IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.,
Petitioner

v.

SHIRE LABORATORIES, INC.,
Patent Owner.

U.S. Patent No. RE42,096 to Burnside *et al.*
Issue Date: Feb. 1, 2011
Title: Oral Pulsed Dose Drug Delivery System

Inter Partes Review No.: IPR2016-XXXX

Petition for *Inter Partes* Review of U.S. Patent No. RE42,096 Under 35 U.S.C. §§ 311-319 and 37 C.F.R. §§ 42.1-.80, 42.100-.123

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TABLE OF CONTENTS

TABLE OF AUTHORITIES

Page(s)

CASES

STATUTES

OTHER AUTHORITIES

Petitioner's Exhibit List

Exhibit #	*Description*
1001	U.S. Patent No. RE 42,096 ("the '096 patent"), "Oral Pulsed Dose Drug Delivery System"
1002	Declaration of David Auslander, Ph.D.
1003	Curricula Vitae of David Auslander, Ph.D.
1004	Amidon *et al.* U.S. Patent No. 5,229,131, "Pulsatile Drug Delivery System"
1005	Mehta *et al.*, U.S. Patent No. 5,837,284, "Delivery of Multiple Doses of Medication"
1006	Physician's Desk Reference 28th edition (1974)
1007	Physician's Desk Reference 47th edition (1993)
1008	Physician's Desk Reference 49th edition (1995)
1009	Physician's Desk Reference 51st edition (1997)
1010	ANSEL, POPOVICH & ALLEN, PHARMACEUTICAL DOSAGE FORMS AND DRUG DELIVERY SYSTEMS 220, 223 (6th ed. 1995)
1011	Gerald L. Brown *et al*, Behavior and Motor Activity Response in Hyperactive Children and Plasma Amphetamine Levels Following a Sustained Release Preparation, *J. Am. Academy of Child Psychiatry*, vol. 19, 255–239 (1980)
1012	Charles S. L. Chiao, Ph.D. & Joseph R. Robinson, PhD., *Sustained-Release Drug Delivery Systems*, 1660-1675, *in* REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY (19th ed. 1995)
1013	W. H. Hartung & J. C. Munch, *Amino Alcohols, VI. The Preparation and Pharmacodynamic Activity of Four Isomeric Phenylpropylamines*, 53 J. AM. CHEM. SOC. 1875, 1875-79 (1931)
1014	Brian B. Hoffman & Robert J. Lefkowitz, *Catecholamines, Sympathomimetic Drugs, and Adrenergic Receptor Antagonists*, in GOODMAN & GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, 199 (9th ed. 1996)
1015	The Merck Index (Susan Budavari, *et al.*, eds., 11th ed. 1989)

Exhibit #	***Description***
1016	Stuart C. Porter, Ph.D., *Coating of Pharmaceutical Dosage Forms*, 1650-1659, 1653 *in* REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY (19th ed. 1995)
1017	Patricia K. Sonsalia, *Central Nervous System Stimulants*, in REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY 1233-34 (19th ed. 1995)
1018	Edward Stempel, *Prolonged-Action Medication*, *in* DISPENSING OF MEDICATION, 1024 (Eric W. Martin ed., 7th ed. 1971)
1019	1995 United States Pharmacopeia and National Formulary, USP 23-NF 18 (1994)
1020	Patent Owner Preliminary Response, dated January 19, 2016
1021	Petition for Inter Partes Review of USPN RE42,096, dated October 1, 2015
1022	Decision Instituting Inter Partes Review of USPN RE42,096, IPR2015-02009
1023	Dahlinder *et al.*, U.S. Patent No. 4,927,640, "Controlled Release Beads Having Glass or Silicon Dioxide Core"
1024	Arwidsson *et al.*, U.S. Patent No. 5,783,215, "Pharmaceutical Preparation"
1025	Select Portions of NDA 11522
1026	"Adderall and Other Drugs for Attention-Deficit/Hyperactivity Disorder" in The Medical Letter (1994)
1027	Physician's Desk Reference 48th edition (1994)
1028	Records from the U.S. Copyright Office for PDR 1997

I. INTRODUCTION

Mylan Pharmaceuticals Inc. ("Petitioner") petition for *Inter Partes* Review, seeks cancellation of claims 1-25 ("challenged claims") of U.S. Patent No. RE42,096 ("the '096 patent") (EX1001), which according to the current records of the USPTO is assigned to Shire LLC ("Patent Owner").

II. OVERVIEW

Generally speaking, the '096 patent purports to claim dosage forms of mixed amphetamine salts, such as the four amphetamine-salt combination of Adderall®, wherein the dosage forms contain an immediate-release dose and a delayed "*pulsed"* enteric-release dose such that the delayed "*pulsed"* enteric-release dose can, in some instances, release "essentially all" of the amphetamine salts within about 60 minutes of initiation. *See* EX1001, Claim 1. The dosage form is purported to be useful for treating Attention Deficit Hyperactivity Disorder (ADHD). *See*, *Id*., 7:51-58.

Prior to the earliest priority date for the '096 patent, the specific pharmaceutically active amphetamine salts used in Adderall® (an immediate-release product), were well known in the art for treating ADHD. Moreover, a person of ordinary skill in the art ("POSA") would have been motivated to modify the immediate-release form of the amphetamine salt products (*i.e*., Adderall®) because it was known that the immediate-release formulations presented problems such as: (i) amphetamine abuse, (ii) the inconvenience of twice-a-day administration, and

(iii) the stigma children felt by the in-school administration of the second dose required by a twice-a-day formulation. EX1002, ¶¶36-37. A POSA would have sought to formulate a once-a-day capsule of the four-amphetamine salt combination of Adderall® to include a delayed pulsed component to avoid such problems. *Id*., at ¶38.

The alleged "invention" of the '096 patent does nothing more than modify then existing prior art amphetamine salt products with well-known techniques to include a so-called delayed "pulsed" release component. In fact, in a related IPR (IPR2015-02009), the patent owner admitted that prior art U.S. Patent No. 5,837,284 ("the '284 patent) (EX1005) teaches the required parameters of a "pulsed" dosage. (EX1020, Patent Owner Preliminary Response, dated January 19, 2016 at 16:12-16); *In re Fout,* 675 F.2d 297, 300 (C.C.P.A. 1982) (explaining that a parties' admissions may create prior art).

With this teaching, all a POSA had to do was follow the directions set forth in U.S. Patent No. 5,229,131 ("the '131 patent") (EX1004) to enable the desired parameters of the '284 patent with a reasonable expectation of success. Specifically, the '131 patent teaches pH-independent enteric "permeability controlled systems" (EX1004, 10:59-11:12) that provide pulsed dosages that release essentially all of the active agent in about 17-50 minutes (*Id*. at 24:43-45). The '131 patent teaches single dose units that "can be tailored to simulate the AUC [area under the curve]

(preferably within 5%) of the immediate-release dosage form administered in divided doses." *Id*., at 24:59-61. In other words, to the extent a POSA would have looked for guidance beyond the '284 patent when making such a formulation disclosed in the '284 patent, the POSA would have only had to look to the '131 patent.

III. STANDING (37 C.F.R. § 42.104(a); PROCEDURAL STATEMENTS)

Petitioner certifies: that (1) the '096 patent is available for IPR; and (2) Petitioner is not barred or estopped from requesting IPR of any claim of the '096 patent on the grounds identified herein. This Petition is filed in accordance with 37 C.F.R. § 42.106(a). Filed herewith are a Power of Attorney and an Exhibit List pursuant to § 42.10(b) and § 42.63(e). The required fee is paid through online credit card, and the Office is authorized to charge any fee deficiencies and credit overpayments to Deposit Acct. No. 160605 (Customer ID No. 00826).

IV. MANDATORY NOTICES (37 C.F.R. § 42.8(a)(1))

A. Each Real Party-In-Interest (37 C.F.R. § 42.8(b)(1))

Mylan Pharmaceuticals Inc., Mylan Inc. and Mylan N.V.

B. Notice of Related Matters (37 C.F.R. § 42.8(b)(2))

1. Judicial Matters

The '096 patent is currently (or was) the subject, as the parent patent or current reissue form, of the following litigations: (1) *Shire LLC v. Amerigen Pharms. Ltd.*,

14-cv-6095 (D.N.J); (2) *Shire LLC v. Corepharma, LLC*, 14-05694 (D.N.J); (3) *Shire LLC v. Par Pharm., Inc.*, 15-cv-01454 (D.N.J); (4) *Shire Labs., Inc. v. Impax Labs, Inc.*, 03-cv-1164 (D. Del.); (5) *Shire LLC v. Sandoz, Inc.*, 07-cv- 197 (D. Colo.); (6) Shire Labs., Inc. v. Barr Labs., Inc., 03-cv-1219,-6632 (SDNY); (7) Shire LLC v. Watson Pharms., Inc., 11-cv-2340 (SDNY); (8) *Shire LLC v. Neos Therapeutics, Inc.*, 13-cv-1452 (N.D. Tx.); (9) *Shire LLC v. Colony, Pharms. Inc.*, 1:07-cv-00718 (D. Md.); (10) *Shire Labs., Inc. v. Andrx Pharms. LLC,* 07-cv-22201 (S.D. Fla.); and (11) *Shire Llc v. Abhai LLC,* 15-cv-13909 (D. Mass.).

2. Administrative Matters

The ’096 patent is currently the subject of *Inter Partes* Review IPR2015-02009. Petitioner is also aware of at least the following related family members: application No. 11/091,011 (“the ’011 application”), now the ’096 patent, is a reissue of application No. 09/176,542 (“the ’542 application”), now U.S. Patent No. 6,322,819. Related family member application 11/091,010 (“the ’010 application”), now U.S. Patent No. RE41,148, is a reissue of application no. 09/807,462 (“the ’462 application”), now U.S. Patent No. 6,605,300.

C. Designation of Lead and Back-Up Counsel and Service (37 C.F.R. §§ 42.8(b)(3), 42.8(b)(4), 42.10(a), and 42.10(b))

Lead Counsel: Jitendra Malik, Ph.D. (Registration No. 55,823; jitty.malik@alston.com). Backup Counsel: Bryan L. Skelton, Ph.D. (Registration

No. 50,893; bryan.skelton@alston.com); James Abe (Registration No. 61,182; james.abe@alston.com); Brianna Kadjo (Registration No. 74,307; brianna.kadjo@alston.com). Please direct all correspondence to lead counsel at the following address: 4721 Emperor Boulevard, Suite 400, Durham, North Carolina 27730. Telephone: (919) 862-2210. Facsimile: (919) 862-2260. Petitioner consents to email service.

V. STATEMENT OF THE PRECISE RELIEF REQUESTED AND THE REASONS THEREFORE (37 C.F.R. § 42.22(a))

Petitioners request IPR and cancellation of claims 1-25. Petitioners' full statement of the reasons for the relief requested is set forth in detail below.

