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Paper 8
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC,
Petitioner,

v.

SHIRE LABORATORIES, INC.,[1]
Patent Owner.

Case IPR2016-01033
Patent RE42,096 E

Before TONI R. SCHEINER, LORA M. GREEN, and SHERIDAN K. SNEDDEN, *Administrative Patent Judges*.

SCHEINER, *Administrative Patent Judge*.

DECISION
Institution of *Inter Partes* Review
37 C.F.R. § 42.108

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[1] The Petition, as filed, identifies Shire Laboratories, Inc. as the Patent Owner. According to Patent Owner, "[t]he real parties-in-interest are Shire Laboratories, Inc. and Shire LLC." Paper 6, 1. We note that Patent Owner has filed Papers 5 and 6 as "Shire Laboratories, Inc.," but filed its Preliminary Response as "Shire LLC."

I. INTRODUCTION

Mylan Pharmaceuticals Inc. ("Mylan" or "Petitioner") filed a Petition (Paper 2, "Pet.") on May 12, 2016, requesting an *inter partes* review of claims 1–25 of U.S. Patent No. RE42,096 E (Ex. 1001, "the '096 patent"). Shire LLC ("Shire" or "Patent Owner") filed a Preliminary Response (Paper 7, "Prelim. Resp.") on August 18, 2016. We have jurisdiction under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted "unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition."

Upon consideration of the arguments and evidence presented in the Petition and the Preliminary Response, we are persuaded that Petitioner has established a reasonable likelihood that it would prevail in its challenges to claims 18–25 of the '096 patent, but not claims 1–17. Accordingly, we institute an *inter partes* review of claims 18–25.

A. Related Proceedings

Petitioner informs us that "[t]he '096 patent is currently (or was) the subject, as the parent patent or current reissue form," of the following: *Shire LLC v. Amerigen Pharms. Ltd.*, 14-cv-6095 (D.N.J.); *Shire LLC v. Corepharma LLC*, 14-05694 (D.N.J.); *Shire LLC v. Par Pharm. Inc.*, 15-cv-01454 (D.N.J.); *Shire Labs., Inc. v. Impax Labs, Inc.*, 03-cv-1164 (D. Del.); *Shire LLC v. Sandoz, Inc.*, 07-cv- 197 (D. Colo.); *Shire Labs., Inc. v. Barr Labs., Inc.*, 03-cv-1219,-6632 (SDNY); *Shire LLC v. Watson Pharms., Inc.*,

11-cv-2340 (SDNY); (8) *Shire LLC v. Neos Therapeutics, Inc.*, 13-cv-1452 (N.D. Tx.); *Shire LLC v. Colony, Pharms. Inc.*, 1:07-cv-00718 (D. Md.); *Shire Labs., Inc. v. Andrx Pharms. LLC,* 07-cv-22201 (S.D. Fla.); and *Shire Llc v. Abhai LLC,* 15-cv-13909 (D. Mass.). Pet. 3–4. Patent Owner identifies the same related matters in its Mandatory Notices under 37 C.F.R. § 42.8(a)(2). Paper 6, 1. In addition, Patent Owner represents that "[t]here is no litigation between the parties concerning the '096 patent." Prelim. Resp. 1.

The parties further inform us that the '096 patent is currently the subject of IPR2015-02009. Pet. 4; Paper 6, 1.

B. The Asserted Ground of Unpatentability

Petitioner asserts the challenged claims are unpatentable under 35 U.S.C. § 103 as obvious over Mehta,[2] PDR 1997,[3] Brown,[4] and Amidon.[5] Pet. 8–58.

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[2] U.S. Patent No. 5,837,284, issued November 17, 1998, to Mehta et al. ("Mehta") (Ex. 1005).

[3] PHYSICIANS' DESK REFERENCE 331, 2209–2211 (51st ed. 1997) ("PDR 1997") (Ex. 1009).

[4] Gerald L. Brown et al., *Behavior and Motor Activity Response in Hyperactive Children and Plasma Amphetamine Levels Following a Sustained Release Preparation*, 19 JOURNAL OF THE AMERICAN ACADEMY OF CHILD PSYCHIATRY 225–239 (1980) ("Brown") (Ex. 1011).

[5] U.S. Patent 5,229,131, issued July 20, 1993, to Amidon et al. ("Amidon") (Ex. 1004).

Petitioner supports its challenges with the Declaration of David E. Auslander, Ph.D., executed May 10, 2016 (Ex. 1002, "Auslander Declaration"). Patent Owner supports its position with the Declaration of Bernhardt L. Trout, Ph.D., executed August 17, 2016 (Ex. 2001, "Trout Declaration").

C. The '096 Patent (Ex. 1001)

The '096 patent, titled "ORAL PULSED DOSE DRUG DELIVERY SYSTEM," is a reissue of U.S. Patent 6,322,819,[6] and "is listed in the FDA's 'Orange Book' of approved drug products for Adderall XR®, which is indicated for Attention Deficit Hyperactivity Disorder (ADHD)." Prelim. Resp. 1 (citing Ex. 2001 ¶ 28; Ex. 2004). Adderall® (also known as Adderall IR®) is an immediate release dosage form containing a mixture of four amphetamine sulfate salts. Adderall XR® contains the same mixture of amphetamine salts, but "uses 'two types of drug-containing beads designed to give a double-pulsed delivery of amphetamines.'" Ex. 1001, 3:5–6; Ex. 2001, 11–12 (citing Ex. 2003 (Orange Book); Ex. 2004, 1; Ex. 2013, 4, 14; Ex. 2019, 12).

The '096 patent teaches that ADHD in children conventionally is treated by administering two separate doses of medication, "one in the morning, and one approximately 4–6 hours later, commonly away from

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[6] U.S. Patent No. 6,322,819, issued November 7, 2001 to Burnside et al. ("the '819 patent") (Ex. 2030).

home under other than parental supervision." Ex. 1001, 3:20–13. Administering two separate doses, however, "is time consuming, inconvenient, and may be problematic for those children having difficulties in swallowing tablet formulations." *Id.* at 3:14–17.

