IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

VANDA PHARMACEUTICALS INC. and AVENTISUB LLC,	)	
	)	C.A. No. 13-1973-GMS
Plaintiffs,	)	(consolidated)
v.	)	**PUBLIC VERSION**
ROXANE LABORATORIES, INC.,	)	
Defendant.	)	

DEFENDANT ROXANE'S RESPONSIVE POST-TRIAL BRIEF

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I. INTRODUCTION

For the reason set forth below and in Roxane's Opening Post-Trial Findings of Fact and Conclusions of Law (D.I. 179), Defendant Roxane requests judgment in its favor on the asserted claims of U.S. Patent Nos. 8,586,610 (the "'610 patent") and RE 39,198 (the "RE'198 patent").

II. ROXANE DOES NOT INFRINGE THE '610 PATENT

Plaintiffs assert that Roxane has infringed the '610 patent under 35 U.S.C. § 271(e) by filing its ANDA. D.I. 178, ¶ 72. Section 271(e) merely provides an "artificial" act of infringement for jurisdictional purposes—the ultimate infringement inquiry is governed by a traditional patent law analysis. *Novartis Pharm. Corp. v. Watson Labs., Inc.*, 611 Fed. Appx. 988, 997 (Fed. Cir. 2015). Plaintiffs' only two proffered theories are contributory and induced infringement, and they have failed to meet their burden of establishing either.

A. Plaintiffs Have Provided No Evidence of Contributory Infringement

Although Plaintiffs assert that they have proven contributory infringement (D.I. 178 ¶ 74), their opening proposed findings are devoid of any support in the facts or the law. Vanda has presented no evidence or testimony that Roxane's proposed product is especially adapted for use in infringing the '610 patent as is required to support such a claim. 35 U.S.C. § 271(c). Likewise, Plaintiffs' experts did not dispute that physicians frequently administer iloperidone without genotyping or in methods that are otherwise not covered by the asserted claims and therefore do not infringe. D.I. 179, ¶¶ 24-25, 32-36. And Plaintiffs' prescribing expert admitted these non-infringing practices are consistent with the iloperidone labeling. D.I. 179, ¶ 24; Tr. 315:6-319:23 (Alva). Having failed to address or provide evidence for these statutory elements of contributory infringement, 35 U.S.C. § 271(c), Plaintiffs' claims fail as a matter of law.

B. Plaintiffs Have Provided Insufficient Evidence To Support a Finding of Induced Infringement

1. Plaintiffs Failed To Establish Direct Infringement

Plaintiffs assert that "[a]ll that is required is that the label teach, suggest, promote, recommend, or instruct a physician to engage in the steps that constitute direct infringement." D.I. 178, ¶ 74 (citing *Takeda Pharm. U.S.A., Inc. v. West-Ward Pharm. Corp.*, 785 F.3d 625, 631 (Fed. Cir. 2015) ("*Takeda II*")). But Plaintiffs overlook the prerequisite element of proof of actual direct infringement, which is necessary, but not sufficient for inducement. *Id.*

Despite the fact that iloperidone has been marketed for many years, Plaintiffs were unable to identify evidence of a single instance of direct infringement—they have not proposed a single finding of fact or conclusion of law that any individual physician has actually practiced the claims of the '610 patent. Not one witness or document evidenced a physician following the claimed method. Indeed, the evidence at trial demonstrates the ***absence*** of any direct infringement. Of the three treating psychiatrists who testified, only one (Dr. Alva) had ever genotyped a patient for whom he prescribed iloperidone. *See* D.I. 179, ¶¶ 20-25. Neither Dr. Kaye nor Dr. Preskorn had ever genotyped a patient in connection with prescribing iloperidone, and Dr. Preskorn had never genotyped *any* patient in his clinical practice. *Id.* ¶ 22. Further, Dr. Preskorn also admitted that he has never practiced any claim of the '610 patent. *Id.*

Even Dr. Alva, who genotyped four of eighteen patients, did not prescribe iloperidone in a manner that is covered by the claims of the '610 patent. Of the patients Dr. Alva genotyped, only one was a poor metabolizer, and that patient was prescribed an initial target iloperidone dose of greater than 12 mg/day. D.I. 179, ¶ 25. Even after genotyping a different patient and determining that patient was an extensive metabolizer, Dr. Alva continued to prescribe 12 mg/day (which is not in the claimed range for extensive metabolizers), for more than two years, until the patient's *symptoms* required an increase. *Id.* This is merely titrating to efficacy rather than adjusting dose based on genotype, which does not infringe. D.I. 179, ¶¶ 13-14.

