IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

VANDA PHARMACEUTICALS INC. and AVENTISUB LLC,	)	
Plaintiffs,	)	Civil Action No. 13-1973-GMS Civil Action No. 14-757-GMS
v.	)	(Consolidated)
ROXANE LABORATORIES, INC.,	)	
Defendant.	)	

MEMORANDUM

I. INTRODUCTION

In this consolidated patent infringement action, plaintiffs Vanda Pharmaceuticals Inc. ("Vanda") and Aventisub LLC ("Aventisub") (collectively "the Plaintiffs") allege infringement by Roxane of U.S. Reissue Patent No. 39,198 ("the '198 Patent") and U.S. Patent No. 8,586,610 ("the '610 Patent"). The two actions were consolidated for purposes of trial on April 13, 2015. The court held a five-day bench trial in this matter on February 29, 2016 to March 4, 2016. (D.I. 171–176.) Presently before the court are the parties' post-trial proposed findings of fact and post-trial briefs concerning the validity of the patents-in-suit and whether Roxane's proposed products infringe the '610 Patent. (D.I. 178, 179, 184, 185.)

Pursuant to Federal Rule of Civil Procedure 52(a), and after having considered the entire record in this case and the applicable law, the court concludes that: (1) all asserted claims of the patents-in-suit are valid; (2) Roxane's proposed products induce infringement of the asserted claims of the '610 Patent; (3) Roxane's proposed products do not contributorily infringe the asserted claims

of the '610 Patent; and (4) each of the parties' Rule 52(c) motions are granted in part and denied in part. These findings of fact and conclusions of law are set forth in further detail below.[1]

II. FINDINGS OF FACT[2]

A. The Parties

1. Plaintiff Vanda is a Delaware corporation with its principal place of business at 2200 Pennsylvania Ave NW, Washington, DC 20037.

2. Plaintiff Aventisub is a Delaware corporation with its principal place of business at 3711 Kennett Pike, Suite 200, Greenville, DE 19807.

3. Defendant Roxane is a Nevada corporation with its principal place of business at 1809 Wilson Road, Columbus, OH 43228.

4. The court has subject matter jurisdiction as well as personal jurisdiction over all parties.

B. Background

5. Genotyping assays are currently commercially available to identify CYP2D6 poor metabolizers.

6. Genotyping assays are laboratory tests.

7. The generic iloperidone described in the Roxane ANDA is literally within the scope of claim 3 of the '198 Patent and infringes claim 3 of the '198 Patent provided that the claim is not proved invalid.

8. Extrapyramidal side effects ("EPS") are undesired side effects of antipsychotic medications.

9. Atypical antipsychotics have fewer extrapyramidal side effects than typical antipsychotics.

C. The Patents-in-Suit

10. The '198 Patent, entitled "Heteroarylpiperidines, Pyrrolidines and Piperazines and Their Use as Antipsychotics and Analgesics," issued on July 18, 2006, and names Joseph T.

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[1] Roxane concedes infringement of claim 3 of the '198 Patent, provided that the claim is not proved invalid. (D.I. 129.)

[2] Prior to trial, the parties submitted an exhibit of uncontested facts in conjunction with their Pretrial Order. (D.I. 154, Ex. 1.) The court takes most of its findings of fact from the parties' uncontested facts. The court has also reordered and renumbered some paragraphs, corrected some formatting errors, and made minor edits for the purpose of concision and clarity that it does not believe alters the meaning of the paragraphs from the Pretrial Order. Otherwise, any differences between this section and the parties' statement of uncontested facts are unintentional.

The court's findings of fact with respect to matters that were the subject of dispute between the parties are included in Part III of this opinion ("Discussion and Conclusions of Law"), preceded by the phrase "the court finds" or "the court concludes."

Strupczewski, Grover C. Helsley, Yulin Chiang, Kenneth J. Bordeau, and Edward J. Glamkowski as the inventors.

11. The '198 Patent was filed on November 15, 2000, and is a reissued patent of U.S. patent no. 5,364,866, filed on October 30, 1992.

12. The '198 Patent claims priority to U.S. Patent Application No. 07/354,411, filed on May 19, 1989.

13. The '198 Patent expires on November 15, 2016.

14. Aventisub is the owner by assignment of the '198 Patent.

15. Vanda holds an exclusive worldwide license to the '198 Patent.

16. The '610 Patent, entitled "Methods for the Administration of Iloperidone," issued on November 19, 2013, and names Curt D. Wolfgang and Mihael H. Polymeropoulos as the inventors.

17. The '610 Patent claims priority to U.S. Provisional Application No. 60/614,798, filed on September 30, 2004.

18. The '610 Patent expires on November 2, 2027.

19. Vanda is the owner by assignment of the '610 Patent.

20. Vanda has standing to sue for infringement of the '610 Patent.

1. The Asserted Claims

a. '198 Patent, Claim 3

Claim 3 of the '198 Patent reads:

A compound as claimed in claim 1, which is 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxyphenyl]ethanone or a pharmaceutically acceptable acid addition salt thereof. The nonproprietary name for 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]- propoxy]-3-methoxyphenyl]ethanone is "iloperidone."

b. '610 Patent, Claims 1-9, 11-13, and 16

Claims 1-9, 11-13, and 16 of the '610 Patent read:

A method for treating a patient with iloperidone, wherein the patient is suffering from schizophrenia, the method comprising the steps of: determining whether the patient is a CYP2D6 poor metabolizer by: obtaining or having obtained a biological sample from the patient; and performing or having performed a genotyping assay on the biological sample to determine if the patient has a CYP2D6 poor metabolizer genotype; and if the patient has a CYP2D6 poor

metabolizer genotype, then internally administering iloperidone to the patient in an amount of 12 mg/day or less, and if the patient does not have a CYP2D6 poor metabolizer genotype, then internally administering iloperidone to the patient in an amount that is greater than 12 mg/day, up to 24 mg/day, wherein a risk of QTc prolongation for a patient having a CYP2D6 poor metabolizer genotype is lower following the internal administration of 12 mg/day or less than it would be if the iloperidone were administered in an amount of greater than 12 mg/day, up to 24 mg/day.

2. The method of claim 1, wherein the performing or having performed the genotyping assay step comprises: extracting or having extracted genomic DNA or mRNA from the biological sample, and sequencing or having sequenced CYP2D6 DNA derived from the extracted genomic DNA or from the extracted mRNA, wherein the sequencing or having sequenced step further comprises: amplifying or having amplified a CYP2D6 region in the extracted genomic B-2 DNA or mRNA to prepare a DNA sample enriched in DNA from the CYP2D6 gene region; and sequencing or having sequenced the DNA sample by hybridizing the DNA sample to nucleic acid probes to determine if the patient has a CYP2D6 poor metabolizer genotype; and wherein the CYP2D6 poor metabolizer genotype is one of the CYP2D6G1846A genotype or the CYP2D6C100T genotype.

3. The method of claim 2, wherein the CYP2D6 poor metabolizer genotype is one of the CYP2D6G1846A (AA) genotype or the CYP2D6G1846A (AG) genotype.

4. The method of claim 3, wherein the CYP2D6 poor metabolizer genotype is the CYP2D6G1846A (AA) genotype.

5. The method of claim 2, wherein the CYP2D6 poor metabolizer genotype is one of the CYP2D6C100T (TT) genotype or the CYP2D6C100T (CT) genotype.

6. The method of claim 5, wherein the CYP2D6 poor metabolizer genotype is the CYP2D6C100T (TT) genotype.

7. The method of claim 1, wherein the step of internally administering iloperidone to the patient in an amount of 12 mg/day or less comprises internally administering iloperidone to the patient in an amount of 6 mg or less b.i.d.

8. The method of claim 2, wherein, if the patient has a CYP2D6 poor metabolizer genotype, then internally administering iloperidone to the patient in an amount of 6 mg b.i.d.

9. A method of treating a patient who is suffering from a schizoaffective disorder, depression, Tourette's syndrome, a psychotic disorder or a delusional disorder, the method comprising: determining if the patient is a CYP2D6 poor metabolizer by obtaining or having obtained a biological sample from the patient, and performing or having performed a genotyping assay on the biological sample to determine whether the patient has a CYP2D6 poor metabolizer genotype, and if the patient is a CYP2D6 poor metabolizer, then internally administering iloperidone to the patient in an amount of up to 12 mg/day, and if the patient is not a CYP2D6 poor metabolizer, then internally administering iloperidone to the patient in an amount of greater than 12 mg/day, up to 24 mg/day.

