IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ALZA CORPORATION and McNEIL-PPC, INC.,	:	
Plaintiffs,	:	
v.	:	Civil Action No. 05-642-JJF
ANDRX PHARMACEUTICALS, LLC, and ANDRX CORPORATION,	:	
Defendants.	:	

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OPINION

March 30, 2009
Wilmington, Delaware

Farnan, District Judge.

This action was brought by Plaintiffs, Alza Corporation ("Alza") and McNeil-PPC, Inc. ("McNeil"), against Defendants, Andrx Pharamceuticals, LLC ("Andrx") and Andrx Corporation ("Andrx Corp.") (collectively, "Andrx"), in connection with the Abbreviated New Drug Applications ("ANDAs") filed by Andrx seeking to market generic versions of CONCERTA®, a drug developed and manufactured by Alza for distribution by McNeil. Joint Statement of Admitted Facts ¶¶ 10-11. Alza is the assignee of U.S. Patent Nos. 6,919,373 (the "'373 patent") and 6,930,129 (the "'129 patent"), which pertain to extended release tablets containing methylphenidate ("MPH") for use in treating Attention Deficit Hyperactivity Disorder ("ADHD"). Id. ¶ 7.

Plaintiffs allege that by filing their ANDAs, Andrx infringes claims 1, 6 and 7 of the '373 patent. Plaintiffs also alleged infringement of claims 1 and 4-6 of the '129 patent, but dismissed these allegations just prior to trial. Andrx contests infringement of all these claims and asserts that they are invalid as obvious, for lack of enablement, and for failure to satisfy the written description requirement. Although Plaintiffs have dismissed their allegations pertaining to the '129 patent, Andrx urges the Court to nevertheless decide all issues related to this patent.

The Court conducted a bench trial, and this Opinion constitutes the Court's Findings of Fact and Conclusions of Law on the issues tried.

BACKGROUND

I. Procedural History

On or before July 22, 2005, Andrx submitted to the FDA an amendment to ANDA No. 76-655 containing a certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) (a "Paragraph IV certification") and seeking approval to engage in the commercial manufacture, use, and sale of a generic version of Plaintiffs' CONCERTA® product prior to the expiration of the '373 patent. Joint Statement of Admitted Facts ¶ 11; D.I 1 ¶¶ 36-37. On August 16, 2005, Andrx submitted to the FDA an amendment to ANDA No. 76-722 containing a Paragraph IV certification and seeking approval to engage in the commercial manufacture, use, and sale of a generic version of Plaintiffs' CONCERTA® product prior to the expiration of the '373 and '129 patents. Joint Statement of Admitted Facts ¶ 11; D.I 1 ¶¶ 36-37; Defendants' Proposed Findings of Fact And Conclusions of Law ("DFF") ¶ 1212. On September 1, 2005, Plaintiffs sued Andrx, alleging that these ANDA filings constituted infringement of the '373 and '129 patents. See D.I. 1.

In response to the Complaint, Andrx filed an Answer and Counterclaims denying infringement and asserting the defense of

invalidity. D.I. 7. Andrx also counterclaimed for a declaratory judgment of noninfringement and invalidity of the '373 and '129 patents. Id.

On the morning of the first day of Trial, Plaintiffs requested the dismissal with prejudice of their own infringement claims and Andrx's declaratory judgment counterclaims on the '129 patent, representing on the record that it would not assert the '129 patent claims against Andrx in connection with products described in Andrx's ANDAs. Tr. (Vol. 1), D.I. 148 at 3:6-9:17. The parties continue to dispute whether the Court has declaratory judgment jurisdiction over Defendants' counterclaims pertaining to the '129 patent.

II. Factual Background

A. The Parties

Alza is a corporation incorporated under the laws of the State of Delaware, with its principal place of business in Mountain View, California. Joint Statement of Admitted Facts ¶ 1. McNeil is a corporation incorporated under the laws of the State of New Jersey with a place of business in Fort Washington, Pennsylvania. Id. ¶ 2.

Andrx is a corporation incorporated under the laws of the State of Delaware with its principal place of business in Weston, Florida. Id. ¶ 3. Andrx Corp. is a corporation incorporated

under the laws of the State of Delaware with its principal place of business in Weston, Florida. Id. ¶ 4.

B. Concerta® And The Patents At Issue

Concerta® is the brand name for a once-daily medication for treating Attention Deficit Hyperactivity Disorder ("ADHD"). Concerta® is manufactured by Alza, while McNeil is the sole authorized distributor of Concerta®. Id. ¶ 10. The active ingredient in Concerta® is a compound called methylphenidate ("MPH"), which has been used in various forms to treat ADHD since the mid-1970s. See Tr. (Vol. 1), D.I. 148 at 24:7-17; PX 575 at 295. However, previously used MPH formulations generally required repeated dosing because the period of efficacy of each dose was relatively short. PX 575 at 295-96. Typical dosing regimes were twice-daily (referred to in the art as "BID" dosing) or three-times-daily (referred to in the art as "TID" dosing). Id. The need for repeated dosing was seen as a particularly significant drawback in the treatment of school-aged children because it necessitated the administration of an MPH dosage form in the middle of the school day. See Tr. (Vol. 1), D.I. 148 at 35:1-36:6.

The Ritalin SR® product, introduced by Ciba-Geigy, was an attempt to provide an effective once-daily dosage form of MPH. See id. at 27:9-19. Briefly, Ritalin SR® was a "sustained release" MPH dosage form that provided an MPH blood plasma

concentration that was considered "constant" or "flat" because it stayed within a certain range over a period of several hours. See id. at 45:5-46:2. It was hoped that by providing a sustained "flat" MPH blood plasma concentration there would be no need for repeated dosing. However, Ritalin SR® ultimately proved to be unreliable and ineffective for the treatment of ADHD, and the prior art BID and TID MPH dosing regimens, though flawed, remained the "gold standard" in ADHD treatment. See Tr. (Vol. 3), D.I. 150 at 810:10-22; Tr. (Vol. 4), D.I. 151 at 1006:12-20, 1021:12-1022:4.

Thus, in 1993, Alza began further investigations into the development of an effective once-daily MPH-based treatment for ADHD. See Tr. (Vol. 1), D.I. 148 at 26:23-30:6. Briefly, the Alza researchers carried out "sipping studies" in which small amounts of MPH were administered to children in 30 minute intervals. By administering the drug in this controlled manner, the Alza researchers were able to simulate particular MPH plasma profiles. See id. at 50:2-51:11. As a result of these investigations, Alza scientists allegedly learned that an MPH blood plasma concentration that ascended over time provided greater efficacy than a concentration that remained constant over time. Id. at 68:9-69:10. Indeed, the efficacy of the ascending plasma profile approached the efficacy associated with conventional multi-dose BID and TID regimens. Id. at 73:7-23.

In addition, Alza contends that the sipping studies established for the first time that MPH was subject to the phenomenon of acute tolerance, which refers to the propensity of a drug to have decreased efficacy over time even though the blood concentration of the drug remains static. Id. at 49:3-18, 76:4-6. By steadily increasing the level of MPH in the blood, an ascending plasma profile overcomes this phenomenon.

Alza then sought patent protection for their alleged discovery, acquiring both the '373 and '129 patents, which share the same specification and same title, "Methods and Devices For Providing Prolonged Drug Therapy." The '373 patent issued on July 19, 2005, to Alza, the assignee of named inventors, Andrew Lam, Padmaja Shivanand, Atul Ayer, Richard Weyers, Suneel Gupta, Diane Guinta, Carol Christopher, Samuel Saks, Lawrence Hamel, Jeri Wright, and Zahedeh Hatamkhany.[1] DTX 1. The '129 patent shares the same inventors as the '373 patent, and issued roughly one month later, on August 16, 2005, to the same assignee as the '373 patent. DTX 2. The common specification explains that "[t]he invention broadly embraces oral sustained-release dosage forms that provide an ascending drug release rate over an extended time period . . . ." As such, the asserted claims of

[1] The inventorship for the '373 patent was corrected on April 29, 2007, removing Andrew Lam, Padmaja Shivanand, Zahedeh Hatamkhany, Jeri Wright, and Richard Weyers as inventors. These individuals do not appear to have been removed as inventors from the '129 patent.

the asserted patents are directed to methods for treating ADHD that include the administration of an MPH dosage form that provides either release of MPH at an ascending rate or an ascending MPH plasma drug concentration. Asserted claim 1 of the '373 patent is the only independent claim of the '373 patent and reads as follows:

> 1. A method for treating ADD or ADHD comprising administering a dosage form comprising methylphenidate that provides a release of methylphenidate at an ascending release rate over an extended period of time.

Each dependent claim of the '373 patent depends from claim 1 and adds one additional limitation over claim 1; specifically, the requirement of a "substantially ascending methylphenidate plasma drug concentration" over a particular time frame.

Alza has since amended its New Drug Application No. 21-121 to identify the '373 and '129 patents as patents "with respect to which a claim of patent infringement could reasonably by asserted if a person not licensed by the owner engaged in the manufacture, use, or sale" of Concerta®. Accordingly, the FDA listed these patents in its list of Approved Drug Products with Therapeutic Equivalence Evaluations ("the Orange Book"). Joint Statement of Admitted Facts ¶ 9.

DISCUSSION

I. Whether The Court Has Declaratory Judgment Jurisdiction Over Defendants' Counterclaims On The '129 Patent

The jurisdictional dispute currently before the Court involves the intricacies of the Hatch-Waxman statutory scheme and a factual scenario that parallels the situation considered by the Court in its recent decision in Dey, L.P. v. Sepracor, Inc., No. 08-372-JJF, 2009 U.S. Dist. LEXIS 7070 (D. Del. Jan. 30, 2009). Sepracor differs from the instant dispute in that there was no question as to which party was the first Paragraph IV ANDA filer. See infra. As a result, the Court's decision in Sepracor does not resolve the jurisdictional question presented here. Nevertheless, the Court refers the reader to Sepracor for a summary of the relevant statutory background, an understanding of which is requisite to an understanding of the instant jurisdictional dispute.

The chronology of the instant jurisdictional dispute is summarized as follows. Alza holds approved New Drug Application ("NDA") No. 21-121 for methylphenidate hydrochloride, which is marketed under the tradename Concerta®. Joint Statement of Admitted Facts ¶ 8. In January 2003, Andrx submitted an ANDA to the FDA seeking permission to market a generic version of Concerta®. DFF ¶ 1207. At some point prior to July 2005, third party Impax Laboratories, Inc. ("Impax") submitted an ANDA of its own. Id. at 1208.

At this point, neither the '373 nor '129 patents had issued. However, on July 19, 2005, the '373 patent issued and, on the same day, Alza filed papers with the FDA to list the '373 patent in the Orange Book for Concerta®. Id. ¶ 1210; Joint Statement of Admitted Facts ¶ 10. Also on the same day, Impax submitted papers to the FDA for the purpose of amending its ANDA to include a Paragraph IV certification on the '373 patent. DFF ¶ 1210. It is unclear which set of documents the FDA received first. Although Andrx ultimately amended its ANDA to include a Paragraph IV certification on the '373 patent, there is no dispute that Impax is the first Paragraph IV filer with respect to the '373 patent.

On August 16, 2005, the '129 patent issued. Id. ¶ 1212. As with the '373 patent, on the same day, Alza filed papers with the FDA to list the '129 patent in the Orange Book for Concerta®. Id. ¶ 1214. Likewise, on the same day, both Andrx and Impax filed papers with the FDA for the purpose of amending their ANDAs to include Paragraph IV certifications for the '129 patent. Id. ¶¶ 1212-13. Of these three sets of documents, it is unclear which set of documents the FDA received first. However, Defendants do not appear to suggest that the FDA did not receive them all on August 16, 2005. See DFF ¶¶ 1212-14. Furthermore, there does not appear to be a dispute that on August 16, 2005,

both Andrx and Impax sent Alza letters notifying Alza of the Paragraph IV certifications. See id. ¶¶ 1212, 1215.

The parties further do not dispute that the pre-MMA version of the Hatch-Waxman Act applies to the instant jurisdictional dispute. See DFF ¶ 1217; D.I. 173 at 3. In these circumstances, a separate 180-day exclusivity period exists for both the '373 and '129 patents. Impax, as the first Paragraph IV ANDA filer on the '373 patent, is entitled to 180-days of market exclusivity on the '373 patent. Given that the parties do not dispute that the Court has jurisdiction over claims pertaining to the '373 patent, this exclusivity may ultimately be triggered by the outcome of the instant litigation. See 21 U.S.C. § 355(j)(5)(B)(iv) (2000). However, if Impax is also considered to be the first filer on the '129 patent, then the FDA will nevertheless prohibit Andrx from taking its generic to market until Impax has also finished enjoying the exclusivity period for the '129 patent. This will not happen until 180 days after either (1) a Court decision on the '129 patent or (2) Impax begins marketing a generic version of Concerta®. Given that there is no indication that Impax will begin marketing its generic, Defendants contend that a decision by this Court on the '129 patent is necessary to remove Impax's possible exclusivity on the '129 patent as a barrier to Andrx's market entry. See DFF ¶ 1226-27. Pointing to the Federal Circuit's recent decision in Caraco Pharm. Labs., Ltd. v. Forest

Labs., Ltd., 527 F.3d 1278 (Fed. Cir. 2008), Defendants contend that this potential for delay is a cognizable injury creating a controversy sufficient to establish declaratory judgment jurisdiction over their counterclaims pertaining to the '129 patent.

In the Court's view, however, the harm to Defendants remains too speculative to establish declaratory judgment jurisdiction. The difficulty with Defendants' position is that they simply do not know whether Impax or Andrx was the first party to submit a Paragraph IV certification for the '129 patent and hence gain entitlement to the 180-day exclusivity period for that patent. According to Defendants, a party is deemed to have "submitted" an ANDA with a Paragraph IV certification when both (1) its Paragraph IV certification papers have been received by the FDA and (2) it has sent notice letters to the NDA holder and patent owner. See id. ¶ 1219. With both Andrx and Impax having done both of these things on August 16, 2005, Defendants contend that the question of who is entitled to exclusivity on the '129 patent boils down to the exact times on August 16, 2005 when the FDA received each party's certification papers. This is so, Defendants contend, because a party's Paragraph IV certification may be invalid if the FDA receives it before receiving the NDA holder's papers requesting that the corresponding patent be listed in the orange book, even if the FDA receives both

documents on the same day. See DFF ¶ 1211, 1222. Thus, whether Impax holds exclusivity on the '129 patent, and hence has the potential to delay Defendants' market entry, hinges on two unknowns: (1) the precise order in which the FDA received the relevant documentation on August 16, 2005 and (2) whether the FDA agrees with Defendants that this order could result in invalidation of one or more party's ANDA. On these facts, the Court concludes that the potential for harm to Defendants remains too speculative to support declaratory judgment jurisdiction.

Alternatively, Defendants' contend that declaratory judgment jurisdiction exists because Alza has a pending patent application that may eventually issue as a patent that may include claims substantially identical to those in the '129 patent. Defendants contend that this patent may eventually pose a litigation threat. See DFF ¶¶ 1228-36. Defendants cite no cases suggesting that this set of circumstances gives rise to declaratory judgment jurisdiction. Accordingly, the Court concludes that this potential injury is also too speculative to support declaratory judgment jurisdiction over Defendants' counterclaims on the '129 patent.

The Court will thus dismiss Defendants' declaratory judgment counterclaims concerning the '129 patent without prejudice. If, at some point, Defendants can confirm that only Impax holds exclusivity on the '129 patent, the Court will reconsider its

dismissal of Defendants' counterclaims. As set forth in the Order accompanying this Opinion, the Court shall permit Defendants to conduct additional limited discovery to gain clarity on this issue.

II. Plaintiffs' Motion To Strike Portions of Defendants' Post-Trial Findings Of Fact (D.I. 188)

By their Motion, Plaintiffs request that the Court strike paragraphs 1179 through 1198 of Defendants' Proposed Findings Of Fact And Conclusions Of Law, which pertain to Defendants' written description defense. Plaintiffs contend that Defendants waived a written description defense by failing to mention such a defense in their pretrial briefing. See D.I. 188 at 2. Plaintiffs further contend that Defendants failed to provide any evidence at trial on a written description defense, noting that Defendants' seven-page section with 20 paragraphs on written description is composed almost entirely of legal argument and includes a mere four record citations. Id. at 4.

