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. RE41,148 to Burnside *et al.*
Issue Date: Feb. 23, 2010
Title: Oral Pulsed Dose Drug Delivery System

Inter Partes Review No.: IPR2016-XXXX

Petition for *Inter Partes* Review of U.S. Patent No. RE41,148 Under 35 U.S.C. §§ 311-319 and 37 C.F.R. §§ 42.1-.80, 42.100-.123

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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)
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I. INTRODUCTION

Mylan Pharmaceuticals Inc. ("Petitioner") petitions for *Inter Partes* Review, and seeks cancellation of claims 1-20 ("challenged claims") of U.S. Patent No. RE41,148 ("the '148 patent") (EX1001), which according to the current records of the USPTO is assigned to Shire LLC ("Patent Owner").

II. OVERVIEW

Generally speaking, the '148 patent purports to cover a mixture of amphetamine base salts, such as the four amphetamine-salt combination of Adderall®, wherein the dosage form contains an both immediate-release and a delayed enteric release dose that is: (1) allegedly sufficient to maintain an effective level of amphetamine base salts in the patient over the course of at least 8 hours without further administration of amphetamine salts; and (2) will produce a plasma concentration versus time curve having an area under the curve (AUC) of about 467 to about 714 ng hr/mL from a "total dose" of 20mg. *See, e.g.*, EX1001 Claim 1. The dosage form is purported to be useful for treating Attention Deficit Hyperactivity Disorder (ADHD). *See, Id.* 8:4-11.

The patentee will not dispute that prior to the earliest priority date for the '148 patent, the specific pharmaceutically active amphetamine salts, such as those used in Adderall® (an immediate-release product), were well-known in the art for treating ADHD. EX1009 at 2210. The '148 patent does nothing more than modify then

existing amphetamine salt products to include a delayed-release component, and then claim the resulting pharmacokinetic parameters. *In re Huai-Hung Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011) (sustaining Board's obviousness determination for a claim that recited pharmacokinetic parameters (*i.e.*, C_{max}) explaining that such parameters are "an inherent property . . . present both in controlled release and immediate release formulations of that drug."); *Santarus, Inc. v. Par Pharm., Inc*., 694 F.3d 1344, 1354 (Fed. Cir. 2012) (an obvious formulation does not "become patentable merely by testing and claiming an inherent property."); *In Re Baxter Travenol Labs*., 952 F.2d 388, 392 (Fed. Cir. 1991) ("Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention."); *In re Prindle*, 297 F.2d 251, 254 (CCPA 1962).

A person of ordinary skill in the art ("POSA"), however, 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, (EX1001 at 3:23-30), and (iii) the stigmatism felt by school children when having to take the second dose in school as part of 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 release component to avoid such problems. *Id.*, at ¶38.

Modifying parameters to control delayed release profiles were known before the priority date of the '148 patent. *See, e.g.*, EX1005, Table 1. For example, by changing parameters such as the ratios of polymers, amount of coating, amount of talc, and curing time, U.S. Patent No. 5,837,284 ("the '284 patent") (EX1005) teaches a delayed release profile that resulted in substantially all of the drug methylphenidate being released after 10 hours. Methylphenidate is "a mild central nervous system stimulant with pharmacological activity qualitatively similar to that of amphetamines," *Id.* at 2:5-16. EX1005, 13:57-60; 14:21-45. Moreover, the '284 patent teaches that the delayed release component can exceed the peak plasma concentration of the immediate release component and other pharmacokinetic parameters such as area under the curve ("AUC") and C_{max}. EX1005, 5:51-56. In fact, in reference to the above discussed '284 patent, in an IPR (IPR2015-02009) for the parent patent (RE42096), the patent owner admitted that the '284 patent teaches the required parameters of a delayed enteric release dosage that lasts for 3-10 hours. (EX1020, Patent Owner Preliminary Response, dated January 19, 2016 at 16:12-16).

To the extent a POSA would have looked at any further guidance beyond the '284 patent, the POSA would have only had to look to U.S. Patent No. 5,229,131 ("the '131 patent") (EX1004) and known pharmacokinetic data (EX1031, Slattum at 1044) to arrive at the alleged invention of the '148 patent with a reasonable expectation of success.

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

Petitioner certifies that (1) the '148 patent is available for IPR; and (2) Petitioner is not barred or estopped from requesting IPR of any claim of the '148 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 an 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 '148 patent is currently the subject, as the parent patent or current reissue form, of the following litigations: *Shire LLC v. Amerigen Pharmaceuticals Ltd.*, No. 1:14-cv-06095-RMB-JS (D.N.J.); *Shire LLC et al v. Abhai LLC*, No. 1:15-cv-13909-WGY (D. Mass.); *Shire LLC v. Par Pharmaceutical, Inc. et al*, No. 1-15-cv-01454 (D.N.J.); *Shire LLC v. CorePharma, LLCC*, No. 1-14-cv-05694 (D.N.J.); *Shire LLC v. Neos Therapeutics, Inc.*, 3-13-cv-01452 (N.D. Tex.); *Shire LLC v. Watson Pharms., Inc., et al*, No. 1-11-cv-02340 (S.D.N.Y.).

2. Administrative Matters

Petitioner is also aware of at least the following related family members: application No. 11/091,010 ("the '010 application"), now the '148 patent, is a reissue of application No. 09/807,462 ("the '462 application"), now U.S. Patent No. 6,605,300, which is a National Stage Entry of PCT/US99/24554, which is a continuation-in-part of 09/176,542 ("the '542 application"), now U.S. Patent No. 6,322,819 ("the '819 patent"). Related family member application 11/091,011 ("the '011 application") is now patented as U.S. Patent No. RE 42,096 ("the '096 patent"). Related family member applications 10/172,705 and 10/758,417 are now abandoned. Petitioners have previously filed, a Petition for *inter partes* review of RE 42,096 (IPR2016-01033). In addition, the '096 patent is currently the subject of *Inter Partes* Review (IPR2015-02009) filed by Petitioner Amerigen.

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

27703. Petitioner consents to email service. 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 1-20. Petitioners' full statement of the reasons for the relief requested is set forth in detail below.

VI. THE '148 PATENT

The '148 patent has two independent claims (claims 1 and 12). Independent claim 1 is directed to a pharmaceutical formulation of amphetamine base salts comprising an immediate release dosage form and a delayed enteric-release dosage form, wherein the formulation is sufficient to maintain an effective level of amphetamine base salts in the patient over at least 8 hours. In addition, other limitations of claim 1 recite that the peak plasma concentration of the amphetamine base salts is higher after the delayed enteric release than after the immediate release, and that the pharmaceutical formulation contains about a total dosage of 20mg resulting in a plasma concentration profile with an AUC of 467 ng hr/mL to 714 ng hr/mL. EX1001, 13:28-55.

Claim 12 is similar to Claim 1, but instead of the total dose and AUC limitation, Claim 12 recites that the enteric release dosage form comprises a coating of thickness greater than 20µm "which comprises dried aqueous dispersion of an

anionic copolymer based on methacrylic acid and acrylic acid ethyl ester, said coating being soluble at a pH of about 5.5 upwards." EX1001 at 14:26-31. A complete analysis of the claims, as well as application of the relevant prior art is presented below.

A. CLAIM CONSTRUCTION

In IPR2015-02009, after considering Petitioner Amerigen's and Patent Owner's arguments, (EX1021), the Board decided the certain terms (provided below) required explicit construction. Petitioner Mylan accepts the Board's constructions for the purposes of this IPR to the extent that the same or similar term appears in the '148 patent:

"Pharmaceutically active amphetamine salt(s)," "amphetamine salts," 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.

Given that "amphetamine base" is included in the Board's prior construction of "amphetamine salt(s)," Petitioner submits that, *"mixture of amphetamine base*

salts" and *"amphetamine base salts"* is included in the construction for "amphetamine salt(s)."

With respect to the term *"enteric release dosage form"* which appears in independent claims 1 and 12 of the '148 patent, the Board previously 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." EX1022 at 15. In line with the Board's prior construction, Petitioner submits that *"enteric release dosage form"* refers to a dosage form that will delay release of a drug until the drug has passed through the stomach and reached the intestines. EX1022 at 15.

With respect to the term "*about*" (which appears in all claims), "about" should be construed to mean "±20%." As explicitly stated in the file history: "[t]he term 'about' has its usual meaning in the field, *e.g*., roughly ± 20%, for example, as used by the FDA in its determinations of bioequivalency." (EX1035, 4/21/2003 Applicant Arguments/Remarks After Final Rejection, US Application No. 09/807,462, at p. 5).