11. The method of claim 9, wherein the CYP2D6 poor metabolizer genotype is one of: B-3 CYP2D6G1846A (AA), CYP2D6G1846A (AG), CYP2D6C100T (TT), or CYP2D6C100T (CT).

12. The method of claim 9, wherein the method comprises: if the patient is a CYP2D6 poor metabolizer, then internally administering the iloperidone to the patient in an amount of 6 mg b.i.d.

13. A method of treating a patient who is suffering from a schizoaffective disorder, depression, Tourette's syndrome, a psychotic disorder or a delusional disorder, the method comprising: determining if the patient is at risk for iloperidone-induced QTc prolongation by obtaining or having obtained a biological sample from the patient, and performing or having performed a genotyping assay on the biological sample to determine whether the patient has a CYP2D6 poor metabolizer genotype, wherein the presence of a CYP2D6 poor metabolizer genotype indicates risk for iloperidone-induced QTc prolongation, and if the patient is at risk for iloperidone-induced QTc prolongation, then internally administering iloperidone to the patient in an amount of up to 12 mg/day, and if the patient is not at risk for iloperidone-induced QTc prolongation, then internally administering iloperidone to the patient in an amount of greater than 12 mg/day, up to 24 mg/day.

16. The method of claim 13, wherein the method comprises: if the patient is at risk for iloperidone-induced QTc prolongation, then internally administering the iloperidone to the patient in an amount of 6 mg b.i.d. claims 1-9, 11-13, and 16 of the '610 Patent.

D. FANAPT® and Roxane's ANDA

20. FANAPT® (iloperidone) is an atypical antipsychotic approved for the treatment of patients with schizophrenia. Vanda offers for sale and sells FANAPT® in the United States.

21. On May 6, 2009, the Food and Drug Administration ("FDA") approved Vanda's new drug application 22-192 for FANAPT® (iloperidone) in its 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg strengths under § 505(b) of the Federal Food, Drug, and Cosmetic Act (the "FFDCA"), 21 U.S.C. § 355(b), for the treatment of schizophrenia ("FANAPT® NDA").

22. Vanda owns the FANAPT® NDA.

23. The prescribing information for FANAPT® ("FANAPT® Label") states in part that "FANAPT® tablets are indicated for the treatment of adults with schizophrenia." § 1.

24. Schizophrenia is a psychotic disorder.

25. The FANAPT® Label states in part that "FANAPT is associated with prolongation of the QTc interval." § 1.

26. The FANAPT® Label states in part that "Prolongation of the QTc interval is associated in some other drugs with the ability to cause torsade de pointes-type arrhythmia, a potentially fatal polymorphic ventricular tachycardia which can result in sudden death." § 1.

27. The FANAPT® Label states in part that "The recommended target dosage of FANAPT tablets is 12 to 24 mg/day administered twice daily." Dosage and Administration.

28. The FANAPT® Label states in part that "The maximum recommended dose [of FANAPT® (iloperidone)] is 12 mg twice daily (24 mg/day)." § 2.1.

29. The FANAPT® Label states in part that "FANAPT dose should be reduced by one-half for poor metabolizers of CYP2D6." § 2.2.

30. The FANAPT® Label states in part that "Iloperidone is metabolized primarily by 3 biotransformation pathways: carbonyl reduction, hydroxylation (mediated by CYP2D6) and O-demethylation (mediated by CYP3A4)." § 12.3.

31. The FANAPT® Label states in part that "Approximately 7% - 10% of Caucasians and 3% - 8% of black/African Americans lack the capacity to metabolize CYP2D6 substrates and are classified as poor metabolizers (PM), whereas the rest are intermediate, extensive or ultrarapid metabolizers." § 12.3.

32. The FANAPT® Label states in part that "PMs of CYP2D6 have higher exposure to iloperidone compared with EMs and PMs should have their dose reduced by one-half. Laboratory tests are available to identify CYP2D6 PMs." § 12.3.

33. The '198 Patent and the '610 Patent are listed in connection with FANAPT® in FDA's publication, "Approved Drug Products with Therapeutic Equivalence Evaluations," referred to as the "Orange Book." The '610 Patent was listed in the Orange Book on or about January 15, 2015, after both of these lawsuits were filed.

34. Roxane filed Abbreviated New Drug Application No. 20-5480 (the "Roxane ANDA") under § 505(j) of the FFDCA to obtain approval to commercially manufacture and sell generic iloperidone tablets in 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg strengths for the treatment of schizophrenia, prior to the expiration of the '198 Patent and the '610 Patent.

35. On October 17, 2013, Roxane sent Novartis and Aventisub II Inc. a Patent Notice pursuant to § 505(j)(2)(B)(ii) asserting that the claims of the '198 patent are invalid under 35 U.S.C. § 103.

36. On May 6, 2015, Roxane sent Vanda a Patent Notice pursuant to § 505(j)(2)(B)(ii) asserting that Roxane's iloperidone label does not induce infringement of any claim of the '610 Patent and that the claims of the '610 Patent are invalid under 35 U.S.C. §§ 101 and 103.

37. If the Roxane ANDA is approved, Roxane will sell generic iloperidone tablets in 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg strengths for the treatment of schizophrenia in the United States.

38. By law, Roxane's label for its generic iloperidone product must include information from the label for the reference listed drug "except for changes required because of differences approved under a petition filed under subparagraph (C) or because the new drug and the listed drug are produced or distributed by different manufacturers." 21 U.S.C. § 355(j)(2)(A)(v).

39. The prescribing information proposed in the Roxane ANDA states in part that "Iloperidone tablets are indicated for the treatment of adults with schizophrenia." § 1.

40. The prescribing information proposed in the Roxane ANDA states in part that "Iloperidone is associated with prolongation of the QTc interval." § 1.

41. The prescribing information proposed in the Roxane ANDA states in part that "Prolongation of the QTc interval is associated in some other drugs with the ability to cause torsade de pointes-type arrhythmia, a potentially fatal polymorphic ventricular tachycardia which can result in sudden death." § 1.

42. The prescribing information proposed in the Roxane ANDA states in part that "The recommended target dosage of iloperidone tablets is 12 to 24 mg/day administered twice daily." Dosage and Administration.

43. The prescribing information proposed in the Roxane ANDA states in part that "The maximum recommended dose [of iloperidone] is 12 mg twice daily (24 mg/day)." § 2.1.

44. The prescribing information proposed in the Roxane ANDA states in part that "Iloperidone dose should be reduced by one-half for poor metabolizers of CYP2D6." § 2.2.

45. The prescribing information proposed in the Roxane ANDA states in part that "Iloperidone is metabolized primarily by 3 biotransformation pathways: carbonyl reduction, hydroxylation (mediated by CYP2D6) and O-demethylation (mediated by CYP3A4)." § 12.3.

46. The prescribing information proposed in the Roxane ANDA states in part that "Approximately 7% to 10% of Caucasians and 3% to 8% of black/African Americans lack the capacity to metabolize CYP2D6 substrates and are classified as poor metabolizers (PM), whereas the rest are intermediate, extensive or ultrarapid metabolizers." § 12.3.

47. The prescribing information proposed in the Roxane ANDA states in part that "PMs of CYP2D6 have higher exposure to iloperidone compared with EMs and PMs should have their dose reduced by one-half. Laboratory tests are available to identify CYP2D6 PMs." § 12.3.

48. By letter dated October 17, 2013 ("Roxane Notice Letter"), Roxane notified Aventisub that Roxane had filed the Roxane ANDA seeking approval to manufacture, use, offer to sell, and sell a generic version of FANAPT® (iloperidone) in 1 mg, 2 mg, 4 mg, 6 mg, 8mg, 10 mg, and 12 mg strengths for the treatment of schizophrenia before the expiration of the '198 Patent.

49. Plaintiffs assert infringement of the following claims against Roxane: claim 3 of the '198 Patent and claims 1-9, 11-13, and 16 of the '610 Patent.

