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Paper 7
Entered: November 5, 2014

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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SHIRE DEVELOPMENT LLC,
Petitioner,

v.

LCS GROUP, LLC,
Patent Owner.

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Case IPR2014-00739
Patent 8,318,813 B2

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Before LINDA M. GAUDETTE, LORA GREEN, and KRISTINA M. KALAN, *Administrative Patent Judges.*

GAUDETTE, *Administrative Patent Judge*.

DECISION
Institution of *Inter Partes* Review
*37 C.F.R. § 42.108*

# I. INTRODUCTION

On May 9, 2014, Shire Development LLC ("Petitioner") filed a Petition (Paper 2, "Pet.") to institute an *inter partes* review of claims 1–13 (the "challenged claims") of U.S. Patent No. 8,318,813 B2 (Ex. 1001, "the '813 patent"). 35 U.S.C. §§ 311–319. LCS Group, LLC ("Patent Owner") timely filed a Preliminary Response (Paper 6, "Prelim. Resp."). We have jurisdiction under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted "unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." Upon consideration of the Petition and Patent Owner's Preliminary Response, we determine Petitioner has established a reasonable likelihood that it would prevail in showing the unpatentability of at least one of the challenged claims. We therefore institute an *inter partes* review as to: (1) claims 1–5, 8–10, 12, and 13 based on the grounds that these claims would have been obvious over (a) Ong, DSM-IV-TR, and Mickle, and (b) Dukarm, DSM-IV-TR, and Mickle; (2) claims 6 and 7 based on the grounds that these claims would have been obvious over (a) Ong, DSM-IV-TR, Mickle, and Marrazzi, and (b) Dukarm, DSM-IV-TR, Mickle, and Marrazzi; and (3) claim 11 based on the grounds that this claim would have been obvious over (a) Ong, DSM-IV-TR, Mickle, and Grilo, and (b) Dukarm, DSM-IV-TR, Mickle, and Grilo. Our factual findings and conclusions at this stage of the proceeding are based on the evidentiary record developed thus far (prior to Patent Owner's Response). This is not a final decision as to patentability of claims for which *inter partes* review is instituted. Our final decision will be based on the record as fully developed during trial.

## II. BACKGROUND

### *A. Related Matters*

Petitioner indicates there are no related judicial or administrative matters that would affect, or be affected by, a decision in this proceeding. Pet. 1.

### *B. The '813 Patent (Ex. 1001)*

The '813 patent relates to a method of treating Binge Eating Disorder (BED) as defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR).[1] *See* Ex. 1001, 25:32–26:51 (claims 1–13). According to the '813 patent, "[b]inge eating disorder is difficult to treat and carries significant medical and psychiatric risks." Ex. 1001, 1:62–63. The background section of the '813 patent explains that known treatments for BED have been of limited success and sometimes worsen binge eating symptoms. *Id.* at 1:63–65. Such known treatments have included administering psychotropic medications such as "antidepressants, antipsychotics, antimanic agents, and mood modulating medications." *Id.* at 1:65–2:1.

The background section of the '813 patent indicates that Attention-Deficit Hyperactivity Disorder (ADHD) and Attention-Deficit Disorder (ADD)[2] are "[p]sychiatric problems associated with, or exacerbated by, binge eating disorder." Ex. 1001, 2:11–12. According to the '813 patent, psychostimulant treatments for ADHD and ADD, including "both amphetamine (e.g. ADDERALL and ADDERALL XR) and methylphenidate (e.g. RITALIN and CONCERTA) preparations," *id.* at 11:44–48, "have been associated with the side effect of appetite suppression," *id.* at 11:3–5. However, the '813 patent indicates that even

[1] Ex. 1010, discussed in Section IV.B, below.

[2] *See* Ex. 1009 (identifying the words that form the acronym "ADD").

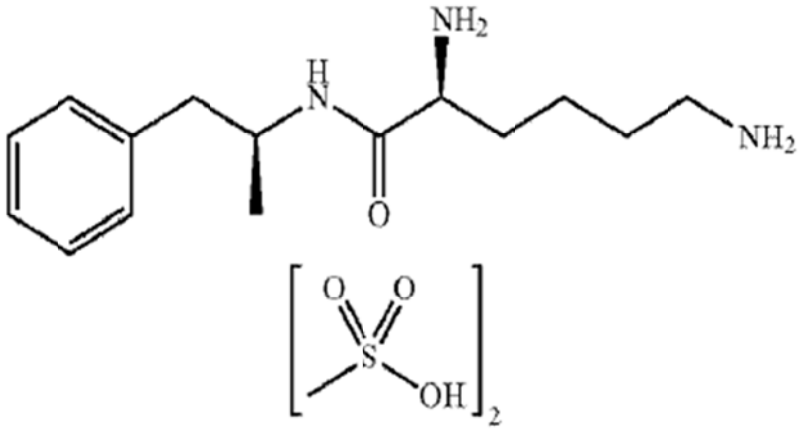
extended release amphetamine (e.g., Adderall XR, *see* Prelim. Resp. 50) or methylphenidate formulations are described by patients as having "a 'wear off' effect for a sufficient part of the day, in which the medication loses its effects including appetite suppressant properties." Ex. 1001, 11:8–12. The "wear off" effect is said to lead to problematic symptoms or side effects, including the urge to have more medication, feeling hungry or eating more, and binge eating. *Id.* at 11:12–16.