Defendants respond that they included the written description defense in their post-trial briefing only in response to new arguments that Plaintiffs raised in their pre-trial briefing, in particular an alleged attempt by Plaintiffs to have the Court re-construe the claim term "dosage form." See D.I. 189 at 5; infra Part IV.B.2.

Because Defendants have the burden of proof on a written description defense, the Court concludes that Defendants were

obligated to raise this defense in their pre-trial briefing. In addition, on review of the record, the Court agrees with Plaintiffs that Defendants did not meaningfully introduce any evidence on written description at trial. Furthermore, to the extent Defendants contend that a written description defense flows from an allegedly overbroad construction of the term "dosage form," the Court notes that Defendants had little trouble putting this theory to use in both their pre-trial brief and at trial with regard to their enablement defense. Accordingly, the Court will grant Plaintiffs' Motion To Strike Portions of Defendants' Post-Trial Findings Of Fact (D.I. 188).

Defendants contend that the Court, having found that Defendants' post-trial briefing on written description was inappropriate, must further find that Plaintiffs' contingent proposed findings of fact and conclusions of law on the '129 patent that appear in Plaintiffs' post-trial briefing are also inappropriate. See D.I. 189 at 14-15. Specifically, Defendants contend that Plaintiffs, after electing to no longer assert the '129 patent, declined to discuss it in their pre-trial papers and should not be allowed to raise it in post-trial briefing. Defendants' thus bring a contingent cross motion to strike Plaintiffs' post-trial briefing on the '129 patent. See D.I. 189. The Court will deny this motion as moot in light of the Court's conclusion that it does not have jurisdiction over

Defendants' counterclaims on the '129 patent. If it becomes necessary for the Court to consider Defendants' counterclaims on the '129 patent, the Court will allow the parties to submit appropriate supplemental findings of fact and conclusions of law.

III. Infringement Of Claims 1, 6, And 7 Of The '373 Patent

A. Applicable Law

A patent is infringed when a person "without authority makes, uses, offers to sell, or sells any patented invention, within the United States, or imports into the United States any patented invention during the term of the patent . . . ." 35 U.S.C. § 271(a). Determining infringement requires a two step inquiry. Step one requires a court to construe the disputed terms of the patent at issue. Step two requires a court to compare the accused products with the properly construed claims of the patent. Step one is a question of law; step two is a question of fact. Markman v. Westview Instruments, Inc., 52 F.3d 967, 979-81 (Fed. Cir. 1995) (en banc), aff'd, 517 U.S. 370 (1996).

Infringement may be proven under either of two theories: literal infringement or the doctrine of equivalents. Literal infringement occurs when each element of at least one claim of the patent is found in the alleged infringer's product. Panduit Corp. v. Dennison Mfg. Co., 836 F.2d 1329, 1330 n.1 (Fed. Cir. 1987). The party asserting infringement has the burden of proof

and must meet its burden by a preponderance of the evidence. SmithKline Diagnostics, Inc. v. Helena Lab. Corp., 859 F.2d 878, 889 (Fed. Cir. 1988) (citations omitted).

B. Discussion

As an initial matter, the Court notes that all asserted claims of the '373 patent are method claims directed to methods for "treating ADD or ADHD." In these circumstances, the Court concludes that Plaintiffs have no cause of action for direct infringement under 35 U.S.C. § 271(a). As the Federal Circuit explained, "pharmaceutical companies do not generally treat diseases; rather, they sell drugs to wholesalers or pharmacists, who in turn sell the drugs to patients possessing prescriptions from physicians. Pharmaceutical companies also occasionally give samples of drugs to doctors and hospitals. In none of these cases, however, does the company itself treat the disease." Warner-Lambert Co. v. Apotex Corp., 316 F.3d 1348, 1363 (Fed. Cir. 2003). Thus, Andrx, a pharmaceutical company that does not treat diseases, can at most be liable as a contributory infringer or an inducer of infringement. However, both these theories of indirect infringement require some underlying direct infringement, most likely by doctors who actually administer the accused products. See DSU Med. Corp. v. JMS Co., 471 F.3d 1293, 1303 (Fed. Cir. 2006). The following analysis is thus carried

out to resolve the issue of whether direct infringement could occur by such means.

Claim 1 of the '373 patent, which is the only independent asserted claim from the '373 patent, requires "an ascending release rate over an extended period of time." The Court construed this phrase to mean "a release of methylphenidate from the dosage form wherein the amount released in a periodic interval is increased over the amount released during the immediately preceding periodic interval starting at t=0 and continuing through at least the midpoint of the T_{90} and for at least three hours. The release rate is as determined by an appropriate in-vitro dissolution test. The ascending release rate does not include release of drug from any immediate-release drug coating that may be applied to the dosage form." D.I. 130. The parties agree that whether the accused products satisfy this limitation is the key dispute with regard to infringement of the '373 patent. See DFF ¶¶ 515-18; Plaintiffs' Proposed Post-Trial Findings Of Fact And Conclusions Of Law ("PFF") ¶ 131.

1. Claim 1

Defendants contend that claim 1 is not infringed because the "ascending release rate" limitation requires infringing MPH dosage forms to, in an appropriate dissolution test, release methylphenidate from a source other than an immediate release ("IR") coating at the very beginning of the dissolution test

(i.e. at t=0). DFF ¶ 517. Put another way, Defendants contend that the "ascending release rate" limitation requires the release of some non-IR MPH during the first measurement interval of an appropriate dissolution test. Id. According to Defendants, although the accused tablets do exhibit immediate release of MPH from an IR-coating, they do not otherwise release MPH until what is typically the second measurement interval of an appropriate dissolution test. Id. ¶¶ 539-44. Hence, according to Defendants, the accused products do not infringe.

Plaintiffs' response is two-fold. First, Plaintiffs contend that Defendants are misinterpreting the Court's claim construction. According to Defendants, "[i]t makes no difference how much, if any, MPH is released in the first interval so long as more is released in the next interval because the claim specifies only an ascending rate." PFF ¶ 240. Second, Plaintiffs contend that even under Defendants' interpretation of the Court's construction, the accused products still infringe because in a substantial fraction of Defendants' tablets some non-IR portion of MPH is released during the initial measurement interval of an appropriate dissolution test. Id. ¶ 253. Thus, to resolve the direct infringement issue, the Court must decide (1) whether the Court's construction requires release of MPH during the initial interval of an appropriate dissolution test,

and (2) if so, whether the accused products release MPH during that interval.

a. Whether The Court's Construction Requires Release of MPH During The Initial Interval of A Dissolution Test

The Court's construction does in fact require release of non-IR MPH during the initial interval of an appropriate dissolution test. The Court's construction is clear that an "ascending release rate" requires, "starting at t=0," the amount of non-IR MPH released per time interval to increase over the immediately preceding time interval. Calling for the "ascending release rate" to begin at "t=0," the Court's construction does not embrace the notion of some indeterminate time interval at the beginning of a dissolution test during which no non-IR drug release occurs. The patent is unequivocal on this point. In clarifying the meaning of "ascending release rate," the patent states the following:

> It will be appreciated that the first periodic release rate measured, e.g., the periodic release rate at t=1 hour (unless equal to 0), will always be greater than the release rate during the preceding period, e.g., the hour before the dosage form was administered, and, thus, the first periodic release rate always constitutes an occurrence of an ascending release rate.

'373 patent at 10:10-16.[2] Thus, to determine if the periodic release rate during the first interval constitutes an "ascending

[2] After reviewing Plaintiffs pre- and post-trial briefing, the Court notes that Plaintiffs do not appear to have directly addressed this passage in the specification.

release rate," the amount of drug released should be compared to the amount of drug released in the interval before the drug was even administered, which, by definition, is none.[3] Accordingly, an "ascending release rate" during the first measurement interval requires a non-zero quantity of drug to be released during that interval. This passage further explains that because the amount of drug released during the initial measurement interval will be greater than the amount of drug released prior to administration, the "first periodic release rate always constitutes an occurrence of an ascending release rate." The one exception to this rule is when the amount of drug released during the first measurement interval is "equal to 0," in which case there is not an "ascending release rate" during the first measurement interval. Consistent with this guidance, every example in the patent describes a dosage form that releases a non-zero quantity of MPH

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[3] Plaintiffs' dissolution expert, Ms. Vivian Gray, testified that this concept was "confusing" and "unheard of." See Tr. (Vol. 1), D.I. 148 at 282:3-302:14. Dr. Gray further testified that the Court's claim construction somehow did not reflect this portion of the patent, responding to a line of questions about this portion of the patent with the statement "[b]ut that's the patent, that's not the claim construction, which was what I followed." Tr. (Vol. 2), D.I. 149 at 312:21-23. Given that the Court adopted Plaintiffs' proposed construction of "ascending release rate" verbatim, and given that Plaintiffs plucked their proposed construction directly from the specification, the Court is skeptical of any suggestion by Plaintiffs that the patent somehow does not reflect the Court's construction. The Court has reviewed Dr. Gray's testimony that the concept set forth in this passage of the specification is "confusing" and concludes that, on the whole, her testimony on this issue lacks credibility.

during the first interval of a dissolution test and affirmatively describes this as an occurrence of an ascending release rate. See '373 patent at Tables 1-5.

Plaintiffs position that "it makes no difference" how much MPH is released during the first interval of a dissolution test "so long as more is released in the next interval" is not only inconsistent with this intrinsic evidence but, in the Court's view, rather difficult to apply. Particularly problematic is that Plaintiffs' position appears to allow for the possibility of an indeterminate time interval following administration during which no non-IR MPH is released. Thus, as an example, Plaintiffs contend that an accused dosage form may still infringe if it does not release any non-IR MPH until the second hour of a dissolution study. According to Plaintiffs, because the amount of non-IR MPH released during the second hour would exceed the amount released during the first hour (i.e., none), there would still be an "ascending release rate." However, if the testing interval is instead taken to be 30 minutes, then such a dosage form would not release any non-IR MPH during the first two intervals of the dissolution study. Under Plaintiffs' understanding of the Court's construction, there would then be no "ascending release rate" starting at "t=0" because the amount of MPH released did not increase on going from the first measurement interval to the second measurement interval. Thus, the determination of whether

there was an "ascending release rate" starting at "t=0" would depend on the length of the testing interval, a result the Court finds unsatisfying.

Indeed, the patent appears to embrace the possibility of using any desired measurement interval. See '373 patent at 8:58-61 (describing "times following administration in appropriate time units, e.g., t=30 minutes or t=2 hours, etc.); id. at 9:66-10:9 (describing hourly measurement intervals as an "example"). In fact, during claim construction, Plaintiffs argued that the testing interval should not be limited to one specific, commonly-used length. D.I. 87 at 23 n. 14 ("Appropriate time units include 30-minute intervals (e.g., t=30 minutes, t=60 minutes; t=90 minutes, etc.), 1-hour intervals and 2-hour intervals.); id. at 27 ("The fact that the specification explicitly refers to and envisions 30-minute and 2-hour intervals demonstrates that the claim term is not limited only to hourly intervals.). Because the patent allows for different length testing intervals, the determination of whether there is an "ascending release rate" should not so strongly depend on the selected testing interval, as it would under Plaintiffs' interpretation of the Court's construction.

Furthermore, the thrust of the '373 patent is to provide an MPH dosage form that overcomes the acute tolerance typically associated with MPH. The patent accomplishes this by providing a

dosage form that releases an amount of MPH that increases over consecutive time intervals. To include a time period where the dosage form releases no MPH - and hence has no therapeutic effect whatsoever - in the evaluation of whether an MPH dosage form provides an "ascending release rate" would be to turn a blind eye to the very purpose and mechanism underlying the invention. Even worse, it would partially eviscerate the "ascending release rate" limitation, which, under the Court's construction, requires at least three hours of ascending MPH release. Indeed, as Plaintiffs' dissolution expert, Ms. Vivian Gray, testified, under the Plaintiffs' interpretation of the Court's construction, an initial time period where a dosage form releases no MPH constitutes a "free pass" towards meeting the three hour requirement. See Tr. (Vol. 2), D.I. 149 at 336:12-19. Thus, according to Dr. Gray, if a hypothetical MPH dosage form provided (1) a two hour period of no MPH release followed by (2) a two hour period of MPH release, the "ascending release rate" limitation would be satisfied, even though there was only one two hour interval of actual MPH release. Id. at 335:23-338:2. As reflected in the intrinsic evidence, the Court's construction of "ascending release rate" simply does not countenance such extended periods of release dormancy as being a part of the "ascending release."

The testimony of Plaintiffs' expert on ADHD pharmacology, Dr. Kennerly Patrick, provides additional confirmation that those of skill in the art would not understand this as being included in the Court's claim construction. Specifically, after reviewing the Court's claim construction, Dr. Patrick testified with respect to Fig. 8 of U.S. Patent No. 5,256,850 to Wong et al., which discloses an oral dosage form that releases no drug in the first two hours after administration, as follows:

> Q. Okay. And when we look at Figure 8, in your opinion, having read that claim construction, how long is it ascending or when does it start ascending?.
>
> A. I would say it started ascending at two hours and ascended to four, at least through four hours when you take the error bars into consideration.
>
> Q. Okay. And to your understanding, is that an ascending release rate from time equals zero?
>
> A. From time two hours to -
>
> Q. Right.
>
> A. - six hours?
>
> Q. Right. My question is that: An ascending release rate from time equals zero, not from time equals two.
>
> A. I - I would not characterize that as that.
>
> Q. And that - why? Because there's no release in the first two hours?
>
> A. Yes.

Tr. (Vol. 4), D.I. 151 at 1077:3-24; see also DTX 634 at Fig. 8 (depicting the release profile with little to no drug release during the first two hours). Thus, according to Dr. Patrick, time periods where a dosage form releases no drug do no constitute occurrences of ascending release.

Having found that Defendants' understanding of the Court's construction is the proper one, the issue of direct infringement is reduced to whether the accused products exhibit release of some non-IR MPH during the first interval of an appropriate dissolution test.

b. Whether The Accused Products Exhibit Release Of Non-IR MPH During The Initial Interval Of An Appropriate Dissolution Test

i. Plaintiffs' Dissolution Studies

As necessary background for analyzing Plaintiffs' infringement allegations, a brief summary of Plaintiffs' dissolution testing of the proposed ANDA products is provided as follows. In general, in vitro dissolution tests involve the placement of a dosage form in a vessel containing a dissolution medium. The dosage form is agitated through rotation or stirring at a specific rate, and samples of the dissolution medium are withdrawn at periodic intervals for testing to determine the amount of drug present therein. See Tr. (Vol. 1), D.I. 148 at 220:8-222:21; PX 726. A publication entitled the U.S. Pharmacopoeia-National Formulary ("USP") is the official compendium of standards for drugs marketed in the United States and sets forth a set of approved dissolution apparatuses. See 21 U.S.C. § 321(j); Tr. (Vol. 1), D.I. 148 at 209:23-211:1. Plaintiffs' dissolution tests utilized USP apparatus 1, which includes storage of the dosage form in a metal basket that is

rotated at 100 RPM and a pH 7.5 phosphate buffer dissolution medium held at a temperature of 37° C. See Tr. (Vol. 1), D.I. 148 at 225:13-226:14, 244:6-245:4, 246:10-17; PX 229. Plaintiffs' dissolution expert, Ms. Vivian Gray, directed dissolution tests on 12 samples of each of three different ANDA products, which contained 27, 36 or 54 mg of MPH. The percentage of MPH released was measured at hourly intervals. See Tr. (Vol. 1), D.I. 148 at 250:4-24. The ANDA products also included an 18 mg dosage form. PX207 at ANDRX 03926. However, during discovery, Defendants were unable to provide samples of these products because they had not yet successfully manufactured a commercial-scale, validated lot of the 18 mg product. See PX 233. Plaintiffs thus have no test results for these proposed products.