50. Plaintiffs commenced Civil Action No. 13-1973 regarding infringement of the '198 Patent on November 25, 2013, within 45 days from Aventisub's receipt of the Roxane Notice Letter.

51. Plaintiff Vanda commenced Civil Action No. 14-757 regarding infringement of the '610 Patent on June 16, 2014.

III. DISCUSSION AND CONCLUSIONS OF LAW

The court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a). Venue is proper under 28 U.S.C. §§ 1391(b), (c), and (d), and 1400 (b). After

having considered the entire record in this case, the substantial evidence in the record, the parties' post-trial submissions, and the applicable law, the court concludes that: (1) all asserted claims of the patents-in-suit are valid; (2) Roxane's proposed products induce infringement of the asserted claims of the '610 Patent; and (3) Roxane's proposed products do not contributorily infringe the asserted claims of the '610 Patent. The court's reasoning follows.

A. Obviousness

1. The Legal Standard

Under 35 U.S.C. § 103(a), a patent may not be obtained "if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art" ("POSA"). 35 U.S.C. § 103(a). Obviousness is a question of law that is predicated on several factual inquires. *See Richardson-Vicks v. Upjohn Co.*, 122 F.3d 1476, 1479 (Fed. Cir. 1997). Specifically, the trier of fact is directed to assess four considerations: (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, acquiescence of others in the industry that the patent is valid, and unexpected results. *See Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

"A patent shall be presumed valid." 35 U.S.C. § 282(a). A party seeking to challenge the validity of a patent based on obviousness must demonstrate by "clear and convincing evidence"[3] that the invention described in the patent would have been obvious to a person of ordinary skill in

[3] "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.'" *Alza Corp v. Andrx Pharms., LLC*, 607 F. Supp. 2d 614, 631 (D. Del. 2009) (quoting *Colorado v. New Mexico*, 467 U.S. 310, 316 (1984)).

the art at the time the invention was made. Importantly, in determining what would have been obvious to one of ordinary skill in the art, the use of hindsight is not permitted. *See KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 421 (2007) (cautioning the trier of fact against "the distortion caused by hindsight bias" and "arguments reliant upon *ex post* reasoning" in determining obviousness). In *KSR*, the Supreme Court rejected the rigid application of the principle that there should be an explicit teaching, suggestion, or motivation in the prior art, the "TSM test," in order to find obviousness. *See id.* at 415. The *KSR* Court acknowledged, however, the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *Id.* at 418.

"Obviousness does not require absolute predictability of success," but rather, requires "a reasonable expectation of success." *See Medichem, S.A. v. Rolado, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (quoting *In re O'Farrell*, 853 F.2d 894, 903–04 (Fed. Cir. 1988)). To this end, obviousness "cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). Moreover, while the Federal Circuit has noted that pharmaceuticals can be an "unpredictable art" to the extent that results may be unexpected, it also recognizes that, per *KSR*, evidence of a "finite number of identified, predictable solutions" *KSR Int'l Co.*, 550 U.S. at 421, "might support an inference of obviousness." *Ortho–McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008).

2. <u>The Level of Ordinary Skill in the Art</u>

With regard to the '198 Patent, the parties agree that a person of ordinary skill in the art working in the field of the '198 Patent would have an advanced degree in medicinal chemistry

and/or pharmacology with some experience with the design and/or synthesis of antipsychotic drugs.[4]

With regard to the '610 Patent, a person of ordinary skill in the art would: (1) understand pharmacogenetics; or (2) have a degree in medicine, pharmacy, pharmacology, or a related field and practical experience in the field of psychiatry and/or clinical pharmacology, including pharmacogenomics. While the parties disagree, the court concludes that the parties' definitions of a person of ordinary skill in the art do not differ in a meaningful way.[5]

3. Nonobviousness of the '198 Patent

Roxane challenges the validity of claim 3 of the '198 Patent, arguing that it is obvious in light of the prior art as of the May 19, 1989 priority date. (D.I. 185 at 10.) The parties agree that at the time of the invention, a person of ordinary skill in the art would have recognized the need for an atypical antipsychotic. Tr. at 672:15–22; 719:22–720:12 (Sargent); 596:5–8 (Ratain); 767:22–768:2 (Strupczewski); 822:4–13 (Bartlett); 893:21–894:6 (Roth). According to Roxane, in 1989, after Janssen Pharmaceuticals announced the discovery of risperidone, a person of ordinary skill in the art searching for an atypical antipsychotic would focus on two compounds, which it labels compounds A and B, because they were known antipsychotics that resembled risperidone. (D.I. 179 at 34.) In particular, Roxane claims that a publication in the *Journal of Medicinal Chemistry* by Robert Duncan and Grover C. Helsley (JX-40), would teach a person of ordinary skill in the art to look to Compounds A and B. Dr. Sargent testified that the discovery of risperidone would lead a person of ordinary skill back to Helsley to experiment with a closely-related compound,

[4] *See* Tr. at 676:7–15 (Sargent); 820:5–13 (Bartlett).

[5] The parties disagree about the level of skill of ordinary skill in the art. Roxane contends that a skilled artisan would understand pharmacogenetics because the '610 Patent is about pharmacogenetics, Tr. at 512:6–12 (Ratain); the Plaintiffs contend that the '610 Patent is about methods of treating schizophrenia patients using iloperidone, and thus a skilled artisan would need to be qualified to administer antipsychotics to patients but would not need a pharmacogenetics background. The difference is insignificant, however. Roxane's expert admits his opinion would not change under either articulation. Tr. at 515:20–23 (Ratain). (*See* D.I. 178 at 17.)

Compound A. Indeed, Compound B was investigated as a potential antipsychotic following the publication of Helsley under the name "lenperone." Finally, according to Dr. Sargent, a person ordinarily skilled in the art could easily modify a butyrophenone compound such as Compound A or B by replacing its benzoyl moiety with a benzisoxazole moiety. (D.I. 185 at 14); Tr. at 692:10–12, 693:10–17 (Sargent). Thus, Roxane contends that a person of ordinary skill in the art had both a lead compound and the motivation to modify the lead compound.

In contrast, the Plaintiffs dispute that Compound B would lead a person of ordinary skill in the art to Compound A. (D.I. 84 at 14.) The Plaintiffs note that lenperone had caused extremely serious side effects, such that the skilled artisan would avoid it and its related compounds. Tr. at 910:5–12 (Roth). In an open-label clinical trial published in 1975, the ten patients treated with lenperone experienced nineteen serious cardiac side effects. Tr. at 908:7–910:3 (Roth) (citing PX-137 (Harris (1975)); 754:10–16 (Sargent). Lenperone was also associated with moderate sedation. Tr. at 754:17–755:6 (Sargent). Moreover, according to the Plaintiffs, lenperone was known to induce catalepsy. Tr. at 904:24–905:3, 906:12–18 (Roth) (citing JX-66).

The Plaintiffs further assert that Compound A was not known to be an antipsychotic. Rather, it was known to have tranquilizing activity and strong sedative effects, neither of which suggests its use as an antipsychotic. Tr. at 898:20–903:23 (Roth) (citing DTX-143; JX-40; JX-63; JX-66). In addition, Dr. Roth testified that Compound A would not be expected to have atypical antipsychotic activity. Tr. at 898:20–903:23 (Roth). Finally, even if a skilled artisan happened to start with Compound A in 1989, the Plaintiffs argue that there would be no motivation to make the bioisosteric substitution out of the many possible modifications to butyrophenones that were known. Tr. at 825:24–830:1 (Bartlett); 664:24–665:11 (Sargent); 839:16–25 (Bartlett).

The court does not find Dr. Sargent's testimony to be credible. Medicinal chemists spent decades and considerable resources trying to find a successor to clozapine, including Dr. Sargent, Tr. at 719:11–21 (Sargent); 894:3–7 (Roth), yet there is no evidence that anyone actually acted in the way that his theory predicts. Tr. at 760:7–11 (Sargent). Instead, the court is persuaded by the Plaintiffs' argument that a person ordinarily skilled in the art in 1989 seeking to synthesize a new atypical antipsychotic would start with a compound known to have atypical activity, which would exclude Compound A. (D.I. 184 at 14–15.) *See Daiichi Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (it is the "possession of promising useful properties in a lead compound that motivates a chemist to make structurally similar compounds."). As the Federal Circuit has cautioned, the reason to select a compound as a lead compound depends on more than just structural similarity, but also knowledge in the art of the functional properties and limitations of the prior art compounds. *See Eli Lilly*, 471 F.3d at 1377–79.

