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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

KVK-Tech, Inc.
Petitioner

v.

Shire PLC
Patent Owner

U.S. Patent No. 8,846,100

PETITION FOR *INTER PARTES* REVIEW

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EXHIBIT LIST

Exhibit	Reference
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1002	U.S. Patent No. 6,605,300 ("Burnside")
1003	PHYSICIANS' DESK REFERENCE® 3144-3146 (58th ed. 2004) ("2004 PDR®")
1004	Declaration of Diane J. Burgess, Ph.D.
1005	Prosecution History of the '100 Patent
1006	Declaration of William J. Jusko, Ph.D.
1007	Rong-Kun Chang et al., *A Review of Aqueous Coating Techniques and Preliminary Data on Release from a Theophylline Product*, 11 Pharm. Tech. 3, 56-68 (1987)
1008	FDA: Center for Drug Evaluation and Research, Application No. 11-522, Approval Letter (Feb. 13, 1996)
1009	ORANGE BOOK: APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS, ADDERALL®, https://www.accessdata.fda.gov/scripts/cder/ob/search_product.cfm. (last visited Aug. 16, 2017)
1010	Christopher J. Kratochvil, MD, *ADHD: Treatment and Outcome*, 4 Managing ADHD 3A, 1-4 (2004)
1011	David J. Heal et al., *Amphetamine, Past and Present - a Pharmacological and Clinical Perspective*, 27 J. Psychopharmacology 6, 479-496 (2013)
1012	C. Bradley, *The Behavior of Young Children Receiving Benzedrine*, 94 Am. J. Psychiatry 1, 154-162 (1937)
1013	Drugs@FDA U.S. Food and Drug Administration, FDA Approved Drugs, Adderall XR®, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=021303 (last visited Aug. 16, 2017).
1014	Simon J. Tulloch et al., *SLI381 (Adderall XR), a Two-Component, Extended-Release Formulation of Mixed Amphetamine Salts: Bioavailability of Three Test Formulations and Comparison of Fasted, Fed, and Sprinkled Administration*, 22 Pharmacotherapy 11, 1405-1415 (2002)
1015	U.S. Patent No. 4,728,512
1016	U.S. Patent No. 5,326,570
1017	U.S. Patent No. 8,313,776
1018	U.S. Patent No. 6,555,136

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1019	U.S. Patent No. 6,322,819
1020	U.S. Food and Drug Administration, Clinical Pharmacology and Biopharmaceutics Review, Application No. 21-303/S-001
1021	ORANGE BOOK: APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS, ADDERALL XR®, https://www.accessdata.fda.gov/scripts/cder/ob/search_product.cfm. (last visited Aug. 25, 2017)
1022	THE PHARMACOLOGICAL BASIS OF THERAPEUTICS 62-83 (Alfred Goodman Gilman et al. eds., 8th ed. 1990)
1023	U.S. Patent Application Publication No. US2004/0059002
1024	Agyilirah, G.A. and Banker, G.S., POLYMERS FOR CONTROLLED DRUG DELIVERY 39-66 (Peter J. Tarcha ed., 1991)
1025	Walter G. Chambliss, "The forgotten dosage form: enteric-coated tablets," *Pharmaceutical Technology*, 7: 124-132, 138-140 (1983)
1026	BIOPHARMACEUTICS AND RELEVANT PHARMACOKINETICS (John G. Wagner et al. eds., 1st ed. 1971)
1027	REMINGTON THE SCIENCE AND PRACTICE OF PHARMACY (Limmer, 20th ed., 2000)
1028	HANDBOOK OF PHARMACEUTICAL EXCIPIENTS (Ainley Wade & Paul J. Weller eds., 2d ed. 1994)
1029	HANDBOOK OF PHARMACEUTICAL EXCIPIENTS (Arthur H. Kibbe ed., 3d ed. 2000)
1030	INTENTIONALLY LEFT BLANK
1031	FDA Adderall XR® Label, 2004 (Published August 2004)
1032	FDA Adderall IR® Label, 2005 (Published June 2005)
1033	Susan B. Clausen et al., *Single- and Multiple-Dose Pharmacokinetics of an Oral Mixed Amphetamine Salts Extended-Release Formulation in* Adults, 10 CNS Spectrums 12 (Suppl 20), 6 (2005)
1034	WO99/66904
1035	WO98/27967
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1038	Clive G. Wilson, GASTROINTESTINAL TRANSIT AND DRUG ABSORPTION, in DRUGS AND THE PHARMACEUTICAL SCIENCE: ORAL DRUG ABSORPTION PREDICTION AND ASSESSMENT (Jennifer Dressman & Hans Lennernäs, Vol. 106, 2000.)

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1039	J. Fallingborg, *Intraluminal pH of the Human Gastrointestinal Tract*, 46 J. Health Sci. 183 (1999)
1040	J. Fallingborg et al., *Measurement of Gastrointestinal pH and Regional Transit Times in Normal Children*, 11 J. Pediatric Gastroenterology & Nutrition 211 (1990)

KVK-Tech, Inc. ("Petitioner") hereby submits this petition for *inter partes* review ("Petition") of U.S. Patent No. 8,846,100 ("the '100 patent") (Ex. 1001). The Petition shows a reasonable likelihood that claims 1-31 of the '100 patent (the "Challenged Claims") are unpatentable on three grounds.

I. INTRODUCTION

This case is about a controlled release composition already disclosed within the experimental examples of a prior patent issued to the same alleged patent owner. The Challenged Claims covering that alleged invention boil down to an amphetamine salt composition comprising three beads: (1) *immediate* release beads; (2) *delayed pulsed* release beads; and (3) *delayed sustained* release beads. Importantly, the delayed sustained release beads served as the basis for allowance of all Challenged Claims.

Yet, the above-mentioned prior art patent – U.S. Patent No. 6,605,300 to Burnside et al. ("Burnside") (Ex. 1002)[1] – teaches each and every single limitation of nearly all Challenged Claims, including the delayed sustained release beads. Indeed, there can be no dispute that Burnside teaches mixed amphetamine salts, which were known 80 years ago. Nor can there be any dispute that Burnside teaches the immediate and delayed release pulsed beads. Finally, Burnside teaches

[1] Burnside reissued as RE41,148 on February 23, 2010.

the delayed sustained release beads, which it dedicates to the public. In fact, Burnside's experimental examples, which teach both delayed pulsed and sustained release beads were largely copied into the '100 patent and serve as the basis of the Challenged Claims. As such, Burnside anticipates the Challenged Claims.

Although the Patent Office withdrew rejections of these claims based on Burnside during prosecution, it did so in view of Applicants' inaccurate representations that Example 4 of Burnside does not teach delayed sustained release beads or a sustained release coating on top of an enteric coating. Shire LLC, the alleged assignee of the '100 patent, has itself demonstrated these representations are inaccurate by admitting in federal court that the formulation of Example 4, "shows a sustained enteric release, occurring over the course of *six* hours." (Ex. 1036 at 12). In addition, and significantly, Petitioner presents new, additional prior art not considered during prosecution. The Challenged Claims thus warrant a fresh look by this tribunal and 35 U.S.C. § 325(d) does not apply here.

At the very least, Burnside alone, or Adderall XR®, in combination with Burnside, renders these claims obvious. Both Burnside and Adderall XR® teach a two-bead system comprising immediate release beads and delayed pulsed release beads, each comprising mixed amphetamine salts. The prior art motivates a person of ordinary skill ("POSA") to add Burnside's sustained release beads to this two-

bead system to prolong the action of the amphetamine actives in patient populations for which the duration of therapeutic efficacy was insufficient.

II. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8

A. Real Parties-in-Interest 37 C.F.R. § 42.8(b)(1)

The real parties-in-interest are KVK-Tech, Inc. and Abhai LLC.

B. Related Matters

Amerigen Pharmaceuticals Limited ("Amerigen") previously petitioned for *inter partes* review of claims 1-31 of the '100 patent on January 13, 2017 (Case No. IPR2017-00665.) Amerigen withdrew its Petition prior to the deadline for Patent Owner's Preliminary Response. Petitioner is also concurrently filing a second petition for *inter partes* review of U.S. Patent No. 9,173,857 based on similar grounds.

C. Lead and Back-Up Counsel 37 C.F.R. § 42.8(b)(3)-(4)

Petitioner designates the following as lead and back-up counsel, both with Axinn, Veltrop & Harkrider LLP:

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A power of attorney is submitted herewith pursuant to 37 C.F.R. § 42.10(b).

III. PAYMENT OF FEES 37 C.F.R. §§ 42.15(A) AND 42.103

Petitioner submits the required fees with this Petition. Please charge any additional fees to Deposit Account No. 013050.

IV. 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 barred or estopped from requesting such review.

V. IDENTIFICATION OF CHALLENGE - PROPOSED GROUNDS

Petitioner challenges claims 1-31 of the '100 patent and requests these claims be found unpatentable in view of the following grounds:

- **Ground 1**: Claims 1-21 and 31 are anticipated by Burnside (Ex. 1002).
- **Ground 2**: Claims 1-31 are obvious in view of Burnside (Ex. 1002).
- **Ground 3:** Claims 1-31 are obvious over: (1) Adderall XR® (Ex. 1003 or Ex. 1031)[2] in view of (2) Burnside (Ex. 1002).

VI. STATE OF THE PRIOR ART AS OF 2006

All aspects of the Challenged Claims were known in the prior art long before the filing of the '100 patent. In fact, mixed amphetamine salts as well as immediate release, delayed pulsed release and delayed sustained release beads

[2] Exhibit 1003 and Exhibit 1031 are alternatives supporting the teachings of Adderall XR®. (Ex. 1004 at ¶¶34-36.)

were known in the art well before the '100 patent. The following prior art published more than one year before the May 12, 2006 filing date of the '100 patent.

A. Amphetamine Was a Well-Known ADHD Treatment

By May 12, 2006, amphetamine salts had been used to treat attention deficit disorder ("ADHD") for about 80 years. (See, e.g., Ex. 1011 at 3; Ex. 1012 at 14.) The specific mixed amphetamine salts ("MAS") of Adderall® – dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate, and amphetamine sulfate – were approved by FDA on February 13, 1996 in an immediate release formulation. (Ex. 1008; Ex. 1004 at ¶¶30-31.) This formulation became known as Adderall IR®. (See Ex. 1004 at ¶¶30-31.) In response to industry desire for a longer-acting dosage form, an immediate release bead was combined with a delayed release bead to produce Adderall XR®. (See id. at ¶32.) Adderall XR®, approved by FDA on October 11, 2001, contained the same amphetamine salts as Adderall IR®. (Ex. 1013 at 1-4; Ex. 1004 at ¶32.) According to the 2004 PDR® for Adderall XR®, "[f]ood does not affect the extent of absorption of [ADDERALL XR®] . . . ." (Ex. 1003 at 5; see also Ex. 1014 at 12.) The 2004 PDR® and Label for Adderall XR® are prior art under 35 U.S.C. § 102(b).