On average, the 54, 36 and 27 mg dosage forms released 24.56%, 24.06%, and 23.44%, respectively, of their total MPH during the first interval of Plaintiffs' dissolution studies. See id. at 271:3-272:7; PX 242; PX 244, PX 246. However, in accordance with the Court's construction, the release of any IR MPH must be excluded before determining whether an accused product exhibits an "ascending release rate." To do this, Plaintiffs relied on the fact that Defendants represented in their ANDAs that 25% of the MPH contained in their proposed products was contained in an immediate-release coating. See,

e.g., PX210 at ANDX206 (Andrx's ANDA "Composition Statement"); Tr. (Vol. 1), D.I. 148 at 251:5-16; 253:4-254:13. Under this assumption, because none of the ANDA products released more than 25% of their MPH during the first testing interval, Plaintiffs' dissolution tests demonstrate that, on average, no non-IR MPH is released during the first interval of an appropriate dissolution test. With regard to the 18 mg ANDA products, Plaintiffs contend that because they are "proportionally equivalent" to the 54 mg tablets they will exhibit equivalent dissolution rates. See Tr. (Vol. 1), D.I. 148 at 261:18-262:10.[4]

Notwithstanding these results demonstrating that, on average, no non-IR MPH is released during the initial interval of Plaintiffs' dissolution studies, Plaintiffs contend that Andrx's ANDA products still infringe. Briefly, Plaintiffs contend that their in vitro dissolution testing demonstrates that in a substantial number of tablets, the amount of MPH recovered during the first testing interval is too large to be attributable solely to the IR portion of the tablet. Hence, Plaintiffs contend that a reasonable conclusion is that some non-IR MPH is in fact released during the first interval. PFF ¶ 253. Plaintiffs further note that although the ANDA products are designed to have

[4] In addition, Plaintiffs conducted an "analysis" of dissolution data contained in Andrx's ANDA from which they conclude that the accused 18 mg ANDA products exhibit an "ascending release rate" over an extended time frame. See id. at 262:11-264:24.

25% of their total MPH in an IR coating, the actual amount of IR MPH can vary from 22.5% to 27.5% of the total MPH. See Tr. (Vol. 5), D.I. 152 at 1310:7-1311:3; DTX 1187 at ANDRX 36308. If one assumes that all of the tested samples are at the lower limit of allowable MPH in the IR layer (22.5%), Plaintiffs' dissolution studies allegedly demonstrate that 31 of the 36 samples tested released some non-IR MPH during the first testing interval. See Tr. (Vol. 5), D.I. 152 at 1314:19-1315:1, 1312:18-1313:19, 1313:20-1314:17, 1314:18; PX 732; PX 733; PX 734. If one assumes that all samples are at the middle of the prescribed range (25%), then seven of the 36 samples tested allegedly released some non-IR MPH during the first testing interval. See Tr. (Vol. 5), D.I. 152 at 1311:17-22; PX 241; PX 243; PX 245. On average, these seven samples released an additional 1.3% of their total MPH during the first interval of the dissolution test. See PX 241; PX 243; PX 245. Finally, if one assumes that all samples are at the upper limit of the allowable range (27.5%), one of the 36 tested samples allegedly released non-IR MPH during the first measurement interval of Plaintiffs' dissolution studies. See Tr. (Vol. 5), D.I. 152 at 1311:4-16. Noting that "an accused product that sometimes, but not always, embodies a claimed method nonetheless infringes . . .," Bell Communications Research v. Vitalink Communications Corp., 55 F.3d 615, 622-623 (Fed. Cir.

1995), Plaintiffs contend that this evidence confirms infringement.

Andrx responds that Plaintiffs' approach of making assumptions regarding the fraction of total MPH contained in the IR-coating is simply wrong. DFF ¶ 550. The correct assumption, Andrx contends, is that "the amount of methylphenidate released in the first hour of the dissolution test is all attributable to the IR portion of methylphenidate," an assumption Andrx terms the "first hour IR assumption." Id. ¶ 551. With the Court's construction of "ascending release rate" requiring the release of some non-IR MPH during the first measurement interval of an appropriate dissolution test, adoption of this assumption would amount to a finding of non-infringement.

ii. Decision

For the reasons set forth below, the Court concludes that substantial evidence supports the "first hour IR assumption," and that Plaintiffs have not adequately rebutted this evidence so as to establish infringement by a preponderance of the evidence.

In support of the "first hour" assumption, Andrx first points to the results of dissolution studies carried out on only the delayed release cores ("DRCs") of the ANDA products (i.e., ANDA products that do not include an IR-MPH coating). These studies demonstrated that in the 27, 36, and 54 mg ANDA products, the DRCs released no MPH in the first hour of a dissolution test

utilizing USP apparatus 1. See DTX 1141; DTX 1142; DTX 1143; Tr. Vol. 1, (D.I. 148) at 558:21-560:16. In fact, on reviewing the results of Andrx's DRC tests, the Court concludes that an appreciable amount of MPH is not released from the DRC until the 90 minute point of the dissolution test, at which point the release rate increases rapidly and then remains relatively constant over roughly the next six hours. See DTX 1141; DTX 1442; DTX 1143.

Plaintiffs contend first that Andrx's DRC dissolution tests are unreliable methods of determining release rate from the DRC core. According to Plaintiffs' expert, Dr. Martyn Davies, the additional manufacturing processes involved in applying the IR coating to a DRC, which include abrading and rubbing of the tablet cores, are likely to increase the rate at which the DRCs release MPH. See Tr. Vol. 5 (D.I. 152), at 1250:9-1251:21. The Court is unconvinced by this testimony. First, Dr. Davies's testimony is unsupported by any experimental evidence or documentation. Second, Dr. Davies testified that it was "likely" that the manufacturing process would cause a change in the release characteristics of the DRCs and that he believed "that's the possibility absolutely" that this would result in an increased rate of MPH release from the DRC. Id. (emphasis added). This language - and the lack of evidence supporting the testimony - suggests that this is merely a theory or hypothesis

of Dr. Davies. Much more is required to establish infringement, and, in the Court's view, Andrx's DRC studies remain compelling evidence of non-infringement.

Plaintiffs further respond to Andrx's DRC studies with evidence of other Andrx dissolution tests that allegedly do, in fact, demonstrate that the ANDA DRCs release MPH during the first interval of an appropriate dissolution test. This evidence, consisting of four documents, was introduced during Plaintiffs' rebuttal case through the testimony of Dr. Davies. See PFF ¶ 268; Tr. (Vol. 5), D.I. 152 at 1252:3-1253:3, 1254:8-1255:11, 1307:7-1308:4; PX 197A at 63300; PX 557 at 46113-114; PX 563 at 66282. However, it is questionable whether the documents Dr. Davies pointed to even correspond to the testing of ANDA products. Indeed, the documents relied upon by Dr. Davies tend to demonstrate that the studies correspond to products that do not actually fall within the ANDA's specification because, at t=4 hours, the samples described in the studies all exhibited an MPH release that exceeded the limits set forth in the ANDAs. See PX 197A at ANDRX 63330 (though lacking a data point at t=4 hours, interpolation suggests that release exceeded the permissible threshold by roughly 5%); PX 557 at ANDRX 46113 (at t=4 hours release exceeded permissible threshold by 28%); PX 557 at ANDRX 46114 (at t=4 hours release exceeded permissible threshold by 14%); PX 563 at ANDRX 66282 (at t=4 hours release exceeded

permissible threshold by 24%). Furthermore, one document Dr. Davies pointed to did not even include a sampling point until 1.5 hours, making it unclear whether any MPH was even released during the first hour of the dissolution test described in the document, as the Court's construction requires. See PX 197A at ANDRX 63300. The three other documents Dr. Davies pointed to are mere excerpts taken from researcher laboratory notebooks that lack a clear connection to the ANDA products. See PX 557 at ANDRX 46081; PX 563 at ANDRX 66189. Accordingly, in the Court's view, these documents do not establish by a preponderance of the evidence that the ANDA DRCs exhibit MPH release within the first interval of an appropriate dissolution test.

As further support for the "first hour" assumption, Andrx points to dissolution studies its researchers carried out on the final ANDA products. These studies included sampling times not just at t=1 hour, but also at t= 30 minutes. See PX 18 at ANDRX 00201-05; PX 25 at ANDRX 04042-43; DTX 388 at ANDRX 46502; DTX 1179. The data from these studies shows that during the first 30 minutes of the dissolution study, roughly 25% of the total MPH is released, while very little MPH, if any, is released during the second 30 minutes of the study. Indeed, with regard to Andrx's dissolution tests on the 18 mg ANDA products, Plaintiffs' dissolution expert, Vivian Gray, testified on cross-examination as follows:

> Q. Okay. But this gives us some information about there is something releasing pretty quickly in the .5 and pretty much nothing releasing in the second period, right, looks like there is a gap there?
>
> A. Yes.

Tr. (Vol. 1), D.I. 148 at 339:3-8. Showing that the ANDA products release essentially no MPH for at least 30 minutes after an initial burst of MPH is released, these studies strongly suggest that any MPH release during the first hour of an appropriate dissolution test is, in fact, attributable to the IR component of the dosage form.

As a final piece of evidence in support of the "first hour IR assumption," Andrx points to "IR overcoat studies," which were carried out by Alza's own testing laboratories. These studies, which focused on the release of MPH from the IR overcoat, utilized USP apparatus 1 and included a sampling point every 15 minutes. See DTX 397A; DTX 1175. Briefly, the studies demonstrated that roughly 23% of the MPH is released within 15 minutes, but that it takes another 75 minutes for the release to exceed 24%, again strongly suggesting that MPH release during the first hour of an appropriate dissolution test is attributable to the IR component. Id.; see also Tr. (Vol. 2), D.I. 149 at 562:21-563:14 (Defendants' expert, Dr. Umesh Bankar, describes the "IR overcoat" studies). With regard to the slight increase in percentage MPH released from t=30 to t=75 minutes, Defendants' expert, Dr. Umesh Banakar, testified that (1) the increase was

within the measurement error of the dissolution tests, and (2) the increase was too small to reflect release from the delayed release core. See Tr. (Vol. 2), D.I. 149 at 563:15-565:3. In light of Andrx's DRC and finished product studies discussed above, the Court finds this testimony credible. Plaintiffs' dissolution expert, Vivian Gray, testified as follows with regard to the "IR overcoat" studies:

> Q. Okay. Does this look like to you as an dissolution expert that what you have got happening here is you have got an IR and basically your ER [sic] starts to begin releasing roughly around the ninety minute time frame?
>
> A. We can't know.
>
> Q. You can't tell?
>
> A. You know, because we don't know exactly which is coming from the tablet core and which is coming from -- but we you can assume when it starts getting above 25 percent that there is --
>
> Q. If we look at just the 25 percent, that also throws us past ninety minutes; correct?
>
> A. Yes

Tr. (Vol. 1), D.I. 148 at 351:22-352:13. Thus, Ms. Gray testified that one could, at most, "assume" that release of MPH from the tablet core does not occur until after the t=90 minute mark, when the percentage of MPH release exceeded 25%. Otherwise, Ms. Gray testified that "[w]e can't know" whether at earlier points MPH was in fact being released from the tablet core, casting doubt on Plaintiffs' theory that, in some fraction of ANDA products, MPH is released during the first interval of an appropriate dissolution test.

In sum, the Court concludes that Plaintiffs have not adequately rebutted the above evidence tending to establish that the ANDA products do not release any non-IR MPH during the first hour of an appropriate dissolution test, which the Court's construction requires. Accordingly, the Court concludes that Plaintiffs have not established that the administration of Andrx's proposed products to treat ADHD would constitute a direct infringement of claim 1 of the '373 patent.

2. Claims 6 And 7

Having concluded that Defendants' ANDA products, if sold, would not infringe claim 1 of the '373 patent, the Court further concludes that Defendants' ANDA products would also not infringe claims 6 and 7, which depend from claim 1.

IV. INVALIDITY

Defendants allege that claims 1, 6 and 7 of the '373 patent are invalid as (1) obvious and (2) not enabled.

A. Obviousness

1. Applicable Law

In pertinent part, 35 U.S.C. § 103 provides that a patent may not be obtained "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious to a person having ordinary skill in the art." 35 U.S.C. § 103. Obviousness is a question of law that is predicated upon several factual

inquiries. Richardson-Vicks v. Upjohn Co., 122 F.3d 1476, 1479 (Fed. Cir. 1997). Specifically, the trier of fact must consider four issues: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed subject matter and the prior art; and (4) secondary considerations of non-obviousness, such as commercial success, long felt but unsolved need, failure of others, and acquiescence of others in the industry that the patent is valid, and unexpected results. Graham v. John Deere Co., 383 U.S. 1, 17-18, (1966)(the "Graham factors"). The Supreme Court, in KSR Intern. Co. v. Teleflex Inc., 550 U.S. 398 (2007), reaffirmed that the Graham factors "continue to define the inquiry that controls" an obviousness analysis.

Because an issued patent is presumed valid, the party seeking to challenge the validity of a patent based on obviousness must demonstrate by clear and convincing evidence that the invention described in the patent would have been obvious to a person of ordinary skill in the art at the time the invention was made. Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1359-60 (Fed. Cir. 2007). Clear and convincing evidence is evidence that places in the fact finder "an abiding conviction that the truth of [the] factual contentions are 'highly probable.'" Colorado v. New Mexico, 467 U.S. 310, 316 (1984).

2. Discussion

The Court will now consider in detail each of the four Graham factors. As set forth below, Defendants' arguments are well taken, and some of the evidence Defendants present does indeed weigh in favor of a finding of obviousness. However, the Court ultimately concludes that Defendants have not met their burden of proving by clear and convincing evidence that the '373 patents is invalid as obvious.

a. The Scope And Content Of The Prior Art

Defendants rely on a number of pieces of prior art in support of their obviousness argument. Plaintiffs dispute the scope of the teachings of this art. The Court will summarize the parties' position on each key piece of prior art in turn and then state its overall conclusion regarding the scope and content of this prior art.

i. Angrist

Defendants point out that the 1987 publication by Burton Angrist on central nervous system ("CNS") stimulants states that "a type of tolerance to CNS stimulants that clearly does occur clinically is an acute tolerance after a single dose, which disappears quickly." DTX 626 at 112-13. Defendants' expert, Dr. Michael Mayersohn, testified that because MPH is a CNS stimulant, one of skill in the art would, upon reviewing the Angrist publication, understand that MPH would likely exhibit acute

tolerance. Tr. (Vol. 3), D.I. 150 at 821:11-825:11. Dr. Mayersohn further testified that amphetamine was a close chemical analog of MPH and one of the first drugs used to treat ADHD. Id.

Plaintiffs respond that the Angrist publication does not mention MPH and was focused on cocaine and d-amphetamine, and, in particular, the binging activity of drug abusers taking these substances. DFF ¶ 481. Plaintiffs' expert, Dr. Kennerly Patrick, testified that, in these circumstances, those of skill in the art seeking to treat children with ADHD would not have looked to the Angrist publication for guidance. Tr. (Vol. 4), D.I. 151 at 1046:5-1047:18. Dr. Patrick further testified that one of skill in the art working on MPH would be unlikely to look to studies focused on cocaine and amphetamine because their physiological mechanism of action differs from that of MPH. Id. at 1048:15-1049:5.

ii. Birmaher

Defendants note that the 1989 publication by Birmaher et al. regarding plasma studies on Ritalin SR® reported a "flattened curve of MPH plasma concentrations after MPH-SR ingestion" and stated that this "raise[d] a question about whether MPH-SR may be more prone to tachyphylaxis" (i.e., acute tolerance). DTX 627 at 771. The Birmaher publication further states that the observed "flattened curve" was similar to what had been previously observed with amphetamines, where tachyphylaxis was a confirmed

phenomenon. Id. Based on this, Defendants contend that the Birmaher publication, like the Angrist publication, confirms that MPH had been associated with acute tolerance prior to the filing of the '373 patent.

In response, Plaintiffs' expert, Dr. Patrick, testified that although tachyphylaxis was mentioned in the Birmaher publication, it was merely mentioned as one of many possible causes for the lack of efficacy of Ritalin SR® compared to Ritalin®. Tr. (Vol. 4), D.I. 151 at 1038:3-1040:13. Other possible causes mentioned in the Birmaher publication include problems with absorption of Ritalin-SR® in the gastrointestinal track, delayed Ritalin SR® absorption, pharmacokinetic differences between Ritalin SR® and Ritalin®, and different brain receptor responses to Ritalin SR® and Ritalin®. DTX 627 at 768. To the extent the authors of the Birmaher publication pointed to tachyphylaxis as a cause, they cited only to a personal communication from another researcher. See id. Dr. Patrick testified that such a citation was unusual and a "peculiar way to substantiate a position." Tr. (Vol. 4), D.I. 151 at 1040:21-1041:10. Furthermore, Plaintiffs note that the Birmaher publication acknowledges that the study described therein was based on less than ideal controls and was not based on a comparison to standard twice-daily MPH dosing. DTX 627 at 771. In these circumstances, Plaintiffs contend that any

conclusions stated in the Birmaher publication should be given little weight. PFF ¶ 447.

iii. Perel

Defendants point to an abstract published by Dr. J. M. Perel at the Ninety-Second Annual Meeting of the American Society for Clinical and Pharmacology and Therapeutics that states that MPH was associated with a phenomenon called "clockwise hysteresis." DTX 153. Defendants pair this with a supplement to an FDA Citizen Petition submitted by Defendant McNeil that explains that acute tolerance is "seen graphically as a clockwise hysteresis in the plasma concentration-effect relationship." PX 266 at Vol. 1 Pg. 8. Thus, according to Defendants, Perel's prior observation of clockwise hysteresis was tantamount to an observation of acute tolerance.

