IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

VANDA PHARMACEUTICALS INC. and AVENTISUB LLC,	)	
Plaintiffs,	)	
v.	)	C.A. No. 13-1973 (GMS) (Consolidated with
ROXANE LABORATORIES, INC.,	)	C.A. No. 14-0757-GMS)
Defendant.	)	REDACTED -- PUBLIC VERSION

VANDA'S POST-TRIAL REPLY BRIEF

MORRIS, NICHOLS, ARSHT & TUNNELL LLP
Jack B. Blumenfeld (#1014)
Karen Jacobs (#2881)
Derek Fahnestock (#4705)
1201 North Market Street
P.O. Box 1347
Wilmington, DE 19899
(302) 658-9200
jblumenfeld@mnat.com
kjacobs@mnat.com
dfahnestock@mnat.com

Attorneys for Plaintiffs

OF COUNSEL:

Nicholas Groombridge
Eric Alan Stone
Kira A. Davis
Josephine Young
Daniel J. Klein
PAUL, WEISS, RIFKIND, WHARTON & GARRISON LLP
1285 Avenue of the Americas
New York, NY 10019
(212) 373-3000

Original Filing Date: May 18, 2016
Redacted Filing Date: May 25, 2016

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I. Vanda Proved That Roxane Infringes the '610 Patent

Roxane's proposed iloperidone label states that genotypic CYP2D6 poor metabolizers "should have their dose reduced by half," where the normal dose is 12mg to 24mg per day. The resultant dose for CYP2D6 poor metabolizers—12mg per day or less—falls within the claims of the '610 patent. As set forth in Vanda's Post-Trial Findings of Fact and Conclusions of Law [D.I. 178], the record evidence establishes infringement of the '610 patent.

To avoid this, Roxane argues that its label is merely educational and does not actually recommend a dosage reduction, that a prescriber following Roxane's label could prescribe iloperidone without practicing the claims of the '610 patent, that doing so is a "substantial non-infringing use" of iloperidone, and that Vanda failed to prove that any physician has ever actually practiced the claims of the '610 patent. These premises are wrong both legally and factually, and Roxane's evidentiary arguments flow from these errors.

A. Vanda Proved That Roxane's Label Encourages, Recommends, and Promotes the Steps of the '610 Patent Claims

Induced infringement in an ANDA case turns on the proposed label for the generic drug. Where the label "instructs," "encourages," "recommends," "suggests," or "promotes" the acts that constitute infringement, the generic induces infringement. *Takeda Pharm. U.S.A., Inc.* v. *West-Ward Pharm. Corp.*, 785 F.3d 625, 631 (Fed. Cir. 2015) (encourages, recommends, or promotes); *AstraZeneca LP* v. *Apotex Corp.*, 633 F.3d 1042, 1060 (Fed. Cir. 2010) (instructs).

Roxane's label tells prescribers—twice—to reduce the dose by one-half for CYP2D6 poor metabolizers. In the "Dosage in Special Populations" section, Roxane's label states that "Iloperidone dose <u>should be reduced by one-half</u> for poor metabolizers of CYP2D6." JX-13 § 2.2 (emphasis added). And in Section 12.3, after defining the term "PMs" for genotypic

CYP2D6 poor metabolizers, Roxane's label states: "PMs should have their dose reduced by one-half." *Id.* § 12.3 (emphasis added).

Roxane now adopts the testimony of its expert Dr. Neal Kaye that the phrase "should have their dose reduced by half" is merely "educational informational language" from FDA, and not an instruction, suggestion, encouragement, promotion, or recommendation to reduce the dose by half. Tr. at 462:1-464:11. The Court does not need expert testimony to conclude that "should have their dose reduced" is an encouragement, or a suggestion, or a recommendation. Indeed, Dr. Kaye's understanding of the word "should" is dangerous; he admitted that even if the label said poor metabolizers "should not" receive a dose above 12mg, that too would be merely educational and not a suggestion or recommendation. Tr. at 464:5–11. That may be why Roxane's other expert, Dr. Ratain, flatly contradicted Dr. Kaye on this point (in testimony Roxane omits from its brief), and agreed that the label "recommends that the dose be reduced" in patients known to be poor metabolizers. Tr. at 548:12–549:7 (Ratain) (emphasis added). He explicitly called it a "dosing recommendation." *Id.* at 569:18–20 (emphasis added). Vanda's expert agreed as well. Tr. at 230:8–231:19 (Preskorn).