VI. THE '096 PATENT

At a high level, the challenged claims of the '096 patent are directed to a "pulsed" dose drug delivery system for pharmaceutically active amphetamine salts. The '096 patent has seven independent claims (claims 1, 2, 5, 8, 11, 13, and 18). Independent claim 1 is directed to a pharmaceutical formulation of mixed amphetamine salts comprising an immediate-release dosage form and a delayed enteric-release dosage form, wherein the delayed pulsed enteric-release dosage form releases "essentially all" of the mixed amphetamine salts within about 60 minutes of initiation of the delayed pulsed enteric-release. EX1001, 12:53-67.

As to the remaining independent claims: Claim 2 is similar to claim 1, but

does not require that the amphetamine salts be mixed and adds a limitation wherein the enteric-release coating has a thickness of at least 25 μ. EX1001, 13:1-13. Claim 5 is similar to claim 1, but does not require that the amphetamine salts be mixed and adds a limitation wherein the immediate-release and enteric-release dosage forms are present on a single core. EX1001, 13:21-37. Claim 8 is similar to claim 1, but adds a limitation wherein the delayed release provides a blood level that is greater than the blood level provided by the immediate release. EX1001, 13:45-64. Claim 11 is similar to claim 8, but adds a limitation wherein the immediate-release and enteric-release dosage forms are present on a single core. EX1001, 14:4-25. Claim 13 is similar to claim 1, but does not require that the amphetamine salts be mixed and adds a limitation wherein the composition includes a protective layer over the enteric-release coating. EX1001, 14:32-45. Claim 18 is similar to claim 13, but the protective layer limitation is more specific, reciting that a "protective layer" exists "between the at least one pharmaceutically active amphetamine salt and the enteric-release coating." EX1001, 14:63-15:11.

A. CLAIM CONSTRUCTION

In IPR2015-02009, after considering Petitioner Amerigen's and Patent Owner's arguments, Petition for Inter Partes Review of USPN RE42,096, dated October 1, 2015 (EX1021), the Board decided the following terms (provided below) required explicit construction. Petitioner Mylan accepts the Board's constructions

for the purposes of this IPR:

"Pharmaceutically active amphetamine salts," "amphetamine salt," and "mixed amphetamine salts": "Pharmaceutically active amphetamine salts" includes non-salts, such as "amphetamine base" and "methylphenidate," as well as salts of amphetamine base and methylphenidate. "Amphetamine salt(s)" includes "amphetamine base" and "methylphenidate," as well as salts of amphetamine base and methylphenidate. "Mixed amphetamine salts" means made up of pharmaceutically active amphetamine salts of more than one kind.

"*Enteric-release coating":* "Enteric-release coating" refers to a coating that will delay release of a drug until the drug has passed through the stomach and reached the intestines.

"Essentially all": "Essentially all" to mean "less than 100%, and not less than 80%."

In Petitioner's view, all other claim terms should be given their broadest reasonable interpretation in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b).

VII. PERSON OF ORDINARY SKILL IN THE ART ("POSA") & STATE OF THE ART

With respect to the '096 patent, a POSA would have had education and/or experience in the field of drug delivery systems, with knowledge of the scientific

literature concerning the same, including some understanding of pharmaceutical formulations for administering amphetamine salts as of 1998. The education and experience levels may vary between persons of ordinary skill, with some persons holding a basic Bachelor's degree, but with 5-10 years of relevant work experience, or others holding more advanced degrees—*e.g.*, Ph.D..—but having fewer years of experience. A person of ordinary skill may work as part of a multi-disciplinary team and draw upon not only his or her own skills, but also take advantage of certain specialized skills of others in the team, to solve a given problem. Declaration of David Auslander, Ph.D, (EX1002 ¶¶17-18).

VIII. IDENTIFICATION OF CHALLENGE (37 C.F.R. § 42.104(b))

Petitioners respectively request IPR of claims 1-25 of the '096 patent on the ground of unpatentability outlined below. Per 37 C.F.R. § 42.6(d), copies of the references are filed herewith. In support of the proposed grounds, this Petition includes the declaration of a technical expert, David E. Auslander, Ph.D. (EX1002), explaining what the art would have conveyed to a POSA as of the priority date. Dr. Auslander is an expert in the field of pharmaceutical formulations and has offered a declaration from the perspective of a POSA.

Ground	References	Basis	Claims Challenged
1	The '284 patent in light of the PDR 1997, Brown and the '131 patent	103	1-25

Prior art references in addition to the primary references listed above provide further background, further motivation to combine the teachings of these references and/or further support for why a POSA would have a reasonable expectation of success to arrive at the invention recited in the challenged claims.

A. The Scope and Content of the Prior Art

1. The '284 Patent

U.S. Patent No. 5,837,284 ("the '284 patent" (EX1005)) entitled "Delivery of Multiple Doses of Medication" was issued on November 17, 1998, from application serial No. 08/892,190, filed on July 14, 1997, and therefore qualifies as prior art under 35 U.S.C. § 102(e) (pre-AIA). The '284 patent was disclosed during prosecution of the '096 application.

The '284 patent teaches a pharmaceutically active amphetamine salt, *i.e.* methylphenidate, for treating ADHD, where the dosage form contains "an immediate dosage and a delayed second dosage [which] provides for reduced abuse potential, improved convenience of administration, and better patient compliance, especially when [it] is used to treat certain central nervous system disorders." EX1005, 1:26-46. The '284 patent teaches using methylphenidate, "a mild central nervous system stimulant with **pharmacological activity qualitatively similar to that of amphetamines**," and its pharmaceutically acceptable salts to treat ADHD. *Id.* at 2:5-16 (emphasis added).

In reference to its release profile, the '284 patent explains "the [t]wo releases can be referred to as 'pulses', and such a release profile can be referred to as 'pulsatile.'" *Id.* at 5:35-36. To attain the desired release profile, according to the '284 patent, as an example, the composition may include "a dosage form containing two groups of particles, each containing the methylphenidate drug." *Id.* at 3:3-7. "The first group of particles provides a substantially immediate dose of the methylphenidate drug," while "[t]he second group of particles comprises coated particles … [which] provide a delay of from about 2 hours to about 7 hours following ingestion before release of the second dose." *Id.* at 3:7-19. This "eliminates the need for a patient, for example a child being treated for ADD, to carry a second dose for ingestion several hours after ingestion of a first dose." *Id.* at 5:18-21.

Moreover, the second group of particles "comprise methylphenidate drug in admixture with one or more binders, wherein the amount of methylphenidate drug is from about 2% to about 75%, preferably from about 2.5% to about 50%, and more preferably from about 5% to about 20%, by weight of the second group of particles, and a coating comprising an ammonio methacrylate copolymer in a quantity sufficient to provide a dose of methylphenidate delayed by from about 2 hours to about 7 hours following ingestion." *Id.* at 4:12-21.

Immediate release is "release within about a half hour following ingestion, preferably about 15 minutes, and more preferably within about 5 minutes following

ingestion." *Id.* at 6:5-8. Delayed pulse release is "a drug release profile which includes a period during which no more than about 10 percent of the drug in a particular dosage form is released, followed by a period of from about 0.5 hour to about 2.5 hours, preferably about 1.5 hours, more preferably about 1 hour, in which no less than about 70 percent, **preferably no less than about 80 percent, and more preferably no less than about 90 percent, of the drug is released**." *Id.* at 6:8-16 (emphasis added).

An initial immediate dosage may be prepared by "incorporating the methylphenidate drug into a form which allows for substantially immediate release of the drug once the dosage form is ingested by a patient," such as "powders, coated and uncoated pellets, and coated and uncoated tablets" for administration "in a tablet or capsule form which may also include the delayed dose." *Id.* at 7:1-6. "The delayed dose of a methylphenidate drug in the dosage forms of the present invention is provided in part by the use of certain copolymers referred to as 'ammonio methacrylate copolymers,'" which "comprise acrylic and/or methacrylic ester groups together with quaternary ammonium groups." *Id.* at 7:12-19. The acrylic groups are preferably derived from monomers selected from C_1-C_6 alkyl esters of acrylic acid and C_1-C_6 alkyl esters of methacrylic acid," and specific examples include: "methyl acrylate, ethyl acrylate, methyl methacrylate, and ethyl methacrylate." *Id.* at 7:25-31.

The specification indicates that the dosage forms preferably contain the drug in the form of small particles or pellets. *Id.* at 9:23-49. Following the formation of suitable particles, the delayed-release particles are coated with a polymer-containing coating. *Id.* at 10:16-24. The amount of coating is determined by the delay required and the amount of drug to be delivered. *Id.* at 10:16-37. "The appropriate amount of coating can advantageously be determined using in vitro measurements of drug release rates obtained with selected amounts of coatings." *Id.*

2. PDR 1997

The Physician's Desk Reference 51st edition (1997) (hereinafter "PDR 1997" (EX1009)) was published on November 1996 (EX1028), and provides the Adderall® label from "May 1996," and qualifies as prior art under 35 U.S.C. § 102(b). PDR 1997 was disclosed to the PTO during prosecution of the '096 application. PDR 1997 indicates that Adderall® containing 10 or 20 mg of mixed amphetamine salts (d-amphetamine saccharate, amphetamine aspartate, d-amphetamine sulfate and amphetamine sulfate) was approved for the treatment of ADHD. EX1009, 2209-10. To provide some context, in 1994, the predecessor of Shire changed the name of a product called Obetrol® to Adderall®, and began promoting Adderall® for the treatment of ADHD. EX1026; EX1027 (noting Obetrol® could be used for ADHD in addition to obesity); EX1002, ¶42. Adderall® has the exact same amphetamine mixture as Obetrol®. (*Compare* EX1009 *with*

EX1026). Thus, the specific mixture of amphetamines in the same proportion for the treatment of ADHD was known as early as 1994, *i.e*., before any relevant priority date. EX1025; EX1001, 3:5-7 (describing prior art Adderall® and characterizing it as the "current" treatment); EX1002, ¶42.

3. Brown

Brown *et al*., Behavior and Motor Activity Response in Hyperactive Children and Plasma Amphetamine Levels Following a Sustained Release Preparation, *J. Am. Academy of Child Psychiatry* 19, 255–239 (1980) (hereinafter "Brown" (EX1011)) was published in 1980 and qualifies as prior art under 35 U.S.C. § 102(b). Brown was disclosed to the PTO during prosecution of the '096 application.

Brown explains that "[a]mphetamines have been used for over 40 years to treat children with aggressive, impulsive behavioral disturbances." EX1011, 225 (internal quotations omitted). Brown discloses a single-dose study of sustained-release *d*-amphetamine capsules in nine hyperactive children. *Id*. at 227. Brown found that "like earlier single-dose amphetamine studies in hyperactive children, [sustained-release d-amphetamine] shows significant behavior and motor activity responses to the medication only during the absorption phase, and these responses are not correlated with specific plasma levels of *d*-amphetamine." *Id.* at 237. Brown further explains, compared to the immediate-release tablet, "it is clear that the peak plasma level occurs later and lasts longer with sustained-release (up to h 8), though

this later occurrence and more plateau-like peak plasma level is not accompanied by a longer period of significant response to the medication." *Id.* at 234.