B. Drug Coating Release Timings and Characteristics Were Well-Known In the Prior Art

The use of coating agents to modulate the release time and rate of active drugs, as in Adderall XR®, was also well-known. (Ex. 1004 at ¶¶23-29; Ex. 1024 at 4; Ex. 1025 at 2; Ex. 1026 at 4.) It was known as of at least 2000 that coating agents used for delayed pulsed or sustained release could be applied to subunits of dosage forms to achieve desired drug-release profiles. (Ex. 1027 at 8-9.) Enteric coating agents (e.g., EUDRAGIT® L 30-D-55), for triggering delayed pulsed release, and sustained release coating agents (SURELEASE®), for triggering sustained release of active pharmaceutical agents are extremely old in the art. (Ex. 1004 at ¶¶27-29 (citing Ex. 1024 at 4, Ex. 1028 and Ex. 1029).)

The prior art reports numerous triple-bead systems containing these types of coating agents, especially for active drugs traditionally administered multiple times per day, but modified for once-daily administration. This is especially true for drugs requiring an extended duration of action. (See, e.g., Ex. 1015 at 1:68-2:8.) In the case of propranolol HCl, for example, U.S. Patent No. 4,728,512 ("Mehta") taught a once-daily dosage form comprising (i) "uncoated" beads (immediate release beads), (ii) beads "coated with a pH sensitive coat" (pulsed release beads with an enteric coating) and (iii) beads "coated with a pH independent coat" (sustained release beads). (Ex. 1015 at [57]; (Abstract).) The prior art taught

similar dosage forms for various other active drugs. (See, e.g., Ex. 1016; Ex. 1017.)

C. Adderall IR® and Adderall XR®

The prior art taught these same types of systems for mixed amphetamine salts.

Some brief history may be helpful here. As previously mentioned, FDA approved the commercial manufacture and sale of Adderall IR® for the treatment of ADHD on February 13, 1996. (Ex. 1008; Ex. 1004 at ¶31.) Clinicians recognized the need for an extended duration of action for the treatment of ADHD so children could forego a second dose during the school day. (See, e.g., Ex. 1002 at 3:13-28; Ex. 1004 at ¶32.) In response, FDA approved Adderall XR® on October 11, 2001. (Ex. 1004 at ¶32; Ex. 1013.) Adderall XR® combined immediate release beads with delayed pulsed release beads containing enteric coatings so the children would not be required to take a second dose of Adderall IR® during the school day. (See, e.g., Ex. 1002 at 3:13-28; Ex. 1010 at 2; see also Ex. 1004 at ¶¶32, 37-38.)

Clinicians recognized, however, that a proportion of patients treated with Adderall XR®, especially adolescents and adults, still required additional treatment to extend the daily therapeutic effect. (Ex. 1001 at 3:26-45.) In many cases, clinicians instructed those patients to augment Adderall XR® with a later dose of

Adderall IR®. (Id.) A prior art article by Kratochvil described this same problem and solution. (Ex. 1010 at 2) ("Give . . . Adderall XR early and IR around 6 PM").

D. Amphetamine Formulations with Sustained Release Beads

The prior art disclosed a solution to the Adderall XR®-Adderall IR® dosing regimen: a sustained release system. (Ex. 1004 at ¶¶40-45.) Burnside, issued August 12, 2003, is prior art under 35 U.S.C. § 102(b).[3] (Ex. 1002 at [45].) Burnside teaches immediate release, delayed pulsed release and delayed sustained release beads in its experimental examples. Example 1 of Burnside teaches immediate release beads containing mixed amphetamine salts. (Ex. 1002 at 10:30-57.) Each of Examples 2 and 3 of Burnside teach delayed pulsed release beads containing these same amphetamine salts coated with enteric polymers (i.e., EUDRAGIT® L 30D-55 and EUDRAGIT® 4110D, respectively). (Id. at 10:58-11:57.) And Example 4 of Burnside teaches delayed sustained release beads, building on either Examples 2 or 3 by adding a sustained release coating (i.e., SURELEASE®) over the enteric coating. (Id. at 11:58-12:26; see also id. at Figure 6 (illustrating the sustained release profile); Ex. 1001 at 7:36-40.) Burnside also teaches that "[t]he drug delivery system . . . comprises one or a number; of beads

[3] Burnside is a continuation in-part of and claims priority to U.S. Patent No. 6,322,819 ("the '819 patent"), issued November 27, 2001 (Ex. 1019.)

or beadlets in a dosage form . . . ." (Id. at 6:32-35; Abstract ("The product can be composed of either one or a number of beads in dosage form . . . .") Example 5 of Burnside describes a non-limiting embodiment combining the beads of Example 1 with those of Examples 2 or 3. (Id. at 12:27-48.) Petitioner provides further teachings from Burnside below in Section X.

U.S. Patent Application Publication No. US2004/0059002 by Couch et al. ("Couch") also teaches formulations containing immediate and sustained release beads of mixed amphetamine salts. (Ex. 1023 at ¶¶10, 19-20.)

VII. THE '100 PATENT

A. Summary of the '100 Patent Specification

The '100 patent relates to a multi-dose composition comprising pharmaceutically active amphetamine salts for the treatment of ADHD. (Ex. 1004 ¶50.) The Background of the '100 patent describes Adderall XR® as prior art. According to admitted prior art in the Background of the '100 patent, Adderall XR® was designed to "me[e]t the need for a dosage form, which c[ould] be administered once, in place of the two oral doses which are needed using the conventional drug delivery formulations of the prior art." (Ex. 1001 at 3:27-30.) "However, clinicians have noted that a proportion of patients treated with these formulations require additional treatment with a short-acting stimulant to extend

the daily therapeutic effect." ("Admitted Prior Art").[4] (Id. at 3:31-41.)

The specification of the '100 patent describes the alleged invention as comprising "an immediate release amphetamine component, a delayed pulsed release amphetamine component and a sustained release amphetamine component. . . ." (Id. at 5:20-22.) This composition is allegedly bioequivalent to "ADDERALL XR® followed by an immediate release amphetamine formulation administered 8 hours later[.]" (Id. at 4:9-11.)

The experimental examples of the '100 patent describe various configurations of these three components, typically in the form of beads or beadlets, as well as certain pharmacokinetic studies. Example 1 teaches immediate release beads. (Id. at 18:60-19:22.) Example 3 teaches delayed pulsed release beads. (Id. at 19:62-20:30.) And Example 4, building on Example 2, teaches sustained release beads. (Id. at 20:31-21:38.) The combination of these three beads in a capsule appears in Example 6. (Id. at 22:15-33.) Example 8 is a study in humans comparing the pharmacokinetics of (1) the 37.5 mg capsule of Example 6 with (2) a single 25 mg dose of Adderall XR® followed by a 12.5 mg immediate release dose of Example 1 eight hours later. (Id. at 23:1-26:10.) The

[4] The statement constitutes admitted prior art. See In re Nomiya, 509 F.2d 566, 571 n.5 (C.C.P.A. 1975).

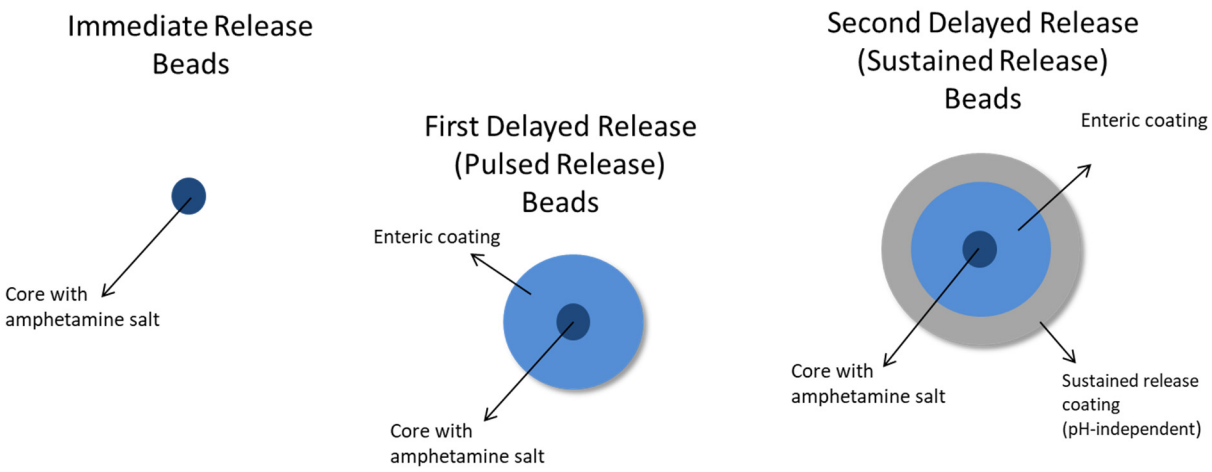
pharmacokinetic data, i.e., AUC, C_{max}, T_{max}, as measured in Example 8, appears at Table 10. (Id. at 25:36-26:6.)

B. Summary of the '100 Patent Claims

Claim 1, the lone independent claim of the '100 patent, recites:

> 1. A pharmaceutical composition comprising: (a) an immediate release bead comprising at least one amphetamine salt; (b) a first delayed release bead comprising at least one amphetamine salt; and (c) a second delayed release bead comprising at least one amphetamine salt; wherein 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; 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, wherein the sustained release coating is pH-independent; and wherein the first delayed release bead and the second delayed release bead comprise an enteric coating.

(Ex. 1001 at 31:59-32:37.) The beads of claim 1 look like this (Ex. 1004 at ¶52.):



Dependent claims 2-31 recite various additional characteristics of the composition, including features of the enteric coating, pharmacokinetic data, use of a protective layer, specific amphetamine salts, lack of food effect and dosage strength. (Ex. 1001 at 32:38-34:27; Ex. 1004 at ¶53.)

C. Summary of the '100 Patent Prosecution History

The '100 patent was filed as application serial no. 11/383,066 ("the '066 application") on May 12, 2006. (Ex. 1005 at 1, 51-58.) The original independent claim of the '066 application recited immediate release, delayed release and sustained release beads. (Id. at 51.)

The Examiner initially rejected all claims as anticipated and obvious based on Burnside. The Examiner explained: "[Burnside] teaches an oral pulsed release formulation comprising a combination of immediate release and delayed release amphetamine beads (abstract)," and cited the experimental examples for the sustained release beads. (Id. at 480-485, 482.) The Examiner asserted that the

claimed physiological effects of the dosage form (T_{max}, C_{max}, and AUC of a 37.5 mg dose) are "merely functional limitations that are the result of the instant compositional components." (Id. at 483.) The Examiner also rejected all claims as obvious in view of Burnside. (Id. at 483-485, 484.)

In response, Applicants argued that "[Burnside] discloses immediate release beads and delayed pulsed release beads, but not sustained release beads." (Id. at 535, 536.) Applicants further argued Burnside teaches use of a delayed pulsed release formulation as opposed to a sustained release formulation. (Id. at 536.) Applicants' characterization, however, was false. The '066 application states that the "sustained release" coating is a polymer or combination of polymers and provides a list of suitable polymers, including SURELEASE®. (Id. at 23.) Example 4 of Burnside discloses a bead coated with amphetamine salts, followed by an enteric coating and then SURELEASE®. (Ex. 1002 at 11:58-12:26; Ex. 1004 at ¶¶46-47.) As mentioned, the assignee on the '100 patent, admitted in federal court that Burnside Figure 6, which provides the release profile for the formulation of Example 4, "shows a sustained enteric release, occurring over the

course of *six* hours."[5] (Shire LLC et al. v. Abhai, LLC, 1:15-cv-13909-WGY (D. Mass. July 21, 2016), D.I. 73 (Ex. 1036 at 12).)