Roxane also relies on Dr. Kaye's testimony that in stating that "Laboratory tests are available to identify CYP2D6 PMs," the label does not specify genotyping tests, and thus that Roxane does not induce infringement of the '610 claims, which all require genotyping. Here, too, Roxane's argument is at odds with the overwhelming preponderance of the evidence. "PMs" are defined in the preceding paragraph: "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." JX-13 § 12.3. The label refers to people who "lack the capacity" to

metabolize CYP2D6 substrates, and breaks out the percentages by ethnicity, precisely because it is referring to genetic (*i.e.*, genotypic) variations, not to phenotypic variations. In fact, Dr. Kaye himself admitted that "lack the capacity to metabolize" refers to poor metabolism caused by genetics, and thus that the defined term "PMs" refers to genotypic, not phenotypic poor metabolizers. Tr. at 439:10–12, 442:12–21. He further admitted that genotyping is preferable to phenotyping: "In today's world, with technology, I don't think there is any doubt, if we can get the genotype itself, that that is going to be our first choice over the phenotypic approach." Tr. at 451:5–11. While Roxane now proposes that a psychiatrist could determine a patient's metabolizer status by asking about the patient's history (*see* Roxane Br. [D.I. 179] ¶ 15), a patient history is not a "laboratory test." And Roxane's other expert, Dr. Ratain, admitted that in stating that "laboratory tests" are available to identify poor metabolizers, the label is referring to "genotyping tests" and "not phenotyping." Tr. at 567:5–568:2. And again, Vanda's experts agreed. *See* Tr. at 234:15–235:13 (Preskorn); 174:7–24, 198:4–200:7 (Kricka).

B. Vanda Does Not Need to Prove That the Treatment of Every Patient Will Result in Infringement

Roxane offers scenarios by which a psychiatrist might prescribe iloperidone but not practice the claims of the '610 patent. Roxane notes that (i) its label does not require genotyping; (ii) its label recommends titrating up to an effective dose, and that a psychiatrist might stop at 12mg/day without genotyping; (iii) its label does not require that CYP2D6 poor metabolizers never exceed 12mg/day, so a doctor might exceed that dose in a poor metabolizer; (iv) its label recommends a minimum dose of 12 mg/day for patients who are not poor metabolizers, so a doctor might give such a patient exactly 12mg/day, rather than "greater than 12 mg/day" as claimed by the '610 patent; and (v) its label does not recommend dosage adjustment for CYP2D6 intermediate metabolizers. Roxane Br. ¶¶ 14–15, 24–27, 32–36.

That a doctor can follow Roxane's label without practicing the claims of the '610 patent, however, does not absolve Roxane from a finding of infringement. *AstraZeneca* makes this clear. *See* 633 F.3d at 1047. There, AstraZeneca's patents covered only once-daily administration of its budenoside product, but its drug label provided for either once- or twice-daily administration, with an instruction to "'titrate down' to the lowest effective dose." *Id.* To avoid infringing AstraZeneca's patents, Apotex removed from its own proposed label any reference to once-daily administration. FDA, however, required Apotex to include the downward-titration language. *Id.* The district court found that the downward-titration language "would lead many users to directly infringe the asserted method claims because titrating down from the recommended starting doses would necessarily lead to once-daily usage" for some patients, and held that "the proposed label provided evidence of Apotex's affirmative intent to induce infringement." *Id.* at 1049. The Federal Circuit agreed that because the downward-titration language in Apotex's label "would inevitably lead some consumers to practice the claimed method" of once-daily dosing, Apotex induced infringement. *Id.* at 1060 (emphasis added). The court repeatedly referred to infringement by "some users" as sufficient. *See id.*