Plaintiffs expert, Dr. Patrick, however, testified that, like the Birmaher publication, the Perel abstract would not have been of interest to those working on ADHD treatment because of flaws in Perel's study. In particular, Dr. Patrick testified that the Perel study involved MPH doses irrelevant to the treatment of pediatric ADHD patients and involved drawing blood from children using needles. The latter factor, Dr. Patrick explained, undermined the study because the effect of the subject observing blood being drawn would be difficult to "separate" from the underlying ADHD. Tr. (Vol. 5), D.I. 152 at 1040:21-1041:10.

iv. Fung

Defendants contend the 1984 article of Ho-Leung Fung on the use of nitrates to treat angina recognized that acute tolerance was associated with nitrates and proposed addressing that problem by providing an ascending release rate. Specifically, Fung stated that to overcome nitrate tolerance "an alternate input mode might be one that involves escalating rates of drug delivery so that increasing systemic nitrate concentrations may be acheived." DTX 631 at 25. Defendants expert, Dr. Mayersohn, testified that the long-acting nitrates were particularly relevant because, like CNS stimulants, they have a "very high body clearance" and that one of skill in the art would be "encouraged" by the Fung article. Tr. (Vol. 3), D.I. 150 at 842:23-851:6.

Plaintiffs respond that the Fung article explicitly stated the "escalating rate" dosing proposal was made in a "speculative fashion" and admitted that the "dosing approach [had] to be experimentally tested." DTX 631 at 25. Furthermore, Plaintiffs' expert, Dr. Patrick, testified that the novel dosing mode proposed in Fung provided a nitrate concentration far in excess of that provided with the conventional nitrate dosing mode and that, if this approach were taken with MPH, there would be intolerable side effects. See Tr. (Vol. 4), D.I. 151 at 1059:22-1060:6. Indeed, according to Dr. Patrick, providing an MPH

concentration so far in excess of the conventional dose, as proposed in Fung, could pose a safety concern and even lead to hospitalization. Id. at 1060:18-1061:3.

Dr. Patrick, further testified that in subsequent patents and publications Fung had, in fact, abandoned this approach in favor of a constant release rate of a related class of drugs. See Tr. (Vol. 4), D.I. 151 at 1064:14-1065:22; PX 420 at 2:3-7. Likewise, over a decade after making his "escalating rate" dosing proposal, Fung admitted in a publication that the efficacy of the "escalating rate" dosing approach compared to intermittent therapy had not been evaluated. See DTX 1221 at 1143. Dr. Patrick testified that this fact was consistent with his conclusion that those of skill in the art would not have viewed prior art pertaining to nitrates as being relevant to treating ADHD. See Tr. (Vol. 5), D.I. 152 at 1191:13-1192:8.

v. Bayer

U.S. Patent No. 4,956,181 issued to Bayer et al., like Fung, dealt with nitrate therapy. Notably, Bayer includes a passage specifically discussing Fung, which explained that Fung had previously disclosed "escalating rates of drug delivery." See DTX 632 at 1: 42-61. Bayer further disclosed a transdermal nitrate delivery system in which, following a "washout period," the delivery rate is increased during a "ramp-up" time of about 8 to 21 hours. Id. at 3:10-50. Plaintiffs' expert, Dr. Martyn

Davies, testified that this system could have been used with MPH to provide an ascending release rate. Tr. (Vol. 5), D.I. 152 at 1245:12-18. In addition, Bayer explained that "pills, tablets, capsules, and caplets for oral administration" could be adapted for use "in accordance with the invention." DTX 632 at 8:51-57.

Dr. Patrick, testified that one of skill in the art trying to develop a once-a-day treatment for MPH would not, however, have found Bayer useful because (1) it dealt with a 24-hour time frame and (2) pertained to nitrates, which have a much higher margin of safety than MPH. See Tr. (Vol. 4), D.I. 151 at 1062:13-24. Dr. Patrick further explained that Bayer did not disclose an ascending release through the midpoint of the T_{90} of a dosage form. Id. at 1063:1-5.

vi. Wong

U.S. Patent No. 5,156,850 to Wong et al. specifically taught methods of manufacturing osmotic dosage forms that,[5] after an initial period of no release, provided ascending release for at least three hours and through the midpoint of the T_{90}. See,

[5] Briefly, osmotic dosage forms are a species of oral dosage forms that "utilize osmotic pressure to generate a driving force for imbibing fluid into a compartment formed, at least in part, by a semipermeable wall that permits free diffusion of fluid but not drug or osmotic agent(s), if present. A substantially constant rate of drug release can be achieved by designing the system to provide a relatively constant osmotic pressure and having suitable exit means for the drug formulation to permit the drug formulation to be released at a rate that corresponds to the rate of the fluid imbibed as a result of the relatively constant osmotic pressure." '373 patent at 3:15-25.

e.g., DTX 634 at 18:36-51, Figs. 10-11. Wong lists MPH as a drug that could be used in conjunction with the methods disclosed therein. Id. at 10:16-29. Furthermore, Defendants' expert, Dr. Mayersohn, testified that one of the drugs Wong discusses at length, verapimil, has a solubility similar to MPH. One of skill in the art, Dr. Mayersohn testified, would thus expect MPH to be released from the Wong dosage forms similarly to verapimil. Tr. (Vol. 4), D.I. 151 at 888:15-21.

However, Dr. Patrick testified that the drugs discussed in Wong have a different mechanism of action from MPH. Id. at 1067:24-1068:16. Dr. Patrick further questioned the relevance of Wong because certain release profiles set forth in Wong would lead to very little drug reaching the bloodstream during the hours shortly after administration and also include an extended period of steady release. Such a profile, Dr. Patrick explained, would be ineffective for ADHD treatment because it would provide inadequate therapy during the early portion of a child's school day and, conversely, provide too much therapy when a child eats dinner and prepares for sleep. Id. at 1069:3-19. Finally, Plaintiffs point out that Defendants' expert, Dr. Mayersohn, testified that Wong included no mention of using the methods described therein to treat either acute tolerance or ADHD. Id. 970:5-971:13.

vii. Statements By The Patentees Regarding The Scope And Content Of The Prior Art

Defendants contend that the patentees made statements in provisional patent applications confirming that those in the art understood that acute tolerance was associated with MPH prior to the filing of their patent application. Specifically, Defendants note that in the "Background of the Invention" section of provisional application 60/030,514 the patentees stated that "[f]or drugs that act on the central nervous system, like methylphenidate . . . the patient often develops an acute tolerance to the drug . . . ." DTX 152 at PALZ 0007772:19-000773:2. Dr. Mayersohn testified that this confirmed his view that acute tolerance was known for CNS stimulants like MPH. Tr. (Vol. 3), D.I. 150 at 825:12-826:18. Defendants further note that Dr. Diane Guinta, a named inventor of the patent-in-suit, testified with regard to the provisional application that this statement meant that before she did her work it was "known clinically" that patients often develop an acute tolerance to MPH. Tr. (Vol. 1), D.I. 148 at 120:10-122:9.

viii. The Court's Conclusions Regarding The Scope And Content Of The Prior Art

Defendants' general position on obviousness is that the prior art, taken as a whole, sets forth both a known problem (acute tolerance to MPH) and a known solution (MPH dosage forms

that provide ascending MPH release). The Court will address the extent to which the prior art includes both of these concepts.

In light of Angrist, Birmaher, and Perel, the Court finds that, prior to the filing of the '373 patent, those of skill in the art were familiar with the concept of acute tolerance and were aware of the possibility that this could occur with MPH. However, the Court also finds that the suggestion of acute tolerance with MPH had not gone far beyond the stage of being a hypothesis. Indeed, Angrist did not mention MPH specifically, referring only to CNS stimulants generally. Given the complex and unpredictable behavior of pharmaceutical compounds, the Court cannot conclude that Angrist confirmed that acute tolerance was associated with MPH. Likewise, Birmaher merely "raised a question" as to whether acute tolerance occurred with MPH. DTX 627 at 771.

In noting the phenomenon of "clockwise hysteresis" in connection with MPH, the Perel abstract provides the most definitive suggestion that MPH might be associated with acute tolerance. Though Plaintiffs note potential deficiencies in the study associated with the Perel abstract, such deficiencies do not change the fact that Perel unequivocally linked "clockwise hysteresis" and MPH. Indeed, in a supplement to an FDA Citizen Petition, Plaintiff McNeil cited Perel as a study showing "that [MPH's] pharmacodynamic effects were predominant in the early

part of the absorption phase and were weaker after methylphenidate had reached its peak concentration." PX 266 at Vol. 1 Pg. 9. However, as Defendants note, even after Perel, other possible explanations for the relative lack of efficacy of MPH-SR remained in play. For instance a 1992 publication by Dr. Laurance L. Greenhill, who was an author on the Perel abstract, mentioned "tachyphylaxis" (i.e., acute tolerance) along with poor compliance at home with taking medication, unpredictable release of MPH from the dosage form core, change in the patient's weight, and new stress in the environment as possible explanations. DTX 630 at 6. Where, after publication of the Perel abstract, one of its authors remained unable to fully discount something so straightforward as compliance issues as being the cause of MPH-SR's inefficacy, the Court cannot conclude that Perel settled the issue of whether MPH was associated with acute tolerance. Nevertheless, the Court does not fully discount the suggestions in the prior art that MPH may be associated with acute tolerance, and finds that they are deserving of some weight.

With respect to whether, prior to the time of filing, there was a known solution to the acute tolerance problem, the Court finds that the general concept of providing increasingly larger doses of the relevant drug was, in fact, suggested as a possible solution to the acute tolerance problem with nitrates. Indeed, Bayer, citing to Fung as background information, explicitly

disclosed the use of an increasing drug release rate to overcome tolerance to nitrates. See generally DTX 632.

Though Bayer was focused on transdermal delivery means, shortly thereafter, Wong disclosed means for preparing oral osmotic dosage forms that seemingly could be used to provide an ascending release rate. Wong further stated that the methods described therein could be used with MPH. However, on reviewing Wong, the Court finds that there is no suggestion that the periods of ascending release provided by the disclosed dosage forms would have any utility to the acute tolerance problem. Indeed, Wong does not mention acute tolerance at all. Furthermore, the Court finds that Wong's reference to MPH as a drug that could be used with the disclosed dosage forms carries little weight given the number of drugs listed in Wong. See DTX 634:48-68 (disclosing an undifferentiated laundry list of drugs that could be used with the disclosed dosage forms). Likewise, although Wong discloses release profiles for verapamil and nicardipine, the Court is not persuaded that one of skill in the art would conclude that MPH would necessarily exhibit similar release profiles when used in conjunction with the Wong dosage forms. The testimony on this issue by Defendants' expert, Dr. Mayersohn, was vague and conclusory. See Tr. (Vol. 3), D.I. 150 at 858:15-24. In the Court's view, the Wong reference would have provided, at the very most, a possible starting point for one of

skill in the art to begin development of oral osmotic dosage forms that provide an ascending release of MPH.

With respect to Fung, the Court disagrees with Plaintiffs that Fung's patents and publications during the 1990s demonstrates that Fung abandoned his 1984 suggestion to overcome acute tolerance to nitrates by providing "escalating rates of drug delivery." Indeed, Fung states in a 1997 publication that "[t]he concept of dosage escalation to overcome nitroglycerin tolerance is well accepted clinically" and states that their "simulations similarly predict that rising input functions would improve the efficacy of a given dose of NTG administered over 12 hours." DTX 1221 at 1144.

Nevertheless, the Court finds that the overall scope of the prior art pertaining to overcoming acute tolerance to MPH is quite limited. In the Court's view, though identifying the nitrate art, Defendants have not identified any additional art suggesting the use of escalating release to overcome acute tolerance to a meaningful range of drugs. Significantly, the Court finds no art that suggests the use of escalating release to overcome acute tolerance to MPH. Similarly, outside of the transdermal dosage form of Bayer, which is intended to be used with nitrates, the Court sees no additional art explicitly setting forth other dosage forms specifically intended to provide ascending release for the purpose of overcoming acute tolerance.

Plaintiffs argue strenuously that the prior art teaches away from the claimed invention. For instance, Plaintiffs' expert, Dr. Patrick, testified that experience with the prior art BID dosing regimen taught that certain features of the plasma profile it produced were essential. In particular, Dr. Patrick testified that the BID dosing regimen resulted in an MPH blood plasma profile with a mid-day trough, which was thought to be critical to avoid lunch-time appetite suppression, a know side effect of MPH. See Tr. (Vol. 4), D.I. 151 at 1017:23-1019:3. Recognizing this, Dr. Patrick testified, one of skill in the art attempting to develop a once-a-day ADHD treatment would have tried to duplicate the BID plasma profile. Id. at 1023:2-19. Furthermore, according to Dr. Patrick, even if one of skill in the art was fully aware that MPH was associated with acute tolerance, such a person attempting to develop a once-a-day treatment for ADHD would still try to mimic the BID profile because the mid-day trough allowed dissipation of drug tolerance. Id. at 1042:7-20. Dr. Patrick further testified that, compared to the relatively ineffective Ritalin-SR, the BID dosing regimen produced an MPH plasma profile that initially ascended somewhat more quickly. Dr. Patrick referred to this initial rapid ascension as the "ramp effect" and suggested that even small deviations from the BID plasma profile could lead to large changes in effectiveness. Id. at 1017:4-22. According to Dr.

Patrick, one of skill in the art, recognizing the importance of this "ramp effect," would not try to develop an extended-release MPH drug product with an ascending release rate because, for such a product to maintain the "ramp effect," a lethal dose of MPH would be required. Id. at 1049:6-1052:3. As further evidence of the prior art teaching away from the claimed invention, Plaintiffs point to a 1996 study by the National Institutes of Mental Health, which recommended MPH dosing three times daily, with the last dose being smaller than the first two. See PX 593 at 5. According to one of the inventors, Dr. Diane Guinta, had it been known that acute tolerance was an issue with MPH, those of skill in the art would not have recommended a dosing regimen with decreasing dose size. Tr. (Vol. 1), D.I. 148 at 161:7-162:12. Dr. Patrick further testified that the smaller third dose was perceived to be necessary to avoid late-day side effects, such as appetite suppression and insomnia. See Tr. (Vol. 4), D.I. 151 at 1020:2-22.

Defendants general response to Plaintiffs' "teaching away" argument is that although providing the pulsatile MPH plasma profiles of the BID and TID dosing regimens presented one obvious solution to the acute tolerance problem, the mere availability of this solution does not necessarily teach away from other equally obvious solutions. According to Defendants' expert, Dr. Mayersohn, this is particularly so because the prior art BID and

TID dosing regimens established dosage bounds that ensured both safety, efficacy, and avoidance of side effects. See Tr. (Vol. 3), D.I. 150 at 860:22-862:22. Concerns over efficacy and side effects would not discourage someone of skill in the art, Dr. Mayersohn explained, from pursuing an ascending plasma concentration to overcome acute tolerance so long as they proposed treatments that produced plasma profiles within these established bounds. Id. Indeed, inventor Diane Guinta testified that before carrying out the studies that led to the '373 patent, Alza scientists assumed there would be no issues with side effects or safety because they were staying within these established boundaries. Tr. (Vol. 1), D.I. 148 at 138:6-140:14. With regard to the perceived importance of the "ramp effect" of prior art BID dosing, Defendants note that Dr. Patrick testified that it was a "stretch" to view the "ramp effect" as the explanation for the efficacy of BID dosing and that this was "simply one of many speculations" on the issue. Tr. (Vol. 4), D.I. 151 at 1017:4-15. As to the importance of the mid-day trough associated with prior art BID and TID dosing, Defendants contend that there were reasons to believe such a trough was undesirable and that it should not necessarily be mimicked in a once-a-day ADHD treatment. Specifically, Defendants note that Plaintiffs' expert, Dr. Feifel, testified at deposition that there are adverse effects associated with downward transitions in

MPH blood plasma profiles. See Feifel Dep. Tr. at 170:22-171:8. Likewise, Defendants note that there was an undesirable "rebound effect" associated with the wearing off of the effects of individual MPH doses in BID and TID dosing plans. See, e.g., DTX 1146 at ALZ0095074.