In addition, Roxane fails to demonstrate that benzisoxazole modifications were then known to solve any of the demonstrated side effects associated with Compound B. *See Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007) (finding it necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound). The court concludes that Roxane's argument is highly influenced by hindsight bias. *See Daiichi Sankyo Co.*, 619 F.3d at 1354 ("the attribution of a compound as a lead compound after the fact must avoid hindsight bias; it must look at the state of the art at the time the invention was made to find a motivation to select and then modify a lead compound to arrive at the claimed invention.") (citing *Ortho–McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008)).

4. <u>Nonobviousness of the '610 Patent</u>

Here, the court feels it necessary to provide a brief background about the claimed invention. Genetic mutations for the enzyme CYP2D6 are associated with an increased risk of iloperidone-induced QTc prolongation. JX-1. Many people are CYP2D6 poor metabolizers. JX-1 at 1:53–61. This can alter both the performance and side-effect profile of the drug. *See, e.g.*, Tr. at 912:3–7 (Roth). Iloperidone is metabolized into the P95 metabolite by the enzyme CYPD26. The claimed invention relies on the relationship between the ratio of P95 and P88 metabolites in the iloperidone metabolic pathway in the blood and the risk of QTc prolongation in iloperidone patients. JX-1.

Roxane asserts the '610 Patent invention is obvious because a POSA would have known to study the implications for iloperidone metabolism of mutations in the genes for the CYP2D6 enzyme. (D.I. 179 at 22.) Roxane relies on the prior art teachings from E. Mutlib & J. T. Klein, "Application of Liquid Chromatography/Mass Spectrometry in Accelerating the Identification of Human Liver Cytochrome P450 Isoforms Involved in the Metabolism of Iloperidone," in light of 1999 FDA Guidance for Industry. JX-68; DTX-118. According to Roxane, Mutlib taught that iloperidone had completed Phase II clinical trials as a potential atypical antipsychotic with a lower risk of side effects. Tr. at 528:14-529:3 (Ratain); JX-68 at 1285. Mutlib also taught that CYP2D6 was important in the metabolism of iloperidone. Tr. at 530:23-531:13 (Ratain). Mutlib reported the results of a study of the metabolism of iloperidone in human liver microsomes to define its metabolic pathways, Tr. at 531:14-20 (Ratain); JX-68 at Abstract, and Mutlib disclosed that metabolites 2 and 4 were formed by CYP3A4 and by the polymorph CYP2D6, respectively. Tr. at 531:21-23 (Ratain); JX-68 at Abstract. Dr. Ratain testified that, because it was known that CYP2D6 is important for the metabolism of iloperidone, a person ordinarily skilled in the art would be motivated to study it further. Tr. at 532:22–25 (Ratain) (citing JX-68).

Roxane also reasons that the '610 Patent is obvious because the FDA would have required clinical pharmacology studies to examine how the drug is metabolized. Tr. at 115:9-16 (Polymeropoulos), 977:24-979:4 (Guengerich); 533:1-24 (Ratain); DTX-76; DTX-118. Roxane posits that as of September 2004, these types of studies would be performed for any drug for which CYP2D6 was an important metabolic route of elimination. Tr. at 534:6-11 (Ratain). This process is exactly what Novartis did in its iloperidone clinical program. Tr. at 534:12-16 (Ratain).

The Plaintiffs respond that the prior art does not teach that CYP2D6 is important in iloperidone metabolism in the body (in vivo). (D.I. 84 at 11); Tr. at 967:7–25, 968:13–17 (Guengerich). According to the Plaintiffs, although Mutlib discloses that CYP2D6 plays a role in metabolizing iloperidone in vitro, the authors did not recover any meaningful in vivo results. Tr. at 592:18–593:14 (Ratain); 967:7–969:1 (Guengerich). The FDA warns that "When a difference arises between findings in vitro and in vivo, the results in vivo should always take precedence over studies in vitro." DTX-118. Vanda further contends the prior art suggested that CYP2D6 was not important in the metabolism of iloperidone. *See, e.g.*, PX-154; JX-95; DTX-53.

Moreover, the Plaintiffs argue that it is often the case that no dosage adjustment is needed for CYP2D6 poor metabolizers. (D.I. 184 at 12.) *See, e.g.*, DTX-122 at 9; Tr. at 607:2–17, 607:25–608:4 (Ratain). According to the Plaintiffs, it was unpredictable whether any dosage adjustment would be needed for CYP2D6 poor metabolizers, much less the amount of adjustment needed to achieve the pharmacokinetic profile seen in normal metabolizers. *See, e.g.*, Tr. at 605:7–606:3 (Ratain) (citing JX-95 at 11); 609:15–610:24 (Ratain) (citing JX-79 at 7); 938:6–16 (Roth). Nor was it clear that a dose adjustment would reduce QTc prolongation, claim the Plaintiffs, because not all side effects are dose-dependent. Tr. at 939:16–22 (Roth); 1008:6–10 (Guengerich). Furthermore, the Plaintiffs contend that because QTc side effects were so risky, a person ordinarily

skilled in the art would be deterred from further investigation. Tr. at 939:2–15 (Roth) ("when we saw prolongation of a QT interval that was induced by a drug, we stopped the drug. We did not give -- we did not lower the dose. We stopped it.").

The court concludes that the level of clinical testing required and inherent unpredictability in this field make certain that the invention was not obvious. The court is particularly persuaded by the fact that Novartis abandoned iloperidone in development because of QTc prolongation. Tr. at 85:14–18 (Polymeropoulos); 366:11–368:4 (Economou); 529:23–530:3 (Ratain) (citing DTX-53). Even if Mutlib provided a basis for a POSA to focus a study on the implications for iloperidone metabolism of mutations in the genes for the CYP2D6, it would have been impossible to predict the results. Tr. at 915:22–916:2, 919:10–13 (Roth). A solution is not obvious simply because it was obvious to conduct experiments to try to solve the problem. *In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988) ("[S]elective hindsight is no more applicable to the design of experiments than it is to the combination of prior art teachings."). In conclusion, the '610 Patent is not invalid as obvious.

5. Secondary Considerations of Nonobviousness

Roxane has failed to make a *prima facie* showing of obviousness under § 103. However, even if Roxane had met its burden, the Plaintiffs effectively make the case that secondary considerations weigh against a finding of obviousness. *See Graham*, 383 U.S. at 17–18. Specifically, the Plaintiffs offer evidence of a long-felt need. As the Plaintiffs points out, Novartis abandoned iloperidone and sold it to Vanda for an up-front payment of $500,000. Tr. at 84:6–85:13 (Polymeropoulos). Subsequently, Vanda was able to get FDA approval for iloperidone, based at least in part on Polymeropoulos's and Wolfgang's invention to reduce the side effects associated with QTc prolongation in order to safely treat patients suffering from schizophrenia. Tr. at 84:15–

22 (Polymeropoulos). After iloperidone was approved, Novartis paid Vanda $200,000,000 to reacquire rights to iloperidone and to market FANAPT® in the U.S. Tr. at 84:6–85:13 (Polymeropoulos). The forty-fold increase in Novartis's valuation of the franchise is highly indicative of non-obviousness. While Roxane argues that schizophrenia continues to be difficult to treat, (D.I. 85 at 11), the court's analysis must consider whether the claimed invention represents an improvement from the prior art at the time, not whether the problem has been totally eliminated.

B. Subject Matter Eligibility of the '610 Patent

1. The Legal Standard

Section 101 describes the general categories of patentable subject matter as "any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof." 35 U.S.C. § 101. There are, however, exceptions to these broad classifications. Under § 101, "laws of nature, natural phenomena, and abstract ideas" are not patentable. *Diamond v. Diehr*, 450 U.S. 175, 185 (1981). The contours of these exceptions have been the subject of much debate in recent years. *See id.* ("[W]e tread carefully in construing this exclusionary principle lest it swallow all of patent law. At some level, all inventions . . . embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas." (internal citation and quotations marks omitted)).