The inventor of the '813 patent is said to have "discovered that amphetamine prodrugs, including lisdexamfetamine dimesylate, methylphenidate prodrugs, and certain methylphenidate analogs, are useful for treating binge eating disorders, obesity resulting from binge eating behavior, and depression." *Id.* at 2:62–66. As used in the '813 patent,

> [t]he terms "amphetamine prodrug" and "methylphenidate prodrug" refer to any product that contains either an amphetamine (CAS Reg. No. 300-62-9) or methylphenidate (CAS Reg. No. 113-45-1) compound conjugated to a chemical moiety such that the conjugated amphetamine or methylphenidate must undergo a conversion in a patient's body to become the active amphetamine or methylphenidate form. "Amphetamine" includes dextro [(d- or dex)] and levo amphetamine forms and all pharmaceutically acceptable amphetamine salts.

*Id.* at 6:55–63. "Lisdexamfetamine dimesylate, CAS Reg. No. 608137-32-3, (2S)-2, 6-diamino-N-[(1S)-1-methyl-2-phenylethyl]hexanamide dimethanesulfonate, is an amphetamine prodrug in which L-lysine is covalently bound to

d-amphetamine."[3] Ex. 1001, 7:3–8. Lisdexamfetamine dimesylate has the chemical formula:




*Id.* at 7:8–20. The '813 patent states that "Lisdexamfetamine dimesylate, sold under the trade name VYVANSE (Shire), is FDA approved for the treatment of Attention–Deficit Hyperactivity Disorder." *Id.* at 11:42–44.

*C. Illustrative Claims*

Independent claim 1, reproduced below, is illustrative of the claimed subject matter:

> 1. A method of treating Binge Eating Disorder, comprising diagnosing a patient as having Binge Eating Disorder, wherein the patient exhibits Binge Eating Disorder as defined in the DSM -IV-TR and administering a therapeutically effective amount of lisdexamfetamine dimesylate to the patient, wherein the lisdexanlfetamine dimesylate is the only active agent administered or is administered together with one or more additional active agents.

[3] Dr. Brewerton uses the term "LDX dimesylate," *see* Ex. 2009, 14, ¶ 28, and Mickle uses the term "L-lysine-d-amphetamine dimesylate," *see* Ex. 1023, discussed in Section V.A.2, below, in describing this compound.

Of the remaining challenged claims, claims 8 and 13 are independent, and similarly recite methods of treating Binge Eating Disorder comprising a step of administering lisdexamfetamine dimesylate to a patient.

*D. Evidence Relied Upon*

Petitioner's patentability challenges are based on the following references:

| **References** | **Patents/Printed Publications** | **Exhibit** |
|---|---|---|
| DSM-IV-TR | American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition, Text Revision, Washington, D.C., American Psychiatric Association, 583–595, 785–787 (2000). | Ex. 1010 |
| Ong | Y.L. Ong, et al., *Suppression of Bulimic Symptoms with Methylamphetamine*, 143 Brit. J. Psychiatry, 288–293 (1983). | Ex. 1017 |
| Dukarm | Carolyn P. Dukarm, *Bulimia Nervosa and Attention Deficit Hyperactivity Disorder: A Possible Role for Stimulant Medication,* 14(4) J. Womens Health, 345–350 (2005). | Ex. 1019 |
| Appolinario | Jose C. Appolinario, et al., *Pharmacological Approaches in the Treatment of Binge Eating Disorder*, 5(3) J. Curro Drug Targets, 301–307 (2004). | Ex. 1020 |
| Mickle | Mickle et al. U.S. Patent Publication No. US 2007/0042955 A1, pub. Feb. 22, 2007 | Ex. 1023 |
| Marrazzi | Mary Ann Marrazzi, et al., *Binge Eating Disorder: Response to Naltrexone,* 19(2) Int. J. Obes., 143–145 (1995). | Ex. 1024 |

| References | Patents/Printed Publications | Exhibit |
|---|---|---|
| Grilo | Carlos M. Grilo, et al., *Reliability of the Eating Disorder Examination in Patients with Binge Eating Disorder*, 35(1) Int. J. Eat, Disord., 80–85 (2004). | Ex. 1025 |

Petitioner also relies on the Declaration of Dr. Timothy D. Brewerton (Ex. 1009 ("the Brewerton Declaration")) in support of its patentability challenges. Patent Owner does not dispute that Dr. Brewerton is "an expert in the field of eating disorders and related comorbidities, including their associated neurobiology and psychopharmacology, . . . at least since 1987," Ex. 1009 ¶ 2. *See generally*, Prelim. Resp. Dr. Brewerton testified that, throughout his career, he has "diagnosed and treated hundreds of patients of all ages having eating disorders and related comorbidities, including anorexia nervosa ('AN'), bulimia nervosa ('BN'), eating disorders not otherwise specified ('EDNOS'), and specifically binge eating disorder ('BED')." Ex. 1009 ¶ 12.

*E. Asserted Grounds of Unpatentability*

Petitioner challenges the patentability of the '813 patent claims based on the following grounds:

| References | Basis | Claims Challenged |
|---|---|---|
| Appolinario and Mickle | § 103(a) | 1–5, 8–10, 12, and 13 |
| Appolinario, Mickle, and Marrazzi | § 103(a) | 6 and 7 |
| Appolinario, Mickle, and Grilo | § 103(a) | 11 |
| Ong, Mickle, and DSM-IV-TR | § 103(a) | 1–5, 8–10, 12, and 13 |

| References | Basis | Claims Challenged |
|---|---|---|
| Ong, Mickle, DSM-IV-TR, and Marrazzi | § 103(a) | 6 and 7 |
| Ong, Mickle, DSM-IV-TR, and Grilo | § 103(a) | 11 |
| Dukarm, Mickle, and DSM-IV-TR | § 103(a) | 1–5, 8–10, 12, and 13 |
| Dukarm, Mickle, DSM-IV-TR, and Marrazzi | § 103(a) | 6 and 7 |
| Dukarm, Mickle, DSM-IV-TR, and Grilo | § 103(a) | 11 |

