In the United States Patent and Trademark Office

Before the Patent Trial and Appeal Board

AMERIGEN PHARMACEUTICALS LIMITED,

Petitioner,

v.

SHIRE LLC,

Patent Owner

U.S. Patent No. 8,846,100 to Shojaei *et al.*
Appln. No. 11/383,066, filed May 12, 2006
Issue Date: September 30, 2014

Title: CONTROLLED DOSE DRUG DELIVERY SYSTEM

Inter Partes Review No. Unassigned

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 8,846,100 UNDER 35 U.S.C. §§ 311-319 AND 37 C.F.R. §§ 42.100 *et. seq*.

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Ex. 1066 Approval Letter from Russell Katz, M.D., Director, Div. of Neuropharm. Drug Products, Office of Drug Eval., to Tami Martin, Vice Pres. of Reg. Affairs, Shire Labs., Inc. (Oct. 11, 2001) (on file at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/21303_Adderall_Approv.pdf)

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I. INTRODUCTION.

Amerigen Pharmaceuticals Limited requests *inter partes* review under 35 U.S.C. §§ 311–319 of claims 1–31 of U.S. Patent No. 8,846,100 ("the '100 patent," Ex. 1001).

The '100 patent claims a pharmaceutical composition containing *three* different beads of amphetamine salts: (1) a bead for *immediate* release, (2) a bead for *delayed* and *pulsed* release, and (3) a bead for *delayed* and *sustained* release. The '100 patent contains just *one* example of each of these beads. *See* Ex. 1018 ¶ 70. Each of these beads, however, is not new in any way – the *exact same* amphetamine-containing beads (immediate, delayed pulsed, and delayed sustained release) were *literally* duplicated from examples in U.S. Patent No. 6,322,819 ("the '819 patent," Ex. 1002) and U.S. Patent No. 6,605,300 ("the '300 patent," Ex. 1003). Including these three amphetamine-containing beads in a single pharmaceutical formulation is not new or novel because such inclusion is explicitly contemplated by the '819 and '300 patents. Although the '300 patent was discussed during the prosecution of the '100 patent, the Applicant made factually incorrect statements about the '300 patent in an effort to distinguish the reference, which materially affected the course of prosecution and warrants additional consideration by the Board.

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

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

The real party-in-interest is Amerigen Pharmaceuticals Limited ("Amerigen" or "Petitioner").

B. Related Matters [37 C.F.R. § 42.8 (b)(2)]:

There are no judicial matters that would affect, or be affected by, a decision in the proceeding. Related pending patent applications include U.S. Patent Application No. 14/790,446. Related issued patents include U.S. Patent No. 9,173,857.

C. Designation of Lead and Back-Up Counsel [37 C.F.R. § 42.8 (b)(3)]:

Lead counsel is Marc R. Wezowski (Reg. No. 73,825) and back-up counsel is Philip D. Segrest, Jr. (Reg. No. 39,021).

D. Service Information [37 C.F.R. § 42.8(b)(4)]:

Papers concerning this matter should be served on the following:

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Petitioner consents to service by email at:

Marc.Wezowski@huschblackwell.com and Philip.Segrest@huschblackwell.com.

E. Fee Payment and Power of Attorney [37 C.F.R. §§ 42.10(b), 42.103]:

The Office is authorized to charge petition fees and deficiencies to Deposit Acct. No. 23-0920, Cust. ID No. 24628. A Power of Attorney is being filed concurrently.

III. REQUIREMENTS FOR *INTER PARTES* REVIEW.

A. Grounds for Standing [37 C.F.R. § 42.104(a)]:

Petitioner certifies that the ’100 patent is available for inter partes review and that Petitioner is not estopped or barred from requesting inter partes review of the ’100 patent on the grounds identified herein.

B. Identification of the Challenge [37 C.F.R. § 42.104(b)]:

Petitioner requests inter partes review of claims 1–31 of the ’100 patent and asks that those claims be found unpatentable under 35 U.S.C. § 102 and/or § 103.

1. Relevant Information Regarding the ’100 Patent.

The ’100 patent issued September 30, 2014, from Application No. 11/383,066, with a filing date of May 12, 2006. Ex. 1018 ¶ 23.

a. Specification.

The ’100 patent relates to a multiple dose composition for pharmaceutically active amphetamine salts pertaining to the treatment of Attention Deficit Hyperactivity Disorder (ADHD). Ex. 1018 ¶ 58. The Background section describes various drug delivery systems for immediate, constant, sustained, pulsed, and delayed release are described. Ex. 1001, 1:53-3:49. Adderall® is an immediate-release (IR) mixture of amphetamine salts (“MAS”): dextroamphetamine sulfate; dextroamphetamine saccharate; amphetamine aspartate monohydrate; and amphetamine sulfate. Ex. 1018 ¶¶ 71–72; Ex. 1001, 3:6–10. Adderall® XR an extended release version that can be administered once daily instead of twice daily as needed for immediate release Adderall®. Ex. 1001, 3:13–25; Ex. 1018 § 193. Adderall® XR and another drug, Concerta® (methylphenidate), last up to twelve hours, but the effect can be extended further by later administering an IR dose of the same medication . Ex. 1001, 3:31–41.

The ’100 patent describes a drug delivery system with a core and coating layers (each of which may or may not be loaded with drug) and/or a layer that controls the onset and characteristics of the drug release. Ex. 1018 ¶ 60–61; Ex. 1001, 12:64–13:10. Example 1 describes an immediate release formulation bead, and the other Examples, namely Examples 2–4, describe various delayed release beads. Ex. 1018 ¶¶ 62–68; Ex. 1001, 18:50–21:34. Figure 3 illustrates a

capsule containing an immediate release bead and two delayed release beads, which is also described in Examples 5–7. Ex. 1018 ¶¶ 69–70; Ex. 1001, 21:35–22:67. Examples 8–10 describe pharmacokinetic studies. *Id*., 23:1–31:67.

b. Claims.

Independent claim 1 recites a pharmaceutical composition comprising an immediate release bead comprising at least one amphetamine salt, a first delayed release bead comprising at least one amphetamine salt, and a second delayed release bead comprising at least one amphetamine salt. Ex. 1001, 31:59–63; *See* Ex. 1018 ¶ 50. The claim further recites that the first delayed release bead provides pulsed release of the at least one amphetamine salt and the second delayed release bead provides sustained release of the at least one amphetamine salt. Ex. 1001, 31:63–67. The claim also recites that the second sustained release bead comprises at least one amphetamine salt layered onto or incorporated into a core, a delayed release coating layered onto the amphetamine core, and a the sustained release coating layered onto the delayed release coating, where the sustained release coating is pH-independent, and the first and second delayed release beads comprise an enteric coating. *Id*., 32:29–37.

Claims 2–4 add that the enteric coating is pH-dependent and that the different beads comprise different enteric coatings or the same enteric coatings, respectively. Ex. 1001, 32:38–45; Ex. 1018 ¶ 51. Claims 5–12 recite certain

pharmacokinetic features of the claimed bead combination. Ex. 1001, 32:46–33:14; Ex. 1018 ¶ 51. Claims 13–18 add that the immediate release bead and the at least one delayed release bead are on the same core or are on different cores, that the amphetamine salt is coated onto a core or incorporated into a core, and that there is a protective layer over at least one enteric coating, or that there is a protective layer between the amphetamine salt and at least one enteric coating, respectively. *Id*., 32:15–30. Claims 19–20 recite the inclusion of one or more specific amphetamine salts. Ex. 1001, 33:31–34:7. Claim 21 specifies the lack of a food effect. *Id*., 34:8–9. Claims 22–30 recite the amount of amphetamine salt that is present in the dosage form. *Id*., 34:10–27. Claim 31 recites a protective coating layered between the delayed release coating and the sustained release coating. *Id*., 34:28–31.

c. Prosecution History.

The ’100 patent was submitted as application serial no. 11/383,066 (“the ’066 application,” Ex. 1004) on May, 12, 2006, with 58 claims. Ex. 1003, 1; 48–55. Two preliminary amendments were filed, cancelling claims 33–58, and adding new claims 59–61. Ex. 1005; Ex. 1006. The first Office Action rejected all of the claims as anticipated and/or rendered obvious by the ’300 patent stating that “the ’300 patent teaches an oral pulsed release formulation comprising a combination of immediate release and delayed release amphetamine beads.” Ex. 1007 p.4. The

Action further stated regarding the ’300 patent disclosure:

> The formulation can comprise a coated core comprising an immediate release portion of the amphetamine salts, along with an enterically coated delayed release bead (claim 1). The enteric polymers include pH dependent enteric polymers (col. 8, lin. 43–68); the formulation further comprises a protective coating to the core between the drug layers, or at the enteric layer (col. 8, lin. 10–30). The amphetamine is coated to an inert seed material (Example 1). This coated seed is then coated with various polymers, forming a core with the amphetamine incorporated (Examples 2 and 3). The formulation can comprise multiple coated delayed core comprises [sic] different enteric polymers or the same polymers such as Eudragit L or 4110D (Examples 1–4). The formulation comprises a combination of immediate release beads and controlled release beads (Example 4). The formulation can comprise up to 20 mg of a mixture of amphetamine salts … A single immediate release bead can be coated with a delayed release bead coating solution and combined with a second delayed release formulation so that the immediate and delayed release portions are present in the same bead and on different beads (Example 4).

Id. p.4–5. The Action stated that the physiological effects of the dosage form (food, T_{max}, AUC, and C_{max} values) “<u>are merely functional limitations</u> that are the result of the instant compositional components,” which are “<u>inherent properties of the composition</u> … since a compound and its properties cannot be separated.” *Id.* p.5 (emphasis added). Speaking to a

37.5 mg dose, the Action stated that these limitations "merely recite a future intended use for the composition." *Id.* p.5 (emphasis added).

The Action also rejected all the claims as obvious in view of the '300 patent stating that "the '300 patent discloses a controlled release dosage form comprising immediate release bead sand [sic] delayed release beads where the delayed release beads comprise enter[ic] polymers and protective coating." *Id.* p.6. The Action noted that the '300 patent teaches amphetamine salts at a concentration of at least 20 mg and that increasing the dosage of a well-known pharmaceutical dependent upon the patient is well within the limits of a person skilled in the art. *Id.* The Action further stated that because the general claim conditions were met, it was not inventive to discover the optimum ranges by routine experimentation, citing *In re Aller*, 220 F.2d 454 (C.C.P.A. 1955) and *In re Russell*, 439 F.2d 1228 (C.C.P.A. 1971). Ex. 1007 p.6–7.