In the second Office Action, the Examiner maintained the same rejections. (Ex. 1005 at 551-557.) In response, Applicants acknowledged Example 4 of Burnside teaches coating the beads of Examples 2 or 3 with SURELEASE®. (Id. at 569-570.) Applicants failed, however, to inform the Examiner that the release profile of Example 4 (shown in Figure 6) was, as Patent Owner later admitted, that of a sustained release bead.

In the third Office Action, the Examiner again maintained the same rejections. (Id. at 587-588.) Applicants asserted that the claimed "second delayed release bead" has an "atypical construction," not taught in Burnside, and amended claim 1 to recite "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. at 645-646.)

Here again, Applicants mischaracterized the teachings of Burnside, stating that the bead of Example 4 did not have a sustained release coating *over* the

[5] Shire was citing to Figure 6 in RE41148, the reissued '100 patent. The Figure is the same in the '100 patent.

enteric coating. Applicants' statement was misleading because Example 4 of Burnside teaches this very construction. That is, Example 4 teaches a core, coated with amphetamine, followed by an enteric coating, and then a sustained release coating. (Id. at 646; Ex. 1002 at 11:58-12:26.)

In the fourth Office Action, in response to Applicants' false representation that Burnside did not teach the second delayed sustained release bead recited by the pending claims, the Examiner withdrew the anticipation rejection and maintained obviousness rejections against some of the claims based on additional art. (Ex. 1005 at 663-670.)

After another rejection and Interview, a Notice of Allowance was mailed with an Examiner's Amendment that included the following additional limitation to claim 1: "wherein the sustained release coating is pH-independent." (Id. at 784-786, 785.) The '100 patent issued on September 30, 2014. (Ex. 1001 at [45].)

VIII. LEVEL OF ORDINARY SKILL IN THE ART

A POSA to whom the patent is addressed has at least a Bachelor of Science Degree in Pharmacy, Chemistry, or Chemical Engineering, or similar field, and experience in the field of pharmaceutics (including pharmaceutical formulation or pharmacokinetics or a similar technical field of study). (Ex. 1004 ¶21.) This person also has access to and may consult with a pharmacologist with experience

in pharmacokinetics and/or an M.D. with experience with ADHD and pharmacological treatments for ADHD. (Id. at ¶21.) Declarations from Dr. Burgess (Ex. 1004), an expert in the field of formulation science and drug delivery, and Dr. Jusko (Ex. 1006), a pharmacokinetics expert, support the Grounds set forth in this Petition.

IX. CLAIM CONSTRUCTION

For purposes of this Petition, each claim term, including the terms "no food effect" and "about,"[6] should be construed consistent with its broadest reasonable interpretation ("BRI") in light of the specification of the '100 patent. See 37 C.F.R. § 42.100(b); Cuozzo Speed Techs., LLC v. Lee, 136 S. Ct. 2131, 2146 (2016). The '100 patent defines "no food effect" as "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," and provides that "'about' can mean a range of up to 20% . . . of a given value." (Ex. 1001 at 11:61-64; 11:65-12:6.) These express statements provide the BRI for the two terms. (Ex. 1004 at ¶¶51, 54-57.)

X. DETAILED EXPLANATION OF GROUNDS

As discussed below, Burnside anticipates claims 1-21 and 31 of the '100

[6] For the purposes of this Petition, no other claim term is expected to require interpretation.

patent. All Challenged Claims are also obvious in view of Burnside alone or Adderall XR® in view of Burnside.

A. Ground 1: Burnside Anticipates Claims 1-21 and 31

Burnside anticipates claims 1-21 and 31 of the '100 patent. Burnside teaches and enables the pharmaceutical composition of claim 1 of the '100 patent. Claim 1 is the sole independent claim and the only subject matter relied upon by the Examiner during prosecution in granting allowance. The remaining claims recite features known in the prior art expressly taught by Burnside.

It bears noting that the Challenged Claims are based on Examples 1-4 of the '100 patent, which are virtually identical to Examples 1-4 in Burnside:

'100 Patent Claims	'100 Patent Examples	Burnside Examples
Immediate Release Bead	Example 1	Example 1
Delayed Pulsed Release Bead[7]	Example 3	Example 2
Delayed Sustained Release Bead	Example 4	Example 4

As Dr. Burgess explains, the only differences between the experimental examples

[7] Example 2 of the '100 patent corresponds to Example 3 of Burnside and reflects another version of the delayed pulsed release bead. (Compare Ex. 1001 at 19:15-51 with Ex. 1002 at 11:25-57.)

of the '100 patent and Burnside are inconsequential and relate to varying concentrations as well as use of an overcoating and talc.[8] (Ex. 1004 at ¶¶59, 87.)

As set forth more fully below, Burnside teaches each of the claimed features in the '100 patent.

1. Independent Claim 1

There can be no dispute that Burnside teaches each of the three beads recited by lone independent claim 1 of the '100 patent. Applicants largely copied Examples 1-4 from Burnside and pasted them into the '100 patent. As shown in the chart below, each and every limitation of claim 1 of the '100 patent is disclosed in Burnside:

Claim	'100 Patent	Burnside
1	A pharmacological composition comprising:	"This invention pertains to a multiple unit dosage form delivery system comprising one or more amphetamine salts . . . ." (Ex. 1002 at 1:9-11.) "[T]he present invention provides an oral multiple unit pulsed dose delivery system for amphetamine salts and mixtures thereof." (Id. at 3:33-35.) "The drug delivery system of the present invention . . . comprises one or a number of

[8] The '100 patent also switches the order of Examples 2 and 3 relative to Burnside. (Compare Ex. 1001 at Examples 2-3 with Ex. 1002 at Examples 2-3.)

Claim	'100 Patent	Burnside
		beads or beadlets in a dosage form . . . ." (Id. at 6:32-35.) "The product can be composed of either one or a number of beads in a dosage form . . . ." (Id. at [57] (Abstract).)
	(a) an immediate release bead comprising at least one amphetamine salt;	"Example 1 Immediate Release Formulation The following formulation was used to layer the drug onto sugar spheres. . . . The suspension of mixed amphetamine salts (MAS) . . . was sprayed onto the seed under suitable conditions . . . ." (Id. at 10:30-57.) "Example 5 A pulsatile delivery system can be achieved by combining the immediate release pellets (Example 1) with delayed release pellets (Example 2 or Example 3)." (Id. at 27-31.)
	(b) a first delayed release bead comprising at least one amphetamine salt; and	"Example 2 [C]oat the mixed amphetamine salt loaded (MASL) pellets from Example 1 with the EUDRAGIT® L 30D-55 . . . coating dispersion. . . . [T]he enteric coating delayed the drug release from the coated pellets . . . ." (Id. at 10:58-11:25.) "Example 3 [C]oat the MASL pellets from Example 1 with the EUDRAGIT® 4110D . . . . coating dispersion. . . . The enteric coating delayed the drug release for several hours from the coated pellets . . . ." (Id. at 11:26-57.) "Example 5 A pulsatile delivery system can be achieved by combining the immediate release pellets

Claim	'100 Patent	Burnside
		(Example 1) with delayed release pellets (Example 2 or Example 3)." (Id. at 27-31.)
	(c) a second delayed release bead comprising at least one amphetamine salt;	"Example 4 [C]oat the enteric coated MASL pellets . . . from Example 2 or coated MASL pellets from Example 3. . . . The coating dispersion was prepared by mixing SURELEASE® (Colorcon) and water . . . . The 8% SURELEASE® coating slightly sustained the drug release from EUDRAGIT® L 30D-55 coated pellets at pH 7.5 buffer, while the SURELEASE® coating delayed the drug release . . . ." (Id. at 11:58-12:13.) "This invention pertains to a multiple unit dosage form delivery system comprising one or more amphetamine salts . . . ." (Ex. 1002 at 1:9-11.) "[T]he present invention provides an oral multiple unit pulsed dose delivery system for amphetamine salts and mixtures thereof." (Id. at 3:33-35.) "The drug delivery system of the present invention . . . comprises one or a number of beads or beadlets in a dosage form . . . ." (Id. at 6:32-35.) "The product can be composed of either one or a number of beads in a dosage form." (Id. at [57] (Abstract).)
	wherein the first delayed release bead provides pulsed release of the at least one amphetamine salt	"The drug release profile of the coated pellets of this example [Example 2] is shown in FIG. **4**." (Id. at 11:21-23.)

Claim	'100 Patent	Burnside
		"The drug release profile of coated pellets of this example [Example 3] is shown in FIG. **5**." (Id. at 11:55-57.) "The present invention provides a composition in which there is immediate release of drug and enteric release of drug wherein the enteric release is a pulsed release and wherein the drug includes one or more amphetamine salts and mixtures thereof." (Id. at 3:63-67.)
	and the second delayed release bead provides sustained release of the at least one amphetamine salt;	"Example 4 [C]oat the enteric coated MASL pellets ... from Example 2 or coated MASL pellets from Example 3... The coating dispersion was prepared by mixing SURELEASE® (Colorcon) and water... . The 8% SURELEASE® coating slightly sustained the drug release from EUDRAGIT® L 30D-55 coated pellets at pH 7.5 buffer, while the SURELEASE® coating delayed the drug release ... The drug release profile of coated pellets from this example [Example 4] is shown in FIG. **6**." (Id. at 11:58-12:26.) "Sustained-release coatings commonly known to one skilled in the art can be used. . . . For example, the following materials can be used . . . SURELEASE® . . . ." (Id. at 9:6-22.)
	wherein the second delayed release bead comprises at least one amphetamine salt layered onto or incorporated into a core;	"Example 1 Immediate Release Formulation The following formulation was used to layer the drug onto sugar spheres . . . . The suspension of mixed amphetamine salts (MAS) . . . was sprayed onto the seed

Claim	'100 Patent	Burnside
		under suitable conditions." (Id. at 10:30-42.)
	a delayed release coating layered onto the amphetamine core;	"Example 2 [C]oat the mixed amphetamine salt loaded (MASL) pellets from Example 1 with the EUDRAGIT® L 30D-55 . . . coating dispersion. . . . The results showed that the enteric coating delayed the drug release from the coated pellets." (Id. at 10:58-11:25.)
	and a sustained release coating layered onto the delayed release coating,	"Example 3 [C]oat the MASL pellets from Example 1 with the EUDRAGIT® 4110D . . . coating dispersion. . . . The enteric coating delayed the drug release for several hours from the coated pellets. . . ." (Id. at 11:26-57.) "Example 4 [C]oat the enteric coated MASL pellets ... from Example 2 or coated MASL pellets from Example 3... The coating dispersion was prepared by mixing SURELEASE® (Colorcon) and water... . The 8% SURELEASE® coating slightly sustained the drug release from EUDRAGIT® L 30D-55 coated pellets at pH 7.5 buffer, while the SURELEASE® coating delayed the drug release ... ." (Id. at 11:58-12:26.)
	wherein the sustained release coating is pH-independent;	"Example 4 [C]oat the enteric coated MASL pellets ... from Example 2 or coated MASL pellets from Example 3... The coating dispersion was prepared by mixing SURELEASE® (Colorcon) and water... . The 8% SURELEASE® **coating** slightly sustained the drug release from EUDRAGIT® L

Claim	'100 Patent	Burnside
		30D-55 coated pellets at pH 7.5 buffer, while the SURELEASE® coating delayed the drug release ... The drug release profile of coated pellets from this example is shown in FIG. 6." (Id. at 11:58-12:26 (emphasis added).)
	and wherein the first delayed release bead and the second delayed release bead comprise an enteric coating.	"Example 2 [C]oat the mixed amphetamine salt loaded (MASL) pellets from Example 1 with the EUDRAGIT® L 30D-55. . . . The results showed that the enteric coating delayed the drug release from the coated pellets." (Id. at 10:58-11:25.) "Example 3 [C]oat the MASL pellets from Example 1 with the EUDRAGIT 4110D . . . coating dispersion. . . . The enteric coating delayed the drug release for several hours from the coated pellets . . . ." (Id. at 11:26-57.) "Example 5 A pulsatile delivery system can be achieved by combining the immediate release pellets (Example 1) with delayed release pellets (Example 2 or Example 3)." (Id. at 27-31.) "Example 4 [C]oat the enteric coated MASL pellets ... from Example 2 or coated MASL pellets from Example 3... The coating dispersion was prepared by mixing SURELEASE® (Colorcon) and water... . The 8% SURELEASE® coating slightly sustained the drug release … ." (Id. at 11:58-12:26.)