Thus, although it is possible that some psychiatrists treating some patients using Roxane's iloperidone may follow Roxane's label but not infringe the claims of the '610 patent, that is the wrong inquiry. The question for induced infringement is whether "some" physicians following the label would inevitably practice those claims. Vanda has shown, by far more than the required preponderance of the evidence, that the answer is "yes."[1]

[1] Nor does it matter, as Roxane notes, that the labels for other drugs use different language to recommend genotyping tests. As Dr. Kaye admitted, FDA has not been consistent with its use of language from drug to drug. Tr. at 465:13–16. To shore up this argument, Roxane relies on PharmGKB's categorization of iloperidone as a drug for which genotyping is not required, but—as Dr. Ratain admitted—PharmGKB assesses whether genotyping is required before the patient

C. Vanda Proved That There Is No Substantial Non-Infringing Use for Iloperidone

Roxane also argues that the ways in which a doctor might prescribe iloperidone on-label without infringing the '610 patent are "substantial non-infringing uses" of iloperidone. But as used in ANDA cases in the context of induced infringement, where the label instructs, recommends, promotes, encourages, or suggests the steps of the patented method, "it is irrelevant that some users may ignore the warnings in the proposed label." *AstraZeneca*, 633 F.3d at 1060. This does not constitute a substantial non-infringing use.

The Federal Circuit likewise has held that off-label uses of a drug are not "non-infringing" uses sufficient to defeat a finding of contributory infringement for "a product that is authorized to be sold solely for the infringing use." *Eli Lilly & Co.* v. *Actavis Elizabeth LLC*, 435 Fed. Appx. 917, 927 (Fed. Cir. 2011). And this Court has found no contributory infringement in an ANDA case where the drug was approved for treating multiple stages of cancer, but the patents covered only a subset of those approved indications. *See Bone Care Int'l, L.L.C.* v. *Roxane Labs., Inc.*, C.A. No. 09-cv-285 (GMS), 2012 WL 2126896, at *32 (D. Del. June 11, 2012). Here, however, iloperidone is approved for only the treatment of schizophrenia. Iloperidone has only one authorized "use." And unlike in a multiple-indications context, where a generic can choose to "carve out" a patented indication from its label to avoid infringement, *see, e.g.*, 21 U.S.C. § 355(j)(2)(A)(viii), Roxane could not choose to omit from its label the language that CYP2D6 poor metabolizers should have their dose reduced by half. As Dr. Ratain admitted, FDA would not allow Roxane to carve that language out of its label because it reflects a safety

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receives the very first dose. Tr. at 560:19–561:19. Because iloperidone must be titrated from a starting dose of 2 mg/day to avoid orthostatic hypotension (JX-13 § 2.1; Tr. at 161:24–162:10 (Polymeropoulos)), and because the need for genotyping arises only at doses above 12 mg/day, all parties agree that genotyping is not required before commencing iloperidone treatment. That is why Vanda (accurately) told foreign regulators that iloperidone has been safely prescribed in the United States without a requirement of genotyping prior to administration.

concern. Tr. at 569:11–570:20. Thus, if Roxane wants FDA approval to sell iloperidone for the treatment of schizophrenia, Roxane must include the label language regarding the steps that are covered by the '610 patent claims. There is no substantial non-infringing use of iloperidone.

D. Vanda Proved Infringement of the Dependent Claims

Roxane makes a token effort to argue that Vanda did not prove infringement of the dependent claims, which further specify certain aspects of genotyping and particular genetic mutations in the CYP2D6 genes. Roxane Br. [D.I. 179] ¶¶ 39-40. Contrary to Roxane's assertions, Dr. Preskorn went through every one of the dependent claims and explained how each matches up with the label, Dr. Kricka explained that the commercially available laboratory tests cover all of the claimed specific mutations, and Roxane provided no contrary evidence. Tr. at 234:15–235:7, 235:18–23, 236:15–20, 237:20–239:5, 239:24–240:7, 240:13–17 (Preskorn); 190:14–193:12 (Kricka).