In response, the Applicant argued that "[t]he '300 patent discloses immediate release beads and delayed pulsed release beads, *but not sustained release beads*." Ex. 1008 p.8 (emphasis added); *see also id.*, 9 ("The '300 patent does not disclose a sustained release bead."). However, this statement is not true and is a clear **mischaracterization of the '300 patent.**

The '066 application describes what is meant by a "sustained release bead": a "sustained release formulation of the present invention comprises at least one

amphetamine salt layered onto, or incorporated into, a core; a delayed release coating layered onto the amphetamine core; a sustained release coating layered onto the delayed release coating; and, optionally, a protective coating." Ex. 1004 p.9. The '066 application states that the delayed pulse release component can include an enteric coating and provides a list of enteric coatings including EUDRAGIT® L30D-55 and EUDRAGIT® 4110D. *Id.* p.22–23. The '066 application further states that the sustained release coating is a polymer or combination of polymers and provides a list of suitable polymers, including SURELEASE®. *Id.* p.23.

Example 4 of the '300 patent derives from Examples 1–3. Ex. 1003, 10:32–12:26. Example 1 discloses an immediate release bead made of amphetamine salts layered onto a core; Examples 2 and 3 disclose delayed release beads having an enteric coating applied over the sustained release bead of Example 1. Example 4 adds a sustained release coating of SURELEASE® and a coating of OPADRY® over the beads of Examples 2 or 3. Thus, Example 4 discloses an immediate release bead covered by layers of a delayed release coating, a sustained release coating, and an OPADRY® coating, respectively. *Id.*

The Applicant further misconstrued the teachings of the '300 patent by arguing that the '300 patent teaches that "a pulsed dose delivery system … is something to be used in place of a sustained release preparation." Ex. 1008 p.8.

This is not what the ’300 patent states in the referenced passage, which is, in reality, a general discussion of the problems associated with prior art systems. Ex. 1003, 1:13–2:12.

Further mischaracterizing the art, the Applicant represented that “the ’300 patent teaches that sustained release [beads] do not work for amphetamines.” Ex. 1008 p.9. The Applicant did not provide a citation as to where the ’300 patent stated such, but instead argued that there were problems with sustained release amphetamine formulations, without citing the ’300 patent. *Id.*. The Applicant stated that “the ’300 patent teaches: (1) not to use sustained release amphetamine formulations and (2) to use a delayed pulsed release formulation instead,” without citing the ’300 patent. *Id*.

In the second Office Action (Ex. 1009), the Action **maintained the anticipation and obviousness rejections** stating that the formulation of the ’300 patent comprises the same immediate and delayed release beads, the same polymers, and the same arrangement of the formulation such that the formulations must also have the same bioequivalence and blood plasma concentrations. *Id*. p.4. The Action stated that that the ’300 patent teaches a dosage form comprising a plurality of beads including immediate release beads and coated controlled release beads. *Id*. p.7. The Action further stated that since the ’300 patent discloses multiple beads, both immediate release uncoated beads and enteric coated beads,

the claims remain fully anticipated and obvious. *Id*. The Action mentioned that Figure 3 of the ’066 application discloses a sustained release formulation achieved through the use of various enteric and protective coatings. *Id*. p.8. The Action stated that the Background section describes the problems of the prior art and that it would be obvious to optimize the coating disposition and concentration to provide an optimal release profile through routine experimentation. *Id.*.

The Applicant responded that the ’066 claims were not anticipated or obvious but acknowledged that Example 4 of the ’300 patent describes coating the beads of Examples 2 or 3 with SURELEASE®. Ex. 1010 p.3. The Applicant argued that in the ’300 patent, the beads of Examples 2 and 3 were of the delayed pulsed release type, and acknowledged that Figures 4 and 5 both illustrated a delayed pulsed release profile. Ex. 1010 p.2. The Applicant failed, however, to inform the Examiner that the release profile of the other bead disclosed in Example 4 and shown in Figure 6, was that of a sustained release bead. Ex. 1003, 11:59–12:26. Yet again, the Applicant mischaracterized the’300 patent.

In the third Office Action (Ex. 1011), the Action **maintained the anticipation and obviousness rejections**, stating that the ’300 patent teaches a dosage form comprising a plurality of beads and that the coating materials of the beads is the same as that recited in the claims of the ’066 application. Ex. 1011 p.7. The Examiner therefore concluded that the beads of the ’300 patent were the

same as the beads recited in the claims and the claims remain anticipated. *Id*. The Action also maintained its rejection because the pharmacokinetic properties are functional limitations determined by the compositional components and the '300 patent's beads would inherently have these same properties since "**the compositional components of the bead is [sic] identical**." *Id*. p.7–8 (emphasis added).

The Applicant responded that the second delayed release bead has an *atypical* construction, which is neither disclosed nor suggested in the prior art. Ex. 1012 p.8. This was yet another attempt to mislead the Examiner because the Applicant offered no evidence other than its own formulations, PD0149-0120 and PD0149-124. *Id.*, p.8–9 (citing [0023] of the published patent application (Ex. 1038)).

The Applicant yet again mischaracterized the teachings of the '300 patent by stating that the bead of Example 4 had a "typical" construction, which the Applicant defined as an enteric coating *over* a sustained release coating. Ex. 1012 p.9. However, this statement is false because, the bead of Example 4 has a sustained release coating (SURELEASE®) *over* the enteric coating. Ex. 1003, Example 4, 11:58–12:28. The Applicant admitted that "[t]he '300 patent teaches … delayed release beads having a drug-containing core coated with an enteric polymer which, in turn, is coated with SURELEASE." Ex. 1012 p.9.

Applicants amended Claim 1 to include "wherein the second delayed release

bead comprises at least one amphetamine salt layered onto or incorporated into a core; a delayed release coating layered onto the amphetamine core; and a sustained release coating layered onto the delayed release coating." *Id.* p.3 (underlining omitted).

In the fourth Office Action (Ex. 1013), the anticipation rejection was withdrawn and the obviousness rejections against some of the claims were maintained with additional art cited. The Action restated that coatings and their arrangement were known and substituting various known active agents in different release formulations was also known. *Id* p.4

The Applicant responded the claims require a second delayed release bead that provides sustained release with a construction where a delayed release coating is layered onto the amphetamine core and a sustained release coating is layered onto the delayed release coating. Ex. 1014 p.7. The Applicant argued the prior art did not teach the same—essentially repeating the Applicant's previous mischaracterization to the Office. *Id.* p.7–9.

In fifth Office Action (Ex. 1015), the Examiner maintained the obviousness rejections, stating that the previous arguments were not persuasive.

The Applicant responded that the cited art did not make the instant claims obvious. Ex. 1016 p.7. The Applicant stated that "[a] sustained release, outer coating according to the instant claims may be, as exemplified in Example 4,

ethylcellulose (SURELEASE)." *Id.* p.11.

Following an Interview, a Notice of Allowance (Ex. 1017) was mailed with an Examiner's Amendment that included this additional limitation to claim 1: "wherein the sustained release coating is pH-independent" (underlining omitted). *Id.* p.6. The '100 patent issued on September 30, 2014. Ex. 1001 at [45].

d. Person of Ordinary Skill in the Art.

A person of ordinary skill in the art ("POSA") is presumed to be aware of all pertinent art, thinks along conventional wisdom in the art, and is a person of ordinary creativity. A POSA may work as part of a multidisciplinary team and draw upon not only his or her own skills, but also take advantage of certain specialized skills of others in the team, to solve a given problem. For example, a clinician may be part of the team. Petitioner submits herewith the declaration of Dr. Edmund J. Elder, Jr. in support hereof (Ex. 1018).

A POSA in 1998 would have a professional or graduate degree (Pharm.D., M.S. or Ph.D.) in pharmacy, chemistry, chemical engineering, or a related discipline, with experience in formulating drugs. Ex. 1018 ¶ 56. The POSA would also have a general understanding of drugs used to treat ADHD, background information regarding their chemistry, and the formulation approaches successfully applied to these drugs. *Id.* ¶ 57. The POSA would also have knowledge regarding the gastrointestinal tract, including differences between the fed and fasted states,

gastrointestinal transit and pH. *Id*.

2. Statement of Precise Relief Requested. [37 C.R.F. § 42.104(b)(1)]

Petitioner challenges the validity of claims 1–31 of the '100 patent and requests claims 1–31 of the '100 patent be found unpatentable.

Petitioner requests *inter partes* review ("Request") and cancellation of all claims of the '100 patent (Ex. 1001) based on one or more of the grounds under 35 U.S.C. § 102 or § 103 set forth herein. This request shows a reasonable likelihood that the petitioner would prevail on at least one of the claims challenged in this petition because the request shows that each limitation of at least one claim of the '100 patent are taught in the prior art. Each reference is non-redundant and has particular unique relevance. For those Grounds under 35 U.S.C. § 103(a), the motivation to combine is provided. Petitioner's detailed statement of the reasons for the relief requested is set forth below.

3. Specific Statutory Grounds On Which The Challenge Is Based And Prior Art References Relied Upon. [37 C.F.R. §§ 42.104(b)(2) and (b)(4)]

Ground 1: Claims 1–31 are anticipated under 35 U.S.C. § 102(b) by the '819 patent (Ex. 1002).

Ground 2: Claims 1–31 are obvious under 35 U.S.C. § 103 over the '300 patent (Ex. 1003) in view of Kratochvil (Ex. 1019).

4. Challenged Claim Construction.

[37 C.F.R. § 42.104(b)(3)]

"A claim in an unexpired patent … shall be given its broadest reasonable construction in light of the specification of the patent in which it appears." 37 C.F.R. § 42.100(b); *see Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2146 (2016). Claim terms are given their ordinary and customary meaning as would be understood by one of ordinary skill in the art in the context of the entire disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257-58 (Fed. Cir. 2007). An inventor may rebut that presumption by providing a definition of the term in the specification with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994). In the absence of such a definition, limitations are not to be read from the specification into the claims. *In re Van Geuns*, 988 F.2d 1181, 1184 (Fed. Cir. 1993).

