IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SHIRE DEVELOPMENT LLC
Petitioner
v.
LCS GROUP, LLC
Patent Owner

U.S. Patent No. 8,318,813 to Sanfilippo
Issue Date: November 27, 2012
Title: Method of Treating Binge Eating Disorder

Inter Partes Review

Declaration of Dr. Timothy D. Brewerton

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I, Timothy David Brewerton, do hereby declare as follows:

I. INTRODUCTION

1. I have been retained as an expert witness on behalf of the petitioner Shire Development LLC ("Petitioner") in connection with the above-captioned *inter partes* review (IPR) petition. I understand that the IPR petition involves U.S. Patent No. 8,318,813 ("the '813 patent") (Ex.1001). I have been informed by counsel for the Petitioner ("counsel") that the sole inventor of the '813 patent is Louis Sanfilippo and that the patent is currently assigned to LCS Group, LLC. I have been engaged to opine on certain matters regarding the '813 patent. Specifically, I have been asked to determine whether claims 1-13 of the '813 patent would have been obvious in light of the prior art. I am being compensated for my time in this matter at my standard consulting rate, which is $350 per hour.

II. BACKGROUND, EXPERIENCE, AND QUALIFICATIONS

2. I am an expert in the field of eating disorders and related comorbidities, including their associated neurobiology and psychopharmacology, and I have been an expert in this field at least since 1987. Beginning in 1974, when I entered medical school, I have accumulated significant training and experience in this and related fields. Throughout the remainder of this declaration, I will refer to the field of eating disorders and related comorbidities, including their associated neurobiology and psychopharmacology, as the "relevant field." In

formulating my opinions, I have relied upon my training, knowledge, and experience in the relevant field. A copy of my current curriculum vitae is provided as Exhibit 1034, and it provides a comprehensive description of my academic and employment history.

3. As an expert in the field, I am qualified to provide an opinion as to what a person of ordinary skill in the art ("POSA") would have understood, known or concluded as of September 13, 2007, which counsel has informed me is the date of the invention. (*See* Ex.1001, '813 patent, cover page).

4. I received a B.Sc. from Louisiana State University in Baton Rouge, LA in 1974.

5. I received an M.D. from Tulane University School of Medicine in New Orleans, LA in 1978.

6. I completed my internship and residency training in psychiatry at the University of California at San Francisco Hospitals and Clinics in 1982.

7. After completing my residency, I held an appointment as Assistant Clinical Professor of Psychiatry at the University of Hawaii in Honolulu, HI. I worked as Staff Psychiatrist and Senior Staff Psychiatrist at Hawaii State Hospital in Kaneohe, HI as part of my debt to the U. S. Public Health Service, National Health Service Corps.

8. From 1984 to 1987 I was a Medical Staff Fellow at the National Institute of Mental Health (NIMH) in the Laboratory of Clinical Science, Section on Biomedical Psychiatry in Bethesda, MD. During this time I worked on the NIMH Eating Disorders Inpatient Program, was Coordinator of the Eating Disorders Outpatient Clinic, and was involved in multiple research protocols studying the neurobiology and psychopharmacology of eating disorders.

9. In 1987, I joined the faculty of the Medical University of South Carolina (MUSC) in Charleston, SC as Assistant Professor of Psychiatry and Behavioral Sciences and as Director and Founder of the Eating Disorders Program at the Institute of Psychiatry.

10. During my time at MUSC, I advanced in rank to Associate Professor (1990) and then to full Professor (1997) with tenure (1999). I remain at MUSC as Clinical Professor.

11. I am Board Certified by the American Board of Psychiatry and Neurology in General Psychiatry (1984), Child and Adolescent Psychiatry (1996, recertified 2006), and Forensic Psychiatry (1998, recertified 2008).

12. Throughout my career I have 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"). I have

treated these patients in inpatient, residential, partial hospital, and outpatient settings. Furthermore, I have supervised or consulted with many professionals across several disciplines about the diagnosis and treatment of eating disorders and related comorbidities, including BED.

13. My accomplishments in the relevant field have been widely recognized. For example, I was endowed as a Distinguished Fellow of the American Psychiatric Association, a Distinguished Fellow of the American Academy of Child and Adolescent Psychiatry, and a Founding Fellow of the Academy of Eating Disorders. I have also been an active member of a number of other professional organizations throughout my career.

14. I am a past president of the Eating Disorders Research Society and the South Carolina Psychiatric Association, and a former member of the Board of Directors of the Academy of Eating Disorders.

15. I have co-authored over 125 peer-reviewed publications and book chapters on various topics in psychiatry, particularly in the relevant field.

16. In addition to gaining expertise via my educational training, professional experiences, and research experiences described above, I have kept abreast of the relevant field by reading scientific literature, attending or presenting at scientific conferences, and attending or presenting at academic symposia.

17. In addition to writing and publishing numerous scientific articles as listed in my current curriculum vitae (Ex.1034, Brewerton CV, pp.42-50), I have been invited to participate in the peer review process for at least 36 scientific journals in which I have reviewed manuscripts submitted by other scientists relating to the relevant field. Some of the scientific journals for which I have reviewed manuscript submissions include: *American Journal of Psychiatry, Annals of Clinical Psychiatry, Archives of General Psychiatry, Appetite, Behavioral and Brain Sciences, Behaviour Research and Therapy, Biological Psychiatry, British Journal of Medical Psychology, CNS Spectrums, Comprehensive Psychiatry, Drug Metabolism and Drug Interactions, Eating and Weight Disorders, European Eating Disorders Review, Expert Opinion in Investigational Drugs, Harvard Review of Psychiatry, Human Psychopharmacology, International Journal of Neuropsychopharmacology, International Journal of Neuroscience, Journal of Clinical Psychiatry, Journal of Consulting and Clinical Psychology, Journal of Pediatrics, Journal of Psychiatric Practice, Journal of Psychiatric Research, Journal of Psychiatry and Neuroscience, Journal of Psychosomatic Research, Journal of the American Academy of Child and Adolescent Psychiatry, Journal of the American College of Nutrition, Journal of Women's Health, Molecular Psychiatry, Neuropsychiatric Genetics, Neuropsychiatry, Neuropsychopharmacology, Neuroscience & Biobehavioral Reviews, New*

England Journal of Medicine, Obesity Research, Psychiatry Research, Psychological Medicine, and *Psychosomatic Medicine.*

18. Further, I have served on the Editorial Boards of several scientific journals, including the *International Journal of Eating Disorders* (1998-present), *Eating Disorders: The Journal of Treatment and Prevention* (1996-present), *Current Food and Nutrition Science* (2004-present), and the *Annals of Clinical Psychiatry* (1993-2004).

19. I have edited or co-edited two books on eating disorders, including the "*Clinical Handbook for Eating Disorders: An Integrated Approach*" (2004), and "*Eating Disorders, Substance Use Disorders and Addictions: Research, Clinical and Treatment Aspects*" (2014).

20. I have received numerous awards recognizing my accomplishments in the relevant field, including the 2013 *Craig Johnson Award for Clinical Practice and Training* by the National Eating Disorders Association, the *Honorary Certified Eating Disorder Specialist* award by the International Association of Eating Disorder Specialists, *Best Doctors in America*, *America's Top Psychiatrists, Who's Who in America*, *Who's Who in the World*, and numerous teaching awards.

21. Furthermore, I have collaborated with or have communicated with many of the researchers in the relevant field. Accordingly, I am a recognized expert in the relevant field.

22. As an expert in the relevant field, I am qualified to provide an opinion as to what a POSA would have understood, known, or concluded as of 2007 regarding issues in the relevant field.

III. BASIS AND SUMMARY OF OPINIONS

A. List of Documents Considered in Forming My Opinions

23. In preparing this declaration, I have considered the exhibits listed in the table below.

Exhibit Number	Exhibit Name
1001	U.S. Patent No. 8,318,813 to Sanfilippo. ("'813 patent")
1002	Prosecution History of U.S. Patent No. 8,318,813 (certified) obtained from the U.S. Patent and Trademark Office. ("'813 PH")
1003	July 21, 2011 Office Action for U.S. Application Serial No. 12/666,460. ("July 2011 OA")
1004	January 23, 2012 Response to Office Action for U.S. Application Serial No. 12/666,460. ("Jan. 2012 Resp.")
1005	April 18, 2012 Final Office Action for U.S. Application Serial No. 12/666,460. ("Apr. 2012 OA")
1006	June 18, 2012 Response to Final Office Action for U.S. Application Serial No. 12/666,460. ("June 2012 Resp.")
1007	June 21, 2012 Examiner-Initiated Interview Summary for U.S. Application Serial No. 12/666,460. ("June 2012 Int. Sum.")
1008	July 20, 2012 Notice of Allowance for U.S. Application Serial No. 12/666,460. ("July 2012 NOA")
1010	American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*. Washington, DC: American Psychiatric Association: 2000; 583-595, 785-787. ("DSM-IV-TR")

Exhibit Number	Exhibit Name
1011	Ioannides-Demos LL., et al., Pharmacotherapy for Obesity. *Drugs*. 2005; 65(10): 1391-1418. ("Ioannides-Demos")
1012	Jimerson DC, et al., Low Serotonin and Dopamine Metabolite Concentrations in Cerebrospinal Fluid From Bulimic Patients With Frequent Binge Episodes. *Arch. Gen. Psychiatry*. 1992; 49(2): 132-138. ("Jimerson")
1013	Epstein LH, et al., Dopamine Transporter Genotype as a Risk Factor for Obesity in African-American Smokers. *Obes. Res*. 2002; 10(12): 1232-1240. ("Epstein")
1014	Samanin R, et al., Neurochemical Mechanism of Action of Anorectic Drugs. *Pharmacol. Toxicol*. 1993; 73(2): 63-68. ("Samanin")
1015	Blundell JE, et al., Serotonin and Appetite Regulation: Implications for the Pharmacological Treatment of Obesity. *CNS Drugs*. 1998; 9(6): 473-495. ("Blundell")
1016	Drimmer EJ, Stimulant Treatment of Bulimia Nervosa With and Without Attention-Deficit Disorder: Three Case Reports. *Nutrition*. 2003; 19(1): 76-77. ("Drimmer")
1017	Ong YL, Suppression of Bulimic Symptoms with Methylamphetamine. *Brit. J. Psychiatry*. 1983; 143: 288-293. ("Ong")
1018	Sokol MS, et al., Methylphenidate Treatment for Bulimia Nervosa Associated with a Cluster B Personality Disorder. *Int. J. Eat. Disord*. 1999; 25(2): 233-237. ("Sokol")
1019	Dukarm CP, Bulimia Nervosa and Attention Deficit Hyperactivity Disorder: A Possible Role for Stimulant Medication. *J. Womens Health*. 2005; 14(4): 345-350. ("Dukarm")
1020	Appolinario JC, et al., Pharmacological Approaches in the Treatment of Binge Eating Disorder. *Curr. Drug Targets*. 2004; 5(3): 301-307. ("Appolinario")
1021	Appolinario JC, et al., An Open-Label Trial of Sibutramine in Obese Patients with Binge-Eating Disorder. *J. Clin. Psychiatry*. 2002; 63(1): 28-30. ("Appolinario 2002")

Exhibit Number	Exhibit Name
1022	Milano W, et al., Use of Sibutramine, an Inhibitor of the Reuptake of Serotonin and Noradrenaline, in the Treatment of Binge Eating Disorder: A Placebo-Controlled Study. *Adv. Ther*. 2005; 22(1): 25-31. ("Milano")
1023	U.S. Publication No. 2007/0042955 to Mickle et al. ("Mickle")
1024	Marrazzi MA, et al., Binge Eating Disorder: Response to Naltrexone. *Int. J. Obes*. 1995; 19(2): 143-145. ("Marrazzi")
1025	Grilo CM, et al., Reliability of the Eating Disorder Examination in Patients with Binge Eating Disorder. *Int. J. Eat. Disord*. 2004; 35(1): 80-85. ("Grilo")
1026	American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. Washington, DC: American Psychiatric Association: 1994; 545-550, 729-731. ("DSM-IV")
1027	Fairburn CG, et al., The Natural Course of Bulimia Nervosa and Binge Eating Disorder in Young Women. *Arch. Gen. Psychiatry*. 2000; 57(7): 659-665. ("Fairburn 2000")
1028	Fairburn CG, et al., Cognitive Behaviour Therapy for Eating Disorders: a "Transdiagnostic" Theory and Treatment. *Behav. Res. Ther.* 2003; 41: 509-528. ("Fairburn 2003")
1029	Grilo CM, et al., Efficacy of Cognitive Behavioral Therapy and Fluoxetine for the Treatment of Binge Eating Disorder: A Randomized Double-Blind Placebo-Controlled Comparison. *Biol. Psychiatry*. 2005; 57(3): 301-309. ("Grilo 2005")
1030	Arnold LM, et al., A Placebo-Controlled, Randomized Trial of Fluoxetine in the Treatment of Binge-Eating Disorder. *J. Clin. Psychiatry*. 2002; 63(11): 1028-1033. ("Arnold")
1031	American Psychiatric Association, *Practice Guideline for the Treatment of Patients with Eating Disorders, Third Ed*. 2006. ("Practice Guideline")

Exhibit Number	Exhibit Name
1032	National Institute for Clinical Excellence, *Eating Disorders: Core Interventions in the Treatment and Management of Anorexia Nervosa, Bulimia Nervosa, and Related Eating Disorders*. January 2004. ("NICE")
1034	Dr. Timothy D. Brewerton's Curriculum Vitae. ("Brewerton CV")
1035	McCarthy LP, et al., Revising Psychiatry's Charter Document DSM-IV. *Written Communication*. 1994; 11(2): 147-192. ("McCarthy")
1036	American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders, Third Edition*. Washington, DC: American Psychiatric Association. 1980; 67-71. ("DSM-III")
1037	Brewerton TD, Binge Eating Disorder: Diagnosis and Treatment Options. *CNS Drugs*. 1999; 11(5): 351-361. ("Brewerton")
1038	American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders, Third Edition-Revised*. Washington, DC: American Psychiatric Association: 1987; 65-71. ("DSM-III-R")
1039	Russell G, Bulimia Nervosa: An Ominous Variant of Anorexia Nervosa. *Psychol. Med*. 1979; 9(3): 429-448. ("Russell")
1040	Stunkard A, Eating Patterns and Obesity, *The Psychiatry Quarterly*. 1959; 33(1): 284-295. ("Stunkard 1959")
1041	Messner E, Methylphenidate Treatment of Bulimia Nervosa After Surgery. *Can. J. Psychiatry*. 1989; 34(8): 824-826. ("Messner")
1042	Schweickert LA, et al., Efficacy of Methylphenidate in Bulimia Nervosa Comorbid with Attention-Deficit Hyperactivity Disorder: A Case Report. *Int. J. Eat. Disord*. 1997; 21(3): 299-301. ("Schweikert")
1043	Hudson JI, et al., The Prevalence and Correlates of Eating Disorders in the National Comorbidity Survey Replication. *Biol. Psychiatry*. 2007; 61(3): 348-358. ("Hudson")

Exhibit Number	Exhibit Name
1044	Stunkard A, et al., d-Fenfluramine Treatment of Binge Eating Disorder. *Am. J. Psychiatry*. 1996; 153(11): 1455-1459. ("Stunkard 1996").
1045	Wilfley DE, et al., Efficacy of Sibutramine for the Treatment of Binge Eating Disorder: A Randomized Multicenter Placebo-Controlled Double-Blind Study. *Am. J. Psychiatry*. 2008; 165(1): 51-58. ("Wilfley")
1046	Appolinario JC, et al., A Randomized, Double-Blind, Placebo-Controlled Study of Sibutramine in the Treatment of Binge-Eating Disorder. *Arch. Gen. Psychiatry*. 2003; 60(11): 1109-1116. ("Appolinario 2003")
1047	Devlin MJ, et al., Open Treatment of Overweight Binge Eaters with Phentermine and Fluoxetine as an Adjunct to Cognitive-Behavioral Therapy. *Int. J. Eat. Disord*. 2000;28(3):325-332. ("Devlin")
1048	McCann UD, et al., Successful Treatment of Nonpurging Bulimia Nervosa With Desipramine: A Double-Blind, Placebo-Controlled Study. *Am. J. Psychiatry*. 1990; 147(11): 1509-1513. ("McCann")
1049	Malhotra S, et al., Venlafaxine Treatment of Binge-Eating Disorder Associated With Obesity: A Series of 35 Patients. J. *Clin. Psychiatry*. 2002; 63(9): 802-806. ("Malhotra")
1050	Schepers RJF, et al., Methamphetamine and Amphetamine Pharmacokinetics in Oral Fluid and Plasma after Controlled Oral Methamphetamine Administration to Human Volunteers. *Clin. Chem*. 2003; 49(1): 121-132. ("Schepers")
1051	Sulzer, D. Mechanisms of Neurotransmitter Release by Amphetamines: A Review. *Prog. Neurobiol*. 2005; 75(6): 406-433. ("Sulzer")
1052	Fleckenstein AE, New Insights into the Mechanism of Action of Amphetamines. *Annu. Rev. Pharmacol. Toxicol*. 2007; 47: 681-698. ("Fleckenstein")
1053	June 10, 2011 Response to Office Action for U.S. Application Serial No. 12/666,460. ("June 2011 Resp.")