On reviewing the evidence presented by the parties, the Court concludes that the prior art did not significantly teach away from the claimed invention. The Court agrees with Plaintiffs that there were perceived virtues of the BID and TID dosing regimens, including safety, efficacy, and a general avoidance of side effects. However, the Court is unconvinced that the virtues of these dosing schemes suggested that other solutions, including an ascending release rate, would not work. With regard to the mid-day trough associated with BID dosing, the Court finds that those of skill in the art hypothesized that it conferred both benefits and drawbacks, not that it was necessary. Dr. Patrick's testimony on the importance of the "ramp effect" in BID dosing was equivocal and inconclusive. To the extent the prior art BID dosing regime guided later work, the Court finds that it did so by teaching an acceptable therapeutic dosing range. In the Court's view, such a teaching may have set constraints on ascending-release dosage forms, which, though possibly assisting in the development of such dosage forms, would not necessarily have taught away.

The most compelling evidence Plaintiffs present of the prior art teaching away from "ascending release" is the 1996 study by the National Institute of Mental Health, which recommended TID dosing with the third dose being half as large as the first two doses. The Court agrees with Plaintiffs that the recommendation of decreasing dose size provides some additional evidence that those in the art were not aware in 1996 that MPH was associated with acute tolerance. However, the Court disagrees that the possibility of this smaller dose size reducing side effects taught away from the claimed invention. Indeed, as Defendants note, the specification of the '373 patent explains that the standard TID regimen included three equal 5 mg doses of Ritalin® and led to a peak in the plasma drug concentration at roughly the 9-hour mark. See '373 patent at 21:25-22:45, Fig. 4. Inventor Dr. Diane Guinta testified that "people supposed" that MPH plasma concentrations remaining below this peak would be acceptable in terms of insomnia. Dr. Guinta further testified that insomnia remains a problem with Concerta® and that concerns over insomnia did not stop the Alza researchers from going forward with their studies on ascending release. See Tr. (Vol. 1), D.I. 148 at 148:15-150:6. Accordingly, the Court is not persuaded that the MTA study would dissuade those of skill in the art as from looking into ascending release of MPH as a means for treating ADHD.

b. The Level Of Ordinary Skill In The Art

According to Defendants' expert, Dr. Mayersohn, a person of ordinary skill in the art would have at least a B.S. or Pharm.D. in Pharmacy or a B.S. in chemistry, biology, or engineering or a related scientific subject area. A person of skill in the art would also have several additional years training either through coursework or work experience. This experience would pertain to the development and evaluation of pharmaceuticals and involve an understanding of pharmacokinetics, pharmacodynamics, and possibly clinical medicine. Tr. (Vol. 3), D.I. 150 at 871:10-872:10; Tr. (Vol. 4), D.I. 151 at 896:20-900:17.

Plaintiffs demand more of one of skill in the art than Defendants do. Indeed, Plaintiffs' expert, Dr. Patrick, testified that one of skill in the art would have an M.D. or a Ph.D. in clinical pharmacology, clinical psychology, or a comparable scientific field. A person of skill in the art would further have at least two years of practical experience gained through residency, post-doctoral research, or the like. Tr. (Vol. 1), D.I. 148 at 112:4-114:4. This advanced clinical training would imbue one of skill in the art with an understanding of the causes of ADHD, the primary patient population, and the treatment options that were available to treat ADHD. Tr. (Vol. 4), D.I. 4 at 1010:12-1011:1. According to Dr. Patrick, without this level of advanced training, one

cannot fully understand the complex nature of ADHD and the nuances of treating it. Id. at 1010:12-1011:1.

Thus, the dispute between the parties appears to have two parts. First, the parties dispute whether one of skill in the art must have particularized knowledge relating to ADHD. Second, the parties dispute whether an M.D. or Ph.D. plus at least two years of additional training is required to attain this knowledge. A non-exhaustive list of factors the Court may consider in determining the level of ordinary skill in the art is as follows: (1) the educational level of the inventor; (2) the type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational levels of active workers in the field. Daiichi Sankyo Co. Ltd. v. Apotex, Inc., 501 F.3d 1254, 1256 (Fed. Cir. 2007).

The Court does not agree with Plaintiffs that one of skill in the relevant art must necessarily have clinical knowledge and experience treating ADD or ADHD. As Defendants note, there is no evidence offered by Plaintiffs that any of the inventors had such knowledge when embarking on the work that led to the '373 patent. Indeed, inventor Diane Guinta testified that when she began this work she thoroughly reviewed the literature and did market research to educate herself about MPH and ADHD, suggesting that she did not previously have the level of particularized knowledge

regarding ADHD that Plaintiffs contend is required of one skilled in the art. See Tr. (Vol. 1), D.I. 148 at 32:6-11. Furthermore, although the claims pertain to ADHD, the specification of the '373 patent is much broader and is not focused strictly on ADHD. The "BACKGROUND OF THE INVENTION" states generally that "the invention is directed to methods and devices that provide drug release within the gastrointestinal tract at an ascending release rate over an extended time period." '373 patent at 1:26-29. To the extent the specification discusses ADHD, it is careful to explain that this an "exemplary" disorder that can be treated using the invention of the '373 patent. Id. at 5:48-53, 6:53-65. The specification further explains that "[t]here are numerous clinical situations and drug therapies that could be improved with the use of dosage forms that provide a sustained and ascending release rate over an extended time period." Id. at 28-32. The specification then lists a series of drugs including, among others, analgesics, anesthetics, vasodilators and decongestants, none of which appear related to the treatment of ADD or ADHD. Id. 5:35-47. In these circumstances, the Court finds that one of skill in the art need not have specific knowledge in the field of ADHD.

Having concluded that particularized knowledge of ADHD is not required of one of ordinary skill in the art, the Court further finds that an M.D. or Ph.D. in a clinical science is

likewise not required. On reviewing the specification of the '373 patent, the Court concludes that it is focused to a large degree on the details of preparing dosage forms that provide particular release profiles. Indeed, the specification describes the structure of exemplary dosage forms in detail, including descriptions of component layers, "push layers," semipermeable membranes, and orifices for releasing the drug. See, e.g., '373 patent at 11:53-12:8, Fig. 1. The seven examples in the specification further detail the composition of these components and describe the technique for preparing the dosage form. See, e.g., id. at 13:63-14:11. Results of dissolution studies for each of the exemplary dosage forms are then summarized. See, e.g., id. at 14:15-35. However, Plaintiffs' expert, Dr. Patrick, testified that neither a typical practicing M.D. nor clinical psychologist would have experience with such dissolution tests. See Tr. (Vol. 4), D.I. 151 at 1101:16-23. Furthermore, not all of the originally named inventors earned an M.D. or Ph.D. in the clinical sciences. For instance, Jeri Wright, Atul Ayer, and Lawrence Hamel have no such degree. Although Ms. Wright was removed as an inventor on the '373 patent, she remains an inventor on the '129 patent, which shares the same specification as the '373 patent. Similarly, Padmaja Shivanand, who was also removed as an inventor on the '373 patent but remains an inventor on the '129 patent, holds a Ph.D. degree but had little

experience, if any, at the time she began working on Alza's methylphenidate project. Shivanand Dep. Tr. at 185:3-12, 185:24-186:10. The involvement of these individuals in the development of Concerta® and their status as inventors on a patent with the same specification as the '373 patent suggests that one of skill in the art need not, as Plaintiffs contend, have both a Ph.D. or M.D. and several years of experience.

The Court further finds no evidence in the record to suggest that an M.D. or clinical psychologist would have significant experience with the formulation of pharmaceutical dosage forms, a topic addressed at length in the '373 patent. Specifically, there is no evidence that such individuals would have knowledge regarding numerous details set forth in the specification such as the structural breakdown of dosage forms, the devices used to prepare dosage forms, and the processes for preparing dosage forms, including, for example, the number of newtons of force that must be applied to granulations to yield suitable capsules. See, e.g., '371 patent at 19:19-21:23. On the contrary, Plaintiffs' expert, Dr. David Feifel, a psychiatrist who treats patients with ADHD, testified at deposition that a "reasonable possibility" for overcoming acute tolerance would be to increase drug plasma levels. However, he testified that he would not know how to accomplish this task, and that it was outside his area of expertise. See Feifel Dep. Tr. at 91:10-92:8.

In sum, the Court finds that neither advanced experience related to ADHD nor an M.D. or Ph.D. in the clinical sciences is required of one of skill in the art. Based on the problem addressed in the '373 patent (i.e., the preparation of dosage forms that provide ascending release rates) and the fact that the inventors were employed by a drug company engaged in the development of new pharmaceuticals, the Court concludes that someone of skill in the art would have several years of practical experience related to drug development, including evaluation of pharmaceuticals, an understanding of pharmacokinetics and pharmacodynamics, and possibly some understanding of clinical medicine. As Defendants' expert, Dr. Mayersohn, testified, such experience could be in the form of coursework or practical experience.[6] See Tr. (Vol. 3), D.I. 150 at 871:10-872:10; see also Tr. (Vol. 1), D.I. 148 at 112:4-114:14 (Plaintiffs' expert, Dr. Patrick, testified that other than experience in "research drug development," nothing else came to mind as relevant experience for Plaintiffs' proposed M.D. or Ph.D. having ordinary skill in the art). Furthermore, having found that an M.D. or Ph.D. is not required of one of skill in the art, the Court concludes, as Defendants contend, that one of skill in the art

[6] The Court notes that this practical experience could be in the form of coursework and/or training that is required to acquire either an M.D. or Ph.D. in a clinical science.

need only have either a Pharm.D. or B.S. in a relevant field, such as chemistry or the biological sciences.[7]

c. The Differences Between The Claimed Subject Matter And The Prior Art

Defendants contend that there are only small differences between the prior art and the claimed invention. Defendants contend that the prior art taught (1) the treatment of ADHD with MPH dosage forms, (2) that acute tolerance was associated with MPH, (3) that this acute tolerance could be dealt with through the use of an ascending release rate, (4) methods for making dosage forms that provide ascending drug release rates, and (5) the acceptable ranges of MPH plasma concentrations that provide safe, effective treatment of ADHD. See DFF ¶ 742. To the extent the prior art, in particular Fung, fails to teach the claimed time frame for how long the MPH dosage form should provide ascending release, Defendants contend that aspects of the relevant time frame could be pieced together based on experience with the prior art BID and TID dosing schemes. For instance,

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[7] In the Court's view, neither party has clearly explained the pertinence of their definition of the ordinary level of skill in the art to the obviousness analysis. Plaintiffs seem to take the position that an individual with an M.D. or Ph.D plus additional particularized experience treating ADHD would disregard art outside the ADHD field, such as art pertaining to the treatment of nitrates with angina. Though the Court has declined to adopt Plaintiffs' definition for one of skill in the art, the Court nevertheless notes that it seems unlikely that someone of such skill and training would disregard teachings slightly outside the narrow field of the problem he or she is trying to solve.

Defendants contend that one of skill in the art would recognize that a once-a-day treatment for ADHD should release 90% of its MPH within about 8-9 hours, which is shortly before the last peak in the traditional TID treatment. Otherwise, according to Defendants' expert, Dr. Mayersohn, sleep patterns could be affected due to the ongoing presence of MPH in the bloodstream. See Tr. (Vol. 3), D.I. 150 at 862:8-863:19. Nevertheless, Defendants seem to acknowledge that the prior art does not explicitly teach ascending release for the greater of 3 hours or the midpoint of the T_{90}, as required by the claims. See DFF ¶ 786. Defendants contend that such a teaching is not required for a finding of obviousness because (1) Plaintiffs are asserting that their claims are entitled to the priority date of on earlier-filed patent application that does not recite ½ the T_{90} as a required time period, and (2) Defendants have put forth no rebuttal evidence to suggest that there is something non-obvious about this time frame. DFF ¶¶ 786-87.

In addressing this Graham factor, Plaintiffs largely reiterate their arguments that the prior art (1) did not show that MPH was associated with acute tolerance and (2) taught away from the claimed invention. See PFF ¶¶ 544-51, 564-65. The Court has set forth its findings on both of these issues above. See supra Parts IV.A.2.a.viii, IV.A.2.c. The Court discerns the following additional evidence in support of Plaintiffs'

positions on this Graham factor. Most notably, Plaintiffs point to the testimony of Defendants' expert witnesses indicating the limited development of ascending release dosage forms in the mid-1990s. For instance, Plaintiffs point to the testimony of Dr. Thomas Needham, who explained that during this time frame there were no drugs that exhibited an ascending release rate for three or more hours. See Tr. (Vol. 3), D.I. 150 at 663:10-14, 693:11-16, 709:2-9, 730:10-731:1. Likewise, Dr. Mayersohn testified that in 1997 he was not aware of any product that had been developed that overcame acute tolerance with a single dosing regimen. See Tr. (Vol. 4), D.I. 151 at 960:20-961:3. Testimony to a similar effect was provided by Plaintiffs' own expert witnesses. See id. at 1072:9-1-73:3

With regard to this Graham factor, Defendants devote a great deal of attention to their contention that Alza researchers were the first to confirm that MPH was associated with acute tolerance. However, the Court finds that this issue is of limited relevance to this Graham factor. Indeed, the claims are drawn to a method for treating ADHD with a dosage form that provides an escalating release rate. Though the claims may presuppose that MPH is associated with acute tolerance, Plaintiffs do not - indeed cannot - hold a patent on this piece of general knowledge. In these circumstances, the Court finds it difficult to meaningfully consider this issue in a comparison of

the scope and content of the prior art and the scope of the claims. However, as set forth above, the Court has considered this issue when analyzing the scope and content of the prior art.

In sum, having reviewed the evidence and argument on this factor, the Court identifies the following key differences between the prior art and the claimed invention:

- Though suggesting the use of escalating release as a method for addressing acute tolerance in nitrates, the prior art does not specifically disclose using escalating release to deal with acute tolerance when treating ADHD with MPH-based dosage forms.
- Though disclosing a transdermal dosage form for providing an escalating release of nitrates, the prior art does not disclose additional dosage forms intended to overcome acute tolerance by providing escalating release. The prior art does not disclose a proven method of providing an ascending release of MPH.
- Though disclosing a broad range of therapeutically acceptable MPH dosages for treating ADHD, the prior art does not specifically disclose that an ascending release MPH dosage form should provide ascending release for at least three hours and through the midpoint of the T_{90}.

d. Secondary Considerations Of Non-Obviousness

Plaintiffs contend that five secondary considerations support non-obviousness: (1) the long-felt need of others, (2) the failure of others in attempting to meet the need, (3) unexpected results, (4) copying, and (5) commercial success. The Court will consider each of these secondary considerations in turn.

i. The Long Felt Need Of Others And The Failure Of Others

With respect to these factors, which Plaintiffs consider together, Plaintiffs note that Ritalin SR® was introduced in 1984 as a once-daily MPH dosage form for treating ADHD, but was not widely adopted and was considered to be ineffective compared to the traditional BID dosing regimen. See Tr. (Vol. 4), D.I. 912:24-913:21; Tr. (Vol. 5), D.I. 5 at 1021:12-1022:1; DTX 630 at 5-6. According to Plaintiffs' expert, Dr. Patrick, it was not until Plaintiffs introduced Concerta® in 2000 that the need for a truly effective once-daily ADHD treatment was satisfied. See Tr. (Vol. 5), D.I. 5 at 1006:12-1008:11. Defendants' response to this position focuses on the 1997 Fung article which, as explained above, confirmed that Fung had not abandoned his earlier suggestion regarding the possibility of using escalating release to overcome acute tolerance. See DTX 631; DTX 1221; supra Part IV.A.2.a.viii. As Fung states in his 1997 article, his delay in pursuing his earlier suggestion was attributable to an inability to test complex dosing profiles, a situation that was remedied with the advent of computer-controlled delivery systems. DTX 631 at 1143-44. Thus, according to Defendants, failure to satisfy any long felt need was merely based on a need for technical advances in other fields, such as computer simulation. DFF ¶ 799-800. Defendants provide no additional evidence or expert witness testimony in support of this position,

and the Court remains unconvinced that this explains the failure to meet the long felt need for an effective once-daily ADHD treatment. In particular, the Court remains unconvinced that advanced computer techniques are required to test the effects of non-linear dosing schemes. Indeed, inventor Dr. Diane Guinta testified that a range of plasma profiles could be explored through "sipping studies," for instance. See Tr. (Vol. 1), D.I. 148 at 50:2-51:11. Accordingly, the Court finds that this factor weighs in favor of a finding of non-obviousness.

ii. Unexpected Results

Plaintiffs contend that those of skill in the art would have been surprised by the efficacy and minimal side effects associated with ADHD treatment methods involving steadily increasing plasma profiles. See, e.g., Tr. (Vol. 1), D.I. 148 at 34:17-24. For instance, based on the increase of insomnia and appetite suppression with Ritalin SR®, which produces a "flat" MPH plasma profile, Plaintiffs contend that one of skill in the art surely would have expected even more serious side effects with a product where the MPH plasma profile steadily increases. Defendants respond that, based on experience with prior art TID dosing, one could ensure safety, efficacy, and avoidance of side effects so long as the MPH plasma profile begins at the effective plasma level and ascends but stays below the last peak in the TID regimen. DFF ¶ 806. Defendants note, and the Court agrees, that

inventor Diane Guinta testified to this effect. See Tr. (Vol. 1), D.I. 148 at 139:18-140:14, 148:23-150:6. In light of this testimony, the Court agrees with Defendants that this considerations does not support a finding of non-obviousness.

iii. Copying

Plaintiffs contend that Defendants' copying of Concerta® and its delivery profile support the non-obviousness of the asserted claims. In support of their copying allegation, Plaintiffs point out that Defendants have informed the FDA that their ANDA products have a similar plasma profile to Concerta® and that Andrx scientists testified during deposition that the ANDA products were designed to be a generic bioequivalent to Concerta®. See PX 40; Cheng Dep. Tr. at 276-278, 280.