The '096 patent, thus, discloses a pharmaceutical composition comprising "an oral multiple pulsed dose delivery system for amphetamine salts and mixtures thereof" (*id.* at 3:22–24), "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 3:53–57). In other words, "[t]he immediate release component releases the pharmaceutical agent in a pulsed dose upon oral administration of the delivery system" (*id.* at 3:58–60), while "[t]he enteric release coating layer retards or delays the release of the pharmaceutical active or drug for a specified time period ("lag time") until a predetermined time, at which time the release of the drug is rapid and complete" (*id.* at 3:61–64).

According to the '096 patent, "overcoming two conflicting hurdles for pulsatile formulation development, i.e., lag time and rapid release" was particularly challenging (*id.* at 2:5–8), but it was "[s]urprisingly . . . found that using a thicker [enteric] coating on the formulation allowed for the second pulsed dose to be released only and completely at the appropriate time in the desired predetermined area of . . . the intestine" (*id.* at 4:31–35). In this regard, the '096 patent teaches that the enteric coating may comprise

pH-dependent polymers, which will not dissolve "in the acidic stomach environment of approximately below pH 4.5, but [are] not limited to this value." *Id.* at 8:12–19. In addition, the specification teaches "[i]n a preferred embodiment, the lag time period is only time-dependent, i.e., pH independent" and "[t]he lag time is preferably within 4 to 6 hours after oral administration of the delivery system." *Id.* at 3:61–4:8.

> In accordance with a preferred embodiment . . . there is provided a pharmaceutical composition for delivering one or more pharmaceutically active amphetamine salts that includes:
>
> (a) one or more pharmaceutically active amphetamine salts that are covered with an immediate release coating, and
>
> (b) one or more pharmaceutically active amphetamine salts that are covered with an enteric release coating wherein (1) the enteric release coating has a defined minimum thickness and/or (2) there is a protective layer between the at least one pharmaceutically active amphetamine salt and the enteric release coating and/or (3) there is a protective layer over the enteric release coating.

Id. at 3:28–42.

According to the '096 patent, plasma levels of the pharmaceutically active amphetamine salts "will reach a peak fairly rapidly after about 2 hours, and after about 4 hours a second pulse dose is released, wherein a second fairly rapid additive increase of plasma drug levels occurs which slowly decreases over the course of the next 12 hours." *Id.* at 10:4–9. Thus, "the multiple dosage form of the . . . invention can deliver rapid and complete dosages of pharmaceutically active amphetamine salts to achieve

the desired levels of the drug in a recipient over the course of about 8 hours with a single oral administration." *Id.* at 9:66–10:3.

Finally, the '096 patent teaches that

> 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; methylphenidate, all chemical and chiral derivatives and salts thereof; phenylpropanolamine and its salts; and all other compounds indicated for the treatment of attention deficit hyperactivity disorder (ADHD).

Id. at 7:50–57.

D. Illustrative Claims

Petitioner challenges claims 1–25 of the '096 patent, of which claims 1, 2, 5, 8, 11, 13, and 18 are independent claims. Claims 1 and 18, reproduced below, are illustrative.

> 1. A pharmaceutical composition for delivery of one or more pharmaceutically active amphetamine salts, comprising:
>
> (a) one or more pharmaceutically active amphetamine salts covered with an immediate release coating;
>
> (b) one or more pharmaceutically active amphetamine salts that are covered with an enteric release coating that provides for delayed pulsed enteric release,
>
> wherein said enteric release coating releases essentially all of said one or more pharmaceutically active amphetamine salts coated with said enteric coating within about 60 minutes after initiation of said delayed pulsed enteric release;
>
> wherein the pharmaceutically active amphetamine salts in (a) and (b) comprise mixed amphetamine salts.

Ex. 1001, 12:53–67.

> 18. A pharmaceutical composition for delivery of one or more pharmaceutically active amphetamine salts comprising:
>
> (a) one or more pharmaceutically active amphetamine salts covered with an immediate release coating;
>
> (b) one or more pharmaceutically active amphetamine salts that are covered with an enteric release coating that provides for delayed pulsed enteric release, wherein said enteric release coating releases said one or more pharmaceutically active amphetamine salts coated with said enteric coating within about 60 minutes after initiation of said delayed pulsed enteric release; and
>
> (c) a protective layer between the at least one pharmaceutically active amphetamine salt and the enteric release coating.

Ex. 1001, 14:63–15:11.

II. ANALYSIS

A. Claim Construction

In an *inter partes* review, claim terms in an unexpired patent are given their broadest reasonable interpretation in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b). Under this standard, we presume that a claim term carries its "ordinary and customary meaning," which "is the meaning the term would have to a person of ordinary skill in the art in question" at the time of the invention. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). *See also Trivascular, Inc. v. Samuels*, 812 F.3d 1056, 1062 (Fed. Cir. 2016) ("Under a broadest reasonable interpretation, words of the claim must be given their plain meaning, unless

such meaning is inconsistent with the specification and prosecution history."). Any special definition for a claim term must be set forth in the specification with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994). Finally, only terms which are in controversy need to be construed, and then only to the extent necessary to resolve the controversy. *Vivid Techs., Inc. v. Am. Sci. & Eng'g. Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999).

For purposes of this Decision, and on this record, only the following terms require explicit construction.[7]

1. "pharmaceutically active amphetamine salts"

The term "pharmaceutically active amphetamine salts" is explicitly defined in the '096 patent as follows:

> Pharmaceutical[ly] active amphetamine salts contemplated to be within the scope of the present invention include amphetamine base, all chemical and chiral derivatives and salts thereof; methylphenidate, all chemical and chiral derivatives and salts thereof; phenylpropanolamine and its salts; and all other compounds indicated for the treatment of attention deficit hyperactivity disorder (ADHD).

Ex. 1001, 7:50–57.

[7] We note that there is considerable discussion on this record concerning the broadest reasonable interpretation of the claim term "*mixed amphetamine salts*" (appearing in independent claims 1 and 8). *See* Pet. 7; Prelim. Resp. 13–18; Ex. 2001 ¶¶ 37–55. However, we determine it is not necessary to construe this term for purposes of this decision.