Exhibit Number	Exhibit Name
1054	Carter WP, et al., Pharmacologic Treatment of Binge Eating Disorder. *Int. J. Eat. Disord*. 2003; 34 Suppl: S74-S88. ("Carter")
1055	Cortese S, et al., Attention-Deficit/Hyperactivity Disorder (ADHD) and Binge Eating. *Nutr. Rev*. 2007;65(9):404-411. ("Cortese")
1056	Corstorphine E, et al., Trauma and Multi-impulsivity in the Eating Disorders. *Eat. Behav*. 2007; 8: 23-30. ("Corstorphine")
1057	Nasser JA, et al., Impulsivity and Test Meal Intake in Obese Binge Eating Women. *Appetite*. 2004; 43(3): 303-307. ("Nasser")

24. The opinions expressed in this declaration are based upon the materials I have reviewed as well as my academic experience, training, expertise in the relevant field, and continuing education in the field of eating disorders.

B. Summary of Grounds of Obviousness

25. As described in detail below, it is my opinion that claims 1-13 of the '813 patent would have been obvious over the references discussed herein. The following chart summarizes the grounds for obviousness described in detail in the paragraphs that follow.

Grounds	Claims	Prior Art
1	1-5, 8-10, 12, and 13	Appolinario (Ex.1020) in view of Mickle (Ex.1023)
2	6 and 7	Appolinario (Ex.1020) in view of Mickle (Ex.1023) in view of Marrazzi (Ex.1024)

Grounds	Claims	Prior Art
3	11	Appolinario (Ex.1020) in view of Mickle (Ex.1023) in view of Grilo (Ex.1025)
4	1-5, 8-10, and 12-13	Ong (Ex.1017) in view of Mickle (Ex.1023) in view of DSM-IV-TR (Ex.1010)
5	6 and 7	Ong (Ex.1017) in view of Mickle (Ex.1023) in view of DSM-IV-TR (Ex.1010) in view of Marrazzi (Ex.1024)
6	11	Ong (Ex.1017) in view of Mickle (Ex.1023) in view of DSM-IV-TR (Ex.1010) in view of Grilo (Ex.1025)
7	1-5, 8-10, and 12-13	Dukarm (Ex.1019) in view of Mickle (Ex.1023) in view of DSM-IV-TR (Ex.1010)
8	6 and 7	Dukarm (Ex.1019) in view of Mickle (Ex.1023) in view of DSM-IV-TR (Ex.1010) in view of Marrazzi (Ex.1024)
9	11	Dukarm (Ex.1019) in view of Mickle (Ex.1023) in view of DSM-IV-TR (Ex.1010) in view of Grilo (Ex.1025)

IV. PERSON OF ORDINARY SKILL IN THE ART

26. I understand that a POSA is a hypothetical person having the combined understanding of those of ordinary skill in the various fields pertinent to the subject matter of the ’813 patent. I further understand that a POSA is presumed to be knowledgeable of all relevant prior art.

27. In my opinion, a POSA with respect to the ’813 patent would be a medical doctor (M.D.) specializing in psychiatry. This POSA would have clinical experience in the diagnosis and psychopharmacology of eating disorders, specifically BED. I came to this opinion by analyzing the ’813 patent, and then considering the following factors provided to me by counsel: (i) the educational level of the inventor; (ii) the types of problems encountered in the art; (iii) prior-art solutions to those problems; (iv) rapidity with which innovations are made; (v) sophistication of the technology; and (vi) educational level of active workers in the field.

28. The claims of the ’813 patent deal with the treatment of BED, which includes diagnosing the disorder and administering the drug lisdexamfetamine (LDX) dimesylate. (*See e.g.*, Ex.1001, ’813 patent, claim 1). The educational level of the person who would be undertaking these activities would be a medical doctor in psychiatry who has clinical experience in the field of eating disorders and related comorbidities. I have been informed by counsel that the sole inventor identified on the front of the patent is Louis Sanfilippo, who is a psychiatrist. At the time of the invention of the ’813 patent (i.e., September 13, 2007), because BED was a diagnostic entity that was the focus of significant research and clinical activity, the POSA would need to be familiar with the diagnosis, etiology, and

developing psychopharmacology of eating disorders in general, and BED specifically.

V. THE STATE OF THE ART AS OF SEPTEMBER 13, 2007

29. A psychiatrist having clinical experience in the field of eating disorders in 2007 would be well aware of the history of the diagnosis and psychopharmacology for the treatment of such disorders. I summarize that history below, with a focus on the diagnosis and treatment of BN, BED, and obesity.

A. The Diagnostic and Statistical Manual of Mental Disorders and Its Recognition of BN and BED

30. The Diagnostic and Statistical Manual of Mental Disorders, commonly referred to as "DSM," was first published in 1952, and has been updated periodically. (Ex.1035, McCarthy, p.10). DSM is widely regarded as the gold standard for diagnosing mental disorders, including eating disorders. (*See* Ex.1035, McCarthy, p.2).

31. While some eating disorders were identified in the earliest editions of DSM, the first acknowledgement by DSM of a "bulimic" disorder appeared in the third edition, which was published in 1980 (*see* Ex.1036, DSM-III, pp.5-7; *see also* Ex.1037, Brewerton, p.2). DSM-III provided a diagnostic criteria for "bulimia" and described its essential features to include, among other things, episodic binge eating. (Ex.1036, DSM-III, pp.5-7). Self-induced vomiting or other inappropriate

compensatory measures could be present, but were not required. (Ex.1036, DSM-III, pp.5-7).

32. As a result of the continued development of the understanding of bulimia generated from research and clinical studies, the revised edition of DSM-III, i.e., DSM-III-R (1987), changed the term "bulimia" to "bulimia nervosa" (BN) (*see* Ex.1038, DSM-III-R, pp.6-8), which is in keeping with the description and nomenclature set forth in 1979 by Gerald Russell. (Ex.1039, Russell, pp.17-18; *see also* Ex.1037, Brewerton, p.2). Also in line with Russell's thinking, in DSM-III-R the diagnostic criteria for BN not only included binge eating (similar to DSM-III), but also required that it be followed by recurrent inappropriate compensatory behavior. (Ex.1038, DSM-III-R, p.6).

33. DSM-IV introduced BED in the appendix under the category of EDNOS. (*See* Ex.1026, DSM-IV, pp.9-11). The EDNOS category is for eating disorders that do not meet the criteria for any specific eating disorder. (*See* Ex.1026, DSM-IV, p.8). Although compulsive overeating by obese patients was first described by Stunkard in 1959 (Ex.1040, Stunkard 1959, pp.4-12), it was not recognized as a distinct disorder by DSM until 1994 (*see* Ex.1026, DSM-IV, pp.9-11; *see also* Ex.1037, Brewerton, pp.1-2).

34. DSM-IV provides that the essential features of BED are recurrent episodes of binge eating, which are associated with subjective and behavioral

indicators of impaired control over, and significant distress about, the binge eating. (Ex.1026, DSM-IV, p.9). In the Research Criteria for BED "[a]n 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[,]" and "(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[.]" (Ex.1026, DSM-IV, p.11). The Research Criteria additionally requires that the binge eating episodes be 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." (Ex.1026, DSM-IV, p.11). The patient must also experience marked distress regarding binge eating. (Ex.1026, DSM-IV, p.11). Further, the binge eating must occur, on average, at least 2 days a week for 6 months. (Ex.1026, DSM-IV, p.11). Finally, the binge eating must not be associated with the regular use of inappropriate compensatory behaviors (e.g., purging, fasting, excessive exercise). (Ex.1026, DSM-IV, p.11).

35. A text revision of DSM-IV (DSM-IV-TR) was published in 2000. (*See* Ex.1010, DSM-IV-TR). The specific criteria for the diagnosis of BN and BED remained the same between the fourth edition and its text revision. (*Compare* Ex.1026, DSM-IV, pp.3-8, 9-11, *with* Ex.1010, DSM-IV-TR, pp.9-15, 16-18).

B. The Essential Diagnostic Criteria of Binge Eating for BN and BED Are the Same

36. BED and BN have recurrent episodes of binge eating as a central diagnostic criterion. (*See* Ex.1010, DSM-IV-TR, pp.14, 18). The main diagnostic distinction between the two is that with BED there is no regular use of inappropriate compensatory behavior, such as self-induced vomiting, laxative misuse, fasting, and excessive exercise that are characteristic of BN. (*See* Ex.1010, DSM-IV-TR, pp.10, 18). Some researchers have even characterized BED as a bulimic binge without the compensatory behaviors of purging or laxative abuse. (*See* Ex.1024, Marrazzi, p.2, Abstract).

37. In the diagnostic criteria for both BED and BN, DSM-IV-TR provides the same description of recurrent episodes of binge eating. (*See* Ex.1010, DSM-IV-TR, p.14, 18). In addition, in the text for BED, DSM-IV-TR directs the physician to the text for BN and states that "[t]he characteristics of a binge episode are discussed in the text for Bulimia Nervosa (p.589)." (Ex.1010, DSM-IV-TR, p.16).

38. Because of the overlapping symptom of binge eating between BN and BED, in my clinical practice I have determined and opined that the two disorders tend not to be distinct disorders but rather exist on a continuum, and that patients may move in and out of specific eating disorders over time. (*See* Ex.1037, Brewerton, p.2).

C. Centrally Acting Psychostimulants Are Effective for Treating the Symptom of Binge Eating

39. At least since 1983, publications have described the use of stimulants to treat binge eating. Ong administered the centrally acting psychostimulant methylamphetamine to BN patients who experienced immediate suppression of bulimic symptoms (overeating). (Ex.1017, Ong, pp.1, 5).

40. In 1989, Messner reported on the use of the centrally acting psychostimulant, methylphenidate to treat a patient with BN. (Ex.1041, Messner, p.3, Abstract). Importantly, the patient reported (i) an absence of the temptation to binge, and (ii) a calm emotional state with no adverse effects. (Ex.1041, Messner, p.3, Abstract).

41. Other case reports showed similar effects of centrally acting psychostimulants. Schweickert in 1997 reported that following administration of methylphenidate, a patient with ADHD who would binge and purge up to five times per day while under stress, had complete cessation of binge eating. (Ex.1042, Schweickert, p.2).

42. Two years later, Sokol recognized that many BN patients with cluster B personality disorders (having impulsivity as a personality trait) respond poorly to psychotherapy and investigated whether the ADHD-like symptoms of impulsivity, affective instability, and inattention might respond to psychostimulants. (Ex.1018, Sokol, p.3). The patients responded well to methylphenidate and had substantial decreases in binge eating and impulsivity. (Ex.1018, Sokol, pp.4-5).

43. In 2003, Drimmer investigated the use of methylphenidate or mixed amphetamine salts (Adderall) in patients having comorbid BN and attention-deficit disorder (ADD), and also studied d-amphetamine (Dexedrine) in a patient presenting with only BN. (Ex.1016, Drimmer, p.2). In each case, Drimmer reported that either the binge eating ceased or the frequency was reduced. (Ex.1016, Drimmer, p.2).

44. Subsequently, Dukarm investigated dextroamphetamine (also known as d-amphetamine) in BN patients comorbid with ADHD and found that all six patients reported a positive response with a decreased desire to binge, decreased anxiety about food, and an improved attention and mood. (Ex.1019, Dukarm, pp.3-5).

45. The chart below summarizes these clinically relevant studies that demonstrate the successful use of psychostimulants to treat the symptom of binge eating.

Year/Author	Active Agent	Effective in the Suppression of Binge Eating?
1983 Ong	Methylamphetamine	Yes
1989 Messner	Methylphenidate	Yes
1997 Schweichert	Methylphenidate	Yes
1999 Sokol	Methylphenidate	Yes
2000 Drimmer	Methylphenidate Mixed amphetamine salts d-Amphetamine	Yes
2005 Dukarm	d-Amphetamine	Yes

D. Centrally Acting Anti-Obesity Agents Are Effective for Treating BED

46. Many patients with BED are obese (*see* Ex.1043, Hudson, p.4; *see also* Ex.1044, Stunkard 1996, p.2), and the literature describes that anti-obesity agents were explored as potential treatments for BED (*see* Ex.1020, Appolinario, p.3). Anti-obesity agents have been successfully used for the treatment of BED, including d-fenfluramine and sibutramine. (Ex.1020, Appolinario, p.3*; see also* Ex.1045, Wilfley, p.1, Abstract). The anticonvulsant topiramate has also been found to have anti-obesity and anti-bulimic effects in patients with BED. (*See* Ex.1020, Appolinario, pp.4).

47. In 1996, the first clinical trial report on the use of an anti-obesity agent for the treatment of BED was published by Stunkard et al. (Ex.1044,

Stunkard 1996, p.2, Abstract). They reported that d-fenfluramine "significantly reduced the frequency of binge eating in women suffering from binge eating disorder." (Ex.1044, Stunkard 1996, p.4).

48. The anti-obesity agent sibutramine was investigated in BED patients as reported in Appolinario 2003. (Ex.1046, Appolinario 2003, p.2, Abstract). Appolinario 2003 conducted a placebo-controlled trial using sibutramine in individuals diagnosed with BED according to DSM-IV criteria. (Ex.1046, Appolinario 2003, p.3). Compared to placebo, sibutramine produced significant decreases in binge episodes per week. (Ex.1046, Appolinario 2003, pp.4-8). These results were later confirmed in two subsequent placebo-controlled clinical trials, in which sibutramine was found to be superior to placebo for the reduction in body mass index, binge frequency, and binge days, and was associated with greater global clinical improvement. (*See* Ex.1022, Milano, pp.4-5; *see also* Ex.1045, Wilfley, pp.4-6).

E. Antidepressants Are Effective for Treating BED

49. The use of antidepressants to treat BED is supported by the following lines of evidence: (i) antidepressants have been shown to be effective in BN, and (ii) those with BED display a high prevalence of a lifetime diagnosis of major depressive disorder. (Ex.1020, Appolinario, p.2). Appolinario cites several examples of studies involving the treatment of BED that show that antidepressants,

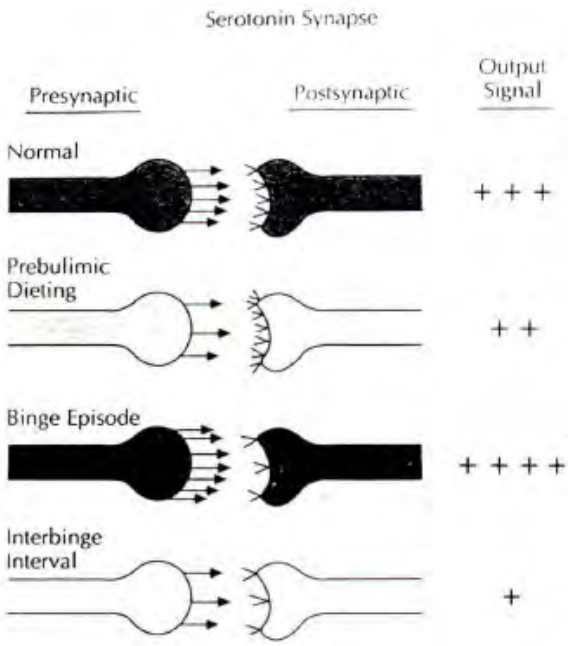
including desipramine and selective serotonin reuptake inhibitors (SSRIs) such as fluvoxamine, sertraline, fluoxetine, and citalopram are effective. (Ex.1020, Appolinario, p.2).