The Supreme Court's decision in *Alice* reaffirmed the framework first outlined in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012), used to "distinguish[ ] patents that claim laws of nature, natural phenomena, and abstract ideas from those that claim patent-eligible applications of those concepts." *Alice Corp. Pty. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2355 (2014).

> First, we determine whether the claims at issue are directed to one of those patent-ineligible concepts. If so, we then ask, what else is there in the claims before us? To

> answer that question, we consider the elements of each claim both individually and as an ordered combination to determine whether the additional elements transform the nature of the claim into a patent-eligible application.

Id. (quoting *Mayo Collaborative Services,* 132 S. Ct. at 1296–98 (internal citations, quotations marks, and alterations omitted). Thus, the court must determine (1) if the patented technology touches upon ineligible subject matter, and (2) whether there are sufficient inventive elements such that the invention is "'significantly more' than a patent on an ineligible concept." *See DDR Holdings, LLC v. Hotels.com, L.P.,* 773 F.3d 1245, 1255 (Fed. Cir. 2014) (quoting *Alice,* 134 S. Ct. at 2355); *see also Alice,* 134 S. Ct. at 2354 ("[A]n invention is not rendered ineligible for patent simply because it involves an abstract concept.").

2. The CYP2D6 Reaction

Roxane's subject matter ineligibility argument is based upon the contention that the '610 Patent is directed toward a patent ineligible subject, specifically a law of nature that it applies in a way that is routine and conventional. Roxane asserts that the patent embodies two laws of nature: (1) that mutations in the CYP2D6 genes can alter enzymatic activity, and (2) that a patient's CYP2D6 enzymatic activity affects their metabolism of iloperidone. Tr. at 621:19–622:2 (Ratain). Thus, according to Roxane, all of the method-of-treatment claims depend on natural processes. (D.I. 184 at 9.) To this, Roxane insists that the Plaintiffs merely add a dose adjustment to reduce the risk of a side effect, which Roxane claims is routine and conventional activity. (D.I. 185 at 10); Tr. at 521:6-522:10 (Ratain). According to Roxane, a person ordinarily skilled in the art would naturally discover the invention in performing FDA-mandated studies. (D.I. 179 at 17); Tr. at 604:13–19 (Ratain). Roxane's expert, Dr. Ratain, cited the prior art teaching from Goodman & Gilman's textbook as support for this view. DTX-79.

The Plaintiffs respond that § 101 forbids patent claims "directed to" patent-ineligible concepts, not claims that merely "*involve* a patent ineligible concept, because essentially every routinely patent-eligible claim involving physical products and actions involves a law of nature and/or natural phenomenon . . . ." *See Enfish, LLC v. Microsoft Corp.*, No. 2015-1244, 2016 WL 2756255, at *4 (Fed. Cir. May 12, 2016). The Plaintiffs argue that they have not sought to claim the use of biological sampling, or genotyping, or the relationship between iloperidone, CYP2D6 metabolism and QTc prolongation. (D.I. 178 at 23–24.) According to the Plaintiffs, the '610 Patent was not the result of routine and conventional testing. Specifically, the Plaintiffs' expert, Dr. Charles McCulloch, testified that clinical-study design is not routine or conventional. *See* Tr. at 629:15–21, 649:19–650:7 (McCulloch). The Plaintiffs also cite evidence that adjusting the dose for CYP2D6 poor metabolizers does not actually lower the risk of QTc prolongation for many drugs, including for antipsychotics that are structurally similar to iloperidone. *See* Ex. A, Guengerich ¶¶ 84–144, 155–60; Ex. B, Roth ¶¶ 144–62. Finally, the Plaintiffs point out that the U.S. Patent Office explicitly considered subject matter eligibility of the '610 Patent claims in light of *Mayo Collaborative Services*, and upheld the patentability of the claims after specific doses were added to the claims. Tr. at 521:6-21 (Ratain); JX-94 at 21; JX-20 at 2; DTX-82 at 2.

The court is persuaded that the asserted claims depend upon laws of nature. The '610 Patent describes the invention in terms of multiple natural relationships:

> The present invention describes an association between genetic polymorphisms in the CYP2D6 locus, corresponding increases in the concentrations of iloperidone or its metabolites, and the effect of such increases in concentrations on corrected QT (QTc) duration relative to baseline.

JX-1 at 2:34-38. The claims depend on the relationship between iloperidone, CYP2D6 metabolism, and QTc prolongation.

The issue is whether the claims incorporate some additional step sufficient to transform the claims, making them valid. In *Mayo Collaborative Services*, the Supreme Court considered patent claims describing the relationship between the ways in which thiopurine compounds are metabolized by the body and determined that this was a law of nature. *Id.* at 1297. The court found that to this law of nature, the claims merely added an "administering" step, a "determining" step, and a "wherein" step. *Id.* The Court wrote that the "determining" step in that case instructed the practitioner to determine the level of the relevant metabolites in the blood, "through whatever process the doctor or the laboratory wishes to use." *Id.* Thus, this step told doctors "to engage in well-understood, routine, conventional activity previously engaged in by scientists who work in the field." *Id.* at 1298. The Court wrote: "We need not, and do not, now decide whether were the steps at issue here less conventional, these features of the claims would prove sufficient to invalidate them." *Id.* at 1302.

The patent-at-issue in this case addresses natural relationships to which the claims add conducting CYP2D6 genotyping tests to determine the appropriate dose of iloperidone to reduce QTc-related risks. According to Roxane, these dosage adjustment limitations steps were routine and conventional activity. (D.I. 179 at 17.) Roxanne argues that Dr. Ratain testified that while exact dose reduction may not necessarily be ascertained without doing studies, the studies to determine the correct dose adjustment were routine. Tr. at 524:24-525:4 (Ratain). The Plaintiffs disagree, arguing that the tests to determine the dosage adjustments were far from routine; indeed Novartis' clinical trials attempted but failed to determine the relationship between QTc prolongation and CYP2D6 metabolism, a discovery it was highly motivated to find. Tr. at 617:18–618:19 (Ratain).

The court finds that while it may have been conventional to investigate for side-effects, Roxane has not proven by clear and convincing evidence that the precise test and the discovered results were routine or conventional. The court finds it persuasive that the dosage step in the '610 Patent does not apply to all patients, but only a specific patient population based upon their genetic composition. The dosage step requires applying genetic tests in a highly specified way. Moreover, the process of using this genetic test to inform the dosage adjustment recited in the claims was not routine or conventional and amounted to more than a mere instruction to apply a natural relationship. This combination of elements is sufficient to ensure that the claims amount to significantly more than just a natural law. As the Federal Circuit instructed in *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, No. 2015-1570, 2016 WL 3606624 (Fed. Cir. July 5, 2016), a "particular 'combination of steps'" can lead to valid patent claims that depend upon a natural relationship. *Id.* at *4 (quoting *Diehr*, 450 U.S. at 188). This is true even though the individual steps may have been well known. *Id.* at *7 "To require something more . . . would be to discount the human ingenuity that comes from applying a natural discovery in a way that achieves a 'new and useful end.'" *Id.* (quoting *Alice*, 134 S. Ct. at 2354). Finally, the court is persuaded that the concern articulated in *Mayo* that "patent law not inhibit further discovery by improperly tying up the future use of laws of nature" does not apply here, because the '610 Patent will not preempt biological sampling or genotyping. *Mayo Collaborative Servs.*, 132 S. Ct. at 1301; (D.I. 178 at 24). Thus, the patent-at-issue is not invalid for lack of patentable subject matter.

C. Written Description of the '610 Patent

1. The Legal Standard

To meet the written description requirement of 35 U.S.C. § 112, the application must show that, as of the filing date, the applicants were in possession of the invention in question. *See Vas-*

Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563–64 (Fed. Cir. 1991). "[T]he test for sufficiency is whether the disclosure of the application relied upon *reasonably conveys* to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (emphasis added). Although an exact definition of "possession" can be elusive, in essence, "the specification must describe an invention understandable to [a] skilled artisan and show that the inventor actually invented the invention claimed." *Id.* To this end, support in the written description must be based on what actually is disclosed, and not on an obvious variant of what is disclosed. *See id.* at 1352 (citing *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1571–72 (Fed. Cir. 1997)). Whether the written description requirement is met is a question of fact. *Id.* at 1351 (citing *Ralston Purina Co. v. Far-Mar-Co, Inc.*, 772 F.2d 1570, 1575 (Fed. Cir. 1985)). The party challenging the sufficiency of a written description must establish by clear and convincing evidence that the claim is invalid or not entitled to an asserted filing date. *See Tech. Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1329–30 (Fed. Cir. 2008).