As detailed above, the combination of MAS beads in the Examples of Burnside satisfies each and every limitation recited by claim 1 of the '100 patent. (Ex. 1004 at ¶¶60-79.) The beads of Example 1 are the immediate release beads. (Id. at ¶¶62-63.) The beads of Examples 2 or 3 are the "first delayed release beads." (Id.) The beads of Example 4, which coat the delayed pulsed release beads of either Example 2 or 3 with SURELEASE®, are the "second delayed release beads." (Id.) Example 5 combines the beads of Example 1 with those of Examples 2 or 3.

Regarding the claim limitation requiring pulsed release by the first delayed release bead, Figures 4 and 5, which correspond to Examples 2 and 3, demonstrate a pulsed release. (Ex. 1002 at Figs. 4 and 5.) Indeed, Applicants admitted during prosecution that Burnside discloses delayed pulsed release beads. (Ex. 1004 at ¶¶76-77; Ex. 1005 at 569.)

Further, and contrary to statements made by Applicants to the Patent Office, Example 4 teaches the claimed sustained release beads, comprising at least one amphetamine salt on a core, a delayed release (enteric) coating on the amphetamine salt and a sustained release (SURELEASE®) coating *over* the delayed (enteric) release coating. (Ex. 1004 at ¶¶46-49, 68-75.) Regarding the claim limitations "sustained release" and "pH independent," a POSA would know that they are met by SURELEASE®. Burnside expressly states that SURELEASE®

is a sustained release coating, and Example 4 states that it provides sustained drug release. (Ex. 1002 at 9:6-22, 12:8-13.) Figure 6 illustrates the expected sustained release profile of beads described in Example 4. (Ex. 1002 at 6:58-61, 12:24-26; Ex. 1004 at ¶74.) Indeed, the prior art, including the Handbook of Pharmaceutical Excipients, teaches that SURELEASE®, at levels between 3% to 20%, is a sustained release polymer. (Ex. 1028 at 4-8; Ex. 1029 at 4-8.)

Further, SURELEASE® was known as a pH independent coating. (Ex. 1004 at ¶¶72-75.) WO 99/66904 to Patel et al. ("Patel"), for example, teaches that SURELEASE® is a sustained release coating containing ethylcellulose and a plasticizer.[9] (Ex. 1034 at 11:8-9.) Patel further states that this coating "gives the desired pH independent solubility of the active drug." (Id. at 13:12-13.) Other prior art also expressly characterizes ethylcellulose as a pH independent coating agent. (EX1035 at 11:18-25.) Furthermore, and as Dr. Burgess explains, a POSA would understand the 8% coating thickness of SURELEASE® in Example 4 necessarily means SURELEASE® is pH independent. (Ex. 1004 at ¶ ¶73-74; Ex. 1002 at 6:3-7.) Consistent with the above and other prior art, which also expressly reports that SURELEASE® is pH independent (Ex. 1007 at 6), Dr.

[9] Patel's filing date is June 25, 1998, around the same time the '819 patent and Burnside were filed.

Burgess has always regarded this polymer as exhibiting pH independence. (Ex. 1004 at ¶74.)

Burnside also teaches the combination of the beads of Examples 1-4. (Id. at ¶¶50, 64-67; Ex. 1002 at 1:9-11, 3:33-41, 6:32-35.) As such, a POSA would recognize that Burnside's teachings are "arranged or combined in the same way as in the claim." Blue Calypso, LLC v. Groupon, Inc., 815 F.3d 1331, 1341 (Fed. Cir. 2016) (internal citations omitted). As Blue Calypso explained, anticipation does not turn on whether the reference has an express discussion of the actual combination:

> [A] reference need not always include an express discussion of the actual combination to anticipate. Instead, a reference may still anticipate if that reference teaches that the disclosed components or functionalities may be combined and [the reference is enabling].

Blue Calypso, 815 F.3d at 1344 (internal citations omitted). A prior art reference anticipates a claim when it (1) provides a "discussion of combining [the] features disclosed," and (2) presents those features in a "limited number," such that a POSA would "at once envisage" the combination. Id. (quoting Kennametal, Inc. v. Ingersoll Cutting Tool Co., 780 F.3d 1376, 1381 (Fed. Cir. 2015)).

In this case, Burnside teaches combining a limited number of features – immediate release beads, enteric release beads and sustained release beads – in the same way as the Challenged Claims. (Ex. 1004 at ¶¶64-67.) Burnside expressly

states "the drug delivery system of the present invention preferably comprises one or a number of beads or beadlets in a dosage form . . . ." (Ex. 1002 at 6:33-35.) It also states "the present invention provides an oral **multiple unit** pulsed dose delivery system for amphetamine salts." (Id. at 3:33-35; 1:9-11 (emphasis added).) Example 5, which combines the beads of Example 1 with those of either Examples 2 or 3, confirms that Burnside teaches combining the different beads disclosed in the experimental examples. Further, Burnside specification teaches only four different bead configurations: immediate release, delayed pulsed release, sustained release, and delayed release with an immediate release component beads, which provide only eleven possible two, three, and four bead composition combinations combined. (Ex. 1004 at ¶65.) A POSA would thus at once envisage the beads of Burnside's experimental examples as arranged in the claims. (Id. at ¶¶66-67.)

Finally, Burnside indisputably enables the composition of claim 1 of the '100 patent. (Ex. 1004 at ¶¶58, 60, 62, 104-108.) The experimental examples of Burnside provide detailed instructions in this regard. (Id.)

2. Claims 2-4

Claim	'100 Patent	Burnside
2	The pharmaceutical composition of claim 1, wherein the enteric coating is pH dependent.	See claim 1 above. "The enteric coating layer is applied onto the cores… . All commercially available pH-sensitive polymers are included… . Enteric polymers include … EUDRAGIT®

Claim	'100 Patent	Burnside
		L 30D-55, … EUDRAGIT® preparation 4110D… ." (Id. at 8:31-55.)
3	The pharmaceutical composition of claim 1, wherein the first delayed release bead and the second delayed release bead comprise different enteric coatings.	See claim 1 above with respect to Examples 2 and 3. "Example 4 The following formulation was selected to coat the enteric coated MASL pellets. Coated MASL pellets from Example 2 [EUDRAGIT® L 30D-55] **or** coated MASL pellets from Example 3 [EUDRAGIT® 4110D]… ." (Id. at 11:59-62, Example 4 (emphasis added).)
4	The pharmaceutical composition of claim 1, wherein the first delayed release bead and the second delayed release bead comprise the same enteric coatings.	See claim 3 above.

Burnside's experimental examples also teach all limitations recited by dependent claims 2-4. (Ex. 1004 at ¶¶80-85.) A combination of delayed pulsed release beads from Example 2 with the delayed sustained release beads from Example 4 (coated beads of Example 3) would provide different enteric coatings on the first and second delayed release beads, as recited by claim 3. (Ex. 1004 at ¶82-83.) And a combination of delayed pulsed release beads from Example 2 with delayed sustained release beads from Example 4 (coated beads from Example 2) would provide the same enteric coatings, as recited by claim 4. (Id.)

3. Claims 5-12

The pharmacokinetic limitations of claims 5-12 are inherent in the anticipated composition of claim 1. (See Ex. 1006 at ¶¶18, 21-29, 47.) It is well-settled that "[p]roducts of identical chemical composition cannot have mutually exclusive properties." In re Spada, 911 F.2d 705, 709 (Fed. Cir. 1990).

In this case, Examples 1, 3 and 4 of the '100 patent, which appear in near duplicate fashion in Burnside, serve as the basis for the pharmacokinetic parameters recited by claims 5-12. (Ex. 1004 at ¶86-89; Ex. 1006 at ¶¶25-27.) Indeed, the claimed pharmacokinetic data appears in Table 10 of the '100 patent, which is based upon a 37.5 mg capsule combining the beads of Examples 1, 3 and 4, as in Example 6. (Ex. 1006 at ¶28.) Because the patent drafter essentially lifted Examples 1, 3 and 4 of the '100 patent from Examples 1, 2 and 4 of Burnside, the prior art teaches a composition identical to the claimed composition. (Ex. 1004 at ¶87.) Petitioner's experts agree that the claimed pharmacokinetic properties are inherent. (Ex. 1004 at ¶87; Ex. 1006 at ¶¶18, 21-29, 47.)

Further, the wherein clauses of claims 5-12 require a pharmacokinetic profile "after administration of a 37.5 mg dose of the pharmaceutical composition" of claim 1. These claims do not affirmatively require that the pharmaceutical composition actually contain the specific dose, just that the pharmacokinetics are present *when* it is administered. (Ex. 1004 at ¶88.)

4. Claims 13-18 and 31

Claim	'100 Patent	Burnside
13	The pharmaceutical composition of claim 1, wherein the immediate release bead and at least one delayed release bead are present on a single core.	See claim 1 above. "In one embodiment, the immediate release and enteric release portions of the composition are present on the same core." (Ex. 1002 at 3:53-55.)
14	The pharmaceutical composition of claim 1, wherein the immediate release bead and at least one delayed release bead are present on different cores.	See claim 1 above. "In another embodiment, the immediate release and enteric release components are present on different cores." (Id. at 3:56-57.)
15	The pharmaceutical composition of claim 1, wherein the at least one amphetamine salt is coated onto a core.	See claim 1 above. "[A] core seed can be coated with one or more layers of one or more pharmaceutically active amphetamine salts." (Id. at 5:14-16.)
16	The pharmaceutical composition of claim 1, wherein the at least one amphetamine salt is incorporated into a core.	See claim 1 above. "[O]ne or more pharmaceutically active amphetamine salts can be provided within or as part of a core seed… ." (Id. at 5:11-13.)
17	The pharmaceutical composition of claim 1, which further comprises a protective layer over at least one enteric coating.	See claim 1 above. "In accordance with a preferred embodiment of the present invention, there is provided a pharmaceutical composition … that includes … one or more pharmaceutically active amphetamine salts that are covered with an enteric release coating wherein … there is a protective layer over the enteric release coating." (Id. at 3:38-52.)