2. The Label Does Not Encourage, Recommend or Promote a Physician to Perform the Claimed Method

Plaintiffs' brief failed to identify evidence that Roxane's label will recommend, encourage or promote infringement. Claim 1, for example, recites "determining whether the patient is a CYP2D6 poor metabolizer" by first "obtaining or having obtained a biological sample from the patient" and then "performing or having performed a genotyping assay … to determine if the patient has a CYP2D6 poor metabolizer genotype." JX-1, at 11. Every claim requires that the prescriber first perform or have performed such genotyping assay, and ***then***, based on the results, administer doses within specified ranges. The claim is unambiguous: based on the results of a genotyping assay, the prescriber must administer doses within particular specified ranges. Tr. 130:14-131:3 (Polymeropoulos), 396:16-398:3 (Kaye); *see* D.I. 178, ¶ 23.

"[I]n the Hatch-Waxman Act context . . . [t]he label must encourage, recommend, or promote infringement." *Takeda II*, 785 F.3d at 631. Plaintiffs have failed to prove that Roxane's proposed label will induce any physician to practice that method.

Plaintiffs have offered no evidence that Roxane's label in any way recommends or promotes taking a biological sample for purposes of performing a genotyping assay, which is the first mandated method step. D.I. 179, ¶ 19. The most that Plaintiffs can propose is that "[a]ll commercially available laboratory tests to determine whether a patient is a genotypic CYP2D6 poor metabolizer involve obtaining a biological sample from the patient" (D.I. 178, ¶ 33), which is facially insufficient to prove inducement. The label plainly contains no ***recommendation*** to obtain a biological sample for genotyping, and Vanda does not assert otherwise. D.I. 179, ¶ 19. And the testimony of various experts who addressed the issue confirms the absence of any such recommendation. *Id.* Plaintiffs' claims fail for this reason alone.

As to the second step, Plaintiffs baldly assert that Roxane's proposed label recommends

genotyping, but notably provide no citation to any evidence for that assertion. D.I, 178, ¶ 32. The evidence in fact showed that the plain meaning of the lone label language cited by Vanda—that laboratory tests "are available"—is not a recommendation, but merely informative. D.I. 179, ¶ 17. The FDA has mandated language in other drug labels that specifies genotyping and recites that genotyping ***is*** "recommended" in connection with prescribing those drugs. D.I. 179, ¶ 18. And the language in Roxane's label makes no reference to genotyping at all, much less recommends dosing based on the results of a genotyping assay. The absence of such language in the iloperidone label shows that the Roxane label does not contain such a recommendation.

Indeed, Plaintiffs' conclusory assertion that the label "recommends that practitioners perform . . . a genotyping assay" is impugned by a host of objective reviews of the label—by PharmGKB, Vivot, and Plaintiffs' own consultant, Dr. Weiden—which conclude otherwise. D.I. 179, ¶ 26-31. That proof—which parallels the inducement inquiry—squarely and objectively refutes Plaintiffs' claim of inducement. Plaintiffs' claim is also belied by Vanda's statements to the EMA that the iloperidone label contains no restrictions on use of the drug and has been used safely for years "in the absence of genotyping." D.I. 179, ¶ 26.

Plaintiffs' corollary assertion that "[t]he only commercially available laboratory tests to determine whether a patient is a genotypic CYP2D6 poor metabolizer are genotyping tests" (D.I 178, ¶ 32), is both circular and does not satisfy the requirement that the label "recommend" the method step of performing or having performed a genotyping assay in any event.

At bottom, Vanda asserts that a physician could discern from the label that assays are available and could learn from information outside the label that commercially available tests typically involve genotyping, which in turn would utilize a biological sample. D.I. 178, ¶¶ 32-33. But that theory fails to establish that Roxane's label recommends or promotes infringement.