The terms in the claims of the '100 patent, with the two exceptions noted below, should therefore be given their broadest reasonable interpretation consistent with the specification.[1]

[1] Claim construction resolves the meanings of disputed terms in a patent to clarify and, when necessary, explain the claims. *O2 Micro Int'l Ltd. v. Beyond Innovation Tech. Co., Ltd.*, 521 F.3d 1351, 1362 (Fed. Cir. 2008). Claim terms, however, need only be construed "to the extent necessary to resolve the controversy." *Vivid Techs.,*

"**About**" (claims 5–12, 22–30): The patentee attempted to define "about" in the specification:

> The term "about" or "approximately" means within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, i.e., the limitations of the measurement system, i.e., the degree of precision required for a particular purpose, such as a pharmaceutical formulation. For example, "about" can mean within 1 or more than 1 standard deviations, per the practice in the art. Alternatively, "about" can mean a range of up to 20%, preferably up to 10%, more preferably up to 5%, and more preferably still up to 1% of a given value. Alternatively, particularly with respect to biological systems or processes, the term can mean within an order of magnitude, preferably within 5-fold, and more preferably within 2-fold, of a value.

Inc. v. Am. Sci. & Eng'g, Inc., 200 F.3d 795, 803 (Fed. Cir. 1999). Claim construction "is not an obligatory exercise in redundancy." *U.S. Surgical Corp. v. Ethicon, Inc.*, 103 F.3d 1554, 1568 (Fed. Cir. 1997). For purposes of this petition, no other disputed issue is expected to involve the interpretation of any other claim term. Should the patent owner introduce additional terms for which construction is necessary, Petitioner reserves the right to request that these additional terms be construed.

Ex. 1001, 11:65-12:12. Therefore, using the "broadest reasonable construction" to define this term, "about" encompasses *at least* a 20% variance of the claimed numerical value and/or, with respect to biological systems or processes, "about" means within "an order of magnitude" (*i.e.*, the nearest power of 10). Ex. 1018, ¶¶ 124-126. Amerigen reserves the right to assert that a stated alternative definition permits an even greater variance.

"Food effect" (claim 21): The patentee explicitly defined "food effect" in the specification:

> "Food effect," as used herein, means a significant difference in the bioavailability of a drug in a patient when the drug is administered in a fasted state compared to a fed state. "No food effect" means that there is no significant difference in the bioavailability of a drug in a patient when the drug is administered in a fasted state compared to a fed state.

Ex. 1001, 11:59–64. Therefore, the absence of a food effect specified by claim 21 means that "there is no significant difference in the bioavailability of a drug in a patient when the drug is administered in a fasted state compared to a fed state." Ex. 1018, ¶¶ 127-128. Thus, using the broadest reasonable construction, the definition of "food effect," in the patent refers only to the requirement of similar +/- 20% AUC when the drug is administered in the fed or fasted stated. Ex. 1018, ¶ 128.

IV. DETAILED DESCRIPTION OF THE PRIOR ART UPON WHICH THE CHALLENGE IS BASED.

A. Technology Background.

1. Amphetamine Was A Well-Known ADHD Treatment.

The use of amphetamine to treat the symptoms of ADHD has been known for about 80 years. Ex. 1020. The specific mixture of amphetamine salts (MAS) of the '100 patent, namely that of dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate, and amphetamine sulfate, *i.e.*, Adderall® (Ex. 1001, 5:28–31), has been in use since FDA approval in 1960 for an immediate release capsule (Ex. 1021) and in 2001 for the extended release capsule, Adderall® XR (Ex. 1022). Ex. 1018, ¶¶ 71-73.

2. The Science of Drug Coatings, Release Timing, And Release Rates Was Well-Known.

The use of various coatings to modulate the release time and release rate of amphetamine was also well-known. *Id.*, ¶¶ 75-77. An earlier patent listing one of the same inventors as the '100 patent (Richard Couch), and also assigned to the owner of the '100 patent, acknowledged this by stating:

> Details of using the foregoing constructs and others to achieve a desired plasma profile as discussed above are fully conventional and can be determined by those of skill in the art with at most a few routine experiments, and conventional adjustments, e.g., involving identities of polymers and mixtures thereof, relative amounts of components, coating thicknesses, bead diameters, number of layers,

> and compositions thereof, etc. Thus, for example, for a given construct, (e.g., one of those in the examples herein) dissolution profiles can be determined and in vivo plasma profiles measured. The latter can then conventionally be compared to the target plasma profile (e.g., that of Adderall XR®) and differences compensated by fully conventional formulation and dissolution profile adjustments such as but not limited to those mentioned.

Ex. 1023, 3:64–4:11 (emphasis added); *see also* Ex. 1018, 152. The coatings mentioned include immediate release, sustained release, and delayed release. Ex. 1023, 2:11-3:63. Many other prior art patents described controlled release coatings for amphetamines. *E.g.*, Exs. 1024–1028.

Triple bead combinations were known for MAS, methylphenidate (Ex. 1029), carbamazepine (Ex. 1030), antibiotics (Ex. 1031), phenylpropanolamine, and other drugs that normally would be administered in divided doses of two or more times per day (Exs. 1032–1034). Each abstract states

> A therapeutic preparation consisting of three groups of spheroids containing an active medicinal substance. The first group of spheroids is uncoated and rapidly disintegrates upon ingestion to release an initial dose of medicinal substance[s], a second group of spheroids is coated with a pH sensitive coat to provide a second dose, and a third group of spheroids is coated with a pH independent coat to provide a third dose.

E.g., Ex. 1032 at [57].

3. "Sculpting The Dose" Was Well-Known.

Clinicians recognized the need for a longer duration of action for the treatment of ADHD because ADHD lasts all day, not just during school hours. Ex. 1019, S162; *see also* Ex. 1018, ¶¶ 177. Some individuals require more than 10–12 hour coverage. Ex. 1019, S163. Clinicians had been optimizing the medical response to amphetamines by giving short acting formulations, intermediate formulations, long acting formulations, and combinations thereof ("sculpting the dose") to manage ADHD. *Id.*, Figure 1. With Adderall® XR, clinicians recognized a need for two doses of the drug during the school day and combined those two separate doses into one extended release formulation, an *in vivo* plasma release profile equivalent to that of the two separate doses. Ex. 1003, 3:13–28; 12:29–49.

B. Printed Publications Relied Upon.

1. The '819 Patent.

The'819 patent issued on November 27, 2001, from an application filed on October 21, 1998. Ex. 1002. It is prior art under 35 U.S.C. § 102(a), (b), and (e) to the '100 patent, which has an effective filing date of May 12, 2006. Ex. 1001. The '819 patent was not discussed during prosecution of the '100 patent but is listed its face, along with about 214 other documents. *Id.* The '819 patent is the parent of the '300 patent, which was filed as a continuation-in-part application. Ex. 1003. Key aspects of the '300 patent were materially misrepresented to the

Examiner as discussed above. Exs. 1004–1017.

The ’819 patent discloses a multiple dose drug delivery system for pharmaceutically active amphetamine salts, composed of one or a number of types of beads in a dosage form. Ex. 1002 at [57]. “The product can be composed of either one or a number of beads in a dosage form ….” *Id*.. A POSA would understand this disclosure to teach that the pharmaceutical dosage form can include one type of bead or a combination of several different types of beads depicted in the examples of the invention. Ex. 1018 ¶ 101.

The ’819 patent states: “The following examples are presented to illustrate and do not limit the invention.” Ex. 1002, 10:4–5 (emphasis added). Example 1 describes an immediate release bead having a nonpareil seed directly coated by a MAS layer. *Id.,* 10:8–30. Example 2 describes a delayed release bead where the beads of Example 1 were further coated by the enteric coating, EUDRAGIT® L 30D-55. *Id.,* 10:31–63. Example 3 describes a different delayed release bead than Example 2, where the bead of Example 1 was further coated by the enteric coating, EUDRAGIT® 4110D. *Id.,* 10:64–11:28. Example 4 describes a different delayed release bead than Examples 2 or 3 where the bead of Examples 2 or 3 was further coated by the sustained release coating, SURELEASE®. *Id.,* 11:31–67; Ex. 1036.

In vitro drug release profiles of those different types of beads are described in the Figures. The immediate release bead of Example 1 has an immediate release

profile shown in Figure 3. *Id.*, 10:29–30. The delayed release beads of Examples 2 and 3 are described to have a delayed pulsed release profile and *in vitro* testing results are shown in Figures 4 and 5. Ex. 1002, 10:61–62; 11:28–29. The delayed release bead of Example 4 has a delayed sustained release profile, shown in Figure 6. *Id.*, 11:66–67. Thus, three different types of beads having three different drug release profiles including immediate release, delayed pulsed release, and delayed sustained release are taught in the '819 patent.

The '819 patent further states: "It is also contemplated that the composition may include a **combination** of the hereinabove referred to cores …" *Id.*, 3:44–48 (emphasis added). The '819 patent further teaches that the exemplary beads can be combined in a dosage form to create a single dosage form that replicates taking two separate doses administered, one in the morning and one approximately 4–6 hours later. *Id.*, 3:5–9, 15–22 & Fig. 1; 6:22–25. The '819 patent is listed in the *FDA Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations* in reference to Adderall® XR. Ex. 1040.

2. The '300 Patent.

The '300 patent issued August 12, 2003, from the national stage entry of a PCT application filed October 20, 1999. Ex. 1003. It claims priority to the '819 patent and is prior art under 35 U.S.C. § 102(a), (b), and (e) to the '100 patent. Ex. 1003, *Cover.* The '300 patent was discussed during prosecution of the '100 patent

and the Applicant made material misrepresentations regarding the content and position of the coatings of the sustained release bead. Ex. 1004–1017. Because the Applicant made material misrepresentations that materially affected prosecution of the ’100 patent, further review and consideration of this reference is warranted.

The most significant disclosure in the ’300 patent that was not present in the ’819 patent is Example 5, which describes human testing of compositions comprised of the immediate and delayed release beads from Examples 1 and 2 and from Examples 1 and 3. Ex. 1003,12:28–48. The results of human testing are the plasma release profiles of Figures 7 and 8. *Id.*, 6:62–7:2. The Applicant revised the “Summary of the Invention” section to state: “the present invention provides an oral multiple **unit** pulsed dose delivery system for amphetamine salts and mixtures thereof.” *Compare id.*, 3:30–32 (emphasis added) *with* Ex. 1002, 3:18-20. It is to be understood that all the limitations described as being taught for the ’819 patent, above, are also taught in the ’300 patent.