Claim	'100 Patent	Burnside
18	The pharmaceutical composition of claim 1, which further comprises a protective layer between the amphetamine salt and at least one enteric coating.	See claim 1 above. "In accordance with a preferred embodiment of the present invention, there is provided a pharmaceutical composition … wherein … there is a protective layer between the at least one pharmaceutically active amphetamine salt and the enteric release coating. . . ." (Id. at 3:38-52.)
31	The pharmaceutical composition of claim 1, wherein a protective coating is layered between the delayed release coating and the sustained release coating.	See claims 1 and 17 above. "In accordance with a preferred embodiment of the present invention, there is provided a pharmaceutical composition … wherein … there is a protective layer over the enteric release coating." (Id. at 3:38-52.) "In another embodiment, the pulsed enteric release is accomplished by employing a protective layer over the enteric coating." (Id. at 5:43-45.) "Example 4 [C]oat the enteric coated MASL pellets ... from Example 2 or coated MASL pellets from Example 3... The coating dispersion was prepared by mixing SURELEASE® (Colorcon) and water... . The 8% SURELEASE® coating slightly sustained the drug release from EUDRAGIT® L 30D-55 coated pellets at pH 7.5 buffer ... ." (Id. at 11:58-12:12.)

Burnside expressly teaches the limitations of claims 13-18 and 31, calling for the immediate release and a delayed release bead on the same or different cores

and protective layers between the amphetamine actives and the enteric coating as well as over the enteric coating. A POSA would read the terms "present invention" and "embodiment" in Burnside as connecting these cited teachings with Examples 1-4, which are likewise representative and preferred embodiments of Burnside's alleged "invention." (Ex. 1004 at ¶94.) Because these features are also limited in number, a POSA would also at once envisage the claimed subject matter of the '100 patent. (Id. at ¶90-96.)

5. Claims 19-20

Claim	'100 Patent	Burnside
19	The pharmaceutical composition of claim 1, 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.	See claim 1 above. "Pharmaceutical 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 at 8:2-5.) "[S]aid amphetamine base salts comprise dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate and amphetamine sulfate … ." (Id. at 13:38-41, 14:38-41.)
20	The pharmaceutical composition of claim 19, wherein the at least one amphetamine salt is a mixture of dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine	See claim 19 above.

Claim	'100 Patent	Burnside
	aspartate monohydrate, and amphetamine sulfate.	

Burnside provides a definition of "pharmaceutically acceptable salts" that includes the salts in Adderall® and goes on to list expressly those specific salts, as recited by claims 19 and 20 of the '100 patent. (Ex. 1004 at ¶97-101.) Burnside expressly claims these salts, signaling they are explicitly contemplated as part of its alleged invention and thus applicable to Examples 1-4. (Id.; Ex. 1002 at 13:38-41, 14:38-41.) A POSA would at once envisage them because they are also the only specific salts identified in Burnside. (Ex. 1004 at ¶99.)

6. Claim 21

Similar to the pharmacokinetic limitations of claims 5-12, the lack of "food effect" recited by claim 21 is inherent in the anticipated composition of claim 1. According to the Federal Circuit, "'food effect' is an inherent property of [the drug] itself, present both in controlled release and immediate release formulations of that drug." In re Huai-Hung Kao, 639 F.3d 1057, 1070 (Fed. Cir. 2011).

Here, Burnside teaches each and every limitation of the composition of claim 1, and would therefore necessarily meet the limitation in claim 21 requiring that the "composition does not exhibit a food effect." (Ex. 1004 at ¶¶102-103.) Further, as Dr. Jusko explains, the absence of a food effect is attributable to the

mixed amphetamine actives taught by Burnside and claimed in the '100 patent. (Ex. 1006 at ¶¶18, 30-33, 47; Ex. 1003 at 5.)

B. The Obviousness Grounds - Ground 2 (Burnside alone) and Ground 3 (Adderall XR® in view of Burnside)

Either Burnside alone, or Adderall XR® (based on either the 2004 PDR® or the 2004 Label for Adderall XR®) in combination with Burnside renders claims 1-31 obvious. (See Ex. 1004, at ¶¶109-172.) As discussed above, Burnside Example 5 teaches a dosage form comprising immediate release beads and delayed release beads. Similarly, Adderall XR® teaches a two-bead system with immediate release and delayed pulsed release components for delivering the specific mixed amphetamine salts recited in the claims of the '100 patent. A POSA would have been motivated to modify Example 5 and Adderall XR® by adding the sustained release beads of Burnside Example 4 with a reasonable expectation of success. Well before the filing of the '100 patent, clinicians recognized a need to extend the duration of the two-bead system in Adderall XR® (Ex. 1010 at 2.), a need satisfied by the sustained release beads of Burnside. Accordingly, claims 1-31 are obvious and should be canceled.

Petitioner sets forth below (1) the scope and content of the prior art; (2) a limitation-by-limitation analysis of the prior art disclosures for each claim of the '100 patent; (3) the rationales for combining the teachings of the prior art; (4) the

reasonable expectation(s) of success; and (5) evidence demonstrating a lack of secondary considerations.

1. Scope and Content of the Prior Art

As discussed above in Section VI ("State of the Prior Art as of 2006"), the scope and content of the prior art points directly to the claimed subject matter of the '100 patent.

2. Limitation-by-Limitation Analysis

As discussed in detail below, Burnside alone and/or Adderall XR® in view of Burnside teach each and every limitation of the Challenged Claims.

a. Ground 2: Burnside Alone

i. *Claim 1*

As shown by the claim charts and accompanying discussions in Section X(A)(1) above for Ground 1, Example 5 of Burnside teaches each and every limitation associated with the immediate and first delayed release beads of claim 1 and Example 4 teaches the second delayed release beads of claim 1.

ii. *Claims 2-21 and 31*

Similarly, as shown above in Sections X(A)(2-6), Burnside teaches each and every limitation recited by claims 2-21 and 31. Dependent claims 5-12 and 21 warrant brief additional discussion.

With respect to claims 5-12, the pharmacokinetic limitations recited by those claims are inherent in the obvious composition of claim 1 and are the results a POSA would have expected or predicted as claimed. (See Ex. 1006 at ¶¶18, 21-29, 47.) As the Federal Circuit has held, "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).

For the reasons set forth in Section X(A)(3) above, the obvious pharmaceutical composition of claim 1 would necessarily produce the expected pharmacokinetic characteristics recited by claims 5-12 when administered in a dose of 37.5 mg. Pharmacokinetic data does not rescue Patent Owner's otherwise obvious composition.

For the reasons set forth in Section X(A)(6) above, the absence of a food effect is also inherent in the obvious composition of claim 1. According to the Federal Circuit, a "'food effect' is an inherent property of [the drug] itself." Huai-Hung Kao, 639 F.3d at 1070. Once again, the absence of a food effect, which a POSA would have expected or predicted, is attributable to the mixed amphetamine salts of Burnside, which would necessarily meet claim 21. (Ex. 1006 at ¶¶18, 30-33, 47.)

iii. *Claims 22-30*

The dosage-strength limitations recited by claims 22-30 are result-effective variables subject to routine optimization. As the C.C.P.A. long ago explained, "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." In re Aller, 220 F.2d 454, 456 (C.C.P.A. 1955); see also In re Applied Materials, Inc., 692 F.3d 1289, 1295-96 (Fed. Cir. 2012). That is, optimization of result-effective variables is "within the grasp of one of ordinary skill in the art." Id.

As an initial matter, a POSA would have recognized that dosage strength is a result-effective variable because it balances efficacy with safety. (Ex. 1004 at ¶135; Ex. 1022 at 7-11.) To determine optimal dosage strengths for the mixed amphetamine salts in Burnside, a POSA would have looked to the prior art. (Ex. 1004 at ¶136.) FDA approved Adderall IR® and Adderall XR® in various dosage strengths, including 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg, 20 mg, and 30 mg (Adderall IR®) and 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, and 30 mg (Adderall XR®). (Ex. 1003 at 4; Ex. 1031 at 1; Ex. 1032 at 1.) Adderall XR® was reported to provide linear pharmacokinetics in either children or adult patients at a dosage range of 5 mg to 60 mg. (Ex. 1031 at 2; Ex. 1033 at 11.) Petitioner discusses the motivation to explore a range from 10 mg to 90 mg for augmented Adderall XR® below at Section X(B)(3)(e).

Petitioner is unaware of any criticality or unexpected results attributable to the claimed dosage strengths. (Ex. 1004 at ¶139.) Indeed, many of the dosage strengths for Adderall® overlap with the claimed dosage strengths. (Ex. 1009; Ex. 1004 at ¶¶136, 139.) Applicant thus never claimed the dosage strengths were critical during prosecution. Further, the claimed dosage strengths use the term "about," which covers up to a 20% variance. Such var7iance applied to the claimed dosages provides a dosage range from 10 to 90 mg. (Ex. 1006 at ¶46.)

b. Ground 3: Adderall XR® in view of Burnside

i. *Independent claim 1*

In addition, the commercial product Adderall XR® includes the immediate release and first delayed release beads of claim 1. And Burnside teaches the second delayed release (delayed sustained release) beads.

Claim	'100 Patent	Adderall XR® and Burnside
1	A pharmacological composition comprising:	"[Adderall XR®] is a once daily extended-release, single entity amphetamine product." (Ex. 1003 at 4; Ex. 1031 at 1.)

Claim	'100 Patent	Adderall XR® and Burnside
	(a) an immediate release bead comprising at least one amphetamine salt;	"A single dose of [Adderall XR®] 20 mg capsules provided comparable plasma concentration profiles of both d-amphetamine and l-amphetamine to [Adderall®] (immediate-release) 10 mg bid [bis in die or twice a day] administered 4 hours apart." (Ex. 1003 at 5; Ex. 1031 at 2.) "Based on bioequivalence data, patients taking divided doses of immediate release [Adderall®] , for example twice a day, may be switched to [Adderall®] at the same total daily dose taken once daily." (Ex. 1003 at 6; Ex. 1031 at 9-10.)
	(b) a first delayed release bead comprising at least one amphetamine salt; and	"[Adderall XR®] combines the neutral sulfate salts of dextroamphetamine and amphetamine, with the dextro isomer of amphetamine saccharate and d,l-amphetamine asparate monohydrate." (Ex. 1003 at 4; Ex. 1031 at 1.) "The [Adderall XR®] capsule contains two types of drug-containing beads designed to give a double-pulsed delivery of amphetamines, which prolongs the release of amphetamine from [Adderall XR®] compared to the conventional [Adderall®] (immediate-release) tablet formulation." (Ex. 1003 at 4; Ex. 1031 at 1.) "Based on bioequivalence data, patients taking divided doses of immediate-release [Adderall®], for example twice a day, may be switched to [Adderall XR®] at the same total daily dose taken once daily." (Ex. 1003 at 6; Ex. 1031 at 9-10.)