4. The '131 Patent

U.S. Patent No. 5,229,131 ("the '131 patent" (EX1004)) was issued on July 20, 1993, and therefore qualifies as prior art under 35 U.S.C. § 102(b) (pre-AIA)). The '131 patent was disclosed to the PTO during prosecution of the '096 application. The '131 patent discloses a drug delivery system that includes individual drug-containing subunits for releasing 'pulsed' doses. EX1004, 6:59-65. The term "pulsed dose" describes the rapid delivery of a dose at specific times analogous to the rate of release from an immediate-release dosage form administered according to an appropriate dosing schedule. *Id.* at 7:1-6. The '131 patent teaches dissolution profiles can be controlled by using: (1) pH-sensitive enteric coatings which are eroded in response to the pH, or (2) permeability-controlled systems which are subject to disruption in response to absorption of water from the environment. *Id.* at 7:17-31.

IX. Invalidity Analysis

A. Ground 1: Claims 1-25 Would Have Been Obvious Over the '284 Patent in Light of the PDR 1997, Brown and the '131 Patent

In IPR2015-02009, the Board concluded that "given the teachings of Mehta [the '284 patent] and the Adderall® PDR, one of ordinary skill in the art would have been motivated to make a dosage form—with either Mehta's methylphenidate

(Ritalin®), or the amphetamine salts in Adderall®—comprising an immediate-release component and a delayed-release component that releases essentially all of the amphetamine salts or salts within about 60 minutes after initiation of the delayed release." EX1022, 32-33. However, in IPR2015-02009, the Board only instituted the IPR against the '096 patent on claims 18-21, 23, and 25, explaining that the Board was "persuaded that the Petition establishes a reasonable likelihood that Petitioner would prevail in showing that claims 18–21 and 23 of the '096 patent are unpatentable under 35 U.S.C. § 102 as anticipated by [the '284 patent], and that claims 18–21, 23, and 25 are unpatentable under 35 U.S.C. § 103(a) [as is obvious in view of [the '284 patent] and the Adderall® PDR]." EX1022, 37, 38.

Although the instant petitioner makes use of the '284 patent, the invalidity rationale set forth below is different from the grounds the Board addressed in IPR2015-02009. EX1002, ¶¶93-94. Based on the teachings of the'284 patent in light of the PDR 1997, Brown and the '131 patent, claims 1-25 of the '096 patent would have been obvious to a POSA for the following reasons.

1. Differences Between the Claims and the Prior Art

a. Independent Claim 1 and Its Dependent Claims 3, 4, 6 and 7

(i) Claim 1

Claim 1 would have been obvious to a POSA for the reasons explained below. EX1002, ¶95. A POSA would have been led by the prior art as shown in the

following claim chart:

Claim 1	The Prior Art
1. A pharmaceutical composition for delivery of one or more pharmaceutically active amphetamine salts, comprising:	Pharmaceutical dosage forms containing mixed amphetamine salt and/or d-amphetamine were known *See,* PDR 1997 (EX1009), *see also,* the '096 patent (EX1001), 3:5-7, (discussing the prior art product containing the four amphetamine sulfate salts of Adderall®).
(a) one or more pharmaceutically active amphetamine salts covered with an immediate-release coating; and	Example 1 teaches an immediate release with a first layer of methylphenidate (MPD) and a second seal layer of HPMC. The '284 patent (EX1005), 12:53 to 13:8; *see also* Board Decision (EX1022) 8 ("the term "pharmaceutically active salts" includes non-salts, such as "amphetamine base" and "methylphenidate" as well as salts of amphetamine base and methylphenidate.").
(b) one or more pharmaceutically active amphetamine salts that are covered with an enteric-release coating that provides for delayed pulsed enteric release,	The layered pellets comprising methylphenidate prepared in Example 1 are then coated with the enteric-release coating described in Example 2. Specifically, the '284 patent at Example 2 describes a delayed pulse enteric release using Eudragit RS and RL. The '284 patent (EX1005), 13:10-35; *see also* Board Decision (EX1022) at 28 (explaining that "Mehta [the '284 patent] discloses formulations with delay periods long enough to release the drug enterically, *i.e*., in the intestines, rather than the stomach."). "One disadvantage of the pH-dependent system is that release of the drug in vivo is affected by the variable pH in the small intestine. Moreover, release time is affected by gastric emptying. Therefore, a second approach which is pH independent is set forth in detail hereinbelow. However, as the results shown hereinabove indicate, pulse time can be controlled by careful choice of core composition, coating composition, and coating curing process variables." The '131 patent (EX1004), 10:59-11:2.

Claim 1	The Prior Art
wherein said enteric-release coating releases essentially all of said one or more pharmaceutically active amphetamine salts coated with said enteric coating within about 60 minutes after initiation of said delayed pulsed enteric [release] *release*;	The '131 patent discloses enteric-release coating: "Permeability-controlled systems are generally based on polymeric coatings which are water-permeable to permit water from the aqueous environment in the gastrointestinal tract of a living being to enter into a coated drug-containing core at a controllable rate and to displace air from the core followed by a build-up of pressure as the core contents expand until the coating is ruptured at the appropriate time." EX1004, 11:5-12. "a drug release profile which includes a period during which no more than about 10 percent of the drug in a particular dosage form is released, followed by a period of from about 0.5 hour to about 2.5 hours, preferably about 1.5 hours, more preferably about 1 hour, in which no less than about 70 percent, preferably no less than about 80 percent, and more preferably no less than about 90 percent, of the drug is released." The '284 patent (EX1005), 6:10-17; (emphasis added). "The term pulsed dose is used herein to describe the rapid delivery of a dose of drug (F_1, F_2, . . . , F_n) at specific respective times (T_1, T_2, . . . , T_n) into the portal system which is analogous to the rate of release from an immediate-release dosage form administered according to an appropriate dosing schedule." '131 patent (EX1004), 6:68-7:6. "By devising a drug dosage delivery form which will release pulsed doses at rates comparable to immediate-release forms, bioavailability will not be compromised by a decreased release rate as has been observed in conventional sustained release dosage forms for these drugs …." The '131 patent (EX1004), 7:11-16.
wherein the pharmaceutically active amphetamine	Prior art Adderall® contains the exact mixed amphetamine salts. *See,* PDR 1997 (EX1009); *see also,* the '096 patent (EX1001), 3:5-7.

Claim 1	The Prior Art
salts in (a) and (b) comprise mixed amphetamine salts.	

As admitted by the '096 patent, Adderall® IR was a known pharmaceutical composition used for the treatment of ADHD. EX1002, ¶96; EX1001, 3:5-7; *In re Fout,* 675 F.2d at 300 (explaining that a parties' admissions may create prior art). The PDR 1997 teaches that "mixed amphetamine salts" are administered in a twice daily dose, with a starting dose of 5 mg followed by a second dose that is administered 4 to 6 hours after the first. EX1002, ¶97; EX1009, 2209-10.

Brown (EX1011) teaches the pharmacokinetics associated with the administration of amphetamine salts for the treatment of ADHD. EX1002, ¶98. It was known that both behavioral and motor responses were greatest during the absorption of the amphetamines associated with rising plasma *d*-amphetamine values. EX1011, 233. Compared to the immediate-release tablet, the peak plasma level of the sustained release dosage form occurs later and lasts longer, though this later occurrence and more plateau-like peak plasma level is not accompanied by a longer period of significant response to the medication. *Id.* at 234. Put another way, the data in Brown, would have indicated to a POSA that *sustained-release d*-amphetamine **would not have** led to a prolonged clinical response. EX1002, ¶99. Thus, a POSA seeking to develop a once-a-day Adderall® formulation would not

have looked to available sustained-release formulations. *Id*. Rather, a POSA would have been motivated to look at a **pulsed** delivery because such a formulation would have had the same release profile as taking Adderall® immediate-release formulation two times a day (*i.e*., the approved dosing regimen). *Id*. at ¶100.

Therefore, a POSA would look to other art in the field of attention deficit disorders to find an approach that provided for an immediate dosage and a delayed second dosage, whereby, the second dosage is released in a quick manner (*i.e*., pulsed). *Id*. The POSA would have been aware of the '284 patent which describes a methylphenidate dosage form that is effective for treating ADHD. *Id*., at 101. The fact the '284 patent focuses on using methylphenidate rather than amphetamines would not have detracted the POSA from the teachings of the '284 patent because as the patent explains methylphenidate is "a mild central nervous system stimulant with pharmacological activity qualitatively similar to that of amphetamines." *Id.*; EX1005, 2:5-16.

The dosage form described in the '284 patent allows for an immediate-release component followed by a second delayed pulse dosage:

> The release of the first dose preferably occurs substantially immediately; for example, within about 30 minutes following administration. Following a period of little or substantially no drug release, the second dose is released. The two releases can be referred to as "pulses," and such a release profile can be referred to as "pulsatile."

EX1005, 5:31-36. The '284 patent further provides motivation to use this pulsed

dosage form for ADHD (and similar disorders) because it would lead to reduced abuse potential, improved convenience of administration, and better patient compliance. EX1002, ¶103; EX1005, 1:26-29.

a) There Would Have Been a Reasonable Expectation of Success

Moreover, there would have been a reasonable expectation of success because the '284 patent is directed to the very same conditions, *i.e.*, ADHD, (EX1005, 3:67) and teaches the parameters needed to achieve a successful pulsed-release dosage form, while the '131 patent would have provided detailed formulation information about how to achieve this objective. EX1002, ¶104.

Specifically, the '131 patent teaches pH independent enteric "permeability controlled systems" that provide pulsed dosages that release "*essentially all*" of the active agent in 20-40 minutes. EX1002, ¶105; EX1004, 11:3-34. The *in vivo* data disclosed in the '131 patent for such enteric "permeability controlled systems" shows a pulsed release lasting about 20-50 minutes. *See, e.g.*, Figures 8, 9, 10 & 11 (showing that the decrease in pH (labeled "DDT") corresponds to essentially all of the active ingredient being released in under 60 minutes). In reference to these figures, the '131 patent states that: "The disintegration dissolution (DDT) was ~17 minutes in three of the dogs and about 50 minutes in the fourth." EX1004, 24:43-45. As the '131 patent explains, the disclosed dosage forms "will release pulsed

doses at rates comparable to immediate-release forms." EX1002, ¶105; EX1004, 7:11-13.[1]

Moreover, a skilled artisan would know that the '131 patent is not limited to

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[1] As the '131 patent teaches:

> The term pulsed dose is used herein to describe the rapid delivery of a dose of drug (F_1, F_2, . . . , F_n) at specific respective times (T_1, T_2, . . . , T_n) into the portal system which is analogous to the rate of release from an immediate-release dosage form administered according to an appropriate dosing schedule.
>
> * * *
>
> By devising a drug dosage delivery form which will release pulsed doses **at rates comparable to immediate-release forms**, bioavailability will not be compromised by a decreased release rate as has been observed in conventional sustained-release dosage forms for these drugs ….