2. <u>Dosage Range</u>

Roxane argues that there is no support for a dosage range of 12 mg/day or less. (D.I. 185 at 11–12); Tr. at 535:24–536:2, 5419–17 (Ratain); 630:6–9 (McCulloch). Specifically, Roxane contends that the data in the patent do not support the asserted claims. Tr. at 630:4–9; 631:11–632:11 (McCulloch); 535:20–536:2 (Ratain). Dr. McCulloch testified that the 12 mg/day or less dosage threshold in the '610 Patent is not supported because the claims are based on indirect relationships that lack statistical significance. Tr. at 637:23–25 (McCulloch).

The Plaintiffs dispute this assertion. (D.I. 184 at 25.) The Plaintiffs point out that the '610 Patent discloses a trend for higher QTc prolongation among genotypic CYP2D6 poor metabolizers

given a 24 mg daily dose. Tr. at 647:22–648:2 (McCulloch) (citing Table 6 of the '610 Patent (JX-1 at 8:50–66)). In addition, Drs. Polymeropoulos and Wolfgang determined that the intermediate biomarkers for CYP2D6 poor metabolism are the ratios of P88 to P95 concentrations in the blood, correlated to higher QTc, and thus support the conclusion that genotypic CYP2D6 poor metabolizers had increased risk of QTc prolongation. Tr. at 976:19–977:13 (Guengerich) (citing JX-1 at col. 10). According to the Plaintiffs, the '610 Patent explicitly discloses the appropriate dosage range based on the P88 to P95 ratio in the blood. (D.I. 84 at 13.) *See, e.g.*, JX-1 at 11:25–28; 9:42–47 ("an individual with a genotype associated with decreased CYP2D6 activity may receive a reduced dosage of 18, 12, or 6 mg per day"); 9:34–42. Table 3 of the '610 Patent demonstrates that CYP2D6 poor metabolizers have 1.5 to 3.5 times higher P88 concentrations than non-poor metabolizers, which supports a 1.5 to 3.5 reduction in dose for CYP2D6 poor metabolizers. JX-1 at 70:50–60; Tr. at 106:16–107:17 (Polymeropoulos).

The court must agree with the Plaintiffs that this data is sufficient to support possession of the claimed dosage range, even if not statistically significant. The patent need only "reasonably convey[] to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharm. Inc.*, 598 F.3d at 1351 (en banc). Indeed, the statute does not recognize "examples or an actual reduction to practice." *Alcon Research Ltd.* v. *Barr Labs., Inc.*, 745 F.3d 1180, 1190 (Fed. Cir. 2014) (quoting *Ariad*, 598 F.3d at 1350)). Thus, Roxane has failed to prove that the '610 Patent is invalid for lack of written description.

D. Infringement

1. The Legal Standard

The determination of whether an accused method infringes a claim in a patent has two steps: (1) construction of the claim to determine its meaning and scope; and (2) comparison of the properly

construed claim to the method at issue. *See Tanabe Seiyaku Co. v. United States Int'l Trade Comm'n,* 109 F.3d 726, 731 (Fed. Cir. 1997) (citing *Markman v. Westview Instruments, Inc.,* 52 F.3d 967, 976 (Fed. Cir. 1995) (en banc), *aff'd* 517 U.S. 370 (1996)). The patent owner has the burden of proving by a preponderance of the evidence that "every limitation of the patent claims asserted to be infringed is found in the accused [method], either literally or by an equivalent." *SmithKline Diag., Inc. v. Helena Lab. Corp.,* 859 F.2d 878, 889 (Fed. Cir. 1988). Under this standard, a patent owner does not have to produce definite proof of infringement, but must instead demonstrate that "infringement was more likely than not to have occurred." *See Warner-Lambert Co. v. Teva Pharms., USA, Inc.,* 418 F.3d 1326, 1341 n.15 (Fed. Cir. 2005) (citing *Advanced Cardiovascular Sys., Inc. v. Scimed Life Sys., Inc.,* 261 F.3d 1329, 1336 (Fed. Cir. 2001)). The application of a patent claim to an accused product is a fact-specific inquiry. *See Kustom Signals, Inc. v. Applied Concepts, Inc.,* 264 F.3d 1326, 1332 (Fed. Cir. 2001).

In the ANDA context, 35 U.S.C. § 271(e)(2)(A) provides that it shall be an act of infringement to submit an ANDA "if the purpose of such submission is to obtain approval . . . to engage in the commercial manufacture, use, or sale of a drug . . . claimed in a patent or the use of which is claimed in a patent before the expiration of such patent." 35 U.S.C. § 271(e)(2)(A). More specifically, as it relates to the instant matter, 35 U.S.C. § 271(b) states that "[w]hoever actively induces infringement of a patent shall be liable as an infringer." 35 U.S.C. § 271(b). Inducement requires "actively and knowingly aiding and abetting another's direct infringement." *C.R. Bard, Inc. v. Advanced Cardiovascular Sys., Inc.,* 911 F.2d 670, 675 (Fed. Cir. 1990). In the Hatch-Waxman context, "[s]tatements in a package insert that encourage infringing use of a drug product are alone sufficient to establish intent to encourage direct infringement" for purposes of inducement to infringe under 35 U.S.C. § 271(b). *Abraxis Bioscience, Inc. v. Navinta, LLC,* 640 F. Supp. 2d

553, 570 (D.N.J. 2009), rev'd and vacated on other grounds, 625 F.3d 1359 (Fed. Cir. 2010) (citing *AstraZeneca LP v. Apotex, Inc.,* 623 F.Supp. 2d 579, 570 (D.N.J. 2009). *See 3M Co. v. Chemque, Inc.,* 303 F.3d 1294, 1305 (Fed. Cir. 2002) (defendant who is aware of a patent and supplies a product to a customer with instructions for use, which when followed lead to infringement, has encouraged acts constituting direct infringement).

Importantly, however, mere knowledge of possible infringement does not constitute inducement. Rather, the patentee must prove that the defendant's actions "induced infringing acts *and* that [the defendant] knew or should have known that [its] actions would induce actual infringement." *See Manville Sales Corp. v. Paramount Sys., Inc.,* 917 F.2d 544, 553 (Fed. Cir. 1990). In ANDA cases, the court must consider whether "the proposed label instructs users to perform the patented method," as well as whether the proposed label encourages others to practice the patented method. *AstraZeneca LP v. Apotex, Inc.,* 633 F.3d 1042, 1060 (Fed. Cir. 2010) (citing *Vita-Mix Corp. v. Basic Holdings, Inc.,* 581 F.3d 1317, 1329 n.2 (Fed. Cir. 2009).

With respect to contributory infringement, under 35 U.S.C. § 271(c), "[w]hoever offers to sell or sells within the United States or imports into the United States a component of patented . . . manufacture, combination or composition, or a material . . . for use in practicing a patented process, constituting a material part of the infringement, knowing the same to be especially made or especially adapted for use in infringement of such patent, and not a staple article or commodity of commerce suitable for substantial noninfringing use," shall be considered "a contributory infringer." 35 U.S.C. § 271(c). The Federal Circuit has clarified that, to establish contributory infringement, the patent owner must prove that: (1) there is direct infringement; (2) the accused infringer had knowledge of the patent at issue; (3) the component has no substantial noninfringing uses; and (4) "the component is a material part of the invention." *Fujitsu Ltd. v. Netgear Inc.,* 620

F.3d 1321, 1326 (Fed. Cir. 2010). *See also Lucent Techs. Inc. v. Gateway, Inc.*, 580 F.3d 1301, 1320 (Fed. Cir. 2009).