Petitioner contends that "'[p]harmaceutically active amphetamine salts' includes non-salts, such as 'amphetamine base' and 'methylphenidate,' as well as salts of amphetamine base and methylphenidate." Pet. 7.

Patent Owner contends that the definition of "pharmaceutically active amphetamine salts" in the '096 patent is a "special definition" and agrees that the term includes amphetamine (α-methylphenethylamine), methylphenidate, and chiral derivatives (enantiomers) and salts thereof. Prelim. Resp. 13 (citing Pet. 7; Ex. 1002 ¶ 33; Ex. 2001 ¶ 33–36).

Given the specification's explicit definition, we agree with the parties that the term "pharmaceutically active amphetamine salts" includes non-salts, such as "amphetamine base" and "methylphenidate," as well as salts of amphetamine base and methylphenidate. *See* Ex. 1001, 70:50–57: Pet. 7; Prelim. Resp. 12–13.

2. "enteric release coating"

Petitioner and Patent Owner agree that the claim term "'[e]nteric-release coating' refers to a coating that will delay release of a drug until the drug has passed through the stomach and reached the intestines.'" Pet. 7; *see* Prelim. Resp. 18 (citing Pet. 7; Ex. 2001 ¶¶ 56–57; Ex. 1022, 14–15).

We see nothing in the specification or prosecution history of the '096 patent inconsistent with this joint definition, and determine, for purposes of this proceeding, that the broadest reasonable interpretation of "enteric release coating" is a coating that will delay release of a drug until the drug has passed through the stomach and reached the intestines.

3. "essentially all"

The term "essentially all" is not defined in the '096 patent. Petitioner contends that the claim term "essentially all" means "less than 100%, and not less than 80%." Pet. 7.

Patent Owner contends that "[t]he plain meaning of 'essentially all' includes an amount less than strictly 'all.'" Prelim. Resp. 19. According to Patent Owner, "[a] 'complete' release includes leeway, which typically is at least (not less than) about 80% of a drug dose, *e.g.*, as measured in dissolution testing." *Id.* at 19–20 (citing Ex. 2024, 6, 8, 12 (discussing testing "until either 80% of the drug from the drug product is released or an asymptote is reached")).

Petitioner's and Patent Owner's constructions are essentially the same, and at this stage of the proceeding, we see nothing in the specification or prosecution history of the '096 patent inconsistent with this construction, and are persuaded, for purposes of this decision, that one of ordinary skill in the art would understand "essentially all" to mean "less than 100%, and not less than 80%."

B. Asserted Obviousness of Claims 1–25

Petitioner contends that the subject matter of claims 1–25 would have been obvious over the combined teachings of Mehta, PDR 1997, Brown, and Amidon. Pet. 14–57. Patent Owner disagrees. Prelim. Resp. 34–57. We begin our discussion with the teachings of the prior art.

1. Mehta (Ex. 1005)

Mehta discloses that methylphenidate hydrochloride, "available commercially as, e.g., Ritalin®," is commonly used to treat the symptoms of attention deficit disorder (ADD) and ADHD in children. Ex. 1005, 1:35–42.

Mehta teaches that methylphenidate exists as four separate optical isomers—l-threo, d-threo, l-erythro, and d-erythro—and that "the threo pair of enantiomers of methylphenidate hydrochloride [the dl-threo racemate] is generally administered for the treatment of ADD and ADHD." *Id.* at 1:48–65, 2:5–7. Mehta teaches that the dl-threo racemate "is a mild central nervous system stimulant with pharmacological activity qualitatively similar to that of amphetamines" (*id.* at 2:14–16), and "is a Schedule II controlled substance [that] produces a euphoric effect when administered through . . . ingestion, and thus carries a high potential for abuse." *Id.* at 2:19–22.[8]

Further according to Mehta:

> An additional problem is that children being treated with dl-threo methylphenidate must generally take one or more doses during the day. This creates a problem for school administrators who must store a controlled substance on school premises, with the associated risk that it may be stolen for illicit use. Furthermore, children may be traumatized by ridicule from peers when they must take medication at school.

Id. at 2:34–41.

[8] Mehta also notes that the dl-threo racemate of methylphenidate is associated with "[u]ndesirable side effects . . . includ[ing] anorexia, weight loss, insomnia, dizziness and dysphoria." Ex. 1005, 2:16–18.

Mehta notes that

> Sustained release formulations of dl-threo methylphenidate have been developed, which provide for slow release of the drug over the course of the day. However, it has been observed that peak plasma concentrations of the drug are lower when sustained release formulations are used. In some studies, sustained release formulations of methylphenidate have been shown to have lower efficacy than conventional dosage forms.

Id. at 2:42–49.

In order to "eliminate the risk of theft or loss of the second dose, while minimizing undesirable side effects and maximizing ease of administration" (*id.* at 2:56–58), Mehta proposes "administer[ing] only the active d-threo form of the drug" (*id.* at 2:29–32), in "a dosage form which provides, in one administration, an initial release followed, at a predictable delay, by a second release, of maximally effective methylphenidate" (*id.* at 2:53–56). Though Mehta emphasizes the advantages of administering a composition comprising only the d-threo isomer of methylphenidate hydrochloride, the administration of the dl-threo racemate is also disclosed. *See e.g.*, *id.* at 15:5–10, 16:10–11.

Mehta teaches that "[t]he release of the first dose preferably occurs substantially immediately; for example, within about 30 minutes following administration." *Id.* at 5:31–33. Then, "[f]ollowing a period of little or substantially no drug release, the second dose is released." *Id.* at 5: 33–35. The period of delay between the first and second doses is "from about 2 hours to about 7 hours following ingestion before release of the second

dose." *Id.* at 3:18–19. According to Mehta, "the two releases can be referred to as 'pulses', and such a release profile can be referred to as 'pulsatile'." *Id.* at 5:35–36. Moreover, Mehta distinguishes between "sustained delivery . . . i.e., for the relatively constant administration of a drug," and "pulsatile release of the drug, a very distinct phenomenon." *Id.* at 7:53–60.