At best, Vanda contends that a physician could learn how to practice the claimed methods by reading the label and consulting information concerning "commercially available" genotyping tests, but that runs squarely into the Federal Circuit's determination that "[m]erely 'describing' an infringing mode is not the same as 'recommed[ing]." *Takeda II*, 785 F.3d at 631 (citation omitted). And the Federal Circuit has likewise rejected a theory of induced infringement in the ANDA context that is predicated on a "look outside the label to understand the alleged implicit encouragement in the label." *Id.* at 634.

Moreover, Vanda's theory is also an example of what the Federal Circuit has warned against—"vague label language cannot be combined with speculation about how physicians may act to find inducement." *Id.* at 632. The real-world evidence belies any assertion that physicians follow the claimed method, and Vanda's supposition as to how a hypothetical physician could act is insufficient to establish inducement. *Id.*

Nor does the label recommend dosing based CYP2D6 status as required by the claims. In fact, Roxane's label mandates a different way to determine the appropriate dose: titration to efficacy. D.I. 179, ¶ 13. Physicians must start all patients at a low dose (below 12 mg/day) and slowly increase the dose to avoid side effects. *Id.* ¶ 58. No genotype information is required to titrate to efficacy. *Id.* ¶ 13. And by mandating titration "to an effective dose," the label means that the physician must stop the titration process at the lowest dose necessary to achieve efficacy. Tr. 401:23-402:10 (Kaye); *see also* 316:4-318:12 (Alva). This also does not require any genotype information. Physicians use the label's "target" range of 12 to 24 mg/day information in the context of titrating to efficacy—it is the patient's response to the drug that informs the dosing decision. This explicit, mandatory label requirement conflicts with the claim requirement that the results of a genotyping assay determine the dosing amount.

Even if a physician were inclined to determine a patient's CYP2D6 status, the testimony at trial overwhelmingly established that a physician can determine or deduce that a patient may be a CYP2D6 poor metabolizer from (i) the patient's history with other drugs (ii) the patient's response to iloperidone during titration to efficacy (iii) measuring the patient's blood levels of iloperidone and its relevant metabolites, and/or (iv) other phenotype laboratory tests like those described but not claimed in the '610 patent. D.I. 179, ¶¶ 15-17. The statement that PMs should have their dose reduced by one-half is entirely consistent with the uniform testimony at trial that physicians dose based on their clinical judgment, not based on genotyping tests. *Id.*¶¶ 20-25. For example, Plaintiffs' expert conceded that in titrating to efficacy, consistent with the label, the final dose can be below or above the target range. *Id.* ¶ 24.

Finally, even if Plaintiffs' theory regarding the practice of physicians were correct, the numerical ranges that would result from that practice do not correspond to the claimed ranges: (1) EMs are not restricted by the label to "greater than 12 mg/day," but may receive 12 mg/day, or may receive less if efficacy is achieved at a lower dose during titration, D.I. 179 ¶ 24; (2) IMs/heterozygotes are included within the patent's definition of poor metabolizers, but would not have their dose reduced under Plaintiffs' interpretation of the label, *id.* ¶ 34; and (3) titrating to efficacy can result in a dose of more than 12 mg/day for a CYP2D6 poor metabolizer—a practice Dr. Alva testified was consistent with the iloperidone labeling, *id.* ¶ 24.

3. Plaintiffs Presented No Evidence of Intent to Induce Infringement

Plaintiffs' Proposed Findings of Fact make no mention of the intent element of their claims of infringement. D.I. 178 at *passim*. That failure of proof itself is sufficient to enter judgment in Roxane's favor on the issue. *See Takeda II*, 785 F.3d at 631 (inducement requires "evidence [of] 'intent to encourage infringement'") (citation omitted).

Plaintiffs offer the stray statement that "Roxane agrees that its expectations for use are

laid out in its Proposed Label," but they do not tether that proposed finding to the requisite intent to encourage infringement. D.I. 178, ¶ 26. Moreover, Roxane's interpretation of the label, as set forth in its notice letter, is that the label does not recommend genotyping. D.I. 179, ¶ 38. Given that Roxane's notice letter is consistent with a host of objective evidence presented in this case, its interpretation of the label is entirely reasonable and belies any suggestion that Roxane intends to encourage infringement. *Id.* ¶¶ 26-31, 47.