50. Also, the combination of the anti-obesity agent phentermine and the antidepressant fluoxetine was investigated by Devlin et al. in 2000. (Ex.1047, Devlin, p.1, Abstract). The results showed "reduction of binge frequency and weight loss in the short term." (Ex.1047, Devlin, p.6).

F. Neurochemical Bases for the Successful Treatment of Binge Eating with Agents that Influence Neurotransmitters

51. Eating 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.1011, Ioannides-Demos, p.5). It is postulated that a major cause of binge eating is a decrease in NT levels in the synaptic cleft between neurons. (Ex.1012, Jimerson, p.5). It has been said that "[DA] is one of the most important neurotransmitters involved in the reinforcing value of food and regulation of food intake." (Ex.1013, Epstein, p.1). Moreover, there is evidence that stimulation of certain 5-HT, DA, and NE receptors in the hypothalamus leads to suppression of eating. (Ex.1014, Samanin, p.4; Ex.1015, Blundell, p.8, 13). Patients diagnosed with binge eating have been found to have diminished levels of NE and metabolites of DA and 5-HT in their cerebrospinal fluid. (*See* Ex.1016, Drimmer, p.3; Ex.1012, Jimerson, pp.3-5).

52. The figure below shows a schematic of four different neuronal models of a serotonin synapse, which is representative of how NTs (e.g., DA and NE) generally function. (Ex.1012, Jimerson, p.4). Each model has two neurons, one presynaptic and one postsynaptic. The presynaptic neuron releases NT (depicted by the arrows) into the synaptic cleft and the NT is received at receptors (depicted by a ">") located on the postsynaptic cleft. Depending on the amount of NT released and the availability of postsynaptic receptors, the output signal (which measures the degree of stimulation in the brain) varies accordingly.



(Ex.1012, Jimerson, p.4, Fig. 3).

53. Under normal circumstances (top model), a basal level of NTs exist between the presynaptic and postsynaptic neurons, and the output signal is considered normal. (Ex.1012, Jimerson, p.4, Fig. 3). By contrast, in binge eating

patients prior to the binge episode (prebulimic dieting), there is a lower-than-normal level of NT and an up-regulation of postsynaptic receptors. (Ex.1012, Jimerson, p.4, Fig. 3). At this point, the signal output is lowered and the patient feels the need to binge. (Ex.1012, Jimerson, p.4, Fig. 3). During a binge episode, elevated levels of NT are released from the presynaptic neurons, which cause a down-regulation of postsynaptic neurons. (Ex.1012, Jimerson, p.4, Fig. 3). The result is an elevated output signal and an over-stimulation of the brain. (Ex.1012, Jimerson, p.4, Fig. 3). The down-regulation eventually produces lowered levels of NT and a low output signal during the interbinge interval thereby resulting in dysphoria. (Ex.1012, Jimerson, p.4, Fig. 3). The cycle then begins again.

54. In theory, drugs that increase the NT and postsynaptic receptor levels during the interbinge interval should sustain satiety and should counteract the dysregulation that leads to a binge eating episode in BED and BN. (Ex.1015, Blundell, pp.16-17). Also, drugs that inhibit NT reuptake on postsynaptic neurons may play a role in BED. (Ex.1015, Blundell, pp.16-17).

55. The mechanisms of several psychopharmacological drugs that have been used in the treatment of binge eating are described below.

G. The Biochemical Mechanism of Action of Certain Agents Explains Their Usefulness in the Treatment of BED

1. Amphetamine and Amphetamine Analogs

56. Because amphetamine has been researched and even studied clinically for decades, much is known about its biochemical mechanism of action, as well as the mechanism of various structurally related compounds. Amphetamine and amphetamine-like analogs increase NE levels in the synaptic cleft, resulting in the stimulation of post-synaptic receptors and the inhibition of feeding. (Ex.1011, Ioannides-Demos, p.6). Also, amphetamine blocks DA reuptake on post-synaptic receptors, which increases the levels of DA in the synaptic cleft and reinforces the suppression of hunger. (Ex.1011, Ioannides-Demos, p.6). Stimulants that can increase the dopaminergic and noradrenergic tone in the brain may help reduce food cravings. (Ex.1016, Drimmer, p.3). Because all of these mechanisms address what is believed to be a main dysfunction in BED, namely abnormally low levels of NTs in the brain, a POSA would expect that amphetamine and amphetamine analogs would be successful in suppressing binge eating. However, it is also known that increasing the levels of DA can increase the potential for abuse. (Ex.1011, Ioannides-Demos, p.6).

2. Anti-obesity Agents

57. The anti-obesity agent d-fenfluramine modulates 5-HT levels in the brain resulting in the feeling of fullness and loss of appetite. (*See* Ex.1015,

Blundell, pp.11-13; s*ee also* Ex.1014, Samanin, pp.2-3). As a 5-HT agonist and a mild 5-HT reuptake inhibitor, the likely mechanism of the anorectic action of d-fenfluramine is to increase the availability of 5-HT at central synapses and indirectly stimulate postsynaptic receptors. (Ex.1014, Samanin, p.2). These mechanisms likely explain d-fenfluramine's therapeutic efficacy in the treatment of BED.

58. Sibutramine is a mixed 5-HT and NE reuptake inhibitor and was approved for the treatment of obesity. (*See* Ex.1021, Appolinario 2002, p.2; *see also* Ex.1022, Milano, p.3). Before sibutramine was examined in BED, I postulated that "its usefulness in the treatment of BED *per se* has not yet been reported, even in open studies, but it nevertheless holds promise on theoretical grounds." (Ex.1037, Brewerton, p.8). Indeed, my expectation was realized in 2003 when Appolinario et al. published a study showing the effectiveness of sibutramine in treating patients with BED. (Ex.1046, Appolinario 2003, p.2, Abstract). Even in 2002, Appolinario et al. mentioned that "[b]ecause all these agents interfere with serotonergic and/or noradrenergic pathways, one possible mechanism of binge-eating reduction related to sibutramine may be a direct central effect on eating behavior." (Ex.1021, Appolinario 2002, p.4).

3. Antidepressants

59. The basis for the effectiveness of antidepressants in BED lies in their ability to modulate the same NTs that are responsible for satiety. For example, the antidepressant desipramine is a NE reuptake inhibitor that showed a reduction in binge frequency by 63% compared to an increase of 6% in patients who received placebo. (Ex.1048, McCann, p.4). Venlafaxine is a 5-HT and NE reuptake inhibitor and has been reported to be effective in treating BED in an open study. (Ex.1049, Malhotra, pp.2-3, Abstract). SSRIs such as fluoxetine, sertraline, fluvoxamine, and citalopram, have all shown efficacy in the treatment of BED (Ex.1020, Appolinario, p.2), perhaps due to their serotonergic effect.

VI. THE '813 PATENT

60. The '813 patent relates to methods of treating BED, obesity resulting from binge eating behavior, and depression with amphetamine prodrugs. (Ex.1001, '813 patent, col.1, ll.11-15). The '813 patent focuses on the use of the amphetamine prodrug LDX dimesylate in the treatment of these disorders, particularly BED. (Ex.1001, '813 patent, col.11, ll.18-67).

61. The '813 patent also discusses methods in which the amphetamine prodrugs are combined with another active agent. (Ex.1001, '813 patent, col.13, ll.50-67). The patent lists numerous agents that may be used in a combination therapy, including weight-loss drugs, anti-diabetes drugs, anti-psychotics, anti-

obesity agents, antidepressants, anticonvulsants, etc. (Ex.1001, '813 patent, col.14, l.9-col.16, l.36).

62. The '813 patent provides six case studies, or examples, of patients with BED or associated symptoms, ADHD, depressive episodes, obsessive compulsive behavior, and/or anxiety disorder, who were treated with LDX dimesylate. (Ex.1001, '813 patent, col.19, l.5-col.25, l.30).

63. The claims of the '813 patent are directed to a method of treating BED with LDX dimesylate. The '813 patent contains three independent claims. They are:

> 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 lisdexamfetamine dimesylate is the only active agent administered or is administered together with one or more additional active agents.
>
> 8. 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 lisdexamfetamine dimesylate is the only active agent administered.

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

64. Dependent claims 2, 9, 10, and 12 recite specific dosage ranges of LDX dimesylate to be administered to the patients.

65. Dependent claims 3-7 relate to the administration of LDX dimesylate together with one or more additional active agents.

66. Finally, dependent claim 11 states that the effective amount of LDX dimesylate is an amount effective to decrease the number of binge eating episodes per month or decrease the number of days in a month in which the patient experiences a binge eating episode.

VII. CLAIM CONSTRUCTION

67. Counsel has informed me that before analyzing whether the claims of a patent would have been obvious, one must understand the meaning of the claim terms.

68. Counsel has further informed me that when determining the meaning of a claim term in the context of an IPR, the claim term receives the broadest reasonable construction in light of the specification of the patent in which it

appears. Additionally, counsel has informed me that the patent and prosecution history are typically the most helpful sources to determine the proper meaning of a claim term.

69. In my opinion there is only one claim term in the '813 patent that requires explanation through the eyes of a POSA: "therapeutically effective amount." This term appears in claims 1, 8, and 13. I noted that the claims of the '813 patent do not provide any details regarding the term "therapeutically effective amount." I then turned to the rest of the patent for additional information regarding the meaning of this term.

70. In column 8, the '813 patent provides guidance on the interpretation of this term because it gives the following definition:

> The **term 'therapeutically effective amount'** or 'effective amount' **means** an amount effective, when administered to a human or non-human patient, to provide any therapeutic benefit. A therapeutic benefit may be an amelioration of symptoms, e.g., **an amount effective to decrease the symptoms of binge-eating disorder** or a major depressive disorder. In certain circumstances a patient may not present symptoms of a condition for which the patient is being treated. Thus a therapeutically effective amount of a compound is also an amount sufficient to provide a significant positive effect on any indicia of a disease, disorder or condition

> e.g. **an amount sufficient to significantly reduce the frequency and severity of binge eating behavior** or depressive symptoms.

(Ex. 1001, ’813 patent, col.8 ll.48-61) (emphasis added).

71. The ’813 patent discusses a method of treating BED along with a method of treating depression. As a result, the above quotation provides a definition of “therapeutically effective amount” that is applicable to the treatment of both BED and depression. However, because the claims of the ’813 patent are directed to the treatment of BED, only the emphasized portions of the quotation—which relate specifically to BED—should be used when interpreting the claim term “therapeutically effective amount.” It therefore follows that the broadest reasonable interpretation of “therapeutically effective amount” is *an amount effective to decrease the symptoms of BED or an amount sufficient to significantly reduce the frequency and severity of binge eating behavior*.

72. I reviewed the prosecution history of the ’813 patent (Ex.1002), which confirms this interpretation of “therapeutically effective amount.” The term was added to claim 1 in the January 23, 2012 Amendment and Response. (Ex.1004, Jan. 2012 Resp., p.2). In the Remarks, the Applicant stated that support for the amendment could be found in the above-quoted paragraph of the patent. (Ex.1004, Jan. 2012 Resp., p.6).

73. In sum, in my opinion, the meaning of "therapeutically effective amount" provided in paragraph 71 above is consistent with the broadest reasonable construction of the term in view of the specification and the prosecution history of the '813 patent. Therefore, I have adopted this construction for the purpose of my analysis in this declaration.

VIII. THE CLAIMS OF THE '813 PATENT WOULD HAVE BEEN OBVIOUS IN 2007

A. Legal Standard for Obviousness

74. It has been explained to me by counsel that once prior art is identified, an obviousness analysis involves comparing a properly construed claim to the prior art to determine whether the claimed invention would have been obvious to a POSA in light of that art, and in light of the general knowledge in the art. I also understand that in order to assess whether a claim would have been obvious in light of the prior art, I must step backward in time and into the shoes worn by the hypothetical POSA at the time of the invention, which I understand is September 13, 2007 with respect to the '813 patent. In view of all factual information, I must then make a determination whether the claimed invention as a whole would have been obvious to that person.

75. I have also been informed that obviousness can be established by combining or modifying the teachings of the prior art to achieve the claimed invention. It is my understanding that where there is a reason to modify or

combine the prior art to achieve the claimed invention, there must also be a reasonable expectation of success for a finding of obviousness. It is also my understanding that a finding of obviousness involves analyzing secondary considerations of nonobviousness, such as unexpected results and long-felt but unmet need.

76. Applying these understandings of obviousness, I set forth below the reasons why I believe claims 1-13 of the '813 patent would have been obvious.

B. The Prior-Art Use of Anti-Obesity Agents to Treat BED Demonstrates that It Would Have Been Obvious to Use LDX Dimesylate to Treat BED

1. Ground 1: Claims 1-5, 8-10, 12, and 13 Would Have Been Obvious over Appolinario in View of Mickle

77. As laid out below, it is my opinion that claims 1-5, 8-10, 12, and 13 would have been obvious to a POSA in light of the disclosures in Appolinario and Mickle.

a. Independent Claim 1

78. Appolinario discusses pharmacotherapies used for the treatment of BED. (*See* Ex.1020, Appolinario, p.1, Abstract). Appolinario also describes the diagnostic criteria for BED as provided in DSM-IV[1] and further teaches the diagnosis of BED according to such criteria. (*See* Ex.1020, Appolinario, pp.1, 4).

1 As described above in paragraph 35, DSM-IV and DSM-IV-TR provide the same diagnostic criteria for BED. Thus, a POSA would have understood that Appolinario discloses diagnosing BED as defined in DSM-IV-TR.

Appolinario identifies three categories of medications that have been studied in the treatment of BED: antidepressants, anti-obesity agents, and anticonvulsants. (*See* Ex.1020, Appolinario, p.1, Abstract).

79. According to Appolinario, the rationale for "[t]he use of anti-obesity agents in the treatment of BED is supported by several lines of evidence: (1) binge eating is characterized by increased appetite and reduced satiety, (2) BED is frequently associated with overweight, obesity, and depression, (3) some anti-obesity agents reduce appetite, increase satiety, induce weight loss, and may reduce depressive symptoms." (*See* Ex.1020, Appolinario, p.3) (internal citations omitted). Appolinario describes a BED treatment study using d-fenfluramine, which resulted in a high rate of remission (80%) of binge eating. (*See* Ex.1020, Appolinario, p.3). In addition, Appolinario discusses both an open trial and randomized controlled trial (RCT) with sibutramine in which sibutramine was found to significantly reduce binge eating frequency, body weight, and associated depressive symptoms. (*See* Ex.1020, Appolinario, p.3). The RCT resulted in a 52% rate of remission of binge eating. (*See* Ex.1020, Appolinario, p.5, Table 1).

80. As described above, both d-fenfluramine and sibutramine act on the central nervous system by impacting NTs that are responsible for hunger and satiety. (*See* above at ¶¶ 57-58). Because of the success of these centrally acting anti-obesity agents in the treatment of BED, a POSA would have had a reasonable

expectation that other centrally acting anti-obesity agents would similarly reduce binge eating behavior. Therefore, from Appolinario, a POSA would have learned to treat BED by diagnosing a patient with BED as defined in DSM-IV-TR, and administering a centrally acting anti-obesity agent to the patient.

81. Despite the positive results of d-fenfluramine and sibutramine in treating BED, a POSA would also have been aware of the potential limitations of their use. Appolinario notes that d-fenfluramine was withdrawn from the market for its association with cardiac valve lesions and pulmonary hypertension. (*See* Ex.1020, Appolinario, p.3). With respect to sibutramine, in the RCT the sibutramine cohort had a 52% remission from binge eating at the end of treatment, while the placebo group had a 32% remission. (*See* Ex.1020, Appolinario, p.5, Table 1). Therefore, although sibutramine was efficacious in the treatment of BED, the net difference in the percentage of patients with remission of binge eating at the end of the clinical study that can be attributable to sibutramine was only 20%. (*See* Ex.1020, Appolinario, p.5).