Claim	'100 Patent	Adderall XR® and Burnside
	(c) a second delayed release bead comprising at least one amphetamine salt;	"Example 4 [C]oat the enteric coated MASL pellets … from Example 2 or coated MASL pellets from Example 3… . The coating dispersion was prepared by mixing SURELEASE® (Colorcon) and water… . The 8% SURELEASE® coating slightly sustained the drug release from EUDRAGIT® L 30D-55 coated pellets at pH 7.5 buffer, while the SURELEASE® coating delayed the drug release… ." (Ex. 1002 at 11:58-12:26.)
	wherein the first delayed release bead provides pulsed release of the at least one amphetamine salt;	"The [Adderall XR®] capsule contains two types of drug-containing beads designed to give a double-pulsed delivery of amphetamines, which prolongs the release of amphetamine from [Adderall XR®] compared to the conventional [Adderall®] (immediate-release) tablet formulation." (Ex. 1003 at 4; Ex. 1031 at 1.)
	and the second delayed release bead provides sustained release of the at least one amphetamine salt;	"Example 4 [C]oat the enteric coated MASL pellets ... from Example 2 or coated MASL pellets from Example 3... The coating dispersion was prepared by mixing SURELEASE® (Colorcon) and water... . The 8% SURELEASE® coating slightly sustained the drug release from EUDRAGIT® L 30D-55 coated pellets at pH 7.5 buffer, while the SURELEASE® coating delayed the drug release ... ." (Ex. 1002 at 11:58-12:26.) "Sustained-release coatings commonly known to one skilled in the art can be used … . For example, the following materials

Claim	'100 Patent	Adderall XR® and Burnside
		can be used … SURELEASE® … ." (Id. at 9:6-22.)
	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,	"Example 1 Immediate Release Formulation The following formulation was used to layer the drug onto sugar spheres… . The suspension of mixed amphetamine salts (MAS) … was sprayed onto the seed under suitable conditions." (Id. at 10:30-42.) "Example 2 [C]oat the mixed amphetamine salt loaded (MASL) pellets from Example 1 with the EUDRAGIT® L 30D-55… . The results showed that the enteric coating delayed the drug release from the coated pellets … ." (Id. at 10:58-11:25.) "Example 3 [C]oat the MASL pellets from Example 1 with the EUDRAGIT® 4110D coating dispersion… . The enteric coating delayed the drug release for several hours from the coated pellets… ." (Id. at 11:26-57.) "Example 4 [C]oat the enteric coated MASL pellets … from Example 2 or coated MASL pellets from Example 3… . The coating dispersion was prepared by mixing SURELEASE® (Colorcon) and water… . The 8% SURELEASE® coating slightly sustained the drug release from EUDRAGIT® L 30D-55 coated pellets at pH 7.5 buffer, while the SURELEASE® coating delayed the drug release… ." (Id. at 11:58-12:26.)

Claim	'100 Patent	Adderall XR® and Burnside
	wherein the sustained release coating is pH-independent; and	"Example 4 [C]oat the enteric coated MASL pellets ... from Example 2 or coated MASL pellets from Example 3... . The coating dispersion was prepared by mixing SURELEASE® (Colorcon) and water. . . . The 8% SURELEASE® **coating** slightly sustained the drug release from EUDRAGIT® L 30D-55 coated pellets at pH 7.5 buffer, while the SURELEASE® coating delayed the drug release... . The drug release profile of the coated pellets from this example is shown in FIG. **6**." (Id. at 11:58-12:26 (emphasis added).)
	wherein the first delayed release bead and the second delayed release bead comprise an enteric coating.	"The inactive ingredients in [Adderall XR®] capsules include … methacrylic acid copolymer …. ." (Ex. 1003 at 4; Ex. 1031 at 1.) "Enteric polymers include . . . co-polymerized methacrylic acid . . . ." (Ex. 1002 at 8:44-51.) "Example 4 [C]oat the enteric coated MASL pellets . . . from Example 2 or coated MASL pellets from Example 3. . . . The coating dispersion was prepared by mixing SURELEASE® (Colorcon) and water. . . . The 8% SURELEASE® coating slightly sustained the drug release from EUDRAGIT® L 30D-55 coated pellets at pH 7.5 buffer, while the SURELEASE® coating delayed the drug release … ." (Id. at 11:58-12:26.)

Regarding the limitations associated with the first delayed release beads of claim 1, Adderall XR® expressly or inherently teaches them all. (Ex. 1004 at ¶¶142-146.) The PDR® and Label for Adderall XR® expressly characterize mixed amphetamine salts as the active agent and state that the product contains two types of beads to provide "double-pulsed delivery" of these amphetamine salts. (Ex. 1003 at 4; Ex. 1031 at 1.) The first pulsed delivery is the result of immediate release beads and the second pulsed delivery is the result of delayed pulsed release beads. Plasma-concentration graphs comparing Adderall IR® and XR® confirm this point. (Ex. 1003 at 6, 7; Ex. 1031 at 2.)

Further, Adderall XR® includes an enteric coating. (Ex. 1004 at ¶144.) A POSA would have known that methacrylic acid copolymer is a well-known pH-dependent enteric coating agent and that such coatings were employed as a matter of course. (Id.) The plasma-concentration graphs comparing Adderall IR® and XR® confirm this point as well. (Ex. 1003 at 5, 7; Ex. 1031 at 2.) Indeed, Burnside states "[e]nteric polymers include . . . co-polmerized methacrylic acid . . . ." (Ex. 1002 at 8:44-49.) The fact that Adderall XR® provides a delayed pulsed release also confirms that methacrylic acid copolymer serves as an enteric coating surrounding the amphetamine sugar spheres in the second set of beads. (Ex. 1004 at ¶144.) Further, the Orange Book lists the '819 patent for Adderall XR®, and all independent claims of the '819 patent require an enteric release coating that

provides for delayed pulsed enteric release. (Ex. 1021; Ex. 1019 at claims.) Likewise, the Summary Basis of Review published on the FDA web site characterizes the delayed release pellets of Adderall XR® as "enteric-coated." (Ex. 1020 at 1.)

Regarding the limitations associated with the second delayed release beads of claim 1, Burnside satisfies them. As set forth more fully in Section X(A)(1) above, Example 4 of Burnside expressly teaches these limitations.

ii. *Dependent claims 2-4*

Claims 3-4 address the nature of the enteric coating and whether it must be the same or different for the first and second delayed release beads. While a matter of design choice, Burnside teaches these aspects. (Id. at ¶126.)

Claim	'100 Patent	Adderall XR® and Burnside
2	The pharmaceutical composition of claim 1, wherein the enteric coating is pH dependent.	See claim 1 above. "The inactive ingredients in [Adderall XR®] capsules include … methacrylic acid copolymer … ." (Ex. 1003 at 4; Ex. 1031 at 1.) Figure 1 (Ex. 1003 at 5, 7; Ex. 1031 at 2.) "The enteric coating layer is applied onto the cores … by conventional coating techniques… . All commercially available pH-sensitive polymers are included… . Enteric polymers include … co-polymerized methacrylic acid EUDRAGIT® L 30D-55, …

Claim	'100 Patent	Adderall XR® and Burnside
		EUDRAGIT® preparation 4110D … ." (Ex. 1002 at 8:31-55.) "Example 4 [C]oat the enteric coated MASL pellets … from Example 2 or coated MASL pellets from Example 3 … . The coating dispersion was prepared by mixing SURELEASE® (Colorcon) and water … ." (Id. at 11:58-66.)
3	The pharmaceutical composition of claim 1, wherein the first delayed release bead and the second delayed release bead comprise different enteric coatings.	See claim 1 above. "Example 2 The following formulation was used to coat the mixed amphetamine salts loaded (MASL) pellets from Example 1 [immediate release] with the EUDRAGIT® L 30D-55 … coating dispersion. " (Ex. 1002 at 10:60-11:24.) "Example 3 The following formulation was used to coat the MASL pellets from Example 1 [immediate release] with the EUDRAGIT® 4110D … coating dispersion." (Id. at 11:26-29.) "Example 4 [C]oat the enteric coated MASL pellets … from Example 2 or coated MASL pellets from Example 3 … . The coating dispersion was prepared by mixing SURELEASE® (Colorcon) and water … ." (Id. at 11:58-66.)
4	The pharmaceutical composition of claim 1, wherein the first delayed release bead and the second	See claim 3, above.

Claim	'100 Patent	Adderall XR® and Burnside
	delayed release bead comprise the same enteric coatings.	

Claims 2-4 are likewise obvious over Adderall XR® in view of Burnside. The enteric polymers taught in Adderall XR® and Burnside are undeniably pH dependent. (Ex. 1004 at ¶125, 148.) Examples 2-4 of Burnside make clear that the enteric polymers employed with the first and second delayed release beads may be the same or different. (Ex. 1004 at ¶126.) This is also an obvious matter of design choice. See In re Harza, 274 F.2d 669, 671 (C.C.P.A. 1960).

iii. *Dependent claims 5-12*

For the reasons set forth at Section X(A)(3) above, the pharmacokinetic limitations of claims 5-12 are inherent in the obvious composition of claim 1 and would have been expected as claimed. (See Ex. 1006 at ¶¶18, 21-29, 47.)

iv. *Dependent claims 13-18 and 31*

Dependent claims 13-18 and 31 specify various configurations of the immediate release and delayed release beads. Burnside expressly discloses each and every one of these configurations.

Claim	'100 Patent	Adderall XR® and Burnside
13	The pharmaceutical composition of claim 1, wherein the immediate	See claim 1 above.

Claim	'100 Patent	Adderall XR® and Burnside
	release bead and at least one delayed release bead are present on a single core.	"In one embodiment, the immediate release and enteric release portions of the composition are present on the same core." (Ex. 1002 at 3:53-55.)
14	The pharmaceutical composition of claim 1, wherein the immediate release bead and at least one delayed release bead are present on different cores.	See claim 1 above. "In another embodiment, the immediate release and enteric release components are present on different cores." (Id. at 3:56-57.)
15	The pharmaceutical composition of claim 1, wherein the at least one amphetamine salt is coated onto a core.	See claim 1 above. "The inactive ingredients in [Adderall XR®] capsules include … sugar spheres … ." (Ex. 1003 at 4; Ex. 1031 at 1.) "[A] core seed can be coated with one or more layers of one or more pharmaceutically active amphetamine salts." (Ex. 1002 at 5:14-16.)
16	The pharmaceutical composition of claim 1, wherein the at least one amphetamine salt is incorporated into a core.	See claim 1 above. "The inactive ingredients in Adderall XR™ capsules include … sugar spheres … ." (Ex. 1003 at 4; Ex. 1031 at 1.) "[O]ne or more pharmaceutically active amphetamine salts can be provided within or as part of a core seed … ." (Ex. 1002 at 5:11-13.)
17	The pharmaceutical composition of claim 1, which further comprises a protective layer over at least one enteric coating.	See claim 1 above. "In accordance with a preferred embodiment of the present invention, there is provided a pharmaceutical composition … that includes … one or more pharmaceutically active amphetamine salts that are covered with an enteric release coating wherein … there is a protective

Claim	'100 Patent	Adderall XR® and Burnside
		layer over the enteric release coating." (Id. at 3:38-52.)
18	The pharmaceutical composition of claim 1, which further comprises a protective layer between the amphetamine salt and at least one enteric coating.	See claim 1 above. "In accordance with a preferred embodiment of the present invention, there is provided a pharmaceutical composition for delivering one or more pharmaceutically active amphetamine salts that includes … one or more pharmaceutically active amphetamine salts that are covered with an enteric release coating wherein … there is a protective layer between the at least one pharmaceutically active amphetamine salt and the enteric release coating … ." (Id. 3:38-52.)
31	The pharmaceutical composition of claim 1, wherein a protective coating is layered between the delayed release coating and the sustained release coating.	See claims 1 and 17 above. "Example 2 [C]oat the mixed amphetamine salt loaded (MASL) pellets from Example 1 with the EUDRAGIT® L 30D-55… . The results showed that the enteric coating delayed the drug release from the coated pellets... ." (Id. at 10:58-11:10.) "A multiple pulsed dose drug delivery system for pharmaceutically active amphetamine salts … wherein … there is a protective layer over the enteric release coating … ." (Id. at [57] (Abstract)) "Example 4 [C]oat the enteric coated MASL pellets … from Example 2 or coated MASL pellets from Example 3 … . The coating dispersion was prepared by mixing

Claim	'100 Patent	Adderall XR® and Burnside
		SURELEASE® (Colorcon) and water … . The 8% SURELEASE® coating slightly sustained the drug release from EUDRAGIT® L 30D-55 coated pellets at pH 7.5 … ." (Id. at 11:58-12:11.)