Defendants respond that claim 1 of the '373 patent does not require a particular plasma profile, only an "ascending release rate," which, as explained above, the Court has construed to require release of some non-IR MPH during the first interval of a dissolution test. However, the ANDA products, Defendants contend, are, unlike Concerta®, designed specifically to not release MPH during the first interval of a dissolution test. Thus, Defendants contend that they could not have copied Plaintiffs' commercial embodiment of the '373 patent. In light of the Court's claim construction and the Court's conclusions as to whether Defendants' ANDA products release MPH during the first

hour of a dissolution test, the Court agrees with Defendants that this secondary consideration does not support a finding of non-obviousness.

iv. Commercial Success

Plaintiffs devote great attention to this particular secondary consideration. By way of summary, the Court understands Plaintiffs as identifying the following key pieces of evidence demonstrating the commercial success of Concerta®:

- From August 2000 through 2006, there have been over 42 million Concerta® prescriptions resulting in over $4 billion in sales. See Tr. (Vol. 5), D.I. 152 at 1346:13-1348:13; PX 499.
- The compound annual growth rate of dollar sales of Concerta® has been approximately 23%, which is substantially faster than the growth of other MPH products. See Tr. (Vol. 5), D.I. 152 at 1360:13-1361:15.
- By 2006, use of Concerta® had grown to the point that total prescriptions and new prescriptions of Concerta® were four times greater than the total prescriptions and new prescriptions of the next closest MPH-based ADHD treatment. See Tr. (Vol. 5), D.I. 152 at 1354:16-1356:11; PX 505; PX 506.
- Given Concerta®'s overall market share, it must have displaced the traditional BID and TID dosing regimens. See Tr. (Vol. 5), D.I. 152 at 1352:18-1354:15.

However, "[e]vidence of commercial success, or other secondary considerations, is only significant if there is a nexus between the claimed invention and the commercial success." Ormco Corp. v. Align Tech., Inc., 463 F.3d 1299, 1311-12 (Fed. Cir. 2006). Pointing to the testimony of their expert witnesses, Plaintiffs

contend that such a nexus is established because Concerta® is within the scope of the asserted claims. See Tr. (Vol. 5), D.I. 152 at 1316:1-1319:10; Tr. (Vol. 2), D.I. 149 at 448:6-451:2. Furthermore, as Defendants' economic expert, Dr. Richard Rozek, testified, no other MPH based ADHD treatment besides Concerta® provides the delivery profile set forth in the '373 patent. See Tr. (Vol. 5), D.I. 152 at 1367:7-1368:2.

Defendants offer numerous responses to Plaintiffs' commercial success argument. First, Defendants dispute that all the claims cover Concerta®. Defendants note that Plaintiffs' expert, Dr. Martin Angst, testified that in an analysis of the plasma profiles of 77 individuals treated with Concerta®, less than 60% of the profiles met the limitations of claim 6 and less than 40% met the limitations of claim 7. See Tr. (Vol. 2), D.I. 149 at 449:15-23, 450:5-12. It is illogical, Defendants contend, to argue that the success of Concerta® is due to the subject matter of these claims when Concerta® does not always meet the claim limitations. However, Plaintiffs do not appear to dispute Dr. Angst's testimony that the mean plasma profile data meets the limitation of both claims. Id. at 448:6-451:2. Furthermore, Defendants do not appear to dispute the testimony of Plaintiffs' dissolution expert, Ms. Vivian Gray, that Concerta® meets the limitations of claim 1 of the '373 patent.

Nevertheless, Defendants further contend that other considerations besides the subject matter of the claims explains the commercial success of Concerta®. Specifically, Defendants contend that, as compared to other ADHD drugs, Concerta® was the subject of greater marketing efforts. See DTX 1223, Exhs. 29-31. In addition, Defendants note that Plaintiffs' expert, Dr. Feifel, testified at deposition that Concerta's success could be attributed, in part, to a reduced possibility of it being abused recreationally by virtue of it being constructed from an unwieldy paste/gel. See Feifel Dep. Tr. at 192:7-193:9. Likewise, Defendants contend that the testimony of Dr. Feifel suggests that Concerta®'s success may have been due, in part, to the fact that Concerta® was the first branded ADHD product in many years. In these circumstances, doctors, after becoming comfortable that Concerta® performed adequately, may have had little motivation to try a later-developed product, such as Ritalin LA®, See id. at 31:6-19, 23:17-24:24, 30:6-16.

As another possible explanation for Concerta®'s success, Defendants note that Dr. Rozek himself attributed the success of Concerta® to its rapid onset of action. This, however, results from the IR coating, which is categorically not part of the claimed subject matter. See Tr. (Vol. 5), D.I. 152 at 1407:11-22. Finally, Defendants contend that Plaintiffs overstate the level of Concerta®'s commercial success. Plaintiffs note that

although Concerta® may be the most successful MPH-based treatment for ADHD, the most successful overall ADHD drug is Adderall XR®, which has 6% more market share than Concerta®. See PX 520.

Having reviewed the evidence on this secondary consideration, the Court finds that this consideration weighs slightly in favor of a finding of non-obviousness. Given that Defendants do not rebut that Concerta® embodies claim 1 of the '373 patent and given the mean data showing substantially ascending MPH plasma concentrations for about 8 hours (and in approximately 40% of individual patients), the Court finds that there is a nexus between the claimed subject matter and the commercial success of Concerta®. Furthermore, the Court is not persuaded that the commercial success of Concerta® is simply attributable to the fact that it was the first branded ADHD product to have been introduced in many years. In the Court's view, evidence that doctors chose to try Concerta® at a time when other treatments for ADHD were available, and thereafter chose not to try later-developed alternatives, speaks to the merit of Concerta®.

However, after considering the evidence presented by the parties regarding marketing of ADHD drugs, see DTX 1223, the Court observes that among all ADHD drugs there appears to be a strong correlation between marketing expenditures and overall commercial success. For instance, as Defendants argue, the ADHD

drugs that appear to be by far the most commercially successful (i.e., Adderall XR®, Concerta®, and Strattera®) are also the ADHD drugs that are most heavily marketed. In these circumstances, the Court is reluctant to conclude that marketing does not play a role in the commercial success of Concerta®. Similarly, in the Court's view, the fact that Concerta® has not displaced Adderall XR® as the most commercially successful ADHD treatment somewhat limits commercial success as an indicator of non-obviousness.

e. Decision

Having considered the evidence, the Court finds that the '373 patent is not invalid as obvious. Defendants' general approach to obviousness is that the prior art sets forth both a known problem (acute tolerance to MPH) and a known solution (MPH dosage forms that provide ascending MPH release). See DFF ¶ 705 ("In other words, what the patents in suit claim was merely an obvious solution i.e., an increasing drug release rate and/or the associated ascending plasma profile, to a known problem, i.e., acute tolerance exhibited with methylphenidate."). However, as discused above, the Court has found that the occurrence of acute tolerance with MPH, though hypothesized in the literature, was not definitively confirmed at the time of the invention. See supra Part IV.A.2.a.viii. Nevertheless, the Court concluded that the multiple suggestions of acute tolerance were entitled to some weight in the obviousness analysis. Accordingly, the Court will

proceed on the assumption that those of skill in the art knew that MPH exhibited acute tolerance.

On making this assumption, the Court still cannot conclude that the claims of the '373 patent are obvious. Though the art suggested that in some situations escalating release could be used to address acute tolerance (e.g., when using nitrates to treat angina), the Court sees no evidence that escalating release was ever proposed as a method for dealing with acute tolerance to MPH when treating ADHD. Indeed, the limited overall scope of art in this area during the relevant time frame was confirmed by Defendants' expert, Dr. Mayersohn, who testified on cross-examination as follows:

> Q. We talked about this prior art, but you are not aware as you sit here today of actual products that would produce an ascending plasma concentration and that had been made and tested and shown to overcome acute tolerance with a single dosing regimen?
>
> A. I am not aware of any such product.

Tr. (Vol. 4), D.I. 151 at 960:20-961:3. Likewise, another of Defendants' expert, Dr. Needham, testified as follows:

> Q. Now, as you sit here, can you think of any examples of dosage forms that were in use in the mid 1990s that had an ascending rate of release of drug over three or four hours or more?
>
> A. Not off the top of my head, no.
>
> Q. Well, you have been working in the field for a long time, and you're an expert in pharmaceutical formulations and work with a lot of them and you teach them, but as you sit here, you can't give me a single example of a formulation that was actually in use in the mid 1990s that involved an

ascending rate of release of the drug over three or four hours or more; is that correct?

A. That's correct.

Q. And in formulating your opinions in this case you didn't come across examples of actual drug formulations of that kind; correct?

A. Correct.

Tr. (Vol. 4), D.I. 150 at 730:10-731:5.

Notwithstanding the apparent absence of products utilizing ascending release to address acute tolerance, the Court will take into full consideration the teachings of Fung and Bayer on the use of escalating release to overcome acute tolerance to nitrates. On doing this, the Court remains unable to conclude that this limited nitrate art presented a predictable, off-the-shelf solution to overcoming acute tolerance with MPH. As Plaintiffs' expert, Dr. Patrick, testified, nitrates are different from MPH in many significant ways: (1) nitrates are a pro-drug while MPH is a drug in its own right; (2) nitrates do not cross the blood-brain barrier while MPH does; (3) nitrates act on the heart and vasculature while MPH is a CNS stimulant; and (4) nitrates have a much higher margin of safety than MPH. Tr. (Vol. 4), D.I. 151 at 1053:21-1055:24, 1060:17-1061:8. Defendants' expert, Dr. Mayersohn, further confirmed on cross-examination that there were "certainly" important differences between MPH and nitrates in terms of pharmacology, chemistry,

clinical results, therapeutic results, and the way the two drugs work in the body. Id. at 946:15-24.

In fact, Fung's 1984 article, which first suggested the use of escalating release of nitrates to treat angina, acknowledges at the outset that "the pharmacokinetic properties of [nitrates] were quite unusual . . . ." DTX 631 at 22. Further, though the Court does not find that Fung's 1997 article showed that he abandoned the concept of treating angina with escalating release of nitrates, it is notable that the Fung's 1997 article unequivocally states that "nitrate tolerance is a well recognized clinical problem that has not yet been resolved." DTX 1221 at 1143. The article further states that "[t]he current clinical approach to minimize tolerance employs an intermittent NTG regime, which imposes a 8-12 hour nitrate-free interval." Id. (emphasis added). Thus, there is evidence that in 1997, which is after the earliest possible priority date of the '373 patent, there remained some level of uncertainty over whether escalating release of nitrates could be used to treat angina.[8] In these circumstances, the Court cannot conclude that one of skill in the

[8] The Court acknowledges that the 1997 Fung publication also states that "[t]he concept of dosage escalation to overcome nitroglycerin tolerance is well accepted clinically." DTX 1221 at 1144. However, that the Fung publication can simultaneously state that (1) dosage escalation to overcome tolerance is "well accepted clinically" and (2) that, even "after over a century of clinical use," the problem of nitrate tolerance "has not yet been resolved" simply underscores the level of uncertainty in this area.

art would be able to generalize the limited experience with nitrates to MPH such that escalating release would be "obvious to try" or present a "predictable" solution to the problem of acute tolerance with MPH, which, as explained above, is a problem that the Court finds was not even particularly well-defined at the relevant time.

In Abbott Labs. v. Sandoz, Inc., 544 F.3d 1341, 1352 (Fed. Cir. 2008),[9] the Federal Circuit instructed as follows:

> The [Supreme] Court in KSR did not create a presumption that all experimentation in fields where there is already a background of useful knowledge is "obvious to try," without considering the nature of the science or technology. The methodology of science and the advance of technology are founded on the investigator's educated application of what is known, to intelligent exploration of what is not known. Each case must be decided in its particular context, including the characteristics of the science or technology, its state of advance, the nature of the known choices, the specificity or generality of the prior art, and the predictability of results in the area of interest.

In light of the testimony of both Dr. Patrick and Dr. Mayersohn regarding the significant differences between nitrates and MPH, the degree to which Defendants' key prior art is specifically directed to nitrate tolerance, the limited scope of the art in the area of ascending release dosage forms, and the almost total

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[9] In Abbott Labs the Federal Circuit was reviewing for abuse of discretion a district court's decision to grant a preliminary injunction. The grant of a preliminary junction was based, in part, on the grounds that the asserted patents were unlikely to be held invalid as obvious. Though this case is in a different procedural posture, the Court nevertheless finds the Federal Circuit's guidance in Abbott Labs helpful.

absence of art addressing acute tolerance to MPH, the Court finds this guidance particularly instructive.

Further evidence supporting a finding of non-obviousness is the fact that none of the prior art cited by Defendants discloses the particular claimed release profile that can be used to treat MPH. Specifically, none of the prior art discloses a release profile that ascends for at least three hours and through the mid-point of the T_{90} as a means for overcoming acute tolerance. Though Wong happens to disclose a release profile with a section that meets these parameters, there is no suggestion in Wong that this profile would be useful for overcoming acute tolerance and no clear guidance that this particular release profile could be easily achieved with MPH as the active ingredient.

Finally, the Court finds that, on the whole, the secondary considerations - in particular, the long felt need of others and commercial success - favor a finding of non-obviousness.

B. Enablement

1. Applicable Law

The statutory basis for the enablement requirement is found in 35 U.S.C. § 112, ¶ 1, which provides in relevant part:

> The specification shall contain a written description of the invention and of the manner and process of making and using it, in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

For a patent to satisfy the enablement requirement, the specification must enable "those skilled in the art to make and use the full scope of the claimed invention without 'undue experimentation.'" Genentech, Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1365 (Fed. Cir. 1997) (quoting In re Wright, 999 F.2d 1557, 1561 (Fed. Cir. 1993)). As the Federal Circuit has explained, "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable . . . . Tossing out the mere germ of an idea does not constitute enabling disclosure." Id. at 1366.

In determining whether undue experimentation is required to practice the claimed invention, the Court is guided by several factors, including: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance disclosed in the patent; (3) the presence or absence of working examples in the patent; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (6) the predictability of the art; and (7) the breadth of the claims. In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988). Consideration of each of these factors, however, is not a mandatory part of the Court's analysis. Rather, the Court is only required to consider those factors which are relevant to the facts of each case. See, e.g., Amgen, Inc. v. Chugai Pharm. Co., Ltd., 927 F.2d 1200, 1213

(Fed. Cir. 1991). Although underlying factual inquiries must be made to determine whether a patent is enabled, enablement is ultimately a question of law. Enzo Biochem, Inc. v. Calgene, Inc., 188 F.3d 1362, 1369 (Fed. Cir. 1999).