## III. CLAIM CONSTRUCTION

Claims of an unexpired patent are interpreted using the broadest reasonable construction in light of the specification of the patent. *See* Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,766 (Aug. 14, 2012); 37 C.F.R. § 42.100(b). At this stage of the proceeding, we determine no express construction of the claim language is needed for this Decision. However, we note that the parties indicate the claim term "therapeutically effective amount" should be interpreted in a manner consistent with the definition in the '813 patent: "an amount effective to decrease the symptoms of BED or an amount sufficient to significantly reduce the frequency and severity of binge eating behavior." Pet. 10; *see* Prelim. Resp. 13; Ex. 1001, 8:48. The parties do not propose constructions for any other claim terms. *See* Pet. 9–11; Prelim. Resp. 13.

## IV. STATE OF THE ART AS OF SEPTEMBER 13, 2007[4]

### *A. Person of Ordinary Skill in the Art (POSA)*

Dr. Brewerton opined that a person of ordinary skill in the art ("POSA") "with respect to the '813 patent" as of September 13, 2007, "would [have been] a medical doctor (M.D.) specializing in psychiatry," and "would have [had] clinical experience in the diagnosis and psychopharmacology of eating disorders, specifically BED." Ex. 1009 ¶¶ 27–28. Patent Owner does not disagree with Dr. Brewerton's description of the POSA, but adds that the POSA would also have had clinical experience in the treatment of eating disorders. Prelim. Resp. 13.

### *B. BED and Bulimia Nervosa (BN)*

Patent Owner agrees with Dr. Brewerton's characterization of the DSM-IV-TR (Ex. 1010) "as the gold standard for diagnosing mental disorders, including eating disorders," Ex. 1009 ¶ 30; Pet. 27 (citing Ex. 1009 ¶ 30); Prelim. Resp. 5 (citing Ex. 1009 ¶ 30). The DSM-IV-TR describes binge-eating disorder as "recurrent episodes of binge eating in the absence of the regular use of inappropriate compensatory behaviors characteristic of Bulimia Nervosa." Ex. 1010, 595. The DSM-IV-TR lists the following research criteria for BN:

> A. Recurrent episodes of binge eating. An episode of binge eating is characterized by both of the following:
>
> (1) eating, in a discrete period of time (e.g., within any 2-hour period), an amount of food that is definitely larger than most people would eat in a similar period of time under similar circumstances
>
> (2) a sense of lack of control over eating during the episode (e.g., a feeling that one cannot stop eating or control what or how much one is eating)

[4] The '813 patent claims benefit of the September 13, 2007 filing date of Provisional Application No. 60/972,046. Ex. 1001, Related U.S. Application Data.

B. Recurrent inappropriate compensatory behavior in order to prevent weight gain, such as self-induced vomiting; misuse of laxatives, diuretics, enemas, or other medications; fasting; or excessive exercise.

C. The binge eating and inappropriate compensatory behaviors both occur, on average, at least twice a week for 3 months.

D. Self-evaluation is unduly influenced by body shape and weight.

E. The disturbance does not occur exclusively during episodes of Anorexia Nervosa.

**Purging Type:** during the current episode of Bulimia Nervosa, the person has regularly engaged in self-induced vomiting or the misuse of laxatives, diuretics, or enemas

**Nonpurging Type:** during the current episode of Bulimia Nervosa, the person has used other inappropriate compensatory behaviors, such as fasting or excessive exercise, but has not regularly engaged in self-induced vomiting or the misuse of laxatives, diuretics, or enemas

*Id.* at 594. The DSM-IV-TR lists the following research criteria for BED:

A. Recurrent episodes of binge eating. An episode of binge eating is characterized by both of the following:

(1) eating, in a discrete period of time (e.g., within any 2-hour period), an amount of food that is definitely larger than most people would eat in a similar period of time under similar circumstances

(2) a sense of lack of control over eating during the episode (e.g., a feeling that one cannot stop eating or control what or how much one is eating)

B. The binge-eating episodes are associated with three (or more) of the following:

(1) eating much more rapidly than normal
(2) eating until feeling uncomfortably full
(3) eating large amounts of food when not feeling physically hungry
(4) eating alone because of being embarrassed by how much

one is eating

(5) feeling disgusted with oneself, depressed, or very guilty after overeating

C. Marked distress regarding binge eating is present.

D. The binge eating occurs, on average, at least 2 days a week for 6 months.

**Note:** The method of determining frequency differs from that used for Bulimia Nervosa; future research should address whether the preferred method of setting a frequency threshold is counting the number of days on which binges occur or counting the number of episodes of binge eating.

E. The binge eating is not associated with the regular use of inappropriate compensatory behaviors (e.g., purging, fasting, excessive exercise) and does not occur exclusively during the course of Anorexia Nervosa or Bulimia Nervosa.

*Id.* at 787; *see also* Ex. 1001, 4:46–5:5 (citing the DSM-IV-TR in describing BED).