Plaintiffs' proposed Conclusions assert that Roxane's non-inducement argument requires that physicians fail to follow the label. D.I. 178, ¶ 74. As set forth above, the label does not recommend the claimed method. Plaintiffs' reliance on *AstraZeneca* for the notion that "it is irrelevant that some users may ignore the warnings in the proposed label," is therefore misplaced. *See AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1060 (Fed. Cir. 2011). *AstraZeneca* holds that "the pertinent question is *whether the proposed label instructs users to perform the patented method.*" 633 F.3d at 1060. In that case, the district court determined that the dosing regimen "would *inevitably* lead some consumers to practice the claimed method." *Id.* (emphasis added). The Federal Circuit also noted the district court's finding that "there was insufficient evidence to establish that any non-infringing use of the generic drug was substantial." *Id.* at 1059-60. Further, the Court noted that Apotex was aware of an infringement problem but proceeded with its ANDA. *Id.* The Court found no abuse of discretion in granting a preliminary injunction—it did not hold that inducement had been established. *Id.* at 1061.

Here, the objective evidence that the iloperidone label does not recommend genotyping, combined with Roxane's Notice Letter statements to the same effect, refutes any potential suggestion that there was any infringement "problem" of which Roxane was aware. D.I. 179, ¶ 38. Further, the non-infringing uses proven at trial do not require that users ignore the

warnings in the proposed label—they are entirely consistent with the label. *Id.* ¶¶ 20-25, 32-36. Nor is there any legitimate dispute that those non-infringing uses are substantial— for instance, heterozygotes vastly outnumber PMs, Dr. Preskorn has used phenotyping but not genotyping, and there is evidence of extensive metabolizers receiving 12 mg/day (lower than the patents recite for such metabolizers) whereas there is no evidence of actual infringement. *Id.* ¶ 35. The existence of such non-infringing uses warrants rejecting Plaintiffs' conclusory assertion of intent. *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1365 (Fed. Cir. 2003); *Takeda Pharm. USA, Inc. v. West-Ward Pharm. Corp.*, 72, F. Supp. 3d 539, 543-44 (D. Del 2014), *affirmed by Takeda II.*

III. THE ASSERTED CLAIMS OF THE '610 PATENT ARE INVALID UNDER 35 U.S.C. § 101 FOR LACK OF PATENTABLE SUBJECT MATTER

Plaintiffs' proposed findings of fact regarding patentable subject matter contain not a single citation to any testimony of their own experts—none of those experts provided any testimony on this issue. This is despite the fact that Vanda resisted summary judgment because "[t]he Court will hear conflicting fact and expert testimony about these issues." D.I. 140, at 1. But there was no conflicting testimony—Dr. Ratain's factual testimony was unrebutted.

Plaintiffs dispute Dr. Ratain's testimony that the more iloperidone a patient has in his system, the higher the side effects would be, relying on the Novartis 0104 study. D.I. 178, ¶ 62. But Plaintiffs cannot dispute that the purported "discovery" of the '610 patent is that increased blood levels of iloperidone result in increased QTc prolongation—indeed, that is the lone basis for their assertion that they have satisfied the written description requirement. *Id.* ¶¶ 65, 98; *see also* D.I. 179, 111. That is precisely the type of law of nature found unpatentable in *Mayo*, which conclusively established that "relationships between concentrations of certain metabolites in the blood and the likelihood that a dosage of a [] drug will prove ineffective or cause harm"

are not patentable under 35 U.S.C. § 101. *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289, 1296-97 (2012). Essentially, Plaintiffs argue that because it was unknown how blood levels correlated to the presence of side effects, discovering that correlation is somehow patentable. However, the purported discovery of a natural phenomenon or law of nature is not patentable, even if previously unknown. *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107, 2117 (2013).

Plaintiffs concede that the asserted claims "depend, in part, on how the body metabolizes iloperidone." D.I. 178, ¶ 63. Plaintiffs then assert that merely because the '610 patent allegedly claims useful applications of that natural processes, they are patent eligible subject matter. *Id.* This is not sufficient. Instead, if the claims are directed toward patent-ineligible subject matter, the court must "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." *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2355 (2014) (citation omitted). The claims of the '610 patent do not satisfy that requirement.