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); *Cuozzo Speed Techs., LLC v. Lee*, 579 U.S. ___, No. 15-446, 2016 WL 3369425, at *14 (2016).

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

With respect to the '148 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, such as those with knowledge of pharmacokinetics, to solve a given problem. Declaration of David Auslander, Ph.D, (EX1002 ¶¶16-19); Declaration of Anthony Palmieri, Ph.D, (EX1029, ¶¶17-20).

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

Petitioners respectfully request IPR of claims 1-20 of the '148 patent on the specific 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 technical experts, David E. Auslander, Ph.D. (EX1002) and Anthony Palmieri, Ph.D, (EX1029), explaining what the art would have conveyed to a POSA as of the priority date.

Ground	References	Basis	Claims Challenged
1	The ’284 patent in light of the PDR 1997, Brown, the ’131 patent, and Slattum	103	1-20

Prior art references in addition to the primary references listed above provide further background in the art, further motivation to combine the teachings of these references and/or further support for why a POSA would have had 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(b) (pre-AIA).[1] The ’284 patent was disclosed during prosecution of the ’148 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

[1] The ’284 patent is 102(b) prior art because of the new matter added to the ’148 patent, otherwise, the ’284 patent would be prior art under 102(e).

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 teaches a formulation comprising immediate release and delayed release enteric dosage forms: "a dosage form containing two groups of particles, each containing the methylphenidate drug." *Id*. at 3:3-7. "The two releases can be referred to as 'pulses', and such a release profile can be referred to as 'pulsatile.'" *Id*. at 5:35-36. "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.

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 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.

The '284 patent also provides a "schematic representation of the plasma concentration of drug resulting from a release profile." *Id.* at 5:37-38; Fig. 2. The schematic shows the maximum concentration of two doses ($C_1$and C_2), along with their respective time. The '284 patent teaches that the maxima of the two releases can differ by no more than 20%, however, "embodiments in which maxima of the two releases differ by more than 40 percent are within the scope of the invention." *Id.* at 5:60-63; *Merck & Co. v. Biocraft Labs., Inc*., 874 F.2d 804, 807 (Fed. Cir. 1989) ("the fact that a specific [embodiment] is taught to be preferred is not controlling, since all disclosures of the prior art, including unpreferred embodiments, must be considered."). The '284 patent further discloses that a POSA can readily determine the appropriate relative amounts of drug in each release to obtain the desired maxima. EX1005 at 6:55-64.

2. PDR 1997

The Physician's Desk Reference 51st edition (1997) (hereinafter "PDR 1997" (EX1009)) was published in 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 '148 application. PDR 1997 indicates that Adderall® containing 10 or 20mg 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, 3:27-30 (describing prior art Adderall® and characterizing it as the "current" treatment); EX1002, ¶43.

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 '148 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 '148 application. The '131 patent discloses a drug delivery system that includes individual drugs 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 that the lag time between the immediate release dose and the delayed dose can be controlled by using: (1) pH-sensitive enteric coatings which are eroded in response to the pH (*i.e*., pH dependent), or (2) permeability-controlled systems which are subject to disruption in response to absorption of water from the environment (*i.e*., pH independent). *Id*. at 7:17-31.

The '131 patent also teaches that the AUC (area under the curve) of a pulsed dosage form can simulate the AUC of an immediate-release dosage form administered in divided doses. *Id.*, at 24:59-61. The experimental examples in the '131 patent used the drug propranolol, but as the '131 patent explains, "the principles of the invention are applicable to any other drug." *Id*. at 25:5-8.

5. Slattum

Slattum, *et al*., Comparison of Methods for the Assessment of Central Nervous System Stimulant Response after Dextroamphetamine Administration to Healthy Male Volunteers, *J. Clin. Pharmacol.*, vol. 36 no. 11 (1996) (hereinafter "Slattum" (EX1031)) was published in 1996 and qualifies as prior art under 35 U.S.C. § 102(b). Slattum was disclosed to the PTO during prosecution of the '148 application.

Slattum discloses a study that measures the pharmacokinetics, including the serum concentration-time profile, of an immediate dose of d-amphetamine. EX1031

at 1040. The immediate dose was administered to eight healthy male volunteers in 5mg, 10mg, and 20mg doses of Dexedrine tablets. EX1031 at 1040-42. The pharmacokinetic results were summarized in Table II and disclosed a mean AUC of 575 ± 115 ng hr/mL for a 20mg dose of dextroamphetamine:

TABLE II

Pharmacokinetic Parameters for Dextroamphetamine

Parameter	Dextroamphetamine Dose		
	5 mg (n = 9)	10 mg (n = 8)	20 mg (n = 8)
k hr^{-1}	0.107 ± 0.022	0.099 ± 0.021	0.094 ± 0.012
C_{max} (ng/mL)	15.4 ± 3.7	30.8 ± 5.3	54.8 ± 16.3
t_{max} (hrs)	2.1 ± 0.7	2.6 ± 0.7	2.8 ± 0.7
Cl/F (L/hr/kg)	0.42 ± 0.06	0.45 ± 0.06	0.43 ± 0.07
$AUC_{0-\infty}$ (ng/mL · hr)	149 ± 31	275 ± 42	575 ± 115

Values are presented as the mean ± standard deviation. k, terminal elimination rate constant; C_{max}, maximum concentration; t_{max}, time to maximum concentration; Cl/F, apparent total body clearance; $AUC_{0-\infty}$, area under the concentration–time curve extrapolated to infinity.

EX1031 at 1044.

IX. Invalidity Analysis

A. Claims 1-20 Would Have Been Obvious Over the '284 Patent in Light of the PDR 1997, Brown, the '131 Patent, and Slattum

1. Differences Between the Claims and the Prior Art

a. Independent Claim 1 and Its Dependent Claims 2-11 and 15-20

(i) Claim 1

Claim 1 would have been obvious to a POSA for the reasons explained below. EX1002, ¶¶95-115; EX1029, ¶¶56-71. 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 formulation for delivery of a mixture of amphetamine base salts effective to treat ADHD in a human patient comprising:	Pharmaceutical formulation containing a mixture of amphetamine base salts effective to treat ADHD in a human patient were known. *See*, PDR 1997 (EX1009), *see also*, the '148 patent (EX1001), 3:16-21 (discussing the prior art product containing the four amphetamine salts of Adderall®).
(a) an immediate release dosage form that provides immediate release upon oral administration to said patient;	The '284 patent teaches a formulation comprising immediate release and delayed release enteric dosage forms: "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."
(b) a delayed enteric release dosage form that provides delayed release upon oral administration to said patient;	"The 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; *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.").
(c) a pharmaceutically acceptable carrier;	Using pharmaceutically acceptable carriers with delayed enteric release dosage was commonly known. *See* the '284 patent (EX1005), 12:38-42 (providing "the dosage forms of the present invention may include, in either or both of the first dose and any delayed dose, pharmaceutically acceptable carriers…")
(d) wherein said amphetamine base salts compromise dextroamphetamine	Prior art Adderall® contains the mixed amphetamine salts. *See*, PDR 1997 (EX1009); *see also*, the '148 patent (EX1001), 3:16-21.

Claim 1	The Prior Art
sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate and amphetamine sulfate;	
(e) wherein said pharmaceutical formulation is sufficient to maintain an effective level of amphetamine base salts in the patient over the course of at least 8 hours without further administration of amphetamine base salt, and the peak plasma concentration of amphetamine base salts reached after release of said delayed enteric release dosage form exceeds the peak plasma concentration previously reached after release of said immediate release dosage form; and	Table 1 from the '284 reflects that by varying the enteric coating parameters (amount of coating, ratio of two polymers, amount of talc, and curing time), release profiles for up to 10 hours were obtained. EX1005 at Table 1; 13:57-60. "[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." EX1005, 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

Claim 1	The Prior Art
	second dose can provide from about 70 percent to about 30 percent of the active agent).[2]
(f) wherein said pharmaceutical formulation, when containing about a total dose of 20mg, will produce in a human individual a plasma concentration versus time curve (ng/mL versus hours) having an area under the curve (AUC) of about 467 to about 714 ng hr/mL.	PDR 1997 discloses that Adderall® was available as 10 mg or 20 mg tablets. EX1009 at 2209-10. Slattum reported an average AUC of 575 ng hr/ml, with an AUC range of 460 to 690 ng hr/mL, for a 20mg dose of dextroamphetamine. EX1031 at 1044. The '131 patent teaches that the AUC of a pulsed dosage form can match the AUC of the immediate-release dosage form administered in divided doses. EX1004 at 24:59-61.