Dr. Brewerton cites an article entitled "Pharmacotherapy for Obesity," by Ioannides-Demos (Ex. 1011) in support of his testimony that "[e]ating disorders have been linked to the dysfunction of three primary neurotransmitter (NT) systems found in the brain, namely serotonin (5-HT), dopamine (DA), and norepinephrine (NE)." Ex. 1009 ¶ 51. Dr. Brewerton also cites Ioannides-Demos in support of his testimony that "amphetamine blocks DA reuptake on post-synaptic receptors, which increases the levels of DA in the synaptic cleft and reinforces the suppression of hunger." *Id.* at 26, ¶ 56. Ioannides-Demos discloses that "[m]ost medications prescribed for obesity regulate satiety through an effect on serotonergic, noradrenergic or dopaminergic receptor systems in the hypothalamus[,] . . . lead[ing] to reduced appetite or hunger and, thus, decreased food-seeking behaviour." Ex. 1011, 1394 (citations omitted). According to the

DSM-IV-TR, "[s]imple obesity is included in the International Classification of Diseases (ICD) as a general medical condition but does not appear in DSM-IV because it has not been established that it is consistently associated with a psychological or behavioral syndrome." Ex. 1010, 583. Dr. Brewerton cites Drimmer (Ex. 1016), which describes studies of BN patients, in support of his testimony that "[s]timulants that can increase the dopaminergic and noradrenergic tone in the brain may help reduce food cravings." Ex. 1009 ¶ 56. Dr. Brewerton testified that BED is listed in the EDNOS category because it does not meet the DSM-IV-TR criteria for a specific eating disorder, Ex. 1009 ¶ 33, e.g., BN.

Dr. Brewerton testified that as early as 1983, centrally acting psychostimulants had been successfully used to treat binge eating. Ex. 1009 ¶ 39. In support of this statement, Dr. Brewerton cites the published case studies of Ong (Ex. 1017), Messner (Ex. 1041), Schweickert (Ex. 1042), Sokol (Ex. 1018), Drimmer (Ex. 1016), and Dukarm (Ex. 1019). *Id.* at 19–21, ¶¶ 39–45. The cited publications report decreases in binge eating in BN patients through the use of methylamphetamine (Ex. 1017), methylphenidate (Exs. 1041, 1042, 1018, 1016), d-amphetamine (Exs. 1016, 1019), and mixed amphetamine salts (Ex. 1016). *See* Ex. 1016, 77; Ex. 1017, 288; Ex. 1018, 233, Abstract; Ex. 1019, 345, Abstract; Ex. 1041, 824, Abstract; Ex. 1042, 299.

## V. ANALYSIS

Independent claims 1, 8, and 13 recite methods for treating BED comprising administering a therapeutically effective amount of lisdexamfetamine dimesylate to a patient.

*A. Asserted obviousness of claims 1–5, 8–10, 12, and 13 over Appolinario in view of Mickle*

*1. Appolinario (Ex. 1020)*

Appolinario is a 2004 publication reviewing "available pharmacological treatment studies of BED and related conditions." Ex. 1020, 301 (Abstract). Appolinario states: "it is important to point out that the mechanism of action of pharmacological agents on BED is unknown." *Id.* at 305, col. 1. Appolinario notes that "[a]lthough the diagnosis of BED is not linked to weight, it is associated with overweight and obesity. Thus, many persons seeking treatment for BED are overweight or obese." *Id.*, col. 2.

According to Appolinario, "there are three classes of drugs with potential for use in the treatment of BED: antidepressants, anti-obesity agents, and anticonvulsants." *Id.* at 306, col. 1. Appolinario discloses that

> antidepressants are the best studied class of agents in BED, and SSRIs represent the best studied class of antidepressants in this condition. The use of SSRIs in BED has been associated with a modest but clinically significant and consistent decrease in binge eating behavior and weight over periods ranging from six to nine weeks.

*Id.* at 306, col. 1. Appolinario also discloses that the anti-obesity agents d-fenfluramine and sibutramine have been used successfully in the treatment of BED. *Id.* at 303, col. 1.

According to Appolinario, d-fenfluramine was found to promote binge-eating suppression in patients with BED and obesity. *Id.* However, although d-fenfluramine provided a high rate of remission of binge eating, a reduction in body weight was not observed. *Id.* Appolinario notes that d-fenfluramine was withdrawn from the market due to its association with cardiac valve lesions and pulmonary hypertension. *Id.*

Appolinario discloses that "[s]ibutramine is a serotonin [(5-HT)] and noradrenaline reuptake inhibitor (SNRI)" and, unlike d-fenfluramine, "does not induce serotonin release, and has not been implicated in the development of valvular heart disease." *Id.* Appolinario notes sibutramine's "efficacy for inducing initial weight-loss and subsequent weight maintenance in obesity is well proven in short and long-term clinical trials." *Id.* According to Appolinario, in a randomized controlled trial, "[t]reatment of BED with sibutramine addressed the three main aspects of the syndrome: abnormal eating behavior, overweight, and associated depressive symptoms." *Id.* "The most frequently described adverse effects with sibutramine (dry mouth and constipation) were mild and benign." *Id.* at 303, col. 1.

*2. Mickle (Ex. 1023)*

Mickle describes abuse-resistant amphetamine prodrugs for treating a patient having "any disease that may benefit from amphetamine-type drugs." Ex. 1023 ¶ 124. Mickle states that "[p]referred indications include ADD, ADHD, narcolepsy, and obesity, with ADHD being most preferred." *Id.* The amphetamine prodrugs comprise a chemical moiety covalently attached to an amphetamine, which can be any of the sympathomimetic phenethylamine derivatives which have central nervous system stimulant activity, including d-amphetamine, methamphetamine, and methylphenidate. *Id*. ¶¶ 85, 96–97.

The amphetamine prodrugs are said to be abuse-resistant, because they remain inactive until oral administration releases the amphetamine from the chemical moiety, and exhibit reduced bioavailability when administered via parenteral routes often employed by abusers. *Id*. ¶¶ 114, 118. Mickle discloses that "[a]mphetamines stimulate the central nervous system (CNS)," *id*. ¶ 3, and "it is believed that the amphetamine prodrug is inactive because the attachment of the

chemical moiety reduces binding between the amphetamine and its biological target sites (e.g., human dopamine ('DAT') and norepinephrine ('NET') transporter sites)," *id.* ¶ 118.