E. Although Not Required, Vanda Demonstrated Direct Infringement

Finally, Roxane tries very hard to disprove that Dr. Alva has practiced the steps claimed by the '610 patent, *see, e.g.*, Roxane Br. [D.I. 179] ¶ 25, to argue that Vanda has not shown direct infringement and thus cannot prove induced or contributory infringement. That is wrong as a matter of law and fact. The act of infringement in an ANDA case is the filing of the ANDA, under 35 U.S.C. § 271(e)(2). By definition there has not been actual, direct infringement of the patent, because the infringing product—Roxane's iloperidone—is not yet even available for sale. Physicians who have prescribed Vanda's FANAPT® have not infringed the claims of the '610 patent, because FANAPT® is sold by the assignee of the '610 patent and thus its use is not "without authority." 35 U.S.C. § 271(a). In ANDA cases, direct infringement by the end user is "hypothetical": "[T]he substantive determination whether actual infringement or inducement will take place is determined by traditional patent infringement analysis, just the same as it is in

other infringement suits, including those in a non-ANDA context, the only difference being that the inquiries now are hypothetical because the allegedly infringing product has not yet been marketed." *Warner-Lambert Co.* v. *Apotex Corp.*, 316 F.3d 1348, 1365 (Fed. Cir. 2003); *accord Bristol-Myers Squibb Co.* v. *Royce Labs., Inc.*, 69 F.3d 1130, 1135 (Fed. Cir. 1995) ("Thus, section 271(e)(2)(A) makes it possible for a patent owner to have the court determine whether, if a particular drug *were* put on the market, it *would* infringe the relevant patent." (emphases in original)).

It is thus not Vanda's burden to prove that any physician actually practiced the claims of the '610 patent. If that were Vanda's burden, however, Vanda met it. Dr. Alva testified that he genotypes his patients—the record evidence reveals over 300 patients, including patients prescribed iloperidone, for whom he ordered genotype tests—and specifically identified, and discussed at length in testimony elicited by Roxane's counsel, 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. Roxane's expert, Dr. Kaye, agreed at his deposition that in treating this patient Dr. Alva practiced the steps of claim 1 of the '610 patent (Tr. at 454:11–460:7), but then sought to change his testimony at trial, after he had submitted his errata sheet and without any notice to Vanda (*id.* at 460:9–18). His last-minute change of heart undermines his credibility, but it does not alter the facts: Dr. Alva's patient records and testimony confirm that he has practiced the steps of the '610 patent claims.

II. Roxane Failed to Show by Clear and Convincing Evidence That the '610 Patent Is Directed to Unpatentable Subject Matter

Roxane seeks to shift to Vanda the burden of disproving Roxane's Section 101 argument, asserting that Vanda "offered no testimony whatsoever directed to § 101." Roxane Br. [D.I. 179] ¶ 50. That is wrong. Although it was not its burden to do so, Vanda offered extensive fact and

expert evidence refuting the purported laws of nature that Roxane advanced. For example, Dr. Ratain argued that it is a law of nature "that the more iloperidone you have in your system the higher the side effects would be" (Tr. at 582:23–583:2), yet Dr. Polymeropoulos testified that for many side effects of iloperidone, poor metabolizers do not experience increased side effects (Tr. at 100:15–25, 110:15–111:14). For additional testimony from Vanda's experts refuting Roxane's Section 101 argument, *see, e.g.*, Tr. at 910:20–911:23, 912:22–914:24, 938:20–939:22 (Roth); 987:15–988:22, 989:6–994:13, 1007:8–1008:10 (Guengerich).

The problem with Roxane's Section 101 argument, however, runs far deeper than dueling testimony (though that would be sufficient to defeat a defense that Roxane must prove by clear and convincing evidence). Roxane's argument fails because there is no law of nature claimed by the '610 patent, which is what the Patent Office explicitly found in assessing the patent application under its post-*Mayo* Section 101 guidelines.