2. Direct Infringement

As a preliminary matter, Roxane argues there is no evidence of direct infringement of the '610 Patent. (D.I. 185 at 2.) Direct infringement is a required element to establish induced infringement. *i4i Ltd. P'ship v. Microsoft Corp.*, 598 F.3d 831, 851 (Fed. Cir. 2010). To satisfy the direct infringement requirement, the patentee "must either point to specific instances of direct infringement or show that the accused device necessarily infringes the patent in suit." *ACCO Brands, Inc. v. ABA Locks Mfr. Co.*, 501 F.3d 1307, 1313 (Fed. Cir. 2007) (citing *Dynacore Holdings Corp. v. U.S. Philips Corp.*, 363 F.3d 1263, 1275–76 (Fed. Cir. 2004)). The Plaintiffs contend that Roxane's Proposed Label for iloperidone is the same as Vanda's FANAPT® Label and establishes that Roxane's product will infringe the asserted claims. Tr. at 368:11–16 (Economou); 373:15–374:4 (Smith); 569:21–23 (Ratain).

The evidence at trial demonstrated that Roxane's Proposed Label satisfies claims 1–9, 11–13, 16 of the '610 Patent as construed in the court's *Markman* order. (D.I. 125.) Roxane's Label recommends that practitioners use iloperidone to treat patients suffering from schizophrenia. JX-13 at § 1. The label recommends oral administration of iloperidone tablets at 12 to 24 mg/day to non-genotypic CYP2D6 poor metabolizers and 12 mg/day or less to genotypic CYP2D6 poor metabolizers. JX-13 at § 2.1-2.2. It also recommends that practitioners perform or have performed a genotyping assay to determine whether patients are CYP2D6 poor metabolizers. JX-13 at § 12.3. Section 5.2 of the label states that in an open-label study, "iloperidone was associated with QTc prolongation of 9 msec at an iloperidone dose of 12 mg twice daily," that "under conditions of metabolic inhibition for both 2D6 and 3A4, iloperidone 12 mg twice daily was associated with a

mean QTc increase from baseline of about 19 msec," and therefore "caution is warranted when prescribing iloperidone . . . in patients with reduced activity of CYP2D6." JX-13 at § 5.2. Section 12.3 states that "PMs of CYP2D6 have higher exposure to iloperidone compared with EMs and PMs should have their dose reduced by one-half." JX-13 at § 12.3; Tr. at 231:20–234:4 (Preskorn). The court is persuaded that the testimony presented at trial demonstrated by the preponderance of the evidence that when the label states that "laboratory tests" are available to identify poor metabolizers, the label is referring to "genotyping tests." Tr. at 567:5–568:2 (Ratain); 234:15–235:13 (Preskorn); 174:7–24, 198:4–200:7 (Kricka). Tr. at 190:14–193:12 (Kricka); 235:18–23, 236:15–19 (Preskorn) (all commercially available laboratory tests to determine whether a patient is a genotypic CYP2D6 poor metabolizer involve genotyping). Under 35 U.S.C. § 271(e)(2)(A), it is an act of infringement to file an ANDA application "for a drug claimed in a patent or the use of which is claimed in a patent." 35 U.S.C. § 271(e)(2)(A). Thus, Roxane's submission of a paragraph IV certification for the '610 Patent is an act of infringement. *See, e.g.*, *Bristol-Myers Squibb Co.* v. *Royce Labs.*, 69 F.3d 1130, 1131 (Fed. Cir. 1995) ("Inclusion of a paragraph IV certification in an ANDA, however, is deemed an act of infringement.").

Roxane argues that it is impossible for its products to infringe the asserted claims because doctors do not actually administer a genotyping test and administer up to 12 mg/day of iloperidone to genotypic CYP2D6 poor metabolizers and therefore do not infringe all of the claims. (D.I. 185 at 2.) The Plaintiffs disagree, relying on the testimony of Dr. Alva. (D.I. 184 at 6–7.) Dr. Alva's patient records and testimony confirm that he has practiced the steps of the '610 Patent claims. (*Id.*) He testified that he genotypes his patients and he specifically identified a patient for whom he exceeded 12mg/day of iloperidone only after determining through genotyping that the patient was

not a poor metabolizer. Tr. at 322:7–326:17 (Alva). The court found Dr. Alva's testimony credible. Thus, the court finds that there is sufficient evidence to establish direct infringement.

3. Induced Infringement

The Plaintiffs argue that Roxane's proposed products induce infringement of the '610 Patent because Roxane's proposed product labels instruct users to perform each element of the claimed patented method. (D.I. 184 at 1.) According to the Plaintiffs, Roxane's Proposed Label recommends that prescribers perform each step of the claimed methods, including genotyping their patients and administering up to 12 mg/day of iloperidone to genotypic CYP2D6 poor metabolizers. (*Id.*)

Roxane responds that the dosage reduction on the label is merely educational language and that its label does not encourage a physician to perform or dose a patient based on a CYP2D6 genotyping test. (D.I. 185 at 3.) Roxane relies on the testimony of Dr. Kaye. Dr. Kaye testified that there is no mandate for genetic testing and that the language "should have their dose reduced by half" is not a recommendation or suggestion to reduce the dosage in CYP2D6 PMs. Tr. at 462:1-464:11 (Kaye). The court did not find the testimony of Dr. Kaye to be credible. Roxane's other expert, Dr. Ratain, and the Plaintiffs's expert, Dr. Preskorn, testified that these words have their plain meaning and are a recommendation to reduce the dosage in this patient population. Tr. at 539:15–25, 548:12–16 (Ratain); 231:14–19 (Preskorn). The court rejects Roxane's argument that this information is merely informative.

Roxane contends that while the '610 claims require genotyping testing, the label does not specify that the tests to determine poor metabolizers must be genotyping tests. (D.I. 185 at 3.) Poor metabolizers can also be identified by laboratory tests that determine a patient's phenotype, such as measuring iloperidone concentrations. Tr. at 144:13-146:5 (Polymeropoulos); 211:14-215:7

(Kricka); 285:14-289:8 (Preskorn); 409:13-410:17, 411:17-413:16, 419:10-12 (Kaye); DTX-19 at 2; DTX-20 at 4; DTX-356; DTX-501; DTX-502; JX-36 at 7. According to Roxane, the label itself describes metabolizer status by reference to serum levels of iloperidone—a measure of phenotype—not by reference to any allele or genetic variant. Tr. at 407:13-408:1 (Kaye); JX-11 at 21. Dr. Kaye explained that he had never genotyped a patient in connection with prescribing iloperidone. Tr. at 381:21-382:4 (Kaye). He further explained that a physician would not genotype a patient in order to determine what dose of a drug to use, because "genotyping does not predict efficacy or dose response." Tr. at 390:17-392:7 (Kaye). According to Dr. Kaye, phenotyping is more clinically helpful than CYP2D6 genotyping. Tr. at 412:11-413:16 (Kaye). In addition, Roxane posits that its label mandates titration to efficacy to determine the appropriate dosage. (D.I. 179, ¶ 13.) Dr. Kaye testified that in accordance with the label's titration requirement, physicians always titrate to efficacy rather than rely on genotyping. Tr. at 394:9-398:3, 400:6-403:20 (Kaye).

The evidence presented at trial suggests that as a practical matter, doctors may not rely on genotyping tests because of the resources and time they require. However, to determine whether there is induced infringement, the court is tasked with interpreting whether the label "encourage[s], recommend[s], or promote[s] infringement." *Takeda Pharm. U.S.A., Inc. v. West-Ward Pharm. Corp.*, 785 F.3d 625, 631 (Fed. Cir. 2015). Roxane argues that because some prescribers of iloperidone will not follow the steps of the '610 Patent by not genotyping their patients, there are substantial noninfringing uses and Roxane does not induce infringement. The court rejects this argument. "The pertinent question is whether the proposed label instructs users to perform the patented method. If so, the proposed label may provide evidence of [Roxane]'s affirmative intent to induce infringement." *AstraZeneca LP v. Apotex Corp.*, 633 F.3d 1042, 1060 (Fed. Cir. 2010). Moreover, the existence of a substantial non-infringing use does not preclude a finding of

inducement. *Erbe Elektromedizin GmbH v. Canady Tech. LLC,* 629 F.3d 1278, 1284 (Fed. Cir. 2010); *Toshiba Corp. v. Imation Corp.*, 681 F.3d 1358, 1364 (Fed. Cir. 2012) (holding that the district court's conclusion that a finding of a substantial non-infringing use precludes a finding of induced infringement was legal error). The court concludes that Roxane's label induces infringement of the '610 Patent.