The '131 patent (EX1004), 6:68-7:6; 7:11-16 (emphasis added).

any particular active agent, but can be applied to "any other drug":

> It is to be understood that although the examples herein have been given in terms of propranolol, the principles of the invention are applicable to **any other drug**. The process of determining the effect of core contents and coating formulations, as set forth herein, will enable one of ordinary skill in the art to fabricate a pulsatile drug delivery system for any given drug and dosing schedule or combination of drugs and respective dosing schedules.

EX1004, 25:5-10 (emphasis added); EX1002, ¶106. In fact, the '131 patent provides a list of other active agents. EX1004, 25:20-44; EX1002, ¶107. As Dr. Auslander explains, these active agents have various different properties further substantiating that the pulsed dosage forms of the '131 patent could have been applied to other known active agents including methylphenidate and amphetamines. EX1002, ¶¶106-107.

With respect to the '284 patent, it teaches delivering a dosage form containing two groups of particles, each containing methylphenidate for the treatment of ADHD. EX1002, ¶108; EX1005, 3:3-7. The initial immediate release occurs "within about a half hour following ingestion, preferably about 15 minutes, and more preferably within about 5 minutes following ingestion." EX1005, 6:5-8. The second, delayed release is a pulsed release because "a drug release profile which includes a period during which no more than about 10 percent of the drug in a particular dosage form is released, followed by a period of from about 0.5 hour to about 2.5 hours, preferably about 1.5 hours, **more preferably about 1 hour, in which no less than**

about 70 percent, preferably no less than about 80 percent, and more preferably no less than about 90 percent, of the drug is released." *Id.*, 6:10-17; EX1002, ¶109.

Indeed, the patent owner has admitted that the '284 patent teaches the required parameters of the claim. EX1020, 16:12-16; EX1002, ¶110. While admitting in a related IPR that the '284 patent teaches the pulsed parameters of "no less than 70%, 80%, or preferably 90 percent within a period of 0.5 to 2.5 hours or 1.5 hours, preferably 1 hour," the patent owner could only aver that "these parameters are a wish-list, at most a goal." EX1020, 16:12-16; EX1002, ¶110.

Yet, in combination with the '131 patent, which is focused on providing pulsed dosage forms, the skilled artisan would have had all the necessary guidance to practice the parameters plainly set forth in the '284 patent. *See, e.g.*, EX1004, 11:35-25:15 (providing guidance); EX1002, at ¶111. Accordingly, it would have been a matter of routine experimentation to prepare a pulsed dose where more than 80% of the active agent is released (*i.e.*, "essentially all") within sixty minutes after initiation of the pulsed dosage. Accordingly, claim 1 would have been obvious. EX1002, ¶¶111-12.

(ii) Claim 3

Claim 3 depends on claim 1 and merely further requires that the "one or more pharmaceutically active amphetamine salts are coated onto a core." The '284 patent

teaches coating its active agent, methylphenidate, onto a core. EX1005, 12:50-13:8 ("The first solution was sprayed onto 25/30 mesh non-pareil seeds"); EX1002, ¶¶113-14.

The Patent Owner may try to argue that although the '284 patent teaches coating its active agent onto a core, in contrast, the '131 patent discloses incorporating its active ingredient into the core. EX1002, ¶115; EX1004, 11:8-9; 12:15-31; 19:34-36. In other words, the Patent Owner may allege that the teachings of the '284 and '131 patents cannot be reconciled, and, as a result, the element reciting "one or more pharmaceutically active amphetamine salts are coated onto a core" cannot be obvious using any combination of the '284 and '131 patents. Such an argument would be incorrect. EX1002, ¶115.

As Dr. Auslander explains, the '131 patent's "permeability controlled systems" use water-permeable polymeric coatings that allow water from the gastrointestinal tract to enter into the core causing a build-up of pressure within the core. EX1002, ¶116; EX1004, 6:11-19. As the core pressure builds up, it causes the external water-permeable polymeric coating to rupture. EX1002, ¶116; *see also*, EX1004, 4:59-5:3. It is the rupturing of the water-permeable polymeric coating that results in the release of the active agent. EX1002, ¶116; EX1004, 5:2-3. Put another way, so long as the water-permeable polymeric coating remains intact, the active agent will not be released. EX1002, ¶116; EX1004, 11:25-27, ("The polymeric

coating for the permeability-controlled system must be impermeable to the drug and permeable to the intake of water. . . .").

From this, the POSA would have understood that it does not matter whether the active agent is "coated onto a core" (claim 3) or "incorporated into a core" (e.g., claim 4). EX1002, ¶117. Rather, *the relevant parameter* would be maintaining the integrity of the water-permeable polymeric coating. As to controlling when the water-permeable polymeric coating would rupture, as Dr. Auslander explains, the '131 patent teaches how to "control the physical and mechanical properties of the films which in turn controls the pulse time and rate of release from the delivery system." EX1002, ¶117; EX1004 22:22-25; see also *Id*. at 11:4-22:22 (disclosing formulation and process parameters to when control water-permeable polymeric coating would rupture). Accordingly, whether the active agent is coated on a core as in the '284 patent, or whether the active agent is incorporated into a core as in the '131 patent, would not have mattered to the POSA. EX1002, ¶117. The obvious end result is the same.

Accordingly, claim 3 would have been obvious for the same reasons discussed above with respect to claim 1. EX1002, ¶118. The following claim chart shows the prior art teaching of the additional element of claim 3:

Claim 3	Prior Art
3. The pharmaceutical	Example 1 of the '284 patent describes coating methylphenidate onto an inert core. The '284 patent

Claim 3	Prior Art
composition of claim 1 wherein the one or more pharmaceutically active amphetamine salts are coated onto a core.	(EX1005), 12:50-13:8.

(iii) Claim 4

Claim 4 depends on claim 1 and merely further requires that the "one or more pharmaceutically active amphetamine salts are incorporated into a core." The '131 patent teaches that a compressed core contains the active agent. Accordingly, claim 4 would have been obvious for the same reasons discussed above with respect to claims 1 and 3. EX1002, ¶¶119-20. The following claim chart shows the prior art teaching of the additional element of claim 4:

Claim 4	Prior Art
4. The pharmaceutical composition of claim 1 wherein the one or more pharmaceutically active amphetamine salts are incorporated into a core.	A compressed core *containing* the active agent for pulsed release that is coated with an enteric coating. The '131 patent (EX1004), 12:15-31; *see also id*. at 11:8-9 ("coated drug-containing core"); *Id*. at 19:34-36.

(iv) Claim 6

Claim 6 depends on claim 1 and merely further requires that "the one or more pharmaceutically active amphetamine salts covered with an immediate-release

coating and the one or more pharmaceutically active amphetamine salts covered with an enteric-release coating are present on different cores." The '284 patent teaches an oral dosage form including a first group of particles providing immediate release and a second group of particles providing delayed release. EX1005, 3:3-16. Accordingly, claim 6 would have been obvious for the same reasons discussed above with respect to claim 1. EX1002, ¶¶121-23. The following claim chart shows the prior art teaching of the additional element of claim 6:

Claim 6	Prior Art
The pharmaceutical composition of claim 1 wherein	*See*, *supra* at 16-18.
the one or more pharmaceutically active amphetamine salts covered with an immediate-release coating and the one or more pharmaceutically active amphetamine salts covered with an enteric-release coating are present on different cores.	An oral dosage form including a first group of particles providing immediate release and a second group of particles providing delayed release The '284 patent (EX1005), 3:3-16.

(v) Claim 7

Claim 7 depends on claim 1 and further requires that the "enteric-release coating is a non-pH dependent enteric-release coating." As explained above, the Board in IPR2005-02009 has determined that "enteric-release coating" refers to a

coating that will delay release of a drug until the drug has passed through the stomach and reached the intestines. EX1002, ¶¶124-25; EX1022, 14-15. The '284 patent and the '131 patent teach non-pH dependent coatings that release the active agent in the intestines, *i.e.*, an enteric release. EX1005, 3:16-19; EX1004, 10:65-11:2. Accordingly, claim 7 would have been obvious for the same reasons discussed above with respect to claim 1. EX1002, ¶¶126-27. The following claim chart shows the prior art teaching of the additional element of claim 7:

Claim 7	Prior Art
The composition of claim 1 wherein	*See*, *supra* at 16-18.
said enteric release coating is a non-pH dependent enteric release coating.	The '284 patent teaches enteric-release coatings that are non-pH dependent. EX1002, ¶127. The '131 patent teaches that the "permeability-controlled systems" employ "pH independent" coatings. The '131 patent (EX1004), 10:65 to 11:2.

b. Independent Claim 2

The limitations of claim 2 are similar to those set forth in claim 1. Claim 2 differs from claim 1 in that claim 2 does not include the wherein clause reciting mixed amphetamine salts. EX1002, ¶128; EX1001, 12:53-13:13. Instead, claim 2 recites "wherein said enteric-release coating has a thickness of at least 25 μ," *i.e.*, a range of 25 μm *or greater*. EX1001 at 13:12-13; EX1002, ¶128.

For the very same reasons as set forth above with respect to claim 1, a POSA

would have had motivation to modify the prior art to achieve a once-a-day Adderall® product, which would have had an immediate-release component and a delayed pulsed-release component. EX1002, ¶129. Also as discussed above, this person would have had a reasonable expectation of success in doing so. For brevity, that discussion is not repeated here. EX1002, ¶¶129-30. A POSA would have been led by the prior art as shown in the following claim chart:

Claim 2	Prior Art
2. A pharmaceutical composition for delivery of one or more pharmaceutically active amphetamine salts, comprising:	Pharmaceutical dosage forms containing mixed amphetamine salt and/or d-amphetamine were known *See,* PDR 1997 (EX1009); *see also,* the '096 patent (EX1001), 3:5-7, (discussing the prior art product containing the four amphetamine sulfate salts of Adderall®).
(a) one or more pharmaceutically active amphetamine salts covered with an immediate-release coating; and	Example 1 teaches an immediate release with a first layer of methylphenidate (MPD) and a second seal layer of HPMC. The '284 patent (EX1005), 12:53 to 13:8; *see also* Board Decision (EX1022) at 8 ("the term "pharmaceutically active salts" includes non-salts, such as "amphetamine base" and "methylphenidate" as well as salts of amphetamine base and methylphenidate.").
(b) one or more pharmaceutically active amphetamine salts that are covered with an enteric-release coating that provides for delayed pulsed enteric release,	The layered pellets comprising methylphenidate prepared in Example 1 are then coated with the enteric-release coating described in Example 2. Specifically, the '284 patent at Example 2 describes a delayed pulse enteric release using Eudragit RS and RL. The '284 patent (EX1005), 13:10-35; *see also* Board Decision (EX1022) at 28 (explaining that "Mehta [the '284 patent] discloses formulations with delay periods long enough to release the drug enterically, *i.e.*, in the intestines, rather than the stomach.").

