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Paper No. 25
Entered: December 9, 2015

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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NEPTUNE GENERICS, LLC.,

Petitioner,

v.

AUSPEX PHARMACEUTICALS, INC.,

Patent Owner.

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Case IPR2015-01313
Patent 7,456,317 B2

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Before LORA M. GREEN, DEBORAH KATZ, and
JACQUELINE WRIGHT BONILLA, *Administrative Patent Judges*.

GREEN, *Administrative Patent Judge*.

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

# I. INTRODUCTION

Neptune Generics, LLC ("Petitioner") filed a Petition requesting an *inter partes* review of claims 1–10 of U.S. Patent No. 7,465,317 B2 (Ex. 1001, "the '317 patent"). Paper 1 ("Pet."). Auspex Pharmaceuticals, Inc. ("Patent Owner") filed a Preliminary Response to the Petition. Paper 13 ("Prelim. Resp.").

An *inter partes* review may not be instituted "unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314. Upon considering the Petition and the Preliminary Response, we determine that Petitioner has not shown a reasonable likelihood that it would prevail in showing the unpatentability of claims 1–10. Accordingly, we decline to institute an *inter partes* review of the challenged claims.

## *A. Related Proceedings*

Petitioner states that it "is unaware of any other matters related to the '317 patent." Pet. 6; *see also* Paper 7 (stating that there "is no related litigation pending," and "no related *inter partes* or other administrative review proceedings pending").

## *B. The '317 Patent (Ex. 1001)*

The '317 patent issued on November 25, 2008, with Thomas G. Gant and Sepehr Sarshar as the listed inventors. Ex. 1001. The claims of the '317 patent are drawn to a deuterated form of venlafaxine ("VF"), an inhibitor of monoamine neurotransmitters. *Id.* at 69:30–70:38, 1:20–34.

The '317 patent teaches that the human body expresses several enzymes that aid in breaking down or solubilizing nutrients and chemicals that have been absorbed into the blood, producing novel intermediates or

metabolites. *Id.* at 1:37–42. Those enzymes include cytochrome P-450 enzymes (also referred to as "CYPs"), esterases, proteases, reductases, and others. *Id.* at 1:39–41. As taught by the '317 patent:

> Some of the most common metabolic reactions of pharmaceutical compounds involve the oxidation of a carbon-hydrogen (C–H) bond to either a carbon-oxygen (C–O) or carbon-carbon (C–C) π-bond. The resultant metabolites may be stable or unstable under physiological conditions, and can have substantially different pharmacokinetic, pharmacodynamic, acute and long-term toxicity profiles relative to the parent compounds. For most drugs, such oxidations are generally rapid and ultimately lead to administration of multiple or high daily doses. There is therefore an obvious and immediate need for improvements of such drugs.

*Id.* at 1:43–53.

The '317 patent teaches that the chemical bond between a carbon and deuterium (an isotope of hydrogen) is stronger than the bond between a carbon and hydrogen. *Id.* at 2:45–53. Thus, if breaking a carbon-hydrogen bond is a rate limiting step in a reaction, substituting the hydrogen with deuterium will decrease the reaction rate, slowing the reaction down. *Id.* That phenomenon is known as the deuterium kinetic isotope effect, and can range from a value of 1, with no isotope effect, to over 50, in which the substitution of deuterium with hydrogen makes the reaction proceed 50 times more slowly. *Id.* at 2:54–58.

According to the '317 patent, "[d]euteration of pharmaceuticals to improve pharmokinetics (PK), pharmacodynamics (PD), and toxicity profiles, has been demonstrated previously with some classes of drugs." *Id.* at 3:47–49. The '317 patent teaches that the method, however, may not be applicable to all classes of pharmaceuticals due to the phenomenon of metabolic switching, which can lead to different proportions of known

metabolites, as well as the production of new metabolites, which may impart more or less toxicity. *Id.* at 3:52–65.

During prosecution of the '317 patent, in the statement of the reasons for allowance, the Examiner noted:

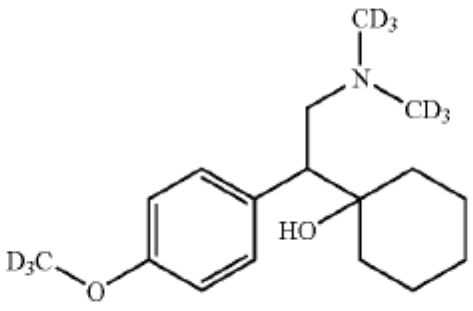
> The prior art neither teaches, nor suggests the limitations of Applicant's claims . . . . Nor would it have been obvious to modify the prior art's venlafaxine to arrive at the instantly claimed invention. There is no teaching in the prior art that correlates improvements in the pharmacological properties of venlafaxine with the instantly claimed D-9 deuterated derivatives of venlafaxine. In addition, venlafaxine has 27 positions that can be deuterated, along with 134,217,727 potential deuterated analogs of venlafaxine. Because of the large number of possible deuterated analogs of venlafaxine, it would not be "obvious to try" to synthesize the instantly claimed D-9 deuterated derivative of venlafaxine.