Mehta further specifies that:

> "Immediate release" . . . means release within about a half hour following ingestion, preferably about 15 minutes, and more preferably within about 5 minutes following ingestion. "Delayed release" . . . refers to a drug release profile which includes a period during which no more than about 10 percent of the drug in a particular dosage form is released, followed by a period of from about 0.5 hour to about 2.5 hours, preferably about 1.5 hours, more preferably about 1 hour, in which no less than about 70 percent, preferably no less than about 80 percent, and more preferably no less than about 90 percent, of the drug is released.

Id. at 6:5–16.

Mehta discloses preparation of layered pellets containing d-threo-methylphenidate (d-MPD) cores, coated with a sealant comprising hydroxypropyl methylcellulose, and further coated with varying amounts and ratios of ammoniomethacrylate polymers (Eudragit® RS30D and Eudragit® RL30D) in Examples 1–3, or with Eudragit® NE30D in Example 4. Ex. 1005, 12:50–14:10. The results of the dissolution measurements are presented in Table 1, reproduced below.

TABLE 1

RELEASE TIMES

Trial No.	% coat	Ratio	Delay	Talc, %	Cure time	Time for 85% release
1	40	90:10	none	20.0	24 hrs	1.0
2	30	95:5	4.0	20.0	"	8.0
3	30	95:5	4.0	20.0	"	8.0
4	30	93:7	1.0	20.0	"	3.0
5	40	93:7	1.0	20.0	"	4.0
6	30	93.5:6.5	2.0	20.0	"	5.0
7	40	"	2.0	20.0	"	5.0
8	30	94.5:5.5	2.0	20.0	"	8.0
9	40	"	1.0	20.0	"	5.0
10	30	94:6	2.0	20.0	"	5.0
11	40	"	2.0	20.0	"	5.0
12	30	95:5	2.0	40.0	"	5.0
13	40	"	3.0	40.0	"	8.0
14	30	96:4	4.0	40.0	"	10.0
15	40	"	5.0	40.0	"	10.0
16	30	"	4.0	40.0	7 days	10.0
17	20	95:5	2.0	40.0	"	5.0
18	30	"	3.0	40.0	"	6.0
19	30	"	3.0	40.0	"	6.0
20	30	"	2.0	40.0	"	6.0
21	40	"	3.0	40.0	"	8.0

Ex. 1005, 14:21–45. Table 1 presents results of dissolution measurements for the various types of layered and coated pellets produced in Mehta's Examples 1–3. Trial 1 is the pellet of Example 4—in which "no delay was observed; substantially all of the drug was released within approximately one hour." *Id.* at 14:8–10. Trials 2–21 are delayed release formulations. According to Mehta, "[t]he results indicate that the amount of drug released is influenced by: amount of coating, ratio of the two polymers, amount of talc, and curing time." *Id.* at 13:58–60.

Finally, Mehta teaches that particles (pellets) providing substantially immediate release and particles providing delayed release can be combined in a capsule, or the two groups of particles can be compressed into a tablet.

Id. at 11:55–60. Alternatively, Mehta discloses a layered dosage form comprising "a single group of particles providing both a substantially immediate dose of a methylphenidate drug, and a delayed dose." *Id.* at 11:66–12:10, 15:57–16:9.

2. PDR 1997 (Ex. 1009)

PDR 1997 discloses Adderall® tablets containing, in combination, the neutral sulfate salts of dextroamphetamine and amphetamine, as well as the dextro isomer of amphetamine saccharate and d,l-amphetamine aspartate. The recommended dosage and administration for treatment of ADHD in school age children is a first dose on awakening, with one or two additional doses given at intervals of 4 to 6 hours. Adderall tablets carry a black box label warning of the potential for abuse of the drug. Ex. 1009, 2209–2210.

3. Brown (Ex. 1011)

Brown describes the results of a study "undertaken to review pharmacokinetic differences between tablets and sustained-release *d*-amphetamine following single-dose administration" to hyperactive children. Ex. 1011, 226. According to Brown, sustained-release *d*-amphetamine, "like earlier single-dose amphetamine studies in hyperactive children, shows significant behavior and motor activity responses to the medication only during the absorption phase, and these responses are not correlated with specific plasma levels of *d*-amphetamine." *Id.* at 237. Brown further explains, compared to immediate-release tablets, "the peak plasma level occurs later and lasts longer with sustained-release

(up to h 8), though this later occurrence and more plateau-like peak plasma level is not accompanied by a longer period of significant response to the medication (in fact, the significant response appears to be shorter)." *Id.* at 234. That is, "there is no evidence that a prolonged clinical response results from the use of the sustained-release preparation." *Id.* at 237.

4. *Amidon (Ex. 1004)*

Amidon discloses a drug delivery system "which delivers pulsed doses at predetermined time intervals to achieve a bioavailability which is equivalent to immediate release dosage forms administered in divided doses." Ex. 1004, 1:15–20. According to Amidon:

> The drug delivery system, or dosage form . . . has one or more . . . individual drug-containing units (also referred to herein as "subunits") in a unitary drug depot which dissolve at different sites and/or times in the gastrointestinal tract to release "pulse doses." The drug delivery system . . . is an extended interval dosage form as compared to a conventional sustained release dosage form which provides a slow, steady release of drug over a long period of time. The term pulse dose is used herein to describe the rapid delivery of a dose of drug (F_1, F_2, . . . , F_n) at specific respective times (T_1, T_2, . . . , T_n) into the portal system which is analogous to the rate of release from an immediate release dosage form administered according to an appropriate dosing schedule.

Id. at 6:59–7:6.

Further according to Amidon:

> This drug delivery system has significant advantages for the oral administration of first-pass metabolized drugs which exhibit a non-linear relationship between input rate of the drug

> into the portal system and bioavailability. By devising a drug dosage delivery form which will release pulsed doses at rates comparable to immediate release forms, bioavailability will not be compromised by a decreased release rate as has been observed in conventional sustained release dosage forms for these drugs (e.g., INDERAL-LA).

Id. at 7:7–16.