As admitted by the '148 patent, Adderall® IR was a known pharmaceutical composition used for the treatment of ADHD. EX1002, ¶¶42-43; EX1001, 3:16-21;

[2] As Dr. Palmieri explains, the POSA would have known that dosage is proportional to plasma peaks. EX1029, ¶62. For example, in prior art reference Angrist, two sets of men were given either 0.25 mg/kg or 0.5 mg/kg of d-amphetamine. The plasma peaks of the men who were given 0.5 mg/kg were "approximately twice those seen in the first group." EX1037 at 1357. Thus, Angrist is an example of a reference that shows that dosage is proportional to plasma peaks. Moreover, as Dr. Palmieri explains, this is consistent with the data in Slattum.

In re Fout, 675 F.2d 297, 300 (C.C.P.A. 1982) (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 followed by a second dose that is administered 4 to 6 hours after the first. EX1002, ¶99; EX1009, 2209-10.

Brown (EX1011) teaches the pharmacokinetics associated with the administration of amphetamine salts for the treatment of ADHD. EX1002, ¶100. 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 using a *sustained-release d*-amphetamine formulation only would not have led to a prolonged clinical response. EX1002, ¶101. 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 ¶102.

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 rapid 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*., ¶103. The fact that 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 '284 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, ¶105; EX1005, 1:26-29.

Moreover, the '284 patent teaches delivering a dosage form containing two groups of particles, each containing methylphenidate for the treatment of ADHD. EX1002, ¶111; 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, ¶112. While 1.5 hours is preferable in the '284 patent, Table 1 shows that by varying the parameters, release profiles for up to **10 hours** were obtained. EX1005 at Table 1; 13:57-60 (delay times were extended based on the amount of coating, ratio of two polymers, amount of talc, and curing time); EX1002, ¶112.

In view of the teachings of the '284 patent, it would have been obvious to "maintain an effective level of amphetamine base salts in the patient over the course of at least 8 hours without further administration of amphetamine base salt." *Id.*; *see also* EX1005 at 6:55-61 (describing how the dosage amounts of the immediate release and delayed release doses can be adjusted); *id.* at 13:57-60 (drug release "is

influenced by: amount of coating, ratio of the two polymers, amount of talc, and curing time."); EX1004 at 7:25-29 (lag time is controlled by adjusting "[v]ariation of process variables and coating and core compositions").[3]

In addition, the '284 patent teaches effective levels of amphetamine base salts and providing for a dosage form where the second concentration peak associated with the delayed pulsed dosage provides a concentration maxima that is greater than, equal to, or less than the first concentration peak. EX1005, 6:45-61 ("the second dose may have

[3] Indeed, in another IPR to a related family member, the patent owner has explained 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 further admitted that "Mehta's delayed pellets, with lag times of 1-5 hours, released 85% of their methylphenidate in 3-10 hours." EX1020, 16:12-16; EX1002, ¶113. The patent owner recognizes that the second pulsed release may extend to 10 hours, thus embracing the claims of the '148 patent. *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003) ("A *prima facie* case of obviousness typically exits when the ranges of a claimed composition overlap the ranges disclosed in the prior art.").

to be adjusted to provide more of the drug than the first dose, to compensate for any competition between drug release and drug metabolism.").[4]

Finally, turning to the recited pharmacokinetic parameters: Slattum discloses that a 20mg total dose of d-amphetamine has an average AUC of 575 ng hr/mL, with a range of 460 ng hr/mL (*i.e.*, 575-115) to 690 ng hr/mL (*i.e.*, 575 +115) (EX1031 at 1044, Table II). Both the average AUC and the AUC range disclosed in Slattum falls within the claimed range.[5] *In re Peterson*, 315 F.3d at 1329 ("A *prima facie* case of obviousness

[4] For example, the '284 patent teaches that the first dosage could contain "about 30 – 50 percent of the patient's daily requirement of the drug and the second providing the remainder of the patient's daily requirement." EX1005, 6:26-28. A POSA would understand the basic pharmacokinetic principle that peak blood plasma concentration is proportional to the dose. EX1029, ¶62; EX1032, Benet at p. 118. In a 30/70 scenario, the blood concentration peak for the second dosage of 70% would be greater than the first peak. EX1029, ¶81.

[5] The claimed range of "about 467 to about 714 ng hr/mL" would encompass the range of 374 to 857 ng hr/mL because, as the Applicants explained, "[t]he term "about" has it usual meaning in the field, e.g., roughly $\pm$ 20%, for example as used by the FDA in its determinations of bioequivalency." *See* EX1035, 4/21/2003

typically exits when the ranges of a claimed composition overlap the ranges disclosed in the prior art.").

TABLE II

Pharmacokinetic Parameters for Dextroamphetamine

	Dextroamphetamine Dose		
Parameter	**5 mg (n = 9)**	**10 mg (n = 8)**	**20 mg (n = 8)**
k hr^{-1}	0.107 ± 0.022	0.099 ± 0.021	0.094 ± 0.012
C_{max} (ng/mL)	15.4 ± 3.7	30.8 ± 5.3	54.8 ± 16.3
t_{max} (hrs)	2.1 ± 0.7	2.6 ± 0.7	2.8 ± 0.7
Cl/F (L/hr/kg)	0.42 ± 0.06	0.45 ± 0.06	0.43 ± 0.07
$AUC_{0-\infty}$ (ng/mL · hr)	149 ± 31	275 ± 42	575 ± 115

While it is true that Slattum provides pharmacokinetic data for a 20mg 'immediate release' formulation, but as in claim 1, the "total dose" of Slattum would be 20mg. Thus, the claimed AUC of the 20mg dose is nothing more than what would have been expected given the known AUC data of 20mg immediate release dose of d-amphetamines as reported by Slattum. EX1029, ¶¶66-68; *In re Huai-Hung Kao*, 639 F.3d at 1070 (sustaining Board's obviousness determination for a claim that recited pharmacokinetic parameters (*i.e.*, C_{max}) explaining that such parameters are "an inherent

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Applicant Arguments/Remarks After Final Rejection, US Application No. 09/807,462, at p. 5.

property . . . present both in controlled release and immediate release formulations of that drug.").

Significantly, the patent owner even admitted the expected nature of AUC recitations during prosecution. When discussing amendments to the AUC limitation, the applicant stated that "when the formulation contains a total dose of 20mg, then it will produce the recited AUC. When it contains other total doses, it will, of course, proportionally produce other AUC's" and that this proportional relationship was "**known for amphetamines**." EX1036, 6/10/2003 Applicant Arguments/Remarks Made in Amendment, US 09/807,462, at p. 6 (emphasis added); *In Re Kubin,* 561 F.3d 1351, 1357 (Fed. Cir. 2009) (stating "[applicant's] application itself instructs that [the limitation] is not an additional requirement imposed by the claims on the [claimed invention], but rather a property necessarily present in [the claimed invention]."); *In re Fout*, 675 F.2d at 300 (explaining that a parties' admissions may create prior art);

Put simply, the patentee has does nothing more than claim an AUC that had already been established in the prior art for amphetamines for the same total dose.[6]

[6] In any event, it would have been obvious to a POSA that a pulsified dose divided into immediate and delayed release components would be pharmacokinetically the same as an immediate release for a given total dose. Prior

Santarus, Inc., 694 F.3d at 1354 (an obvious formulation does not "become patentable merely by testing and claiming an inherent property."); *In Re Baxter Travenol Labs*., 952 F.2d at 392 (Fed. Cir. 1991) ("Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention."); *In re Prindle*, 297 F.2d at, 254; *Biomarin Pharmaceticals Inc. v. Genzyme Therapeutics Products Ltd*., IPR2013-00534, Paper 81 (Final Written Decision) at p. 15 ("All that remained to be achieved over the prior art was the determination that a specific dose within a previously suggested dose range, and its corresponding dosing schedule, would have been safe and effective for the treatment of human patients."); *In re Peterson*, 315 F.3d at 1329-30; *In re Woodruff*, 919 F.2d 1575, 1578 (Fed. Cir. 1990). Accordingly, claim 1 would have been obvious. EX1002, ¶¶114-15.

