the intra-group variability affects the quality of the data. Pet. at 44-45; Ex. 1004 ¶¶ 69-72. But she does not explain why this "calls into question the reliability of the Hirose Data and its conclusions." Ex. 1004 ¶¶ 71-72. Instead, she asserts incorrectly that the Examiner raised the issue, but Applicants did not address it. Ex. 1004 ¶ 71. Dr. Au cites the wrong Office Action. *Id.* (citing Ex. 1076 at 1185). The citation should have referred to Ex. 1076 at 1229-30. And Applicant did address that point. Ex. 1076 at 1266. Applicant noted that the testing involved an *in vivo* assay in an animal model as opposed to an *in vitro* test. *Id*. Thus, the range of precision and accuracy depends on numerous factors.

Dr. Au, like the Examiner, also questioned the data in the lithium groups (4 and 9). Ex. 1004 ¶¶ 73-79; Ex. 1076 at 1230. Applicant again addressed the Examiner's comments on the record. Ex. 1076 at 1266. Specifically, Applicant noted that the range generated from the mean ± S.E.M. overlapped between the two control groups (4 and 9 in table above), which means that any difference is not

statistically significant.[5, 6] *Id*. Dr. Au argues that Applicant's data seems to be contrary to "what is known and expected in the field" for lithium's affects in the methamphetamine mouse model. Ex. 1004 ¶ 76. What Dr. Au overlooks, however, is that Dr. Hirose's experimental paradigm used sub-therapeutic doses of

[5] Dr. Au also quibbles with Applicant's definition of "range," asserting—without citation—that "range" is "normally" understood to represent the difference between the highest and lowest of all of the observed values. Ex. 1004 ¶¶ 84-85. Instead, Applicant clearly defined "range" to represent the mean value plus one S.E.M. Ex. 1076 at 1264-65. Dr. Au readily understood this definition upon considering the Table and Applicant's comments. Ex. 1004 ¶ 53 (citing Ex. 1076 at 1264-65).

[6] Petitioner and Dr. Au assert that Applicant has defined statistical significance depending on whether the range of mean ± S.E.M. overlaps or not. Pet. at 47; Ex. 1004 ¶¶ 103-04. Applicant did not define statistical significance that way. Although it is true that an overlapping range means that there is no statistical significance between the two groups, the converse, *i.e.*, ranges that do not overlap, is not automatically statistically significant. Applicant did not argue that. Instead, Dr. Hirose applied Dunnett's test, and the only group to show statistical significance was Group 5 compared to Group 2. Ex. 1076 at 1162-63.

lithium chloride. Ex. 1076 at 1208, *see also* 1265-66. In other words, Groups 4 and 9 were *not* supposed to demonstrate a difference from the methamphetamine control Groups 2 and 7.

The literature that Dr. Au uses in support of her position is consistent. For the Hirose data, one dose of *25 mg/kg* of lithium chloride was administered *20 minutes* before the start of the measurement. Ex. 1076 at 1161. In contrast, the doses of lithium chloride that exhibited locomotor suppression effect in the documents cited by Dr. Au were either higher or were administered for longer periods of time. *See* Ex. 1004 at Appendix D; Exs. 1036, 1037, 1050, 1038, 1051, 1039, and 1052. For example, in Ex. 1036, mice were administered 22 mg/kg, 67 mg/kg, and 200 mg/kg for 21 days. Ex. 1036 at 2. Only at 67 mg/kg and 200 mg/kg was suppression observed. *Id*. at 3. The 22 mg/kg dose did not result in a significant effect at the earlier time points. *Id*.; *see also* Exs. 1037 (not a methamphetamine model; also administered chlordiazepoxide), 1050 (170 mg/kg), 1038 (significant for 25 mg/kg only after 60 mins.), 1051 (pretreatment for 14 days with 47.5 mg/kg twice a day), 1039 (10-300 mg/kg; no separation from placebo with lowest dose), and 1052 (47.5 mg/kg). Thus, Dr. Au's arguments are irrelevant when one considers the experimental conditions that were used and clearly explained to the Examiner. Ex. 1076 at 1208, 1265-66.