Mickle describes a clinical evaluation in which the pharmacokinetics and oral bioavailability of the abuse-resistant prodrug L-lysine-d-amphetamine dimesylate was compared to the amphetamine extended release products Adderall XR® and Dexedrine Spansule®, used in the treatment of ADHD. *Id.* ¶¶ 338–347 (Example 33). According to Mickle, "[o]ver the course of twelve hours, typically the time needed for effective once-daily treatment of ADHD, the bioavailability for L-lysine-d-amphetamine was approximately equivalent to that of Adderall XR® [(a mixture of d-amphetamine and l-amphetamine salts (equal amounts of d-amphetamine sulfate, d-/l-amphetamine sulfate, d-amphetamine saccharate, and d-/l-amphetamineaspartate))] and over twenty percent higher than that of Dexedrine Spansule®." *Id.* ¶ 341. Based on the results of the clinical testing, Mickle concluded "L-lysine-d-amphetamine would be an effective once-daily treatment for ADHD." *Id.*

*3. Analysis*

Petitioner contends one of ordinary skill in the art at the time of the invention would have recognized from Appolinaro that d-fenfluramine and sibutramine can be used successfully to treat BED. Pet. 14. Petitioner further contends the ordinary artisan would have understood that d-fenfluramine and sibutramine act on the central nervous system by impacting neurotransmitters (NTs) responsible for hunger and satiety, and would have expected other centrally acting anti-obesity agents to be useful in the treatment of BED. *Id.* at 14–15. Petitioner maintains the ordinary artisan would have been aware from Appolinaro that d-fenfluramine was withdrawn from the market due to cardiopulmonary risks

and that sibutramine had limited effectiveness in achieving remission from binge eating. *Id.* at 15 (noting Appolinario reports "the net difference in the percentage of patients with remission from binge eating at the end of the trial was only 20%"). Petitioner argues one of ordinary skill in the art would have been motivated to find alternative centrally acting anti-obesity agents to treat BED due to the limitations of d-fenfluramine and sibutramine. *Id.* at 17. Petitioner contends one of ordinary skill in the art would have been motivated to use LDX dimesylate to treat BED, and would have had a reasonable expectation of success in so doing, based on Mickle's disclosure that LDX dimesylate is an anti-obesity agent, and that d-amphetamine increases NE and DA levels in the brain, which would address what is believed to be the main dysfunction in BED, namely, low levels of NTs. *Id.* at 16–17.

Patent Owner disagrees with Petitioner's contention that one of ordinary skill in the art would have understood from Appolinario that any compound which acts on the NTs responsible for hunger and satiety would be useful in treating BED. Prelim. Resp. 20. Patent Owner concedes the ordinary artisan would have had some expectation that drugs which act by raising 5-HT levels would be effective in treating BED, based on Appolinario's disclosure that SSRI antidepressants, and fenfluramine, and sibutramine, all of which increase 5-HT, are effective in treating BED. *Id*. at 21. However, Patent Owner argues one of ordinary skill in the art would not have assumed that because sibutramine, a 5-HT and NE reuptake inhibitor, is effective in treating BED, LDX dimesylate, which raises NE and DA levels, also would be effective in treating BED. *Id.* (noting "Appolinario does not provide data or analysis of the effects of drugs that raise DA and NE levels, but do not affect 5-HT levels"). Patent Owner further contends the ordinary artisan would not have assumed from reading Mickle that all of the

disclosed inventive amphetamine prodrugs are anti-obesity agents. *Id*. at 18. Patent Owner argues the ordinary artisan would have first turned "to the VYVANSE (LDX dimesylate) prescribing information (Ex. 2008)" and would have concluded, based on the lack of clinical data for treating obesity, that LDX dimesylate would not be useful as an anti-obesity agent. *Id.*

We agree with Patent Owner that the evidence relied on by Petitioner does not support Petitioner's contention that one of ordinary skill in the art would have been motivated to use LDX dimesylate to treat BED based on the combined teachings of Appolinario and Mickle. Even assuming Petitioner is correct in stating that one of ordinary skill in the art would have understood from Mickle that LDX dimesylate is an anti-obesity agent, the evidence is insufficient to support its contention that the ordinary artisan would have assumed that LDX dimesylate would have been effective in treating BED. As argued by Patent Owner, Appolinario's disclosure of anti-obesity agents effective in treating BED is limited to fenfluramine and sibutramine. Fenfluramine and sibutramine, like the antidepressants described by Appolinario as effective in treating BED, impact 5-HT levels. By contrast, LDX dimesylate affects DA and NE levels. Ex. 1023 ¶ 118. Petitioner has not directed us to persuasive evidence which establishes that one of ordinary skill in the art would have expected an anti-obesity agent which does not affect 5-HT levels, e.g. LDX dimesylate, to be effective in treating BED.