Amidon teaches that means of controlling dissolution include "(1) pH-sensitive enteric coatings which are eroded in response to the pH of the aqueous environment in the gastrointestinal tract and (2) permeability-controlled systems which are subject to disruption in response to absorption of water from the environment which creates a pressure as the core contents expand." *Id.* at 7: 19–25. "Variation of process variables and coating and core compositions . . . enables precise tailoring of the dissolution, or pulse, time of the individual unit cores . . . [which] are combined into a unitary depot which may be single tablet or a gelatin capsule or any other form known in the art. *Id.* at 7:25–31.

Amidon provides an extensive list of formulation and process variables "which must be taken into consideration in the successful design of a permeability-controlled drug delivery system." *Id.* at 11:31–33; *see id.* at 11:35–12:10. For example, formulation variables include "the choice of polymer and plasticizer as well as their initial and final concentration in the polymer coat" and representative polymers include cellulose acetate, ethyl acetate latexes, ethyl cellulose and . . . Eudragit RS and Eudragit E 30 D." *Id.* at 11:60–62. "[P]rocess variables for the coating include spray rate,

spray distance, atomization pressure, drying temperature and rate, and pan rotation speed." *Id.* at 12:6–8. Amidon further proposes a theoretical model for permeability-controlled embodiments which incorporates variables such as film thickness (*see id.* at 11:35–12:10, 19:30–22:22; *see also id.* at 20:27).

Amidon exemplifies a polymer coated dosage form comprising a tablet core containing propranolol HCl and citric acid. *Id.* at 22:26–62. In vitro and in vivo "dissolution testing was performed to demonstrate that the coating would withstand transit through the acidic pH environment of the stomach." *Id.* at 22:66–68.

Finally, according to Amidon, although the examples involve propranolol, "the principles of the invention are applicable to any other drug" and the disclosed formulation and process variables "will enable one of ordinary skill in the art to fabricate a pulsatile drug delivery system for any given drug and dosing schedule or combination of drugs and dosing schedules." *Id.* at 25:6–13.

5. Analysis

Claims 1, 3, 4, 6, and 7

Petitioner contends essentially that the subject matter of independent claim 1—a dosage form that delivers an immediate dose of mixed amphetamine salts, followed by a delayed pulsed enteric release of essentially all of a second dose of mixed amphetamine salts within about sixty minutes of the enteric release—would have been obvious over the combined teachings of Mehta, PDR 1997, Brown, and Amidon. Pet. 14–23.

Specifically, Petitioner cites Mehta as disclosing "methylphenidate, 'a mild central nervous system stimulant with **pharmacological activity qualitatively similar to that of amphetamines,**'" used to treat ADHD, in a dosage form containing an immediate dose and a delayed second dose which "provides for reduced abuse potential, improved convenience of administration, and better patient compliance." Pet. 9 (citing Ex. 1005, 1:26–46, 2:5–16); *see also id.* at 20 (citing Ex. 1002 (Auslander Declaration) ¶ 103; Ex. 1005, 1:26–29).

Petitioner notes that Adderall®, containing "mixed amphetamine salts" in an instant release dosage form, also "was a known pharmaceutical composition used for the treatment of ADHD," and was "administered in a twice daily dose, with a starting dose of 5 mg followed by a second dose that is administered 4 to 6 hours after the first." Pet. 18 (citing Ex. 1001, 3:5–7; Ex. 1002 ¶¶ 96–97; Ex. 1009, 2209-2210).

Petitioner further cites Brown's study of the pharmacokinetics of single-dose administration of sustained-release *d*-amphetamine capsules in hyperactive children. Pet. 13. Petitioner notes in particular, Brown's observation that "significant behavior and motor activity responses to the medication [occur] only during the absorption phase, and these responses are not correlated with specific plasma levels of *d*-amphetamine." *Id.* (citing Ex. 1011, 237). Moreover, Petitioner notes that Brown teaches that "[c]ompared to the immediate-release tablet, the peak plasma level of the sustained release dosage form occurs later and lasts longer, though this later

occurrence and more plateau-like peak plasma level is not accompanied by a longer period of significant response to the medication." *Id.* at 18 (citing Ex. 1011, 234). According to Petitioner's declarant, Dr. Auslander,

> [p]ut another way, the data in Brown would have indicated to a POSA that *sustained-release d*-amphetamine would not have led to a prolonged clinical response, *i.e*. that making a sustained release dosage form would not have led to longer period of significant response to the medication. Therefore, the POSA would have had to look for an alternative solution if they were seeking to develop a once-a-day Adderall® formulation (and would not have looked to available sustained release formulations).

Ex. 1002 ¶ 99.

Petitioner contends, therefore, that a person of ordinary skill in the art, "seeking to develop a once-a-day Adderall® formulation . . . would have been motivated to look at a **pulsed** delivery because such a formulation would have had the same release profile as taking Adderall® immediate-release formulation two times a day." Pet. 18–19 (citing Ex. 1002 ¶ 100). Essentially, Petitioner contends that one of ordinary skill in the art would have "look[ed] to other art in the field of attention deficit disorders to find an approach that provided for an immediate dosage and a delayed second dosage, whereby, the second dosage is released in a quick manner (*i.e*., pulsed)." *Id*. at 19 (citing Ex. 1002 ¶ 101).

Petitioner contends that Mehta "teaches delivering a dosage form containing two groups of particles, each containing methylphenidate for the treatment of ADHD." *Id.* at 22 (citing Ex. 1002 ¶ 108; Ex. 1005, 3:3-7).

According to Petitioner, Mehta's dosage form provides an initial immediate release of methylphenidate and a "second, delayed release, [which] is a pulsed release" because "a period during which no more than about 10 percent of the drug in a particular dosage form is released, [is] followed by a period of from about 0.5 hour to about 2.5 hours, preferably about 1.5 hours, **more preferably about 1 hour, in which no less than about 70 percent, preferably no less than about 80 percent, and more preferably no less than about 90 percent, of the drug is released**." *Id.* at 22-23 (citing Ex. 1005, 6:5–8, 10–17; Ex. 1002 ¶¶ 108, 109). Moreover, Petitioner contends that Mehta's teachings, although directed to methylphenidate rather than amphetamines, would have been relevant to one of ordinary skill in the art because Mehta teaches that methylphenidate is "a mild central nervous system stimulant with pharmacological activity qualitatively similar to that of amphetamines." *Id.* (citing Ex. 1005, 2:5–16).