4. Dr. Au's Synergy Model Would Not Have Been Appropriate

Dr. Au asserts that the Hirose experiments were not designed to establish synergy, and that Applicant should have used the Loewe Additivity model. Pet. at 47-48; Ex. 1004 ¶¶ 93-101, Appendix A. That model, however, "assumes that drugs in combination are merely different dilutions of the same agent and that an agent cannot interact with itself." Ex. 1004 at Appendix A ¶ 13. Stated differently, this model assumes that lithium and either aripiprazole or olanzapine have the same mechanisms of action. There is no evidence they do. Indeed, Tohen speculates that olanzapine *may* have "unique effects" or mood stabilizing properties. Ex. 1006 at 7-8. Thus, Dr. Au's criticisms of Dr. Hirose's experimental design are unfounded.

5. Dr. Au's Arguments Strongly Suggest that a Person of Ordinary Skill in the Art Would Not Have Had a Reasonable Expectation of Success

According to Dr. Au, to establish synergy, one must first establish the additive effect of the drugs and then compare that with the experimentally combined effect. Ex. 1004 ¶ 90. To even begin generating those results, however, she asserts that one would need to understand the dose response curves for all of the active ingredients—alone *and* together. *Id*. at ¶ 91, Appendix A ¶¶ 17-19, 21, 22. She states "[t]o be clear, determination of the nature of drug interactivity

requires the concentration-effect of dose response curves of single agents and their combinations obtained at multiple concentration or dose levels." Ex. 1004 at Appendix A ¶ 22. She also indicates that the experiments would need to account for different drug effects at different time points. *Id*. at ¶¶ 94-96.

Petitioner has not established that *any* of the data it asserts is *required* data was known. Petitioner has not shown that there was a clearly defined dose-response curve for lithium alone, olanzapine alone, aripiprazole alone, or any of the agents together. Nor has Petitioner established that lithium and the atypical antipsychotics have the same mechanism of action. In fact, Tohen clarifies only that olanzapine *may* have mood stabilizing properties. Ex. 1006 at 8. And Petitioner has provided no evidence that olanzapine and aripiprazole are interchangeable. *Supra* § III.A.2. Dr. Au asserts that "drug interactivity is highly complex and the nature of the interactivity can vary from synergy to antagonism depending on the effect level and drug concentration" (Ex. 1004 at Appendix A ¶ 20), *i.e.*, it is highly unpredictable. The Examiner agreed. Ex. 1076 at 1026 ("It is generally recognized in the art that biological compounds often react unpredictably under different circumstances"). Thus, Petitioner's own evidence establishes that a person of ordinary skill in the art would have had little to no expectation of success regarding the therapeutic benefit of lithium and aripiprazole in patients nonresponsive to the mood stabilizers of the claims. Absent a reasonable

expectation of success, which neither the Office then nor Petitioner now has established, the submission of any data was unnecessary. And given the paucity of dose-response data in the art, Applicant's data in the Hirose declaration appropriately served as a "barometer" to assist the Examiner. *Id*. at 1270.

For all of the foregoing reasons, the Board should exercise its discretion under § 325(d) to deny institution.

V. Petitioner's Six Grounds of Unpatentability Are Redundant of One Another

"[M]ultiple grounds, which are presented in a redundant manner by a petitioner who makes no meaningful distinction between them, are contrary to the regulatory and statutory mandates, and therefore are not all entitled to consideration." *Liberty Mutual Ins. Co. v. Progressive Casualty Ins. Co.*, CBM2012-00003, Paper 7 at 3 (P.T.A.B. Oct. 25, 2012). Here, Petitioner introduces its grounds "as independent and not redundant" (Pet. at 24), yet it does not even attempt to make a meaningful distinction among them. Instead, the Petition suffers from both horizontal and vertical redundancy.

A. All Grounds Are Horizontally Redundant

Horizontal redundancy occurs when a petition (1) relies on allegedly distinct documents to "provide essentially the same teaching to meet the same claim limitation" and (2) fails to "explain why one reference more closely satisfies the

claim limitation at issue in some respects than another reference, and vice versa." *Id.* Here, all of the proposed grounds rely on "Keck (Ex. 1007) or BMS/Otsuka Press Release (Ex. 1028)" (Grounds 1-4 and 6) or Citrome (Ex. 1008) (Ground 5) for an alleged disclosure of aripiprazole. The grounds then pair those documents—without meaningful distinction—with either APA Practice Guidelines (Ex. 1009), Tohen (Ex. 1006), Expert Consensus (Ex. 1026), or a combination thereof as allegedly providing the *same* teaching: an antipsychotic combined with a mood stabilizer.

As the Board has explained,

> [t]he proper focus of a redundancy designation is not whether the applied prior art disclosures have differences, for it is rarely the case that disclosures of different prior art references will be literally identical. Rather, the focus is on whether the petitioner articulated a meaningful distinction in terms of ***relative strengths and weaknesse****s* with respect to application of the prior art disclosures to one or more claim limitations.