Vanda's Proposed Findings of Fact and Conclusions of Law catalogued Roxane's ever-shifting articulation of the "law of nature" supposedly claimed by the '610 patent, non-semantic changes caused by Roxane's previously proposed "laws of nature" being simply wrong. Roxane's arguments highlight the Supreme Court's concern that in addressing Section 101 challenges, the courts should "tread carefully in construing this exclusionary principle lest it swallow all of patent law." *Alice Corp.* v. *CLS Bank Int'l*, 134 S. Ct. 2347, 2416 (2014). That concern is only heightened now, because Roxane has proposed yet another articulation of its supposed law of nature in its post-trial submission.

Roxane now argues that obtaining a biological sample is a law of nature, that genotyping the biological sample is another law of nature, and that adjusting the iloperidone dose based on genetic status is routine and conventional. Roxane Br. [D.I. 179] ¶ 53. Neither obtaining a

biological sample nor genotyping that sample, however, is a law of nature within the meaning of Section 101; phlebotomy devices, buccal swabs, and DNA-sequencing equipment are man-made inventions. And as the Federal Circuit recently confirmed, what Section 101 forbids is 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—after all, they take place in the physical world." *Enfish, LLC* v. *Microsoft Corp*, -- F.3d--, No. 2015-1244, Slip Op. at 10 (Fed. Cir. May 12, 2016) (emphases in original). Vanda has not sought to claim, and thus preempt the use of, biological sampling, or genotyping, or even the relationship between iloperidone, CYP2D6 metabolism, and QTc prolongation. All that Vanda claims in the '610 patent is a specific method of treating a specific patient population with a specific drug at specified doses, which the Patent Office found to be patentable.

Without any appreciable law of nature, Roxane's assertions about the routine and conventional nature of dosing adjustments are of no importance in a Section 101 analysis. But Roxane cannot sustain its burden in any event. Vanda's witnesses testified extensively that arriving at the claimed dosages in the '610 patent was not routine or conventional, *see, e.g.*, Tr. at 85:14–18, 110:15–111:14 (Polymeropoulos); 911:16–23, 912:25–914:24, 938:6–16, 939:1–22 (Roth); 988:18–24, 1007:1–1008:5 (Guengerich). As Roxane admits, the "exact dose reduction may not necessarily be ascertained without doing studies." Roxane Br. [D.I. 179] ¶ 62. Although Roxane's expert, Dr. Ratain, believes the studies to determine the correct dose adjustment were routine, he could not offer any explanation for why Novartis, an interested and sophisticated company, failed to achieve what was purportedly so routine. Tr. at 617:18–618:17.

Roxane's Section 101 challenge appears to reduce down to an attack on all method-of-

treatment claims that depend on an interaction between a drug and some process in a patient's body (which is to say, an attack on all medication method-of-treatment claims). If that is Roxane's point, it is wrong. *Enfish* makes that clear. So, too, does the recent guidance from the USPTO to the Patent Examiner corps on applying Section 101 to method-of-treatment claims, which confirmed yet again that claims like those of the '610 patent are patentable after *Mayo*, *Myriad*, and the other recent Section 101 cases. *See* USPTO May 2016 Update: Subject Matter Eligibility Examples: Life Sciences at, *e.g.*, 10-11, 14-16, *available at* http://www.uspto.gov/sites/default/files/documents/ieg-may-2016-ex.pdf.

III. Roxane Failed to Show by Clear and Convincing Evidence That the Claims of the '610 Patent Are Obvious

Roxane's expert, Dr. Ratain, agrees that prior to the work leading to the '610 patent, it was not known what role, if any, CYP2D6 metabolism played in iloperidone-induced QTc prolongation or whether it was possible to reduce the risk of QTc prolongation in patients taking iloperidone or what dosage, if any, would be both efficacious in treating schizophrenia but also safe in terms of QTc prolongation. *See, e.g.*, Tr. at 602:3–16, 607:22-608:18, 609:18–610:23, 614:2–16, 620:3–16. Roxane's whole obviousness argument is that because it was allegedly known that CYP2D6 played a major role in the metabolism of iloperidone, and because QTc prolongation is a significant side effect that will bar FDA approval, it was obvious to investigate whether CYP2D6 played a role in iloperidone-induced QTc prolongation and, if so, to then determine a safe and effective dose. Roxane has not offered evidence even remotely close to clear and convincing to support that strained theory.