2. The Parties' Contentions

Defendants contend that the claims of the '373 patent are invalid under a number of theories of the enablement doctrine. In general, Defendants' position is that during claim construction, Plaintiffs requested an exceedingly broad construction for the claim term "dosage form," and, having received that construction, Plaintiffs now cannot show that the specification supports the full scope of the claims. In particular, at Plaintiffs' suggestion, the Court construed the term "dosage form" to mean "a pharmaceutical composition that includes a dose of methylphenidate." Defendants contend that this construction does not require that a "dosage form" be a tablet, capsule, transdermal, or oven that the dosage form necessarily be oral. Indeed, Defendants contend that, under the Court's construction, a "dosage form" could be such things as an aerosol, capsule, cream, emulsion, gel, injection, lozenge, suppository, etc. DFF ¶ 907. According to Defendants, in these circumstances, the claims of the '373 patent define the invention as the use of any MPH dosage form that has the functional requirement of the claims, which is to provide an ascending

release rate and/or substantially ascending MPH plasma profile. Id. ¶ 906. Covering essentially all means to achieve a desired result, Defendants contend that the claims are analogous to "single means" claims and are thus invalid as a matter of law. See, e.g., Fiers v. Revel, 984 F.2d 1164, 1170 (Fed. Cir. 1993) (explaining that a count that claimed "all DNA's that achieve a result without defining what means will do so" is "analagous to a single means claim, which has been held not to comply with the first paragraph of section 112").

Plaintiffs respond that the claims are not as broad as Defendants contend. In particular, Plaintiffs point out that the Court construed the claim term "ascending release rate" to require both an appropriate dissolution test and the exclusion of any immediate release coating from the analysis of the whether the dosage form provides an ascending release rate. Thus, Plaintiffs contend that one of skill in the art would understand that the claims are limited to oral dosage forms, such as tablets

and capsules, which may be subject to a dissolution test.[10] See PFF ¶ 623.

Defendants reply that even if one assumes the claims should be limited to oral dosage forms such as tablets and capsules, the claims are still not enabled for their full scope. In particular, Defendants contend that many oral dosage forms, such as chewable tablets and buccal tablets, are subject to dissolution testing, yet are not enabled by the '373 patent. See

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[10] Defendants argue at length that this position represents a change from Plaintiffs' position during claim construction, which was that the term "dosage form" should be understood broadly to encompass any MPH dosage form that exhibits an ascending release rate. See DFF ¶¶ 891-907. After reviewing the record on this issue, the Court agrees with Defendants that Plaintiffs have dramatically altered their position as to the meaning of the term "dosage form." As just one of many examples of how Plaintiffs have altered their position, Plaintiffs stated during claim construction that "the specification indicates that the terms 'dosage form' and 'pharmaceutically acceptable composition' broadly encompass pharmaceutical compositions containing methylphenidate that can be adapted for administration to an individual." D.I. 87 at 16. Likewise, Plaintiffs stated that "[the patents-in-suit], expressly state[] that the claimed methods are not limited to methods that use dosage forms described in the examples, but instead encompass use of any dosage form that exhibits an ascending rate of release or provides a substantially ascending methylphenidate blood plasma concentration." D.I. 94 at 18 (emphasis added). However, in a significant curtailment of this position, Plaintiffs now contend that "[a] person of ordinary kill in the art would understand the asserted claims to require the use of oral dosage forms, and in particular extended-release oral tablets and capsules." PFF ¶ 621. Though the Court finds that Plaintiffs have significantly altered their claim construction position, the Court notes that this has little relevance, if any, to the enablement analysis. The Court shall conduct its enablement analysis based on the overall scope of the claims as reflected in the Court's construction of all the disputed claim terms.

DFF ¶¶ 903, 1012-14. Furthermore, even if one concludes that claims are not directed to dosage forms like chewable tablets and buccal tablets, there is still an enablement issue because the '373 patent is "actually of no aid other than with regard to making an osmotic dosage form." Id. ¶ 1037. Proceeding under this assumption, the parties do not appear to dispute that the enablement issue reduces to a question of fact as to whether undue experimentation is required to make oral dosage forms other than osmotic dosage forms that meet the limitations of the claims.

3. Discussion

In light of the parties' latent dispute over the scope of the claims, the Court will clarify the proper scope of the claims before addressing the enablement issue.

a. The Scope Of The Claims

The Court agrees with Plaintiffs that the Court's construction of the term "ascending release rate" narrows the scope of the claims of the '373 patent such that they do not, as Defendants contend, encompass any and all MPH dosage forms that provide the required ascending release rate. In particular, because the Court's construction of "ascending release rate" calls for an "appropriate dissolution test," the Court's construction limits the scope of the claims to dosage forms that may reasonably be subject to such a dissolution test. However,

the component of the Court's construction referring to an immediate release coating does not place additional limitations on the dosage forms covered by the claims. The language at issue states that "[t]he ascending release rate does not include release of drug from any immediate-release drug coating that may be applied to the dosage form." D.I. 130 ¶ 2. This language, on its face, does not strictly require that the claims be limited to dosage capable of receiving an immediate release coating, and, during claim construction, Plaintiffs did not advance any argument that this was the case. Rather, in light of Plaintiffs' arguments during claim construction, which were ultimately accepted by the Court, this language must be viewed as simply clarifying that in the case of dosage forms capable of receiving an immediate release coating, such coating is not included in the ascending release.

Unfortunately, even after providing clarification, the Court lacks the expertise to enumerate a complete and exhaustive list of the dosage forms encompassed by the claims. However, the following conclusions can be drawn with certainty. First, there appears to be no dispute that the claims encompass oral tablets and capsules. Second, the Court also does not detect a dispute that chewable tablets and buccal tablets may be subject to dissolution tests. The same is true of lozenges, which appear to be categorized as distinct dosage forms from capsules and

tablets. See DTX 656 at 1942, 1945, 1949. Third, the testimony of Plaintiffs' expert witnesses confirms that suppositories, creams, ointments, and transdermals may be subject to dissolution tests. See Tr. (Vol. 2), D.I. 149 at 369:23-371:22 (Ms. Gray confirms that suppositories, creams, and ointments may be subject to a dissolution test); Tr. (Vol. 5), D.I. 152 at 1213:11-15 (Dr. Davies confirms that in 1996 dissolution tests were available for transdermals). Accordingly, the Court concludes that at least the following dosage forms are within the scope of the claims: oral tablets (including chewable and buccal tablets) and capsules, suppositories, creams, ointments, and transdermals.

With respect to suppositories, creams, ointments, lozenges, and buccal tablets, Plaintiffs point out that Defendants' expert, Dr. Needham, testified that those of skill in the art would be unlikely to use such dosage forms to carry out the claimed invention. See Tr. (Vol. 3), D.I. 150 at 737:4-741:24. Specifically, with regard to creams and ointments,[11] Dr. Needham

[11] The Court is not certain whether it is possible to achieve ascending release with ointments and creams. Further, the parties have not presented meaningful evidence regarding whether creams and ointments can be used for this purpose. Therefore, the Court cannot exclude ointments and creams from the scope of the claims simply on the basis of its own speculation that it may not be possible to achieve ascending release through such dosage forms. With respect to chewable tablets, Defendants' expert, Dr. Needham, testified that it would be very difficult to reduce to practice a chewable tablet that provided the required ascending release. See Tr. (Vol. 3), D.I. 150 at 703:9-18. However, Dr. Needham also testified that he could "probably come up with a concept or an idea" for doing this. On the basis of

testified that a child being treated for ADHD would be unlikely to keep a cream or ointment on their arm for three to five hours. Id. at 740:18-26. Likewise, with regard to a buccal tablet or lozenge, Dr. Needham testified that it would be unlikely for a child with ADHD to keep such a dosage form in his or her mouth for a long time. Id. at 740:15-741:10. Dr. Needham testified similarly on the use of suppositories to treat ADHD. Id. at 740:1-10. Pointing to this testimony, Plaintiffs contend that "common sense" would, as a practical matter, limit the types of dosage forms that one of skill in the art would used to practice the invention. See PFF ¶ 625. The Court agrees that this may well be the case. However, the difficulty with this argument is that the claims are not so narrowly drawn. Indeed, the claims include nothing to suggest that they are limited to only the most pleasant or most optimal dosage forms that provide the required ascending release. Similarly, the claims are not limited to a method of treating ADHD in children. Furthermore, during claim construction, Plaintiffs did not argue that "common sense" should operate to limit the scope of the claims. At this stage, the Court declines to selectively apply Plaintiffs' version of "common sense" to winnow the claims to a set of dosage forms that

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this testimony, the Court is also unable to exclude chewable tablets from the scope of the claims.

one of skill in the art would most likely use to practice the invention.

b. Whether The Claims Of The '373 Patent Are Enabled

Although the Court has clarified that the claims encompass dosage forms other than oral capsules and tablets, the Court concludes that the enablement issue may nevertheless be resolved in Defendants' favor even under the assumption that the claims are limited to oral tablets and capsules. Indeed, after considering the Wands factors, the Court concludes that one of skill in the art, after reading the specification, could not prepare non-osmotic tablets and capsules that meet the limitations of the claims without undue experimentation.

i. The Quantity Of Experimentation Necessary

The Court finds that this factor suggests that undue experimentation would be required to develop non-osmotic dosage forms that meet the limitations of the claims. Turning first to the intrinsic evidence, the specification states the following:

- "With the discovery that administration of drug at a release rate that is substantially ascending provides improved drug therapy, a need arises for sustained-release oral dosage forms adapted to provide such a release rate over a suitable extended time period." '373 patent at 4:19-24 (emphasis added).
- "It has been surprisingly discovered that oral osmotic dosage forms exhibiting an ascending drug release rate for an extended time period can be achieved." Id. at 4:30-32 (emphasis added).

- "The achievement of an ascending release rate for an extended time period of at least 50% of the T_{90} period is not found within the prior art." Id. at 10:62-65.
- "In addition to the above-described bi-layer osmotic dosage forms, it has been surprisingly discovered that oral osmotic dosage forms exhibiting an ascending drug release rate for an extended time period can also be achieved with a novel tri-layer tablet core surrounded by a semipermeable membrane and having suitable exit means for releasing drug formulation through the semipermeable membrane." Id. at 12:9-16 (emphasis added).

Explaining that there was a newly arising need for ascending release dosage forms, that dosage forms providing such ascending release were "not found within the prior art," and that the discovery that such release rates could be provided with the newly disclosed osmotic dosage forms was "surprising," the specification strongly suggests that, at the time of filing, the field of ascending release dosage forms was not mature.

The prosecution history of the '373 patent confirms this. Indeed, the provisional applications to which the '373 patent claims priority include additional language describing the nascent state of the art in this area. For instance, Provisional Application 60/031,741, filed on November 25, 1996, explains:

> [A] long-felt need exists for a dosage form for (1) delivering a drug in a sustained-ascending rate that simultaneously reduces or eliminates the need for frequency of daily dosing; for (2) delivering a drug in a sustained-compensating dose to substantially compensate for acute tolerance to the drug and thereby maintain a preselected clinical profile; for (3) administering the drug in an increasing dose to lessen or eliminate acute or chronic tolerance to the drug to

> provide effective therapy; and (4) for delivering the drug in a sustained, ascending-controlled profile clinically indicated for both medical and psychomedical effects.

DTX 1144 at PALZ 000829:10-19. The provisional application further provides:

> In accordance with the practice of this invention, it has now been discovered [that] a novel dosage form can be made available characterized by an ascending rate of drug delivery over time. The dosage form provided by this invention delivers a drug at a continuously increasing rate for a predetermined period of time. The dosage form of this invention is unexpected and it is a breakaway from the prior art existing dosage form technologies that deliver a drug at a constant zero-order unchanging rate over time. The dosage form of this invention avoids delivery at a zero order rate as it delivers a drug continuously in an ascending rate over time. The profile of the prior art dosage form consists of a short start-up in delivery, followed by a constant unchanged rate. The profile of this invention departs from the prior art by making available a dosage form wherein the drug release rate follows an ascending profile to achieve a desired drug delivery pattern. The dosage form of this invention achieves the ascending pattern by combining the dimensions of the dosage form with the internal formulation of the dosage form.

Id. at PALZ 000832:20 - 000832:4 (emphasis added). Explaining again that there was a "long felt need" for ascending release dosage forms and that they were a "breakaway" from the prior art, the prosecution history provides further confirmation that, at the time of filing, the preparation of ascending release dosage forms was, in general, not routine. See also id. at PALZ 000829:2-19.

Consistent with the intrinsic evidence, Defendants have put forth additional evidence suggesting that Plaintiffs had tried and failed to produce non-osmotic dosage forms, such as matrix systems, that provided the claimed ascending release. In particular, Defendants point to the deposition testimony of Mr. Andrew Lam, who currently is a senior director of liquid OROS®[12] technology at ALZA and who worked on formulation and product development from roughly 1987 to 1999. Mr. Lam, though originally named as an inventor on the '373 patent, was removed as an inventor in April 2007. Nevertheless, he remains an inventor on the '129 patent, which shares the same specification as the '373 patent. Mr. Lam testified that Alza's early work on ascending release involved attempts to create ascending release using non-osmotic matrix design dosage forms. According to Mr. Lam, Alza attempted to make this work for roughly one to two months, preparing matrix formulations using different ingredients, but was unable to achieve ascending release through such preparations. See Lam Dep. Tr. at 805-07. Likewise, Mr. Lam further testified that as part of Alza's development efforts they tested 21 different dosage form designs, including matrix designs, and none of the non-OROS formulations yielded the desired ascending release rate. Id. at 866-67.

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[12] "OROS" is the trade name for Plaintiffs' osmotic delivery technology. See PFF ¶ 605.

Consistent with Mr. Lam's deposition testimony, Plaintiffs' expert, Dr. Davies, testified that in November of 1996 it would have taken a few months to develop an MPH dosage form that had an ascending release and that this would involve testing plus additional fine tuning. See Tr. (Vol. 5), D.I. 152 at 1240:16-1241:9. Though Dr. Davies attempted to characterize such efforts as "routine experimentation," the Court cannot agree, particularly in light of Mr. Lam's testimony indicating that Alza had in fact tried and failed for a few months to produce non-osmotic ascending release dosage forms.[13] Furthermore, in arguing the issue of obviousness, Plaintiffs elicited testimony from Defendants' expert, Dr. Needham, that he could not think of "a single example of a formulation that was actually in use in the

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[13] Relying on the testimony of Alza scientist Atul Ayer, Plaintiffs argue that Alza had in fact produced non-osmotic dosage forms that produced an ascending release profile. See Tr. (Vol. 1),D.I. 148 at 171:20-174:4. In particular, Mr. Ayer pointed to a laboratory notebook page that allegedly showed that Alza had generated a non-osmotic ascending release dosage form for pseudoephedrine. See id. at 188:14-189:1, 194:22-198:4; DTX 1151 at ALZ00012323. However, the Court has reviewed this notebook page and finds that it refers to the "POP" of an "osmotic" agent. See DTX 1151 at ALZ00012323. Thus, the notebook page may well be referring to an osmotic dosage form. More importantly, the notebook page provides no confirmation that an ascending release was actually achieved with the dosage form described therein. See Tr. (Vol. 1), D.I. 148 at 190:1-16. In fact, Mr. Ayers testified that although Alza keeps laboratory notebooks, he did not have any notebook confirming that Alza had actually produced a non-osmotic dosage form that provided an ascending release rate. Id. at 192:17-194:13. In this respect, the testimony of Mr. Ayer actually tends to confirm that the preparation of such dosage forms was not a routine matter.

mid 1990s that involved an ascending rate of release of the drug over three or four hours or more . . . ." Tr. (Vol. 3), D.I. 150 at 730:10-731:1; supra Part IV.A.2.e. Yet additional evidence that significant experimentation would be required to prepare non-osmotic ascending release dosage forms comes from the deposition of Mr. Lawrence Hamel, who is an inventor on the '373 patent and was head of all Alza formulators. Mr. Hamel testified that it was a challenge to achieve the targeted ascending release with Alza's own tri-layer osmotic dosage form, which the specification describes in detail. In particular, Mr. Hamel testified that at the relevant time the technology was brand new and that, as a result, certain tools were unavailable, making it difficult to achieve the appropriate viscosity balance and weight uniformity and then control these parameters to achieve a targeted release profile. Mr. Hamel described this as a "significant technical challenge." See Hamel Dep. Tr. at 750-51. As Defendants argue, if, as Plaintiffs contend, it were truly routine to achieve ascending release with a variety of non-osmotic dosage forms, it is difficult to believe that Alza would instead undertake the technical challenges of preparing an osmotic ascending release dosage form.