In this regard, we note Petitioner relies on Dr. Brewerton's testimony that a person having ordinary skill in the art would have expected LDX dimesylate to be effective in treating BED because such person would have known that "d-amphetamine increases NE and DA levels in the brain, which would address what is believed to be the main dysfunction in BED, namely, low levels of NTs." Pet. 14–15 (citing Ex. 1009 ¶ 56). Petitioner's statement is not, however, supported by

paragraph 56 of the Brewerton Declaration, wherein Dr. Brewerton states that abnormally low levels of NTs in the brain are believed to be a main dysfunction in BED, but does not identify evidence which directly supports Petitioner's contention that a person of ordinary skill in the art as of September 13, 2007, would have understood that low levels of the specific neurotransmitters NE and DA are a main dysfunction in BED. *See* Ex. 1009 ¶ 56 (citing Ex. 1011, discussing pharmacotherapy for the management of obesity, and Ex. 1012, relating to studies involving BN patients) and Ex. 1010 (noting that simple obesity has not been consistently associated with a psychological or behavioral syndrome), discussed above in Section IV.B; *compare* Ex. 1010 (criteria B. (3), indicating a binge-eating episode in BED may be associated with eating large amounts of food even when not feeling physically hungry) *with* Ex. 1009 ¶ 56 (stating that the effect of amphetamines on levels of DA may reinforce suppression of hunger and that the increase in dopaminergic and noradrenergic tone in the brain may reduce food cravings). Moreover, Petitioner's statement is contradicted by Appolinario's disclosure that "the mechanism of action of pharmacological agents on BED is unknown." Ex. 1020, 305, col. 1. In addition, there is no persuasive evidence to support Petitioner's contention that one of ordinary skill in the art reasonably would have assumed that LDX dimesylate would have been more effective and/or had fewer drawbacks than sibutramine in treating BED.

As noted by Patent Owner, Mickle's disclosure is devoid of any data or testing showing the efficacy of LDX dimesylate, or any other amphetamine prodrug, as an anti-obesity agent or treatment for BED. Prelim. Resp. 23. Further, as argued by Patent Owner, LDX dimesylate is a Schedule II drug, and there is no evidence that one of ordinary skill in the art would have considered a Schedule II drug a more desirable alternative to sibutramine, the side effects of which were

considered mild and benign. *See* Ex. 1020, 303, col. 1.

In sum, Petitioner has not provided sufficient articulated reasoning with rational underpinning as to why the ordinary artisan, at the time of the invention, would have had a reason to combine the teachings of Appolinario and Mickle in the manner required by claims 1–5, 8–10, 12, and 13, or how one would have done so with a reasonable expectation of success. Therefore, Petitioner has not established a reasonable likelihood that it would prevail in showing the unpatentability of claims 1–5, 8–10, 12, and 13 based on the combined teachings of Appolinario and Mickle.

*B. Asserted obviousness of claims 1–5, 8–10, 12, and 13 over Ong in view of Mickle and DSM-IV-TR*

*1. Ong (Ex. 1017)*

Ong describes a study in which eight patients with BN were given methylamphetamine or a placebo intravenously. Ex. 1017, Summary. Ong reports methylamphetamine, a stimulant, reduced self-ratings of hunger and quantity of food ingested by the study patients. *Id.* at 292, col. 2.

*2. Analysis*

Petitioner contends one of ordinary skill would have recognized from DSM-IV-TR that BN and BED display many overlapping characteristics. *See* Pet. 27. Petitioner notes, for example, that BN and BED share the features of "recurrent episodes of binge eating (eating a definitely large amount of food in a short period of time) associated with indicators of impaired control over, and significant distress about, the binge eating." *Id.* Petitioner maintains that "[s]ince Ong discloses that methylamphetamine administered to [test] patients resulted in suppression of the bulimic or binge eating symptoms, a POSA would have had a reasonable expectation of success in treating BED with methylamphetamine." *Id.*

at 28. In further support of this contention, Petitioner cites paragraphs 39–45 of the Brewerton Declaration, wherein Dr. Brewerton testified that, prior to September 13, 2007, several publications had described the successful use of stimulants to treat binge eating in BN patients. *Id.*; Ex. 1009 ¶¶ 39–45 (citing Messner (Ex. 1041), Schweicker (Ex. 1042), Sokol (Ex. 1018), Drimmer (Ex. 1016), and Dukarm (Ex. 1019)).

Petitioner notes Ong cautions that "drugs with stimulant and euphoric effects carry the dangers of dependence and drug induced psychosis." Pet. 28 (quoting Ex. 1017, 292, col. 2). Petitioner contends that, given this precaution, the ordinary artisan would have been motivated to use LDX dimesylate to treat BED in view of Mickle's teaching that LDX dimesylate is an amphetamine prodrug that has the beneficial pharmacological properties of amphetamines, but without the associated abuse liability. *Id.* at 28–29 (citing Ex. 1023, ¶ 114).

Patent Owner argues one of ordinary skill in the art would have understood from Ong that the binge eating symptom of BN is inextricably linked to compensatory behavior, and would not have expected a drug which treats BN to have efficacy in treating BED, defined by the absence of inappropriate compensatory behavior. Prelim. Resp. 26–28. Patent Owner further argues a POSA reading Ong would not have known whether methylamphetamine is useful for treating the symptom of binge eating in BN or BED because the Ong study did not go beyond a single dose administration and, therefore, it is unclear from Ong whether methylamphetamine would be effective in controlling recurrent episodes of binge eating, which are a characteristic of both BN and BED. *Id.* at 29–30.

Ong reports that methylamphetamine reduced the quantity of food ingested by BN study patients, Ex. 1017, 292, col. 2, i.e., it reduced binge eating behavior in the BN study patients, *see* Ex. 1010, 589 ("A *binge* is defined as eating in a

discrete period of time an amount of food that is definitely larger than most individuals would eat under similar circumstances."). The DSM-IV-TR's reference to the text for BN for the characteristics of a binge eating episode in BED, *see* Ex. 1010, 785 ("The characteristics of a binge episode are discussed in the text for Bulimia Nervosa (p. 589)"), supports Petitioner's contention that the ordinary artisan would have had a reasonable basis for concluding the same drug Ong used to successfully treat binge eating behavior in a BN patient could also be used to successfully treat binge eating behavior in a BED patient.