The Supreme Court expressly determined that adjusting the dose of a drug to reduce the risk of a side effect is routine and conventional activity. *Mayo*, 132 S. Ct. at 1297-98; *see also Endo Pharm. Inc. v. Actavis Inc.*, C. A. No. 14-1381-RGA, 2015 WL 7253674, at *1, 3 (D. Del. Nov. 17, 2015). Plaintiffs assert that determining the appropriate dose requires empirical research, but courts have held that mere empirical confirmation of appropriate dosage information is not patentable. *Hoffmann-LaRoche Inc. v. Apotex, Inc.*, C. A. No. 07-4417 (SRC)(MAS), 2012 WL 4661588, at *7 (D.N.J. Oct. 1, 2012). Moreover, although Plaintiffs conflate the 101 and 102 inquiries, the question for 101 is not whether the results would have been predictable, but merely whether the application of natural laws is routine and conventional.

Dr. Ratain provided unrebutted testimony that the dosages recited in the claims qualify because FDA requires studies to determine the appropriate dose adjustments based on CYP2D6 status and other genetic factors. D.I. 179, ¶ 61.

Finally, Plaintiffs assert that Novartis's 0104 study demonstrates that the dosage adjustments were not routine or conventional, alleging that Novartis failed to identify that any dose adjustment was necessary. D.I. 178, ¶ 58. But the salient point is that Novartis performed the study pursuant to the FDA Guidance, which shows that it is conventional. Tr. 524:10-525:10, 533:6-534:16 (Ratain). Dr. Polymeropoulos conceded that the data from that Novartis study supported the claimed subject matter of reducing the dose of iloperidone. D.I. 179, ¶ 95. Thus, Plaintiffs cannot contend that Novartis failed to determine that dose adjustments were necessary when Vanda relied on that Novartis data in support of its proposed dose adjustments.

IV. THE ASSERTED CLAIMS OF THE '610 PATENT ARE INVALID AS OBVIOUS

Plaintiffs suggest that because one study (Mutlib) failed to recover meaningful amounts of the CYP2D6 metabolite *in vivo*, a skilled artisan would have assumed that CYP2D6 was not a major pathway despite the *in vitro* evidence showing CYP2D6 was involved. But Subramanian disclosed that the CYP2D6 metabolite identified by Mutlib was further metabolized to form P95—an inactive metabolite of iloperidone that was recovered in the study. Tr. 979:20-982:25 (Guengerich). Thus, Mutlib, in combination with Subramanian, suggested that iloperidone was metabolized by CYP2D6. As a result, the 1997 FDA guidance directed a skilled artisan to determine iloperidone pharmacokinetics in relation to CYP2D6 metabolism. D.I. 179, ¶ 81.

Plaintiffs' non-obviousness assertions rest primarily on the allegation that whether and to what extent dose reductions would result in decreased QTc prolongation would have been unpredictable. But Dr. Ratain explained that the studies to determine the appropriate dose adjustments were routine, as confirmed by the prior art. D.I. 179, ¶ 62. The FDA Guidance

expressly required those studies. *Id.* Moreover, while Kirchheiner showed a range of possible dose adjustments for various drugs and notes that for certain drugs prescribed by psychiatrists, 50% was the most prevalent reduction. *Id.* ¶ 60. Thus Kirchheiner taught skilled artisans the likely range of dose adjustments, with a 50% reduction being a predictable result. *Id.* ¶¶ 59-62.

Plaintiffs' alleged secondary considerations are unpersuasive. Plaintiffs assert that a long-felt, unmet need existed for atypical antipsychotics, but they presented no evidence that iloperidone satisfied any need. Indeed, Plaintiffs' experts conceded that schizophrenia continues to be difficult to treat. Tr. 307:22-309:21 (Alva.) Plaintiffs' reliance on the transactions between Novartis and Vanda to support non-obviousness (D.I. 178, ¶ 59) omit that Novartis received additional compensation besides the $500,000 up-front payment. Vanda overtook responsibility for further development and commercialization, while Novartis was to receive a 10% royalty and milestones. Tr. 84:6-14 (Polymeropoulos). Further, Plaintiffs failed to establish any nexus between those transactions and the '610 patent claims: Novartis could not have been motivated by the '610 patent, REDACTED. D.I. 179, ¶ 6.

V. THE ASSERTED CLAIMS OF THE '610 PATENT ARE INVALID FOR LACK OF WRITTEN DESCRIPTION

Plaintiffs' written description arguments cannot be reconciled with their positions asserting nonobviousness and patentable subject matter. Plaintiffs contend that the prior art provided insufficient information for a skilled artisan to determine whether or how much to reduce the dose for poor metabolizers, but wholly ignore that the '610 patent contains no more information than the prior art.