Petitioner further contends that Amidon discloses detailed formulation and process parameters for producing "pH independent enteric 'permeability controlled systems' that provide pulsed dosages that release '*essentially all*' of [an] active agent in 20–40 minutes." *Id.* at 20 (citing Ex. 1004, 11:3–34; Ex. 1002 ¶ 5). In support of this assertion, Petitioner points to an *in vivo* trial of a dosage form containing propranolol and citric acid in four dogs, showing that "[t]he disintegration dissolution [time] (DDT) was ~17 minutes in three of the dogs and about 50 minutes in the fourth." *Id.* at 20 (citing Ex. 1004, 24:43–45).

Moreover, Petitioner contends that Amidon teaches that its systems, although exemplified using propranolol, "can be applied to 'any other drug.'" *Id.* at 22–23 (citing Ex. 1004, 25:5–10; Ex. 1002 ¶¶ 106, 107). In this regard, Dr. Auslander, testifies that the various active agents (i.e., other drugs) listed by Amidon "have various different properties further substantiating that the pulsed dosage forms . . . could have been applied to other known active agents including methylphenidate and amphetamines." Ex. 1002 ¶ 107.

Finally, Dr. Auslander notes Amidon's extensive list of formulation and process variables, as well as Amidon's mathematical model for producing permeability-controlled systems that provide pulsed dosages that "simulate the AUC [area under the curve] (preferably within 5%) of the immediate release dosage form administered in divided doses." Ex. 1002 ¶ 41 (citing Ex. 1004, 11:5–12:10, 19:30–22:25). Dr. Auslander testifies that to the extent one of ordinary skill in the art would have had any difficulty in making the pulsed dosage forms described by Mehta, Amidon "would have had all the necessary guidance to practice the parameters plainly set forth in" Mehta. Ex. 1002 ¶ 111 (citing Ex. 1004, 11:35–25:15); *see also id.* ¶ 41 (citing Ex. 1004, 22:21–25 (Amidon stating "[b]y optimizing the formulation and process variables by application of the principles of the invention, it is possible to control the physical and mechanical properties of the films which in turn controls the pulse time and rate of release from the delivery system.")). According to Dr. Auslander,

"[u]sing the teachings and guidance of the '131 patent [Amidon], it would have been a matter of routine experimentation to prepare a [delayed] pulsed dose where more than 80% of the active agent is released (*i.e.*, "essentially all") within sixty minutes after initiation of the pulsed dosage." Ex. 1002 ¶ 41.

Patent Owner, supported by the testimony of its declarant, Dr. Trout, contends on the other hand, that the references provide "no expectation of success, only undue experimentation" and "no guidance to solve the nagging problem of a delay and a rapid and complete pulse, only impermissible hindsight from the '096 disclosure." Prelim. Resp. 48 (citing Ex. 2001 ¶¶ 103–104, 190–191, 208, 223–229).

Specifically, Patent Owner contends that "Mehta provides an immediate dose of methylphenidate followed by at least one delayed dose at a predetermined time . . . us[ing] a polymer coating to delay a second release by 2-7 hours." Prelim. Resp. 20 (citing Ex. 1005, 3:8-19). Patent Owner acknowledges that "[t]he two releases can be referred to as pulses" (*id.* (citing Ex. 1005, 5:35-36)), but contends that "Mehta's second release always takes very long and is a delayed sustained release, not a 60 minute pulse." *Id.* at 20–21 (citing Ex. 1005, Example 3 (Table 1), Fig. 1, Example 5; Ex. 2001 ¶¶ 99–100, 213–220). Patent Owner contends that "Mehta does refer to 'delayed release' as including a period of 0.5 to 2.5 hours or 1.5 hours, preferably 1 hour, in which no less than 70%, 80%, or preferably 90%, of the drug is released," but "Mehta's examples and teachings never

came anywhere near such results." *Id.* at 21–22 (citing Ex. 2001 ¶¶ 99–100, 213–220).

Patent Owner contends that one of Mehta's samples (No. 1) is from Example 4 and had no delay. Of the remaining samples:

> Three have a 1-hour delay (Nos. 4, 5, 9), which is less than Mehta's targeted 2–7 hours and is not enteric. Eight have a 2-hour delay (Nos. 6–8, 10–12, 17, 20). Nine (Nos. 2, 3, 13–16, 18, 19, 21) have delays of 3–5 hours. The delayed release in these examples is *sustained over many hours*. It is not a rapid and complete pulse of "essentially all" (≥80%) the drug "within about 60 minutes." The fastest is 3 hours, with a 1-hour delay (No. 4). Other 1-hour pellets release in 4–5 hours (Nos. 5, 9). The 2-hour pellets release in 5, 6, or 8 hours (Nos. 6–8, 10–12, 17, 20). The 3–5 hour pellets release in 6, 8, or 10 hours.

Prelim. Resp. 40 (citing Ex. 1005, 14, Table 1; Ex. 2001 ¶¶ 101, 213–214).

Accordingly, Patent Owner contends that "Mehta is evidence of a continuing long-felt need for the '096 invention and shows a <u>failure</u> . . . to achieve it." Prelim. Resp. 24 (citing Ex. 2001 ¶¶ 105–110, 243–246). Patent Owner argues that Petitioner "ignores all of this and relies on 'optimizing' and <u>unrealized</u> 'delayed release' in Mehta that wishes for 70%, 80%, or 90% of the total drug in a dosage form to release within 0.5 to 2.5 hours, preferably 1.5 or 1 hour." *Id.* at 43 (citing Pet. 22–23).

As for PDR 1997, Patent Owner contends that "[t]here is nothing in this reference to guide the artisan toward a successful once-daily dosage form to replace two spaced-apart immediate doses" and "[t]he PDR does not help Mehta provide a 60-minute pulse for amphetamine or for

methylphenidate." Prelim. Resp. 24. Moreover, Patent Owner contends that Brown, far from motivating one of skill in the art to develop a pulsed-release delivery system, "actually motivated incrementally improving the 'available sustained-release formulations.'" *Id.* at 31 (citing Ex. 2001 ¶¶ 81, 92–97).