Claim 2	Prior Art
	"One disadvantage of the pH-dependent system is that release of the drug in vivo is affected by the variable pH in the small intestine. Moreover, release time is affected by gastric emptying. Therefore, a second approach which is pH independent is set forth in detail hereinbelow. However, as the results shown hereinabove indicate, pulse time can be controlled by careful choice of core composition, coating composition, and coating curing process variables." The '131 patent (EX1004), 10:59-11:2.
wherein said enteric-release coating releases essentially all of said one or more pharmaceutically active amphetamine salts coated with said enteric coating within about 60 minutes after initiation of said delayed pulsed enteric release;	The '131 patent discloses enteric-release coating: "Permeability-controlled systems are generally based on polymeric coatings which are water-permeable to permit water from the aqueous environment in the gastrointestinal tract of a living being to enter into a coated drug-containing core at a controllable rate and to displace air from the core followed by a build-up of pressure as the core contents expand until the coating is ruptured at the appropriate time." EX1004, 11:5-12. "a drug release profile which includes a period during which no more than about 10 percent of the drug in a particular dosage form is released, followed by a period of from about 0.5 hour to about 2.5 hours, preferably about 1.5 hours, more preferably about 1 hour, in which no less than about 70 percent, preferably no less than about 80 percent, and more preferably no less than about 90 percent, of the drug is released." The '284 patent (EX1005), 6:10-17. (emphasis added). "The term pulsed dose is used herein to describe the rapid delivery of a dose of drug (F_1, F_2, . . . , F_n) at specific respective times (T_1, T_2, . . . , T_n) into the portal system which is analogous to the rate of release from an immediate-release dosage form administered according to an appropriate dosing schedule." The '131 patent (EX1004), 6:68-7:6.

Claim 2	Prior Art
	"By devising a drug dosage delivery form which will release pulsed doses at rates comparable to immediate-release forms, bioavailability will not be compromised by a decreased release rate as has been observed in conventional sustained release dosage forms for these drugs …." The '131 patent (EX1004), 7:11-16.
wherein said enteric-release coating has a thickness of at least 25 μ.	See discussion of this element below.

It is axiomatic that simply modifying the thickness of the coating is a routine modification to a POSA. EX1002, ¶131. The '131 patent discloses an optimization of the enteric coating to provide the desired delayed pulse dosage. EX1004, 19:30-22:25; EX1002, ¶131. As the '131 patent teaches, "[b]y optimizing the formulation and process variables by application of the principles of the invention, it is possible to control the physical and mechanical properties of the films which in turn controls the pulse time and rate of release from the delivery system." EX1004, 22:21-25. In fact, the '131 patent explicitly states that film thickness is one of the relevant performance criteria. EX1004, 20:27-28 ("L_p in turn will be a function of **film thickness**, plasticizer content and processing variables.") (emphasis added); EX1002, ¶131.

Clearly, the physical and mechanical properties of the coating are related to

the thickness of the enteric coating. EX1004, 22:21-25; 20:27-28. Moreover, as Dr. Auslander explains, a POSA would have known that the varying coating thickness of an enteric coating would result in a change in the release profile. EX1002, ¶132. Moreover, as Dr. Auslander explains, citing Remington (EX1025 at p. 1668), the claimed range, *i.e.*, 25 μ and greater, overlaps with typical ranges (less than 1 μ to 200 μ) disclosed in the prior art. EX1002, ¶132. Overlapping ranges establish a *prima facie* case of obviousness. *In re Peterson,* 315 F.3d 1325, 1329-30 (Fed. Cir. 2005); *In re Woodruff*, 919 F.2d 1575, 1578 (Fed. Cir. 1990). Moreover, optimizing the coating thickness of the delayed-release profile disclosed in the '131 patent would have been a matter of routine skill and would have resulted in a thickness of at least 25 μ. EX1002, ¶132; *In re Aller*, 220 F.2d 454, 456-57 (C.C.P.A. 1955) (holding that "where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation"). Accordingly, claim 2 would have been obvious. EX1002, ¶¶131-33.

c. Independent Claim 5

Claim 5 is similar to claim 1, but adds a limitation "wherein the amphetamine salts covered with an immediate-release coating and the amphetamine salts covered with an enteric-release coating are present on a single core." EX1002, ¶134. With respect to the additional limitation of a single core, the '284 patent teaches a particle

having a single core, which is coated with a delayed dose of methylphenidate and a delayed-release coating, which is coated with an outer layer for immediate release of methylphenidate. EX1005, 12:1-9. Accordingly, a POSA would have been taught of a single core having the immediate-release component and the delayed pulsed-release component. EX1002, ¶¶135-36. A POSA would have been led by the prior art as shown in the following claim chart:

Claim 5	Prior Art
5. A pharmaceutical composition for delivery of one or more pharmaceutically active amphetamine salts, comprising:	Pharmaceutical dosage forms containing mixed amphetamine salt and/or d-amphetamine were known *See,* PDR 1997 (EX1009); *see also,* the '096 patent (EX1001), 3:5-7, (discussing the prior art product containing the four amphetamine sulfate salts of Adderall®).
(a) one or more pharmaceutically active amphetamine salts covered with an immediate-release coating; and	Example 1 teaches an immediate release with a first layer of methylphenidate (MPD) and a second seal layer of HPMC. The '284 patent (EX1005), 12:53 to 13:8; *see also* Board Decision (EX1022) at 8 ("the term "pharmaceutically active salts" includes non-salts, such as "amphetamine base" and "methylphenidate" as well as salts of amphetamine base and methylphenidate.")
(b) one or more pharmaceutically active amphetamine salts that are covered with an enteric-release coating that provides for delayed pulsed enteric release,	The layered pellets comprising methylphenidate prepared in Example 1 are then coated with the enteric-release coating described in Example 2. Specifically, the '284 patent at Example 2 describes a delayed pulse enteric release using Eudragit RS and RL. The '284 patent (EX1005), 13:10-35; *see also* Board Decision (EX1022), 28 (explaining that "Mehta [the '284 patent] discloses formulations with delay periods long enough to release the drug enterically, *i.e.*, in the intestines, rather than the stomach.").

Claim 5	Prior Art
	"One disadvantage of the pH-dependent system is that release of the drug in vivo is affected by the variable pH in the small intestine. Moreover, release time is affected by gastric emptying. Therefore, a second approach which is pH independent is set forth in detail herein below. However, as the results shown hereinabove indicate, pulse time can be controlled by careful choice of core composition, coating composition, and coating curing process variables." The '131 patent (EX1004), 10:59-11:2.
wherein said enteric-release coating releases essentially all of said one or more pharmaceutically active amphetamine salts coated with said enteric coating within about 60 minutes after initiation of said delayed pulsed enteric release;	The '131 patent discloses enteric-release coating: "Permeability-controlled systems are generally based on polymeric coatings which are water-permeable to permit water from the aqueous environment in the gastrointestinal tract of a living being to enter into a coated drug-containing core at a controllable rate and to displace air from the core followed by a build-up of pressure as the core contents expand until the coating is ruptured at the appropriate time." EX1004, 11:5-12. "a drug release profile which includes a period during which no more than about 10 percent of the drug in a particular dosage form is released, followed by a period of from about 0.5 hour to about 2.5 hours, preferably about 1.5 hours, more preferably about 1 hour, in which no less than about 70 percent, preferably no less than about 80 percent, and more preferably no less than about 90 percent, of the drug is released." The '284 patent (EX1005), 6:10-17; (emphasis added). "The term pulsed dose is used herein to describe the rapid delivery of a dose of drug (F_1, F_2, . . . , F_n) at specific respective times (T_1, T_2, . . . , T_n) into the portal system which is analogous to the rate of release from an immediate-release dosage form administered according to an appropriate dosing schedule." The '131 patent (EX1004), 6:68-7:6.

Claim 5	Prior Art
	"By devising a drug dosage delivery form which will release pulsed doses at rates comparable to immediate-release forms, bioavailability will not be compromised by a decreased release rate as has been observed in conventional sustained-release dosage forms for these drugs …." The '131 patent (EX1004), 7:11-16.
wherein the one or more pharmaceutically active amphetamine salts covered with an immediate-release coating and the one or more pharmaceutically active amphetamine salts covered with an enteric-release coating are present on a single core.	"As discussed, the dosage form can comprise a single group of particles providing both a substantially immediate dose of a methylphenidate drug, and a delayed dose of methylphenidate drug." The '284 patent (EX1005), 11:66 to 12:2.

d. Independent Claim 8 and Its Dependent Claims 9, 10, and 12

(i) Claim 8

Claim 8 is similar to claim 1, but further requires the blood level of amphetamine salt is higher after the delayed enteric pulsed release than after the immediate release. EX1002, ¶137. With respect to the additional limitation related to the relative blood levels, the '284 patent teaches this very same concept:

> For example, the first dose can provide from about 30 percent to about 70 percent of a patient's daily prescribed intake of the drug and the **second dose provides from about 70 percent** to about 30 percent. . . . However, as will be apparent to one skilled in the art, the effect of drug

> metabolism in the body may require adjustment of the relative amounts of each dose, so that, for example, **the second dose may have to be adjusted to provide more of the drug than the first dose, to compensate for any competition between drug release and drug metabolism**.

EX1005, 6:45-61 (emphasis added); *see also id*. at 6:61-64 (explaining that Figure 2 "represents the blood plasma level of a drug, such as a methylphenidate drug."); EX1002, ¶137.

Indeed, the '284 patent explicitly teaches that relative maxima of the immediate-release component and the delayed-pulsed enteric-release component can "differ by more than 40 percent," explaining further that "[t]he appropriate relative amounts of drug in each release can be readily determined by one skilled in the art." EX1005, 5:61-65. In other words, the '284 patent teaches an adjustment that would provide a blood level of amphetamine salt can be higher relative to the immediate release. EX1002, ¶138.

Indeed, in light of the data in Brown discussed above showing that sustained release of an amphetamine would not have led to the desired clinical response, a POSA would have adjusted the dosages to provide for higher blood levels relative to the immediate release. EX1002, ¶139. That is, the point of a delayed enteric pulsed delivery is to produce an increase in amphetamine level that would have mimicked taking a second immediate-release dose but without requiring the undesirable routine of having to administer a second dosage form during the day.

The result is the entirely expected additive increase in the plasma levels of the amphetamine salts when the delayed release adds to the pre-existing plasma levels already existing from the immediate release. *Id*.