Ex. 2032, 3.

### *C. Illustrative Claim*

Petitioner challenges claims 1–10 of the '317 patent. Claim 1 is the only independent claim, is illustrative, and is reproduced below, with the symbol "D" in the structural formula indicating a deuterium:

1. A compound having the structural formula:




or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

### *C. The Asserted Grounds of Unpatentability*

Petitioner challenges the patentability of claims 1–10 of the '317 patent on the following grounds (Pet. 7–8):

| References | Basis | Claims Challenged |
|---|---|---|
| Fogelman[1] and Miwa[2] | § 103(a) | 1 |
| Fogelman, Miwa , and Platteeuw[3] | § 103(a) | 2 and 8 |
| Fogelman, Miwa , Platteeuw, and Jerussi[4] | § 103(a) | 3–7, 9, and 10 |

## II. ANALYSIS

### *A. Claim Construction*

In an *inter partes* review, claim terms in an unexpired patent are interpreted according to their broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1276–79 (Fed. Cir. 2015); Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,766 (Aug. 14, 2012). Claim terms also are given their ordinary and customary meaning, as would be understood by one of ordinary skill in the art in the context of the entire disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249,

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[1] Fogelman et al. ("Fogelman"), *O- and N-demethylation of Venlafaxine In Vitro by Human Liver Microsomes and by Microsomes from cDNA-Transfected Cells: Effet of Metabolic Inhibitors and SSRI Antidepressants*, 20 NEUROPSYCHOPHARMACOLOGY 480–490 (1999) (Ex. 1003).
[2] GERALD T. MIWA AND ANTHONY Y. H. LU ("MIWA"), *Kinetic Isotope Effects and 'Metabolic Switching' in Cytochrome P450-Catalyzed Reactions*, 7 BIOESSAYS 215–19 (1987) (Ex. 1004).
[3] Platteeuw et al. ("Platteeuw), US 2003/0190351 AI, published Oct. 9, 2003 (Ex. 1005).
[4] Jerussi et al., ("Jerussi"), US 6,197,828 B1, issued Mar. 6, 2001(Ex. 1006).

1257 (Fed. Cir. 2007). Only terms which are in controversy need to be construed, and then only to the extent necessary to resolve the controversy. *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999). We determine that explicit construction of any specific claim term is not necessary to determine whether to institute a trial in this case.

### *B. Obviousness of Claim 1 Over the Combination of Fogelman (Ex. 1003) and Miwa (Ex. 1004)*

Petitioner asserts that claim 1 is rendered obvious by the combination of Fogelman and Miwa. Pet. 22–30.

#### *i. Overview of Fogelman (Ex. 1003)*

Fogelman studied the transformation of VF into its two major metabolites—O-desmethylvenlafaxine ("ODV") and N-desmethylvenlafaxine ("NDV"). Ex. 1003, Abstract. Fogelman teaches that VF is transformed in the liver to ODV, NDV, and N,O-didesmethylvenlafaxine ("N,O-DV"). *Id.* at 481. According to Fogelman, "ODV has a receptor affinity profile similar to its parent compound VF, while the latter two metabolites have little if any affinity for the . . . receptor sites." *Id.*

Table 4 of Fogelman is reproduced below.

**Table 4.** Formation of ODV and NDV by Microsomes Containing Human Cytochromes Expressed by cDNA-Transfected Human Lymphoblastoid Cells

| | 2C9 | 2C19 | 2D6 | 3A4 |
|---|---|---|---|---|
| | | O-demethylation (ODV formation) | | |
| $V_{max}$ [a] | 0.58 | 3.78 | 6.48 | — |
| $K_m$ [b] | 3119 | 293 | 23.2 | — |
| $K_s$ [c] | 5708 | — | 8704 | — |
| $V_{max}/K_m$ [d] | 0.187 | 12.9 | 278.7 | — |
| Relative contribution at low substrate concentrations[e] | 1% | 10% | 89% | |
| | | N-demethylation (NDV formation) | | |
| $V_{max}$ | 10.33 | 7.56 | — | 1.23, 5.39 |
| $K_m$ | 2250 | 398 | — | 556, 11836 |
| $K_s$ | 6337 | — | — | — |
| $V_{max}/K_m$ | 4.59 | 19.04 | — | 2.67[f] |
| Relative contribution at low substrate concentrations[e] | 31% | 33% | | 36% |