As is the case with the ’819 patent, the ’300 patent includes MAS beads having an immediate release coating (Ex. 1003, 3:42–44; Example 1, *id.*, 10:30–57); delayed release beads having “one or more pharmaceutically active amphetamine salts that are covered with an enteric release coating” (*id.*, 3:45–46; Examples 2 and 3, *id.*, 10:58–11:57); and one or more pharmaceutically active amphetamine salts that are covered with an enteric release coating having “a

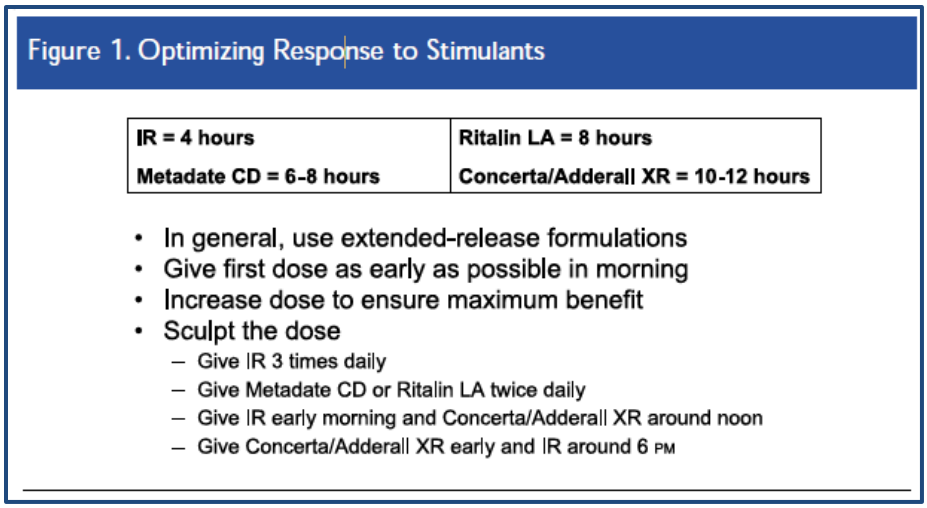
protective layer over the enteric release coating (*id.*, 3:45–52; Example 4, *id.*, 11:60–12:27). A protective layer can consist of a water penetration layer successively coated onto an enteric coated MAS bead to reduce the water penetration rate thus increasing the lag time of drug release. *Id.*, 9:1–6. SURELEASE® is listed as a sustained release coating. *Id.*, 9:6–17. Example 4 describes this third type of bead where an enteric coated MAS bead of Example 2 or 3 is further coated with SURELEASE®, which sustains the delayed release from EUDRAGIT® L 30-D55 coated pellets at pH 7.5, and delayed the drug release by up to 2 hours after the buffer was switched from pH 1 to pH 7.5. *Id.*, 11:59–12:26. The sustained release coating described in Example 4, SURELEASE®, is ethyl cellulose which is a pH independent polymer. *Id.*, 8:22-30; Ex. 1036. The '300 patent also teaches the enteric coated pellets of Example 3 (EUDRAGIT® 4110D) are coated with SURELEASE®. Ex. 1003, 11:25-31; *id.*, 11:60-67.

3. Kratochvil.

Kratchovil is prior art that was not considered during prosecution of the '100 patent and details the medical treatment of the symptoms of ADHD from a clinician's perspective. Ex. 1019. "Like other chronic health problems, attention deficit hyperactivity disorder (ADHD) must be approached as a disorder that causes difficulties throughout the day, every day." Ex. 1019, S162. "Historically, one limitation of stimulant drugs was their short-acting profile." *Id.* "Extended

release stimulants are advantageous because they are approved for first-line use in children and adolescents and have a 7- to 12-hour action profile…However, they provide limited coverage in late evenings or early mornings…" *Id.*

Kratchovil teaches the necessity of "[s]culpting the dose" to match the needs of individual patients. *Id.*, S163. "Several factors come into play in optimizing the response to stimulants…the dose must be high enough to ensure full efficacy…" *Id.* "[D]uration of action is an important consideration. How much time elapses before the drug becomes effective, and when do the effects wear off?" *Id.* "ADHD lasts all day, and management should extend beyond the school hours." *Id.* (emphasis added). "Sculpting the dose of the stimulants can be accomplished in several ways (Figure 1)." *Id.* As shown below, Kratochvil teaches that coverage for an entire day can be provided by either giving a morning dose of immediate release ("IR") and a noon dose of Adderall® XR, or, alternatively, giving a morning dose of Adderall® XR and a 6 pm dose of IR. *Id.*, Figure 1. Kratochvil provides the options for optimizing response to stimulants, shown in the figure below:



4. Additional Prior Art Confirming the General Knowledge of the Ordinarily-Skilled Artisan.

In addition to the prior art discussed above, Dr. Elder addresses additional prior art confirming the general knowledge of a person of ordinary skill ("POSA") in May 2006. A POSA would understand that the amount of amphetamine contained in a commercial formulation would be set in appropriate intervals to permit administration "at the lowest effective dosage." Ex. 1018, ¶¶ 119-120. For example, the June 2005 package insert for immediate-release Adderall® shows the formulation was available in tablets separated by 2.5 mg increments (5, 7.5, 10, 12.5, 15, 20, 25 and 30 mg). Ex. 1042. Similarly, the May 2005 package insert for Adderall® XR, which was intended as a substitute for twice-a-day dosing of Adderall, shows the formulation was available in capsules with 5.0 mg dosage increments (5, 10, 15, 20, 25 and 30 mg). Ex. 1043; Ex. 1018, ¶ 120. The dosing increments were functional to facilitate titration of dosing by the treating physician

to dose "at the lowest effective dosage." Ex. 1052, 2210.

V. THE CONSTRUED CLAIMS ARE UNPATENTABLE, 37 C.F.R. § 42.104(b)(4).

A. Standard of Invalidity under 37 C.F.R. § 42.104(b)(4).

The claims of the '100 patent are anticipated by the teachings of the '819 patent or, alternatively, rendered obvious by the teachings of the '300 patent in view of Kratochvil.

A *prima facie* case of either anticipation or obviousness has been established when the claimed and prior art products are identical or substantially identical in structure or composition. *In re Best*, 562 F.2d 1252, 1255 (C.C.P.A. 1977).

The '819 patent anticipates claims 1–31 of the '100 patent under 35 U.S.C. § 102(a), (b), and (e) because each and every limitation is disclosed therein, either expressly or inherently. *Verdegaal Bros., Inc. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987); *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 958 (Fed. Cir. 2014). The presence of a claim limitation in a reference must be determined from the perspective of a POSA. *Dayco Prods., Inc. v. Total Containment, Inc.*, 329 F.3d 1358,1368–1369 (Fed. Cir. 2003).

A prior art reference may anticipate without explicitly disclosing a feature of the claimed invention if that missing characteristic is inherently present in the single anticipating reference. *Continental Can Co. U.S.A., Inc. v. Monsanto Co.*,

948 F.2d 1264, 1268 (Fed. Cir. 1991). "Common sense" can be applied in interpreting anticipatory prior art when a claim limitation is not disclosed verbatim. *King Pharms., Inc. v. Eon Labs, Inc.*, 616 F.3d 1267, 1276–77 (Fed. Cir. 2010) (holding claim was anticipated despite specific times not being disclosed in the prior art); *see also Perfect Web Techs., Inc. v. InfoUSA, Inc.*, 587 F.3d 1324, 1330 (Fed. Cir. 2009) (holding that common sense can be applied to provide a limitation admittedly missing from prior art when the limitation "simply recites repetition of a known procedure until success is achieved").

Anticipation does not require "actual performance of suggestions in a disclosure." *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1379 (Fed. Cir. 2001); *In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009). "[A] patent need not teach, and preferably omits, what is well known in the art." *Hybritech Inc. v. Monoclonal Antibodies,*, 802 F.2d 1367, 1384 (Fed. Cir. 1986).

Reciting measured properties of prior art disclosures adds "nothing of patentable consequence" because "merely discovering and claiming a new benefit of an old process cannot render the process again patentable." *In re Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011) (quoting *King*, 616 F.3d at 1275–76). "The initial blood serum concentration resulting from administering [a drug] is an inherent property of the formulation, and an obvious formulation cannot become nonobvious simply by administering it to a patient and claiming the resulting

serum concentrations." *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012). "To hold otherwise would allow any formulation—no matter how obvious—to become patentable merely by testing and claiming an inherent property." *Id.*

Furthermore, a generic disclosure will anticipate a claimed species covered by that disclosure when the species can be "at once envisage[d]" from the disclosure. *In re Petering,* 301 F.2d 676, 681 (C.C.P.A .1962). When a claimed compound is not specifically named in a reference, but instead it is necessary to select from a group of alternatives and combine them, anticipation can be found if the alternatives are sufficiently limited or well delineated. *Ex parte A,* 17 U.S.P.Q.2d 1716, 1718 (B.P.A.I. 1990).

If not anticipated by the '819 patent, the claims of the '100 patent are rendered obvious by the '300 patent in view of Kratochvil. Ex. 1018, ¶¶ 239–367. The '300 patent teaches three discrete types of pellets containing at least one amphetamine: (a) immediate release; (b) delayed-pulsed release; and (c) delayed-sustained release. The '300 patent further teaches combining pellets having different release profiles in order to provide targeted relief and show success in replacing a twice a day administration of immediate release Adderall® with a single formulation of different types of coated or uncoated drug-containing beads. Ex. 1018, ¶¶ 239-251. Similarly, Kratochvil teaches the need to provide all-day relief

to patients suffering from ADHD and suggests administering an extended release tablet followed several hours later by an immediate release pellet (or vice versa). *Id.* A POSA would understand the '300 patent's disclosure in view of these problems and solutions disclosed in Kratochvil to teach the claims of the '100 patent. *Id.*

The Examiner's prior consideration of the '300 patent is immaterial. The Applicant of the '100 patent misrepresented several crucial facts about of the '300 patent in order to get around the '300 patent. *Id.* ¶ 109. Furthermore, prior art that has been previously considered by an examiner during prosecution is not "substantially the same" when supplemented with new prior art references, evidence, or expert testimony. *Heartland Tanning, Inc. v. Sunless, Inc.*, IPR2014-00018, Paper 15 at 18–20, 2014 WL 1253151, at *12 (P.T.A.B., Mar. 13, 2014) (instituting review when one reference was added to two prior art references considered by the examiner).[2]

New combinations of previously-considered prior art provide sufficient

[2] *See also Micron Tech., Inc. v. Board of Trustees of the Univ. of Ill.*, IPR2013-00008, Paper 24 at 6-7, 2013 WL 5970124, at *4 (Mar. 13, 2013) (instituting review when expert testimony supplemented previously-considered prior art reference).

bases for institution, as do new arguments applied to the same art. *Nuvasive, Inc. v. Neurovision Med. Products, Inc.*, IPR2015-00502, Paper 15 at 7–8, 2015 WL 4381727, at *4 (P.T.A.B., July 16, 2015). Examiner error also allows the reconsideration of previously analyzed prior art. *Macauto U.S.A. v. BOS GmbH & KG*, No. IPR2012-00004 (TLG) Paper 18 at 17–19, 2013 WL 5947694, at *8–*10 (P.T.A.B., Jan. 24, 2013). Here Applicant's material misrepresentations lead to an erroneous conclusion by the Examiner.