82. As a result, a POSA would have been motivated to identify another centrally acting anti-obesity agent with positive properties, such as LDX dimesylate as described by Mickle.

83. Mickle teaches amphetamine prodrugs, such as LDX dimesylate, that are indicated for the treatment of certain disorders, including obesity. (Ex.1023,

Mickle, Abstract, ¶ [0098]). In fact, obesity is identified as a preferred indication. (Ex.1023, Mickle ¶ [0124]). Mickle teaches that following oral administration of LDX dimesylate, the centrally acting stimulant d-amphetamine is released. (*See, e.g.*, Ex.1023, Mickle ¶¶ [0003], [0085], [0096], [0358]). Mickle also teaches that LDX dimesylate has the attractive properties of reduced abuse potential and sustained release. (*See, e.g.*, Ex.1023, Mickle ¶¶ [0114], [0226]-[0231], [0355]-[0360]). In addition, Mickle provides "methods for treating a patient comprising administering a therapeutically effective amount of an amphetamine prodrug, i.e., an amount sufficient to prevent, ameliorate, and/or eliminate the symptoms of a disease." (*See* Ex.1023, Mickle ¶ [0124]). Given the positive properties of LDX dimesylate provided in Mickle, it is my opinion that a POSA would have been motivated to replace centrally acting anti-obesity agents d-fenfluramine and sibutramine of Appolinario with the centrally acting anti-obesity agent LDX dimesylate of Mickle for the treatment of BED.

84. In light of the teachings of Appolinario together with Mickle, a POSA would have diagnosed BED according to DSM-IV-TR and would have had a reasonable expectation of success in treating BED with LDX dimesylate. Thus, it is my opinion that claim 1 would have been obvious over the combination of Appolinario and Mickle.

b. Claims 2-5, 8-10, 12, and 13

85. Claim 2 depends on claim 1, and therefore I incorporate by reference my analyses and opinions laid out above for claim 1. Claim 2 further requires a dosage of 15 to 70 mg of LDX dimesylate administered daily. Mickle teaches administration of amphetamine prodrugs, such as LDX dimesylate, in daily doses of about 10 mg to about 100 mg. (Ex.1023, Mickle ¶ [0153]). Mickle also provides for administration of LDX dimesylate in dosages of 30 mg, 50 mg, and 70 mg per day. (*See, e.g.*, Ex.1023, Mickle ¶¶ [0348], [0353]). Based on these teachings, it would have been obvious to a POSA to administer LDX dimesylate in daily dosage amounts of 15 to 70 mg for the treatment of BED. As such, it is my opinion that claim 2 would have been obvious over the combination of Appolinario and Mickle.

86. Claim 3 depends on claim 1, and therefore I incorporate by reference my analyses and opinions laid out above for claim 1. Claim 3 further requires that LDX dimesylate be administered together with one or more other active agent(s), although the additional active agent(s) is not specified. Mickle teaches that the amphetamine prodrugs, e.g., LDX dimesylate, can be administered in combination with one or more therapeutic agents. (Ex.1023, Mickle ¶ [0125], Table 1). Therefore, in light of this disclosure in Mickle, taken together with my analyses for

claim 1, it is my opinion that claim 3 would have been obvious over the combination of Appolinario and Mickle.

87. Claim 4 is dependent on claim 3, and therefore I incorporate by reference my analyses and opinions laid out above for claim 3. Claim 4 further requires that the one or more other active agents being administered with LDX dimesylate be from particular classes of active agents; the list of classes includes SSRIs. Appolinario teaches that BED is frequently associated with depression and additionally identifies antidepressants such as SSRIs as useful for the treatment of BED. (*See* Ex.1020, Appolinario, p.2). Further, Mickle discloses that amphetamine prodrugs, e.g., LDX dimesylate, can be administered with antidepressants including SSRIs. (*See* Ex.1023, Mickle ¶ [0125], Table 1). As such, it would have been obvious to combine LDX dimesylate with SSRIs when treating BED. Hence, it is my opinion that claim 4 would have been obvious over the combination of Appolinario and Mickle.

88. Claim 5 is dependent on claim 4, and therefore I incorporate by reference my analyses and opinions laid out above for claim 4. Claim 5 further requires that the additional active agent being administered with LDX dimesylate be from a list of specific agents that includes citalopram, fluoxetine, fluvoxamine, and sertraline. Appolinario teaches that BED is frequently associated with depression and identifies these SSRIs as useful for the treatment of BED. (*See*

Ex.1020, Appolinario, p.2). Further, Mickle discloses that amphetamine prodrugs, e.g., LDX dimesylate, can be administered with antidepressants such as fluoxetine (Prozac®) and sertraline (Zoloft®). (*See* Ex.1023, Mickle ¶ [0125], Table 1). As such, when treating BED, it would have been obvious to combine LDX dimesylate with one of the SSRIs listed above. Hence, it is my opinion that claim 5 would have been obvious over the combination of Appolinario and Mickle.

89. Claim 8 is an independent claim and is the same as claim 1, except that claim 8 requires that LDX dimesylate be the only active agent administered. I incorporate by reference my analyses and opinions laid out above for claim 1 here for claim 8, since the difference between the two claims does not impact in any substantive way such analyses and opinions. As such, it is my opinion that claim 8 would have been obvious over the combination of Appolinario and Mickle for the same reasons that claim 1 would have been obvious over the combination of Appolinario and Mickle.

90. Claim 9 depends on claim 8, and therefore I incorporate by reference my analyses and opinions laid out above for claim 8. Claim 9 further requires a dosage of 2.5 to 200 mg of LDX dimesylate administered daily. Mickle teaches administration of amphetamine prodrugs, such as LDX dimesylate, in daily doses of about 2.5 mg to about 500 mg and about 10 mg to about 250 mg. (Ex.1023, Mickle ¶ [0153]). Mickle also provides for administration of LDX dimesylate in

dosages of 30 mg, 50 mg, and 70 mg per day. (*See, e.g.*, Ex.1023, Mickle ¶¶ [0348], [0353]). Based on these teachings, it would have been obvious to a POSA to administer LDX dimesylate in daily dosage amounts of 2.5 to 200 mg for the treatment of BED. As such, it is my opinion that claim 9 would have been obvious over the combination of Appolinario and Mickle.

91. Claim 10 depends on claim 8, and therefore I incorporate by reference my analyses and opinions laid out above for claim 8. Claim 10 further requires a dosage of 15 to 100 mg of LDX dimesylate administered once per day. Mickle teaches administration of amphetamine prodrugs, such as LDX dimesylate, in daily doses of about 10 mg to about 100 mg. (Ex.1023, Mickle ¶ [0153]). Mickle also states that "[p]referably, a single dose is administered once daily." (Ex.1023, Mickle ¶ [0155]). Mickle further provides for administration of LDX dimesylate in dosages of 30 mg, 50 mg, and 70 mg once per day in the morning. (*See, e.g.*, Ex.1023, Mickle ¶¶ [0348], [0353]). Based on these teachings, it would have been obvious to a POSA to administer LDX dimesylate in amounts of 15 to 100 mg once per day for the treatment of BED. As such, it is my opinion that claim 10 would have been obvious over the combination of Appolinario and Mickle.

92. Claim 12 depends on claim 8, and therefore I incorporate by reference my analyses and opinions laid out above for claim 8. Claim 12 further requires a dosage of 15 to 70 mg of LDX dimesylate administered daily. Mickle teaches

administration of amphetamine prodrugs, such as LDX dimesylate, in daily doses of about 10 mg to about 100 mg. (Ex.1023, Mickle ¶ [0153]). Mickle also provides for administration of LDX dimesylate in dosages of 30 mg, 50 mg, and 70 mg per day. (*See, e.g.*, Ex.1023, Mickle ¶¶ [0348], [0353]). Based on these teachings, it would have been obvious to a POSA to administer LDX dimesylate in daily dosage amounts of 15 to 70 mg for the treatment of BED. As such, it is my opinion that claim 12 would have been obvious over the combination of Appolinario and Mickle.

93. Claim 13 is an independent claim and is the same as claim 1, except that claim 13 omits the requirement of diagnosing a patient as having BED. I incorporate by reference my analyses and opinions laid out above for claim 1 here for claim 13, since the difference between the two claims does not impact in any substantive way such analyses and opinions. As such, it is my opinion that claim 13 would have been obvious over the combination of Appolinario and Mickle for the same reasons that claim 1 would have been obvious over the combination of Appolinario and Mickle.

2. Ground 2: Claims 6 and 7 Would Have Been Obvious over Appolinario in View of Mickle and Marrazzi

94. Claim 6 depends on claim 5 and claim 7 depends on claim 6; therefore I incorporate by reference my analyses and opinions laid out above for claim 5. Claim 6 further requires that the additional active agent being administered with

LDX dimesylate be from the group orlistat, naltrexone, and zonisamide, while claim 7 further requires that the additional active agent being administered with LDX dimesylate be naltrexone. Marrazzi describes that naltrexone was shown to attenuate BN in a previous controlled clinical trial and was thus administered to a patient having BED, with positive results. (*See* Ex.1024, Marrazzi, p.2, Abstract). Further, Mickle teaches that LDX dimesylate can be administered in combination with one or more therapeutic agents. (Ex.1023, Mickle ¶ [0125], Table 1). Therefore, it would have been obvious to combine LDX dimesylate with naltrexone when treating BED. As such, it is my opinion that claims 6 and 7 both would have been obvious over the combination of Appolinario, Mickle, and Marrazzi.

3. Ground 3: Claim 11 Would Have Been Obvious Over Appolinario in View of Mickle and Grilo

95. Claim 11 depends on claim 8 and further requires that the effective amount be an amount that decreases the number of binge eating episodes per month or the number of days in a month in which the patient experiences a binge. Because claim 11 depends on claim 8, I incorporate by reference my analyses and opinions laid out above for claim 8. In addition, I note that Grilo teaches that the Eating Disorder Examination (EDE) is a reliable method for assessing large binge episodes, as well as the number of days during which large binge episodes occurred. (Ex.1025, Grilo, p.1, Abstract). Grilo also focuses on the binge episodes

occurring in "the previous 28 days." (*See* Ex.1025, Grilo, pp.3, 5). Thus, it is my opinion that claim 11 would have been obvious over Appolinario in view of Mickle and Grilo.

C. The Prior-Art Use of Centrally Acting Stimulants to Treat Binge Eating Demonstrates that It Would Have Been Obvious to Use LDX Dimesylate to Treat BED

1. Ground 4: Claims 1-5, 8-10, 12, and 13 Would Have Been Obvious over Ong in View of DSM-IV-TR and Mickle

96. As laid out below, it is my opinion that claims 1-5, 8-10, 12, and 13 of the '813 patent would have been obvious to a POSA in light of the disclosures in Ong, DSM-IV, and Mickle.

a. Independent Claim 1

97. Ong describes an eight-person double-blind controlled study involving the administration of methylamphetamine to patients diagnosed with BN. (Ex.1017, Ong, p.1, Abstract). Ong focuses on the symptom of bulimia, which is defined as "overeating" and characterized by the "rapid consumption of excessive quantities of food against a mounting experience of distress" (Ex.1017, Ong, p.1, Abstract). Thus, the term "bulimia," i.e., overeating, is a symptom of BN that is distinct from the subsequent symptoms of self-induced vomiting or purgation.

98. The patients enrolled in the study in Ong had frequent recurrent episodes of overeating. (*See* Ex.1017, Ong, p.2, Table 1). All patients received

methylamphetamine and placebo in double-blind fashion on alternating days in random order at least one week apart. (*See* Ex.1017, Ong, pp.2-3). No patient who was administered methylamphetamine experienced bulimia. (Ex.1017, Ong, p.3). Further, caloric consumption and self-ratings for hunger were both significantly lower in patients after administration of methylamphetamine versus placebo. (*See* Ex.1017, Ong, p.3). In reading Ong, a POSA would have recognized that the "most important finding is that bulimia as defined in this report, is suppressed by methylamphetamine." (Ex.1017, Ong, p.5).

99. A POSA would have known that the symptom of bulimia as studied in Ong closely resembles the symptom of binge eating described in DSM-IV-TR for both BN and BED. This is illustrated in the table below.

Bulimia in Ong	**Binge Eating in DSM-IV-TR**
"The symptom of bulimia (rapid, **excessive** and distressing eating) . . . ." (Ex.1017, Ong, p.1, Abstract) (emphasis added). "The characteristic features of bulimia are the rapid consumption of **excessive quantities** of food . . . ." (Ex.1017, Ong, p.1) (emphasis added). "[S]ome patients with bulimia nervosa had a typical episode of bulimia. They rapidly consumed **excessive quantities** of food . . . ." (Ex.1017, Ong, p.5) (emphasis added).	"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 . . . ." (Ex.1010, DSM-IV-TR, p.18) (emphasis added).

Bulimia in Ong	Binge Eating in DSM-IV-TR
"[S]ome patients with bulimia nervosa had a typical episode of bulimia. They . . . experienced a **loss of control** of their eating behaviour . . . ." (Ex.1017, Ong, p.5) (emphasis added).	"An episode of binge eating is characterized by both of the following . . . (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." (Ex.1010, DSM-IV-TR, p.18) (emphasis added).
"The symptom of bulimia (**rapid**, **excessive** and distressing eating) . . . ." (Ex.1017, Ong, p.1, Abstract) (emphasis added). "The characteristic features of bulimia are the **rapid** consumption of **excessive quantities** of food . . . ." (Ex.1017, Ong, p.1) (emphasis added). "[S]ome patients with bulimia nervosa had a typical episode of bulimia. They **rapidly** consumed **excessive quantities** of food . . . ." (Ex.1017, Ong, p.5) (emphasis added). "[R]esponses of the eight patients [when questioned about factors which triggered episodes of overeating] in turn were . . . 'if annoyed, irritated, or **depressed**' (4), 'when tired or **depressed'** (5), 'I enjoy eating forbidden food, so I must **carry on to overeat** . . . ." (Ex.1017, Ong, pp.1-2) (emphasis added).	"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" (Ex.1010, DSM-IV-TR, p.18) (emphasis added).
"The symptom of bulimia (rapid, excessive and **distressing** eating) . . . ." (Ex.1017, Ong, p.1, Abstract) (emphasis added).	"Marked **distress** regarding binge eating is present." (Ex.1010, DSM-IV-TR, p18) (emphasis added).

Bulimia in Ong	Binge Eating in DSM-IV-TR
"The characteristic features of bulimia are the rapid consumption of excessive quantities of food against a mounting experience of **distress** . . . ." (Ex.1017, Ong, p.1) (emphasis added). "[S]ome patients with bulimia nervosa had a typical episode of bulimia. They rapidly consumed excessive quantities of food, experienced a loss of control of their eating behavior, became very **distressed** about this . . . ." (Ex.1017, Ong, p.5) (emphasis added).	

100. Therefore, a POSA reading Ong and DSM-IV-TR would have learned to treat BED by diagnosing the patient and administering methylamphetamine to the patient. And based upon the teachings of Ong and DSM-IV-TR, a POSA would have had a reasonable expectation of success of treating BED with methylamphetamine used in Ong. Moreover, in 2007 a POSA would have been aware of other centrally acting psychostimulants, such as d-amphetamine and methylphenidate, that were shown to be effective for the treatment of binge eating. (*See* above at ¶¶ 39-45).

101. Yet, a POSA would have also recognized from Ong that "drugs with stimulant and euphoric effects carry the dangers of dependence and drug induced psychosis . . . ." (Ex.1017, Ong, p.5). Such a warning would have led and motivated the POSA to seek an alternative stimulant that could provide similar properties as methylamphetamine given its success as a treatment in Ong; but this

alternative stimulant would have needed to carry a lower risk of these side effects. Thus, the POSA would have turned to Mickle and its teachings of amphetamine prodrugs that have a similar impact on the central nervous system as, and avoids the risks associated with, methylamphetamine.