[a] $V_{max}$ (units = pmol/min/pmol CYP) equals the maximal velocity.
[b] $K_m$ (units = μM) is the substrate concentration at which the reaction velocity equal 50% of $V_{max}$.
[c] $K_s$ (units = μM) is a constant indicating the degree of substrate inhibition.
[d] $V_{max}/K_m$ units = (nl/min/pmol CYP).
[e] Relative contributions have been normalized for relative cytochrome abundance as described by Venkatakrishnan et al. (1998a, b).
[f] Sum of two $V_{max}/K_m$ values.

*Id.* at 486. Table 4 provides details of the formation of ODV and NDV by microsomes containing human cytochromes expressed by cDNA-transfected human lymphoblastoid cells. *Id.*

Fogelman found that "[u]sing the $V_{max}//K_m$ ratio as a quantity to estimate intrinsic clearance, approximately 90% of total intrinsic clearance was accounted for by the O-demethylation pathway." *Id.* at 483.

*ii. Overview of Miwa (Ex. 1004)*

Miwa is a review of kinetic isotope effect and "metabolic switching" in cytochrome P-450-catalyzed reactions. Ex. 1004, Summary. Miwa teaches that the carbon-deuterium bond is stronger than the carbon-hydrogen bond, and thus many reactions that involve cleavage of that bond are

retarded by deuterium substitution, a phenomenon known as kinetic isotope effect. *Id.* at 215. Miwa teaches:

> In most enzymic reactions involving a C-H bond cleavage step, the reduction in product formation for the deuterated substrate is accompanied by a concomitant decrease in substrate metabolism. The tight complimentary binding between the substrate and the enzyme active site places severe restrictions on alternative orientations of the substrate, thus limiting metabolism to only a single site. In contrast, an unexpected change in regional selectivity was observed when the products of cytochrome P-450-catalyzed reactions were carefully determined. . . . [T]he term 'metabolic switching' [has been coined] to describe this change in selectivity during the metabolism of deuterated substrates. In this essay, 'metabolic switching' is defined more generally and refers to the increase in substrate flux through alternative pathways, catalyzed by either cytochrome P-450 or alternate enzymes, when the primary pathway for metabolism is reduced by a hydrogen isotope or other substituents.

*Id.* (reference omitted).

Thus, Miwa teaches that for some drugs, isotope substitution (i.e., from hydrogen to deuterium) may reduce the rate of drug metabolism, and, therefore, may reduce the rate of clearance of the drug from the body. *Id.* at 218. Miwa teaches further, however, that for other drugs, isotope substitution may not give rise to significant isotope effects in metabolism or clearance, which may be due to the lack of contribution of C-H bond in the overall metabolism of the drug, or because of metabolic switching, which results in the potentiation of other metabolic pathways. *Id.* When metabolic switching occurs, the pharmacological and toxicological consequences depend on the new metabolic pathway, which may either enhance or inhibit the production of toxic metabolites. *Id.*

*ii. Analysis*

Petitioner asserts that claim 1 is unpatentable as being rendered obvious by the combination of Fogelman and Miwa. Pet. 22–30. Petitioner relies on the Declaration of Dr. William Braunlin (Ex. 1002) to support its obviousness challenge. Patent Owner disagrees. Prelim. Resp. 20–36.

Petitioner relies on Fogelman for teaching that the transformation of VF to ODV is the major pathway for clearance of VF. Pet. 24 (citing Ex. 1002 ¶ 15). Petitioner relies also on Fogelman for teaching the major metabolites of VF, the specific P-450 enzymes responsible for the production of the O-demethylation and N-demethylation metabolism products of VF, as well as the extent of which P-450 enzyme is responsible for the production of those products. *Id.* at 23–24.

Petitioner relies on Miwa for demonstrating that the use of strategic deuteration of the active sites of pharmaceutically active compounds to alter their preferred metabolic route and rate of clearance was known. *Id.* at 24. Miwa is also relied upon for its teaching that the possibility of metabolic switching was known, as well as the factors that may influence its occurrence. *Id.* (citing Ex. 1002 ¶ 16).