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

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art experimentally confirmed that the bioavailability of immediate release d-amphetamine was the same as sustained release d-amphetamine. EX1038, Hinsvark at p. 327; EX1029, ¶¶69-71.

form. And as necessary, the '131 patent would have provided additional information about how to achieve this objective.[7] Furthermore, the '131 patent teaches pulsed released formulations where the peak plasma concentration of the delayed component exceeds the peak plasma concentration previously reached after release of the immediate component. EX1029, ¶¶59-63. As the '131 patent explains, the disclosed dosage forms "will release pulsed doses at rates comparable to immediate-release forms." EX1002, ¶108; EX1004, 7:11-13.[8]

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[7] For example *in vivo* data disclosed in the '131 patent shows a pulsed release lasting about 20-50 minutes. *See, e.g.*, EX1004 at Figures 8, 9, 10 & 11 (showing that the decrease in pH (labeled "DDT") corresponds to 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.

[8] 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.

Moreover, a skilled artisan would know that the '131 patent is not limited to any particular active agent, but can be applied to "any other drug." EX1004, 25:5-10 (emphasis added); EX1002, ¶109. In fact, the '131 patent provides a list of other active agents. EX1004, 25:20-44; EX1002, ¶110. 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 a variety of other known active agents including methylphenidate and amphetamines. EX1002, ¶¶109-10.

Thus, in combination with the '131 patent, 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, ¶114. Accordingly, it would have been a matter of routine experimentation to prepare a pulsed dose that maintained an effective level of amphetamine base salts over a period of at least 8 hours and provide the expected AUC with a reasonable

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* * *

> 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).

expectation of success. Indeed, the '131 patent teaches that pulsed delivery "can be tailored to simulate the AUC (preferably within 5%) of the immediate release dosage form administered in divided doses." EX1004 at 24:58-61.

(ii) Claim 2

Claim 2 depends on claim 1 and additionally requires that the "plasma concentration curve has a maximum concentration (C_{max}) of about 22.5 to about 40 ng/ml for about a total dose of 20mg." By use of the term "about," the claimed range would encompass the range of 18 to 48 ng/mL.[9] Slattum disclosed C_{max} values ranging from 11.7 ng/ml to 71.1 ng/mL for dextroamphetamine doses ranging from 5mg to 20mg. EX1031 at 1044.

As explained by Dr. Palmieri, the immediate release formulations disclosed in Slattum would have a single C_{max} because all of the drug is released at one time. *See, e.g.*, Figure 1 of Slattum showing a single C_{max}; EX1029 at ¶77. In contrast, as shown in the '284 patent, a formulation that contains both an immediate release component and a delayed release component would have two *relative* maxima—one

[9] As the Applicants explained, "[t]he term "about" has it usual meaning in the field, e.g., roughly $\pm$ 20%, for example as used by the FDA in its determinations of bioequivalency." *See* EX1035, 4/21/2003 Applicant Arguments/Remarks After Final Rejection, US Application No. 09/807,462, at p. 5.

representing the *relative* C_{max} immediate release portion and the other representing the *relative* C_{max} of the delayed release component. *See, e.g.*, Figure 2 of the '284 patent showing the presence of two *relative* C_{max} values; EX1029 at ¶78.

Said another way, for the same dose amount (*e.g.*, 20mg), a formulation that only contains an immediate release component will have a higher C_{max} than any of the two *relative* C_{max} values observed when the 20mg total dose is split between the immediate release portion (*e.g.*, 10mg) and a delayed release portion (*e.g.*, 10mg). This is consistent with the basic pharmacokinetic principle that peak blood plasma concentration is proportional to the dose. EX1029, ¶¶77-82; EX1032, Benet at p. 118; EX1037 at 1364; *see also* EX1029, ¶¶60, 67-69, 71, 89, 95-97; EX1036, 6/10/2003 Applicant Arguments/Remarks Made in Amendment, US 09/807,462, at p. 6 ("When it contains other total doses, it will, of course, proportionally produce other AUC's"; this proportional relationship was "known for amphetamines ((e.g., Suk et al., of record, page 587).").

As explained above, the '284 patent teaches the '148 patent recitation where "the peak plasma concentration of amphetamine base salts reached after release of said delayed enteric release dosage form *exceeds* the peak plasma concentration previously reached after release of said immediate release dosage form." EX1001 at 13:45-50. For example, the '284 patent teaches that the first dosage could contain

"about 30– 50 percent of the patient's daily requirement of the drug and the second providing the remainder of the patient's daily requirement." EX1005, 6:26-28.[10]

Looking at two of the dosage proportions disclosed in the '284 patent, *i.e.*, 30/70 and 50/50, in the 30/70 situation for a 20mg dose (see analysis for claim 1 discussing disclosure of 20mg dose), the immediate release component would contain 6 mg (30% of 20mg) of the amphetamines while the delayed release component would contain 14 mg (70% of 20mg).[11] As Dr. Palmieri explains, the data in Slattum would have shown the POSA that the two *relative* C_{max} values would

[10] In fact, the '284 patent discloses dosage splits as lopsided as having 2% of the drug in the first dose and 99% in the delayed dose. See EX1005 at 4:6-7 ("The first dose can contain anywhere from "about 2% to about 99% by weight of the methylphenidate drug.").

[11] The '284 patent discloses an extremely wide range of combinations for how you can split up the active drug in the two dosage forms. The first dose can contain anywhere from "about 2% to about 99% by weight of the methylphenidate drug." EX1005 at 4:6-7.

be approximately 18.4 ng/mL (6mg) and 43.12 ng/mL (14mg).[12] Thus, for the 30/70 situation for a 20mg dose, the C_{max} is 43.12 ng/mL, which falls within the claimed limitation of "**about** 22.5 to about 40 ng/ml for about a total dose of 20mg." Again, as explicitly explained by the patentee, by use of the term "about," the claimed range would encompass the range of 18 to 48 ng/mL.

In the other end of the exemplified range (i.e., 50/50), for a 20mg dose (see analysis for claim 1 discussing disclosure of 20mg dose), the immediate release and delayed release components would have both contained 10mg of the amphetamines. As Dr. Palmieri explains the data in Slattum shows the two observed C_{max} values would be approximately 30.8 ng/mL. However, as Dr. Palmieri explains, the C_{max} of the delayed release component would be higher than the C_{max} of the immediate release component because it would be influenced by plasma levels due to residual

[12] These numbers are calculated by the C_{max} values from either the 5mg or 10mg data in Slattum, and the linear relationship of the data. Using the 20mg data in Slattum, the calculated C_{max} values are 16.44 ng/mL and 38.36 ng/mL. As discussed herein, it does not matter which data values are used, the calculated prior art values all fall within the claimed range. EX1029, ¶¶80-82.

levels of amphetamines released from the immediate release component.[13] EX1029, ¶63; *see, e.g.*, EX1005 at 3, Figure 2 of the '284 patent; *see also* the '284 patent (explaining that methylphenidate have a "pharmacological activity qualitatively similar to that of amphetamines.") EX1005 at 2:13-16. Thus, for the 50/50 situation for a 20mg dose, the C_{max} is approximately 30.8 ng/mL, which falls within the claimed limitation of "about 22.5 to about 40 ng/ml for about a total dose of 20mg."

Since both the 30/70 and 50/50 ranges disclosed in the '284 patent would have had C_{max} that fell within the claimed range, all other dosage splits encompassed within those ranges would have also fallen within the '148 patent's claimed range (e.g., 40/60). *In re Peterson*, 315 F.3d at 1329 ("A *prima facie* case of obviousness typically exits when the ranges of a claimed composition overlap the ranges disclosed in the prior art."). Accordingly, claim 2 would have been obvious.

(iii) Claims 3 and 4

Claim 3 depends on claim 2 and further requires that the "time after said oral administration to reach said C_{max} value is about 7 to about 10 hours." Claim 4

[13] As Dr. Palmieri explains, it was well-known that the elimination half-life of *d*-amphetamine is about seven hours. EX1011, Brown at p. 2. Thus, it was understood that *d*-amphetamine from the immediate dose would still be in the blood 4-6 hours after the immediate release. EX1029, ¶63.

depends on claim 1 and merely further requires that the "time after said oral administration to reach maximum concentration of said plasma concentration curve is about 7 to about 10 hours". Put another way, these claims cover reaching C_{max} during the delayed release portion of the dosage form.

In a related IPR, the patent owner has admitted that the '284 patent teaches the required parameters of the claim. EX1020, 16:12-16; EX1002, ¶113. While admitting 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 further argued that "Mehta's delayed pellets, with lag times of 1-5 hours, released 85% of their methylphenidate in **3-10 hours**." EX1020, 16:12-16 (emphasis added); EX1002, ¶113.[14] *In re Peterson*, 315 F.3d at 1329 ("A *prima facie* case of obviousness typically exits when the ranges of a claimed composition overlap the ranges disclosed in the prior art."). Therefore, claims 3 and 4 are obvious.