102. Namely, Mickle discloses amphetamine prodrugs that exhibit numerous advantages, including reduced overdose potential by exhibiting a reduced pharmacological activity when administered at doses higher than what is therapeutic and reduced abuse potential by exhibiting (i) stability under conditions likely to be employed by illicit chemists attempting to release the amphetamine; and (ii) decreased bioavailability when it is administered via parenteral routes. (*See* Ex.1023, Mickle ¶ [0114]). Thus, Mickle's amphetamine prodrugs may "reduce the euphoric effect associated with amphetamine abuse." (Ex.1023, Mickle ¶ [0114]).

103. Mickle identifies LDX dimesylate as the preferred amphetamine prodrug. (*See* Ex.1023, Mickle ¶ [0098]). Mickle teaches that, following oral administration of LDX dimesylate, d-amphetamine is released. (*See, e.g.*, Ex.1023, Mickle ¶¶ [0085], [0358]). D-amphetamine, like methylamphetamine, is a known central nervous system stimulant. (*See* Mickle at ¶¶ [0003], [0096]). In fact, methylamphetamine breaks down and metabolizes into d-amphetamine. (*See generally* Ex.1050, Schepers). Both d-amphetamine and methylamphetamine have

similar neurobiological mechanisms of action. (*See* Ex.1051, Sulzer, p.2). Specifically, methylamphetamine and d-amphetamine release excess DA into the synaptic clefts of dopaminergic neurons. (Ex.1052, Fleckenstein, p.3; Ex.1051, Sulzer, pp.2, 21). To a lesser extent methylamphetamine and d-amphetamine act as dopaminergic and adrenergic reuptake inhibitors and in high concentrations as monoamine oxidase inhibitors. (Ex.1051, Sulzer, pp.10, 13, 18-19).

104. In addition, Mickle provides methods for treating a patient including the administration of a therapeutically effective amount of an amphetamine prodrug, e.g., LDX dimesylate, that is sufficient to prevent, ameliorate, and/or eliminate the symptoms of a disease. (*See* Ex.1023, Mickle ¶ [0124]). Mickle also discloses administering the amphetamine prodrug with one or more other therapeutic agents, and specifically identifies particular agents to be used in the combination. (*See* Ex.1023, Mickle ¶ [0125], Table 1).

105. A POSA would have been motivated to replace methylamphetamine as disclosed in Ong with the LDX dimesylate of Mickle. As noted above, Ong cautions about the dangers of dependence and drug-induced psychosis for drugs with stimulant and euphoric effects, and LDX dimesylate is designed to exhibit reduced euphoric effects associated with abuse. Further, a POSA would have expected that LDX dimesylate would have the same pharmacological effects as methylamphetamine, because, as described previously, LDX dimesylate and

methylamphetamine bind to the same receptors. To put it simply, a POSA would have replaced methylamphetamine with LDX dimesylate because LDX dimesylate is a safer drug with a similar mechanism of action. Therefore, based on the disclosures in Mickle, a POSA would have had a reasonable expectation of successfully treating BED by replacing methylamphetamine with LDX dimesylate, a stimulant having the beneficial pharmacological properties of methylamphetamine but with reduced abuse potential.

106. In light of the teachings of Ong together with DSM-IV-TR and Mickle, a POSA would have diagnosed BED according to DSM-IV-TR and would have had a reasonable expectation of success of treating BED with LDX dimesylate. Thus, it is my opinion that claim 1 would have been obvious over the combination of Ong together with DSM-IV-TR and Mickle.

b. Claims 2-5, 8-10, 12, and 13

107. Claim 2 depends on claim 1, and therefore I incorporate by reference my analyses and opinions laid out above for claim 1. Claim 2 further requires a dosage of 15 to 70 mg of LDX dimesylate administered daily. Mickle teaches administration of amphetamine prodrugs, such as LDX dimesylate, in daily doses of about 10 mg to about 100 mg. (Ex.1023, Mickle ¶ [0153]). Mickle also provides for administration of LDX dimesylate in dosages of 30 mg, 50 mg, and 70 mg per day. (*See, e.g.*, Ex.1023, Mickle ¶¶ [0348], [0353]). Based on these

teachings, it would have been obvious to a POSA to administer LDX dimesylate in daily dosage amounts of 15 to 70 mg for the treatment of BED. As such, it is my opinion that claim 2 would have been obvious over the combination of Ong, DSM-IV-TR, and Mickle.

108. Claim 3 depends on claim 1, and therefore I incorporate by reference my analyses and opinions laid out above for claim 1. Claim 3 further requires that LDX dimesylate be administered together with one or more other active agent(s), although the additional active agent(s) is not specified. DSM-IV-TR states that "[s]ome individuals report that binge eating is triggered by dysphoric moods, such as depression and anxiety" (Ex.1010, DSM-IV-TR, p.17), suggesting the need for combination drug therapy. Further, Mickle teaches that the amphetamine prodrugs, e.g., LDX dimesylate, can be administered in combination with one or more therapeutic agents. (Ex.1023, Mickle ¶ [0125], Table 1). Therefore, in light of these disclosures in Mickle and DSM-IV-TR, taken together with my analyses for claim 1, it is my opinion that claim 3 would have been obvious over the combination of Ong, DSM-IV-TR, and Mickle.

109. Claim 4 is dependent on claim 3, and therefore I incorporate by reference my analyses and opinions laid out above for claim 3. Claim 4 further requires that the one or more other active agents being administered with LDX dimesylate be from particular classes of active agents; the list of classes includes

SSRIs, which can be used as antidepressants. DSM-IV-TR states that "[s]ome individuals report that binge eating is triggered by dysphoric moods, such as depression and anxiety." (Ex.1010, DSM-IV-TR, p.17), suggesting the need for combination drug therapy with antidepressants. Further, Mickle discloses that the amphetamine prodrugs, e.g., LDX dimesylate, can be administered with antidepressants, including SSRIs. (*See* Ex.1023, Mickle ¶ [0125], Table 1). Hence, it would have been obvious to combine LDX dimesylate with SSRIs when treating BED. As such, it is my opinion that claim 4 would have been obvious over the combination of Ong, DSM-IV-TR, and Mickle.

110. Claim 5 is dependent on claim 4, and therefore I incorporate by reference my analyses and opinions laid out above for claim 4. Claim 5 further requires that the additional active agent being administered with LDX dimesylate be from a list of specific agents that includes citalopram, fluoxetine, fluvoxamine, and sertraline, which all can be used as antidepressants. DSM-IV-TR states that "[s]ome individuals report that binge eating is triggered by dysphoric moods, such as depression and anxiety." (Ex.1010, DSM-IV-TR, p.17), suggesting the need for combination drug therapy with antidepressants. Further, Mickle discloses that amphetamine prodrugs, e.g., LDX dimesylate, can be administered with antidepressants such as fluoxetine (Prozac®) and sertraline (Zoloft®). (*See* Ex.1023, Mickle ¶ [0125], Table 1). Thus, it would have been obvious to combine

LDX dimesylate with one of the SSRIs listed above when treating BED. As such, it is my opinion that claim 5 would have been obvious over the combination of Ong, DSM-IV-TR, and Mickle.

111. Claim 8 is an independent claim and is the same as claim 1, except that claim 8 requires that LDX dimesylate be the only active agent administered. I incorporate by reference my analyses and opinions laid out above for claim 1 here for claim 8, since the difference between the two claims does not impact in any substantive way such analyses and opinions. As such, it is my opinion that claim 8 would have been obvious over the combination of Ong, DSM-IV-TR, and Mickle for the same reasons that claim 1 would have been obvious over the combination of Ong, DSM-IV-TR, and Mickle.

112. Claim 9 depends on claim 8, and therefore I incorporate by reference my analyses and opinions laid out above for claim 8. Claim 9 further requires a dosage of 2.5 to 200 mg of LDX dimesylate administered daily. Mickle teaches administration of amphetamine prodrugs, such as LDX dimesylate, in daily doses of about 2.5 mg to about 500 mg and about 10 mg to about 250 mg. (Ex.1023, Mickle ¶ [0153]). Mickle also provides for administration of LDX dimesylate in dosages of 30 mg, 50 mg, and 70 mg per day. (*See, e.g.*, Ex.1023, Mickle ¶¶ [0348], [0353]). Based on these teachings, it would have been obvious to a POSA to administer LDX dimesylate in daily dosage amounts of 2.5 to 200 mg for the

treatment of BED. As such, it is my opinion that claim 9 would have been obvious over the combination of Ong, DSM-IV-TR, and Mickle.

113. Claim 10 depends on claim 8, and therefore I incorporate by reference my analyses and opinions laid out above for claim 8. Claim 10 further requires a dosage of 15 to 100 mg of LDX dimesylate administered once per day. Mickle teaches administration of amphetamine prodrugs, such as LDX dimesylate, in daily doses of about 10 mg to about 100 mg. (Ex.1023, Mickle ¶ [0153]). Mickle also states that "[p]referably, a single dose is administered once daily." (Ex.1023, Mickle ¶ [0155]). Mickle further provides for administration of LDX dimesylate in dosages of 30 mg, 50 mg, and 70 mg once per day in the morning. (*See, e.g.*, Ex.1023, Mickle ¶¶ [0348], [0353]). Based on these teachings, it would have been obvious to a POSA to administer LDX dimesylate in amounts of 15 to 100 mg once per day for the treatment of BED. As such, it is my opinion that claim 10 would have been obvious over the combination of Ong, DSM-IV-TR, and Mickle.

114. Claim 12 depends on claim 8, and therefore I incorporate by reference my analyses and opinions laid out above for claim 8. Claim 12 further requires a dosage of 15 to 70 mg of LDX dimesylate administered daily. Mickle teaches administration of amphetamine prodrugs, such as LDX dimesylate, in daily doses of about 10 mg to about 100 mg. (Ex.1023, Mickle ¶ [0153]). Mickle also provides for administration of LDX dimesylate in dosages of 30 mg, 50 mg, and 70

mg per day. (*See, e.g.*, Ex.1023, Mickle ¶¶ [0348], [0353]). Based on these teachings, it would have been obvious to a POSA to administer LDX dimesylate in daily dosage amounts of 15 to 70 mg for the treatment of BED. As such, it is my opinion that claim 12 would have been obvious over the combination of Ong, DSM-IV-TR, and Mickle.

115. Claim 13 is an independent claim and is the same as claim 1, except that claim 13 omits the requirement of diagnosing a patient as having BED. I incorporate by reference my analyses and opinions laid out above for claim 1 here for claim 13, since the difference between the two claims does not impact in any substantive way such analyses and opinions. As such, it is my opinion that claim 13 would have been obvious over the combination of Ong, DSM-IV-TR, and Mickle for the same reasons that claim 1 would have been obvious over the combination of Ong, DSM-IV-TR, and Mickle.

2. Ground 5: Claims 6 and 7 Would Have Been Obvious over Ong in View of DSM-IV-TR, Mickle, and Marrazzi

116. Claim 6 depends on claim 5 and claim 7 depends on claim 6; therefore I incorporate by reference my analyses and opinions laid out above for claim 5. Claim 6 further requires that the additional active agent being administered with LDX dimesylate be from the group orlistat, naltrexone, and zonisamide, while claim 7 further requires that the additional active agent being administered with LDX dimesylate be naltrexone. Marrazzi describes that naltrexone was shown to

attenuate BN in a previous controlled clinical trial and was thus administered to a patient having BED, with positive results. (*See* Ex.1024, Marrazzi, p.2, Abstract). Further. Mickle teaches that LDX dimesylate can be administered in combination with one or more therapeutic agents. (Ex.1023, Mickle ¶ [0125], Table 1). Therefore, it would have been obvious to combine LDX dimesylate with naltrexone when treating BED. As such, it is my opinion that both claims 6 and 7 would have been obvious over the combination of Ong, DSM-IV-TR, Mickle, and Marrazzi.

3. Ground 6: Claim 11 Would Have Been Obvious over Ong in View of DSM-IV-TR, Mickle, and Grilo

117. Claim 11 depends on claim 8 and further requires that the effective amount be an amount that decreases the number of binge eating episodes per month or the number of days in a month in which the patient experiences a binge. Because claim 11 depends on claim 8, I incorporate by reference my analyses and opinions laid out above for claim 8. In addition, I note that Grilo teaches that the EDE is a reliable method for assessing large binge episodes, as well as the number of days during which large binge episodes occurred. (Ex.1025, Grilo, p.1, Abstract). Grilo also focuses on the binge episodes occurring in "the previous 28 days." (Ex.1025, Grilo, pp.3, 5). Thus, it is my opinion that claim 11 would have been obvious over Ong in view of DSM-IV-TR, Mickle, and Grilo.

D. The Prior-Art Use of d-Amphetamine to Treat Binge Eating Demonstrates that It Would Have Been Obvious to Use LDX Dimesylate to Treat BED

1. Ground 7: Claims 1-5, 8-10, 12, and 13 Would Have Been Obvious over Dukarm in View of DSM-IV-TR and Mickle

118. As laid out below, it is my opinion that claims 1-5, 8-10, 12, and 13 of the ’813 patent would have been obvious to a POSA in light of the disclosures in Dukarm, DSM-IV-TR, and Mickle.

a. Independent Claim 1

119. Dukarm provides case reports for six patients who were diagnosed with comorbid BN and ADHD and were treated with the stimulant medication, d-amphetamine. (*See* Ex.1019, Dukarm, p.2, Abstract). A review of the case reports reveals that all six patients experienced recurring episodes of binge eating. (*See* Ex.1019, Dukarm, pp.3-5). After administration of d-amphetamine “all of the 6 patients described reported complete abstinence from binge eating . . . .” (Ex.1019, Dukarm, p.5). As a result, Dukarm concluded that “these cases suggest the potential role of psychostimulants in the management of BN because of the high rate of abstinence from bulimic symptoms and the low rate of adverse side effects.” (Ex.1019, Dukarm, p.6). The positive results achieved in the six cases were not surprising in light of the historical summary of the successful use of psychostimulants in the treatment of BN provided in the introduction of Dukarm. (*See* Ex.1019, Dukarm, p.3).

120. Dukarm also discloses the use of DSM-IV-TR to diagnose a patient. (*See* Ex.1019, Dukarm, p.3). At the time of the invention a POSA would have been familiar with DSM-IV-TR. As described in paragraph 30 above, DSM-IV-TR was psychiatry's preeminent diagnostic manual of mental disorders and as a result, a POSA would have relied upon the diagnostic criteria provided therein when diagnosing a patient with BED.

121. As previously discussed, an essential feature of both BN and BED in DSM-IV-TR is "recurrent episodes of binge eating." (Ex.1010, DSM-IV-TR, pp.9, 14, 16, 18). According to DSM-IV-TR a "recurrent episode of binge eating" in BED is the same as a "recurrent episode of binge eating" in BN. (*See* Ex.1010, DSM-IV-TR, p.14 (Diagnostic Criteria for BN), p.18 (Research Criteria for BED); *see also* above at ¶¶ 36-38). The DSM-IV-TR section on BED even specifically points to the section on BN for additional information on the characteristics of a binge episode in BED. (*See* Ex.1010, DSM-IV-TR, p.16).

122. In addition to the recurrent episodes of binge eating, a diagnosis of BED according to DSM-IV-TR also requires three or more indicators of impaired control including "eating very rapidly, eating until feeling uncomfortably full, eating large amounts of food when not hungry, eating alone because of embarrassment over how much one is eating, and feeling disgust, guilt, or depression after overeating." (Ex.1010, DSM-IV-TR, pp.16-17). Although the

diagnostic criteria for BN does not require these indicators of impaired control, most of them are usually present in patients with BN as evidenced in the discussion of the diagnostic features of BN in DSM-IV-TR:

> Individuals with Bulimia Nervosa are **typically ashamed** of their eating problems and attempt to conceal their symptoms. Binge eating usually occurs in **secrecy**, or as inconspicuously as possible. An episode . . . is usually (but not always) characterized by **rapid consumption**. The binge eating often continues until the individual is **uncomfortably, or even painfully, full**. . . . Binge eating may transiently reduce dysphoria, but **disparaging self-criticism and depressed mood** often follow.