The '131 patent enables these very types of formulations that "will release pulsed doses at rates comparable to immediate-release forms . . . ." EX1004, 7:10-16; EX1002, ¶140. In doing so, the '131 patent states that for certain drugs "bioavailability will not be compromised by a decreased release rate as has been observed in conventional sustained-release dosage forms for these drugs." *Id*. According to the '131 patent, by following its teachings, the pulsed dosage can "simulate the AUC (preferably within 5%) of the immediate release." EX1004, 24:58-61; EX1002, ¶140. A POSA would have therefore been led by the prior art to each element of claim 8 as shown in the following claim chart:

Claim 8	Prior Art
8. A pharmaceutical composition for delivery of at least one amphetamine salt, comprising:	Pharmaceutical dosage forms containing mixed amphetamine salt and/or d-amphetamine were known *See,* PDR 1997 (EX1009); *see also,* the '096 patent (EX1001), 3:5-7, (discussing the prior art product containing the four amphetamine sulfate salts of Adderall®).
(a) at least one pharmaceutically active amphetamine salt	*See* above
covered with an immediate-release coating; and	Example 1 teaches an immediate release with a first layer of methylphenidate (MPD) and a second seal layer of HPMC. The '284 patent (EX1005), 12:53 to 13:8; *see also* Board Decision (EX1022), 8 ("the term

Claim 8	Prior Art
	"pharmaceutically active salts" includes non-salts, such as "amphetamine base" and "methylphenidate" as well as salts of amphetamine base and methylphenidate.")
(b) at least one pharmaceutically active amphetamine salt covered with an enteric-release coating,	The layered pellets comprising methylphenidate prepared in Example 1 are then coated with the enteric-release coating described in Example 2. Specifically, the '284 patent at Example 2 describes a delayed pulse enteric release using Eudragit RS and RL. The '284 patent (EX1005), 13:10-35; *see also* Board Decision (EX1022) at 28 (explaining that "Mehta [the '284 patent] discloses formulations with delay periods long enough to release the drug enterically, *i.e.*, in the intestines, rather than the stomach."). "One disadvantage of the pH-dependent system is that release of the drug in vivo is affected by the variable pH in the small intestine. Moreover, release time is affected by gastric emptying. Therefore, a second approach which is pH independent is set forth in detail hereinbelow. However, as the results shown hereinabove indicate, pulse time can be controlled by careful choice of core composition, coating composition, and coating curing process variables." The '131 patent (EX1004), 10:59-11:2.
said component (a) providing for an immediate release of amphetamine salt to provide a first blood level of amphetamine salt and	The '284 patent teaches and claims an oral dosage form including a first group of particles providing immediate release and a second group of particles providing delayed release. EX1005, 3:3-16.
component (b) providing a delayed pulse enteric release of amphetamine salt that increases the blood level of amphetamine salt to a	"[E]mbodiments in which the maxima of the two releases differ by more than 40 percent are within the scope of the invention. The appropriate relative amounts of drug in each release can be readily determined by one skilled in the art." *Id.*, 5:61-65. "[T]he effect of drug metabolism in the body may

Claim 8	Prior Art
second level that is greater than the first level provided by component (a)	require adjustments of the relative amounts of each dose . . . the second dose may have to be adjusted to provide more of the drug than the first dose, to compensate for any competition between drug release and drug metabolism." EX1005, 6:45-61 (explaining that the second dose can provide from about 70 percent to about 30 percent of the active agent).
wherein said enteric-release coating releases essentially all of said one or more pharmaceutically active amphetamine salts coated with said enteric coating within about 60 minutes after initiation of said delayed pulsed enteric release;	The '131 patent discloses enteric-release coating: "Permeability-controlled systems are generally based on polymeric coatings which are water-permeable to permit water from the aqueous environment in the gastrointestinal tract of a living being to enter into a coated drug-containing core at a controllable rate and to displace air from the core followed by a build-up of pressure as the core contents expand until the coating is ruptured at the appropriate time." EX1004, 11:5-12. "a drug release profile which includes a period during which no more than about 10 percent of the drug in a particular dosage form is released, followed by a period of from about 0.5 hour to about 2.5 hours, preferably about 1.5 hours, more preferably about 1 hour, in which no less than about 70 percent, preferably no less than about 80 percent, and more preferably no less than about 90 percent, of the drug is released." The '284 patent (EX1005), 6:10-17; (emphasis added). "The term pulsed dose is used herein to describe the rapid delivery of a dose of drug (F_1, F_2, . . . , F_n) at specific respective times (T_1, T_2, . . . , T_n) into the portal system which is analogous to the rate of release from an immediate-release dosage form administered according to an appropriate dosing schedule." The '131 patent (EX1004), 6:68-7:6. "By devising a drug dosage delivery form which will release pulsed doses at rates comparable to

Claim 8	Prior Art
	immediate-release forms, bioavailability will not be compromised by a decreased release rate as has been observed in conventional sustained release dosage forms for these drugs ….” The ’131 patent (EX1004), 7:11-16.
wherein the pharmaceutically active amphetamine salts in (a) and (b).[2]	Prior art Adderall® contains the exact mixed amphetamine salts. *See,* PDR 1997 (EX1009); *see also,* the ’096 patent (EX1001), 3:5-7.

(ii) Claim 9

Claim 9 depends from claim 8 and merely further requires that the “one or more pharmaceutically active amphetamine salts are coated onto a core.” As such, this claim element is similar to the element in claim 3. As discussed above with respect to claim 3, the ’284 patent teaches coating its active agent, methylphenidate, onto a core. EX1005, 12:50-13:8. Accordingly, claim 9 would have been obvious. EX1002, ¶141.

(iii) Claim 10

Claim 10 depends on claim 8 and merely further requires that the “one or more pharmaceutically active amphetamine salts are incorporated into a core.” The ’131 patent teaches a compressed core that contains the active agent. EX1004 at 12:15-31; *see also id*. at 11:8-9 (“coated drug-containing core”); *id*. at 19:34-36. Accordingly, claim 10 would have been obvious. EX1002, ¶¶142-43.

[2] *See* Certificate of Correction for the ’096 patent.

(iv) Claim 12

Claim 12 depends on claim 8 and merely further requires that "the one or more pharmaceutically active amphetamine salts covered with an immediate-release coating and the one or more pharmaceutically active amphetamine salts covered with an enteric-release coating are present on different cores." The '284 patent teaches and claims an oral dosage form including a first group of particles providing immediate release and a second group of particles providing delayed release. EX1002, ¶¶144-45; EX1005, 3:3-16. Accordingly, claim 12 would have been obvious. EX1002, ¶146.

e. Independent Claim 11

Claim 11 is similar to claim 1, but it also includes the "single core" limitation of claim 5, and the "blood level" limitation of claim 8. EX1002, ¶147. As discussed above, with respect to claims 5 and 8, a POSA would have been taught that the components could be present on a single core and the expected relatively higher blood levels after the delayed, pulsed release adds to the already present blood levels provided by the immediate release. EX1002, ¶¶147-48. A POSA would have been led by the prior art as shown in the following claim chart:

Claim 11	Prior Art
11. A pharmaceutical composition for delivery of at least one amphetamine	Pharmaceutical dosage forms containing mixed amphetamine salt and/or d-amphetamine were known *See,* PDR 1997 (EX1009); *see also,* the '096 patent (EX1001), 3:5-7, (discussing the prior art product

Claim 11	Prior Art
salt, comprising:	containing the four amphetamine sulfate salts of Adderall®).
(a) at least one pharmaceutically active amphetamine salt covered with an immediate-release coating; and	Example 1 teaches an immediate release with a first layer of methylphenidate (MPD) and a second seal layer of HPMC. The '284 patent (EX1005), 12:53 to 13:8; *see also* Board Decision (EX1022) at 8 ("the term "pharmaceutically active salts" includes non-salts, such as "amphetamine base" and "methylphenidate" as well as salts of amphetamine base and methylphenidate.")
(b) at least one pharmaceutically active amphetamine salt covered with an enteric-release coating,	The layered pellets comprising methylphenidate prepared in Example 1 are then coated with the enteric-release coating described in Example 2. Specifically, the '284 patent at Example 2 describes a delayed pulse enteric release using Eudragit RS and RL. The '284 patent (EX1005), 13:10-35; *see also* Board Decision (EX1022) at 28 (explaining that "Mehta [the '284 patent] discloses formulations with delay periods long enough to release the drug enterically, *i.e.*, in the intestines, rather than the stomach."). "One disadvantage of the pH-dependent system is that release of the drug in vivo is affected by the variable pH in the small intestine. Moreover, release time is affected by gastric emptying. Therefore, a second approach which is pH independent is set forth in detail hereinbelow. However, as the results shown hereinabove indicate, pulse time can be controlled by careful choice of core composition, coating composition, and coating curing process variables." The '131 patent (EX1004), 10:59-11:2.
said component (a) providing for an immediate release of amphetamine salt to provide a first blood level of amphetamine salt and	The '284 patent teaches and claims an oral dosage form including a first group of particles providing immediate release and a second group of particles providing delayed release. EX1005, 3:3-16.

Claim 11	Prior Art
component (b) providing a delayed pulse enteric release of amphetamine salt that increases the blood level of amphetamine salt to a second level that is greater than the first level provided by component (a)	"[E]mbodiments in which the maxima of the two releases differ by more than 40 percent are within the scope of the invention. The appropriate relative amounts of drug in each release can be readily determined by one skilled in the art." *Id*., 5:61-65. "[T]he effect of drug metabolism in the body may require adjustments of the relative amounts of each dose . . . the second dose may have to be adjusted to provide more of the drug than the first dose, to compensate for any competition between drug release and drug metabolism." EX1005 6:45-61 (explaining that the second dose can provide from about 70 percent to about 30 percent of the active agent).
wherein said enteric-release coating releases essentially all of said one or more pharmaceutically active amphetamine salts coated with said enteric coating within about 60 minutes after initiation of said delayed pulsed enteric release; and	The '131 patent discloses enteric-release coating: "Permeability-controlled systems are generally based on polymeric coatings which are water-permeable to permit water from the aqueous environment in the gastrointestinal tract of a living being to enter into a coated drug-containing core at a controllable rate and to displace air from the core followed by a build-up of pressure as the core contents expand until the coating is ruptured at the appropriate time." EX1004, 11:5-12. "a drug release profile which includes a period during which no more than about 10 percent of the drug in a particular dosage form is released, followed by a period of from about 0.5 hour to about 2.5 hours, preferably about 1.5 hours, more preferably about 1 hour, in which no less than about 70 percent, preferably no less than about 80 percent, and more preferably no less than about 90 percent, of the drug is released." The '284 patent (EX1005), 6:10-17; (emphasis added). "The term pulsed dose is used herein to describe the rapid delivery of a dose of drug (F_1, F_2, . . . , F_n) at specific respective times (T_1, T_2, . . . , T_n) into the portal

Claim 11	Prior Art
	system which is analogous to the rate of release from an immediate-release dosage form administered according to an appropriate dosing schedule." The '131 patent (EX1004), 6:68-7:6. "By devising a drug dosage delivery form which will release pulsed doses at rates comparable to immediate-release forms, bioavailability will not be compromised by a decreased release rate as has been observed in conventional sustained-release dosage forms for these drugs …." The '131 patent (EX1004), 7:11-16.
wherein the one or more pharmaceutically active amphetamine salts covered with an immediate-release coating and the one or more pharmaceutically active amphetamine salts covered with an enteric-release coating are present on a single core.	"As discussed, the dosage form can comprise a single group of particles providing both a substantially immediate dose of a methylphenidate drug, and a delayed dose of methylphenidate drug." The '284 patent (EX1005), 11:66 to 12:2.

f. Independent Claim 13 and Its Dependent Claims 14, 15, 16 and 17

(i) Claim 13

Claim 13 is similar to claim 1, but adds a limitation in clause "(c)" regarding a protective layer over the enteric-release coating. The '284 patent teaches that dosage forms that can be used include "**coated** and uncoated pellets, and **coated** and

uncoated tablets." EX1002, ¶¶149-50. The dose for immediate release can be administered in a tablet or capsule form which may also include the delayed dose. For example, *two or more groups of pellets may be combined within a hard gelatin capsule* or compressed into a tablet." EX1005, 7:2-9. Therefore, the use of coated pellets and tablets, and encapsulating pellets "*within a hard gelatin capsule*" discloses the limitation of "a protective layer over the enteric-release coating." EX1002, ¶150.