[14] *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.").

(iv) Claim 5

Claim 5 depends on claim 2, 3, or 4 and further requires that the "AUC is **about** 714 ng hr/mL". (Emphasis added). As the Applicants explained, "[t]he term "about" has its usual meaning in the field, e.g., roughly $\pm$ 20%, for example as used by the FDA in its determinations of bioequivalency." EX1035, 4/21/2003 Applicant Arguments/Remarks After Final Rejection, US Application No. 09/807,462, at p. 5. Therefore, the "**about** 714 ng hr/mL" encompasses the range of 571.2-865.8 ng hr/mL. Slattum reported mean AUC of 575 ± 115 ng hr/mL, which falls within the range encompassed by the claim. EX1031 at 1044. Overlapping ranges establish a *prima facie* case of obviousness. *In re Peterson*, 315 F.3d at 1329-30; *In re Woodruff*, 919 F.2d at 1578.[15]

Moreover, there is no evidence of any criticality or unexpected results contained in the specification or the file history of the claimed 714 ng/mL value. Indeed, the 714 ng/mL value never even appears in the specification. *See Application of Tanczyn*, 241 F.2d 731, 733 (C.C.P.A. 1957) (no finding of

[15] Arriving at the desired AUC and C_{max} would be obvious to a POSA that understood that AUC and C_{max} are merely dose proportional. *See* EX1036, 6/10/2003 Applicant Arguments/Remarks Made in Amendment, US 09/807,462, at p. 6; EX1032, Benet at p. 118; EX1037, Angrist at p. 1364.

nonobviousness where applicant failed to discuss unexpected results in specification). Moreover, during prosecution the Applicant admitted that the AUC value for the given total dose of 20mg was expected. *See* EX1036, 6/10/2003 Applicant Arguments/Remarks Made in Amendment, US 09/807,462, at p. 6 ("when the formulation contains a total dose of 20mg, then it will produce the recited AUC. When it contains other total doses, it will, of course, proportionally produce other AUC's"; this proportional relationship was "**known for amphetamines**.") (emphasis added). Therefore, claim 5 would have been obvious.

(v) Claim 6

Claim 6 depends on claim 3 and further requires that the "AUC is about 714 ng hr/mL, the time after said oral administration to reach said C_{max} value is about 7 hours and C_{max} is about 40 ng/mL". The AUC limitation "about 714 ng hr/mL" is discussed above for claim 5, and therefore is obvious for the reasons stated therein.

As to the C_{max} limitation, "*about* 40 ng/mL" would encompass a range of 32 to 48 ng/mL. *See* EX1035, 4/21/2003 Applicant Arguments/Remarks After Final Rejection, US Application No. 09/807,462, at p. 5 (explaining the meaning of the word "about"). Slattum disclosed a C_{max} value of 54.8$\pm$16.3 ng/mL for a dose of 20

mg,[16] which equates to a C_{max} range for a 20mg dose of 38.5 to 71.1 ng/mL. EX1029, ¶87. Thus, the range disclosed in Slattum for a 20mg dose overlaps with the range encompassed by the claim. Overlapping ranges establish a *prima facie* case of obviousness. *In re Peterson*, 315 F.3d at 1329-30; *In re Woodruff*, 919 F.2d at 1578. Furthermore, arriving at the desired AUC and C_{max} would be obvious to a POSA that understood that AUC and C_{max} are merely dose proportional. *See* EX1036, 6/10/2003 Applicant Arguments/Remarks Made in Amendment, US 09/807,462, at p. 6; EX1032, Benet at p. 118; EX1037, Angrist at 1364. "All that remained to be achieved over the prior art was the determination that a specific dose within a previously suggested dose range, and its corresponding dosing schedule, would have been safe and effective for the treatment of human patients." *Biomarin Pharmaceticals Inc.*, IPR2013-00534, Paper 81 (Final Written Decision) at p. 15.

Turning to the 7 hour lag time recitation: in a related IPR, the patent owner admitted that the '284 patent teaches the required lag time parameter. EX1020,

[16] Claim 6 does not recite a dosage, but requires a dosage of 20mg because it depends indirectly on claims 1 and 2, which both recite "about a total dose of 20 mg."

16:12-16; EX1002, ¶110.[17] *In re Peterson*, 315 F.3d at 1329 ("A *prima facie* case of obviousness typically exits when the ranges of a claimed composition overlap the ranges disclosed in the prior art."). Therefore, claim 6 would have been obvious.

Claim 6	Prior Art
6. A formulation of claim 3 wherein said AUC is about 714 ng hr/mL, the time after said oral administration to reach said C_{max} value is about 7 hours and C_{max} is about 40 ng/mL.	Slattum reported an AUC of 460 to 690 ng hr/mL for a 20 mg dose of dextroamphetamine. Slattum also disclosed C_{max} values ranging from 11.7 ng/mL to 71.1 ng/mL for dextroamphetamine doses ranging from 5mg to 20mg. EX1031 at 1044. The '131 patent teaches that the AUC of a pulsed release dosage can match the AUC of an immediate release dosage. EX1004 at 24:58-61. In the prosecution history, the applicant admitted that AUC is dose proportional. When discussing amendments to the AUC limitation, the applicant stated that "when the formulation contains a total dose of 20mg, then it will produce the recited AUC. When it contains other total doses, it will, of course, proportionally produce other AUC's" and that this proportional relationship was "known for amphetamines." EX1036, 6/10/2003 Applicant Arguments/Remarks Made in Amendment, US 09/807,462, p. 6. Table 1 shows that by varying the parameters, release profiles for up to **10 hours** were obtained. EX1004 at Table 1; EX1002, ¶ 109.

[17] *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 6	Prior Art
	"Preferably if two approximately equal doses are released, the release of the two doses provides a plasma concentration profile having two maxima, which differ from each other by no more than about 40 percent in magnitude, preferably by no more than about 30 percent, and more preferably by no more than about 25 percent. This is determined by the relationship: $\|C_1 - C_2\|/C_1$." The '284 patent, 5:51-59. The '284 patent teaches that the second peak concentration can be greater than the first peak concentration by as much as 40 percent in magnitude.

(vi) Claim 7

Claim 7 depends on claim 2 and further requires that the "C_{max} is about 40 ng/mL". The term "*about* 40 ng/mL" would encompass a range of 32 to 48 ng/mL. *See* EX1035, 4/21/2003 Applicant Arguments/Remarks After Final Rejection, US Application No. 09/807,462, at p. 5. Slattum disclosed a C_{max} value of 54.8±16.3 ng/mL for a dose of 20mg.[18] EX1029, ¶87. That equates to a C_{max} range for a 20mg dose of 38.5 to 71.1 ng/mL. Thus, the range disclosed in Slattum for a 20mg dose overlaps with the range encompassed by the claim. To arrive at the precise desired C_{max}, a POSA would understand the basic pharmacokinetic principle that C_{max} is proportional to dose. EX1036, 6/10/2003 Applicant Arguments/Remarks Made in

[18] Claim 7 depends on claim 2, which depends on claim 1, and thus requires a total dose is 20mg. EX1001 at 13:58.

Amendment, US 09/807,462, at p. 6; EX1032, Benet at p. 118; EX1037, Angrist at 1364. Therefore, claim 7 would have been obvious.

(vii) Claim 8

Claim 8 depends on claims 3 or 4 and further requires that the "time is about 7 hours." As stated above, in a related IPR, the patent owner has admitted 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," and the patent owner further argued that "Mehta's delayed pellets, with lag times of 1-5 hours, released 85% of their methylphenidate in **3-10 hours**." EX1020, 16:12-16 (emphasis added); EX1002, ¶113.[19] The patent owner recognizes that the '284 patent teaches the second pulsed release include 7 hours, thus encompassing the lag time limitation. *In re Peterson*, 315 F.3d 1329 ("A *prima facie* case of obviousness typically exits when the ranges of a claimed composition overlap the ranges disclosed in the prior art."). Accordingly, claim 8 would have been obvious.

[19] *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.").