Petition relies on new prior art and new arguments, and the record before the Office is not the same as during prosecution. Petitioner therefore respectfully requests that the Board grant its institution.

B. Explanation Of Ground 1 For Unpatentability: The '819 Patent Anticipates Each of the 31 Claims of the '100 Patent.

The '100 patent contains 31 claims, each of which are anticipated by the'819 patent. Claim 1 of the '100 patent is the only independent claim and is explicitly disclosed in the '819 patent. Claims 2–4, 13–21, and 31 amend the pharmaceutical composition of claim 1 in a way that is explicitly disclosed in the '819 patent. Claims 5–12 add pharmacokinetic ranges and properties that are anticipated inherently, as the same drug containing beads are used in both patents. Claims 22–30 are disclosed by the functional need taught in the '819 patent to create an array of dosage amounts to permit usage of the products.

1. The ’819 Patent Discloses Every Limitation of Independent Claim 1.

The ’819 patent teaches all limitations of claim 1 of the ’100 patent including the preamble, “**a pharmaceutical composition**” that comprises at least three beads. *See* p. 20–21, *supra* (discussing drug release profiles of three types of beads disclosed in the ’819 patent); Ex. 1018, ¶ 131.

The ’819 patent further teaches the first limitation, **an immediate release bead comprising at least one amphetamine salt** by describing “a pharmaceutical composition for delivering one or more pharmaceutically active amphetamine salts [MAS] that includes one or more pharmaceutically active amphetamine salts that are covered with an immediate release coating…” (Ex. 1002, 3:25–30); “and a suspension of mixed amphetamine salts (MAS)…sprayed onto the [nonpareil] seed.” Example 1, *id.,* 10:6–27[3]; Ex. 1018, ¶¶ 132-134.

The second limitation of claim 1, **a first delayed release bead comprising at least one amphetamine salt** is identical to the beads of Example 2 or 3 of the ’819 patent, where the MAS pellets from Example 1 are coated with EUDRAGIT® L 30D-55 (Ex. 1002, 10:32–60) or EUDRAGIT® 4110D. *Id.*, 10:65–11:29.

[3] Both the abbreviation “MASL”, as used in the ’819 and ’300 patents, and the commonly used abbreviation “MAS” refer to “mixed amphetamine salts” that are layered onto a core.

EUDRAGIT® L 30D-5 and EUDRAGIT® 4110D are both enteric polymers. *Id.*, 8:22–35; Ex. 1018, ¶¶ 135-138. The '100 patent illustrates this claim limitation with Example 3, which is the same as'819 patent, Example 2. *Cf* Ex. 1001, 19:52–20:22 *with* Ex. 1002, 10:32–64.

Example 4, shown in Figure 6, of the '819 patent discloses the third limitation of claim 1, **the second delayed release bead provides sustained release of the at least one amphetamine salt.** Figure 6, which illustrates the delayed sustained release profile of the bead coated with MAS, followed by enteric release coating, followed by SURELEASE® coating. Ex. 1002, 11:31–67; Ex. 1018, ¶¶ 139-143. The '100 patent illustrates this claim limitation with Example 4 ("Sustained Release Formulation"), which is the same as Example 4 of the '819 patent. *Cf* Ex. 1001, 20:25–67 *with* Ex. 1002, 11:32–67; Ex. 1018, ¶¶ 139-143. In both Examples, pellets coated with EUDRAGIT® L 30 D-55 are further coated with SURELEASE®. Ex. 1001, 20:25-67; Ex. 1002 11:32-67; Ex. 1018, ¶¶ 139-143.

The third limitation of the '100 patent contains two subparts, both of which the '819 patent discloses. *Id.*, ¶¶ 144-159. The '819 patent discloses the limitation**, wherein the first delayed release bead provides pulsed release of the at least one amphetamine salt**, in Example 2 of the '819 patent. *Ex.* 1002, 10:32–63; Ex. 1018, ¶¶ 145-153. The limitation, **the second delayed release bead**

provides sustained release of the at least one amphetamine salt is disclosed in the ’819 patent, Figure 6. *Id.*, ¶ 157. The two exemplary beads used to illustrate this limitation in the ’100 patent are the same beads disclosed in Examples 2 and 4 of the ’819 patent. *Id.*, ¶¶154-159.

Example 4 also discloses the next limitation, **wherein the second delayed release bead comprises at least one amphetamine salt layered onto or incorporated into a core; a delayed release coating layered onto the amphetamine core; and a sustained release coating layered onto the delayed release coating.** Ex. 1018, ¶¶ 160-164. Example 4 shows where the enteric coated MAS pellets from Example 2 or Example 3 were further coated with SURELEASE®. Ex. 1001, 11:31–63.

The limitation, **wherein the sustained release coating is pH-independent,** is disclosed by “a semi-permeable polymer, which may comprise a low water-permeable pH-insensitive polymer, is layered onto the outer surface of the enteric layer,” in the ’819 patent. Ex. 1002, 5:54–57; Ex. 1018, ¶¶ 163-164.

The final limitation, **wherein the first delayed release bead and the second delayed release bead comprise an enteric coating**, is described in Examples 2, 3, and 4 of the ’819 patent. Ex. 1002, 10:32–60; 10:65–11:29; 11:30–67; Ex. 1018, ¶¶ 165-168.

Also, a POSA would note that the drug release profile of the delayed

sustained release bead of Example 4, described in Figure 6, shows that this bead works longer than eight hours. In addition, the Examples in the '100 patent used to illustrate this limitation are the same as those contained in the '819 patent.

Therefore, the identical triple bead formulation of an immediate release bead, a delayed release bead, and a sustained release bead was taught by the '819 patent. Ex. 1018, ¶¶ 132-168. A POSA would understand that the '819 patent's teaching of "one bead or a number of beads" (*Id.*, Abstract) means "one or a number of **types** of beads." *Id.*, ¶ 169. All of the claims of the '819 patent use "comprising" language to specifically allow for additional types of beads from other examples to be included in the formulation. *Id*. Furthermore, the Applicant amended the specification to recite a "multiple **unit** pulsed dose delivery system for amphetamine salts and mixtures thereof" (*see* Ex. 1003, 3:29–33, emphasis added) when the following '300 patent application was filed. The '819 also stated: "The following examples are presented to illustrate and do not limit the invention," and the specification subsequently provides four Examples of different types of beads. Ex. 1002, 10:4–5; 10:8–11:67. Thus, a POSA would understand that the Examples of the '819 patent illustrate the types of different beads that are useful in combination to deliver the multiple doses of the pharmaceutical composition. Ex. 1018, ¶¶ 169-173. In addition, all of the claims of the '819 patent include "comprising" language, thus including the use of the other drug containing bead

disclosed in the ’819 patent.

Anticipation does not require “actual performance of suggestions in a disclosure.” *Bristol-Meyers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1379 (Fed. Cir. 2001);). The fact that **only three** different release profiles (immediate, delayed, and sustained) are exemplified in the ’819 patent would disclose to a POSA a **three bead** composition representing each one of the **three profiles** for a multidose composition.

The total number of possible bead combinations that a POSA could immediately envisage would be very small (ten). Ex. 1018, ¶ 173. Of the ten potential combinations, a POSA would further understand that only six allow for three-bead combinations. *Id.* A POSA would therefore understand that the ’819 patent teaches a three bead combination having an immediate release bead, a delayed release bead, and a sustained release bead.

The remaining claims of the ’100 patent are dependent upon claim 1 and are likewise anticipated.

2. The ’819 Patent Discloses the Modifications to the Pharmaceutical Composition of Claim 1 That Are Claimed by Dependent Claims 2-4, 13-–21 and Claim 31.

Dependent Claims 2–4, 13–21 and Claim 31 further limit independent claim 1 by modifying the claimed pharmaceutical composition in a variety of ways. Each modification, however, is explicitly disclosed by the ’819 patent, as shown

below.

Claim 2 recites the limitation, **wherein the enteric coating is pH dependent**. This is disclosed in the '819 patent by "[t]he enteric coating layer is applied onto the cores…All commercially available pH-sensitive polymers are included." Ex. 1002, 8:10–15; Ex. 1018, ¶¶ 175-176.

Claim 3 recites the limitation, **wherein the first delayed release bead and the second delayed release bead comprise different enteric coatings.** In Example 2, the '819 patent teaches MAS pellets coated with EUDRAGIT® L 30D-55, an enteric coating. Ex. 1002, 10:32–60; 8:31; Ex. 1018, ¶ 178. This corresponds to a first delayed release bead. Ex. 1018, ¶ 179. In Example 4 of the '819 patent, the enteric coated MAS pellets from Example 3, coated with the enteric coating, EUDRAGIT® 4110D (*id.*, 8:32), are further coated with SURELEASE®, which corresponds to the second delayed release bead having a different enteric coating than that of the first delayed release bead. Ex. 1002, 11:31–67; Ex. 1018, ¶ 180.

Claim 4 recites the limitation, **wherein the first delayed release bead and the second delayed release bead comprise the same enteric coatings.** In Example 2, the '819 patent teaches MAS pellets coated with EUDRAGIT® L 30D-55, an enteric coating. Ex. 1002, 10:32–60; 8:31. This corresponds to a first delayed release bead. Ex. 1018, ¶¶ 183-185. In Example 4 of the '819 patent, the

enteric coated MAS pellets from Example 2, also coated with the enteric coating, are further coated with SURELEASE®, which corresponds to the second delayed release bead having the same enteric coating as the first delayed release bead. Ex. 1002, 11:31–63; Ex. 1018, ¶¶ 184-185.

Claim 13 recites the limitation, **wherein the immediate release bead and at least one delayed release bead are present on a single core**. Likewise, the '819 patent discloses "immediate release and enteric release portions of the composition are present on the same core." Ex. 1002, 3:39–41; Ex. 1018, ¶¶ 200-201.

Claim 14 recites the limitation, **wherein the immediate release bead and at least one delayed release bead are present on different cores**. The '819 patent discloses "immediate release and enteric release components are present on different cores." Ex. 1002, 3:42–43; Ex. 1018, ¶¶ 202-203.