Patent Owner acknowledges that Amidon discloses that "[b]y optimizing the formulation and process variables by application of the principles of [its] invention, it is possible to control the physical and mechanical properties of the films which in turn controls the pulse time and rate of release from the delivery system." Prelim. Resp. 25 (quoting Ex. 1004, 22:20–25 (emphasis added)). Nevertheless, Patent Owner contends that Amidon cannot "lift Mehta from failure to success" (*id.* at 25) because "the problems with combining Amidon and Mehta are legion" (*id.* at 44). For example, Patent Owner contends that "[t]here is no disclosure of how to manage release rate after a delay (T*p*) [in Amidon], only extensive open-ended experimentation." *Id.* at 25.

According to Patent Owner, Amidon tried to address the production of successive divided dosage forms in two ways: "Trial-and-error experiments varied a few component amounts and process variables of a starting-point formulation. Then, Amidon proposed model equations for a given formulation based on assumptions about its makeup." Prelim. Resp. 26.

> In the first approach, Amidon: (1) made a propranolol dosage form and some variations; (2) collected data about certain properties of the samples and their delay times (T*p*); (3) used the data to make more variations; (4) tested samples identify two variables that were impactful for T*p*; (5) made surface plots for

> those variables versus T*p*, such as temperature and percent coating (Fig. 1) or amounts of PEG and a sodium carboxymethyl cellulose excipient (Fig. 3); and (6) tried to fit an equation to the data. . . . [and] Amidon made only one validation of one pH-dependent sample according to a selected T*p* from a surface plot.

Prelim. Resp. 26–27 (citing Ex. 1004, 8:27–10:30, Fig. 1, 12:12–14:24; Ex. 2001 ¶¶ 117–136).

> In a second approach, Amidon speculated upon a "Theoretical Model For Permeability Controlled Embodiments." This is a series of equations that attempt to correlate certain polymer coating variables, like hydraulic permeability (L*p*), with a delay time (T*p*). . . . The equations make various untested assumptions. Numerous constants and formulation properties are needed, but values are not disclosed or readily attainable. . . . No equation is applied to the design and testing of any dosage form. No 60-minute pulse could arise anyway, because the equations target only the T*p* delay, not release rate.

Id. at 27–28 (citing Ex. 1004, 19:30–22:19; EX2001 ¶¶ 143–155, 200-202).

Turning to Amidon's working examples (relied on by Petitioner (Pet. 2, 20–21 (citing Ex. 1002 ¶¶ 41, 105))), Patent Owner notes that the only drug tested was propranolol, and the dosage forms were merely subjected to in vitro and in vivo testing to determine their disintegration dissolution time ("DDT"). Prelim. Resp. 28–29 (citing Ex. 1004, 8:30–10:11, 10:24–28; Ex. 2001 ¶¶ 120–128, 132–142). As Dr. Trout explains at great length, however, DDT testing is not a measure of the release rate of propranolol from the dosage form, and "cannot be related to defined quantities such as release rate." Ex. 2001 ¶ 162; *see id.* ¶¶ 156–168. Having carefully

reviewed his testimony in view of the evidence currently of record, we credit Dr. Trout on this point.

Patent Owner contends that Amidon's "approach was a way to organize laborious experiments with two variables of a given dosage form" but "[t]he entire process . . . of dogged empirical work, surface plots, equation-fitting, and validation, would have to be done from scratch, for each new drug, formulation, and regime." Prelim. Resp. 27.

> Experiments with distinct propranolol formulation variables, to make surface plots, propose equations, and toy with lag time, is arduous and speculative, and anyway is limited to that formulation and those variables. . . . No information leads to controlling release rate, or to a 60-minute pulse. . . . Theoretical models, still constrained to probe lag time, are even more remote and untested. . . . All of this is undue experimentation without anticipated success in a very unpredictable field.

Id. at 46 (citing Ex. 2001 ¶¶ 112–128, 132–134, 143–155, 170–180, 194–222, 226–228: *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988)).

In summary, Patent Owner contends that "[t]he maxim that changing formulation and process variables will change results, noted by Petitioner, is an open call for undue experimentation." Prelim. Resp. 45 (citing Pet. 23, 31–32; Ex. 1002 ¶ 41). Patent Owner contends that "[t]his was not a path to predictability" and "would not have inspired and facilitated a 60-minute pulse [of amphetamine or methyphenidate] after an enteric delay." *Id.* (citing Ex. 1004, 7:46–14:24; Ex. 2001 ¶¶ 115–136, 170–174, 202).

Having considered the arguments and evidence presented by both Petitioner and Patent Owner, we agree with Petitioner that, given the

teachings of the prior art, one of ordinary skill in the art would have been motivated to produce a dosage form—with either Mehta's Ritalin (methylphenidate) or Adderall (a mixture of neutral sulfate salts of dextroamphetamine and amphetamine, as well as the dextro isomer of amphetamine saccharate and d,l-amphetamine aspartate)—comprising an immediate release component and a delayed release component that releases "essentially all" (i.e., less than 100%, and not less than 80%) within about 60 minutes after initiation of the delayed release.

Nevertheless, we agree with Patent Owner that Petitioner has not established that the prior art relied on would have provided one of ordinary skill in the art with a reasonable expectation of success in producing a dosage form that meets *all* the limitations of claim 1.