Petitioner relies on Dr. Braunlin for his statement that an important aspect of the effectiveness of a particular drug "is how long it remains in the body before being metabolized and cleared from the body." *Id.* at 28 (quoting Ex. 1002 ¶ 19). Fogelman teaches that the major pathway of clearance for VF is through the ODV pathway, and that approximately 90% of total intrinsic clearance is through that pathway. *Id.* at 29 (citing Ex. 1002 ¶ 19). Thus, Petitioner contends that "one of ordinary skill in the art would have been motivated to deuterate the drug venlafaxine at the sites acted upon

by cytochrome P-450 enzymes in order to reduce the rate of venlafaxine metabolism, reduce the clearance of venlafaxine from the body and improve the duration of action and peak plasma levels of venlafaxine." *Id.* at 29–30 (quoting Ex. 1002 ¶ 19).

As for a reasonable expectation of success, Petitioner relies on the Declaration of Dr. Braunlin for the explanation that VF has only two cytochrome P-450 enzyme active sites that would be expected to be successful for deuteration, the carboxymethyl oxygen and the two methyl groups on the nitrogen. *Id.* at 30 (citing Ex. 1002 ¶ 20). Thus, Petitioner contends that "a person of ordinary skill in the art would have had a reasonable expectation of success in determining the sites for deuteration that are recited in claim 1 of the '317 patent." *Id.* (citing Ex. 1002 ¶¶ 19–20).

Patent Owner responds that it is not possible to predict whether any given kinetic isotope effect will provide a beneficial change in metabolism without extensive testing. Prelim. Resp. 22 (citing Ex. 2021, [5] 404–406). Specifically, Patent Owner argues that a primary deuterium kinetic isotope effect "will only be observed if the breaking of the carbon-hydrogen bond is the rate-limiting step." *Id.* at 23 (reference omitted) (citing Ex. 2020,[6] 102). According to Patent Owner, the evidence of record demonstrates that the ordinary artisan would not have known, nor been able to predict, the rate-limiting step of P-450 mediated metabolic oxidation of VF. *Id.*

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[5] Scott L. Harbeson and Roger D. Tung ("Harbeson"), *Deuterium in Drug Discovery and Development*, 46 ANNUAL REPORTS IN MEDICINAL CHEMISTRY 403–417 (John E. Macor, Ed., 2011).

[6] Fisher et al. ("Fisher"), *The Complexities Inherent in Attempts to Decrease Drug Clearance by Blocking Sites of CYP-Mediated Metabolism*, 9 CURRENT OPINION IN DRUG DISCOVERY & DEVELOPMENT 101–109 (2006).

Patent Owner cites to evidence that shows that even if the breaking of the carbon-hydrogen bond is the rate-limiting step of P-450 mediated metabolic oxidation of VF, the evidence of record demonstrates further that the ordinary artisan would not have been able to predict the magnitude of the deuterium substitution effect. *Id.* at 24 (citing Ex. 2021, 104). If the effect is too low, there may be no impact on the metabolism of the drug, and if it is too high, metabolic switching may occur. *Id.* (citing Ex. 2020, 102–104). Patent Owner cites to evidence that the ordinary artisan would not have been able to predict the metabolites that would be formed by metabolic switching, nor the impact of those metabolites. *Id.* at 26 (citing Ex. 1004, 218).

Thus, Patent Owner contends that the ordinary artisan would not have had a reasonable expectation of success of deuterating VF to achieve a molecule with improved duration of action and peak plasma levels. *Id.* at 27. In fact, according to Patent Owner, Miwa—relied upon by Petitioner—teaches that "isotope substitution may not give rise to significant isotope effects in metabolism or clearance." *Id.* (quoting Ex. 1004, 218).

As noted above, Petitioner relies on Fogelman for teaching that the major pathway for clearance of VF is oxidation to its major metabolite, ODV. *Id.* at 28. In that pathway, the methoxy group is converted to a hydroxyl, and thus, according to Petitioner, it would have been obvious to replace the -$OH_3$ group with an -$OD_3$ group to replace the rate of clearance of VF. *Id.* Patent Owner argues, however, that "the *exact opposite effect* occurred for two deuterated forms of paroxetine in which methylene hydrogens adjacent to an oxygen were substituted with deuterium." *Id.* (citing Ex. 2021, 413–414). Patent Owner points out that deuterium

substitution of paroxetine, which is also a serotonin reuptake inhibitor, resulted in an increase in metabolism, not a decrease. *Id.* at 28–29.