Claim 15 recites the limitation, **wherein the at least one amphetamine salt is coated onto a core**. The '819 patent discloses "a core seed can be coated with one or more layers of one or more pharmaceutically active amphetamine salts." Ex. 1002, 4:65–67; Ex. 1018, ¶¶ 204-205.

Claim 16 recites the limitation, **wherein the at least one amphetamine salt is incorporated into a core**. The '819 patent describes "one or more pharmaceutically active amphetamine salts can be provided within or as part of a core seed..." Ex. 1002, 4:62–65; Ex. 1018, ¶¶ 206-207.

Claim 17 recites the limitation, **wherein the pharmaceutical composition further comprises a protective layer over at least one enteric coating.** Likewise, the '819 patent teaches: "there is a protective layer over the enteric release coating." Ex. 1002, 3:37–38; Ex. 1018, ¶¶ 208-210.

Claim 18 recites the limitation, **wherein the pharmaceutical composition further comprises a protective layer between the amphetamine salt and at least one enteric coating**. The '819 patent discloses: "there is a protective layer between the at least one pharmaceutically active amphetamine salt and the enteric release coating." Ex. 1002, 3:34–36; Ex. 1018, ¶¶ 211-213.

Claim 19 recites the limitation, **wherein the at least one amphetamine salt is selected from the group consisting of dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate, amphetamine sulfate, and mixtures thereof.** The '819 patent describes: "[p]harmaceutical active amphetamine salts contemplated to be within the scope of the present invention include amphetamine base, all chemical and chiral derivatives and salts thereof…" Ex. 1002, 7:47–50; *see also* Ex. 1003, 13:38–41 (identifying in continuation-in-part of the '819 patent the four claimed salts by name). The '819 patent therefore anticipates this claim. Ex. 1018, ¶¶ 214-217.

Claim 20 recites the limitation, **wherein the at least one amphetamine salt is a mixture of dextroamphetamine sulfate, dextroamphetamine saccharate,**

amphetamine aspartate monohydrate, and amphetamine sulfate. The '819 patent describes: "[p]harmaceutical active amphetamine salts contemplated to be within the scope of the present invention include amphetamine base, all chemical and chiral derivatives and salts thereof…" Ex. 1002, 7:47–50; Ex. 1018, ¶¶ 214-217. It also discloses Adderall® as a mixture of four amphetamine salts (*Id.*, 3:1–3), which contains the four recited amphetamine salts. Ex. 1021.

Claim 21 recites **lack of a food effect**. Food and other biological effects are inherent to the identical composition that is disclosed in the '819 patent. The absence of a food effect means that "there is no significant difference in the bioavailability of a drug in a patient when the drug is administered in a fasted state compared to a fed state." Ex. 1018, ¶ 220. It was previously recognized that the formulations of the '819 patent do not exhibit a "food effect" as defined in the '100 patent. Ex. 1018, ¶ 222; *see also* Ex. 1041, 17; Ex. 1043, 2; Ex. 1047, 16; Ex. 1048, 1406. In addition, claiming an inherent property of the prior art does not make patentable an obvious or anticipated formula. *In re Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011) (affirming rejection of claims as obvious and holding "that the claimed 'food effect' is an inherent property of [the drug] itself, present both in controlled release and immediate release formulations of that drug.").

Furthermore, "[t]he initial blood serum concentration resulting from administering [a drug] is an inherent property of the formulation, and an obvious

formulation cannot become nonobvious simply by administering it to a patient and claiming the resulting serum concentrations. To hold otherwise would allow any formulation—no matter how obvious—to become patentable merely by testing and claiming an inherent property." *Santarus*, 694 F.3d at 1354 (citation omitted).[4]

Claim 31 recites the limitation **wherein a protective coating is layered between the delayed release coating and the sustained release coating**. The '819 patent discloses a "protective layer may be added on top of the pharmaceutical active containing layer and also may be provided between active layers" (Ex. 1002, 7:56–63) and that "[s]uitable materials for the protective layer include… OPADRY®." Ex. 1002, 8:1–8; Ex. 1018, ¶¶ 234-238.

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[4] *In re Best*, 562 F.2d 1252, 1254-55 (C.C.P.A. 1977) ("[W]here the Patent Office has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may, in fact, be an inherent characteristic of the prior art, it possesses the authority to require the applicant to prove that the subject matter shown to be in the prior art does not possess the characteristic relied on." (citation omitted)); *In re Donohue*, 766 F.2d 531, 534 (Fed. Cir.1995) (holding, when compounds in the prior art and purported invention were the same, the properties of the claimed invention were inherently disclosed in the prior art).

To anticipate, the '819 patent need not have an actual example with all three types of beads placed into one capsule and administered to a patient where the drug profile measured. It is enough that a POSA was given sufficient details describing the contemplated modifications of the examples provided. The applicant must look to the whole reference for what it teaches. The applicant cannot merely rely on the examples and argue that the reference did not teach others. *In re Courtright*, 377 F.2d 647, 651–52 (C.C.P.A. 1967).

Furthermore, a generic disclosure will anticipate a claimed species covered by that disclosure when the species can be "at once envisage[d]" from the disclosure. *Petering*, 301 F.2d at 681. As mentioned earlier, three types of beads were exemplified and a POSA would know that these were useful to put into a dosage form. Ex. 1018, ¶¶ 170-173. The number of reasonable permutations would be six. *Id.* The three-bead species can be "at once envisaged" because the number of possible combinations is so small and because there are only three types of beads taught. *Id.* Moreover, when a claimed compound is not specifically named in a reference, but instead it is necessary to select from a group of alternatives and combine them, anticipation can be found if the alternatives are sufficiently limited or well delineated. *Ex parte A,* 17 U.S.P.Q.2d at 1718.

3. Claims 5–12 are anticipated by the '819 patent.

Claims 5–12 of the '100 patent claim pharmacokinetic parameters (AUC,

C_{max}, and T_{max}) for d- and l-amphetamine when the claimed three-bead formulation is administered in a total dosage amount of 37.5 mg. Ex. 1018, ¶ 186. In other words, if the pharmaceutical composition was administered in a dosage of 37.5 mg the claimed parameter would be obtained.

Specifically, claims 5–12 each claim, when administration of the pharmaceutical composition from claim 1 is 37.5 mg, a measurement (AUC, C_{max}, or T_{max}) of d or l-amphetamine that is "about" the claimed value. Ex. 1018, ¶¶ 188-197. As noted above, the '100 patent defines "about" to mean *at least* a 20% variance of the claimed numerical value and/or, with respect to biological systems or processes, means within "an order of magnitude" (*i.e.*, the nearest power of 10). *See* Ex. 1001, 11:65- 12:12; *see also* Ex. 1018, ¶¶ 189-190.. Thus, for example, Claim 5 of the '100 patent, which reads "The pharmaceutical composition of claim 1, wherein administration of a 37.5 mg dose of the pharmaceutical composition to a human patient results in a d-amphetamine C_{max} of about 50 ng/ml," claims a d-amphetamine C_{max} of between 40 ng/ml – 60 ng/ml, or even greater if one deems the achievement of a C_{max} to be a biological process. Ex. 1018, ¶ 189. Each of the claimed parameters are qualified with the term "about."

Each of the limitations in claims 5–12 are each disclosed by the '819 patent and inherent in the prior art three-bead combinations. Ex. 1018, ¶¶ 188-197. As discussed above, the '819 patent discloses each of the three claimed drug

containing beads claimed in the ’100 patent, claim 1. When the claimed and prior art products are identical or substantially identical in structure or composition, a *prima facie* case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255 (C.C.P.A. 1977). The drug containing beads disclosed in the ’819 patent therefore possess the same characteristics as the drug containing beads of the ’100 patent.[5]

Claim 5 recites the limitation, **wherein administration of a 37.5 mg dose of the pharmaceutical composition to a human patient results in a d-amphetamine C_{max} of about 50 ng/ml.** Using the definition of “about” allowing for at least a 20% variance, the claim encompasses values from 40 ng/ml to 60 ng/ml. Ex. 1018, ¶ 189. The ’819 patent discloses as a combination of Examples 1 and 2 what is known as Adderall® XR. Ex. 1018, ¶ 193. Normalized to 37.5 mg dose, the C_{max} for Adderall® XR is 52.74 ± 16.57 ng/ml for d-amphetamine. *Id.*, ¶ 196. A POSA would therefore understand that a C_{max} that includes the range claimed by the ’100 patent, claim 5 is necessarily present in the beads disclosed in

[5] The USPTO Examiner rejected these claims on the basis that the claimed pharmacokinetic parameters “are merely functional limitations that are the result of the components of the composition,” claimed in the ’300 patent, which is a continuation-in-part of the ’819 patent. Ex. 1007, 4.

Example 1 and 2 of the ’819 patent. The ’819 patent therefore anticipates Claim 5.

These same arguments apply equally to claims 6–12, which merely recite additional pharmacokinetic properties, which are inherent to the composition that is disclosed in the ’819 patent. *See* Ex. 1018, ¶¶ 186-198.

4. The ’819 Patent Anticipates Claims 22–30.

Claims 22–30 recite the inclusion of different **amounts of amphetamine salt** in the pharmaceutical formulation, namely 12.5, 18.75, 25, 31.25, 37.5, 43.75, 50, 62.5 and 75 mg. Ex. 1018, ¶¶223-233. The ’819 patent explicitly “pertains to a multiple dosage form delivery system comprising one or more amphetamine salts for administering the amphetamine salts to a recipient.” Ex. 1002, 1:4–6, 3:16–20; 9:60–64. Adjustment of the dose is generally dependent on the weight and age of the patient and should be administered “at the lowest effective dosage.” Ex. 1052, 2210. Administration of a dosage form to a recipient necessarily requires the determination of an appropriate amount of drug. Ex. 1018,¶ 227–228. *See Continental Can*, 948 F.2d at 1269. (“this modest flexibility in the rule that ’anticipation’ requires that every limitation of the claims appear in a single reference accommodates situations in which the common knowledge of technologists is not recorded in the reference…” *Id.*). The prior art Adderall® IR was available in 5, 7.5, 10, 12.5, 15, 20 and 30 mg amounts. Ex. 1042. The prior art Adderall® XR was available in 5, 10, 15, 20, 25 and 30 mg amounts. Ex. 1043.