The numerous publications cited and discussed by Dr. Brewerton in connection with his testimony as to the state of the art prior to September 13, 2007, *see* Ex. 1009 ¶¶ 39–45 (citing Messner (Ex. 1041), Schweicker (Ex. 1042), Sokol (Ex. 1018), Drimmer (Ex. 1016), and Dukarm (Ex. 1019)), support Petitioner's contention that the ordinary artisan would also have been aware of other studies showing the successful use of stimulants to treat the binge eating behavior in BN patients. Pet. 28. For example, Schweickert discloses a patient with comorbid ADHD and BN reported "a complete cessation of her eating binges" when treated with methylphenidate. Ex. 1042, 300. Similarly Drimmer describes a patient who "was more easily satiated and ate only when hungry" when treated with dextroamphetamine sulfate (Dexedrine). Ex. 1016, 76, col. 3.

Patent Owner also argues "Ong at least suggests that" Mickle's amphetamine prodrugs "would not work in the treatment of BN" because they do not produce a euphoric effect. Prelim. Resp. 33. This argument is not supported by Ong, which explains that either the euphoriant effects or the anorectic effects of methylamphetamine may be responsible for its effectiveness in treating bulimic overeating. Ex. 1017, 292, col. 2. Moreover, this argument contradicts Patent Owner's argument that the ordinary artisan would not have expected VYVANSE

to have reduced abuse potential because it was labelled as a Schedule II drug, which is defined by the U.S. Controlled Substances Act as a drug that has a high potential for abuse. *See* Prelim. Resp. 34–35; *cf.* Ex. 1023 ¶ 114 (indicating the euphoric effects of amphetamines create a potential for abuse).

Based on the information presented at this stage of the proceeding, we are persuaded there is a reasonable likelihood Petitioner would prevail in showing independent claims 1, 8, and 13 would have been obvious over Ong in view of Mickle and DSM-IV-TR. Patent Owner has not yet disputed Petitioner's specific contentions with respect to the dependent claims. *See generally*, Prelim. Resp. 24–35. Petitioner has provided claim charts demonstrating where the additional limitations of the dependent claims are described in the references. *See* Pet. 32–37. Therefore, on this record, we also are persuaded there is a reasonable likelihood Petitioner would prevail in showing claims 2–5, 9, 10, and 12 are obvious over Ong in view of Mickle and DSM-IV-TR.

*C. Asserted obviousness of claims 1–5, 8–10, 12, and 13 over Dukarm in view of Mickle and DSM-IV-TR*

*1. Dukarm (Ex. 1019)*

Dukarm is a case report published in 2005 describing a study in which six patients with comorbid BN and ADHD were treated with dextroamphetamine. Ex. 1019, Abstract. The results of the study were that all six patients "reported complete abstinence from binge eating and purging after treatment with psychostimulants, and none of the patients discontinued taking the medication because of side effects. The side effect of decreased appetite proved beneficial in decreasing the desire to binge eat. However, all 6 patients remained within a healthy weight range." *Id.* According to Dukarm, BN and ADHD "share several key features, including impulsivity (lack of impulse control) and low self-esteem."

*Id.* at 345, col. 1. Dukarm notes that prior to the study, it was known that dextroamphetamine was highly effective in treating ADHD, and that antidepressants, such as SSRIs, showed only partial resolution of bulimic symptoms.

*2. Analysis*

Petitioner contends that "[g]iven the teachings of DSM-IV-TR, a POSA would have understood that the characteristics of binge eating episodes in BN and BED are essentially the same." Pet. 40. Petitioner argues "since Dukarm discloses that d-amphetamine administered to patients with BN resulted in abstinence from binge eating, a POSA would have had a reasonable expectation of success in treating BED with d-amphetamine." *Id.* at 40–41. Petitioner notes Mickle teaches that following oral administration of LDX dimesylate, d-amphetamine, the same active ingredient used in the Dukarm study, is released. *Id.* at 41. Petitioner contends the ordinary artisan would have been motivated to use LDX dimesylate to treat BED based on Mickle's teaching that amphetamine prodrugs reduce the euphoric effects associated with amphetamine abuse. *Id.*

Similar to its response to Petitioner's challenge based on obviousness over Ong in view of Mickle and DSM-IV-TR, Patent Owner argues Dukarm's successful treatment of BN with d-amphetamine would not have motivated one of ordinary skill in the art to treat BED with d-amphetamine because "DSM-IV-TR provides that BN and BED are distinct diseases." Prelim. Resp. 41. This argument is not persuasive for the reasons discussed above in Section V.B.2. Patent Owner concedes Dukarm raises concerns about "potential for misuse of stimulant medication by individuals with eating disorders in an attempt at further weight loss," Prelim. Resp. 42 (quoting Ex. 1019, 349, col. 1), but argues that one of ordinary skill in the art would not have been motivated to use LDX dimesylate

based on Mickle's disclosure that amphetamine prodrugs reduce the euphoric effects associated with amphetamine abuse. *Id.* Patent Owner contends "[a]buse of stimulants for weight loss is a different mechanism of abuse than euphoria seeking," and one of ordinary skill in the art would have realized "that the lower abuse potential of LDX dimesylate for ADHD patients may not translate to reduced abuse for eating disorder patients." *Id.* at 42–43. Patent Owner's argument is not convincing because it is not supported by expert testimony or other persuasive evidence.

Patent Owner argues we should deny *inter partes* review based on this ground because Patent Owner overcame the same arguments made during prosecution of the '813 patent. Prelim. Resp. 37. Patent Owner contends the Examiner considered U.S. Application Publication 2005/0038121 A1 (Ex. 2006) and a patent which claim priority to the same provisional as Mickle. Prelim. Resp. 14; *see also id.* at 38 (noting Mickle is a continuation-in-part of U.S. Application Publication 2005/0038121 A1). Patent Owner argues the Examiner "rejected claims over Dukarm in view of American Heritage Medical Dictionary in view of [U.S. Application Publication 2005/0038121 A1]" and "mentioned DSM-IV's description of binge eating disorder" in the rejection. Prelim. Resp. 38.