Indeed, Roxane stumbles at the first step. The evidence is that it was not even known whether CYP2D6 played any significant role in iloperidone metabolism. Roxane relies on a publication by Mutlib. *See* Roxane Br. [D.I. 179] ¶ 80; Mutlib (1998) (JX-68). But—as Vanda's

Dr. Guengerich testified—Mutlib showed only that CYP2D6 is relevant to iloperidone metabolism *in vitro*, while providing only inconclusive evidence about whether CYP2D6 is involved in iloperidone metabolism *in vivo*. Tr. at 967:7–969:1. FDA cautions that "When a difference arises between findings *in vitro* and *in vivo*, the results *in vivo* should always take precedence over studies *in vitro*." FDA Guidance (1997) (DTX-118). And the prior art as a whole taught that CYP2D6 was not important in the metabolism of iloperidone. *See, e.g.*, Caccia (PX-154); Kirchheiner 2004 (JX-95); Raggi (DTX-53). There is no evidence to support Roxane's baseline assumption that a skilled artisan would start from the proposition "that CYP2D6 was important for iloperidone metabolism and that further studies would quantitatively show its role." Roxane Br. [D.I. 179] ¶ 80.

Even accepting that premise, however, Roxane has not provided clear and convincing evidence that a skilled artisan "would have learned quantitatively the difference between CYP2D6 poor metabolizers and individuals that are not poor metabolizers." Roxane Br. [D.I. 179] ¶ 82. After all, Novartis—highly motivated to commercialize iloperidone—wrongly concluded that CYP2D6 poor metabolizers required no dosage adjustment. And Novartis sold the iloperidone franchise to Vanda for $500,000, only to license it back four years later for $200,000,000, after the inventive work leading to the '610 patent. Roxane bears the burden of showing why, in light of the failure by Novartis to solve this very problem, the Court should find, by clear and convincing evidence, that the solution was obvious all along. *See Microsoft Corp.* v. *i4i Ltd.*, 131 S. Ct. 2238, 2245–46 (2011); *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litigation*, 676 F.3d 1063, 1077–79 (Fed. Cir. 2012). Roxane does not even try to answer this question.

On top of that, the solution the '610 patent inventors found was not an obvious one even

to a skilled artisan starting from Roxane's premise. As Dr. Polymeropoulos testified, there might not have been any genetic role in iloperidone-induced QTc prolongation, which is why he tested some 90 variations within about 10 candidate genes without any expectation that one of them, or any of them, would turn out to be important. Tr. at 90:11–91:21. Roxane concedes that "Genotyping cannot predict a patient's response to any particular dose of a drug such as iloperidone." Roxane Br. [D.I. 179] ¶ 10 (citing Tr. at 390:17-391:20 (Kaye)). And even where there is a genetic link between a drug's metabolism and QTc prolongation, it is not obvious to reduce the dose: sometimes a dosage increase is appropriate, sometimes a reduction, sometimes the drug must be stopped entirely, and sometimes no change at all is required. Tr. at 109:13–111:14 (Polymeropoulos), 938:20–939:22 (Roth); 987:15–988:21, 989:6–994:14, 1007:8–1008:10 (Guengerich).

All that Roxane has proven is that it is important to reduce QTc prolongation. But stating the problem does not make the solution obvious. When there is "no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful," courts should reject "hindsight claims of obviousness." *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009). A solution is not obvious merely because it was obvious to conduct experiments to try to solve the problem: "selective hindsight is no more applicable to the design of experiments than it is to the combination of prior art teachings." *In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988).

IV. Roxane Failed to Show by Clear and Convincing Evidence That the Claims of the '610 Patent Lack Written Description

Roxane's written-description arguments ignore the patent specification and the law. Roxane argues that "the '610 patent includes no disclosure of administering 12 mg/day or less to a subject having a CYP2D6 poor metabolizer genotype." Roxane Br. [D.I. 179] ¶¶ 91, 108, 111.