(viii) Claim 9

Claim 9 depends on claims 1-4, 6 or 7 and further requires that the "salts are contained in about equal amounts within each of said dosage forms". Claim 1 recites that there are four amphetamine base salts: (1) dextroamphetamine sulfate, (2) dextroamphetamine saccharate, (3) amphetamine aspartate monohydrate, and (4) amphetamine sulfate. EX1001 at 13:38-41. Claims 2-4, 6, 7 depend directly or indirectly from claim 1. PDR 1997 indicates that the 20 mg Adderall® formulation contained 25% each of d-amphetamine saccharate, amphetamine aspartate, damphetamine sulfate and amphetamine sulfate. EX1009 at 2209. Accordingly, claim 9 would have been obvious.

(ix) Claim 10

Claim 10 depends on claims 1-4, 6, or 7 and further requires that the "delayed enteric release dosage form comprises a coating of a thickness of **[**at least**]** *greater than* 20µm which comprises dried about 30% (dry substance) aqueous dispersion of an anionic copolymer based on methacrylic acid and acrylic acid ethyl ester, said coating being soluble at a pH of about 5.5 upwards".

Turning first to the thickness recitation: It is axiomatic that simply modifying the thickness of the coating is a routine modification to a POSA. EX1002, ¶121. 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. *Id*.

Indeed, as Dr. Auslander explains, citing Remington (EX1012 at 1668), the claimed range, *i.e.*, 20µm and greater, overlaps with typical ranges (less than 1µm to 200µm) disclosed in the prior art. EX1002, ¶121. Overlapping ranges establish a *prima facie* case of obviousness. *In re Peterson*, 315 F.3d at 1329-30; *In re Woodruff*, 919 F.2d at 1578. Moreover, optimizing the coating thickness of the delayed-release profile would have been a matter of routine skill and would have resulted in a thickness of greater than 20µm. EX1002, ¶¶121, 125; *In re Aller*, 220 F.2d at 456-57 (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").

Turning next to polymer coating recitation: The '131 patent discloses "erosion-dependent systems" using pH sensitive polymers:

> Erosion-Dependent Systems
>
> Enteric coatings of **pH-sensitive polymers** are employed to control the time of delivery of a drug-containing core composition to the small intestine of a living mammal.
>
> . . .
>
> In illustrative embodiments, cellulose acetate phthalate (CAP) and/or methyl-methacrylate/methacrylic acid are suitable materials for the enteric coatings contemplated by the invention. These coatings delay release of the drug until the dosage form has passed from the stomach to the small intestine. **In particular, the methyl-methacrylate/methacrylic acid coatings dissolve at a higher pH**

> **than CAP and are capable of extending the time of dissolution to four to eight hours in vitro in simulated intestinal fluid of pH 6.8**. Methyl-methacrylate is sold commercially by Rohm Pharma, W. Germany under the trademark Eudragit S100 and methacrylic acid is sold under the trademark Eudragit L100.

EX1004 at 7:48-8:9 (emphasis added). Moreover, the '131 patent teaches that "[v]arying the relative proportions of Eudragit L100 and Eudragit S100 in the formulation set forth above results in modification of release time." EX1004 at 9:36-37; *see also* EX1033, 6/24/2002 Examiner's Office Action at p.5 (noting that prior art disclosure of Eudragit® L100-55 teaches pH dependent coatings); EX1016, at 1653 ("The action of enteric coatings results from a difference in composition of the respective gastric and intestinal environments in regard to pH and enzymatic properties…. Thus, most currently used enteric coatings are those which remain undissociated in the low pH environment of the stomach, but readily ionize when the pH rises to about 4 or 5.").

Indeed, even Applicants stressed the conventional nature of the use of pH dependent systems: "[T]he pH dependent doses rely, e.g., on **highly conventional** enteric technology to achieve release as the pH changes along the gastrointestinal tract." EX1034, 10/24/2002 Applicant Arguments/Remarks Made in Amendment, US Application No. 09/807,462 at p. 11 (emphasis added). As a further illustration of the conventional nature of these limitations, Applicants admitted that the

limitations were nothing more than what was recited on the conventional tech data sheets:

> [T]he enteric coating composition is based on conventional knowledge of the chemical composition of the enteric material utilized in Example 2, i.e., Eudragit® L 30 D-55. **This can be seen from the attached data sheets** describing this well-known enteric material, e.g., "Eudragit L, Aqueous Dispersion, Data Sheet (Info LD 2/e) Eudragit L 30 D (two pages), at page 1, top and column 1, and Eudragit L, Aqueous Dispersion, Standards Sheet (Info LD-7/e), Eudragit L 30 D" (two pages), at page 1, top and columns 1 and 2. (The notation "55" in the nomenclature used in the specification is an equivalent of the older nomenclature L 30 D, "55" simply refereeing to the pH (5.5) at which the enteric material becomes soluble).

EX1035, 4/21/2003 Applicant Arguments/Remarks Made After Final Rejection, US Application No. 09/807,462 at p. 5 (emphasis added); *see also Id*. at p. 7-10, Tech Data Sheets for Eudragit® L 30 D.

Applicants have admitted that the claim limitations represent nothing more than *copying information* contained on publically available Tech Data sheets for polymers used in "highly conventional enteric technology." *See* EX1034, 10/24/2002 Applicant Arguments/Remarks Made in Amendment, US Application No. 09/807,462 at p. 11. As such, these limitations would have been obvious to a POSA and to the extent there would have been any optimization required by the

skilled artisan (if any, in view of the information provided on the data sheet), such an endeavor would have been a routine exercise. *See Galderma Labs.*, 737 F.3d at 736 (various inactive ingredient limitations for acne medication were obvious where "[t]he specific inactive ingredients of the asserted claims [were] taught by the **Data Sheet**" of a prior art product) (emphasis added).

Furthermore, the use of "about 30% (dry substance) aqueous dispersion" of the anionic copolymer would have also been obvious to a POSA. The patent owner admitted during prosecution that Eudragit® L 30 D, which has 30% dry polymer substance, is conventional. EX1035, 4/21/2003 Applicant Arguments/Remarks Made After Final Rejection, US Application No. 09/807,462 at p. 5; *see also Id*. at p. 7-10. Furthermore, optimizing the amount of dry substance would have been a matter of routine skill and would have resulted in the claimed amount. EX1002, ¶136; *In re Aller*, 220 F.2d at 456-57 (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"). Furthermore, incorporating known products into a formulation based on properties in their publicly available data sheets is obvious. *See Galderma Labs*, 737 F.3d at 736. Accordingly, claim 10 would have been obvious.

(x) Claim 11

Claim 11 depends on claim 10 and further requires that the "thickness is at least 25µm." *See* EX1004, 19:30-20:28. For the same reasons as claim 10's "*greater than* 20µm" recitation, claim 11 is obvious because it is axiomatic that simply modifying the thickness of the coating is a routine modification to a POSA. EX1002, ¶121; EX1012 at 1668; *In re Peterson*, 315 F.3d at 1329-30; *In re Woodruff*, 919 F.2d at 1578; *In re Aller*, 220 F.2d at 456-57. Accordingly, claim 11 would have been obvious.

(xi) Claims 15 and 16

Claim 15 depends on claim 1, and claim 16 depends on claim 2, but both recite that the total dose is 20mg, but without the term "about." Adderall was available in 20mg dosages prior to the '148 patent. EX1009 at 2209-10. Accordingly, claims 15 and 16 are obvious for the same reasons as claims 1 and 2.

(xii) Claim 17

Claim 17 depends on claim 1 and requires that the formulation is "formulated for a total dose different from about 20mg and having an AUC proportional to said 20mg AUC". As to the meaning of this claim recitation, a discussion of the prosecution history is helpful. During prosecution, Applicants explained:

> Claim 103, prior to this amendment, recited an AUC value for the instance where a total dose of 20mg was contained in the generically claimed formulation ("for about a 20mg total dose").

> Straightforwardly, it followed that when the formulation contained other total doses, other proportional AUC's would be produced, as it known for amphetamines (e.g., Suk et al., of record, page 587). The claim stated this: "or an AUC proportional thereto for a total dose other than about 20mg," but did not need to. The new language says the same thing, only non-redundantly. *That is, when the formulation contains a total dose of 20 mg, then it will produce the recited AUC. When it contains other total doses, it will, of course, proportionally produce other AUC's*. . . . New claims 117-120[20] are drawn individually to the two possibilities involved.

EX1036, 6/10/2003 Applicant Arguments/Remarks Made in Amendment, US Application No. 09/807,462 at p. 6 (emphasis added).