Patent Owner argues further that the compound of claim 1 is not just the substitution of an -$OH_3$ group with an -$OD_3$ group, but also replaces the hydrogen with deuterium on two N-methyl groups, making for a total of nine replacements, leaving the other hydrogens on the compound unreplaced. *Id.* at 29. The deuteration of alkyl groups in an N-alkylated compound, Patent Owner contends, is also not predictable. *Id.* at 30. According to Patent Owner, when phentermine was tested, which has a N-di-(tri-deuteromethyl) group similar to VF, no deuterium kinetic isotope effect was observed. *Id.* (citing Ex. 2019,[7] 22–23).

And even if decreased metabolism is observed, Patent Owner argues, there may be no net benefit *in vivo*. *Id.* Patent Owner cites studies of tramadol, which is also a serotonin reuptake inhibitor, and which, Patent Owner argues, shares many structural features with VF, and is also metabolized via O- and N-demethylation. *Id.* at 31. Patent Owner argues that although some of the deuterated versions of tramadol that were prepared, including a $d_9$-tramadol, "exhibited reduced *in vitro* metabolism, *none of the prepared deuterated versions were superior to tramadol* in terms of potency or duration of effect; clearance was not reduced and half-life was not increased." *Id.* (citing Ex. 2026,[8] 692–693). According to Patent Owner, the "deuterated venlafaxine claimed in the '317 patent, however, has

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[7] Allan B. Foster ("Foster"), *Deuterium Isotope Effects in the Metabolism of Drugs and Xenobiotics: Implications for Drug Design*, 14 ADVANCES IN DRUG RESEARCH 1–40 (1985).
[8] Shao et al. ("Shao"), *Derivatives of Tramadol for Increased Duration of Effect*, 16 BIOORGANIC & MEDICINAL CHEMISTRY LETTERS 691–94 (2006).

superior pharmacokinetic properties compared to venlafaxine, including increased half-life, reduced C*max*, and reduced inter-patient variability." *Id.* (citing Ex. 2018[9]).

Patent Owner contends also that "Petitioner provides no credible motivation . . . to modify venlafaxine by deuteration." *Id.* at 31. Petitioner, Patent Owner asserts, relies on the unsupported assertion of its expert that the ordinary artisan would have been motivate to deuterated the sites acted upon by cytochrome P-450 to reduce the rate of metabolism and clearance of VF, thereby improving its peak plasma levels and its duration of action. *Id.* at 32. The prior art, however, teaches that ODV has the same pharmacological activity of VF, but that it has a longer duration of action and is more potent than VF. *Id*. According to Patent Owner, the Petition does not identify a reason why the ordinary artisan would want to deuterate VF to inhibit ODV production given its useful pharmacologic activity, arguing that "[t]his flaw exemplifies the unfounded generalizations that characterize Petitioner's arguments." *Id.*

We recognize that an obvious analysis requires us to consider whether an ordinary artisan would have had a reasonable expectation of success, not absolute predictability of success. *In re O'Farrell*, 853 F.2d 894, 903–904 (Fed. Cir. 1988). We agree with Patent Owner, however, that Petitioner has not demonstrated that the ordinary artisan would have combined Fogelman with Miwa with a reasonable expectation of arriving at the invention claimed by the '317 patent. Although Fogelman teaches that ODV may account for 90% of the pathway for intrinsic clearance of VF (Ex. 1003, 483), Fogelman

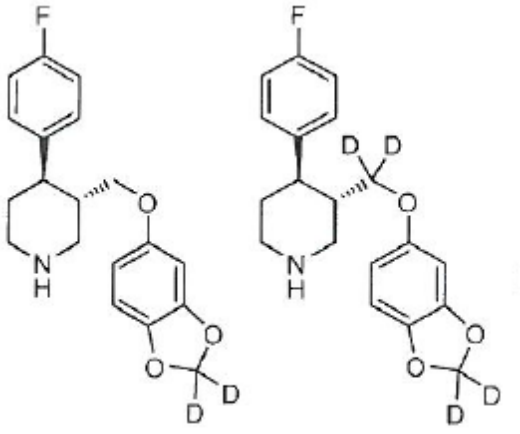
[9] Amanda Yarnell, *Heavy Hydrogen Drugs Turn Heads, Again*, 87(25) Chem, Eng. News 36–39 (2009).

teaches also that ODV has a receptor affinity profile similar to its parent compound VF (*id.* at 481). As noted by Patent Owner (Prelim. Resp. 32), Petitioner has not explained, through evidence or adequate scientific reasoning, why the ordinary artisan would have wanted to prevent the metabolism of VF to its pharmaceutically active metabolite, ODV. Stated differently, because ODV is a desired metabolite, as it has the same pharmacological activity as its parent compound, VF, Petitioner has not explained why the ordinary artisan would have had a reason to prevent VF from being metabolized to ODV, rather than only preventing metabolism to a non-active metabolite, or make a substitution that would prevent the further metabolism of ODV.