The patent discloses precisely that. The '610 patent explicitly states that CYP2D6 poor metabolizers should receive a 75%, 50%, or 25% reduced dose, and specifically refers to giving 24mg/day to non-poor metabolizers and a reduced dose of 18 mg/day, 12 mg/day, or 6 mg/day to CYP2D6 poor metabolizers. JX-1 at 9:34–47, 11:25–28. The patent thus expressly describes the claimed dosage.

Roxane's core argument is not that these words are not in the patent, but that there is no statistically significant clinical data to support the '610 claims. But the law is clear that "there is no requirement that the disclosure contain 'either examples or an actual reduction to practice.'" *Alcon Research Ltd.* v. *Barr Labs., Inc.*, 745 F.3d 1180, 1190-91 (Fed. Cir. 2014) (quoting *Ariad Pharm., Inc.* v. *Eli Lilly & Co.*, 598 F.3d 1336, 1350 (Fed. Cir. 2010)); *see also Alcon Research, Ltd.* v. *Apotex Inc.*, 790 F. Supp. 2d 868, 943 (S.D. Ind. 2011) ("Given the case law that an invention does not actually have to be used, or even made, in order to satisfy the written description requirement, clinical testing cannot be required to satisfy the written description requirement."). Nor does the written description requirement demand that an inventor correctly set forth, or even know, how or why the invention works. *Fromson* v. *Advance Offset Plate, Inc.*, 720 F.2d 1565, 1570 (Fed. Cir. 1983).

To be clear, Roxane has not made a utility or enablement challenge. It has not argued that the method of the '610 patent is ineffective in reducing QTc prolongation, or that a skilled artisan reading the patent would not know how to practice the claims. Roxane has argued only written description, and it has failed to sustain that burden. The '610 patent specification describes a 50% dosage reduction for CYPD26 poor metabolizers from a normal dosage of 12 to 24mg/day, which is what is claimed. No more is required for written description.

V. Roxane Failed to Show by Clear and Convincing Evidence That the Claim of the'198 Patent Is Obvious

As set forth in Vanda's Proposed Findings of Fact and Conclusions of Law [D.I. 178], the '198 patent inventors synthesized a novel chemical compound, satisfying a long-felt need for an atypical antipsychotic where others—including Roxane's own expert, Dr. Sargent, when he headed Booth Pharmaceuticals—had failed for decades.

Roxane has not carried its burden to prove by clear and convincing evidence that this invention was obvious. Its argument is rank hindsight.

Roxane assumes that a skilled artisan in 1989 seeking to synthesize a new atypical antipsychotic would not start with a compound known to have atypical activity, like sulpiride. *See* Roxane Br. ¶ 126. But that is what skilled artisans actually did (including Dr. Sargent).

Even if a skilled artisan were for some reason motivated to start with a less-promising lead compound, as Roxane hypothesizes, that compound would not be AHR-2244 (Compound A). Roxane argues (*id.* ¶ 124) that Vanda's experts, Drs. Roth and Bartlett, admitted that AHR-2244 (Compound A) was a known antipsychotic. That is wrong. Dr. Roth testified that it was not. Tr. at 898:20–903:23. And Roxane admits that AHR-2244 "had never been marketed or put into clinical trials." Roxane Br. [D.I. 179] ¶ 136. Although Roxane argues that lenperone (Compound B) would have led a skilled artisan to AHR-2244, that ignores that lenperone had caused extremely serious and concerning side effects, such that the skilled artisan would run away from it and its related compounds, not towards them. *See Takeda Chem. Indus., Ltd.* v. *Alphapharma Pty., Ltd.*, 492 F.3d 1350, 1359 (Fed. Cir. 2007) ("Significantly, the closest prior art compound . . . exhibited negative properties that would have directed one of ordinary skill in the art away from that compound."). Having failed to show that AHR-2244 had potent or promising activity, Roxane has not demonstrated that one of skill in the art would have selected

AHR-2244 as a lead compound. *See Daiichi Sankyo Co.* v. *Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010); *Otsuka Pharm. Co.* v. *Sandoz, Inc.*, 678 F.3d 1280, 1292 (Fed. Cir. 2012).