To comply with the written description requirement, the specification must describe the entire claimed ranges. *In re Wertheim*, 541 F.2d 257, 263-64 (C.C.P.A. 1976). It is insufficient that the claim an obvious variant; it must be described with all its elements. *Lockwood v. Am.*

Airlines, Inc., 107 F.3d 1565, 1572 (Fed. Cir. 1997). The excerpts Plaintiffs cite (D.I. 179, ¶ 65) do not satisfy that standard—they identify doses of 18 mg/day, 12 mg/day, or 6 mg/day, which provides a description of neither: (i) the claimed range for poor metabolizers of 12 mg/day or less, nor (ii) the claimed range limiting patients who are not poor metabolizers to greater than 12 mg/day, up to 24 mg/day.

Instead, Plaintiffs incorrectly imply that the written description requirement is satisfied if the claimed ranges encompass some of the doses set forth within the specification. Plaintiffs' assertion that Table 3 describes the invention conflicts with their non-obviousness position. Plaintiffs state—with no expert testimony—that Table 3 supports the claims by disclosing a higher iloperidone to metabolite ratio. D.I. 178, ¶ 65. Yet Plaintiffs contend that information regarding blood concentrations is insufficient to determine appropriate dose adjustments, noting that "[n]ot all side effects are dose-dependent." *Id.* ¶ 52; *see also id.* ¶ 54.

Plaintiffs assert that the '610 patent is non-obvious because the prior art allegedly did not teach whether or how dosage adjustments for CYP2D6 poor metabolizers might reduce risk of QTc prolongation. *Id.* ¶¶ 57-58. But the '610 patent specification provides no information showing that reducing the dose below 12 mg/day for poor metabolizers would reduce the risk of QTc prolongation. D.I. 179, ¶¶ 91-108. The specific dosage regimen in the asserted claims is "supported" only by data that was not disclosed in the patent or otherwise..

Further Plaintiffs' reliance on the ratios of iloperidone to its metabolites in the blood also fails because the specification does not correlate those ratios to higher QTc risk, nor to the claimed genotypes. Tr. 641:17-642:1 (McCulloch). The metabolite ratios in Tables 2-4 and 8-9 cannot be used to link the genotype data appearing in only Tables 2-5 with QTc data appearing only in Tables 8-9. Tr. 642:7-11 (McCulloch). Indirectly related variables can have a negative

association even if the individual relationships have a positive correlation. Tr. 644:15-645:16 (McCulloch). Drawing an indirect correlation is particularly inappropriate here because the phenotypic "poor metabolizers" group specifically included individuals who were not genetic "poor metabolizers" within the meaning of the claims. Tr. 1004:2-1005:13 (Guengerich).

VI. THE ASSERTED CLAIM OF THE RE'198 PATENT IS INVALID AS OBVIOUS

Plaintiffs assert that as of 1989, clozapine was "then the sole atypical antipsychotic." D.I. 178, ¶ 9. For that reason, Plaintiffs contend that skilled artisans would have used only known atypical antipsychotics, such as clozapine, as potential lead compounds. *Id.* ¶ 41. Plaintiffs' argument is unpersuasive. First, prominent publications described risperidone as an atypical antipsychotic in 1986, which motivated research directed to atypical antipsychotics that differed from clozapine. D.I. 179, ¶ 121. Thus, as Dr. Sargent explained, risperidone motivated artisans to seek lead compounds from cyclic butryphenones similar to risperidone, and compounds that contained or could be engineered to contain benzisoxazoles. *Id.* ¶ 122.

Plaintiffs assert that a skilled artisan would consider removing the benzisoxazole moiety from risperidone because Strupczewski's 1985 paper showed that the benzisoxazoles were not atypical antipsychotics. But that paper did *not* show lack of atypicality—it contained no data regarding atypicality. Tr. 814:19-21 (Strupczewski), 840:17-841:16; JX-26. Dr. Bartlett did not testify that removing the benzisoxazole group would be desirable—only that he did not believe atypical activity had been attributed to them. Tr. 839:12-840:16 (Bartlett). Lenperone, however, did show signs of atypicality. Tr. 750:19-752:19, 760:19-761:9 (Sargent). Plaintiffs do not explain why Lenperone's side effects would have "cause[d] one to run away from Compound A," while at the same time asserting that skilled artisans would have sought analogues of clozapine, which was likewise known to have serious side effects.