In determining whether to institute an *inter partes* review, we may take into account whether "the same or substantially the same prior art or arguments previously were presented to the Office." 35 U.S.C. § 325(d). In the above-cited rejection, Ex. 1003, 4–7, the Examiner did not rely on the DSM-IV-TR, noting that the claims did not limit binge eating disorder to the DSM-IV-TR classification. *See id.* at 5. As the '813 patent claims explicitly recite "Binge Eating Disorder as defined in the DSM -IV-TR," Ex. 1001, claims 1, 8, 13, and Petitioner relies on DSM-IV-TR in its challenge, we are not convinced that the same or substantially

the same prior art or arguments were previously presented to the Office, and we thus decline to exercise our discretion under 35 U.S.C. § 325(d) to not institute *inter partes* review of the '813 patent on that basis.

In sum, based on the information presented at this stage of the proceeding, we are persuaded there is a reasonable likelihood Petitioner would prevail in showing independent claims 1, 8, and 13 are obvious over Dukarm in view of Mickle and DSM-IV-TR. Patent Owner has not yet disputed Petitioner's specific contentions with respect to the dependent claims. *See generally*, Prelim. Resp. 36–43. Petitioner has provided claim charts demonstrating where the additional limitations of the dependent claims are described in the references. *See* Pet. 44–49. Therefore, on this record, we are also persuaded there is a reasonable likelihood Petitioner would prevail in showing claims 2–5, 9, 10, and 12 are obvious over Dukarm in view of Mickle and DSM-IV-TR.

*D. Asserted obviousness of claims 6 and 7 over Mickle, Marrazzi and (1) Appolinario, (2) Ong and DSM-IV-TR, or (3) Dukarm and DSM-IV-TR; and*

*Obviousness of claim 11 over Mickle, Grilo and (1) Appolinario, (2) Ong and DSM-IV-TR, or (3) Dukarm and DSM-IV-TR*

As explained above, Petitioner has not provided sufficient articulated reasoning with rational underpinning as to why the ordinary artisan, at the time of the invention, would have had a reason to combine the teachings of Appolinario and Mickle in the manner required by independent claims 1–5, 8–10, 12, and 13, or how one would have done so with a reasonable expectation of success. Likewise, Petitioner does not explain adequately how Marrazzi or Grilo might have provided such a reason. *See* Pet. 24–26. Therefore, Petitioner has not demonstrated a reasonable likelihood it would prevail on the ground that claims 6 and 7 are unpatentable over Appolinario, Mickle, and Marrazzi, or on the ground that claim

11 is unpatentable over Appolinario, Mickle, and Grilo.

Patent Owner has not yet disputed Petitioner's specific contentions with respect to the challenges of claims 6 and 7 based on Mickle, DSM-IV-TR, Marrazzi, and either Ong or Dukarm, and claim 11 based on Mickle, DSM-IV-TR, Grilo, and either Ong or Dukarm. *See* Prelim. Resp. 15 ("In this response we do not comment on Marazzi or Grilo, the references relied upon [in] Grounds 2-3, 5-6, and 8-9. Rather we show Grounds 1, 4, and 7 are flawed and cannot render the independent claims obvious."). Petitioner has provided claim charts demonstrating where the additional limitations of the dependent claims are described in Marrazzi and Grilo. *See* Pet. 37–39; 50–52. On this record, we are persuaded there is a reasonable likelihood Petitioner would prevail in showing claims 6 and 7 are unpatentable over Mickle, DSM-IV-TR, Marrazzi, and either Ong or Dukarm, and in showing claim 11 is unpatentable over Mickle, DSM-IV-TR, Grilo, and either Ong or Dukarm.

## VI. CONCLUSION

Petitioner has demonstrated a reasonable likelihood that it would prevail on the grounds that claims 1–5, 8–10, 12, and 13 would have been obvious over: (1) Ong, DSM-IV-TR, and Mickle; and (2) Dukarm, DSM-IV-TR, and Mickle. Petitioner has also demonstrated a reasonable likelihood that it would prevail on the grounds that claims 6 and 7 would have been obvious over the same groups of references in view of Marrazzi, and claim 11 would have been obvious over the same groups of references in view of Grilo.

At this stage of the proceeding, the Board has not made a final determination as to the patentability of any challenged claim.

## VII. ORDER

For the reasons given, it is

ORDERED that, pursuant to 35 U.S.C. § 314(a), *inter partes* review of the '813 patent is instituted on the following grounds:

1) claims 1–5, 8–10, 12, and 13 based on obviousness over Ong, DSM-IV-TR, and Mickle;

2) claims 1–5, 8–10, 12, and 13 based on obviousness over Dukarm, DSM-IV-TR, and Mickle;

3) claims 6 and 7 based on obviousness over Ong, DSM-IV-TR, Mickle, and Marrazzi;

4) claims 6 and 7 based on obviousness over Dukarm, DSM-IV-TR, Mickle, and Marrazzi;

5) claim 11 based on obviousness over Ong, DSM-IV-TR, Mickle, and Grilo; and

6) claim 11 based on obviousness over Dukarm, DSM-IV-TR, Mickle, and Grilo.

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(a), *inter partes* review of the '813 patent is hereby instituted commencing on the entry date of this Order, and pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial.

FURTHER ORDERED that all other grounds raised in the Petition are denied, and no ground other than those specifically granted above is authorized for the *inter partes* review.

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