Moreover, the '284 patent discloses the use of sealant as a physical barrier. EX1002, ¶151; EX1005, 10:38-42. As Dr. Auslander explains, the use of sealants and protective coating was well known to a POSA for decades. EX1002, ¶151; EX1016 (Remington 19th Ed. Ch. 93 at p.1650.) As is known in this field, a sealant or protective coating provides a temporary barrier between the functional coating and the environment to help preserve the integrity of the functional coating until use. EX1002, ¶151; EX1016 at p.1650. As such it would have been obvious to a POSA to select any known protective layer or sealant, such as those disclosed in the '284 or '131 patents, and apply it over the enteric-release coating. EX1016, at 1650. The remaining limitations of claim 13 are discussed above with respect to claim 1. EX1002, ¶¶151-52. A POSA would have been led by the prior art as shown in the following claim chart:

Claim 13	Prior Art
13. A pharmaceutical composition for delivery of one or more pharmaceutically active amphetamine salts, comprising:	Pharmaceutical dosage forms containing mixed amphetamine salt and/or d-amphetamine were known *See,* PDR 1997 (EX1009); *see also,* the '096 patent (EX1001), 3:5-7, (discussing the prior art product containing the four amphetamine sulfate salts of Adderall®).
(a) one or more pharmaceutically active amphetamine salts covered with an immediate-release coating; and	Example 1 teaches an immediate release with a first layer of methylphenidate (MPD) and a second seal layer of HPMC. The '284 patent (EX1005), 12:53 to 13:8; *see also* Board Decision (EX1022) at 8 ("the term "pharmaceutically active salts" includes non-salts, such as "amphetamine base" and "methylphenidate" as well as salts of amphetamine base and methylphenidate.").
(b) one or more pharmaceutically active amphetamine salts that are covered with an enteric-release coating that provides for delayed pulsed enteric release,	The layered pellets comprising methylphenidate prepared in Example 1 are then coated with the enteric-release coating described in Example 2. Specifically, the '284 patent at Example 2 describes a delayed pulse enteric release using Eudragit RS and RL. The '284 patent (EX1005), 13:10-35; *see also* Board Decision (EX1022) at 28 (explaining that "Mehta [the '284 patent] discloses formulations with delay periods long enough to release the drug enterically, *i.e.*, in the intestines, rather than the stomach."). "One disadvantage of the pH-dependent system is that release of the drug in vivo is affected by the variable pH in the small intestine. Moreover, release time is affected by gastric emptying. Therefore, a second approach which is pH independent is set forth in detail herein below. However, as the results shown hereinabove indicate, pulse time can be controlled by careful choice of core composition, coating composition, and coating curing process variables." The '131 patent (EX1004), 10:59-11:2.
wherein said enteric-release coating releases essentially all	The '131 patent discloses enteric-release coating: "Permeability-controlled systems are generally based on polymeric coatings which are water-permeable to permit

Claim 13	Prior Art
of said one or more pharmaceutically active amphetamine salts coated with said enteric coating within about 60 minutes after initiation of said delayed pulsed enteric release;	water from the aqueous environment in the gastrointestinal tract of a living being to enter into a coated drug-containing core at a controllable rate and to displace air from the core followed by a build-up of pressure as the core contents expand until the coating is ruptured at the appropriate time." EX1004, 11:5-12. "a drug release profile which includes a period during which no more than about 10 percent of the drug in a particular dosage form is released, followed by a period of from about 0.5 hour to about 2.5 hours, preferably about 1.5 hours, more preferably about 1 hour, in which no less than about 70 percent, preferably no less than about 80 percent, and more preferably no less than about 90 percent, of the drug is released." The '284 patent (EX1005), 6:10-17; (emphasis added). "The term pulsed dose is used herein to describe the rapid delivery of a dose of drug (F_1, F_2, . . . , F_n) at specific respective times (T_1, T_2, . . . , T_n) into the portal system which is analogous to the rate of release from an immediate-release dosage form administered according to an appropriate dosing schedule." The '131 patent (EX1004), 6:68-7:6. "By devising a drug dosage delivery form which will release pulsed doses at rates comparable to immediate-release forms, bioavailability will not be compromised by a decreased release rate as has been observed in conventional sustained-release dosage forms for these drugs …." The '131 patent (EX1004), 7:11-16.
(c) a protective layer over the enteric-release coating.	EX1005, 7:2-9 (disclosing the use of coated pellets and tablets, and putting groups of pellets "*within a hard gelatin capsule*"); *see also* 10:38-42 (the '284 patent discloses the use sealant as a physical barrier).

(ii) Claim 14

Claim 14 depends on claim 13 and merely further requires that the "one or more pharmaceutically active amphetamine salts are coated onto a core." As such, this claim element is similar to the element in claim 3. As discussed above with respect to claim 3, the '284 patent teaches coating its active agent, methylphenidate, onto a core. EX1005, 12:50-13:8. Accordingly, claim 14 would have been obvious. EX1002, ¶¶153-54.

(iii) Claim 15

Claim 15 depends on claim 13 and merely further requires that the "one or more pharmaceutically active amphetamine salts are incorporated into a core." The '131 patent teaches a compressed core that contains the active agent. EX1004, 12:15-31; *see also id*. at 11:8-9 ("coated drug-containing core"); *id*. at 19:34-36. Accordingly, claim 15 would have been obvious. EX1002, ¶¶155-56.

(iv) Claim 16

Claim 16 depends on claim 13, but adds a limitation "wherein the amphetamine salts covered with an immediate-release coating and the amphetamine salts covered with an enteric-release coating are present on a single core." EX1002, ¶157. With respect to this additional limitation, such a formulation is taught by the '284 patent. The '284 patent teaches a particle having a single core, which is coated with a delayed dose of methylphenidate and a delayed-release coating, which is

coated with an outer layer for immediate release of methylphenidate. EX1005, 11:66-12:2. Accordingly, a POSA would have been taught of a single core having the immediate-release component and the delayed, pulsed-release component. EX1002, ¶157. As such, a POSA would have been led to use a single core to achieve the desired objective of a once-a-day Adderall® having the immediate-release component and the delayed, pulsed-release component. *See Id*.

(v) Claim 17

Claim 17 depends on claim 13 and merely further requires that "the one or more pharmaceutically active amphetamine salts covered with an immediate-release coating and the one or more pharmaceutically active amphetamine salts covered with an enteric-release coating are present on different cores." The '284 patent teaches and claims an oral dosage form including a first group of particles providing immediate release and a second group of particles providing delayed release. EX1005, 3:3-16. Accordingly, claim 17 would have been obvious. EX1002, ¶¶158-59.

g. Independent Claim 18 and Its Dependent Claims 19-24

(i) Claim 18

As discussed above, in IPR2015-2009, the Board has already been persuaded that there is a reasonable likelihood that claims 18-21 and 23, are unpatentable under 35 U.S.C. § 102 as anticipated by the '284 patent or obvious in view of the '284

patent and the Adderall® PDR. EX1022, 37, 38. Claim 18 is similar to claim 1, but adds a limitation in clause "(c)" regarding a protective coating between the amphetamine salt and the enteric-release coating. EX1002, ¶160. The '284 patent teaches this limitation. *See*, EX1005, 10:38-42; 5:45-55. As Dr. Auslander explains, the use of protective coatings and sealants to create a barrier between the drug and the functional coating, or the functional coating and the environment was well known. EX1002, ¶¶151, 160-61. The remaining limitations of claim 18 are discussed above with respect to claim 1, and for brevity are not copied here. EX1002, ¶162. A POSA would have been led by the prior art as shown in the following claim chart:

Claim 18	Prior Art
18. A pharmaceutical composition for delivery of one or more pharmaceutically active amphetamine salts, comprising:	Pharmaceutical dosage forms containing mixed amphetamine salt and/or d-amphetamine were known *See,* PDR 1997 (EX1009); *see also,* the '096 patent (EX1001), 3:5-7, (discussing the prior art product containing the four amphetamine sulfate salts of Adderall®).
(a) one or more pharmaceutically active amphetamine salts covered with an immediate-release coating; and	Example 1 teaches an immediate release with a first layer of methylphenidate (MPD) and a second seal layer of HPMC. The '284 patent (EX1005), 12:53 to 13:8; *see also* Board Decision (EX1022), 8 ("the term "pharmaceutically active salts" includes non-salts, such as "amphetamine base" and "methylphenidate" as well as salts of amphetamine base and methylphenidate.").