Burnside expressly teaches the limitations of claims 13-18 and 31. Claims 13 and 14 cover whether the immediate release and a delayed release bead are on the same or different cores. The two options constitute the only design options as the beads will either be on the same or on different cores. (Ex. 1004 at ¶127.) Likewise, claims 15 and 16 cover whether the active is coated onto or incorporated into the core. Again, these are the only two design options for the active in relation to the core. (Ex. 1004 at ¶130.) Claims 17, 18, and 31 merely cover the design options for the compositions to include either a protective coating over an enteric (delayed release) coating; or between an amphetamine layer and an enteric coating.

v. *Dependent claims 19 and 20*

The specific salts recited by claims 19 and 20 are the same salts listed as the active ingredient in Adderall XR®.

Claim	'100 Patent	Adderall XR® and Burnside
19	The pharmaceutical composition of claim 1, wherein the at least one amphetamine salt is selected from the group consisting of	See claim 1 above. "[ADDERALL XR®] combines the neutral sulfate salts of dextroamphetamine and amphetamine, with the dextro isomer of

Claim	'100 Patent	Adderall XR® and Burnside
	dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate, amphetamine sulfate, and mixtures thereof.	amphetamine saccharate and d,l-amphetamine aspartate monohydrate." (Ex. 1003 at 4; Ex. 1031 at 1.)
20	The pharmaceutical composition of claim 19, wherein the at least one amphetamine salt is a mixture of dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate, and amphetamine sulfate.	See claim 19 above.

vi. ***Dependent claim 21***

Claim 21 is an inherent property of the obvious composition of claim 1.

Claim	'100 Patent	Adderall XR® and Burnside
21	The pharmaceutical composition of claim 1, wherein the composition does not exhibit a food effect.	See claim 1 above. "Food does not affect the extent of absorption of [ADDERALL XR®]… . Opening the capsule and sprinkling the contents on applesauce results in comparable absorption to the intact capsule taken in the fasted state. " (Ex. 1003 at 5; Ex. 1031 at 2.)

The PDR® and Label for Adderall XR® confirm that the active amphetamine salts "exhibit no food effect," as recited by claim 21: "Food does not affect the

extent of absorption of [ADDERALL XR®]. . . . Opening the capsule and sprinkling the contents on applesauce results in comparable absorption to the intact capsule taken in the fasted state." (Ex. 1003 at 5; Ex. 1031 at 2; Ex. 1004 at 33.) It is therefore necessarily true that the modified composition containing the immediate release and delayed release beads of Adderall XR® along with the sustained release beads of Burnside exhibits no food effect. (Ex. 1006 at ¶¶18, 30-33, 47.)

vii. *Dependent claims 22-30*

For the same reasons set forth in Section X(B)(2)(a)(iii) above, the dosage strengths recited by claims 22-30 are obvious in view of the prior art based on routine optimization.

3. Rationales for Combination

a. To Add Sustained Release Beads (Grounds 2 and 3)

The prior art motivates a POSA to prolong the therapeutic efficacy provided by the two-bead systems of Example 5 of Burnside and/or Adderall XR®.[10] The Admitted Prior Art and Kratochvil teach that Adderall XR® is inadequate for a

[10] Because Example 5 of Burnside contains the same type of active ingredient and release profile as Adderall XR®, a POSA would view prior art teachings concerning Adderall XR® as applicable to both.

certain proportion of patients, who would benefit from a composition that prolongs the release of the amphetamine actives longer than Adderall XR®. (Ex. 1001 at 3:26-50; Ex. 1010 at 2.) To address this problem, Kratochvil teaches administration of a second Adderall IR® dose at 6:00 p.m. (Ex. 1010 at 2.)

Thus, the prior art motivates a POSA to create a once-daily oral composition to meet the demand for a longer duration of efficacy than provided by Adderall XR®. To do so, a POSA would add the sustained release beads taught by Example 4 of Burnside to Example 5 of Burnside and/or Adderall XR® . (Ex. 1004 at ¶¶39, 157-168.) As Dr. Burgess and Dr. Jusko explain, the sustained release bead taught in Burnside Example 4 is the *only* formulation in the Burnside Examples capable of releasing additional amphetamine in the patient *after* release of amphetamine active in the two-bead systems of Example 5 and Adderall XR®. (Ex. 1004 at ¶160; Ex. 1006 at ¶¶19, 35, 48.) A POSA would understand that such later release of amphetamine is necessary to provide prolonged therapeutic efficacy. (Ex. 1004 at ¶159; Ex. 1006 at ¶¶34-41.) Not only that, but a POSA would also zero in on Burnside Example 4 because it teaches the only bead in all of the prior art designed for prolonged efficacy of amphetamine salts and already characterized with an *in vitro* release profile. (See Ex. 1002 at Fig. 6.) Burnside also expressly motivates a POSA to combine its beads, stating "the present invention comprises one or a number of beads or beadlets in a dosage form . . . ." (Ex. 1002 at 6:32-35.)

Further, Burnside Example 4 teaches the same active ingredients employed in Example 5 and Adderall XR®. (Id. at 12:17-22.) In fact, the Orange Book lists Burnside as a patent covering Adderall XR®, further motivating a POSA to focus on its teachings. (Ex. 1004 at ¶166.)

Couch, provides still further motivation. As Dr. Burgess explains, a POSA would have recognized that Couch includes formulations containing immediate and sustained release beads of mixed amphetamine salts. (Ex. 1004 at ¶161; Ex. 1023 at ¶¶8, 10, 20, claim 11.) One embodiment of the sustained release beads employed SURELEASE® in the same configuration as Burnside Example 4. (Ex. 1004 at ¶162; Ex. 1023 at ¶37.) Further, Couch teaches that sustained release bead systems with an immediate release component can provide an *in vivo* plasma concentration profile "substantially equivalent" to that achieved by Adderall XR®. (Ex. 1004 at ¶161; Ex. 1023 at ¶1, 8, 10, 20, claim 11.)[11] As Dr. Burgess explains, Burnside's *in vitro* amphetamine release profile for the Example 4 beads together

[11] Although Burnside states that sustained release formulations are not suitable for certain actives, it never specifically applies that teaching to mixed amphetamine salts. Further, Couch recommends sustained release beads for amphetamines, and characterizes them as capable of providing an *in vivo* profile "substantially equivalent to" Adderall XR®. (EX1004 at ¶¶157, 163.)

with Couch's teaching that a sustained release bead can mimic the AUC and C_{max} of a pulsatile system (Adderall XR®) teach that the sustained release beads of Example 4 would prolong the efficacy of prior art two-bead systems. (Ex. 1004 at ¶163; Ex. 1023 at ¶3, 8.)

By extension then, addition of a sustained bead to Adderall XR® would mimic Adderall XR® plus a separate immediate release dose late in the day, per Kratovchil. (Id. at ¶163.) Couch, therefore, further motivates a POSA to add the sustained release bead of Burnside Example 4 to the two-bead system of Burnside Example 5 or Adderall XR®.

Additional prior art also supports just such an addition. According to Mehta, a POSA can eliminate multiple dosing and achieve full-day therapeutic efficacy with a once-daily dosage form comprising (i) "uncoated" immediate release beads , (ii) pulsed beads "coated with a pH sensitive coat" and (iii) beads "coated with a pH independent coat" (sustained release beads). (E.g., Ex. 1015 at [57] (Abstract).)

Finally, a POSA would have added a sustained as opposed to pulsed release third bead for additional reasons. As Dr. Burgess explains, use of a pulsed release third bead would mean release of the amphetamine active in the colon. (Ex. 1004 at ¶167; Ex. 1038 at 7-8.) As was known at the time, reduced drug absorption occurs in the colon because the environment is dry and solids are present and there

were difficulties in achieving constant pulsed release at 8 hours. (Ex. 1004 at ¶167; Ex. 1038 at 5; Ex. 1039 at 185-88; Ex. 1040 at 212-213.) Indeed, the '100 patent itself notes that a delayed pulsed formulation with a lag time of about 8 hours would be unsuitable for this reason. (Ex 1001 at 4:3-8).[12]

Regardless, KSR Rationale E - obvious to try - also leads a POSA directly to the Challenged Claims. The prior art identified a design need with respect to Adderall XR®, namely to prolong its therapeutic efficacy. (Ex. 1004 at ¶159.) The only beads containing amphetamine and capable of satisfying this need appear in Burnside, Couch and Midha. (Id. at ¶157.) In light of Couch and as discussed in detail at Section X(C), a POSA could have evaluated this finite universe of beads with a reasonable expectation of success. (Id. at ¶¶161-172.) Further, the prior art makes clear that adding sustained release beads to existing dosage forms produces the predictable result of prolonging therapeutic efficacy . (Id. at ¶165; Ex. 1015 at

[12] Although U.S. Patent No. 6,555,136 to Midha ("Midha") teaches a triple pulsed bead system for treating ADHD, it does not teach away from the claimed subject matter. To teach away, a reference must "criticize, discredit, or otherwise discourage investigation into the invention claimed." Galderma Labs., L.P. v. Tolmar, Inc., 737 F.3d 731, 738 (Fed. Cir. 2013). This, Midha does not do. (Ex. 1004 at ¶167.)