Plaintiffs have two responses to the above evidence. First, Plaintiffs argue that at the time of filing there were many known ways of achieving ascending release through non-osmotic dosage

forms. Plaintiffs argue that Provisional Application 60/030,514, to which the '373 patent claims priority, describes a number of non-osmotic dosage forms that can allegedly be used to provide ascending release. See PX 477 at PALZ 778-81. However, as Defendants note, these examples were later deleted and do not appear in the patents that resulted from the provisional application. Accordingly, the Court assigns these descriptions little weight. Plaintiffs further point to the testimony of their expert, Dr. Davies, who identified four literature references that, prior to the time of filing, allegedly set forth techniques of achieving ascending release with non-osmotic dosage forms. See PFF ¶¶ 635-61. However, two of the four references Dr. Davies relied upon are, in the Court's view, entirely theoretical in nature and thus not particularly probative of the amount of experimentation necessary to produce an actual, working non-osmotic ascending release dosage form. See PX 472; PX 465. The remaining two references Dr. Davies relied upon were prior art patents. However, for both of these references, Dr. Davies testified that one of skill in the art would need to combine various teachings contained within each of these patents and conduct additional experimentation to arrive at the targeted ascending release. See PX 470; PX 471; Tr. 1233 (Vol. 5), D.I. 152 at 1233:4-1244:11; id. at 1234:12-24. Though Dr. Davies testified that the level of experimentation would not be undue,

the Court nevertheless views Dr. Davies' testimony as conjectural in nature. Furthermore, these two references do not appear directed to ascending release and/or the preparation of MPH dosage forms. In fact, one of the patents relied upon by Dr. Davies, U.S. Patent No. 5,326,570, explicitly states that "[t]he present invention relates to a method of delivery for carbamezepine which will provide steady and constant blood levels of carbamezepine." PX 470 at 1:7-9. Similar to the Wong reference, the Court concludes that the two patent references relied upon by Dr. Davies would provide one of skill in the art with, at most, a possible starting point for the preparation of an oral MPH dosage form that provided the desired ascending release profile.

Furthermore, the Federal Circuit has drawn a distinction between (1) using the knowledge of one of skill in the art to supplement a disclosure and (2) using the knowledge of one of skill in the art to substitute for a basic enabling disclosure. Genentech, Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366 (Fed. Cir. 1997). Put another way, the Federal Circuit has explained that the omission of "minor details" does not lead to a failure to meet the enablement requirement. Id. Here, however, Plaintiffs are not asking the Court to supplement the disclosure with "minor details" known to those in the art, but instead augment the disclosure with swaths of knowledge pertaining to

dosage forms that operate according to mechanisms completely different from those discussed in the patent. In the Court's view, this is impermissible "substitution" and not simple "supplementation." See also Auto. Techs. Int'l, Inc. v. BMW of N. Am., Inc., 501 F.3d 1274, 1283-84 (Fed. Cir. 2007) (rejecting a patentee's attempt to rely on knowledge in the art for enablement when a specification meaningfully disclosed only one of two claimed methods for implementing vehicle crash sensors). Accordingly, the Court will not give Dr. Davies' four prior art references significant weight when considering this Wands factor.

Plaintiffs second response to the above evidence is to discredit the testimony of Mr. Lam. In particular, Plaintiffs rely on the testimony of Mr. Ayer to suggest that Mr. Lam's role in the development of Concerta® was largely administrative and that, to the extent Mr. Lam did experiments, they were merely "ad hoc, personal experimental experiences . . . ." See PFF ¶ 696; Tr. (Vol. 1), D.I. 1 at 177:21-24. However, there is no dispute that Mr. Lam was the product development manager for the Concerta® product. Furthermore, Mr. Lam was originally named as an inventor on the '373 patent, and, the Court understands that he remains a named inventor on the '129 patent. Accordingly, the Court is skeptical of Plaintiffs' efforts to downplay Mr. Lam's testimony.

ii. The Amount Of Direction Or Guidance Disclosed In The Patent And The Presence Or Absence Of Working Examples In The Patent

On reviewing the specification, the Court agrees with Defendants that the specification contains no guidance as to how to achieve ascending release with non-osmotic oral dosage forms. Plaintiffs do not appear to dispute this, arguing instead that the lack of working examples of non-osmotic dosage forms is immaterial. See PFF ¶¶ 689-91. Accordingly, the Court concludes that these Wands factor weigh strongly in favor of a finding that undue experimentation would be required to develop a non-osmotic ascending release dosage form.

iii. The Nature Of The Invention And The Predictability Of The Art

In view of Mr. Lam's testimony regarding Alza's unsuccessful efforts to create non-osmotic matrix based dosage forms that provide ascending release and Mr. Hamel's testimony regarding the technical challenges associated with achieving a desired ascending release with Alza's osmotic release technology, the Court concludes that the art at issue is, in general, unpredictable. Indeed, Mr. Hamel testified with regard to Alza's osmotic release technology as follows:

Q. The first sentence of the section of the e-mail that you believe you wrote at the bottom of the first page beginning achieving the target ascending release profile for methylphenidate has turned out, comma, as expected, comma, to be a significant challenge. Do you see that statement?

A. Yes.

Q. As you sit here today, do you recall why it was a significant challenge?

A. Yes.

Q. And why was that?

A. Of course, this was brand new technology, the LCT. There were no good tablet presses in the world. There were no laser drills. There were no lasers, I mean, that could do that. The viscosity balance that you need between the first and second layers is a very tricky operation. Achieving a tablet with good weight uniformity and content uniformity is difficult, and then to control all those parameters and achieve a target release profile is a significant technical challenge.

Hamel. Dep. Tr. at 751 (emphasis added).

Along these lines, the expert witness testimony indicates a significant level of unpredictability in the field of pharmaceutical product design. Specifically, Defendants' expert, Dr. Needham, testified that the process of pharmaceutical product development was "iterative" in nature, suggesting that a trial-and-error approach is involved. See Tr. (Vol. 3), D.I. 150 at 705:24-710:2. Plaintiffs' expert, Dr. Davies, avoided testifying that drug formulation was "iterative." Nevertheless, Dr. Davies testified that "normal formulation would undertake an approach where one would design a system to achieve a particular release rate, one would make that system, test it, one may need to modify

or tune that system to achieve the release rate . . . ." Tr. (Vol. 5), D.I. 152 at 1288:1-7. Dr. Davies further testified that this process could take "a few months." Id. at 1240:24-1241:9. In the Courts' view, this testimony tends to confirm Dr. Needham's view of the drug formulation process.

Accordingly, the Court concludes that these factors favor a finding that undue experimentation would be required to produce a non-osmotic dosage form exhibiting the claimed ascending release rates.

iv. The Relative Skill Of Those In The Art

As set forth above, see supra Part IV.A.2.b, the Court has concluded that someone of skill in the art would have, in addition to a degree in a relevant field, several years of practical experience related to drug development, including evaluation of pharmaceuticals, an understanding of pharmacokinetics and pharmacodynamics, and possibly some understanding of clinical medicine. Though this level of skill is not as high as Plaintiffs contend it should be, the Court nevertheless views this as a fairly high skill level. Accordingly, this Wands factor weighs against a finding of undue experimentation.

v. The State Of The Prior Art

In light of the evidence set forth above, the Court finds that the prior art in the area of ascending release dosage oral

forms was limited in scope. Specifically, the specification and prosecution history of the '373 patent indicate that there had been a long felt need for ascending release dosage forms and that the development of such dosage forms was a "break away" from prior art constant release dosage forms. See supra Part. IV.B.3.b.i. Likewise, Dr. Needham's testimony that he was unable to think of a single example of a product in the 1990s that provided ascending release over three or four hours tends suggests that such dosage forms were not prevalent in the art. See id. The testimony of Mr. Lam, who described Alza's lack of success in producing non-osmotic ascending release dosage forms, further suggests that there was no well-known prior art solution that could be easily applied to the problem of ascending release. See id. The same may be said with regard to the testimony of Mr. Hamel, who described the serious technical challenges Alza faced in developing an osmotic ascending release dosage form. See supra Part IV.B.3.b.iii.

The Court acknowledges that the parties have identified some prior art addressing oral dosage forms that could possibly be used as a basis for developing an ascending release dosage form. For instance, Plaintiffs, through the testimony of their expert, Dr. Davies, identify four prior art references dealing with non-osmotic oral dosage forms. See PX 472; PX 465; PX 709; PX 471; Tr. 1233 (Vol. 5), D.I. 152 at 1233:4-1244:11; id. at 1234:12-24.

Similarly, in support of their obviousness argument, Defendants point to the Wong reference, which appears to disclose osmotic dosage forms that may provide ascending release. See DTX 634; supra Part IV.A.2.a.vi. In light of these references, the Court finds that the prior art shows that some work had, in fact, been done that was relevant to oral ascending release dosage forms. However, for the reasons set forth above, the Court assigns little weight to the references identified by Dr. Davies. See supra Part IV.B.3.b.i. Furthermore, the Wong reference pertains to osmotic dosage forms and is thus not particularly probative on the issue of whether undue experimentation would be required to produce non-osmotic oral ascending release dosage forms. Nevertheless, the existence of this art limits the overall impact of this Wands factor. Though this factor weighs in favor of a finding of undue experimentation, the Court concludes that it does so only slightly.

vi. The Breadth Of The Claims

The plain language of the claims requires only an MPH dosage form that achieves the claimed ascending release and/or substantially ascending blood plasma profiles. However, the Court has construed the claims of the '373 patent to require an appropriate dissolution test, which, as explained above, limits the scope of the claims to a set of particular dosage forms, including, among other things, oral tablets and capsules,

transdermals, and lozenges. Nevertheless, even if the claims are understood to be limited to only oral tablet and capsules, as Plaintiffs contend they should, the Court would find that this factor weighs in favor of a finding of undue experimentation. Indeed, as Plaintiffs argue, there are many kinds of oral tablets and capsules, including reservoir devices, matrix devices, dissolution systems, osmotic systems, and ion-exchange/resin systems. Within each of these categories there are additional subcategories and combination devices. See Tr. (Vol. 5), D.I. 152 at 1239:20-1240:15; '373 patent at 2:45-62. In this respect, even if the claims are limited to oral tablets and capsules, they still may be viewed as being quite broad. Accordingly, the Court concludes that this factor weighs in favor of undue experimentation.

vii. Decision

The Court first notes that the claims are not, as Defendants contend, "unlimited in nature" by claiming any dosage form or pharmaceutical composition that provides the results of the claim. See DFF ¶ 976. Accordingly, the claims are not invalid as a matter of law for being analogous to single means claims.

However, even if the claims are limited to oral tablets and capsules, the Court finds that seven of the eight Wands factors tilt in favor of a finding that it would take one of skill in the art, after reading the specification, undue experimentation

to prepare a non-osmotic oral dosage form that meets the limitations of the claims. Based on this finding, the Court concludes that the claims of the '373 patent are invalid for lack of enablement.

Instructive in this case is the Federal Circuit's recent decision in Auto. Techs. Int'l, Inc. v. BMW of N. Am., Inc., 501 F.3d 1274 (Fed. Cir. 2007). In Automative Technologies, the patentee claimed vehicle crash impact sensors that detected a crash through the motion of a mass situated in a housing. The district court construed the claim term "means responsive to the motion of said mass" to include both mechanical and electronic side impact sensors. Auto. Techs., 501 F.3d at 1282. With respect to mechanical sensors, the specification included two columns of text and five figures worth of discussion. Id. However, with respect to electronic sensors, the specification included only one figure, which the specification described as "conceptional," and one short paragraph of text, which explained that "[t]he motion of the sensing mass 202 can be sensed by a variety of technologies using, for example, optics, resistance change, capacitance chance or magnetic reluctance change." Id. The Federal Circuit explained that this disclosure provided "little more than . . . an overview of an electronic sensor without providing any details of how the electronics sensor operates." Id. Given that the "novel aspect of the invention is

side impact sensors," the Federal Circuit held that "it is insufficient to merely state that known technologies can be used to create an electronic sensor" and affirmed the judgment of the district court that the claims were invalid as not being enabled for their full scope. Id. at 1283, 1285.

Here, the '373 patent includes roughly 13 columns of text and two figures devoted to osmotic dosage forms. This material discusses nine different examples of osmotic dosage forms. With respect to non-osmotic dosage forms, however, the '373 patent provides even less information than the patent in Automotive Technologies included for electronic impact sensors. Indeed, there is not even a "conceptional" figure devoted to non-osmotic dosage forms and the Court finds no text devoted to the use of non-osmotic dosage forms for providing ascending release. At most, there is language in the "BACKGROUND OF THE INVENTION" section listing a variety of dosage forms that have been previously used to provide sustained release and some additional boilerplate language explaining that "the invention is not limited by the exemplary embodiments." See '373 patent at 2:45-62, 6:1-14. Certainly, there is no example of how to provide the target release profile using a non-osmotic dosage form.

Yet, just as velocity-type side impact sensors were a novel part of the invention in Automotive Technologies, dosage forms that provide an ascending release of MPH are a novel aspect of

the invention here. The claims explicitly require "a dosage form comprising methylphenidate that provides a release of methylphenidate at an ascending release rate . . . ." Id. at 23:12-15 (emphasis added). The specification further confirms that a novel aspect of the invention is the dosage form, explaining, for example, that "other aspects of the present invention include providing oral sustained-release dosage forms that provide an ascending drug release rate over an extended time period, methods of making such dosage forms and methods of using such dosage forms to maintain therapeutic effectiveness for a desired prolonged therapy period." Id. at 4:24-29 (emphasis added). Likewise, the specification goes so far as to explain that "[t]he achievement of an ascending release rate for an extended period of time of at least 50% of the T_{90} period is not found within the prior art." Id. at 10:62-65; see, e.g., also id. at 4:32-36 ("In particular, the present invention is directed to osmotic dosage forms having bi-layer or tri-layer tablet cores that are adapted to provide ascending drug release rates over an extended period."); id. at 5:50-53 ("Accordingly, the present invention also pertains to making oral methylphenidate sustained release dosage forms that provide a sustained and ascending release rate of a drug over an extended time period. "); id. at 10:65-11:2 ("The dosage forms of the present invention are useful for providing continuous effective drug therapy over a prolonged

therapy period without exhibiting a decrease in effectiveness during the after portion of the prolonged therapy period.") (emphasis added).

Because dosage forms that provide an ascending release of MPH are a novel aspect of the invention, such dosage forms must be enabled for their full scope, which, as explained above, includes at least oral tablets and capsules of both the osmotic and non-osmotic variety. As the Federal Circuit explained in Automotive Technologies, in enabling the claims for their full scope "it is insufficient [for Plaintiffs] to merely state that known technologies" could be used to provide non-osmotic dosage forms that provide ascending release. However, this is the very most the Plaintiffs have done. Accordingly, the Court concludes that the claims of the '373 patent are invalid as not being enabled for their full scope.

CONCLUSION

For the reasons discussed, the Court concludes that it does not currently have subject matter jurisdiction over Defendants' declaratory judgment counterclaims pertaining to the '129 patent. Furthermore, the Court will grant Plaintiffs' Motion To Strike Portions of Defendants' Post-Trial Findings Of Fact (D.I. 188) and deny Defendants' Contingent Cross Motion To Strike Portions of Plaintiffs' Post-Trial Findings Of Fact And Conclusions Of Law (D.I. 189). If, at some point, the Court acquires jurisdiction

over Defendants' counterclaims concerning the '129 patent the Court will allow the parties to submit supplemental findings of fact and conclusions of law pertaining to the '129 patent.

The Court concludes that Plaintiffs have not demonstrated by a preponderance of the evidence that Defendants' ANDA products would infringe the asserted claims of the '373 patent. The Court further concludes that Defendants' have not demonstrated by clear and convincing evidence that the '373 patent is invalid for obviousness. However, the Court concludes that Defendants have demonstrated by clear and convincing evidence that the '373 patent is invalid for lack of enablement for the full scope of the claims. Having found the '373 patent both invalid and not infringed, the Court will enter judgment in favor of Defendants on both issues. Defendants shall submit with notice to Plaintiffs a proposed form of Final Judgment Order within ten (10) days of this Opinion.