Thus, this claim covers formulations that contain a total dose *other than 20mg*, but because the total dose is no longer 20mg, unremarkably the resulting AUC is different in some proportion relative to the 20mg total dose formulation. *See* EX1036, 6/10/2003 Applicant Arguments/Remarks Made in Amendment, US Application No. 09/807,462 at p. 6. ("when the formulation contains a total dose of 20 mg, then it will produce the recited AUC. When it contains other total doses, it will, of course, proportionally produce other AUC's").

[20] Claim 119 (as then listed) became claim 17.

Adderall was available in dosages other than 20mg prior to the '148 patent (EX1009). As Dr. Palmieri explains *at length*, the data in Slattum and other references shows that the AUC has a linear (*i.e.*, proportional) relationship with dose amounts of administered amphetamines. EX1029, ¶¶60, 67-69, 71, 82, 89, 95-99. In fact, Dr. Palmieri's observation is consistent with *explicit statements* in Slattum: "[v]alues for . . . dose corrected $AUC_{0\rightarrow\infty}$ . . . were not significantly different among dose levels." EX1031, Slattum at 1044, EX1029, ¶ 99. As Dr. Palmieri explains, the lack of significant differences when $AUC_{0\rightarrow\infty}$ was corrected for dose levels indicates a linear relationship. *Id*. Therefore, because of this linear relationship, when total dose amounts other than 20mg are used, the prior art would have taught that there would be a proportional change in $AUC_{0\rightarrow\infty}$ relative to the 20mg total dose formulation. *Id*.

Indeed, this fact is not controversial and was in fact admitted by the Applicants during prosecution: "it followed that when the formulation contained other total doses, other proportional AUC's would be produced, *as is known for amphetamines* (e.g. Suk et al . . .)." EX1036, 6/10/2003 Applicant Arguments/Remarks Made in

Amendment, US Application No. 09/807,462 at p. 6;[21] *In re Fout*, 675 F.2d at 300 (explaining that a parties' admissions may create prior art). Therefore, claim 17 is obvious.

(xiii) Claim 18

Claim 18 depends on claim 2 and requires a formulation that is "formulated for a total dose different from about 20mg and having a C_{max} proportional to said 20mg C_{max}". Claim 18 is similar to claim 17 except instead of reciting AUC, it recites C_{max}.[22] Therefore, this claim covers formulations that contain a total dose other than 20mg, but because the total dose is no longer 20mg, the resulting C_{max} is

[21] Likewise, Angrist teaches that dosage is proportional to plasma peaks. In an experiment where two sets of men were given either 0.25 mg/kg or 0.5 mg/kg of d-amphetamine, the plasma peaks of the men who were given 0.5 mg/kg were "approximately twice those seen in the first group." EX1037 at 1357.

[22] Indeed, the prosecution excerpt provided above during the discussion of claim 17 applies to claim 18. *See* EX1036, 6/10/2003 Applicant Arguments/Remarks Made in Amendment, US Application No. 09/807,462 at p. 6. The excerpt explicitly makes reference to "claims 117-120," claim 120 became issued claim 18 in the '148 patent.

different in some proportion relative to the 20 mg total dose formulation.

As stated above, Adderall was available in dosages other than 20mg prior to the '148 patent (EX1009). Moreover, as Dr. Palmieri explains, the data in Slattum shows that the C_{max} has a linear (*i.e.*, proportional) relationship with dose amounts of administered amphetamines. EX1029, ¶¶95-99.[23] Dr. Palmieri's observation is consistent with statements in Slattum: "[v]alues for . . . dose corrected C_{max}. . . were not significantly different among dose levels." EX1031, Slattum at 1044; EX1029, ¶99. As Dr. Palmieri explains, the lack of significant differences when C_{max} was corrected for dose levels indicates a linear relationship. *Id*. Therefore, when the total dose is not 20mg, based on the data in Slattum, the resulting C_{max} will be different in some proportion relative to the 20mg total dose formulation. Therefore, claim 18 is obvious.

(xiv) Claim 19

Claim 19 depends on claim 1 and further states that the "delayed release is pH independent". Both the '284 patent and the '131 patent teach the use of pH independent systems. The '284 patent teaches enteric-release coatings that are non-

[23] A POSA would understand the basic pharmacokinetic principle that C_{max} is proportional to dose. EX1032, Benet at p. 118. Given this relationship, it is obvious that the C_{max} for a 20mg dose would be proportional to the C_{max} for a different dose.

pH dependent. EX1005 at 13:61-14:45. EX1002, ¶127. The '131 patent teaches that the "permeability-controlled systems" employ "pH independent" coatings. EX1004, 10:65 to 11:2. Accordingly, claim 19 is obvious for the same reasons as claim 1, because a POSA would have been motivated to use the pH independent delayed release system as disclosed in the '284 patent and the '131 patent.

(xv) Claim 20

Claim 20 depends on claim 1 and requires that the pharmaceutical formulation further contain "a protective coating layer." The '284 patent teaches that dosage forms that can be used include "**coated** and uncoated pellets, and **coated** and uncoated tablets." EX1002, ¶128; EX1005 at 7:2-4. 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, 7:6-8. Therefore, the use of coated pellets and tablets, and encapsulating pellets "*within a hard gelatin capsule*" discloses the limitation of a "protective coating layer." EX1002, ¶128.

Moreover, the '284 patent discloses the use of sealant as a physical barrier. EX1002, ¶129; EX1005, 10:38-42. As Dr. Auslander explains, the use of sealants and protective coating was well known to a POSA for decades. EX1002, ¶129; EX1016 at 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, ¶129; EX1016 at 1650. As such, claim 20 would have been obvious.

b. Independent Claim 12 and Its Dependent Claims 13 and 14

(i) Claim 12

The limitations of claim 12 are similar to those set forth in claim 1. Claim 12 differs from claim 1 in that claim 12 does not include the wherein clause reciting a total dose of 20mg that will produce in a human individual a plasma concentration versus time curve (ng/mL versus hours) having an area under the curve (AUC) of about 467 to about 714 ng hr/mL. Instead, claim 12 limits the delayed enteric dosage to a coating thickness of greater than 20μm and with pH dependency. EX1001 at 14: 19-45; EX1002, ¶130.

For the same reasons 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, ¶130; *see supra* IX.A.1.a(i). 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, ¶¶97-115; *see supra* IX.A.1.a(i)a).

Turning to the enteric coating thickness limitation: It is axiomatic that simply modifying the thickness of the coating is a routine modification to a POSA. EX1002, ¶133. 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, ¶135. Indeed, as Dr. Auslander explains, citing Remington (EX1012 at p. 1668), the claimed range, *i.e.*, 20µm and greater, overlaps with typical ranges (less than 1µm to 200µm) disclosed in the prior art. EX1002, ¶133. Overlapping ranges establish a *prima facie* case of obviousness. *In re Peterson*, 315 F.3d at 1329-30; *In re Woodruff*, 919 F.2d at 1578. Moreover, optimizing the coating thickness of the delayed-release profile would have been a matter of routine skill and would have resulted in a thickness of at least 20µm. EX1002, ¶133; *In re Aller*, 220 F.2d at 456-57 (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").

Turning to the pH dependency limitation: The '131 patent discloses "erosion-dependent systems" using pH sensitive polymers:

> Erosion-Dependent Systems
>
> Enteric coatings of **pH-sensitive polymers** are employed to control the time of delivery of a drug-containing core composition to the small intestine of a living mammal . . . . In illustrative embodiments, cellulose acetate phthalate (CAP) and/or methyl-methacrylate/methacrylic acid

> are suitable materials for the enteric coatings contemplated by the invention. These coatings delay release of the drug until the dosage form has passed from the stomach to the small intestine. **In particular, the methyl-methacrylate/methacrylic acid coatings dissolve at a higher pH than CAP and are capable of extending the time of dissolution to four to eight hours in vitro in simulated intestinal fluid of pH 6.8**. Methyl-methacrylate is sold commercially by Rohm Pharma, W. Germany under the trademark Eudragit S100 and methacrylic acid is sold under the trademark Eudragit L100.

EX1004 at 7:48-8:9 (emphasis added). Moreover, the '131 patent teaches that "[v]arying the relative proportions of Eudragit L100 and Eudragit S100 in the formulation set forth above results in modification of release time." EX1004 at 11:36-37; *see also* EX1033, 6/24/2002 Examiner's Office Action at p.5 noting that prior art disclosure of Eudragit® L100-55 teaches pH dependent coatings; EX1016, 1653 ("The action of enteric coatings results from a difference in composition of the respective gastric and intestinal environments in regard to pH and enzymatic properties…. Thus, most currently used enteric coatings are those which remain undissociated in the low pH environment of the stomach, but readily ionize when the pH rises to about 4 or 5.")