5:1-11; Ex. 1016 at Figure 1; Ex. 1017 at [57] (Abstract); Ex. 1023 at ¶8.) And finally, Couch expressly teaches the predicted *in vivo* behavior of these sustained release beads and Burnside provides *in vitro* data for the Example 4 sustained release beads making them the beads a POSA would zero in on for adding to the two-bead composition of Adderall XR® or Burnside Example 5. (Ex. 1023 at ¶1.)

b. Enteric Coatings (Grounds 2 and 3 - Claims 3 and 4)

In adding the sustained release beads of Burnside Example 4 to Example 5 or the Adderall XR® system, the POSA has two options with respect to the enteric coating - to use either the same or a different enteric coating as the first delayed release bead. (Ex. 1004 at ¶126.) Burnside teaches use of the same or different enteric coatings in designing a multiple-bead system for the prolonged administration of Adderall®. (Id. at ¶¶124, 126; Ex. 1002 at 3:53-57.) A POSA would use the same enteric coating to make the manufacturing process more efficient. (Ex. 1004 at ¶126.) A POSA would use different enteric coatings to influence the pH at which the enteric coating dissolves in the gastrointestinal tract. (Id.)

c. Cores/Protective Layers (Grounds 2 and 3 - Claims 13-18 and 31)

Similar to the enteric coatings, a POSA has two options with respect to the cores – either use the same or a different core for the immediate and delayed release beads. The prior art motivates a POSA to use the same core to eliminate

steps in the manufacturing process, thereby making it more efficient. (Id. at ¶127.) A POSA would use different cores to ensure there exists a clear delineation between the three beads and their respective functions or to provide different dosage strengths for the beads. (Id.)

With respect to the positioning of the amphetamine salt(s), they are either coated onto the core or incorporated into it. The prior art motivates a POSA to coat the amphetamine salt(s) directly onto the core or incorporate them therein because those are the only locations possible. (Ex. 1004 at ¶130.) In addition, the location of the amphetamine salt(s) is largely inconsequential to the overall performance and properties of the composition. (Id.)

With respect to the use of protective layers, such as Opadry®, the prior art motivates a POSA to add them for various reasons. For example, such protective layers can prevent tackiness. (Id. at ¶128.) And they can protect against both physical and chemical activity during passage of the composition through the upper parts of the gastrointestinal tract. (Id.)

A POSA designing a three-bead system for the amphetamine active with one or more protective layers would look to Burnside to determine its location. Burnside teaches that the protective layer can optionally be added to the beads either "between the pharmaceutically active amphetamine salt and the enteric

release coating and/or . . . over the enteric release coating." (Ex. 1002 at [57] (Abstract); Ex. 1004 at ¶129.)

d. Amphetamine Salts (Ground 2 - Claims 19 and 20)

To the extent Patent Owner argues Burnside does not sufficiently teach the mixed amphetamine salts of claims 19 and 20 in Examples 1-4, express disclosure of these salts in the Burnside Background and their express inclusion in Burnside's only independent claims motivates a POSA to use them. (Ex. 1002 at 3:13-18, claims 1and 12; Ex. 1004 at ¶131.) It was, of course, known that these salts were approved by FDA and safe and effective. (Ex. 1004 at ¶131; Ex. 1008.)

e. Dosage Strengths (Grounds 2 and 3 - Claims 22-30)

Because the Admitted Prior Art as well as Kratochvil (Ex. 1010) make clear that augmentation of Adderall XR® with an additional immediate release dose was necessary across certain patient populations, a POSA would have been motivated to explore higher total dosage strengths, including a range up to 90 mg (range of Adderall XR® concentrations providing linear pharmacokinetics plus a single dose of Adderall IR®). (Ex. 1006 at ¶¶20, 42-46, 49.) The motivation to optimize the therapy disclosed in the prior art "flows from the 'normal desire of scientists or artisans to improve upon what is already generally known.'" Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1368 (Fed. Cir. 2007) (quoting In re Peterson, 315 F.3d 1325, 1330 (Fed. Cir. 2003)).

C. Reasonable Expectation of Success (Grounds 2 and 3)

A POSA would have had at least a reasonable expectation of success in making the composition of the claims of the '100 patent. (Ex. 1004 at ¶¶140-141, 169-172.) As the Federal Circuit has repeatedly explained, "[o]bviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." Pfizer, 480 F.3d at 1364.

In this case, Burnside demonstrated that each of the three claimed beads could be successfully made and provided *in vitro* release-profile data for each of the beads. Methods for making each were straightforward and clearly taught in Burnside's experimental examples. (Ex. 1004 at ¶140.) Nor is there anything unusual or challenging about a triple-bead system, as numerous prior art patents demonstrate. (See, e.g., Ex. 1015 at [57] (Abstract); Ex. 1016; Ex. 1017; Ex. 1019; Ex. 1002.)

Furthermore, and as Dr. Jusko explains, a POSA would have also reasonably expected that the addition of the delayed sustained release beads of Example 4 of Burnside would prolong the therapeutic efficacy of the mixed amphetamines salts for hours beyond that of Adderall XR®. (Ex. 1006 at ¶¶19, 34-41, 48.) Specifically, a POSA would have understood that the delayed sustained release beads would release active amphetamine both during and for at least 5 to 6 hours after the release of active amphetamine from the delayed pulsed release beads.

(Ex. 1006 at ¶39.) Based on the "superposition principle" – a basic principle of pharmacokinetics – a POSA would have known that this additional amphetamine would be additive to the amphetamine released by the immediate and delayed pulsed release beads. (Id. at ¶40.) The POSA would therefore have reasonably expected that the addition of the delayed sustained release beads would provide a plasma concentration profile with a higher maximum plasma concentration and sustained higher blood levels for at least 5 or 6 hours after the two-bead system of Adderall XR®. (Id.) This would, in turn, have given the POSA a reasonable expectation that the three-bead system would provide hours of additional therapeutic efficacy as compared to Adderall XR®. (Id. at ¶41.)

The prior art further supports this expectation. First, Mehta teaches that three-bead systems containing immediate, pulsed and sustained release components can provide full-day therapeutic efficacy . (Ex. 1015.) Second, Couch, by extension, teaches a POSA that the right combination of pulsed release components plus sustained release beads may be employed to mimic the plasma concentration profile of Adderall XR® plus a separate immediate release dose late in the day. (Ex. 1004 at ¶163; Ex. 1023 at ¶¶8, 11, 19-21.)

In sum, a POSA would have had a reasonable expectation that addition of the delayed sustained release beads of Example 4 of Burnside to the two-bead

system of Adderall XR® or Example 5 of Burnside would successfully meet the demand for "longer-day" therapeutic relief for ADHD.

D. Alleged Evidence of Secondary Considerations Does Not Support Non-obviousness (Grounds 2 and 3)

Objective evidence of non-obviousness cannot overcome the strong case of obviousness presented here.

Petitioner is not aware of any unexpected results that rebut obviousness. Although the '100 patent specification states that a thicker application of the enteric coating led to a surprising result, the claims do not include any limitations directed to coating thickness and the Burnside specification provides comparable disclosures regarding coating thickness in any event. (Ex. 1002 at 4:44-63.) The '100 patent also states it was unexpected that a sustained release formulation could mimic the bioavailability of Adderall XR® followed by Adderall IR® 8 hours later. (Id. at 4:8-14.) Couch demonstrates this was not unexpected. And the sustained release bead was known in the prior art in any event.

During prosecution of the '100 patent, Applicants argued that it was unexpected that the "atypical" construction of the third bead met the longer-day ADHD treatment requirement when administered with immediate and delayed pulsed release beads. (Ex. 1005 at 646.) However, secondary considerations attributable to features already known in the prior art do not support non-obviousness. See, e.g., Huai-Hung Kao, 693 F.3d at 1068.

Nor can commercial success rescue the '100 patent. To the extent commercial success, if any, exists, it must trace back to the therapeutic activity of the amphetamine actives, which was well-known in the prior art before the '100 patent. (Ex. 1004 at ¶173-180.) Indeed, "if the feature that creates the commercial success was known in the prior art, the success is not pertinent." Ormco Corp. v. Align Tech., Inc., 463 F.3d 1299, 1312 (Fed. Cir. 2006).

XI. THE BOARD SHOULD ADOPT ALL PROPOSED GROUNDS

Petitioner respectfully submits that each of the three grounds is distinct. Ground 1 relies upon a different statute than Grounds 2 and 3. Further, Ground 2 relies exclusively on Burnside for obviousness while Ground 3 relies upon Adderall XR® in combination with Burnside. In particular, Ground 2 relies upon Burnside's experimental examples for each of the three beads recited by independent claim 1 while Ground 3 relies upon Adderall XR® for the immediate release and first delayed release beads. Burnside expressly states that the first delayed bead comprises an enteric coating while the Adderall XR® PDR® and Label do not. Further, use of Adderall XR® as the base reference means motivation to employ the teachings of Burnside for the dependent claims is an additional requirement. On the other hand, Examples 1-5 of Burnside do not expressly mention their association with Adderall XR® for purposes of motivation, though it is a reasonable inference.

XII. SECTION 325(D) DOES NOT APPLY HERE

Finally, while some of the same prior art relied upon in the Grounds was before the Patent Office during prosecution of the '100 patent, this Petition presents new additional prior art and arguments *not* previously presented. The Board should not exercise its discretion under 35 U.S.C. § 325(d) to deny this Petition.

First, the Examiner's amendment leading to allowance reveals that the Examiner was unaware of prior art teaching that SURELEASE® is pH independent. Indeed, the Examiner only allowed the claims of the '100 patent after requiring the following amendment to all claims: "wherein the sustained release coating is pH-independent." The prior art of record did not, however, include Petitioner's Exhibits 1007, 1034 and 1035. These prior art references expressly state SURELEASE® is pH independent and identify SURELEASE® as ethylcellulose, which was known to be pH independent.

S*econd*, the Examiner withdrew the rejections over Burnside in view of statements by Applicants that were false. Patent Owner itself, during district court proceedings, contradicted Applicants' representation that Example 4 of Burnside is not a sustained release formulation. (Supra, at X.) Indeed, Burnside Example 4 expressly teaches a sustained release coating *over* the enteric coating, again contrary to Applicant's representation. (Supra, at VII(C).) Expert testimony by

Dr. Burgess, unavailable during prosecution, also confirms this critical point. (Ex. 1004 at ¶71.)

Third and finally, Petitioner provides an extended and strong case for motivation based upon Burnside, Crouch and Mehta. This stands in sharp contrast to the Examiner's discussion of motivation in the Office Actions rejecting the claims based on Burnside.

XIII. CONCLUSION

Petitioner has established a reasonable likelihood that it will prevail on all Challenged Claims. This Petition should be granted, and claims 1-31 of the '100 patent should be found unpatentable and canceled.

Respectfully submitted,

Dated: December 11, 2017

By: /s/ James T. Evans

Counsel for KVK-Tech, Inc.

CERTIFICATE OF SERVICE

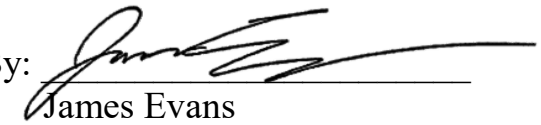
The undersigned hereby certifies that, pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a), a copy of the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 8,846,100, along with all exhibits and other supporting documents, was served on December 8, 2017, by FedEx overnight delivery at the following address:

McDermott Will & Emery LLP
The McDermott Building
500 North Capitol Street, N.W.
Washington, DC 20001

which is the correspondence address of record (37 C.F.R. § 42.105(a)) indicated in the Patent Office's public PAIR system for U.S. Patent No. 8,846,100.

Respectfully submitted,

Date: December 11, 2017

By: 

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