In addition, Miwa teaches that isotope substitution may not give rise to significant isotope effects in metabolism or clearance, which may be due to the lack of contribution of C-H bond in the overall metabolism of the drug. Ex. 1004, 218. Fisher, relied upon by Patent Owner, also states that if cleavage of the C-H bond is the rate-limiting step, the turnover of the drug would depend on deuterium substitution. Ex. 2020, 102. Fisher notes, however, that other steps, such as product release, may be rate-limiting, and thus, suppress any isotope effect. *Id.* Thus, according to Fisher, "deuterium isotope effect theory and the mechanism of CYP enzymes taken together suggest that the strategy will usually not result in significant alterations in overall metabolic clearance of the substrate." *Id.* at 101–102. In addition, Harbeson, also cited by Patent Owner, teaches that "[i]t is difficult to predict *a priori* which effect deuterium may have on a drug's metabolism." Ex. 2021, 404. Harbeson notes that while a deuterium isotope effect has the potential to affect the metabolism of drugs that are metabolized by the

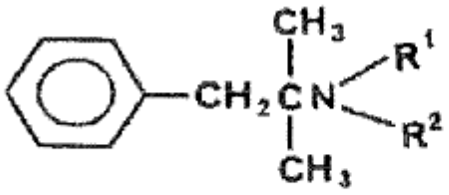
cleavage of a C-H bond, in practice, the effect is often masked. *Id.* at 405. Thus, the evidence of record demonstrates that it was not predictable what would be the effect of replacing one or more hydrogens of VF with deuterium on the metabolism of VF by the P-450 enzymes. That is, although Petitioner argues that it would be obvious to substitute the two main sites of VF acted upon by the P-450 enzymes, that is, -$OCH_3$ and –$N(CH_3)_2$ (Pet. 10–11), due to the presence of other possible rate-limiting steps, as well as the possibility of metabolic switching, the ordinary artisan would not have had a reasonable expectation that substitution of all of the nine hydrogens at those sites for deuterium would result in a deuterated VF derivative having enhanced bioavailability and which maintains its activity for a longer period of time.

That conclusion is supported further by evidence relied upon by Patent Owner. For example, Harbeson, cited by Patent Owner, teaches that while one deuterated analog of paroxetine, whose structure is unknown, mitigated inactivation by a P-450 enzyme in a clinical setting, two other analogs, with structures 16 and 17 showed increased metabolism *in vivo*. Ex. 2021, 413. Structures 16 and 17 are reproduced below.



Patent Owner notes that methylene hydrogens adjacent to an oxygen were substituted with deuterium (Prelim. Resp. 28), which Petitioner argues would have been obvious to do with VF (Pet. 29–30).

Patent Owner notes further that when phentermine was tested, which has a N-di-(tri-deuteromethyl) group similar to VF, no deuterium kinetic isotope effect was observed. Prelim. Resp. 30 (citing Ex. 2019, 22–23). The structures of *N*,*N*-dimethylphenteramine (Formula 87), and its deuterated derivatives (Formulas 88 and 89), are reproduced below:



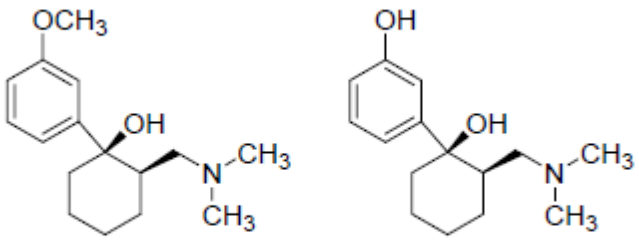
87 $R^1 = R^2 = CH_3$

88 $R^1 = R^2 = CD_3$

89 $R^1 = CH_3$, $R^2 = CD_3$

Ex. 2019, 23. Foster teaches that it was found that the C-H bond did not contribute to the rate-limiting step, and that the N-demethylation could involve a transition state different from that associated with O-demethylation. *Id.*