(*See* Ex.1010, DSM-IV-TR, p.10) (emphasis added). Thus, it would have been clear to a POSA that the characteristics of the binge eating episodes in BED are essentially the same as those in BN.

123. In fact, because of the overlapping symptom of binge eating required for diagnosis of BED and BN, one of the difficulties regarding the diagnosis of BED included differentiating it from bulimia nervosa, nonpurging type, which involved fasting and excessive exercise as compensatory behaviors. (*See* Ex.1037, Brewerton, p.2). In a 1999 publication on BED, I noted: "In clinical practice, these disorders tend not to be distinct entities, but rather exist on a continuum. Patients

may move in and out of specific eating disorder diagnostic criteria over time." (Ex.1037, Brewerton, p.2).

124. Based on the teachings of DSM-IV-TR, it is my opinion that a POSA would have understood that the binge eating of BN is the same as the binge eating of BED. Further, given the evidence in Dukarm demonstrating that d-amphetamine was successful in eliminating the binge eating symptom in patients with BN, a POSA would have had a reasonable expectation of success in treating BED with d-amphetamine. Therefore, a POSA reading Dukarm and DSM-IV-TR would have learned to treat BED by diagnosing the patient and administering d-amphetamine to the patient.

125. Yet, a POSA also would have understood Dukarm's concern of "the risk of abuse of the [psychostimulant] medication," particularly in eating-disorder patients who have an increased risk for substance abuse. (Ex.1019, Dukarm, p.6). This would have motivated a POSA to seek an alternative stimulant with a lower risk of abuse. Thus, a POSA would have turned to Mickle and its disclosure of amphetamine prodrugs that reduce the euphoric effects associated with amphetamine abuse. (*See, e.g.*, Ex.1023, Mickle ¶¶ [0114], [0355]-[0360]).

126. The preferred amphetamine prodrug in Mickle is LDX dimesylate. (*See* Ex.1023, Mickle ¶ [0098]). Mickle teaches that, following oral administration of LDX dimesylate, d-amphetamine is released. (*See, e.g.,* Ex.1023, Mickle ¶¶

[0085], [0358]). A POSA would have recognized that the active ingredient released from LDX dimesylate—d-amphetamine—is the same agent that reduced binge eating in Dukarm.

127. Additionally, Mickle provides methods for treating a patient including the administration of a therapeutically effective amount of an amphetamine prodrug, e.g., LDX dimesylate, that is sufficient to prevent, ameliorate, and/or eliminate the symptoms of a disease. (*See* Ex.1023, Mickle ¶ [0124]). Mickle also discloses administering the amphetamine prodrug with one or more other therapeutic agents, and specifically identifies particular agents to be used in the combination. (*See* Ex.1023, Mickle ¶ [0125], Table 1).

128. A POSA would have been motivated to replace d-amphetamine as disclosed in Dukarm with the LDX dimesylate of Mickle for the treatment of BED. As noted above, Dukarm warns of the risk of abuse of psychostimulants in patients with eating disorders, and LDX dimesylate is an amphetamine prodrug with reduced abuse potential that releases the identical drug used in Dukarm, i.e., d-amphetamine. Therefore, based on the disclosures in Mickle, a POSA would have had a reasonable expectation of successfully treating BED by replacing d-amphetamine with LDX dimesylate.

129. In light of the teachings of Dukarm together with DSM-IV-TR and Mickle, a POSA would have diagnosed BED according to DSM-IV-TR and would

have had a reasonable expectation of success of treating BED with LDX dimesylate. Thus, it is my opinion that claim 1 would have been obvious over the combination of Dukarm together with DSM-IV-TR and Mickle.

b. Claims 2-5, 8-10, 12, and 13

130. Claim 2 depends on claim 1, and therefore I incorporate by reference my analyses and opinions laid out above for claim 1. Claim 2 further requires a dosage of 15 to 70 mg of LDX dimesylate administered daily. Mickle teaches administration of amphetamine prodrugs, such as LDX dimesylate, in daily doses of about 10 mg to about 100 mg. (Ex.1023, Mickle ¶ [0153]). Mickle also provides for administration of LDX dimesylate in dosages of 30 mg, 50 mg, and 70 mg per day. (*See, e.g.*, Ex.1023, Mickle ¶¶ [0348], [0353]). Based on these teachings, it would have been obvious to a POSA to administer LDX dimesylate in daily dosage amounts of 15 to 70 mg for the treatment of BED. As such, it is my opinion that claim 2 would have been obvious over the combination of Dukarm, DSM-IV-TR, and Mickle.

131. Claim 3 depends on claim 1, and therefore I incorporate by reference my analyses and opinions laid out above for claim 1. Claim 3 further requires that LDX dimesylate be administered together with one or more other active agent(s), although the additional active agent(s) is not specified. DSM-IV-TR states that "[s]ome individuals report that binge eating is triggered by dysphoric moods, such

as depression and anxiety" (Ex.1010, DSM-IV-TR, p.17), suggesting the need for combination drug therapy. Further, Mickle teaches that the amphetamine prodrugs, e.g., LDX dimesylate, can be administered in combination with one or more therapeutic agents. (Ex.1023, Mickle ¶ [0125], Table 1). Therefore, in light of these disclosures in Mickle and DSM-IV-TR, taken together with my analyses for claim 1, it is my opinion that claim 3 would have been obvious over the combination of Dukarm, DSM-IV-TR, and Mickle.

132. Claim 4 is dependent on claim 3, and therefore I incorporate by reference my analyses and opinions laid out above for claim 3. Claim 4 further requires that the one or more other active agents being administered with LDX dimesylate be from particular classes of active agents; the list of classes includes SSRIs, which can be used as antidepressants. DSM-IV-TR states that "[s]ome individuals report that binge eating is triggered by dysphoric moods, such as depression and anxiety." (Ex.1010, DSM-IV-TR, p.17), suggesting the need for combination drug therapy with antidepressants. Further, Mickle discloses that amphetamine prodrugs, e.g., LDX dimesylate, can be administered with antidepressants, including SSRIs. (Ex.1023, Mickle ¶ [0125], Table 1). Hence, it would have been obvious to combine LDX dimesylate with SSRIs when treating BED. As such, it is my opinion that claim 4 would have been obvious over the combination of Dukarm, DSM-IV-TR, and Mickle.

133. Claim 5 is dependent on claim 4, and therefore I incorporate by reference my analyses and opinions laid out above for claim 4. Claim 5 further requires that the additional active agent being administered with LDX dimesylate be from a list of specific agents that includes citalopram, fluoxetine, fluvoxamine, and sertraline, which all can be used as antidepressants. DSM-IV-TR states that "[s]ome individuals report that binge eating is triggered by dysphoric moods, such as depression and anxiety." (Ex.1010, DSM-IV-TR, p.17), suggesting the need for combination drug therapy with antidepressants. Further, Mickle discloses that amphetamine prodrugs, e.g., LDX dimesylate, can be administered with antidepressants such as fluoxetine (Prozac®) and sertraline (Zoloft®). (*See* Ex.1023, Mickle ¶ [0125], Table 1). Thus, it would have been obvious to combine LDX dimesylate with one of the SSRIs listed above when treating BED. As such, it is my opinion that claim 5 would have been obvious over the combination of Dukarm, DSM-IV-TR, and Mickle.

134. Claim 8 is an independent claim and is the same as claim 1, except that claim 8 requires that LDX dimesylate be the only active agent administered. I incorporate by reference my analyses and opinions laid out above for claim 1 here for claim 8, since the difference between the two claims does not impact in any substantive way such analyses and opinions. As such, it is my opinion that claim 8 would have been obvious over the combination of Dukarm, DSM-IV-TR, and

Mickle for the same reasons that claim 1 would have been obvious over the combination of Dukarm, DSM-IV-TR, and Mickle.

135. Claim 9 depends on claim 8, and therefore I incorporate by reference my analyses and opinions laid out above for claim 8. Claim 9 further requires a dosage of 2.5 to 200 mg of LDX dimesylate administered daily. Mickle teaches administration of amphetamine prodrugs, such as LDX dimesylate, in daily doses of about 2.5 mg to about 500 mg and about 10 mg to about 250 mg. (Ex.1023, Mickle ¶ [0153]). Mickle also provides for administration of LDX dimesylate in dosages of 30 mg, 50 mg, and 70 mg per day. (*See, e.g.*, Ex.1023, Mickle ¶¶ [0348], [0353]). Based on these teachings, it would have been obvious to a POSA to administer LDX dimesylate in daily dosage amounts of 2.5 to 200 mg for the treatment of BED. As such, it is my opinion that claim 9 would have been obvious over the combination of Dukarm, DSM-IV-TR, and Mickle.

136. Claim 10 depends on claim 8, and therefore I incorporate by reference my analyses and opinions laid out above for claim 8. Claim 10 further requires a dosage of 15 to 100 mg of LDX dimesylate administered once per day. Mickle teaches administration of amphetamine prodrugs, such as LDX dimesylate, in daily doses of about 10 mg to about 100 mg. (Ex.1023, Mickle ¶ [0153]). Mickle also states that "[p]referably, a single dose is administered once daily." (Ex.1023, Mickle ¶ [0155]). Mickle further provides for administration of LDX dimesylate

in dosages of 30 mg, 50 mg, and 70 mg once per day in the morning. (*See, e.g.*, Ex.1023, Mickle at ¶¶ [0348], [0353]). Based on these teachings, it would have been obvious to a POSA to administer LDX dimesylate in amounts of 15 to 100 mg once per day for the treatment of BED. As such, it is my opinion that claim 10 would have been obvious over the combination of Dukarm, DSM-IV-TR, and Mickle.

137. Claim 12 depends on claim 8, and therefore I incorporate by reference my analyses and opinions laid out above for claim 8. Claim 12 further requires a dosage of 15 to 70 mg of LDX dimesylate administered daily. Mickle teaches administration of amphetamine prodrugs, such as LDX dimesylate, in daily doses of about 10 mg to about 100 mg. (Ex.1023, Mickle ¶ [0153]). Mickle also provides for administration of LDX dimesylate in dosages of 30 mg, 50 mg, and 70 mg per day. (*See, e.g.*, Ex.1023, Mickle ¶¶ [0348], [0353]). Based on these teachings, it would have been obvious to a POSA to administer LDX dimesylate in daily dosage amounts of 15 to 70 mg for the treatment of BED. As such, it is my opinion that claim 12 would have been obvious over the combination of Dukarm, DSM-IV-TR, and Mickle.

138. Claim 13 is an independent claim and is the same as claim 1, except that claim 13 omits the requirement of diagnosing a patient as having BED. I incorporate by reference my analyses and opinions laid out above for claim 1 here

for claim 13, since the difference between the two claims does not impact in any substantive way such analyses and opinions. As such, it is my opinion that claim 13 would have been obvious over the combination of Dukarm, DSM-IV-TR, and Mickle for the same reasons that claim 1 would have been obvious over the combination of Dukarm, DSM-IV-TR, and Mickle.

2. Ground 8: Claims 6 and 7 Would Have Been Obvious over Dukarm in View of DSM-IV-TR, Mickle, and Marrazzi

139. Claim 6 depends on claim 5 and claim 7 depends on claim 6; therefore I incorporate by reference my analyses and opinions laid out above for claim 5. Claim 6 further requires that the additional active agent being administered with LDX dimesylate be from the group orlistat, naltrexone, and zonisamide, while claim 7 further requires that the additional active agent being administered with LDX dimesylate be naltrexone. Marrazzi describes that naltrexone was shown to attenuate BN in a previous controlled clinical trial and was thus administered to a patient having BED, with positive results. (*See* Ex.1024, Marrazzi, p.2, Abstract). Further, Mickle teaches that LDX dimesylate can be administered in combination with one or more therapeutic agents. (Ex.1023, Mickle ¶ [0125], Table 1). Therefore, it would have been obvious to combine LDX dimesylate with naltrexone when treating BED. As such, it is my opinion that both claims 6 and 7 would have been obvious over the combination of Dukarm, DSM-IV-TR, Mickle, and Marrazzi.

3. Ground 9: Claim 11 Would Have Been Obvious over Dukarm in View of DSM-IV-TR, Mickle, and Grilo

140. Claim 11 depends on claim 8 and further requires that the effective amount be an amount that decreases the number of binge eating episodes per month or the number of days in a month in which the patient experiences a binge. Because claim 11 depends on claim 8, I incorporate by reference my analyses and opinions laid out above for claim 8. In addition, I note that Grilo teaches that the EDE is a reliable method for assessing large binge episodes, as well as the number of days during which large binge episodes occurred. (Ex.1025, Grilo, p.1, Abstract). Grilo also focuses on the binge episodes occurring in "the previous 28 days." (Ex.1025, Grilo, pp.3, 5). Thus, it is my opinion that claim 11 would have been obvious over Dukarm in view of DSM-IV-TR, Mickle, and Grilo.

IX. THE APPLICANT'S ARGUMENTS DURING PROSECUTION DO NOT DEMONSTRATE NONOBVIOUSNESS OF THE CLAIMS

A. A Brief Summary of the Relevant Sections of the Prosecution History

141. As outlined above with respect to grounds 7-9, it is my opinion that claims 1-13 would have been obvious to a POSA primarily in view of Dukarm and Mickle. I understand that the Examiner also relied primarily on Dukarm during prosecution when rejecting an earlier set of claims directed to the treatment of BED. (*See* Ex.1003, July 2011 OA, pp.5-6). I also understand that in this rejection the Examiner additionally relied on Mickle 2005. (*See* Ex.1003, July 2011 OA,

pp.5-6). Just like Mickle (relied on in my opinions above), Mickle 2005 is a patent application publication that discloses amphetamine prodrugs with reduced abuse potential, such as LDX. At the time of the rejection, claim 1 had been amended as follows:

> 1. (Currently Amended) A method of treating binge eating disorder or ~~obesity resulting from binge eating behavior~~, comprising diagnosing a patient as having a binge eating disorder ~~or obesity resulting from binge eating behavior~~ and providing an effective amount of an amphetamine prodrug~~, methylphenidate prodrug, or methylphenidate analog~~ to the patient, wherein the amphetamine prodrug~~, methylphenidate prodrug, or methylphenidate analog~~ is provided as the only active agent or is provided together with one or more additional active agents.

(*See* Ex.1053, June 2011 Resp., p.2).

142. The basic points of the rejection were that (i) "binge eating disorder" as claimed encompassed BN, and (ii) the teachings of Dukarm to treat the binge eating in BN could be applied to the treatment of BED. (*See* Ex.1003, July 2011 OA, pp.5-6; *see also* Ex.1004, Jan. 2012 Resp., p.8).

143. The Applicant provided a response to the rejection, including an amendment to the claims that incorporated a description of BED found in DSM-IV-TR in order to distinguish BED from BN. (*See* Ex.1004, Jan. 2012 Resp., p.8). At this time, claim 1 was amended as follows:

1. (Currently Amended) A method of treating Bbinge Eating Ddisorder, comprising diagnosing a patient as having ~~a~~ Bbinge Eeating Ddisorder, wherein the Bbinge Eating Ddisorder comprises binge eating episodes ~~are~~ characterized by three or more of the following symptoms: eating until uncomfortable full, eating large amounts of food when not physically hungry, eating much more rapidly than normal, eating alone on account of embarrassment over how much one is eating, and feeling disgusted, depressed or guilty after overeating and ~~providing~~ administering ~~an~~ a therapeutically effective amount of ~~an amphetamine prodrug~~ lisdexamfetamine dimesylate to the patient, wherein the lisdexamfetamine dimesylate~~amphetamine prodrug~~ is ~~provided as~~ the only active agent administered or is ~~provided~~ administered together with one or more additional active agents.

(Ex.1004, Jan. 2012 Resp., p.2).

144. The Applicant then made arguments as to why he thought that the claims would not have been obvious over the Dukarm and Mickle 2005 references. (Ex.1004, Jan. 2012, pp.8-13). Subsequently, the Examiner withdrew the rejection. (*See* Ex.1005, Apr. 2012 OA, p.4). For the reasons outlined below, it is my opinion that the Applicant's arguments do not detract from my obviousness analysis in grounds 7-9, which rely upon Dukarm and Mickle.