Indeed, even Applicants stressed the conventional nature of the use of pH dependent systems: "[T]he pH dependent doses rely, e.g., on **highly conventional** enteric technology to achieve release as the pH changes along the gastrointestinal

tract." EX1034, 10/24/2002 Applicant Arguments/Remarks Made in Amendment, US Application No. 09/807,462 at p. 11. (Emphasis added). As a further illustration of the conventional nature of these limitations, Applicants admitted that the limitations were nothing more than what was recited on the conventional tech data sheets:

> [T]he enteric coating composition is based on conventional knowledge of the chemical composition of the enteric material utilized in Example 2, *i.e.*, Eudragit® L 30 D-55. This can be seen from the attached data sheets describing this well-known enteric material, *e.g.*, "Eudragit L, Aqueous Dispersion, Data Sheet (Info LD 2/e) Eudragit L 30 D (two pages), at page 1, top and column 1, and Eudragit L, Aqueous Dispersion, Standards Sheet (Info LD-7/e), Eudragit L 30 D" (two pages), at page 1, top and columns 1 and 2. (The notation "55" in the nomenclature used in the specification is an equivalent of the older nomenclature L 30 D, "55" simply refereeing to the pH (5.5) at which the enteric material becomes soluble).

EX1035, 4/21/2003 Applicant Arguments/Remarks Made After Final Rejection, US Application No. 09/807,462 at p. 5; *see also Id*. at p. 7-10, Tech Data Sheets for Eudragit® L 30 D. Accordingly, claim 12 would have been obvious.

A POSA would have been led by the prior art as shown in the following claim chart:

Claim 12	The Prior Art
1. A pharmaceutical formulation for delivery of a mixture of amphetamine base salts effective to treat ADHD in a human patient comprising:	Pharmaceutical formulation containing a mixture of amphetamine base salts effective to treat ADHD in a human patient were known. *See*, PDR 1997 (EX1009), *see also*, the '148 patent (EX1001), 3:16-21 (discussing the prior art product containing the four amphetamine sulfate salts of Adderall®).
(a) an immediate release dosage form that provides immediate release upon oral administration to said patient;	The '284 patent teaches a formulation comprising immediate release and delayed release enteric dosage forms: "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."
(b) a delayed enteric release dosage form that provides delayed release upon oral administration to said patient,	"The 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; *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 12	The Prior Art
(c) wherein said enteric release dosage form comprises a coating of a thickness of **[**at least**]** *greater than* 20μm which comprises dried aqueous dispersion of an anionic copolymer based on methacrylic acid and acrylic acid ethyl ester, said coating being soluble at a pH of about 5.5 upwards; and	"Encapsulated dissolution systems can be prepared either by coating particles or granules of drug with varying thicknesses of slowly soluble polymers or, by [sic] microencapsulation. . . . The coating materials may be selected from a wide variety of natural and synthetic polymers, depending on the drug to be coated and the release characteristics desired. The most commonly used coating materials include gelatin, carnauba wax, shellacs, ethylcellulose, cellulose acetate phthalate or cellulose acetate butyrate. Drug release from microcapsules, is a mass-transport phenomenon; and *can be controlled by adjusting the size of microcapsules, thickness of coating materials* and the diffusivity of core materials. The coating thickness of microcapsules is normally very thin, and fora given coating-core ratio, it decreases rapidly as the microcapsule size decreases. *The thickness can be varied from less than 1 μm to 200 μm by* changing the amount of coating material from 3 to 30% of the total weight." EX1012 at 1668 (emphasis added).
	"Enteric coatings of pH-sensitive polymers are employed to control the time of delivery of a drug-containing core composition to the small intestine of a living mammal . . . . In illustrative embodiments, cellulose acetate phthalate (CAP) and/or methyl-methacrylate/methacrylic acid are suitable materials for the enteric coatings contemplated by the invention. These coatings delay release of the drug until the dosage form has passed from the stomach to the small intestine. In particular, the methyl-methacrylate/methacrylic acid coatings dissolve at a higher pH than CAP and are capable of extending the time of dissolution to four to eight hours in vitro in simulated intestinal fluid of pH 6.8. Methyl-methacrylate is sold commercially by Rohm Pharma, W. Germany under the trademark Eudragit S100 and methacrylic acid is sold under the trademark Eudragit L100." EX1004 at 7:48-8:9.

Claim 12	The Prior Art
	"Varying the relative proportions of Eudragit L100 and Eudragit S100 in the formulation set forth above results in modification of release time." EX1004 at 11:36-37. Suitable enteric polymers include methacrylic acid-methacrylic acide ester copolymers. EX1016, at 1653 ("The action of enteric coatings results from a difference in composition of the respective gastric and intestinal environments in regard to pH and enzymatic properties…. Thus, most currently used enteric coatings are those which remain undissociated in the low pH environment of the stomach, but readily ionize when the pH rises to about 4 or 5.")
(d) a pharmaceutically acceptable carrier;	Using pharmaceutically acceptable carriers with delayed enteric release dosage was commonly known. *See* the '284 patent (EX1005), 12:38-42 (providing "the dosage forms of the present invention may include, in either or both of the first dose and any delayed dose, pharmaceutically acceptable carriers…")
(e) wherein said amphetamine base salts compromise dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate and amphetamine sulfate;	Prior art Adderall® contains the mixed amphetamine salts. See, PDR 1997 (EX1009); see also, the '148 patent (EX1001), 3:16-21.
(f) wherein said pharmaceutical formulation is sufficient to maintain an effective level of amphetamine base salts in the patient over the course of at least 8 hours without further administration of	"[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

Claim 12	The Prior Art
amphetamine base salts reached after release of said delayed enteric release dosage form exceeds the peak plasma concentration of said salts previously reached after release of said immediate release dosage form.	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).[24] Table 1 from the '284 reflects that by varying the enteric coating parameters (amount of coating, ratio of two polymers, amount of talc, and curing time), release profiles for up to 10 hours were obtained. EX1005 at Table 1; 13:57-60.

(ii) Claim 13

Claim 13 depends on claim 12 and further requires that the thickness is at least 25μm. As discussed in claims 11 and 12, the optimum thickness is readily determined. EX1004, 19:30-20:28. Accordingly, claim 13 would have been obvious, because it is axiomatic that simply modifying the thickness of the coating is a routine modification to a POSA. EX1002, ¶135; EX1012 at 1668; *In re Peterson*, 315 F.3d at 1329-30; *In re Woodruff*, 919 F.2d at 1578; *In re Aller*, 220 F.2d at 456-57.

[24] Angrist teaches that dosage is proportional to plasma peaks. In an experiment where two sets of men were given either 0.25 mg/kg or 0.5 mg/kg of d-amphetamine, the plasma peaks of the men who were given 0.5 mg/kg were "approximately twice those seen in the first group." EX1037 at 1357.

(iii) Claim 14

Claim 14 depends on claim 12 and further requires that the "dried aqueous dispersion of an anionic copolymer that is a (sic) dried about 30% (dry substance) aqueous dispersion of an anionic copolymer." As discussed for claim 10, the use of "about 30% (dry substance) aqueous dispersion" of the anionic copolymer would have also been obvious to a POSA. The patent owner admitted during prosecution that Eudragit® L 30 D, which has 30% dry polymer substance, is conventional. EX1035, 4/21/2003 Applicant Arguments/Remarks Made After Final Rejection, US Application No. 09/807,462 at p. 5; *see also Id*. at p. 7-10. Furthermore, optimizing the amount of dry substance would have been a matter of routine skill and would have resulted in the claimed amount. EX1002, ¶136; *In re Aller*, 220 F.2d at 456-57 (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"). Furthermore, incorporating known products into a formulation based on properties in their publicly available data sheets is obvious. *See Galderma Labs.,* 737 F.3d at 736.

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 '148 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, ¶106.

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 1-20 of the '148 patent are unpatentable as obvious.

RESPECTFULLY SUBMITTED,
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Date: October 4, 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 13,983 words, according to the word count tool in Microsoft Word™.

Respectfully submitted,

ALSTON & BIRD LLP

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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 4th day of October 2016, a complete copy of the foregoing Petitioner's Petition for *Inter Partes* Review of U.S. Patent No. RE 41,148, Power of Attorney, and all supporting exhibits were served via UPS® to the Patent Owner by serving the correspondence address of record for the '148 patent:

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