EMC Corp. v. PersonalWeb Techs., LLC, IPR2013-00082, Paper 33 at 3-4 (P.T.A.B. June 5, 2013) (emphasis added). Petitioner makes no attempt to justify its repetitive and burdensome grounds by articulating why each ground has strength and weakness relative to the others. APA Practice Guidelines, Tohen, and Expert Consensus are factually redundant (and deficient). APA Practice Guidelines and Tohen report the same preliminary finding that *olanzapine* in

combination with lithium or valproate may provide additional efficacy compared to monotherapy. Ex. 1009 at 31, under "Combination therapy"; Ex. 1006 at 7, right col., bottom para. And while Petitioner relies on Expert Consensus as an alternative to those two documents, Expert Consensus does not mention the preliminary data involving olanzapine or data on any atypical antipsychotic used in combination with a mood stabilizer. Petitioner provides no basis for subjecting the Board and Patent Owner to its horizontally redundant grounds.

B. Grounds 1 and 4, Grounds 2 and 4, and Grounds 2 and 6 Are Vertically Redundant

"Vertical redundancy exists when there is assertion of an additional prior art reference to support another ground of unpatentability when a base ground already has been asserted against the same claim without the additional reference and the Petitioner does not explain what are the relative strength and weakness of each ground." *Liberty Mutual*, CBM2012-00003, Paper 7 at 13. Under these circumstances, "[t]o move forward with such a multiplicity of grounds, Petitioner must articulate a reasonable basis to believe that from a certain perspective the base ground is stronger, and that from another perspective the ground with additional reference is stronger." *Id.*

Here, each of Grounds 1 and 2 is vertically redundant of Ground 4. In one instance, Ground 4 adds Tohen (Ex. 1006) to the identical combination of

documents asserted in Ground 1. In the second instance, Ground 4 adds APA Practice Guidelines (Ex. 1009) to the identical combination of documents asserted in Ground 2. Similarly, in Ground 6, the Petition adds Citrome (Ex. 1008) to the identical combination of documents asserted in Ground 2. In each occurrence, Petitioner does not argue that the base ground has anything not found in the ground that follows. In fact, the later grounds (4 and 6) repeatedly use the phrase "[a]s discussed above" indicating that Petitioner is merely repeating the same discussion from the base grounds. Pet. at 34, 35, 39, 40. Accordingly, because Petitioner fails to articulate anything distinct for Grounds 1 and 2 over Grounds 4 and 6, Grounds 1 and 2 should be denied.

VI. Conclusion

For these reasons, Petitioner has not shown that it is reasonably likely to succeed on its challenge to claims 2, 6, 7, and 9 of the '939 patent. The Board should therefore deny the Petition and not institute *inter partes* review.

Dated: February 28, 2017

By: /Erin M. Sommers/

Erin M. Sommers, Reg. No. 60,974
James B. Monroe, Reg. No. 33,971
Christopher L. McDavid, Reg. No. 70,809
FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.
901 New York Avenue, NW
Washington, DC 20001-4413
Telephone: 202-408-4000;
Facsimile: 202-408-4400

Counsel for Patent Owner
Otsuka Pharmaceutical Co., Ltd.

CERTIFICATE OF COMPLIANCE

The undersigned certifies that a copy of the foregoing **Patent Owner's Preliminary Response** contains 13,831 words, excluding those portions identified in 37 C.F.R. § 42.24(a), as measured by the word-processing system used to prepare this paper.

Dated: February 28, 2017

By: /Erin M. Sommers/
Erin M. Sommers, Reg. No. 60,974

CERTIFICATE OF SERVICE

The undersigned certifies that a copy of the foregoing **Patent Owner's Preliminary Response** and **Exhibits 2001-2008** were served electronically via email on February 28, 2017, in their entirety, on the following:

Theresa C. Kavanaugh
Nicholas K. Mitrokostas
GOODWIN PROCTER LLP
100 Northern Avenue
Boston, MA 02210
tkavanaugh@goodwinlaw.com
nmitrokostas@goodwinlaw.com

Carolyn S. Elmore
ELMORE PATENT LAW GROUP, P.C.
484 Groton Road
Westford, MA 01886
celmore@elmorepatents.com

Petitioner has agreed to electronic service.

Dated: February 28, 2017

By: /Erin M. Sommers/
Erin M. Sommers, Reg. No. 60,974