Plaintiffs' assertion that persons of ordinary skill in the art would have continued to seek

analogues of clozapine ignores the fact that such attempts had been ongoing for decades, and failed. Tr. 672:23-675:25 (Sargent).

Further, a skilled artisan would have modified compound A to arrive at the claimed invention. Plaintiffs acknowledge that "[c]hemists use bioisosteric changes to modify compounds while preserving the activity of the compound." D.I. 178, ¶ 82. A skilled artisan would have sought to preserve antipsychotic activity by making small structural changes. D.I. 179, ¶ 116. This is exactly what happened, as could be expected, by the benzisoxazole substitution.

Plaintiffs primarily rely on the assertion that whether a substitution would result in atypicality was unpredictable. This argument assumes an incorrect legal standard. The RE'198 patent claims the iloperidone compound, and contains no limitations requiring atypicality. D.I. 179, ¶ 132. Nor does the RE'198 specification contain any data suggesting atypicality. *Id.* All that is required is a reasonable expectation that iloperidone would preserve the antipsychotic activity of the prior art compound, a result which is unsurprising. In the cases Plaintiffs cite, the claimed inventions were established to demonstrate "unexpected results," which Plaintiffs did not asserted here. *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1079 (Fed. Cir. 2008); *Daiichi Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1352 (Fed. Cir. 2010).

VII. EVEN TO THE EXTENT PLAINTIFFS PREVAIL, THEY ARE NOT ENTITLED TO INJUNCTIVE RELIEF PAST THE EXPIRATION OF THE RE'198 PATENT

Plaintiffs assert that if they prevail, the Court should order the effective approval date of Roxane's ANDA no sooner than the expiration of the '610 patent, under 35 U.S.C. § 271(e)(2). The only case Plaintiffs cite for this proposition addressed post-expiration injunctive relief based on FDA market exclusivity. *In re Omeprazole Patent Litig.*, 536 F.3d 1361, 1367 (Fed. Cir. 2008). That circumstance is wholly inapplicable here.

Another court recently declined to alter the effective date of an ANDA under circumstances similar to the present case. *Endo Pharm. Inc. v. Amneal Pharm. Inc.,* 12 Civ. 8115 (TPG), 2016 WL 1732751 (S.D.N.Y. Apr. 29, 2016). The *Endo* court determined that plaintiffs were not entitled to relief under 35 U.S.C. § 271(e)(4)(A) based on patents that issued after defendants filed their ANDAs. The court held that the statute's use of the past-tense in defining the act of infringement—submitting an ANDA for "a drug claimed in a patent or the use of which is claimed in a patent"— refers to "a patent that has already been issued at the time of the ANDA's submission." *Endo*, 2016 WL 1732751 at *3.

Roxane's ANDA was filed before the '610 patent issued. U.F. ¶¶ 10, 29; F.O.F. ¶167. Under the reasoning of *Endo*, Plaintiffs are not entitled to relief under 35 U.S.C. § 271(e)(4)(A).

Plaintiffs' alternate request for a permanent injunction contains not one citation to factual evidence. D.I. 178, ¶¶ 100-102. It relies on attorney argument that Vanda allegedly will suffer irreparable harm that cannot be compensated by money damages. Not only has Vanda failed to substantiate these claims, it makes no attempt to tie them to the '610 patent. The '610 patent does not claim *all* uses of iloperidone—it claims only particular dosage adjustments based on genotyping. In light of the undisputed evidence that the majority of physicians prescribe iloperidone without genotyping, Plaintiffs cannot establish that any *de minimis* alleged infringement would inflict irreparable harm. Moreover, the public interest would be particularly disserved by excluding generic drugs from the market based on a patent that does not cover the majority of the drug's uses. Plaintiffs' requests for injunctive relief should be denied.

VIII. CONCLUSION

Accordingly, Roxane does not infringe the asserted claims of the '610 patent, and the asserted claims of the '610 patent and asserted claim 3 of the RE'198 patent are invalid for the reasons stated above and in Roxane's proposed findings of fact and conclusions of law.

Respectfully submitted,

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