(b) one or more pharmaceutically active amphetamine salts that are covered with an enteric-release coating that provides for delayed pulsed enteric release,	The layered pellets comprising methylphenidate prepared in Example 1 are then coated with the enteric-release coating described in Example 2. Specifically, the '284 patent at Example 2 describes a delayed pulse enteric release using Eudragit RS and RL. The '284 patent (EX1005), 13:10-35; *see also* Board Decision (EX1022), 28 (explaining that "Mehta [the '284 patent] discloses formulations with delay periods long enough to release the drug enterically, *i.e.*, in the intestines, rather than the stomach.") "One disadvantage of the pH-dependent system is that release of the drug in vivo is affected by the variable pH in the small intestine. Moreover, release time is affected by gastric emptying. Therefore, a second approach which is pH independent is set forth in detail herein below. However, as the results shown hereinabove indicate, pulse time can be controlled by careful choice of core composition, coating composition, and coating curing process variables." The '131 patent (EX1004), 10:59-11:2.
wherein said enteric-release coating releases essentially all of said one or more pharmaceutically active amphetamine salts coated with said enteric coating within about 60 minutes after initiation of said delayed pulsed enteric release;	The '131 patent discloses enteric-release coating: "Permeability-controlled systems are generally based on polymeric coatings which are water-permeable to permit water from the aqueous environment in the gastrointestinal tract of a living being to enter into a coated drug-containing core at a controllable rate and to displace air from the core followed by a build-up of pressure as the core contents expand until the coating is ruptured at the appropriate time." EX1004, 11:5-12. "a drug release profile which includes a period during which no more than about 10 percent of the drug in a particular dosage form is released, followed by a period of from about 0.5 hour to about 2.5 hours, preferably about 1.5 hours, more preferably about 1 hour, in which no less than about 70 percent, preferably no less than about 80 percent, and more preferably no less than about 90 percent, of the drug is released." The '284 patent

	(EX1005), 6:10-17; (emphasis added). "The term pulsed dose is used herein to describe the rapid delivery of a dose of drug (F_1, F_2, . . . , F_n) at specific respective times (T_1, T_2, . . . , T_n) into the portal system which is analogous to the rate of release from an immediate-release dosage form administered according to an appropriate dosing schedule." The '131 patent (EX1004), 6:68-7:6. "By devising a drug dosage delivery form which will release pulsed doses at rates comparable to immediate-release forms, bioavailability will not be compromised by a decreased release rate as has been observed in conventional sustained release dosage forms for these drugs …." The '131 patent (EX1004), 7:11-16.
(c) a protective layer between the at least one pharmaceutically active amphetamine salt and the enteric-release coating	The '284 patent discloses the use sealant as a physical barrier. EX1005, 10:38-42 ("After deposition of the drug, a sealant can be applied to any and/or all of the particles, prior to application of the polymeric coating. A sealant provides a physical barrier between the drug and the coating").

(ii) Claim 19

Claim 19 depends on claim 18 and recites "wherein [t]he delayed pulsed release is from 4 to 6 hours after administration of the pharmaceutical composition." EX1002, ¶163. The '131 patent discloses that "drug delivery systems can be constructed to deliver drugs dosed every 4 to 6 hours, for example, in a once-a-day dosage form." EX1004, 15:65-68. Therefore, the '131 patent discloses the very same range claimed in claim 19, rendering claim 19 *prima facie* obvious. *See In re*

Peterson, 315 F.3d 1325, 1329-30 (Fed. Cir. 2005); *In re Woodruff,* 919 F.2d 1575, 1578 (Fed. Cir. 1990); *In re Malagari,* 499 F.2d 1297, 1303 (C.C.P.A. 1974). Likewise, the '284 has a similar disclosure. EX1002, ¶¶163-64; EX1005, 5:14–18. The following claim chart shows the prior art teaching of the additional element of claim 19:

Claim 19	Prior Art
The pharmaceutical composition of claim 18	*See*, *supra* at 50-52.
wherein the delayed pulsed release is from 4 to 6 hours after administration of the pharmaceutical composition.	The '284 patent teaches that the second dose can be delayed most preferably by about 4 to about 5 hours. The '284 patent (EX1005), 5:14–18. "With this wide range of pulse times, drug delivery systems can be constructed to deliver drugs dosed every 4 to 6 hours, for example, in a once-a-day dosage form." The '131 patent (EX1004), 15:65-68.

(iii) Claim 20

Claim 20 depends on claim 18 and recites "wherein the delayed pulsed enteric release, releases the amphetamine salt in about 30 to 60 minutes after initiation of the release." The '131 patent defines "pulsed dose" as "the rapid delivery of a dose of drug (F_1, F_2, …, F_n) at specific respective times (T_1, T_2, … , T_n) into the portal system which is analogous to the rate of release from an immediate-release dosage form administered according to an appropriate dosing schedule." EX1004, 7:1-6;

EX1002, ¶¶165-66. In connection with the pH-independent enteric "permeability controlled systems," the '131 patent provides that pulsed dosages release "essentially all" of the active agent in 20-50 minutes. EX1004, 24:43-49. As Dr. Auslander explains, the *in vivo* data disclosed in the '131 patent for such enteric "permeability controlled systems" shows a pulsed release lasting about 20-50 minutes. EX1002, ¶105, (referring to Figures 8, 9, 10 & 11 of the '131 patent, each of which shows that the decrease in pH (labeled "DDT") corresponds to essentially all of the active ingredient being released in under 60 minutes). Specifically, in reference to these figures, the '131 patent states that: "The disintegration dissolution (DDT) was ~17 minutes in three of the dogs and about 50 minutes in the fourth." EX 1004, 24:43-45; EX1002, ¶166.

Claim 20	Prior Art
The pharmaceutical composition of claim 18	*See*, *supra* at 50-52.
wherein the delayed pulse enteric release, releases the amphetamine salt in about 30 to 60 minutes after initiation of the release.	*See, e.g.*, Figures 8, 9, 10 & 11 of the '131 patent (showing that the decrease in pH (labeled "DDT") corresponds to essentially all of the active ingredient being released in under 60 minutes). "The disintegration dissolution (DDT) was ~17 minutes in three of the dogs and about 50 minutes in the fourth." EX 1004, 24:43-45.

(iv) Claim 21

Claim 21 depends on claim 18 and merely further requires that the "one or more pharmaceutically active amphetamine salts are coated onto a core." As discussed in connection with claim 3, the '284 patent teaches coating its active agent, methylphenidate, onto a core. EX1005, 12:50–64. Accordingly, claim 21 would have been obvious. EX1002, ¶¶167-68.

(v) Claim 22

Claim 22 depends on claim 18 and merely further requires that the "one or more pharmaceutically active amphetamine salts are incorporated into a core." The '131 patent teaches that a compressed core contains the active agent. EX1004 '131 patent, 12:15-31; *see also id*. at 11:8-9 ("coated drug-containing core"); *id*. at 19:34-36. Accordingly, claim 22 would have been obvious. EX1002, ¶¶169-70.

(vi) Claim 23

Claim 23 depends on claim 18, but adds a limitation "wherein the amphetamine salts covered with an immediate-release coating and the amphetamine salts covered with an enteric-release coating are present on a single core." EX1002, ¶171. With respect to this additional limitation, such a formulation is taught by the '284 patent. The '284 patent teaches a particle having a single core, which is coated with a delayed dose of methylphenidate and a delayed-release coating, which is coated with an outer layer for immediate release of methylphenidate. EX1005,

11:66-12:9. Accordingly, a POSA would have been taught of a single core having the immediate-release component and the delayed, pulsed-release component. EX1002, ¶172. As such, a POSA would have been led to use a single core to achieve the desired objective of a once-a-day Adderall® having the immediate-release component and the delayed, pulsed-release component. *Id*.

(vii) Claim 24

Claim 24 depends on claim 18 and merely further requires that "the one or more pharmaceutically active amphetamine salts covered with an immediate-release coating and the one or more pharmaceutically active amphetamine salts covered with an enteric-release coating are present on different cores." EX1002, ¶173. The '284 patent teaches and claims an oral dosage form including a first group of particles providing immediate release and a second group of particles providing delayed release. EX1005, 3:3-16. Accordingly, claim 24 would have been obvious. EX1002, ¶¶174-75.

a. Dependent Claim 25

Dependent Claim 25 depends on any one of claims 2, 13, or 18-20 and recites "wherein the one or more pharmaceutically active amphetamine salt in (a) and (b) comprises mixed amphetamine salts." As discussed above, in IPR2015-2009, the Board has already preliminary been persuaded that claim 25 is obvious in view of the '284 patent and the Adderall® PDR. EX1022, 37, 38; EX1002, ¶176.

As discussed above with respect to claim 1, the '096 patent admits that the prior art formulation, Adderall® IR, contains the so-called "mixed amphetamine salts," which comprise a mixture of four amphetamine sulfate salts. EX1001, 3:5-6; *see also* EX1009. For the same reasons discussed above, the prior art would have led a POSA to modify the immediate-release formulation of the mixed amphetamine salts of Adderall® to achieve the desired objective of a once-a-day Adderall® having the immediate-release component and the delayed, pulsed-release component. EX1002, ¶178. Accordingly, claim 25 would have been obvious.

B. Objective Indicia of Non-Obviousness

Although objective indicia of nonobviousness must be taken into account, they do not necessarily control an obviousness determination. *Newell Cos., Inc. v. Kenney Mfg. Co*., 864 F.2d 757, 768 (Fed. Cir. 1988). A strong case of obviousness, such as the instant case, cannot be overcome by objective evidence of non-obviousness. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1372 (Fed. Cir. 2008).

Petitioner addresses below potential objective indicia arguments that Patent Owner may raise. To the extent Patent Owner does assert any objective indicia in this proceeding, detailed consideration of such evidence should not be undertaken until Petitioner has had an opportunity to respond to it. *Amneal Pharmaceuticals, LLC v. Supernus Pharmaceuticals, Inc*., IPR2013-00368 [Paper 8, pp. 12-13].

1. No Unexpected Results Over the Closest Prior Art

Allegations of unexpected results are insufficient to rebut a strong *prima facie* case of obviousness. The claims of the ’096 patent are obvious because they cover nothing more than modifying an immediate-release amphetamine formulation to include a delayed pulse-release dosage form that had been applied to a pharmacologically similar drug used to treat the same condition. EX1002, ¶96.

2. Other Objective Indicia

A showing of “copying in the ANDA context where a showing of bioequivalence is required for FDA approval” is not compelling evidence of nonobviousness. *Purdue Pharma Prods. L.P. v. Par Pharm., Inc.,* 377 Fed App’x 978, 983 (Fed. Cir. 2010). As to commercial success, such any alleged success requires the patentee to provide data establishing commercial success (*e.g.*, market share data, market growth, and comparative sales volume) and, more importantly, “[a] nexus must be established between the merits of the claimed invention and the evidence of commercial success before that issue becomes relevant to the issue of obviousness.” *Vandenberg v. Dairy Equip. Co.*, 740 F.2d 1560, 1567 (Fed. Cir. 1984). There is no evidence linking the claims to any alleged commercial success.

X. CONCLUSION

Petitioner has demonstrated by a preponderance of the evidence that claims 1-25 of the ’096 patent are unpatentable as obvious.

RESPECTFULLY SUBMITTED,
ALSTON & BIRD LLP

Date: May 12, 2016

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CERTIFICATION OF WORD COUNT

Pursuant to 37 C.F.R. §§ 42.24, the undersigned certifies that the argument section of this Petition (Sections I-II, V-X) has a total of 13,913 words, according to the word count tool in Microsoft Word™.

Respectfully submitted,

ALSTON & BIRD LLP

By: /Jitendra Malik/
Jitendra Malik, Ph.D.
Reg. No. 55,823

CERTIFICATION OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e), 42.8(b)(4) and 42.105, the undersigned certifies that on the 12th day of May 2016, a complete copy of the foregoing Petitioner's Petition for *Inter Partes* Review of U.S. Patent No. RE 42,096, Power of Attorney, and all supporting exhibits were served via UPS® to the Patent Owner by serving the correspondence address of record for the '096 patent:

Joseph R. Robinson
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