Roxane also has not shown that a skilled artisan who happened to start with AHR-2244 would then modify it to produce iloperidone. Roxane does not, and cannot, argue that a skilled artisan had a reasonable expectation that a bioisosteric modification to a compound that might have typical antipsychotic properties would yield an atypical antipsychotic compound. *See* Roxane Br. [D.I. 179] ¶ 140; *see also Takeda Chem.*, 492 F.3d at 1360 (affirming district court's rejection that a person of skill would be motivated to make a modification with any expectation of success because "'homologation had no tendency to decrease unwanted side effects' and thus researchers would have been inclined 'to focus research efforts elsewhere'").

Fundamentally, Roxane's core argument is that because the '198 patent does not claim atypicality or explicitly provide data proving that the compound is atypical, Roxane need not demonstrate that a skilled artisan would have been motivated to modify its lead compound to maintain or achieve atypical properties. That is incorrect. It is undisputed that the problem that skilled artisans were trying to solve at the time of the invention was to invent an atypical antipsychotic. Roxane Br. [D.I. 179] ¶ 112. The '198 patent specifically notes the side-effect drawbacks of typical antipsychotics. Its inventors were motivated to find an antipsychotic without those side effects, *i.e.* an atypical antipsychotic. Roxane cannot demonstrate obviousness by changing the problem the inventors sought to solve.

CONCLUSION

For the foregoing reasons, and those set forth in Vanda's Proposed Post-Trial Findings of Fact and Conclusions of Law [D.I. 178], and on the record before the Court at trial, Vanda respectfully requests that the Court enter judgment in Vanda's favor with respect to the '610 and '198 Patents.

MORRIS, NICHOLS, ARSHT & TUNNELL LLP

/s/ Karen Jacobs

Jack B. Blumenfeld (#1014)
Karen Jacobs (#2881)
Derek J. Fahnestock (#4705)
1201 North Market Street
P.O. Box 1347
Wilmington, DE 19899
(302) 658-9200
jblumenfeld@mnat.com
kjacobs@mnat.com
dfahnestock@mnat.com

Attorneys for Plaintiffs

OF COUNSEL:

Nicholas Groombridge
Eric Alan Stone
Kira A. Davis
Josephine Young
Daniel J. Klein
PAUL, WEISS, RIFKIND, WHARTON & GARRISON LLP
1285 Avenue of the Americas
New York, NY 10019
(212) 373-3000

May 18, 2016

CERTIFICATE OF SERVICE

I hereby certify that on May 18, 2016, I caused the foregoing to be electronically filed with the Clerk of the Court using CM/ECF, which will send notification of such filing to all registered participants.

I further certify that I caused copies of the foregoing document to be served on May 18, 2016, upon the following in the manner indicated:

David E. Moore, Esquire — *VIA ELECTRONIC MAIL*
Bindu A. Palapura, Esquire
Stephanie E. O'Byrne. Esquire
POTTER ANDERSON & CORROON LLP
Hercules Plaza, 6th Floor
1313 North Market Street
Wilmington, DE 19801
Attorneys for Roxane Laboratories, Inc.

Kenneth G. Schuler, Esquire — *VIA ELECTRONIC MAIL*
Emily C. Melvin, Esquire
Timothy J. O'Brien, Esquire
LATHAM & WATKINS LLP
330 North Wabash Avenue, Suite 2800
Chicago, IL 60611
Attorneys for Roxane Laboratories, Inc.

Michael R. Seringhaus, Esquire — *VIA ELECTRONIC MAIL*
LATHAM & WATKINS LLP
140 Scott Drive
Menlo Park, CA 94025
Attorneys for Roxane Laboratories, Inc.

Daniel G. Brown, Esquire — *VIA ELECTRONIC MAIL*
LATHAM & WATKINS LLP
885 Third Avenue
New York, NY 10022
Attorneys for Roxane Laboratories, Inc.

Damion Jurrens, Esquire
LATHAM & WATKINS LLP
505 Montgomery Street, Suite 2000
San Francisco, CA 94111
Attorneys for Roxane Laboratories, Inc.

VIA ELECTRONIC MAIL

/s/ Karen Jacobs

Karen Jacobs (#2881)