B. The Applicant's Position that Dukarm's Teachings Would Not Extend to BED Is Not Persuasive

145. Dukarm presents case reports for six patients with comorbid BN and ADHD treated with the stimulant d-amphetamine. (*See* Ex.1019, Dukarm, p.2, Abstract). All six patients reported complete abstinence from binge eating over an extended period of time. (*See* Ex.1019, Dukarm, pp.3-5).

146. The Applicant made various arguments as to why a POSA would not apply Dukarm's teachings—the use of stimulants to decrease the symptom of binge eating in patients with BN—to the treatment of BED: (i) BED and BN are recognized as separate disorders; (ii) because the BN patients treated in Dukarm were comorbid with ADHD, it was impossible to know which disorder was being treated; and (iii) drugs useful for treating BN are not necessarily effective for treating BED. (*See* Ex.1004, Jan. 2012 Resp., pp.8-11). While it is not disputed that BN and BED are separate disorders, it is the fact that they share the symptom of binge eating that is relevant to this analysis. As discussed in detail above, one need only look to DSM-IV-TR to recognize that the binge eating episodes required for a diagnosis of BN are the same as the binge eating episodes required for a diagnosis of BED. (*See* above at ¶¶ 36-38). I explain below why none of the arguments presented by the Applicant would have dissuaded a POSA from applying Dukarm's results to the treatment of BED, especially if one considers the complete teachings of Dukarm.

1. The Fairburn 2000 Reference Would Not Have Deterred a POSA from Applying the Teachings of Dukarm to the Treatment of BED

147. The Applicant raised Fairburn 2000 for the purpose of showing that BN and BED have separate courses and outcomes. (*See* Ex.1004, Jan. 2012 Resp., pp.8-9). Based upon the results and discussion in Fairburn, the Applicant proposed that a POSA "would not have extrapolated Dukarm's teaching that stimulants decreased binging behavior in BN patients to the treatment of Binge Eating Disorder." (Ex.1004, Jan. 2012 Resp., p.9). I disagree.

148. Fairburn 2000 opens by stating that "[f]undamental to the classification of psychiatric disorders and their management is knowledge of their course and outcome." (*See* Ex.1027, Fairburn 2000, p.1). I read this as providing a rationale for the work reported in the publication, which followed BN and BED patients over a five-year prospective study. (*See* Ex.1027, Fairburn 2000, p.1, Abstract). Fairburn concluded that BN and BED have different courses and outcomes. (*See* Ex.1027, Fairburn 2000, p.1, Abstract).

149. Based upon Fairburn 2000's opening statement, a POSA first would have asked, "How does the finding by Fairburn 2000 that BN and BED have different courses and outcomes impact, if at all, the classification and management of these disorders?" Regarding their classification, Fairburn 2000 considered BN and BED as separate disorders (*see* Ex.1027, Fairburn 2000, p.6). Yet, it was

known by POSAs, and recognized by Fairburn, that the binge eating symptom, an "objective bulimic episode," is the essential feature of both disorders. (*See* Ex.1027, Fairburn 2000 , p.1). Even after Fairburn 2000 (i.e., 2003), experts in the field of eating disorders were still noting that "[p]atients with BED display symptoms that are similar to those of individuals with bulimia nervosa." (*See, e.g.,* Ex.1054, Carter, p.2).

150. In explaining Fairburn 2000 to the Examiner, the Applicant stated that "Fairburn noted several differences in the binge eating behavior and obesity between the two cohorts." (*See* Ex.1004, Jan. 2012 Resp., p.9). But Table 2 of Fairburn 2000 demonstrates that the same characteristic of "objective bulimic episodes" was measured for both the BN and BED cohorts. (*See* Ex.1027, Fairburn 2000, p.4). Fairburn 2000 does not present any differences in the frequency or severity of objective binge episodes between the two disorders at recruitment. Rather, the differences noted by Fairburn 2000 are with respect to the course and outcome, and these differences do not address the symptom of binge eating articulated in DSM-IV-TR.

151. With respect to management of BN and BED, nowhere does Fairburn 2000 suggest, let alone conclude, that treatments useful in BN cannot or should not be used for the treatment of BED. Fairburn 2000 does not even consider treatment options for these disorders. To this point, none of the three main implications that

Fairburn 2000 identifies as a result of the findings of his study implicate treatment options for BN or BED. (*See* Ex.1027, Fairburn 2000, p.6).

152. Notably, in a subsequent publication in 2003, Fairburn himself formulated the transdiagnostic model for the etiology and treatment of all eating disorders, including AN, BN, and EDNOS, such as BED. The transdiagnostic model is based upon Fairburn's observations that all of these eating disorders "share the same distinctive psychopathology" and that "patients move between these diagnostic states over time." (Ex.1028, Fairburn 2003, p.12). Furthermore, "[t]hese two characteristics, together with the clinical observation that shared clinical features tend to be maintained by similar psychopathological processes, suggest that *common mechanisms are involved in the persistence of bulimia nervosa, anorexia nervosa and the atypical eating disorders*." (Ex.1028, Fairburn 2003, p.12). With respect to treatment, he ultimately concludes that "[t]he patient's specific eating disorder diagnosis is not of relevance to the treatment." (Ex.1028, Fairburn 2003, p.14).

153. In my opinion, the arguments presented by the Applicant with respect to Fairburn do not detract from the teachings of Dukarm and would not have deterred a POSA from applying the teachings of Dukarm for the treatment of BED, especially in light of Fairburn 2003.

2. The Comorbidity in Dukarm Would Not Have Prevented a POSA from Applying the Teachings of Dukarm to the Treatment of BED

154. In attempting to disqualify the teachings of Dukarm, the Applicant asserted that it was not clear which disorder Dukarm was treating because the patients were comorbid with BN and ADHD. (*See* Ex.1004, Jan. 2012 Resp., pp.9-10).

155. As an initial matter, I point out that the Applicant inaccurately characterized the patients in Dukarm by stating that "Dukarm presents a study of **ADHD patients who happen also to be suffering from BN**, limiting the applicability of Dukarm's findings." (*See* Ex.1004, Jan. 2012 Resp., p.8) (emphasis added). There is nothing in Dukarm to support this statement, and a POSA reading Dukarm would never have characterized the patients in such a manner. The Applicant appears to be minimizing the medical significance of the BN in patients who were specifically seeking treatment for their eating disorder. (Ex.1019, Dukarm, pp.3-5).

156. Contrary to the Applicant's implication, the fact that the patients had BN was not a trivial aspect of the analysis in Dukarm. The treatment of the binge eating symptom was the primary focus of the publication. In addition, the Applicant's position that the findings in Dukarm cannot support a method of treating BN independent of ADHD is inconsistent with Dukarm's ultimate

conclusion, which did not limit the findings to situations where patients have comorbid BN and ADHD: "[T]hese cases suggest a potential role of psychostimulants in the management of bulimia because of the high rate of abstinence from bulimic symptoms and the low rate of adverse side effects." (Ex.1019, Dukarm, p.2, Abstract).

157. In the "Discussion" section, Dukarm hypothesizes as to the various reasons why treatment of these patients with the psychostimulant d-amphetamine resulted in the complete abstinence of binging and purging: (i) BN and ADHD share a common causal factor or several common factors; (ii) symptoms of BN are the result of untreated ADHD; and (iii) the appetite-suppressant effects of stimulants resulted in a decreased desire to binge eat and, therefore, a decrease in compensatory purging. (*See* Ex.1019, Dukarm, p.5). A POSA would have understood Dukarm to be explaining the basis for the significant and uniform response of these patients to d-amphetamine. Providing hypotheses, in my view, is standard practice when authoring a scientific publication, particularly in a "Discussion" section. The Applicant suggests that these hypotheses would somehow derail a POSA from applying the unequivocal results of Dukarm to the treatment of BED. I disagree because a POSA would have made a determination based on scientific data and not hypothetical explanations. In addition, I note that

while the Applicant emphasized the first two hypotheses, he failed to address the third, which is that d-amphetamine was treating binge eating in the first instance.

158. A POSA would have understood that it is not uncommon for patients with BED and BN to experience impulsivity as an associated psychopathology. (*See* Ex.1020, Appolinario, p.2; Ex.1056, Corstorphine, p.2; Ex.1057, Nasser, pp.1, 4, Abstract). Based on available data, Cortese reviewed several hypotheses that could have explained the link between ADHD and binge eating. (Ex.1055, Cortese, p.3, Abstract). One hypothesis was that inattention and/or impulsivity promoted binge eating. (Ex.1055, Cortese, p.6). Another hypothesis put forward by Cortese was that ADHD and binge eating share common neurobiological bases, such as a dopaminergic defect that might predispose toward a reward deficiency syndrome. (Ex.1055, Cortese, p.6). Cortese stated, "obese patients with abnormal eating behaviors and ADHD may present with common genetically determined dysfunctions in the dopaminergic system." (Ex.1055, Cortese, p.6). In patients with ADHD and binge eating, Cortese also noted that both conditions might benefit from common therapeutic strategies, such as stimulants. (Ex.1055, Cortese, p.7). Specifically, they noted, "ADHD medications might act both on the brain pathways involved in ADHD and on those that mediate abnormal eating behaviors." (Ex.1055, Cortese, p.9). Thus, the fact that the patients in Dukarm had comorbid ADHD and BN and were successfully treated with the

psychostimulant d-amphetamine, may provide further support for the successful use of psychostimulants in BED whether or not the patient satisfies the diagnostic criteria for ADHD.

159. It is my opinion that even in view of the hypothetical commentary made by Dukarm in an attempt to explain her results, a POSA still would have had a reasonable expectation of success in treating BED with the psychostimulant d-amphetamine, particularly in view of the information in Dukarm that neither the Applicant nor the Examiner considered. I discuss this information below.

3. The Applicant and the Examiner Did Not Address Key Disclosures in Dukarm

160. During the prosecution of the ’813 patent, the discussions between the Examiner and the Applicant failed to take into account a significant aspect of Dukarm. Specifically, Dukarm provides a historical summary (with reference to the original publications) of the successful use of psychostimulants in the treatment of BN. (*See* Ex.1019, Dukarm, p.3). I display below in a chart what I believe reflects Dukarm’s teachings with respect to the successful use of psychostimulants prior to Dukarm’s study.

Author, Date	Psychostimulant	Study Results	Patient Population
Ong, 1983	Methylamphetamine	Decreased hunger and food consumption	Four patients with BN
Messner, 1989	Methylphenidate	Decreased desire to binge eat	One bulimic patient

Author, Date	Psychostimulant	Study Results	Patient Population
Schweickert, 1997	Methylphenidate	Complete resolution of binge eating and purging	One patient with BN and ADHD
Sokol, 1999	Methylphenidate	Significant improvement	Two patients with BN
Drimmer, 2003	Stimulants	All demonstrated favorable response	Two patients with comorbid BN and ADHD, and one patient with BN without comorbid ADHD

(*See* Ex.1019, Dukarm, p.3).

161. In other words, the result of Dukarm that the stimulant d-amphetamine is useful in treating binge eating symptoms in BN patients comorbid with ADHD, would not be read in a vacuum. A POSA would have understood **directly** from Dukarm that, before Dukarm's data were presented, over two decades of prior publications reported the successful use of psychostimulants in the treatment of bulimic episodes in BN patients, including some that were not comorbid with ADHD (specifically, Ong and Drimmer).

162. It is my opinion that given the overlapping symptom of binge eating in BN and BED described by DSM-IV-TR, together with the extensive data demonstrating the successful use of psychostimulants in the treatment of binge eating described in Dukarm, a POSA would have had a reasonable expectation of success in extending the teachings of Dukarm to the treatment of BED.

4. The Applicant Incorrectly Argued that Drugs Useful for Treating BN Are Not Effective for Treating BED

163. The Applicant incorrectly concluded that because fluoxetine, an SSRI useful for the treatment of BN, did not demonstrate efficacy in one study of patients with BED, a POSA would not have had a reasonable expectation of success that drugs useful for treating BN would be effective in treating BED. First, in support of this argument the Applicant relied on the results of one study while ignoring other data clearly available to POSAs. Specifically, the Applicant cited to Grilo 2005, a study concluding that Cognitive Behavioral Therapy (CBT), but not fluoxetine, demonstrated efficacy for the behavioral and psychological features of BED. (*See* Ex.1004, Jan. 2012 Resp., pp.10-11). The Applicant compared these results to an unrelated study that reported on the reduction of binge eating behavior in BN following fluoxetine treatment. (*See* Ex.1004, Jan. 2012, pp.10-11). However, a POSA would have been aware of countervailing data demonstrating positive results for the treatment of BED with fluoxetine. (*See* Ex.1030, Arnold, p.2, Abstract; *see also* Ex.1054, Carter, p.1, Abstract). In addition, both the American Psychiatric Association and the National Institute for Clinical Evidence suggest antidepressant medications, particularly SSRIs such as fluoxetine, as one possible evidence-based treatment option for patients with BED. (Ex.1031, Practice Guideline, p.21, 56, 86; Ex.1032, NICE, p.20).

164. In addition, I note that when describing the results from Grilo 2005 in support of his argument that positive results for the treatment of BN cannot be applied with any reasonable expectation of success in the treatment of BED, he stated that "clinical data showed that drugs useful for treating Bulimia Nervosa are not necessarily efficacious for treating Binge Eating Disorder and its associated binge eating symptoms, and **may actually worsen** binge eating behavior." (Ex.1004, Jan. 2012 Resp., p.10) (emphasis added). I do not find a rational basis for what appears to be an overstatement describing the results in Grilo 2005. Although fluoxetine was not deemed superior to placebo in the study, specific comparisons of the treatments revealed that fluoxetine did not significantly differ from placebo, and in fact, the frequency of binge eating in both the placebo and fluoxetine groups improved. (*See* Ex.1029, Grilo 2005, pp.4-5). There is no indication that the patient population that was administered fluoxetine experienced a worsened condition as a result of treatment.

165. In my opinion, the Applicant's generalization that positive results for the treatment of BN cannot be applied with any reasonable expectation of success to the treatment of BED based on a single article concerning a fluoxetine study is flawed.

C. There Was a Reasonable Expectation that LDX Dimesylate Would Have Been Effective in Reducing Binge Eating Based on Dukarm and in View of the Extensive Information about LDX Dimesylate Provided By Mickle

166. During the prosecution of the '813 patent, the Applicant stated with respect to Mickle 2005 that "there was no reasonable expectation that the amino acid amphetamine prodrugs discussed by Mickle would provide the same benefits for Bulimia Nervosa patients as the d-amphetamine used by Dukarm." (Ex.1004, Jan. 2012 Resp., p.11). This argument does not detract from my opinions that rely on Mickle.

167. The premise of the Applicant's argument was two-fold: (i) LDX dimesylate is a long-acting stimulant with a markedly different pharmacokinetic profile from the short-acting d-amphetamine utilized by Dukarm; and (ii) Mickle 2005 is silent as to the appetite suppressant properties of LDX, which are well-established for the short-acting stimulant d-amphetamine. (*See* Ex.1004, Jan. 2012 Resp., pp.11-12). I address below both of these positions as they would apply to my obviousness opinions relying on Mickle as opposed to Mickle 2005, which was relied on by the Examiner.

168. First, the Applicant's argument focused on the fact that LDX dimesylate is a long-acting stimulant and d-amphetamine is a short-acting stimulant. However, as the Applicant notes, the patients in Dukarm were

administered d-amphetamine multiple times a day (Ex.1004, Jan. 2012 Resp., p.11; *see also* Ex.1019, Dukarm, pp.3-5), thus mimicking a long-acting effect.

169. Second, a POSA would have recognized from Mickle that following administration of LDX dimesylate, the pharmacologically active agent that is released from the prodrug is d-amphetamine (*see e.g.*, Ex.1023, Mickle ¶ 0118)—the same d-amphetamine used in Dukarm.