Thus, claiming dosages amounts beginning at "about 12.5 mg" (claim 22) and increasing the dose amount repeatedly by about 6.25 mg to reach dosage amounts of 75 mg (claims 23–30) would be understood as disclosed to the POSA by the '819 patent because it is necessary to "administer[] the amphetamine salts to a recipient." Ex. 1002, 1:4–6; *see also* Ex. 1018, ¶¶ 232-233. Routine dosage determination is not patentable. *E.g., Merck & Co. v. Biocraft Labs., Inc.*, 874 F.2d 804, 809 (Fed. Cir. 1989) ("[T]hough requiring time and care, the experimentation needed to arrive at the claimed dosages was nothing more than routine."); *see also In re Applied Materials, Inc.*, 692 F.3d 1289, 1295 (Fed. Cir. 2012) ("[D]iscovery of an optimum value of a result effective variable…is ordinarily within the skill of the art."). Thus, the list of claimed dosages at intervals necessary to permit dose titration to the lowest effective dose is necessary to administer the dosage forms disclosed in the '819 patent and thus anticipates claims 22–30 of the '100 patent. Ex. 1018, ¶¶ 232-233.

C. Explanation Of Ground 2 For Unpatentability: Claims 1–31 Are Obvious Over The '300 Patent In View Of Kratochvil.

Claims 1–31 are obvious over the '300 patent and Kratochvil. A patent shall not issue "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the

subject matter pertains." *KSR Int'l Co. v. Teleflex Inc*., 550 U.S. 398, 406–07 (2007) (quoting 35 U.S.C. § 103(a)). The question of obviousness turns on underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). An obviousness analysis "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR*, 550 U.S. at 418. *Prima facie* obviousness occurs when the prior art itself suggests the claimed subject matter to a POSA. *In re Rinehart*, 531 F.2d 1048, 1051 (C.C.P.A. 1976).

1. A POSA Would Be Motivated to Combine the '300 Patent With Kratochvil.

Kratochvil explained that some people with ADHD need therapy beyond the eight hour school day and taught "sculpting the dose" by combining various stimulant fomulations to match the patient's needs. Ex. 1019, S163; *see also* Ex. 1018, ¶¶ 240-251 (discussing a POSA's motivation to combine the '300 patent and Kratochvil). Figure 1 of Kratochvil illustrates drug combinations to provide therapeutic coverage for about 16 hours, including: three Adderall® IR doses per day; one Adderall® IR dose in the morning and one Adderall® XR around noon; and one Adderall® XR in the morning and one Adderall® IR around six PM. Ex. 1019,

S163. Kratochvil would have motivated a POSA to create a triple bead formulation of MAS to compensate for the inadequacies of Adderall® XR. Ex. 1018, ¶¶ 240-251. A POSA would have had a reasonable expectation of success because this strategy had been used successfully in the development of Adderall® XR. *Id.*, ¶ 251. "Obviousness does not require absolute predictability of success…all that is required is a reasonable expectation of success." *In re O'Farrell*, 853 F.2d 894, 903–04 (Fed. Cir. 1998). Moreover, a triple bead formulation of methylphenidate, another ADHD amphetamine, was known. Ex. 1029. Thus, there was significant motivation to create a MAS triple bead combination and a known technique to make it. Ex. 1018, ¶¶ 240-251. A POSA would not even have to develop any new beads because the '300 patent already described three beads that could provide full-day coverage shown by the delayed sustained profile in Figure 6 and Example 4. Ex. 1003, 11:58-12:6. The '300 patent also taught matching a desired plasma profile with a multi-bead formulation having an equivalent plasma profile to get the therapeutic coverage of Example 5. *Id.*, 12:28–48. Kratochvil, in Figures 1 and 2 described the desired plasma profile equivalent to IR 3X a day, having an immediate pulse, a delayed pulse around noon, then the last dose around 6 pm. Ex. 1019, S163-64. The '300 patent taught everything necessary to achieve this plasma profile and provided examples of each of the three required beads; immediate release, delayed release, and sustained release. Ex. 1018, ¶¶ 360–364.

The rationale to combine references is signficantly stronger when the references seek to solve the same problems, come from the same field, and corrrespond well. *In re Inland Steel Co*., 265 F.3d 1354, 1362 (Fed. Cir. 2001). Here, a POSA had reason to combine the '300 patent and Kratochvil because they both relate to treatment of ADHD with multiple unit formulations of MAS.

The rationale to combine is also stronger where the prior art is analagous; that is, reasonably pertinent to the particular problem with which the invention is involved. *In re Wood*, 599 F.2d 1032, 1036 (C.C.P.A. 1979). The '300 patent and Kratochvil address the same problem at issue in the '100 patent: treatment of ADHD with multi-unit MAS dosage forms and matching them to the desired plasma profile, which Kratochvil taught was akin to three immediate release doses. Ex. 1018, ¶¶ 240-251. It follows that a POSA would look to the '300 patent as analagous art, which teaches various release multi-bead MAS formulations, to solve the problem created by the lack of a single dose formulation of MAS providing full-day coverage. *Id.*

Kratochvil teaches that ADHD lasts the whole day and appropriate coverage is needed. Ex. 1019, S162. Kratochvil illustrates the inadequacies of Adderall® XR, which has to be supplemented with an IR dose at 6 pm. *Id.*, Figure 1. Kratochvil teaches "sculpting the dose" according to the needs of the patient. *Id*., S163. Specifically, Kratochvil teaches that the dosing profile for full day

coverage should be equivalent to 3 IR doses comprised of an early morning dose, a noon dose, and a 6 PM dose. *Id*. A POSA facing this problem would look to art directed to multiple dose ADHD drugs generally and to Adderall® specifically, like the '300 patent. Ex. 1003, 3:13–28.

2. The '300 Patent, In View of Kratochvil, Teaches Each Element of Claim 1.

The '300 patent teaches all limitations of claim 1 of the '100 patent including "**a pharmaceutical composition comprising: (a) an immediate release bead comprising at least one amphetamine salt**." *See* Ex. 1003, 3:39–44; *id.*, Example 1; *id.*, 10:32–54[6]; *see also* Ex. 1018, ¶¶254-256.

The next limitation of claim 1 of the '100 patent, **a first delayed release bead comprising at least one amphetamine salt**, is identical to the beads of Example 2 or 3 of the '300 patent, where the MAS pellets are coated with EUDRAGIT® L 30D-55 (*Id*., 10:60–11:24) or with EUDRAGIT® 4110D, which are enteric polymers. Ex. 1003, 8:44–56; Ex. 1018; ¶¶ 257-262. Figures 4 and 5 illustrate the delayed pulsed release profile of the bead of Examples 2 and 3. Ex. 1003, 6:50-57; Ex. 1018 ¶ 261.

The next limitation of claim 1 of the '100 patent, **a second delayed release**

[6] As everything taught by the '819 patent is included in the '300 patent, Petitioner incorporates Section V.B. in support of Ground 2.

bead comprising at least one amphetamine salt, is disclosed in Example 4 of the '300 patent, in which the coated MAS pellets from either Example 2 or Example 3 are further coated with SURELEASE® (i.e., ethyl cellulose, a pH independent polymer). Ex. 1003, 11:58-12:26; Ex. 1036, 1-2; Ex. 1018, ¶¶274–280. Figure 6 illustrates the delayed sustained release profile of the bead of Example 4. Ex. 1003, 6:58-61; Ex. 1018, ¶266.

The limitation of claim 1, **the second delayed release bead provides sustained release of the at least one amphetamine salt** is disclosed by Figure 6 of the '300 patent. Ex. 1003, Fig. 6; *see also* Ex. 1018, ¶¶ 263-268. The limitation**, wherein the first delayed release bead provides pulsed release of the at least one amphetamine salt**, is disclosed in Example 4 of the '300 patent. Ex. 1002, 11:45-12:14; Ex. 1018, ¶¶ 270-280. The next limitation, **wherein the second delayed release bead comprises at least one amphetamine salt layered onto or incorporated into a core; a delayed release coating layered onto the amphetamine core; and a sustained release coating layered onto the delayed release coating**, is disclosed in the '300 patent Example 4. Ex. 1003, 11:60–12:26; Ex. 1018, ¶¶281-288. The limitation, **wherein the sustained release coating is pH-independent,** is disclosed by "a semi-permeable polymer, which may comprise a low water-permeable pH-insensitive polymer, is layered onto the outer surface of the enteric layer…" in the '300 patent. Ex. 1003, 6:3-6; Ex. 1018, ¶

287. The limitation, **wherein the first delayed release bead and the second delayed release bead comprise an enteric coating**, is described in Examples 2, 3, and 4 in the '300 patent. Ex. 1003, 10:32–12:26; Ex. 1018, ¶¶ 289-291. The remainder of the claims of the '100 patent are dependent upon claim 1 and are likewise obvious.

3. The '300 Patent, In View of Kratochvil, Teaches Each Element of Claims 2–4, 13–21, and 31.

A POSA would understand the '300 patent, viewed in light of the teachings of Kratochvil, to disclose the modified pharmaceutical compositions taught by the '100 patent and therefore to render obvious dependent Claims 2–4, 13–21 and 31.

Claim 2 recites the limitation, **wherein the enteric coating is pH dependent**. The '300 patent discloses "[t]he enteric coating layer is applied onto the cores…All commercially available pH-sensitive polymers are included." Ex. 1003, 8:31–36; Ex. 1018, ¶¶ 293-294.

Claim 3 recites the limitation, **wherein the first delayed release bead and the second delayed release bead comprise different enteric coatings.** In Example 2, the '300 patent teaches MAS pellets coated with EUDRAGIT® L 30D-55, an enteric coating. Ex. 1003, 10:58–11:21; Ex. 1018, ¶ 296–297. This corresponds to a first delayed release bead. Ex. 1018, ¶ 297. In Example 4 of the '300 patent, the enteric coated MAS pellets from Example 3, additionally coated with the enteric coating, EUDRAGIT® 4110D (*id.*, 8:54), are further coated with

SURELEASE®, which corresponds to the second delayed release bead having a different enteric coating than that of the first delayed release bead (EUDRAGIT® L 30D-55 v.s. EUDRAGIT® 4110D). Ex. 1003, 11:58–12:26; Ex. 1018, ¶¶ 298-299.

Claim 4 recites the limitation, **wherein the first delayed release bead and the second delayed release bead comprise the same enteric coatings.** In Example 2, the '300 patent teaches MAS pellets coated with EUDRAGIT® L 30D-55, an enteric coating. Ex. 1003, 10:58–11:21; Ex. 1018, ¶ 303. This corresponds to a first delayed release bead. In Example 4 of the '819 patent, the enteric coated MAS pellets from Example 2, are further coated with SURELEASE®, which corresponds to the second delayed release bead having the same enteric coating as the first delayed release bead. Ex. 1003, 11:58–12:26; Ex. 1018, ¶ 303.