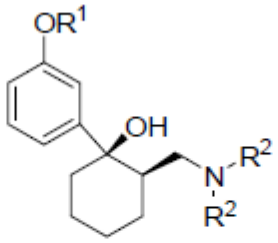
Shao, also cited by Patent Owner (Prelim. Resp. 30–31), demonstrates that even if deuteration slows the formation of major metabolites, there may be no *in vivo* effect. Ex. 2026, 693–94. Shao looked at deuteration of tramadol, which is used in the treatment of moderate to moderately severe pain. *Id.* at 691. The structures of tramadol (Formula 1), and its major metabolite, M1, are reproduced below:




**1** **M1**

*Id.*

Shao attempted to slow CYP450-mediated metabolism by replacing hydrogen with deuterium at metabolically active sites, that is, by replacing the hydrogen atoms at the O-methyl and N-methyl groups, as demonstrated below:




**$D_3$** $R^1 = CD_3$, $R^2 = CH_3$
**$D_6$** $R^1 = CH_3$, $R^2 = CD_3$
**$D_6$ $M_1$** $R^1 = H$, $R^2 = CD_3$
**$D_9$** $R^1 = CD_3$, $R^2 = CD_3$

*Id.*

As reported by Shao:

> In conclusion, the substitution of deuterium for hydrogen in the methyl groups of tramadol did not adversely affect the in vitro binding affinity. In vitro testing in human microsomes confirmed that replacing hydrogen with deuterium in the metabolically labile *O*-methyl position of 1 slowed the formation of the primary metabolite M1 by approximately 5-fold. The deuterated derivatives 7 (D6) and 9 (D9) were active

> analgesics in the rat tail-flick model, but were not superior to tramadol in terms of potency or duration of effect. Deuterium for hydrogen replacement at metabolically active sites had no obvious deleterious effects in vivo but did not result in a longer duration of effect. In this case, deuteration at metabolically active sites produced a pharmacological agent equipotent in vivo with tramadol.

*Id.* at 693–694.

Thus, the evidence of record demonstrates that the effect of the deuteration on the metabolic and pharmacologic properties of a drug are unpredictable, and thereby supports Patent Owner's contention that the ordinary artisan would not have had a reasonable expectation of success at arriving at the invention claimed by the '317 patent. We have considered the Declaration of Dr. Braunlin, relied upon by Petitioner to demonstrate a reasonable expectation of success (Pet. 30), but it does not convince us otherwise.

Dr. Braunlin states:

> It is my opinion that a person of ordinary skill in the art would have had a reasonable expectation of success of achieving the claimed invention. As taught by Miwa, strategic deuteration of active sites on drugs to alter their preferred metabolic route and rate of clearance was known. And, in terms of functionality, there are only two cytochrome P-450 enzyme active sites on venlafaxine that would be expected to be successful sites for deuteration: -CD3 substitution of the carboxymethyl oxygen and -CD3 substitution of the two methyl groups on nitrogen.

Ex. 1002 ¶ 20. Dr. Braunlin opines further that as the primary metabolic pathway involves O-demethylation, "it makes sense to fully deuterate the single O-methyl group to enhance bioavailability and maintain activity for a longer prior to elimination." *Id.* ¶ 21. Relying on a reference to Foster (for

which an exhibit number was not provided nor appear does the reference appear to be made of record), Dr. Braunlin states that O-methyl deuteration has a "very large isotope effect." *Id.* Because the second pathway involved N-demethylation, Dr. Braunlin concludes "a person of ordinary skill in the art would have had a reasonable expectation of success in determining sites for deuteration that are recited in claim 1 of the '317 patent." *Id.*

As discussed above, although Miwa teaches that the use of deuteration to alter drug clearance rate was known, Miwa teaches also that for some drugs, isotope substitution may not give rise to significant isotope effects in metabolism or clearance. Ex. 1004, 218. The lack of a kinetic isotope effect may be due to the lack of contribution of C-H bond in the overall metabolism of the drug, or because of metabolic switching, which results in the potentiation of other metabolic pathways. *Id*. Thus, Miwa supports the unpredictability of the effect of substituting deuterium for hydrogen on the pharmacological and toxicological effects of a drug. Moreover, the reference relied upon by Dr. Braunlin to support his statement that O-methyl deuteration has a "very large isotope effect" was not provided; whereas Shao, relied upon by Patent Owner demonstrates that deuteration of the O-methyl group of tramadol had no *in vivo* effect. Ex. 2026, 693–694.

Patent Owner argues further that the Petition does not demonstrate that it would have been obvious to try deuteration of VF to arrive at the claims of the '317 patent. Prelim. Resp. 32. In particular, Patent Owner notes that there were not a finite number of identified, predictable solutions, as there are approximately $2^{27}$-1, or 124,217,727 deuterated forms of VF, minus some number of forms which are equivalent due to symmetry or rotatable bonds. *Id.* at 32–33, 35. According to Patent Owner, "[t]o explore

all of these possibilities would be to vary all parameters in the bare hope of success." *Id.* at 35.