170. Third, Mickle provided pharmacokinetic details for LDX dimesylate and compared them to the pharmacokinetics of d-amphetamine. These details demonstrate that the pharmacokinetics of these two compounds are not so different such that a POSA would have been persuaded against using LDX dimesylate to reduce binge eating episodes. In fact, aspects of LDX dimesylate pharmacokinetics actually would have been attractive to a POSA for use in treating the binge eating of BN and BED.

171. Mickle compares the pharmacokinetics of LDX dimesylate to d-amphetamine in preclinical studies. The conclusion is that the area under the curve (AUC) for d-amphetamine following administration of LDX dimesylate is **the same** as an equivalent dose of d-amphetamine. (*See* Ex.1023, Mickle ¶¶ [0202]-[0206]) (emphasis added). This demonstrates that the extent of exposure to d-amphetamine is the same, whether LDX dimesylate or d-amphetamine is administered. Mickle also shows that for d-amphetamine, the maximum

concentration (Cmax) is lowered by about 20-30%, and the time-to-maximum-concentration (Tmax) is delayed following administration of LDX dimesylate as compared to an equivalent dose of d-amphetamine. (*See* Ex.1023, Mickle ¶¶ [0202]-[0206]). The blunted Cmax and extended Tmax of d-amphetamine following LDX dimesylate administration results in reduced euphoria (i.e., reduced abuse potential) while at the same time providing a high enough concentration of drug to maintain the desirable stimulant effects needed for treatment. (*See, e.g.*, Ex.1023, Mickle ¶ [0121]).

172. In addition to these basic pharmacokinetic parameters, Mickle also provided other pharmacokinetic data regarding LDX dimesylate that the POSA would have found attractive in a drug used to treat eating disorders. For instance, Mickle demonstrated that at suprapharmacological doses in preclinical studies, blood levels of d-amphetamine were substantially lower after LDX dimesylate administration as compared to following the administration of d-amphetamine, supporting the idea that LDX dimesylate has reduced abuse potential. (*See* Mickle Ex.1023 ¶¶ [0212]-[0214]). The claim of reduced abuse potential was further supported by data from a clinical trial in humans. (*See* Ex.1023, Mickle ¶¶ [0359]-[0360]). Reduced abuse potential is a beneficial feature for a drug that would be used in a patient population prone to substance abuse. (*See* Ex.1019, Dukarm, p.6). Mickle also disclosed that food does not affect the extent of absorption of d-

amphetamine from LDX dimesylate, and that the Tmax for d-amphetamine is delayed by only about one hour after a high-fat meal. (*See* Ex.1023, Mickle ¶ [0350]). These are pharmacokinetic properties a POSA would have found valuable in a drug used to treat binge eating. Additionally, Mickle teaches that "[t]here were no apparent differences" between males and females with respect to extent of exposure or half-life ($t_{½}$). (Ex.1023, Mickle ¶ [0351]).

173. Based on the positive pharmacokinetic attributes of LDX dimesylate described above, it is my opinion that a POSA would have been motivated to replace the d-amphetamine of Dukarm with LDX dimesylate of Mickle.

174. In arguing that there was no reasonable expectation that the LDX dimesylate in Mickle 2005 would provide the same benefits for BN patients as the d-amphetamine in Dukarm, the Applicant also honed in on the issue of the difference in appetite suppressant activity between d-amphetamine and LDX dimesylate. (*See* Ex.1004, Jan. 2012 Resp., pp.11-12). A POSA would not have viewed the difference in this activity as a deterrent to the use of LDX dimesylate for the treatment in BED. Rather, the report of decreased appetite in 39% of ADHD patients receiving LDX dimesylate, along with Mickle's identification of obesity as one of the preferred indications for this prodrug (*see* Ex.1023, Mickle ¶ [0124]), would have provided a POSA with motivation and a reasonable expectation of success for the use of LDX dimesylate to treat BED.

175. In sum, it is my opinion that a POSA would have recognized that the LDX dimesylate in Mickle provides the same benefits for binge eating behavior as the d-amphetamine in Dukarm.

X. NONE OF THE DATA OR ARGUMENTS PRESENTED DURING THE PROSECUTION OF THE '813 PATENT DEMONSTRATE UNEXPECTED RESULTS OR LONG-FELT NEED

176. I understand that during prosecution of the '813 patent the Examiner rejected claims similar to issued claim 1 as obvious over the Mickle '770 patent in view of Mattos and the VYVANSE Package Insert, as evidenced by the RITALIN Package Insert. (*See* Ex.1005, April 2012 OA, pp.5-8). The Applicant's response included arguments that (i) LDX dimesylate shows unexpected efficacy for treating BED, and (ii) there had been a long-felt and unmet need for a BED treatment. (*See* Ex.1006, June 2012 Resp., pp.8-10, 14-15). The Examiner considered these arguments as sufficient to rebut the obviousness case over the claims. (*See* Ex.1007, June 2012 Int. Sum.). However, it is my opinion that a POSA at the time of the invention would have (i) found that the clinical evidence identified by the Applicant regarding the efficacy of LDX dimesylate was not surprising or unexpected, and (ii) been aware of available treatment options effective for BED.

A. Examples 1, 2, and 5 of the '813 Patent Do Not Demonstrate that LDX Dimesylate Showed Unexpected Efficacy for Treating BED

177. The Applicant asserted that it "unexpectedly discovered that while psychostimulants as a class were not found effective for treating Binge Eating Disorder, lisdexamfetamine dimesylate was found unexpectedly effective for treating Binge Eating Disorder." (Ex.1006, June 2012 Resp., p.8). However, as described at length in this Declaration, a POSA would have known that many psychostimulants were successfully used for treating binge eating. (*See* above at ¶¶ 39-45). Thus, a POSA would not have been surprised that the psychostimulant LDX dimesylate would have been an effective treatment for BED.

178. It was well understood in 2007 that centrally acting psychostimulants can successfully treat binge eating as evidenced, for instance, by Ong (reduction in overeating after administering methylamphetamine), Schweickert (reduction in binge eating after administering methylphenidate), Sokol (reduction in binge eating and impulsivity after administering methylphenidate), Drimmer (reduction in binge eating after administering methylphenidate, mixed amphetamine salts, and d-amphetamine), and Dukarm (reduction in binge eating after administering d-amphetamine), to name a few. (*See* above at ¶¶ 39-45). Notably, the psychostimulants involved in these studies—methylamphetamine, methylphenidate, and d-amphetamine—all increase levels of DA (*see* Ex.1052, Fleckenstein, p.3; *see also* Ex.1051, Sulzer, p.2, 21), which as described above "is

one of the most important neurotransmitters involved in the reinforcing value of food and regulation of food intake." (Ex.1013, Epstein, p.1). In turn, a POSA would have expected that psychostimulants as a class, and especially those that affect DA levels, would be effective for treating BED. It follows that a POSA also would have expected LDX dimesylate to effectively treat binge eating and thereby treat BED, since LDX dimesylate is a centrally acting amphetamine prodrug that releases d-amphetamine.

179. Similarly, the positive results shown with respect to BED by the patients given LDX dimesylate from the Examples of the '813 patent would not have been surprising, which is in contrast to the position taken by the Applicant in the Response to the Final Office Action. For instance, regarding Example 1, the Applicant explained that the patient presented with comorbid ADHD, BED, and major depression. Treatment with LDX dimesylate reduced by 75% the number of days on which the patient experienced binge eating episodes. (*See* Ex.1006, June 2012 Resp., p.8). The Applicant regarded this result as unexpected since BED was not the treatment objective. (*See* Ex.1006, June 2012 Resp., p.8). However, Patient 1 was never previously treated with a centrally acting psychostimulant. In light of all the prior art described above that demonstrates the effective use of centrally acting psychostimulants to treat binge eating, a POSA would have expected that LDX dimesylate, also a centrally acting psychostimulant, would have

been effective for the treatment of BED. In my opinion, this result would not have been surprising or unexpected to a POSA.

180. The Applicant also asserted that the results provided in Example 2 were surprising. (*See* Ex.1006, June 2012 Resp., pp.8-9). The Applicant described the patient in Example 2 as having comorbid ADHD and BED and being treated with ADDERALL XR. (*See* Ex.1006, June 2012 Resp., p.8). It appears that ADDERALL XR treatment was not sufficient since LDX dimesylate was initiated "for treatment of the patient's ADHD to address 'wear off' effects from ADDERALL XR in the later afternoons and early evenings." (Ex.1001, '813 patent, col.20, ll.52-55). The example confirms this purpose by later stating that LDX dimesylate treatment was "to provide later coverage into the evening" primarily for the ADHD. (Ex.1001, '813 patent, col.20, l.67-col.21, l.3). Example 2 also notes that the patient "indicated binging behaviors in the evenings." (Ex.1001, '813 patent, col.20, ll.59-60). Treatment with LDX dimesylate successfully addressed the BED. (Ex.1001, '813 patent, col.21, ll.12-17).

181. In reviewing the complete description of Example 2 in the '813 patent, it is specifically noted toward the end "that Patient 2's ADHD symptoms were not at issue at the time lisdexamfetamine dimesylate monotherapy was begun," and that the "ADHD symptoms were adequately addressed with ADDERALL XR treatment." (Ex.1001, '813 patent, col.21, ll.35-39). I find these

statements in direct contradiction to the purpose of the initiation of LDX dimesylate treatment, which was to address ADHD symptoms late in the day. In other words, ADHD symptoms could **not** have been adequately addressed by ADDERALL XR treatment if the patient's ADHD symptoms late in the day were untreated. This inconsistency calls into question the Applicant's comparisons between the effects of ADDERALL XR and LDX dimesylate. With respect to BED, the binge eating episodes occurred primarily in the evening, when the ADDERALL XR wore off. (*See* '813 patent at col.20, ll.55-62). This would have suggested to a POSA that, not surprisingly, this psychostimulant was actually effective in addressing the BED during the day, just as it was effective for managing the daytime ADHD. Upon initiation of LDX dimesylate, daytime **and** evening symptoms of **both** disorders were adequately addressed. This also would not have been surprising, as LDX dimesylate is a centrally acting stimulant that provides sustained release (*See e.g.*, Ex.1023, Mickle, ¶¶ [0122], [0127], [0226]-[0227]).

182. Finally the Applicant also contended that the results provided in Example 5 are surprising. (*See* Ex.1006, June 2012 Resp., p.9). According to the Applicant, the patient was diagnosed with major depressive disorder and severe BED; multiple medications across different classes, including methylphenidate, were unsuccessful in treating the patient. (*See* Ex.1006, June 2012 Resp., p.9).

The Applicant indicated that upon administration of LDX dimesylate, the patient's BED symptoms improved significantly. (*See* Ex.1006, June 2012 Resp., p.9).

183. Again, I disagree that the treatment of the patient in Example 5 is a demonstration of surprising and unexpected results with respect to the successful treatment of BED with LDX dimesylate. The patient was administered seventeen different medications, of which only one (RITALIN, methylphenidate) was a centrally acting psychostimulant. (Ex.1001, '813 patent, col.23, ll.48-66). As I discussed above at length, it would have been obvious to use psychostimulants to treat binge eating and therefore BED. A POSA also would have recognized, however, that a patient will not necessarily respond to every psychostimulant, particularly when that patient has as complex a set of disorders as described in Example 5. Therefore, it would not have been surprising or unexpected that the Example 5 patient's BED symptoms did not improve in response to RITALIN, but did improve in response to LDX dimesylate. It was common in the field of eating disorders to switch medications when an initial pharmacologic intervention was not effective and to find that while one agent may not have provided positive results, another agent from the same class was effective. In fact, in the "Background" section, the '813 patent describes the practice of switching therapies when an initial pharmacologic intervention fails as a treatment. (*See* Ex.1001, '813

patent, col.2, ll.21-29). There is nothing about Example 5 in the '813 patent to suggest that the successful use of LDX dimesylate was surprising or unexpected.

184. Hence, for the reasons provided here, I disagree with the Applicant that the Examples of the '813 patent demonstrate any surprising or unexpected result.

B. In 2007 Treatments Were Available for Binge Eating, Including BED

185. According to the Applicant, at the time of the invention in 2007 there was a long-felt and unmet need for a BED treatment, since (i) BED was the most common eating disorder and (ii) there were no FDA-approved treatments for BED. (*See* Ex.1006, June 2012 Resp., p.14). The Applicant referred to (i) an article showing that BED occurred at a rate of 2.8% of the US population, and (ii) the Mayo Clinic website that indicated there was no medication specifically designed to treat BED. (*See* Ex.1006, June 2012 Resp., p.14). However, based upon my decades of clinical experience in the treatment of eating disorders, it is my opinion that in 2007 there were treatment options available to address BED.

186. First, the Applicant argued that there were "no FDA **approved** treatments for Binge Eating Disorder." (Ex.1006, June 2012 Resp., p.14) (emphasis added). Medical doctors, and in particular POSAs, would have known that FDA approval is not a prerequisite for using drugs for the treatment of various disorders, including BED. To this point, many of the publications cited in this

declaration demonstrate safe and effective off-label drug use for the treatment of eating disorders. In fact, the Applicant himself engaged in the practice of using drugs off-label when he prescribed LDX dimesylate to the patient discussed in Example 5 of the '813 patent. So, the fact that the FDA had not approved a drug for treating BED is irrelevant as to whether effective treatments were available.

187. Second, during prosecution when discussing the use of LDX dimesylate for the treatment of BED, the Applicant stated that "the only known medications are only partially effective (anti-depressants) or have serious side effects (topiramate)" and concluded that LDX dimesylate "thus fulfills a long-felt unmet need." (*See* Ex.1006, June 2012 Resp., p.14). The Applicant ignored the extensive body of published literature that identifies many classes of active agents that were used successfully for the treatment of binge eating, including for BED. I have already mentioned some of those options within this declaration, including in the discussion of Appolinario, which describes the effective use of antidepressants, anti-obesity agents, and anticonvulsants in treating BED. (Ex.1020, Appolinario, p.1, Abstract). In fact, both the American Psychiatric Association (2006) and the National Institute for Clinical Evidence (2004) provided treatment options for BED, including CBT and antidepressant medications, particularly SSRIs such as fluoxetine. (Ex.1031, Practice Guideline, p.21, 56, 85-86; Ex.1032, NICE, p.19-20).

188. Third, the Applicant's evidence of long-felt and unmet need actually suggests that there were treatment options for BED. During prosecution, the Applicant cited to an online Mayo Clinic document for the premise that "[t]here's no medication specifically designed to treat binge-eating disorder." (Ex.1006, June 2012 Resp., p.14). As a starting point, this statement is not equivalent to saying that there were no BED treatment options. To the contrary, the Mayo Clinic document also made clear that "several types of medication may help reduce symptoms, especially when combined with psychotherapy." (Ex.1006, June 2012 Resp., p.76). It is my opinion that psychotherapy, along with pharmacotherapeutic support was in 2007 and still is today, a highly successful treatment for BED.

189. In sum, I disagree that in 2007 there was a long-felt and unmet need for the claimed treatment of BED.

XI. CONCLUSION

190. At least since the early 1980s, studies have shown psychostimulants to be successful in treating the binge eating symptom of BN. Because it was well-established at the time of the invention that the binge eating symptom in BN and BED is the same, a POSA would have had a reasonable expectation of effectively treating the binge eating symptom of BED with a psychostimulant. In addition, prior to the date of the invention, centrally acting anti-obesity agents had been studied for the treatment of BED with positive outcomes. Despite these

encouraging results, it was known that psychostimulants present a risk for abuse, especially in a patient population susceptible to such abuse. It was further known that the studied anti-obesity agents, while exhibiting positive results, presented potential limitations to their use. Thus, a POSA would have been motivated to find an alternative centrally acting stimulant, and therefore would have turned to LDX dimesylate. Disclosed in Mickle, LDX dimesylate was a known centrally acting stimulant with many attractive properties including reduced abuse potential, anti-obesity action, and sustained release. A POSA would have had a reasonable expectation of successfully using LDX dimesylate to treat BED. For at least the reasons detailed in this declaration, it is my opinion that claims 1-13 of the '813 patent would have been obvious to a POSA at the time of the invention.

191. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Respectfully submitted,

Date: 5-8-14

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