Claim 13 recites the limitation, **wherein the immediate release bead and at least one delayed release bead are present on a single core**. Likewise, the '300 patent discloses "immediate release and enteric release portions of the composition are present on the same core." Ex. 1003, 3:5–55; Ex. 1018; ¶¶ 322-323.

Claim 14 recites the limitation, **wherein the immediate release bead and at least one delayed release bead are present on different cores**. The '300 patent discloses "immediate release and enteric release components are present on different cores." Ex. 1003, 3:56–57; Ex. 1018, ¶¶ 324-325.

Claim 15 recites the limitation, **wherein the at least one amphetamine salt**

is coated onto a core. The '300 patent discloses "a core seed can be coated with one or more layers of one or more pharmaceutically active amphetamine salts." Ex. 1003, 5:14–16; Ex. 1018, ¶¶ 326-327.

Claim 16 recites the limitation, **wherein the at least one amphetamine salt is incorporated into a core**. The '300 patent describes "one or more pharmaceutically active amphetamine salts can be provided within or as part of a core seed..." Ex. 1003, 5:11–13; Ex. 1018, ¶¶ 328-329.

Claim 17 recites the limitation, **wherein the pharmaceutical composition further comprises a protective layer over at least one enteric coating.** The '300 patent teaches: "there is a protective layer over the enteric release coating." Ex. 1003, 3:51–52; Ex. 1018, ¶¶330-332.

Claim 18 recites the limitation, **wherein the pharmaceutical composition further comprises a protective layer between the amphetamine salt and at least one enteric coating**. The '300 patent discloses: "there is a protective layer between the at least one pharmaceutically active amphetamine salt and the enteric release coating." Ex. 1003, 3:48–50; Ex. 1018, ¶¶ 333-335.

Claim 19 recites the limitation, **wherein the at least one amphetamine salt is selected from the group consisting of dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate, amphetamine sulfate, and mixtures thereof.** Claim 12 of the '300 patent

discloses mixtures of the four salts claimed in Claim 19. Ex. 1003, 14:21–49; Ex. 1018, ¶¶ 336-339.

Claim 20 recites the limitation, **wherein the at least one amphetamine salt is a mixture of dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate, and amphetamine sulfate.** See above for claim 19; Ex. 1018, ¶¶ 336-339.

Claim 21 recites **lack of a food effect**. The same arguments regarding claim 5 are to be equally applied here, that food and other biological effects are inherent to the identical composition that is disclosed in the '300 patent. Ex. 1018, ¶¶ 342-344. Moreover, the lack of a food effect was well known in the art, including Adderall® XR. *See* Ex. 1041, 17; Ex. 1018, ¶¶ 343-344.

Claim 31 recites the limitation **wherein a protective coating is layered between the delayed release coating and the sustained release coating**. The '300 patent discloses "a semi-permeable polymer, which may comprise a low water-permeable pH-insensitive polymer, is layered onto the outer surface of the enteric layer…Another pH-sensitive layer may be applied onto the surface of a low water-permeability layer." Ex. 1003, 6:3–12; Ex. 1018, ¶¶ 356-359. Furthermore, the '300 patent, like the '819 patent, discloses that "a protective layer may be added on top of the pharmaceutical active containing layer and also may be provided between active layers" (Ex. 1003, 8:10–16) and that "suitable materials

for the protective layer include… OPADRY®." Ex. 1003, 8:22–29; Ex. 1018, ¶¶356-359.

4. The '300 Patent, In View of Kratochvil, Teaches Each Element of Claims 5–12.

Claim 5 recites the limitation, **wherein administration of a 37.5 mg dose of the pharmaceutical composition to a human patient results in a d-amphetamine C_{max} of about 50 ng/ml.** As explained above, these claim limitations relate to d- or l-amphetamine levels achieved upon administering a 37.5 mg dose of the formulation of claim 1. In addition, because this claim term references a biological system or process, the "about" qualification means within "an order of magnitude" (i.e., the nearest power of 10). Ex. 1018, ¶¶ 312-313. Additionally, the pharmacokinetic values claimed here are also inherent to the multiple (three)-bead composition disclosed by the '300 patent, as discussed below. Ex. 1018, ¶¶ 306-320.

The d-amphetamine levels disclosed in claim 2 of the '300 patent describe C_{max} of 22.5 to 40 ng/ml for a 20 mg dose, which, assuming dose proportionality, converts to 42.2 to 75 ng/ml for a 37.5 mg dose. Ex. 1018, ¶¶ 307-314. Considering the range encompassed by "about 50 ng/ml," the C_{max} of the prior art combination would necessarily fall within the claimed range. *Id.*, ¶ 34; *see also* Ex. 1067, 5 ("The values from Figs. 7 and 8 are d-amphetamine levels to one of ordinary skill in the art…").

These same arguments apply equally to claims 6–12, which merely recite additional pharmacokinetic properties, which are inherent to the multiple (three)-bead composition disclosed by the '300 patent. Ex. 1018, ¶ 315. Claims 6 and 7 relate to the d-amphetamine AUC, which is "about" the same as the claimed dose-adjusted range from claim 1 of the '300 patent (AUC of 20 mg dose is 467–714 ng.hr/ml, which corresponds to 875–1339 ng.hr/ml for 37.5 dose). Ex. 1018, ¶ 316. Claim 8 and Claim 12 claim a T*max* of about 8.2 and 8.4 hours, respectively. *Id.*, ¶ 317. These T*max* values overlap with the T*max* claimed by the '300 patent (7–10 hours). *Id.* Claims 9–11 claim the l-amphetamine levels corresponding to an administration of the MAS pellets, which is known to be about 1/3 of the d-amphetamine levels. *Id.*, ¶¶ 318-320; *see also* Ex. 1023; Ex. 1045.

In addition, modifying the beads disclosed in the '300 patent as guided by the dose sculpting taught by Kratochvil (a single dosage form to replace the extended release plus immediate release regimen) would produce a formulation that meets the claimed ranges. As set forth above, it is known that the 20 mg dose of Adderall® IR is bioequivalent (similar Cmax and AUC) to a 10 mg Adderall® XR administered twice a day. Ex. 1018, ¶ 193. Thus, the claimed limitations are inherent in amphetamines, particularly when the breadth of the range claimed is taken into account.

5. The '300 Patent, In View of Kratochvil, Teaches Each Element of Claims 22–30.

Claims 22–30 recite different **dosages of amphetamine salt**, specifically 12.5, 18.75, 25, 31.25, 37.5, 43.75, 50, 62.5 and 75 mg. Ex. 1001. The '819 patent explicitly "pertains to a multiple dosage form delivery system comprising one or more amphetamine salts for administering the amphetamine salts to a recipient." Ex. 1003, 1:9–11, 3:31–35; 10:17–21. Adjustment of the dose is generally dependent on the weight and age of the patient and should be administered "at the lowest effective dosage." Ex. 1052, 2210. Administration of a dosage form to a recipient necessarily requires the determination of an appropriate amount of drug. *See Continental Can*, 948 F.2d at 1269. ("this modest flexibility in the rule that 'anticipation' requires that every limitation of the claims appear in a single reference accommodates situations in which the common knowledge of technologists is not recorded in the reference…"); *see also* Ex. 1018, ¶¶ 349–350. The prior art Adderall® IR was available in 5, 7.5, 10, 12.5, 15, 20 and 30 mg amounts. Ex. 1042. The prior art Adderall® XR was available in 5, 10, 15, 20, 25 and 30 mg amounts. Ex. 1043. Thus, claiming dosages amounts beginning at "about 12.5 mg" (claim 22) and increasing the dose amount repeatedly by about 6.25 mg to reach dosage amounts of 75 mg (claims 23–30) would be understood as disclosed to the POSA by the '300 patent. Ex. 1018, ¶¶ 347-352. Routine dosage determination is not patentable. *E.g., Merck & Co. v. Biocraft Labs., Inc.*, 874 F.2d 804, 809

(Fed. Cir. 1989) ("[T]hough requiring time and care, the experimentation needed to arrive at the claimed dosages was nothing more than routine."); *see also In re Applied Materials, Inc.*, 692 F.3d 1289, 1295 (Fed. Cir. 2012) ("[D]iscovery of an optimum value of a result effective variable…is ordinarily within the skill of the art."). Thus, the list of claimed dosages at intervals necessary to permit dose titration to the lowest effective dose is necessary to administer the dosage forms disclosed in the '300 patent and does not render the claims new or nonobvious.[7] Ex. 1018, ¶ 355.

VI. Conclusion.

For the foregoing reasons, Petitioner submits that there is a reasonable likelihood that it will prevail with respect to at least one of the claims challenged as

[7] No secondary considerations would support any conclusion of nonobviousness. That the '100 patent proclaims that the results were "surprising," is not persuasive. Ex. 1001, 5:11-27. The same observation of alleged "surprising" results was made in both the '819 and '300 patents. *Cf* Ex. 1001, 5:11-27 *with* Ex. 1002, 5:38-46 *and* Ex. 1003, 5:54-62. Moreover, such results were not surprising to a POSA at the time of either the '819 and '300 patents. Ex. 1018, ¶ 367. No secondary considerations were discussed in the prosecution history or relied upon in the notice of allowance. *See generally* Ex. 1004-1017.

unpatentable over the prior art cited herein. Accordingly, Petitioner respectfully requests *inter partes* review of claims 1–31 of the '100 patent.

Respectfully submitted,

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CERTIFICATION UNDER 37 C.F.R. §42.24(d)

Under the provisions of 37 C.F.R. §42.24(d), the undersigned hereby certifies that the word count for the Petition for *Inter Partes Review* of U.S. Patent No. 8,846,100 filed in this proceeding on January 13, 2017, totals 13,952 words, which is less than the 14,000 allowed under 37 C.F.R. § 42.24(a)(i).

January 13, 2017

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CERTIFICATE OF SERVICE

The *Petition for Inter Partes Review* was served by Federal Express, on January 13, 2017, to the owner of the '100 patent, Shire Inc., at their correspondence address of record according to PAIR:

McDermott Will & Emery, LLP
The McDermott Building
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and that additional copies have been delivered to the address of the patent owner and additional counsel at the following addresses:

Shire LLC
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Respectfully,

Dated: January 13, 2017

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