4. Contributory Infringement

In contrast, the Plaintiffs have not established contributory infringement. 35 U.S.C. § 271(c). Here, the Federal Circuit's opinion in *Toshiba Corp. v. Imation Corp.* is instructive on the distinction between contributory and induced infringement. 681 F.3d 1358. An accused infringer may escape liability for contributory infringement if his product is capable of substantial non-infringing use. *Id.* at 1362. On the other hand, if the accused infringer encourages infringing use, the fact that his product is capable of substantial non-infringing use will not save him from inducement liability. *Id.* at 1365–66.

The Plaintiffs contend that Roxane's proposed products contribute to infringement because their proposed labels would contribute to direct infringement of the asserted claim and Roxane's products have no substantial noninfringing uses. The court cannot agree. The evidence presented at trial demonstrates that a physician could prescribe iloperidone without practicing the claims of the '610 Patent by not using a genotyping test. Tr. at 257:4-258:6 (Preskorn), 407:13-406:11 (Kaye), 503:22-504:3 (Ratain); JX-11 at 21. The burden is on the Plaintiffs to prove that there is not a substantial noninfringing use and the Plaintiffs have not met this burden. In this case, the testimony at trial established that the noninfringing uses are not "unusual, far-fetched, illusory, impractical, occasional, aberrant, or experimental." *Vita-Mix Corp.*, 581 F.3d at 1327.

In conclusion, Roxane's generic iloperidone as described in the Roxane ANDA would, if marketed, induce infringement of claims 1-9, 11-13, and 16 of the '610 Patent. However, there are one or more substantially non-infringing uses for Roxane's generic iloperidone that preclude a finding of contributory infringement. Thus, Roxane does not contribute to the infringement of the '610 Patent.

E. Remedies

Pursuant to 35 U.S.C. § 271(e)(4)(B), the court finds that Roxane, its officers, agents, attorneys, and employees, and those acting in privity or concert with any of them, should be enjoined from engaging in the commercial manufacture, use, offer to sell, or sale with the United States, or importation into the United States of Roxane's ANDA Product prior to the expiration of the '198 Patent. 35 U.S.C. § 271(e)(4)(B). The court finds that the Plaintiffs are not entitled to relief pursuant to 35 U.S.C. § 271(e)(4)(A) for the '610 Patent because the '610 Patent did not issue until after the effective date of any FDA approval of the Roxane ANDA of Roxane's ANDA No. 20-5480. Section 271(e)(4)(A) explicitly protects a patent that has already issued at the time of the ANDA's submission. *See Endo Pharm. Inc. v. Amneal Pharm., LLC*, No. 12 CIV. 8060 (TPG), 2016 WL 1732751, at *4 (S.D.N.Y. Apr. 29, 2016). Under § 271(e)(2), it is an act of infringement to submit an ANDA under § 355(j) for "'a drug claimed in a patent or the use of which is claimed in a patent.' Notably, the subject of the sentence is 'a patent,' not a provisional patent application or a patent-pending." *Id.* at *3.

While the Plaintiffs are ineligible for the relief set forth in § 271(e)(4), the court has the general equitable power to issue an injunction based upon the finding of patent infringement under § 271(a)-(c). *See, e.g., eBay Inc. v. MercExchange, LLC*, 547 U.S. 388 (2006). Before the court can enjoin Roxane, the Plaintiffs must demonstrate that such relief would be fair and equitable

pursuant to the Supreme Court's analysis in *eBay*. A patent owner prevailing on the merits in a patent infringement suit is not automatically entitled to an injunction. *eBay*, 547 U.S. at 390. Rather, courts apply traditional equitable principles to determine: (1) whether the patentee would be irreparably harmed without an injunction; (2) whether the patentee has an adequate remedy at law; (3) whether the balance of hardships favors an injunction; and (4) whether granting the injunction is in the public interest. *Id.* at 391. The court will apply these considerations to the facts of this case.

Here, it is clear that Vanda would be irreparably harmed without an injunction. "Where a plaintiff and an infringer directly compete in the same market, an injunction may be warranted to protect the plaintiff from irreparable harm." *Endo Pharm. Inc.*, 2016 WL 1732751, at *5 (citing *Douglas Dynamics, LLC v. Buyers Prods. Co.*, 717 F.3d 1336, 1345 (Fed. Cir. 2013)). Allowing generic products such as Roxane's into the market will no doubt cause harm to Vanda. Without an injunction, Plaintiffs would suffer an incalculable loss of market share and Roxane's generic iloperidone would erode the price for Fanapt®. Vanda would also suffer irreparable harm from being unable to use lost Fanapt® revenue to invest in research and development of new clinical indications for and formulations of Fanapt® and development of other drugs. These irreparable harms would be the direct result of Roxane's sales. (D.I. 178 at 26.) There is no other adequate remedy because these harms are and would continue to be difficult to quantify. On the other hand, Roxane has not demonstrated it would suffer hardship. Therefore, the balance of hardships weighs in favor of enjoining Roxane. Finally, the court finds that the public interest would not be disserved by a permanent injunction. *eBay*, 547 U.S. at 391. Vanda holds a valid patent and the Federal Circuit has "long acknowledged the importance of the patent system in encouraging innovation. Indeed, the 'encouragement of investment-based risk is the fundamental purpose of the patent grant,

and is based directly on the right to exclude.'" *SanofiSynthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1383 (Fed. Cir. 2006) (quoting *Patlex Corp. v. Mossinghoff*, 758 F.2d 594, 599 (Fed. Cir. 1985)).

In conclusion, the four *eBay* factors weigh in favor of issuing an injunction. The Plaintiffs are entitled to a permanent injunction restraining and enjoining Roxane, their officers, agents, servants, employees, attorneys, affiliates, divisions, subsidiaries, and those persons in active concert or participation with any of them from infringing the '610 Patent or inducing anyone to do the same, including the manufacture, use, offer to sell, sale, distribution, or importation of any generic iloperidone product described in the Roxane ANDA, or any amendments or supplements thereto until the expiration of the '610 Patent on November 2, 2027.

IV. CONCLUSION

In sum, the court finds that (1) all asserted claims of the patents-in-suit are valid; (2) Roxane's proposed products induce infringement of the asserted claims of the '610 Patent; (3) Roxane's proposed products do not contributorily infringe the asserted claims of the '610 Patent; and (4) each of the parties' Rule 52(c) motions are granted in part and denied in part.

Dated: August 25, 2016

UNITED STATES DISTRICT JUDGE

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

VANDA PHARMACEUTICALS INC., and AVENTISUB LLC,	)	
Plaintiffs,	)	Civil Action No. 13-1973-GMS Civil Action No. 14-757-GMS
v.	)	(Consolidated)
ROXANE LABORATORIES, INC.,	)	
Defendant.	)	

ORDER

At Wilmington this 25th day of August, 2016, IT IS HEREBY ORDERED THAT:

1. Roxane's ANDA Product infringes claim 3 of the '198 Patent.

2. Roxane's ANDA Product infringes claims 1–9, 11–13, and 16 of the '610 Patent, except with respect to the Plaintiffs' claim of contributory infringement.

3. Claim 3 of the '198 Patent is not invalid as obvious.

4. Claims 1–9, 11–13, and 16 of the '610 Patent are not invalid as obvious.

5. Claims 1–9, 11–13, and 16 of the '610 Patent are not invalid for lack of written description.

6. Claim 1–9, 11–13, and 16 of the '610 Patent are not invalid for failure to claim patentable subject matter.

7. Pursuant to the court's equitable power, Roxane is hereby enjoined from engaging in the commercial manufacture, use, offer to sell, or sale with the United States, or importation into the United States of Roxane's ANDA Product prior to the expiration of the '610 Patent (November 2, 2027) or any applicable exclusivities and extensions.

8. The effective date of any Food and Drug Administration approval of Roxane's ANDA No. 20-5480 shall be a date not earlier than the latest of the expiration of the '610 Patent or any applicable exclusivities and extensions.

9. The Clerk of Court is directed to enter final judgment in favor of the plaintiffs.

10. The parties' Rule 52(c) motions are GRANTED IN PART AND DENIED IN PART.

UNITED STATES DISTRICT JUDGE