We agree. In *In re O'Farrell*, the Federal Circuit set forth two situations in which an "obvious to try" rationale was usually applied improperly. *In re O'Farrell*, 853 F.2d at 903. The first improper situation was to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters are critical or no direction as to which of many possible choices is likely to be successful." *Id.* The second improper situation was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." *Id.; see also In re Kubin*, 561 F.3d 1351, 1358–1360 (Fed. Cir. 2009) (noting that the rationale in *O'Farrell* was "affirmed in the logical inverse" in *KSR*, 550 U.S. at 417, in a statement that "§103 bars patentability unless 'the improvement is more than the predictable use of prior art elements according to their established functions.'").

Based on the above framework, we conclude that it would not have been obvious to try to achieve the invention of claim 1 of the '317 patent. As noted by Patent Owner (Prelim. Resp. 35), and not disputed by Petitioner (*see* Pet. 10–11), there are approximately $2^{27}$-1, or 124,217,727 deuterated forms of VF, minus some number of forms which are equivalent due to symmetry or rotatable bonds. Although Petitioner contends that as P-450 enzymes act on two main sites of VF—that is, -$OCH_3$ and –$N(CH_3)_2$, arguing that it would have been obvious to deuterate only those sites (Pet. 10–11)—as discussed above, the ordinary artisan would not have had a

reasonable expectation that deuteration of those sites would result in enhanced bioavailability and maintaining the activity of VF for a longer period of time. Thus, the ordinary artisan would be left with trying the over 100,000,000 possible deuterated forms of VF until possibly arriving at a successful result.

*iii. Conclusion*

For the reasons set forth above, we conclude that Petitioner has not established a reasonable likelihood that claim 1 is rendered obvious by the combination of Fogelman and Miwa.

*C. Obviousness over the Combination of Fogelman (Ex. 1003), Miwa (Ex. 1004), and Platteeuw (Ex. 1005), and the Combination of Fogelman, Miwa, Platteeuw, and Jerussi (Ex. 1006).*

Petitioner contends that claims 2 and 8 are unpatentable over the combination of Fogelman, Miwa, and Platteeuw (Pet. 31–33), and that claims 3–7, 9, and 10 are unpatentable as obvious over the combination of Fogelman, Miwa, Platteeuw, and Jerussi (Pet. 33–49). Petitioner relies on Platteeuw for teaching a therapeutically effective amount of VF (Pet. 31), and Jerussi for teaching oral, parental, and intravenous infusion (*id.* at 34). Thus, neither Platteeuw nor Jerussi remedy the deficiencies of the combination of Fogelman and Miwa, as discussed above in relation to claim 1, upon which claims 2–10 depend.

As neither Platteeuw nor Jerussi remedy the deficiencies of the combination of Fogelman and Miwa, discussed above, Petitioner has not established a reasonable likelihood that claims 2–10 are rendered obvious by the combination of Fogelman, Miwa, and Platteeuw, or the combination of Fogelman, Miwa, Platteeuw, and Jerussi.

## III. PENDING MOTIONS

Patent Owner filed a Motion for Additional Discovery (Paper 9). In addition, Petitioner filed a Motion to Seal (Paper 18), as well as a Motion to Expunge Paper 17 (Paper 19).

We grant Petitioner's Motion to Expunge. We deny Patent Owner's Motion for Additional Discovery as moot in view of our denial of the Petition. Finally, as we did not rely on the material Petitioner sought to seal, we decline to address the merits of the Motion to Seal. Petitioner is authorized to file a motion to expunge any material that it seeks to keep confidential within thirty (30) days of the date of this decision, or within thirty (30) days of a decision on rehearing, if rehearing is requested.

## IV. CONCLUSION

For the foregoing reasons, we are not persuaded that the Petition establishes a reasonable likelihood that Petitioner would prevail in showing claims 1–10 of the '317 patent are unpatentable under 35 U.S.C. § 103(a).

## V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that the Petition is *denied* as to all of the challenged claims of the '317 patent;

FURTHER ORDERED that Paper 17 is expunged; and

FURTHER ORDERED that Petitioner is authorized to file a motion to expunge any material that it seeks to keep confidential within thirty (30) days of the date of this decision, or within thirty (30) days of a decision on rehearing, if rehearing is requested.

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