Claim 1 also requires that the delayed release coating is an enteric coating, but none of Mehta's delayed release formulations that could be considered to be enteric[9] by virtue of their delay periods (i.e., those with

[9] We recognize that Mehta does not use the word "enteric," or disclose expressly an intent to deliver the delayed dosage to the intestines, rather than the stomach. The '096 patent, however, teaches that the delay (lag time period) may be time dependent, rather than pH dependent, and for a non-pH dependent enteric release, the lag time preferably is within 4 to 6 hours after administration of the drug. Ex. 1001, 3:61–4:8. Mehta discloses formulations that provide delays of 4 or 5 hours. Ex. 1005, Table 1. For purposes of this decision, we agree that Petitioner has shown sufficiently that the Mehta discloses formulations with delay periods long enough to release the drug enterically, i.e., in the intestines, rather than the stomach.

delays of 4 or 5 hours) had release rates of "essentially all" of the drug in anywhere near the required time period. Even if Mehta could be read to suggest that a delay of 4 or 5 hours followed by a release of essentially all of the delayed dose within 60 minutes would be desirable, we are not persuaded that Mehta's disclosure that the amount of drug released is influenced by the amount of coating, the ratio of the two polymers, the amount of talc, and curing time is adequate guidance for one of ordinary skill in the art to achieve such a dosage form. In general, Mehta demonstrates that longer delays are accompanied by longer release times, with formulations that could be considered to provide enteric release (i.e., a release after a 4 or 5 hour delay) having 85% release times of 8 or more hours. *See* Ex. 1005, Table 1.

Nor are we persuaded that Amidon would have provided one of ordinary skill in the art with a reasonable expectation of achieving a delayed enteric release of essentially all of a second dose of drug within about 60 minutes of enteric release. Patent Owner's and Dr. Trout's position on this issue is amply supported by the disclosure of Amidon itself. As discussed above, Amidon provides an extensive list of formulation and process variables, "which must be taken into consideration in the successful design of a permeability-controlled drug delivery system" (Ex. 1004, 11:31–33), but its working examples deal with two variables only, and more specific guidance is not provided. Moreover, the working examples were designed to determine the disintegration dissolution time for the drug delivery

system—a measure of the delay period afforded by the system—not, as explained by Dr. Trout, a measure of the drug release rate. *See* Ex. 2001 ¶¶ 156–168. We agree with Patent Owner that Amidon itself provides evidence of the unpredictability of formulating dosage forms with particular delay and release parameters.

Accordingly, we are not persuaded that Petitioner has established a reasonable likelihood of prevailing in its challenge of claim 1 as unpatentable over Mehta, PDR 1997, Brown, and Amidon, or of claims 3, 4, 6, and 7, which depend from claim 1.

Claims 2, 5, and 8–17

Claims 2, 5, 8, 11, and 13 are independent claims, and, like claim 1, require that the "enteric release coating releases essentially all of said one or more pharmaceutically active amphetamine salts coated with said enteric coating within about 60 minutes after initiation of said delayed pulsed enteric release." Accordingly, we are not persuaded that Petitioner has established a reasonable likelihood of prevailing in its challenge of independent claims 2, 5, 8, 11, and 13 as unpatentable over Mehta, PDR 1997, Brown, and Amidon, or their dependent claims, 9, 10, 12, and 14–17.

Claims 18–25

Claim 18 requires, in relevant part, "one or more pharmaceutically active amphetamine salts that are covered with an enteric release coating that provides for delayed pulsed enteric release, wherein said enteric release coating releases said one or more pharmaceutically active amphetamine salts

coated with said enteric coating within about 60 minutes after initiation of said delayed pulsed enteric release." Notably, unlike claims 1–17, claim 18 and its dependent claims 19–24 and 25 (to the extent that claim 25 depends from claims 18–20), does not require release of "essentially all" of the pharmaceutically active amphetamine salts coated with the enteric coating within about 60 minutes after initiation of the delayed pulsed enteric release. Accordingly, we determine that claims 18–25 (to the extent that claim 25 depends from claims 18–20) encompass release of less than essentially all (i.e., less than 80%) of the drug within 60 minutes after initiation of the delayed pulsed enteric release.

As discussed above, Mehta suggests dosage forms with an immediate release component and a delayed release component that releases a second dose of methylphenidate after a delay of between 2 to 7 hours, and exemplifies dosage forms with delays of 4 or 5 hours, disclosed in the '096 patent as satisfying the "enteric" limitation. *See* section II.B.5, footnote 9.

Patent Owner has not addressed claims 18–24, but does argue with respect to claim 25 that "the claimed 60-minute pulse combined with mixed amphetamine salts are not in the record." *See* Prelim. Resp. 56.

Nevertheless, as discussed above, having considered the arguments and evidence presented by Petitioner, we are persuaded that, given the teachings of the prior art, one of ordinary skill in the art would have been motivated to produce a dosage form—containing either Ritalin (methylphenidate) or Adderall (a mixture of neutral sulfate salts of

dextroamphetamine and amphetamine, as well as the dextro isomer of amphetamine saccharate and d,l-amphetamine aspartate)—comprising an immediate release component and a delayed release component that releases a second dose of drug within about 60 minutes after initiation of the delayed enteric release (i.e., after a delay of 4 to 6 hours), as required, e.g., by claims 18, 19, 20, and 25. Again, unlike claims 1–17, these claims are not limited to release of "essentially all" of the drug within about 60 minutes. With respect to the additional limitations of claims 21–24, we are persuaded that Petitioner has shown sufficiently that the prior art teaches or suggests dosage forms where the pharmaceutically active amphetamine salts are coated on or incorporated in a core, or multiple cores. *See e.g.*, Pet. 49–56.

Accordingly, we determine that Petitioner has established a reasonable likelihood of prevailing in its challenge of claims 18–25 as unpatentable over Mehta, PDR 1997, Brown, and Amidon.

III. CONCLUSION

For the foregoing reasons, on this record, we are persuaded that the Petition establishes a reasonable likelihood that Petitioner would prevail in showing that claims 18–25 of the '096 patent are unpatentable under 35 U.S.C. § 103(a) in view of Mehta, PDR 1997, Brown, and Amidon.

We emphasize that at this stage of the proceeding, we have not made a final determination as to the patentability of any challenged claim or the construction of any claim term.

IV. ORDER

Accordingly, it is

ORDERED that that pursuant to 35 U.S.C. § 314 an *inter partes* review of the '096 patent is hereby instituted on the following ground:

Whether claims 18–25 of U.S. Patent No. RE42,096 are unpatentable under 35 U.S.C. § 103 in view of Mehta, PDR 1997, Brown and Amidon.

FURTHER ORDERED that the trial is limited to the ground identified above and no other ground is authorized; and

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(a), *inter partes* review of the '096 patent is hereby instituted commencing on the entry date of this Order, and pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of trial.

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